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Original Investigation

Transcatheter Aortic Valve Implantation in Failed Bioprosthetic Surgical Valves

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IMPORTANCE Owing to a considerable shift toward bioprosthesis implantation rather than mechanical valves, it is expected that patients will increasingly present with degenerated bioprostheses in the next few years. Transcatheter aortic valve-in-valve implantation is a less invasive approach for patients with structural valve deterioration; however, a comprehensive evaluation of survival after the procedure has not yet been performed.

OBJECTIVE To determine the survival of patients after transcatheter valve-in-valve implantation inside failed surgical bioprosthetic valves.

DESIGN, SETTING, AND PARTICIPANTS Correlates for survival were evaluated using a multinational valve-in-valve registry that included 459 patients with degenerated bioprosthetic valves undergoing valve-in-valve implantation between 2007 and May 2013 in 55 centers (mean age, 77.6 [SD, 9.8] years; 56% men; median Society of Thoracic Surgeons mortality prediction score, 9.8% [interquartile range, 7.7%-16%]). Surgical valves were classified as small (≤21 mm; 29.7%), intermediate (>21 and <25 mm; 39.3%), and large (≥25 mm; 31%). Implanted devices included both balloon- and self-expandable valves.

MAIN OUTCOMES AND MEASURES Survival, stroke, and New York Heart Association functional class.

RESULTS Modes of bioprosthesis failure were stenosis (n = 181 [39.4%]), regurgitation (n = 139 [30.3%]), and combined (n = 139 [30.3%]). The stenosis group had a higher percentage of small valves (37% vs 20.9% and 26.6% in the regurgitation and combined groups, respectively; P = .005). Within 1 month following valve-in-valve implantation, 35 (7.6%) patients died, 8 (1.7%) had major stroke, and 313 (92.6%) of surviving patients had good functional status (New York Heart Association class I/II). The overall 1-year Kaplan-Meier survival rate was 83.2% (95% CI, 80.8%-84.7%; 62 death events; 228 survivors). Patients in the stenosis group had worse 1-year survival (76.6%; 95% CI, 68.9%-83.1%; 34 deaths; 86 survivors) in comparison with the regurgitation group (91.2%; 95% CI, 85.7%-96.7%; 10 deaths; 76 survivors) and the combined group (83.9%; 95% CI, 76.8%-91%; 18 deaths; 66 survivors) (P = .01). Similarly, patients with small valves had worse 1-year survival (74.8% [95% CI, 66.2%-83.4%]; 27 deaths; 57 survivors) vs with intermediate-sized valves (81.8%; 95% CI, 75.3%-88.3%; 26 deaths; 92 survivors) and with large valves (93.3%; 95% CI, 85.7%-96.7%; 7 deaths; 73 survivors) (P = .001). Factors associated with mortality within 1 year included having small surgical bioprosthesis (≤21 mm; hazard ratio, 2.04; 95% CI, 1.14-3.67; P = .02) and baseline stenosis (vs regurgitation; hazard ratio, 3.07; 95% CI, 1.33-7.08; P = .008).

CONCLUSIONS AND RELEVANCE In this registry of patients who underwent transcatheter valve-in-valve implantation for degenerated bioprosthetic aortic valves, overall 1-year survival was 83.2%. Survival was lower among patients with small bioprostheses and those with predominant surgical valve stenosis.

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Group Information: The Valve-in-Valve International Data Registry Investigators are listed in eTable 1 in the Supplement.

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Surgical aortic valve replacements increasingly use bioprosthesis implants rather than mechanical valves.[1] Structural valve deterioration can result in leaflet degeneration and failure, as evidenced by valve stenosis, regurgitation, or a combination of both.[2-4] Owing to a considerable shift toward bioprosthesis implantation, it is expected that patients will increasingly present with degenerated bioprostheses. Treatment of patients with failed bioprostheses is a clinical challenge. Although reoperation is considered the standard of care, these patients are frequently elderly, and repeat cardiac surgery carries significant morbidity and mortality risks.[5,6]

Transcatheter aortic valve replacement has become an alternative, less invasive treatment for patients at high surgical risk with severe symptomatic native aortic valve stenosis.[7-11] Previous reports have demonstrated the feasibility of treating degenerated bioprostheses with transcatheter heart valves inside failed surgical valves (eFigure 1 in the Supplement).[12-16] Preliminary data from the Valve-in-Valve International Data (VIVID) Registry revealed that although procedural success was achieved in 93.1% of patients, the valve-in-valve procedure included several safety and efficacy concerns.[17] However, a comprehensive long-term evaluation of valve-in-valve procedures of a larger group of patients with considerable follow-up has not yet been performed.

