Transcatheter Aortic Valve Replacement for Degenerative Bioprosthetic Surgical Valves

Results From the Global Valve-in-Valve Registry

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Background—Transcatheter aortic valve-in-valve implantation is an emerging therapeutic alternative for patients with a failed surgical bioprosthesis and may obviate the need for reoperation. We evaluated the clinical results of this technique using a large, worldwide registry.

Methods and Results—The Global Valve-in-Valve Registry included 202 patients with degenerated bioprosthetic valves (aged 77.7±10.4 years; 52.5% men) from 38 cardiac centers. Bioprosthesis mode of failure was stenosis (n=85; 42%), regurgitation (n=68; 34%), or combined stenosis and regurgitation (n=49; 24%). Implanted devices included CoreValve (n=124) and Edwards SAPIEN (n=78). Procedural success was achieved in 93.1% of cases. Adverse procedural outcomes included initial device malposition in 15.3% of cases and ostial coronary obstruction in 3.5%. After the procedure, valve maximum/mean gradients were 28.4±14.1/15.9±8.6 mm Hg, and 95% of patients had ≤+1 degree of aortic regurgitation. At 30-day follow-up, all-cause mortality was 8.4%, and 84.1% of patients were at New York Heart Association functional class I/II. One-year follow-up was obtained in 87 patients, with 85.8% survival of treated patients.

Conclusions—The valve-in-valve procedure is clinically effective in the vast majority of patients with degenerated bioprosthetic valves. Safety and efficacy concerns include device malposition, ostial coronary obstruction, and high gradients after the procedure. **(*Circulation*. 2012;126:2335-2344.)**

Key Words: bioprosthesis ■ transcatheter aortic valve implantation ■ valve-in-valve

More than 200 000 surgical aortic valve replacements (SAVR) are performed annually worldwide, with a substantial shift toward the use of bioprostheses rather than mechanical valves.[1] Bioprostheses have limited durability, and most are expected to degenerate and eventually fail within 10 to 20 years.[2–4] As a result, it is estimated that in the subsequent few years, many patients will suffer from failed surgical bioprosthetic valves. Reoperation, the standard of care for these patients, is occasionally a high-risk procedure that carries significant mortality and morbidity risks, especially because many of these patients are elderly and have numerous comorbidities.[5–7]

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Transcatheter aortic valve replacement (TAVR), performed mainly with the use of the Edwards SAPIEN (Edwards Lifesciences, Irvine, CA) and the CoreValve (Medtronic, Minneapolis, MN) devices, was introduced as an alternative to SAVR for the treatment of severe symptomatic native aortic valve stenosis in patients at a high surgical risk.[8–10] In recent years, several reports have suggested that the off-label use of TAVR within failed surgically inserted bioprosthetic valves (valve-in-valve [VIV]) is technically feasible.[11–26] However, all previous reports evaluating the VIV approach have included a small number of cases and are limited in providing measures of efficacy and safety. High postprocedural gradients and several potentially life-threatening complications, such as ostial coronary obstruction, were only reported anecdotally, and there was no comparison between different devices possibly applicable for VIV.[27–29]

The Global Valve-in-Valve Registry was established to mitigate these limitations and further explore the VIV approach. Study objectives were to evaluate the efficacy and safety of this procedure in a large group of patients. In particular, the study sought to examine clinical outcomes, including long-term analysis; to evaluate the results of VIV procedures performed inside different types of surgical bioprostheses; to give correlates for high postprocedural gradients; to supply data on possible rare complications; and to compare the procedural characteristics and clinical results of performing VIV with the use of Edwards SAPIEN and CoreValve devices.

Methods

Registry Design

The Global Valve-in-Valve Registry was initiated in December 2010. The registry is not supported by any external funding and was designed to collect data from centers across the world that had TAVR experience with the use of either CoreValve or Edwards SAPIEN devices. There was retrospective collection of data from cases performed before registry initiation and prospective data collection after that time.

A total of 38 centers from Europe, North America, Australia, New Zealand, and the Middle East contributed all of their VIV experience to the registry (Appendix I in the online-only Data Supplement). Continued communication with involved centers (D.D.) regarding clinical events was initiated. Data were collected with the use of a dedicated case report form. All inconsistencies were resolved directly with local investigators and on-site data monitoring. For each bioprosthesis, we collected the operation year, valve type, label size, and internal diameter. Baseline bioprosthetic valve area, gradients, and degree of regurgitation were gathered from the last echocardiographic study before the procedure. Early postimplantation hemodynamic analysis included data from intraprocedural echocardiographic analysis or from the first echocardiographic evaluation after the procedure. Images from these procedures were collected into a library of VIV procedures. The inclusion of patients included in this registry was approved in each center by a local ethical committee.

Definitions

Bioprosthetic valve mechanism of failure (eg, stenosis or regurgitation) was evaluated according to the criteria of the American Society of Echocardiography.[30] Patients with at least a moderate degree of both stenosis and regurgitation were included in the "combined stenosis and regurgitation" group. Other patients were categorized, according to the primary mechanism of failure, in either the "stenosis" group or the regurgitation group.

Successful VIV implantation was defined as a procedure having all of the following: successful vascular access, delivery, and deployment of a device; successful retrieval of the delivery system; intended performance of the device with neither severe stenosis (mean aortic gradient >40 mm Hg or peak velocity >4 m/s) nor moderate or severe regurgitation; and the patient being transferred alive out of the catheterization suite. Major clinical end points were assessed according to the Valve Academic Research Consortium (VARC) criteria.[31] Follow-up data were collected for patients according to the time frame elapsed from the index VIV procedure to data lock for present analysis.

Statistical Analysis

Statistical analysis was performed with the use of SAS version 9.1 (SAS Institute, Cary, NC). Results are presented as mean±SD for continuous variables with normal distribution, as median and interquartile range (25th, 75th percentiles) for continuous variables without normal distribution, and as percentages for categorical data. Student *t* test was used to compare normally distributed continuous variables between the CoreValve and Edwards SAPIEN groups, and the Wilcoxon rank sum test was used for variables not normally distributed. One-way ANOVA 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. The Kaplan–Meier method and comparison between the CoreValve and Edwards SAPIEN groups were performed with the use of the log-rank statistic. High postprocedural gradients were defined according to the VARC criteria as those having mean gradients ≥20 mm Hg.[31] Changes in valve gradients were evaluated with repeated measures analysis. For multivariable analysis of predictors for high postprocedural gradients, a logistic regression was used. The initial selection of variables entered into the univariate model included the following: sex, age, functional class, baseline echocardiographic parameters (aortic valve area, aortic regurgitation degree, and left ventricular ejection fraction), bioprosthetic type (stented versus stentless), internal diameter, the device used during the VIV procedure (CoreValve versus Edwards SAPIEN), device size, preimplantation valvuloplasty, and postimplantation valvuloplasty. Variables with $P<0.10$ in the univariate analysis, as well as other critical parameters possibly affecting the analysis (eg, bioprosthesis size or performance of postimplantation valvuloplasty), were further examined in a stepwise model. The results of the multivariate analysis are presented as odds ratio with 95% confidence interval (CI). A 2-sided P value <0.05 was considered statistically significant.

The authors are solely responsible for the design and conduct of this study, all analyses, drafting and editing of the manuscript, and its final contents.

Results

Patient Demographics

Table 1 shows the clinical characteristics of 202 patients included in the registry; 124 patients underwent VIV procedure with the use of the CoreValve device and 78 patients with the use of the Edwards SAPIEN device. Patients' mean age was 77.7±10.4 years (distribution, 25–91), and 52.5% were men. The CoreValve group had lower left ventricular ejection fraction and a higher rate of diabetes mellitus than did the Edwards SAPIEN group (49±13% versus 52.8±10.4%, $P=0.03$; 34.7% versus 20.5%, $P=0.03$, respectively).

Degenerated Bioprosthetic Valves

The patients included in the trial had between 1 and 4 previous SAVRs (85.6% had 1 previous surgery). The me-

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

	All (n=202)	CoreValve (n=124)	Edwards SAPIEN (n=78)	P*
Patient characteristics				
Age, y	77.7±10.4	77.4±11	78.3±9.4	0.53
Men, n (%)	106 (52.5)	65 (52.4)	41 (52.6)	1.0
Log EuroSCORE	31.1±16.4	31±16.6	31.2±16.1	0.92
STS score	11.8±9.9	12.8±11	10.2±7.5	0.07
Diabetes mellitus, n (%)	59 (29.2)	43 (34.7)	16 (20.5)	0.03
Peripheral vascular disease, n (%)	41(20.3)	22 (17.7)	19 (24.4)	0.26
Chronic renal failure, n (%)†	94 (46.5)	52 (41.9)	42 (53.8)	0.10
Previous stroke, n (%)	25 (12.4)	16 (12.9)	9 (11.5)	0.77
>1 previous SAVR, n (%)	31 (15.3)	19 (15.3)	12 (15.4)	1.0
NYHA functional class, n (%)				0.39
II	12 (5.9)	6 (4.8)	6 (7.7)	
III	112 (55.4)	66 (53.2)	46 (59)	
IV	78 (38.6)	52 (41.9)	26 (33.3)	
Left ventricular ejection fraction, %	50.5±12.2	49±13	52.8±10.4	0.03
Bioprosthetic valve				
Time since last SAVR, y‡	9 (6, 13)	10 (6, 14)	8 (5, 13)	0.33
Type, n (%)				0.01
Stented	155 (76.7)	87 (70.2)	68 (87.2)	
Stentless	47 (23.3)	37 (29.8)	10 (12.8)	
Size (internal diameter), n (%)				0.27
<20 mm	52 (25.7)	35 (28.2)	17 (21.8)	
≥20 and <23 mm	102 (50.5)	57 (46)	45 (57.7)	
≥23 mm	40 (19.8)	27 (21.8)	13 (16.7)	
Unknown	8 (4)	5 (4)	3 (3.8)	
Mechanism of failure, n (%)				0.25
Stenosis	85 (42.1)	50 (40.3)	35 (44.9)	
Regurgitation	68 (33.7)	47 (37.9)	21 (26.9)	
Combined	49 (24.3)	27 (21.8)	22 (28.2)	

STS indicates Society of Thoracic Surgeons; SAVR, surgical aortic valve replacement; and NYHA, New York Heart Association.

*Comparisons between the CoreValve and Edwards SAPIEN groups.

†Calculated glomerular filtration rate <60 mL/min.

‡Presented as mean (interquartile range, 25th, 75th percentiles).

dian time from the last SAVR to the VIV procedure was 9 years (interquartile range, 6 to 13 years). Implanted bioprostheses were stented in 76.7% of cases (n=155) and stentless in 23.3% (n=47). Edwards SAPIEN was used to treat a higher proportion of stented bioprosthetic valves than CoreValve (87.2% versus 70.2%; $P=0.005$). There was no significant difference between the CoreValve and Edwards SAPIEN groups in the internal diameter size of bioprostheses. Fifty-two patients had small bioprostheses with internal diameter <20 mm (28.2% of CoreValve cases versus 21.8% of Edwards-SAPIEN; $P=0.32$). Appendix II in the online-only Data Supplement includes data on the degenerative bioprostheses included in the registry.

The mechanism of failure was stenosis (n=85; 42.1%), regurgitation (n=68; 33.7%), and combined stenosis and regurgitation (n=49; 24.3%). The distribution of mechanism of failure did not differ between the CoreValve and Edwards SAPIEN groups. The stenosis group had lower aortic valve orifice area and higher maximum/mean valve gradients than the regurgitation and combined groups (0.69±0.3 versus 1.63±0.53 versus 0.91±0.2 cm^2, respectively; 83±24.2/50.5±16.2 versus 34.6±14.1/17.8±7.8 versus 67.7±16.8/38.8±11.1 mm Hg, respectively).

Characteristics of VIV Procedures

Table 2 shows the procedural characteristics and early results of VIV procedures in the total cohort and is further separated into the CoreValve and Edwards SAPIEN groups. In both groups, the majority of devices were of the smallest available size: 26-mm CoreValve (79.8%) and 23-mm Edwards SAPIEN (79.5%). The main access route in the CoreValve group was femoral (91.1%) versus apical in the Edwards SAPIEN group (69.2%). General anesthesia, transesophageal echocardiogram, and preimplantation valvuloplasty use were all more common in the Edwards SAPIEN group.