Methods

Registry Design
The VIVID Registry was initiated in December 2010 and was designed to collect data on valve-in-valve procedures using mainly self-expandable CoreValve (Medtronic) and balloon-expandable Edwards SAPIEN devices (Edwards Lifesciences). Valve-in-valve procedures performed using other transcatheter devices or implanted in positions other than the aortic valve were not included in the current analyses. We collected data retrospectively for cases performed before registry initiation and prospectively thereafter. A total of 55 centers from Europe, North America, Australia, New Zealand, and the Middle East contributed data (eTable 1 in the Supplement). Data were collected for cases performed between 2007 and May 2013 using a dedicated case report form. All inconsistencies were resolved directly with local investigators and on-site data monitoring. All patients gave written informed consent to a transcatheter aortic valve-in-valve procedure. The inclusion of patients was approved in each center by a local ethics committee.

Definitions
Prediction of patient operative mortality after conventional surgical valve replacement was calculated using the Society of Thoracic Surgeons (STS) score (http://riskcalc.sts.org /de.aspx) and the LogEuroSCORE (http://www.euroscore .org/calcold.html). Mechanism of bioprosthetic valve failure (ie, stenosis, regurgitation, or combined) was evaluated according to the criteria of the American Society of Echocardiography.[18] Patients with at least a moderate degree of both stenosis and regurgitation were included in the combined group. Other patients were categorized according to the primary mechanism of failure, either in the stenosis group or in the regurgitation group. Body surface area was calculated using the Mosteller formula. Internal diameter of a surgical valve was derived from its label size and manufacturer charts.[19] In cases for which label size was unknown, internal diameter was defined according to available imaging modes, such as computed tomography or transesophageal echocardiography. Major clinical end points were assessed according to the Valve Academic Research Consortium criteria.[20] Early postimplantation hemodynamic data were obtained from either intraprocedural or first postprocedural echocardiogram. Post–valve-in-valve severe prosthetic-patient mismatch (PPM) was defined in cases that had a postprocedure effective aortic orifice area divided by body surface area of less than 0.65 cm²/m².[21]

Statistical Analysis
Results are presented as mean (standard deviation) for continuous variables with normal distribution, as median (interquartile range) for continuous variables without normal distribution, and as number (percentage) for categorical data. The t test was used to compare normally distributed continuous variables between the devices used during the valve-in-valve procedure and the Wilcoxon rank sum test was used for variables not normally distributed. One-way analysis of variance was used to compare the stenosis, regurgitation, and combined groups for normally distributed continuous variables and the Kruskal-Wallis test was used for non–normally distributed data. The χ^2 and Fisher exact tests were used to compare categorical variables. Time-to-event curves using the Kaplan-Meier method were calculated. Results were compared using the log-rank statistic. High postprocedural gradients were defined as those having mean gradients of at least 20 mm Hg.[20] Variables entered into bivariable models included sex, age, baseline echocardiographic parameters (ie, left ventricular ejection fraction), STS score, baseline renal failure, bioprosthetic type (stented vs stentless) and size, device used during the valve-in-valve procedure, and procedural access. Three semiparametric Cox proportional hazards regression analyses were conducted. The first was an overall analysis and the others were time-segmented analyses. For the latter, the hazard function was used as a guide to determine approximate time points for the end of the early phase of hazard and the beginning of the late phase. This occurred at approximately 30 days. Therefore, piece-wise time-segmented Cox analyses were performed for 2 periods. For one pair of analyses, deaths occurring within the first 30 postoperative days were analyzed, with follow-up beyond that time set to 30 days; then deaths beyond 30 days were analyzed. Characteristics included in the multivariable model for 1-year death were bioprosthesis label size, mechanism of failure, procedural access, and STS score. The results of the multivariable analysis are presented as hazard ratios (HRs) for 1-year mortality with 95% confidence intervals. A 2-sided $P<.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 20.0 statistical software (IBM SPSS Inc).