Table 2. Procedural Characteristics and Early Results

	Total (n=202)	CoreValve (n=124)	Edwards SAPIEN (n=78)	*P**
Procedural characteristics				
Device size, mm, n (%)				NA
23	62 (30.7)	0	62 (79.5)	
26	115 (56.9)	99 (79.8)	16 (20.5)	
29	25 (12.4)	25 (20.2)	0	
Access, n (%)				NA
Transfemoral	137 (67.8)	113 (91.1)	24 (30.8)	
Transapical	54 (26.7)	0	54 (69.2)	
Transaxillary	10 (5)	10 (8.1)	0	
Transaortic	2 (1)	2 (1.6)	0	
General anesthesia, n (%)	132 (65.3)	68 (54.8)	64 (82.1)	<0.0001
Transesophageal echocardiography use, n (%)	105 (52)	49 (39.5)	56 (71.8)	<0.0001
Procedural results, n (%)				
Procedural success†	188 (93.1)	120 (96.8)	68 (87.2)	0.009
Preimplantation valvuloplasty	56 (27.7)	20 (16.1)	36 (46.2)	<0.0001
Attempted device retrieval	11 (5.4)	11 (8.9)	0	NA
Need for a second TAVR valve	17 (8.4)	10 (8.1)	7 (9)	0.82
Postimplantation valvuloplasty	25 (12.4)	21 (16.9)	4 (5.1)	0.01
Ostial coronary obstruction	7 (3.5)	4 (3.2)	3 (3.8)	1.0
Need for an emergent surgery	4 (2)	1 (0.8)	3 (3.8)	0.3
Thirty-day outcome				
Death, n (%)	17 (8.4)	9 (7.3)	8 (10.3)	0.45
Major stroke, n (%)‡	4 (2)	2 (1.6)	2 (2.6)	0.64
Death or major stroke, n (%)	20 (10.4)	11 (8.9)	9 (11.5)	0.48
Major vascular complication, n (%)‡	7 (3.5)	2 (1.6)	5 (6.4)	0.11
Need for a permanent pacemaker, n (%)	15 (7.4)	11 (8.9)	4 (5.1)	0.31
Aortic valve maximal gradients, mm Hg	28.4±14.1	25.3±12.9	33.5±14.5	<0.0001
Aortic valve mean gradients, mm Hg	15.9±8.6	13.9±7.5	19.2±9.2	<0.0001
Aortic regurgitation (≥+2), n (%)	10 (5)	8 (6.5)	2 (2.6)	0.32
Left ventricular ejection fraction, %	51.3±11.8	50.6±12.4	52.4±10.6	0.31
NYHA functional class, n (%)				0.16
I	99 (49)	55 (44.4)	44 (56.4)	
II	71 (35.1)	52 (41.9)	19 (24.4)	
III	13 (6.4)	7 (5.6)	6 (7.7)	
IV	2 (1)	1 (0.8)	1 (1.3)	

TAVR indicates transcatheter aortic valve replacement; NYHA, New York Heart Association; and NA, not applicable.
*Comparisons between the CoreValve and Edwards SAPIEN groups.
†According to the registry definition.
‡According to the Valve Academic Research Consortium definition.

Procedural Results

Table 2 depicts procedural results and 30-day outcome. There were 14 procedural failures (6.9%) according to the registry definition and 83 device failures according to the VARC definition (41.1%). Most of the VARC device failures (62.7%) were secondary to elevated postprocedural gradients of moderate degree (mean gradients, 20–39 mm Hg). Procedural success, according to the registry definition, and device success according to the VARC definition were both higher in the CoreValve group (96.8% versus 87.2%, $P=0.009$ and 64.5% versus 50%, $P=0.04$, respectively).

Thirty-one cases had initial device malposition (15.3%; 16.9% CoreValve versus 12.8% Edwards SAPIEN; $P=0.41$) (Figure 1A and 1B). Additional maneuvers during the procedures included 11 attempts to retrieve the device during CoreValve procedures (8.9%) and implantation of a second TAVR device in 17 cases (8.1% CoreValve versus 9% Edwards SAPIEN; $P=0.82$). Postimplantation valvuloplasty was used in 25 cases (16.9% CoreValve versus 5.1% Edwards SAPIEN; $P=0.01$). Ostial left main coronary obstruction occurred in 7 cases (3.2% of CoreValve cases versus 3.8% of Edwards SAPIEN cases; $P=1.0$) (Figure 1C and 1D). In-hospital mortality in the patients with ostial coronary obstruction was 57.1%. Three cases with ostial coronary obstruction appeared during VIV procedures performed inside Mitroflow stented valves (Sorin Group Inc, Vancouver, British Columbia, Canada), 2

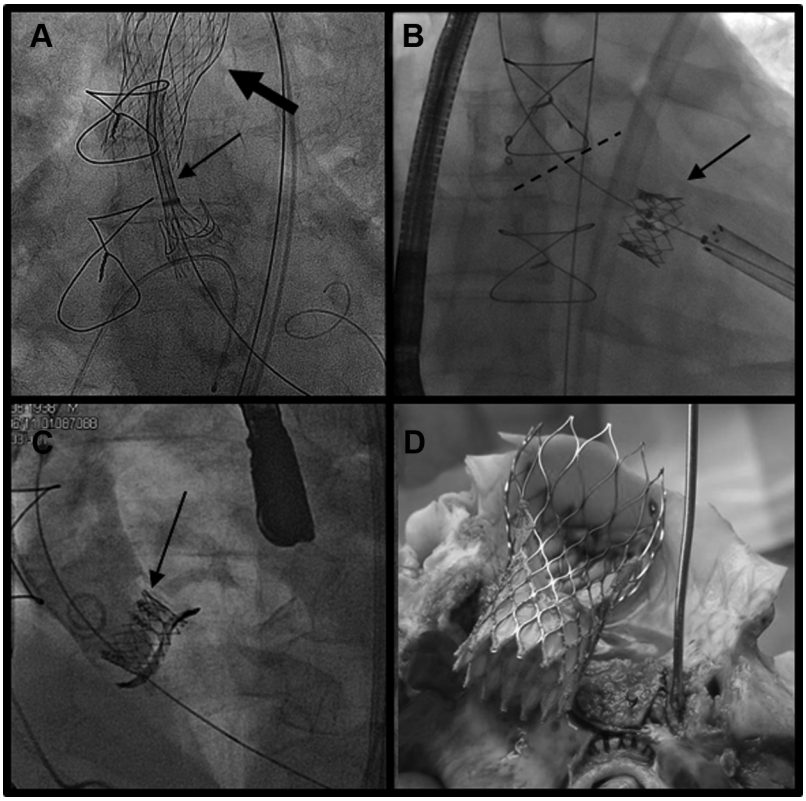

Figure 1. Case examples of device malposition and ostial coronary obstruction during aortic valve-in-valve implantations. **A**, CoreValve embolization during implantation inside a Perimount (Edwards Lifesciences, Irvine, CA) valve (thick arrow) followed by delivery of a second CoreValve in a correct position (thin arrow). **B**, Edwards SAPIEN XT (arrow) dives into the left ventricle during transapical implantation in a Mosaic (Medtronic, Minneapolis, MN) valve (the dotted line illustrates the target for implantation). That device was reimplanted after conversion to open cardiac surgery. **C**, Transapical Edwards SAPIEN implantations in a Mitroflow (Sorin Group Inc, Vancouver, British Columbia, Canada) 25-mm device showing the surgical bioprosthetic valve leaflet (arrow) obstructing the left coronary ostium. That patient had successful coronary revascularization. **D**, Transfemoral CoreValve implantation in a Freedom (Sorin) stentless surgical bioprosthesis. The patient died suddenly on the second postoperative day. Postmortem examination revealed ostial left coronary artery obstructed by a bioprosthesis leaflet.

cases in Freedom stentless valves (Sorin), 1 case in a stentless CryoLife O'Brien valve (CryoLife International, Atlanta, GA), and 1 in a stented Mosaic valve (Medtronic). The rate of ostial coronary obstruction was 0.9% for stented bioprostheses (other than Mitroflow) and 2.2% for stentless bioprostheses (other than Freedom), without a statistically significant difference ($P=0.47$). There was an ostial coronary obstruction event in 7.7% of the Mitroflow cases (more than in other stented valves; $P=0.049$) and in 50% of the Freedom stentless (more than in other stentless valves; $P=0.02$).

Thirty-Day Outcome

Median duration of hospital stay was 8 days (interquartile range, 6–12 days). At 30 days, 185 patients survived, 17 patients died (8.4%), and no patient was lost to follow-up. There were no differences between the CoreValve and Edwards SAPIEN groups in mortality, major vascular complication, or stroke. Overall, postprocedureal aortic valve gradients decreased to 28.4±14.1 mm Hg (maximum) and 15.9±8.6 mm Hg (mean). Mean postprocedural gradients were 5 mm Hg higher in the Edwards SAPIEN group than in the CoreValve group ($P<0.0001$). After the procedure, significant aortic regurgitation (≥+2) appeared in 10 cases (5%), and left ventricular ejection fraction was 51.3±11.8%, which is similar to that measured before the procedure at 50.5±12.2% ($P=0.62$). There was no difference between the CoreValve and Edwards SAPIEN groups in the need for a permanent pacemaker implantation (8.9% versus 5.1%, respectively; $P=0.31$).

Postprocedural Gradients

Postprocedural gradients were assessed in 197 patients (5 patients died during the index procedure before the analysis). High postprocedural gradients (mean gradients ≥20 mm Hg) were recorded in 56 patients (28.4%): 26 in the CoreValve group versus 30 in the Edwards SAPIEN group (Figure 2). The rate of elevated postprocedural gradients was higher after Edwards SAPIEN than after CoreValve implantations (40% versus 21.3%, respectively; $P<0.0001$). There was a significant difference in the rate of high postprocedural gradients between the Edwards SAPIEN and the CoreValve groups for VIV procedures performed inside small surgical bioprostheses (internal diameter <20 mm): 58.8% versus 20%, respectively ($P=0.005$); Figure 3 shows representative case examples. Table 3 shows the results of analysis for predictors for high postprocedural gradients. The only independent predictors were baseline surgical bioprosthetic valve area (odds ratio, 0.87 per 0.1-cm^2 increment; CI, 0.79–0.94; $P=0.001$) and implantation of the Edwards SAPIEN device versus CoreValve (odds ratio, 2.28; CI, 1.17–4.43; $P=0.02$). Preimplantation valvuloplasty and TAVR implantation inside a stented bioprosthesis were not independent predictors for elevated postprocedural gradients in multivariate analysis.

One-Year Clinical Results

The overall patients' Kaplan–Meier survival curve is depicted in Figure 4. Median follow-up time was 285 days (interquartile range, 114–509 days). There were 23 deaths within the first postprocedural year. At 1 year, the total number of patients at risk was 87 (CoreValve, n=48; Edwards SAPIEN, n=39), and the follow-up rate was 54.4%. The calculated 1-year survival was 85.8% (CI, 79.9–91.6%). There was no significant difference in 1-year survival between patients undergoing CoreValve VIV procedures (89%; CI, 82.1–

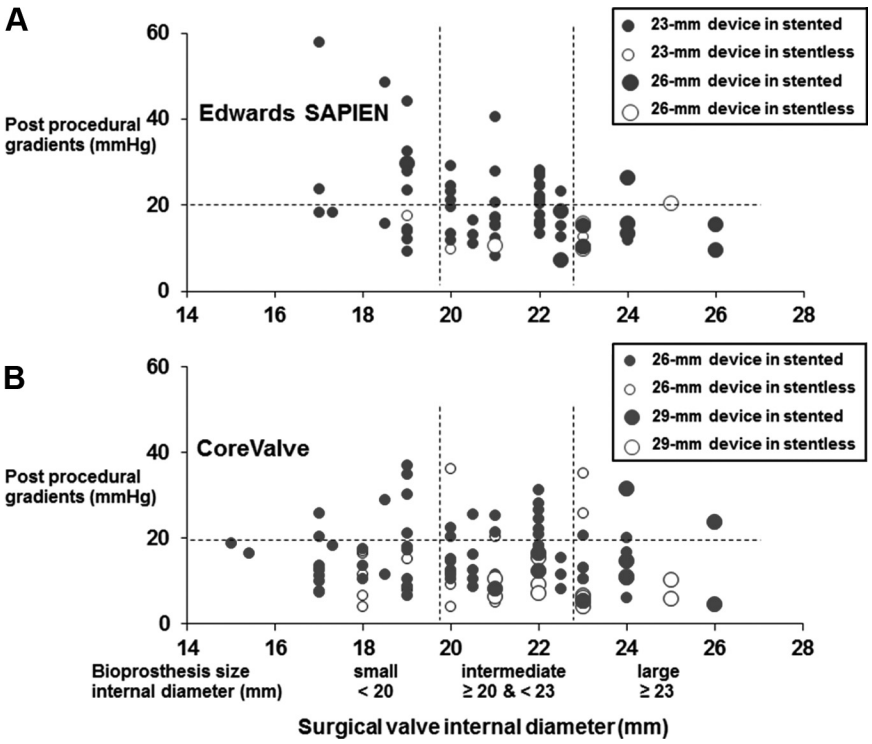

Figure 2. Analysis of high postprocedural gradients (mean gradients ≥20 mm Hg) after valve-in-valve procedures, according to surgical bioprosthesis size: large (internal diameter ≥23 mm), intermediate (≥20 and <23), and small (<20). **A**, Mean gradients after Edwards SAPIEN (red) procedures according to the bioprosthesis size (r=0.353, P=0.28). There was a negative trend between the bioprosthesis size and high postprocedural gradients rates: 23.1%, 37.8%, and 58.8%, respectively. **B**, Mean gradients after CoreValve (blue) procedures according to the bioprosthesis size (r=0.077, P=0.40). Unlike after the Edwards SAPIEN procedures, there was almost no change in the rate of elevated postprocedural gradients after CoreValve procedures: large, 22.2%; intermediate, 22.8%; small, 20%.