Table 1. Baseline Characteristics at the Time of Valve-in-Valve Procedure

Characteristics	All (n = 459)	Mechanism of Surgical Valve Failure				Device Used		
		Stenosis (n = 181)	Regurgitation (n = 139)	Combined (n = 139)	P Value	Self-Expandable (n = 213)	Balloon-Expandable (n = 246)	P Value
Age, mean (SD), y	77.6 (9.8)	78.8 (7.8)	77.1 (10.6)	76.6 (11.1)	.10	77.6 (10)	77.6 (9.7)	.95
Men, No. (%)	257 (56)	87 (48)	93 (66.9)	77 (55.4)	.002	113 (53.1)	144 (58.5)	.25
Height, mean (SD), cm	167.2 (9.8)	167.1 (9.9)	168.1 (9.7)	166.5 (9.8)	.20	166.9 (10)	167.4 (9.7)	.59
Weight, mean (SD), kg	73.9 (15.2)	77.6 (16.5)	72 (13.3)	70.8 (14.1)	<.001	73.7 (15)	74 (15.4)	.84
BMI, mean (SD)[a]	26.4 (4.8)	27.7 (4.8)	25.4 (3.9)	25.5 (4.2)	<.001	26.4 (4.6)	26.3 (4.4)	.78
BSA, mean (SD), m^2	1.85 (0.22)	1.89 (0.24)	1.83 (0.2)	1.8 (0.21)	.002	1.84 (0.22)	1.85 (0.23)	.76
LogEuroSCORE, median (IQR), %[b]	29 (19.1-42.3)	29.8 (20-39.9)	25.7 (16-41.9)	30.3 (22.3-44.7)	.18	29 (18.6-38.7)	29 (19.3-44.2)	.48
STS score, median (IQR), %[b]	10 (6.2-16.1)	9.9 (6.1-13.9)	9.9 (5.8-15.6)	10.8 (7.1-18.4)	.33	11 (6.2-17.3)	9.3 (6.1-14.1)	.13
Diabetes mellitus, No. (%)	125 (28.7)	69 (40.1)	28 (21.2)	28 (21.4)	.001	62 (31.1)	63 (26.5)	.29
Peripheral vascular disease, No. (%)	114 (26.1)	53 (30.6)	31 (23.5)	30 (22.9)	.22	37 (17.4)	77 (31.3)	<.001
Chronic renal failure, No. (%)[c]	224 (48.8)	80 (44.2)	71 (51.1)	72 (51.8)	.37	81 (38)	140 (56.9)	<.001
Previous stroke/TIA, No. (%)	51 (11.7)	23 (13.3)	17 (12.8)	12 (9.2)	.52	24 (12.2)	27 (11.3)	.76
>1 Previous SAVR, No. (%)	62 (13.5)	16 (8.8)	23 (16.5)	23 (16.5)	.06	27 (12.7)	35 (14.2)	.63
NYHA functional class, No. (%)								
II	35 (7.8)	14 (7.7)	10 (7.2)	11 (7.9)	.97	15 (7)	20 (8.1)	.66
III	283 (61.9)	130 (71.8)	78 (56.1)	75 (54)	.001	124 (58.2)	159 (64.6)	.16
IV	141 (30.3)	37 (26.2)	51 (36.7)	53 (38.1)	.001	74 (34.7)	67 (27.2)	.08
Left ventricular ejection fraction, mean (SD), %	50.3 (13.1)	51.7 (12.9)	49.0 (13.1)	49.7 (13.3)	.16	49.1 (13.4)	51.2 (12.8)	.08

Abbreviations: BMI, Body mass index; BSA, body surface area; IQR, interquartile range; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack.

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[b] Prediction of operative mortality after conventional surgical valve replacement (STS score: http://riskcalc.sts.org/de.aspx; LogEuroSCORE: http://www.euroscore.org/calcold.html). Range of scores is 0% to 100%; higher score indicates greater patient risk.

[c] Calculated glomerular filtration rate <60 mL/min.

Results

Patient Demographics

Table 1 shows clinical characteristics of the 459 patients included in the registry. Mean age was 77.6 (SD, 9.8) years (range, 25-92 years) and 56% were men. The mechanism of failure of surgical bioprostheses was stenosis in 181 patients (39.4%), regurgitation in 139 (30.3%), and combined in 139 (30.3%). The balloon-expandable device was used in 246 patients (53.6%) and the self-expandable in 213 patients (46.4%). The distribution of failure mode differed between the balloon-expandable device group (stenosis, n = 106 [43.1%]; regurgitation, n = 61 [24.8%]; combined, n = 79 [32.1%]) and the self-expandable device group (stenosis, n = 75 [35.2%]; regurgitation, n = 78 [36.6%]; combined, n = 60 [28.2%]), as more regurgitant bioprostheses were treated by self-expandable device implantation (P = .02). There were no significant differences in surgical risk scores when patients were stratified according to mechanism of failure or according to the device used during the valve-in-valve procedure. The stenosis group had more women and higher patient body weight, body mass index, and body surface area levels in comparison with the other groups (Table 1).