95.8%) and those undergoing Edwards SAPIEN VIV procedures (81.8%; CI, 71.9–91.6%; log rank P=0.25).

Figure 5 shows hemodynamic and clinical results up to 1 year of follow-up. Thirty-day mean gradients, functional class, and aortic regurgitation results were maintained at 1-year follow-up (P=0.13, P=0.33, P=0.49, respectively).

Discussion

The present study is the first large, comprehensive evaluation of a transcatheter approach for failed surgically inserted aortic bioprostheses. According to the present analysis of high-risk patients with degenerated bioprosthetic valves, in most cases the VIV approach is clinically effective. The improvement in patient functional capacity after device implantation was clear: 84.1% of patients were classified as having New York Heart Association class I/II early after the procedure. Nevertheless, several safety and efficacy concerns emerged, including a relatively high rate of device malposition, a cluster of ostial coronary obstruction events, and a high rate of moderately elevated postprocedural gradients.

Procedural Efficacy

The VIV approach results in considerable hemodynamic improvement, including a decrease in valve gradients and aortic regurgitation level. Clinical results were maintained at 1-year follow-up among analyzed patients and are comparable with other TAVR cohorts.[8–10] Nevertheless, even though implantation success according to the registry definition was high (93.1%), the rate of VARC-defined "device success" was relatively low (58.9%), which was primarily due to elevated postprocedural gradients of moderate degree. It should be emphasized that the VARC definition was created and originally intended for TAVR procedures performed in native aortic valves and not for VIV procedures.

High Postprocedural Gradients

Significantly elevated postprocedural gradients are common after VIV. In the present registry, the rate of high postprocedural gradients (mean, ≥20 mm Hg) was relatively high (28.4%), and the mean postprocedural gradient (15.9 mm Hg) was higher than after procedures performed inside native aortic valves (≈10 mm Hg).[8–10] This is probably due to reduced area available for the functioning valve when implanted inside a surgical bioprosthesis (ie, reduced potential orifice area) or patient-prosthetic mismatch. In an in vitro model of hemodynamic performance of a 23-mm Edwards SAPIEN device within a degenerated surgical bioprosthesis, incomplete stent expansion resulted in leaflet distortion when implanted in 19- and 21-mm Carpentier Edwards bioprostheses.[28]

In the present analysis, the 2 independent predictors for high postprocedural gradients (severity of bioprosthetic stenosis and use of an Edwards SAPIEN device) are both associated with reduced potential orifice area. The difference between Edwards SAPIEN and CoreValve results is probably secondary to the fundamental dissimilarity between the devices: The functioning part of the Edwards SAPIEN valve is located inside the native valve annulus (intra-annular), and that of the CoreValve is usually located above that plane (supra-annular). Consequently, the CoreValve device depends much less on surgical bioprosthesis dimensions, and its functioning part may have larger potential orifice area. In support of this theory, in an in vitro evaluation, a custom-designed supravalvular TAVR device has achieved more favorable hemodynamic measurements.[32] In the present registry, at 1-year follow-up there was no statistically significant increase in valve gradients in comparison to early postprocedural gradients. However, the possible impact of elevated gradients should be examined with longer follow-up.

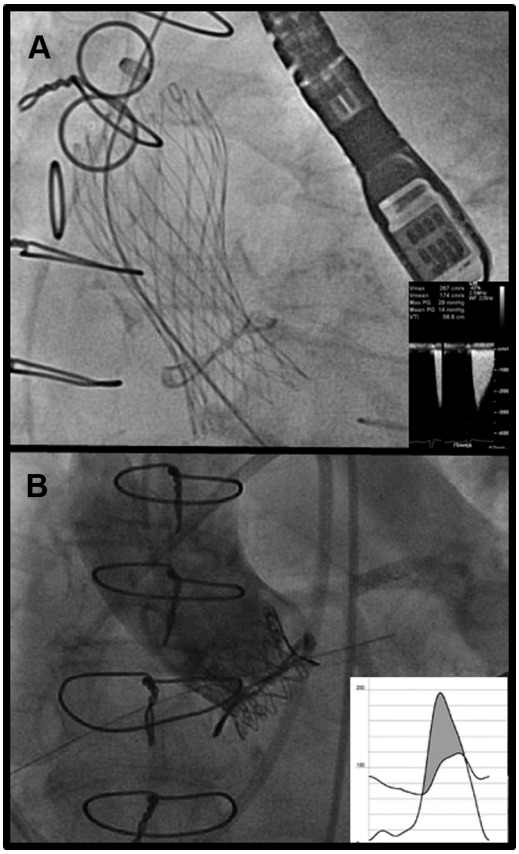

Figure 3. Case examples of valve-in-valve procedures performed inside small surgical bioprostheses. **A**, Transfemoral implantation of 26-mm CoreValve inside a 19-mm Mitroflow valve with an internal diameter of 15.4 mm. Postprocedural maximum/mean gradients were reasonable: 29/14 mm Hg. **B**, Transapical implantation of 23-mm Edwards SAPIEN inside a 21-mm Mitroflow valve with an internal diameter of 17 mm. Postprocedural gradients were very high: 88/58 mm Hg.

Safety Hazards

Thirty-day mortality and stroke rates after VIV procedures (8.4% and 2%, respectively) are comparable to those in other TAVR cohorts.[8–10] Nevertheless, there are 2 major safety concerns when VIV is performed: device malposition and ostial coronary obstruction. The relatively high malposition rate during VIV cases (15.3%) could be secondary to the relative lack of valvular calcification and, in some cases, difficulty in defining the optimal target for implantation during the procedure, particularly in stentless bioprostheses, in which no anatomic markers are available.