Degenerated Bioprosthetic Valves and Characteristics of Valve-in-Valve Procedures

Patients included in the registry had 1 to 4 previous cardiac surgeries (**Table 2** and eTable 2 in the Supplement). Surgical valve sizes were characterized as small (label size ≤21 mm; n = 133 [29%]), intermediate (>21 mm and <25 mm; n = 176 [38.3%]), large (≥25 mm; n = 139 [30.3%]), and unknown (n = 11 [2.4%]). Bioprostheses were either stented (n = 366 [79.7%]) or stentless (n = 93 [20.3%]). The stenosis group had more stented valves (95.6% vs 60.4% in the regurgitation group and 78.4% in the combined group; P < .001) and more small valves (37% vs 20.9% and 26.6%, respectively; P = .005). There was no significant difference between the self-expandable and balloon-expandable device groups in the rate of valve-in-valve procedures performed in small bioprostheses (31.9% vs 26.4%, respectively; P = .19).

Devices used included balloon-expandable 20-mm, 23-mm, 26-mm, and 29-mm sizes (58.9% SAPIEN XT) and self-expandable 23-mm, 26-mm, 29-mm, and 31-mm sizes. eTable3 in the Supplement shows data on valve-in-valve procedural characteristics. Device delivery access included transfemoral (n = 270 [58.8%]), transapical (n = 171 [37.3%]), transaxillary (n = 13 [2.8%]), and direct aortic (n = 5 [1.1%]). The main ac-

Table 2. Surgical Valve Characteristics at the Time of Valve-in-Valve Procedure

| Characteristics | All (n = 459) | Mechanism of Surgical Valve Failure | | | | Device Used | | |
		Stenosis (n = 181)	Regurgitation (n = 139)	Combined (n = 139)	P Value	Self-Expandable (n = 213)	Balloon-Expandable (n = 246)	P Value
Time since last SAVR, median (IQR), y[a]	9 (6-12)	8 (5-11)	10(7-14)	10 (7-14)	.04	9 (7-13)	9 (6-12)	.08
Type, No. (%)					<.001			<.001
Stented	366 (79.7)	173 (95.6)	84 (60.4)	109 (78.4)		152 (71.4)	214 (87)	
Stentless	93 (20.3)	8 (4.4)	55 (29.6)	30 (21.6)		61 (28.6)	32 (13)	
Label size, No. (%)								
≤21 mm	133 (29)	67 (37)	29 (20.9)	37 (26.6)	.005	68 (31.9)	65 (26.4)	.19
>21 mm and <25 mm	176 (38.3)	74 (40.9)	43 (30.9)	59 (42.4)	.09	83 (39)	93 (37.8)	.80
≥25 mm	139 (30.3)	34 (18.8)	65 (46.8)	40 (28.8)	<.001	53 (24.9)	86 (35)	.02
Unknown	11 (2.4)	6 (3.3)	2 (1.4)	3 (2.2)	.54	9 (4.2)	2 (0.8)	.02
Internal diameter, No. (%)								
<20 mm	126 (27.5)	53 (29.3)	32 (23)	41 (41.7)	.37	66 (31)	60 (24.4)	.11
≥20 mm and <23 mm	230 (50.1)	102 (56.4)	64 (34.5)	64 (46)	.10	100 (46.5)	130 (52.8)	.21
≥23 mm	103 (22.4)	26 (14.4)	43 (30.9)	34 (24.5)	.002	46 (21.6)	57 (23.2)	.69
AV area, mean (SD), cm²	0.95 (0.48)	0.69 (0.21)	1.48 (0.6)	0.91 (0.31)	<.001	0.99 (0.49)	0.91 (0.46)	.04
AV index, mean (SD), cm²/m²[b]	0.51 (0.28)	0.38(0.13)	0.83 (0.37)	0.51(0.19)	<.001	0.55 (0.31)	0.49 (0.25)	.05
AV maximum gradient, mean (SD), mm Hg	60.8 (27.4)	75.2 (23.1)	34.3 (17.7)	64.6 (22.8)	<.001	59.7 (27.2)	61.8 (27.6)	.44
AV gradient, mean (SD), mm Hg	36.2 (18.4)	46.4 (16.1)	18.0 (10.1)	37.6 (14.9)	<.001	35 (18.5)	37.3 (18.3)	.21
AV regurgitation of at least moderate degree, No. (%)[c]	296 (64.5)	22 (12.2)	139 (100)	135 (97.1)	<.001	143 (67.1)	153 (63)	.27

Abbreviations: AV, aortic valve; IQR, interquartile range; SAVR, surgical aortic valve replacement.

[a] Time interval between last SAVR and valve-in-valve procedure.

[b] AV index = AV area (cm²)/patient body surface area (m²).

[c] Evaluated according to the criteria of the American Society of Echocardiography.[18]

cess route in the self-expandable device group was transfemoral (n = 197 [92.5%]) while in the majority of the balloon-expandable device group was transapical (n = 171 [69.5%]; *P* < .001). Device retrieval was attempted in 10.3% of self-expandable procedures. A second transcatheter device was implanted in 5.7% of the total patients (self-expandable, 7.5% vs balloon-expandable, 4.1%; *P* = .05). Ostial coronary obstruction following valve-in-valve implantation occurred in 2% and was more frequent in the stenosis group (3.9%; *P* = .02).

Clinical Outcomes

The median duration of hospital stay after the procedure was 8 days (interquartile range, 5-12 days). At 30 days, 35 patients (7.6%) had died. **Table 3** includes data on procedural outcomes. Patients in the stenosis group had a higher 30-day mortality rate (10.5% vs 4.3% in the regurgitation group and 7.2% in the combined group; *P* = .04). There were no differences between the self-expandable and balloon-expandable device groups in terms of mortality or stroke rates. The balloon-expandable device group had more major/life-threatening bleeding and more acute kidney injury events, while the self-expandable device group had more permanent pacemaker implantation. Aortic regurgitation of at least moderate degree was evident in 25 cases (5.4%) after valve-in-valve procedure and was more common in the regurgitation group (9.4% vs 2.8% in the stenosis group and 5% in the combined group; *P* = .04) and in the self-expandable device group (8.9% vs 2.4% in the balloon-expandable device group; *P* = .002).

The degree of postprocedure residual aortic stenosis was higher in the stenosis group, manifested by lower mean orifice area and higher mean gradient (orifice area, 1.37 [SD, 0.33] cm² and mean gradient, 18.5 [SD, 9.8] mm Hg vs 1.56 [SD, 0.51] cm² and 12 [SD, 6.7] mm Hg in the regurgitation group and 1.56 [SD, 0.65] cm² and 16.1 [SD, 8.3] mm Hg in the combined group, respectively; *P* < .001 for each comparison). Postprocedural gradients were assessed in 429 patients. Moderately elevated postprocedural gradients (mean gradients ≥20 mm Hg) were recorded in 115 patients (26.8%) (eFigure 2 in the Supplement). Elevated postprocedural gradients were more common with balloon-expandable devices in comparison with self-expandable devices (HR, 1.87; 95% CI, 1.21-2.9; *P* = .005); for small surgical valves, 41.2% vs 23.4% (*P* = .04) and for intermediate-sized valves, 35.8% vs 19.4% (*P* = .01), respectively. Severe PPM occurred in 31.8% of patients surviving aortic valve-in-valve procedure. The incidence of severe PPM was lower in patients with predominantly bioprosthesis regurgitation at baseline (19.3% vs 36.1% and 36.4% in those with predominant stenosis and combined failure, respectively; *P* = .03) and higher in patients who received a balloon-expandable device vs a self-expandable device (43.8% vs 15.2%, respectively; *P* < .001). One-year survival was not affected by having severe PPM (86.7% [95% CI, 77.6%-95.8%] vs 89.1% [95% CI, 82.2%-96%] in patients without severe PPM; *P* = .69).

Time-to-event curves are depicted in **Figure 1**. No patients were lost to follow-up. Median follow-up time was 301