Ostial left-main obstruction, which is reported only rarely during native valve TAVR, seems to be more common during VIV procedures (3.5%). This complication has a dreadful prognosis. Most of the patients having ostial left-main obstruction died during their hospital stay. The propensity for this complication is clearly related to the spatial geometry of the surgical valve leaflets inside the aortic sinuses and seems to be more common within the Mitroflow and Freedom valves. The Mitroflow leaflets are unique, being relatively long (≈13 mm) and mounted externally over the stent rather than internally, as in most other stented bioprostheses.[29]

Table 3. Predictors for Elevated Gradients After Valve-in-Valve Procedures

	Odds Ratio	95% Confidence Interval	*P*
Univariate analysis			
Patient age (y)	1.00	0.97–1.02	0.77
Female	0.95	0.65–1.48	0.76
LVEF (%)	1.02	1.00–1.04	0.04
NYHA functional class IV	0.47	0.24–0.92	0.03
Baseline aortic valve area*	1.17	1.07–1.27	0.0004
Baseline aortic regurgitation ≥+2	2.71	1.43–5.14	0.002
Stented bioprosthesis	4.18	1.56–11.22	0.004
Small bioprostheses (ID <20 mm)	0.83	0.27–2.52	0.94
Preimplantation valvuloplasty	3.03	1.55–5.93	0.001
Use of Edwards SAPIEN device	2.46	1.31–4.64	0.005
Use of small TAVR device†	2.65	1.04–6.72	0.04
Postimplantation valvuloplasty	0.77	0.29–2.0	0.6
Multivariate analysis			
Baseline aortic valve area*	0.87	0.79–0.94	0.001
Edwards SAPIEN	2.28	1.17–4.43	0.02
NYHA functional class IV	1.00	0.97–1.02	0.83
LVEF (%)	1.02	0.97–1.06	0.13
Baseline aortic regurgitation ≥+2	1.04	0.49–2.17	0.93
Stented bioprosthesis	1.42	0.61–3.31	0.42
Small bioprostheses (ID <20 mm)	1.40	0.63–3.10	0.35
Preimplantation valvuloplasty	1.67	0.93–2.91	0.08
Use of small TAVR device†	2.85	0.41–17.32	0.84
Postimplantation valvuloplasty	1.57	0.62–3.81	0.38

LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association; ID, internal diameter; and TAVR, transcatheter aortic valve replacement.

*Per 0.1-cm^2 increment.

†CoreValve 26 mm (vs 29 mm) and Edwards SAPIEN 23 mm (vs 26 mm).

Implications for VIV Procedures

The VIV procedure is technically demanding and should be reserved for highly experienced centers. Operators should be skilled in the handling of device malposition, retrieval techniques, and implantation of a second TAVR device, if needed. During screening, the Heart Team must have all of the information about and be familiar with the particular characteristics of the surgical bioprosthesis: the mode of degeneration and echocardiographic parameters (isolated paravalvular regurgitation should be excluded); valve size (most importantly, bioprosthesis internal diameter should be used for TAVR device and size selection; because of better hemodynamic results, CoreValve may be preferred in cases of small bioprosthesis with internal diameter <20 mm); valve position (intra-annular versus supra-annular); valve type (stented versus stentless); the relation of the bioprosthetic valve to its radiopaque markers; and the risk for coronary obstruction when VIV is performed inside that specific bioprosthesis.

Operators should be aware of the risk of device malposition, and every effort should be taken to ensure correct localization and overlap with the bioprosthesis sewing ring. One cannot underestimate the importance of having coaxial positioning during the final stage of device deployment. The use of trans-

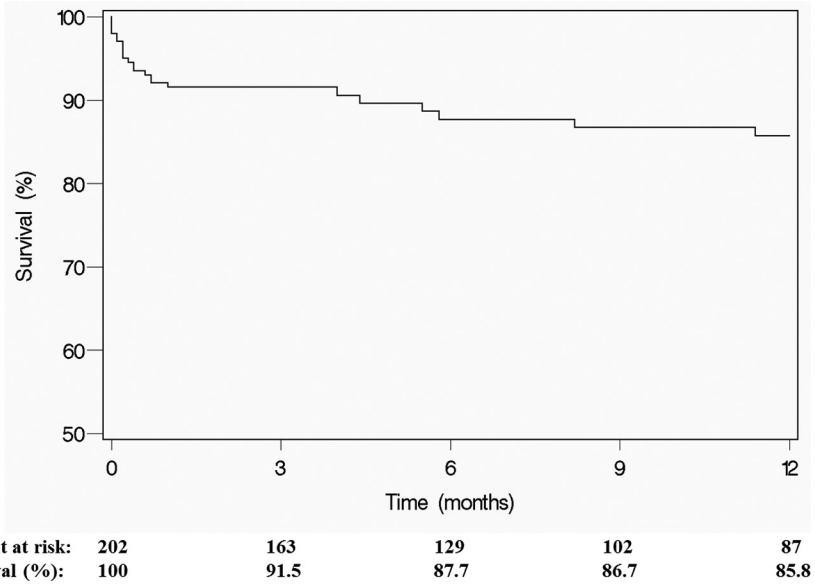

Figure 4. Kaplan–Meier survival curve of patients undergoing transcatheter aortic valve replacement for degenerated bioprosthetic valve (valve-in-valve).

esophageal echocardiography during these procedures is encouraged, especially during procedures performed inside stentless valves, where no radiopaque markers can assist in positioning. The use of software that will possibly enable improved device localization, such as the C-THV (Paieon Inc, Israel) or the Heart Navigator (Philips, Eindhoven, Netherlands), may be helpful and should be further evaluated.[33]

Although no case of acute hemodynamic instability after preimplantation valvuloplasty was encountered in the registry, the practice of balloon dilatation inside degenerative bioprosthesis before valve implantation should be reserved for critically stenotic bioprostheses and probably avoided in patients with severe regurgitation. In comparison with native aortic valve leaflets, surgical valves seem to be susceptible to tearing after balloon valvuloplasty.[34,35] That could lead to acute severe valve regurgitation, debris embolization, and stroke. It must be emphasized, however, that avoiding preimplantation valvuloplasty could result in a need for postimplantation balloon inflation, as occurred in the registry CoreValve group.

When preimplantation valvuloplasty is utilized, the maneuver may be used to examine the risk for ostial coronary obstruction by injecting contrast above the inflated balloon and evaluating the flow into the coronary arteries. Patients at high risk of ostial coronary occlusion should probably be managed conservatively, or, in selected Edwards SAPIEN cases, a preventive wire may be inserted into the left main coronary artery before device implantation.

Interestingly, the rate of pacemaker implantation after the CoreValve VIV procedures (9%) was relatively low compared with that after native aortic valve CoreValve procedures. This is most likely due to some degree of protection created by the surgical bioprosthesis frame, resulting in diminished compression of the TAVR device on the interventricular basal septum.[36] Obviously, strict ECG monitoring should be the standard of care after all TAVR procedures; however, it seems that after CoreValve VIV implantations, prolonged preventive use of a temporary pacemaker is not warranted when no conduction abnormality appears.