Table 3. Clinical Outcomes

Outcomes	All (n = 459)	Mechanism of Surgical Valve Failure, No. (%)				Device Used, No. (%)		
		Stenosis (n = 181)	Regurgitation (n = 139)	Combined (n = 139)	P Value	Self-Expandable (n = 213)	Balloon-Expandable (n = 246)	P Value
Duration of hospital stay, median (IQR), d	8 (5-12)	7 (5-11)	7 (5-12)	8 (6-13)	.21	7 (5-12)	8 (6-13)	.07
Thirty-day outcomes								
Death, No. (%)	35 (7.6)	19 (10.5)	6 (4.3)	10 (7.2)	.04	15 (7)	20 (8.1)	.66
Cardiovascular death, No. (%)	30 (6.5)	16 (8.8)	5 (3.6)	9 (6.5)	.06	12 (5.6)	18 (7.3)	.47
NYHA functional class, No. (%)								
I/II	313 (92.6)	126 (91.3)	100 (94.3)	87 (92.6)	.83	160 (93)	153 (93.3)	.94
III/IV	25 (7.4)	12 (8.7)	6 (5.7)	7 (7.4)	.83	12 (7)	13 (7.8)	.94
Major stroke, No. (%)[a]	8 (1.7)	1 (0.6)	3 (2.2)	4 (2.9)	.26	2 (0.9)	6 (2.4)	.22
Death or major stroke, No. (%)	42 (9.2)	19 (10.5)	9 (6.5)	14 (10.1)	.42	17 (8)	25 (10.2)	.22
Major vascular complication, No. (%)[a]	42 (9.2)	14 (7.7)	10 (7.2)	18 (12.9)	.11	16 (7.5)	26(10.6)	.26
Major/life-threatening bleeding, No. (%)[a]	37 (8.1)	20 (11)	5 (3.6)	12 (8.6)	.01	10 (4.7)	27 (11)	.01
Acute kidney injury type II/III, No. (%)[a]	34 (7.4)	16 (8.8)	10 (7.2)	8 (5.8)	.58	9 (4.2)	25 (10.2)	.02
Permanent pacemaker implantation, No. (%)	38 (8.3)	17 (9.4)	12 (8.6)	9 (6.5)	.63	26 (12.2)	12 (4.9)	.005
AV area, mean (SD), cm²	1.47 (0.5)	1.37 (0.33)	1.56 (0.51)	1.56 (0.65)	.01	1.58 (0.41)	1.38 (0.54)	.001
AV index, mean (SD), cm²/m²[b]	0.77 (0.25)	0.71 (0.15)	0.82 (0.23)	0.84 (0.35)	.004	0.83 (0.19)	0.74 (0.28)	.004
AV maximal gradient, mean (SD), mm Hg	28.3 (14.1)	32.2 (14.7)	22.4 (11.6)	29.1 (13.6)	<.001	26.2 (12.1)	30.3 (15.4)	.002
AV mean gradient, mean (SD), mm Hg	15.8 (8.9)	18.5 (9.8)	12 (6.7)	16.1 (8.3)	<.001	14.1 (7.3)	17.2 (9.7)	<.001
AV regurgitation of at least moderate degree, No. (%)[c]	25 (5.4)	5 (2.8)	13 (9.4)	7 (5)	.04	19 (8.9)	6 (2.4)	.002
Left ventricular ejection fraction, mean (SD), %	51.6 (11.5)	53.7 (9.9)	48.9 (11.6)	51.2 (12.9)	.002	51.2 (12.2)	51.7 (10.8)	.66
One-year outcomes								
Death, No. (%)	62 (16.8)	34 (23.4)	10 (8.8)	18 (16.1)	.01	25 (15)	37 (18.7)	.44
NYHA functional class, No. (%)								
I/II	163 (86.2)	62 (84.9)	46 (85.2)	55 (88.7)	.34	88 (81.6)	75 (82.4)	.89
III/IV	26 (13.8)	11 (15.1)	8 (14.8)	7 (11.3)	.34	10 (18.4)	16 (17.6)	.89
AV area, mean (SD), cm²	1.38 (0.42)	1.28 (0.29)	1.51 (0.48)	1.36 (0.45)	.01	1.55 (0.41)	1.29 (0.39)	.006
AV maximal gradient, mean (SD), mm Hg	30 (14.7)	32.3 (14.9)	25.2 (15.4)	32.1 (12.5)	.005	25.3 (11.9)	33.3 (16)	<.001
AV mean gradient, mean (SD), mm Hg	16.9 (9.1)	18.3 (9.5)	13.8 (8.9)	18.4 (8)	.001	13.5 (7)	19.4 (9.6)	<.001

Abbreviations: AV, aortic valve; IQR, interquartile range; NYHA, New York Heart Association.

[a] According to the Valve Academic Research Consortium definition.

[b] AV index = AV area (cm²)/patient body surface area (m²).

[c] Evaluated according to the criteria of the American Society of Echocardiography.[18]

days (interquartile range, 53-504 days). Overall 1-year Kaplan-Meier survival rate was 83.2% (95% CI, 80.8%-84.7%; 62 death events; 228 survivors). Patients in the stenosis group had worse 1-year survival (76.6%; 95% CI, 68.9%-83.1%; 34 deaths; 86 survivors) vs the regurgitation group (91.2%; 95% CI, 85.7%-96.7%; 10 deaths; 76 survivors) and the combined group (83.9%; 95% CI, 76.8%-91%; 18 deaths, 66 survivors) (P = .01). Similarly, patients with small valves had worse 1-year survival after valve-in-valve procedure (74.8%; 95% CI, 66.2%-83.4%; 27 deaths; 57 survivors) vs with intermediate-sized valves (81.8%; 95% CI, 75.3%-88.3%; 26 deaths; 92 survivors) or with large valves (93.3%; 95% CI, 85.7%-96.7%; 7 deaths; 73 survivors)

(P = .001) (Figure 1, A and B). There was no significant difference in survival between patients undergoing self-expandable and balloon-expandable valve-in-valve procedures (Figure 1C). One-year mortality was higher among patients undergoing transapical procedures, those with STS scores higher than 20%, and those with a baseline left ventricular ejection fraction of less than 45% (eFigures 3-8 in the Supplement).