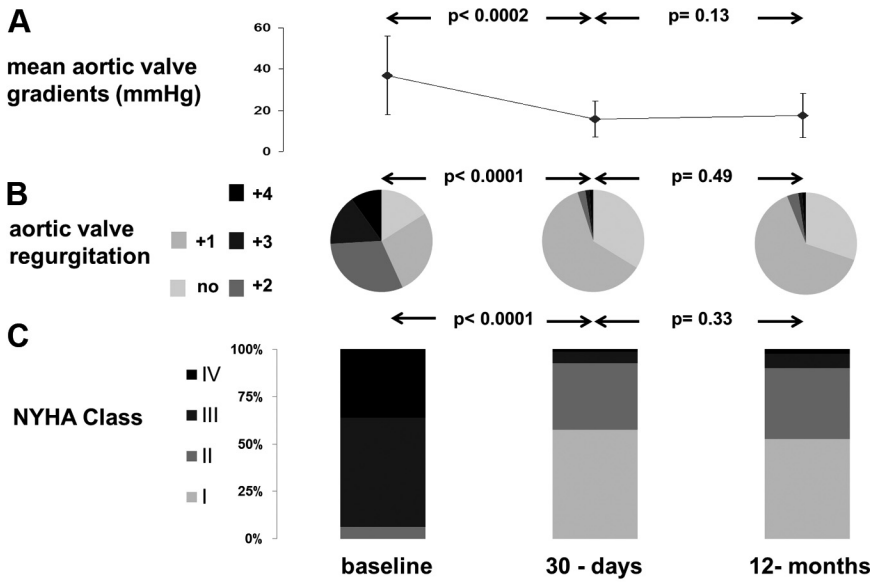

Figure 5. Clinical and hemodynamic results of patients undergoing transcatheter aortic valve replacement for degenerated bioprosthetic valves (valve-in-valve). Thirty-day mean valve gradients (**A**), aortic regurgitation (**B**) and functional class (**C**) results were maintained at 1-year follow-up (obtained in 81 patients). NYHA indicates New York Heart Association.

Implications for Cardiac Surgery

In the future, dependent on expanded clinical data, the VIV approach may affect SAVR practice in several respects: transcatheter treatment of patients with failed bioprosthetic valves with markedly elevated risk for reoperation, selection of valve class (biological much more than mechanical) and valve type (with minimal risk for ostial coronary obstruction) during surgery, and performance of surgical annular dilatation in small aortic roots.

A randomized controlled trial comparing reoperative SAVR and VIV in patients with failed bioprostheses has never been executed, and because VIV treatment is still infrequent, it will be quite difficult to conduct such a trial. As a result, there are not enough data to justify VIV instead of reoperation in most high-risk patients with failed aortic bioprostheses. Nevertheless, VIV could be an acceptable approach in carefully selected high-risk patients and in those considered as having no option (ie, those with no other effective treatment option for their illness).

VIV practice may also affect the selection of valve type during SAVR. A less invasive approach for failed bioprostheses could definitely be an argument in favor of using bioprosthesis in younger patients undergoing SAVR. In addition, surgical valves with increased risk for ostial coronary obstruction after VIV should probably be used less frequently during SAVR because the risk of later bioprosthetic failure and the possible need for a subsequent VIV procedure should be taken into account.

Limitations

Because the VIV approach is novel, 1-year follow-up was reached in only 87 patients, less than half of the original group evaluated. Therefore, long-term results of the registry data should be analyzed with caution. Registry results reveal that elevated gradients are relatively common after VIV procedures. However, the study was not powered to correlate these echocardiographic results and clinical outcomes. For that evaluation, another trial including a larger patient group followed for a longer time period might be beneficial.

Conclusion

The VIV procedure is clinically effective in the vast majority of patients with degenerated stenotic or regurgitant bioprosthetic valves. Short- and intermediate-term results after these procedures are favorable. Safety and efficacy concerns include device malposition, ostial coronary obstruction, and high postprocedural gradients.

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CLINICAL PERSPECTIVE

In the last decade, bioprosthetic valves have been used more commonly during surgical valve replacements; it is estimated that in subsequent years, many patients will suffer from failed surgical bioprostheses. The Global Valve-in-Valve Registry, which includes in the present analysis 202 patients from 38 centers, is the first large, comprehensive evaluation of transcatheter aortic valve replacement with the use of either Edwards SAPIEN (Edwards Lifesciences, Irvine, CA) or CoreValve (Medtronic, Minneapolis, MN) devices for failed surgically inserted aortic bioprostheses, including 1-year clinical and echocardiographic analyses. According to the registry, the valve-in-valve approach is effective and relatively safe. Improvement in patient functional capacity was clear: 84.1% of treated patients were classified as New York Heart Association class I/II early after the procedure. Clinical and hemodynamic results are maintained in 1-year follow-up. Thirty-day mortality and stroke rates (8.4% and 2%, respectively) are comparable to those in other transcatheter aortic valve replacement cohorts. An efficacy concern involved moderately elevated postprocedural gradients, with predictors in multivariate analysis that include the degree of bioprosthesis stenosis and treatment with an Edwards SAPIEN inside a small bioprosthesis. Safety concerns included ostial coronary obstruction (3.5%) and device malposition (15.3%) resulting in relatively high rates of a need for implantation of another transcatheter aortic valve replacement device (8.4%) and retrieval of a CoreValve (8.9%). Operators of valve-in-valve procedures should be skilled in handling device malposition and related technical maneuvers, if needed. The possible impact on cardiac surgery practice includes referral of patients with failed bioprostheses who are at very high surgical risk to valve-in-valve and selection of valve class during surgery (mechanical versus biological), in favor of the use of bioprostheses.