Figure 2 includes data on correlates for mortality within 1 year after valve-in-valve procedures. Independent correlates included small surgical bioprostheses (HR, 2.04; 95% CI, 1.14-3.67; P = .02), baseline surgical bioprosthesis stenosis (vs re-

gurgitation; HR, 3.07; 95% CI, 1.33-7.08; *P* = .008), transapical access (HR, 2.25; 95% CI, 1.26-4.02; *P* = .006), and STS score (per 1% increment; HR, 1.01; 95% CI, 1.00-1.01; *P* < .001). Independent correlates for early mortality (≤30 days) included small surgical bioprostheses (HR, 2.25; 95% CI, 1.03-4.93; *P* = .04) and for late mortality (>30 days) included baseline surgical bioprosthesis stenosis (HR, 3.33; 95% CI, 1.00-11.31; *P* = .05).

Discussion

The VIVID Registry is a multinational comprehensive evaluation of transcatheter valve implantations for failed surgical aortic bioprostheses. Survival after valve-in-valve procedures was associated with surgical valve size and mechanism of failure. Patients with baseline stenosis and those with small surgical valves had worse clinical outcomes after valve-in-valve procedures.

Mechanism of Failure of Bioprosthetic Valves and Valve-in-Valve Procedures

Valve-in-valve implantation should be considered a heterogeneous group of procedures, performed in widely diverse surgical valves with different degeneration modes.[22] Bioprosthesis failure may present as stenosis that occurs as a consequence of calcification, pannus, or, less commonly, thrombosis. Failure may also present as regurgitation secondary to wear and tear or infection.[23,24] The mode of failure in the VIVID registry was relatively balanced among stenosis, regurgitation, and a combination of both. Although there was no difference in patient age or calculated risk scores among the groups, clinical outcomes differed significantly. Higher mortality in the stenosis group could partially be attributed to higher rates of specific life-threatening procedural complications, such as ostial left main obstruction. Nevertheless, long-term dissimilarity between the groups could be a result of differences in baseline characteristics and postprocedural hemodynamics. After valve-in-valve implantation, patients with baseline stenosis had a lower valve area and higher gradients. Prosthetic-patient mismatch occurs when the effective orifice area is physiologically too small in relation to patient body size.[21] In the current analysis, patients with predominantly surgical valve stenosis had larger body size measures (body weight, body mass index, and body surface area); nevertheless, they had smaller surgical valves implanted compared with the other groups. In patients undergoing surgical aortic valve replacement, lower effective orifice area in relation to body size is associated with lower left ventricular mass regression, less recovery in ventricular systolic function, and lower long-term survival.[21,25-28]

Evaluation of Patients for Valve-in-Valve Procedures

Thorough assessment of candidates for valve-in-valve implantation is a key step to obtain optimal results.[22] The current analysis highlights the need for meticulous evaluation of bioprosthesis mechanism of failure before attempting a valve-in-valve procedure. Patients who are diagnosed

Figure 1. Time-to-Event Curves in Patients Undergoing Valve-in-Valve Procedures

A Mechanism of surgical valve failure

No. at risk by type of valve failure

Stenosis	181	112	98	91	86
Regurgitation	139	92	84	78	76
Combined	139	85	76	68	66

B Surgical valve label size[a]

No. at risk by valve label size

Small	133	81	68	61	57
Intermediate	176	116	103	95	92
Large	139	89	82	76	73

C Device used during valve-in-valve implantation

No. at risk by type of device

Balloon-expandable	246	163	146	136	130
Self-expandable	213	126	112	101	98

[a] Surgical valve sizes were as follows: small, label size ≤21 mm; intermediate, >21 mm and <25 mm; and large, ≥25 mm. In 11 patients (2.4%), label size was unknown.

as having failed surgical valves secondary to stenosis should be further separated into those with degenerated valves and those who have elevated gradients and small effective orifice area as a result of severe PPM with their surgical valve. Occasionally, it is clinically difficult to differentiate between

Figure 2. Results of Multivariable Analyses for Correlates for 1-Year Mortality After Valve-in-Valve Implantation

	No. of Events	Total	Hazard Ratio (95% CI)		P Value
Overall mortality					
Surgical valve label size					
≤21 mm	28	133	2.04 (1.14-3.67)		.02
>21 mm	34	315			
Type of valve failure					
Stenosis	34	181	3.07 (1.33-7.08)		.008
Regurgitation	12	139			
Transapical access					
Yes	34	171	2.25 (1.26-4.02)		.006
No	30	288			
STS score (per 1% increment)[a]			1.01 (1.00-1.01)		<.001
Early mortality, ≤30 d					
Surgical valve label size					
≤21 mm	15	133	2.25 (1.02-4.98)		.045
>21 mm	17	315			
Type of valve failure					
Stenosis	18	181	2.97 (0.94-9.37)		.06
Regurgitation	6	139			
Transapical access					
Yes	19	171	2.25 (1.03-4.93)		.04
No	15	288			
STS score (per 1% increment)[a]			1.01 (1.00-1.01)		<.001
Late mortality, >30 d					
Surgical valve label size					
≤21 mm	13	133	1.61 (0.68-3.80)		.28
>21 mm	17	315			
Type of valve failure					
Stenosis	16	181	3.33 (1.00-11.31)		.05
Regurgitation	6	139			
STS score (per 1% increment)[a]			1.01 (1.00-1.04)		.002

0.1   1.0   10
Hazard Ratio (95% CI)

[a] The Society of Thoracic Surgeons (STS) score is a prediction of operative mortality after conventional surgical valve replacement (http://riskcalc.sts.org /de.aspx).

those entities, and a patient may have a combination of both. Small bioprostheses (label size ≤21 mm) have small effective orifice areas and the gradients across them are commonly high, even in the absence of structural degeneration, such as impaired leaflet mobility, significant calcification, or pannus.[29] Therefore, markers for stenosis in bioprostheses should lead to a more detailed assessment of previous echocardiographic examinations and changes in clinical status over years. It seems that the valve-in-valve approach should only be rarely offered to patients after implantation of small surgical valves without signs of valve degeneration, for which gradients are relatively stable over time.

Candidates with surgical valve regurgitation should be evaluated for the location of the leak. Significant paravalvular leak should not be treated by valve-in-valve implantation since no considerable change is expected in regurgitation severity.[22] The current registry reveals an elevated rate of residual leak in the group of patients with baseline regurgitation (9.4%) in comparison with patients with predominantly stenosis (2.8%). Significant postprocedural regurgitation could be attributed to improper treatment of patients with predominantly paravalvular leak at baseline. Transesophageal echo-

cardiography is a key mode during this screening process and should be routinely performed for evaluating leak origin.

Implications for Cardiac Surgery
Increasing global valve-in-valve experience may affect cardiac surgery practice. The valve-in-valve approach may offer an effective, less invasive treatment for patients with failed surgical bioprostheses and, therefore, the trend toward implantation of bioprostheses in younger patients is expected to grow.[1] It is difficult to define an optimal cutoff age for bioprostheses implantation rather than mechanical valves.[30] However, surgeons should be aware that their technique is crucial to allow for the possibility of successful valve-in-valve implantation when bioprosthesis failure occurs years later. According to the VIVID Registry analysis, valve-in-valve outcomes are worse in patients with small surgical valves (label size ≤21 mm) and those with stenosis as the mechanism of failure; an attempt to address these limitations may possibly be made during the index procedure by providing the largest effective orifice area achievable. However, annular enlargement and other related techniques must balance the potential benefit of larger valve against described increase in operative complications.[31-33]

Limitations

The valve-in-valve therapeutic approach represents a widely diverse heterogeneous group of procedures; hence, it is difficult to stratify patients according to each type of the numerous surgical valves treated. Nevertheless, stratification according to mechanism of failure and bioprostheses size showed a major influence on clinical outcomes after valve-in-valve implantation. Since specific label sizes of surgical valves such as the 19 mm were not common (2.4%), we were not powered to compare different surgical valve sizes without clustering cases into subgroups. Nevertheless, dividing surgical bioprostheses into small, intermediate, and large valve sizes, in accordance with previous reports, is clinically relevant and showed clinical significance when defining small valve size as those having a label size of 21 mm or smaller.[34,35]

Study results reveal that PPM of the implanted transcatheter heart valve device during valve-in-valve procedures did not influence 1-year survival. However, analyses were limited by lack of echocardiographic data immediately after surgical implantation (median of 9 years before the valve-in-valve procedure) that would have enabled evaluation of PPM of the implanted surgical valve. Therefore, a clear differentiation between degeneration of the surgical bioprosthesis and PPM is challenging.

Although dozens of baseline medical and echocardiographic parameters were included in the analyses (Table 1, Table 2, and Table 3 and eTables 2 and 3 in the Supplement), analyses is limited by lack of several parameters known to be related to clinical outcomes in patients with structural aortic valve disease, including left ventricular mass index, diastolic function, ischemic cardiomyopathy, and frailty.

Conclusions

In this registry of patients who underwent transcatheter valve-in-valve implantation for degenerated bioprosthetic aortic valves, overall 1-year survival was 83.2%. Survival was lower among patients with small bioprostheses and those with predominant surgical valve stenosis.

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