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Transcatheter Aortic Valve Replacement for Degenerative Bioprosthetic Surgical Valves: Results From the Global Valve-in-Valve Registry

Danny Dvir, John Webb, Stephen Brecker, Sabine Bleiziffer, David Hildick-Smith, Antonio Colombo, Fleur Descoutures, Christian Hengstenberg, Neil E. Moat, Raffi Bekeredjian, Massimo Napodano, Luca Testa, Thierry Lefevre, Victor Guetta, Henrik Nissen, José-María Hernández, David Roy, Rui C. Teles, Amit Segev, Nicolas Dumonteil, Claudia Fiorina, Michael Gotzmann, Didier Tchetche, Mohamed Abdel-Wahab, Federico De Marco, Andreas Baumbach, Jean-Claude Laborde and Ran Kornowski

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SUPPLEMENTAL MATERIAL

Appendix 1. The Global Valve-in-Valve Registry: participating sites and key personnel

Medical Center	Enrolling Physician	# of cases
German Heart Center, Munich, Germany	Sabine Bleiziffer, MD, Rüdiger Lange, MD, Nicolo Piazza, MD, PhD, Domenico Mazzitelli, MD	25
St Paul's, Vancouver, Canada	John Webb, MD, Stefan Toggweiler, MD, Anson Cheung, MD, Jian Ye, MD	15
Sussex Cardiac Centre, Brighton, UK	David Hildick-Smith, MD, Uday H Trivedi, FRCS	13
Hospital Bichat, Paris, France	Alec Vahanian, MD, Dominique Himbert, MD, Fleur Descoutures, MD	12
San Raffaele Scientific Institute, Milan, Italy	Antonio Colombo, MD, Azeem Latib, MD, Matteo Montorfano MD, Alaide Chieffo MD, Francesco Maisano MD	11
Royal Brompton Hospital, UK	Neil E Moat, FRCS, Simon Davies, MD	7
Universitaetsklinikum Regensburg, Germany	Christian Hengstenberg, MD, Michael Hilker, MD, Oliver Husser, MD	7
University of Heidelberg, Germany	Raffi Bekeredjian, MD	7
University of Padova, Italy	Massimo Napodano, MD	7
Rabin Medical Center, Israel	Ran Kornowski, MD, Abid Assali, MD, Hana Vaknin-Assa, MD	6
St George's Hospital, London, UK	Stephen Brecker, MD, David Roy, MD, Marjan Jahangiri, FRCS	6
Hopital Jacques Cartier, Massy, France	Thierry Lefevre, MD, Kentaro Hayashida, MD, PhD	6
Clinical Institute S. Ambrogio, Milan, Italy	Francesco Bedogni, MD, Luca Testa, MD, PhD, Nedy Brambilla, MD, Maria Luisa Laudisa, MD	6
Clinique Pasteur, Toulouse, France	Didier Tchetche, MD, Olivier Vahdat, MD, Bruno Farah, MD, Jean Fajadet, MD	5
Hospital de Santa Cruz, Lisboa, Portugal	Rui Campante Teles, MD, Jose Neves, MD	5
Odense University Hospital, Denmark	Henrik Nissen MD, PhD	5
Hospital Universitario Virgen de la Victoria. Málaga, Spain	José María Hernández-García, MD, PhD, Antonio J. Muñoz-García, MD, PhD, Juan H Alonso-Briales, MD Manuel F Jiménez-Navarro MD, PhD	5
Bergmannsheil Ruhr-University, Bochum, Germany	Michael Gotzmann, MD, Waldemar Bojara, MD	5

Ospedale Niguarda Ca' Granda, Milan, Italy	Federico De Marco, MD, Silvio Klugmann, MD, Giuseppe Bruschi, MD, Jacopo Oreglia, MD	4
Spedali Civili Brescia, Italy	Ettori Federica, MD, Claudia Fiorina, MD	4
Bristol Heart Institute, UK	Andreas Baumbach, MD, Ali Khavandi, MD, Mark Turner, MD	4
Sheba Medical Center, Israel	Victor Guetta, MD, Amit Segev, MD	4
Rangueil University Hospital, Toulouse, France	Nicolas Dumonteil, MD, Bertrand Marcheix, MD, PhD	4
Segeberger Kliniken GmbH, Bad Segeberg, Germany	Mohamed Abdel-Wahab, MD, Gert Richardt, MD	4
Sahlgrenska University Hospital, Gothenburg, Sweden	Dan Ioanes, MD	3
University Hospital Duesseldorf, Germany	Marc W. Merx, MD, Malte Kelm, MD	3
Azienda Policlinico Vittorio Emanuele, Catania, Italy	Marco Barbanti, MD, Gian Paolo Ussia, MD, Corrado Tamburino, MD, PhD	3
Villa Azzurra Hospita, Rapallo, Italy	Paolo Pantaleo, MD	2
Azienda Ospedaliero Universitaria di Bologna Policlinico Sant'Orsola Malpighi, Bologna, Italy	Antonio Marzocchi, MD, Francesco Saia, MD, PhD	2
Hamilton hospital WDHB, New Zealand	Sanjeevan Pasupati, MBChB, FRACP, Gerald Devlin, MBChB, FRACP, Rajesh Nair MBBS, MRCP	2
Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy	Anna Sonia Petronio, MD	2
Medizinische Klinik und Poliklinik II, Universitaetsklinikum Bonn, Bonn, Germany	Jan-Malte Sinning, MD, Nikos Werner, MD, PhD, Georg Nickenig, MD, PhD, Eberhard Grube, MD, PhD	2
AKH Linz, Austria	Michael Grund, MD	1
Alfred Hospital Melbourne, Australia	Antony Walton, MBBS, Stephen Duffy. MBBS	1
Blackpool, UK	David H Roberts, MD	1
Cardiocentre Royal Vineyards, Prague, Czech republic	Viktor Kocka, MD	1
University Hospital of Geneva, Switzerland	Stephane Noble, MD, Marco Roffi, MD,	1
Silesian Center for Heart Diseases in Zabrze, Poland	Piotr Chodor, MD, Krzysztof Wilczek, MD	1

Appendix 2. Degenerated bioprostheses included in the Global Valve-in-Valve Registry

Stented (n= 155)			**Stentless (n= 47)**		
	n	**%**		**n**	**%**
Carpentier Edwards (Edwards Lifesciences, Irvine, CA)	61	39.4	Homograft	14	29.8
Mitroflow (Sorin Group Inc, Vancouver, Canada)	39	25.2	Biocor (St. Jude)	10	21.3
Mosaic (Medtronic, Minneapolis, MN)	15	9.7	Cryolife O'Brien (Cryolife International, Atlanta, GA)	6	12.8
Epic (St. Jude Medical, St. Paul, MN)	13	8.4	Freestyle (Medtronic)	4	8.5
Hancock (Medtronic)	13	8.4	Freedom (Sorin)	4	8.5
Others	14	9.0	Toronto SPV (St. Jude)	4	8.5
			Prima (Edwards)	2	4.3
			Others	3	6.4

Label-size	**n**	**%**
19-mm	6	3
21-mm	47	23.3
23-mm	74	36.6
25-mm	47	23.3
27-mm	9	4.5
Others	19	9.4