Transcatheter mitral valve replacement after surgical repair or replacement comprehensive midterm evaluation of valve-in-valve and valve-in-ring implantation from the VIVID registry

Simonato, M.; Whisenant, B.; Ribeiro, H.B.; Webb, J.G.; Kornowski, R.; Guerrero, M.; ... ; Dvir, D.

Circulation

ORIGINAL RESEARCH ARTICLE

Transcatheter Mitral Valve Replacement After Surgical Repair or Replacement

Comprehensive Midterm Evaluation of Valve-in-Valve and Valve-in-Ring Implantation From the VIVID Registry

Editorial, see p 117; Article see p 178

Matheus Simonato, MD
⋮
Danny Dvir, MD

BACKGROUND: Mitral valve-in-valve (ViV) and valve-in-ring (ViR) are alternatives to surgical reoperation in patients with recurrent mitral valve failure after previous surgical valve repair or replacement. Our aim was to perform a large-scale analysis examining midterm outcomes after mitral ViV and ViR.

METHODS: Patients undergoing mitral ViV and ViR were enrolled in the Valve-in-Valve International Data Registry. Cases were performed between March 2006 and March 2020. Clinical endpoints are reported according to the Mitral Valve Academic Research Consortium (MVARC) definitions. Significant residual mitral stenosis (MS) was defined as mean gradient ≥10 mm Hg and significant residual mitral regurgitation (MR) as ≥ moderate.

RESULTS: A total of 1079 patients (857 ViV, 222 ViR; mean age 73.5±12.5 years; 40.8% male) from 90 centers were included. Median STS-PROM score 8.6%; median clinical follow-up 492 days (interquartile range, 76–996); median echocardiographic follow-up for patients that survived 1 year was 772.5 days (interquartile range, 510–1211.75). Four-year Kaplan-Meier survival rate was 62.5% in ViV versus 49.5% for ViR (P<0.001). Mean gradient across the mitral valve postprocedure was 5.7±2.8 mm Hg (≥5 mm Hg; 61.4% of patients). Significant residual MS occurred in 8.2% of the ViV and 12.0% of the ViR patients (P=0.09). Significant residual MR was more common in ViR patients (16.6% versus 3.1%; P<0.001) and was associated with lower survival at 4 years (35.1% versus 61.6%; P=0.02). The rates of Mitral Valve Academic Research Consortium–defined device success were low for both procedures (39.4% total; 32.0% ViR versus 41.3% ViV; P=0.01), mostly related to having postprocedural mean gradient ≥5 mm Hg. Correlates for residual MS were smaller true internal diameter, younger age, and larger body mass index. The only correlate for residual MR was ViR. Significant residual MS (subhazard ratio, 4.67; 95% CI, 1.74–12.56; P=0.002) and significant residual MR (subhazard ratio, 7.88; 95% CI, 2.88–21.53; P<0.001) were both independently associated with repeat mitral valve replacement.

CONCLUSIONS: Significant residual MS and/or MR were not infrequent after mitral ViV and ViR procedures and were both associated with a need for repeat valve replacement. Strategies to improve postprocedural hemodynamics in mitral ViV and ViR should be further explored.

The full author list is available on page 114.

Key Words: heart valve disease ■ hemodynamics ■ mitral valve ■ mitral valve insufficiency ■ mitral valve stenosis

Sources of Funding, see page 115

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- Residual stenosis is common after mitral valve-in-valve/valve-in-ring procedures, especially in patients with small devices and large body size, and is associated with a need for repeat mitral valve replacement.
- Residual regurgitation was especially common in mitral valve-in-ring procedures.
- The suboptimal survival of patients having mitral valve-in-ring procedures extends to 4 years with ≈50% mortality.

What Are the Clinical Implications?

- Suboptimal hemodynamics of mitral valve-in-valve and mitral valve-in-ring should lead to procedural strategies to improve postimplantation hemodynamics, aiming to optimize device durability.
- Alternative therapies to mitral valve-in-ring in patients with mitral valve failure after surgical repair should be considered.

Mitral valve (MV) disease is associated with substantial morbidity and mortality.[1] Patients with severe MV disease are increasingly treated with bioprosthetic valves or repaired with annuloplasty rings.[2] Bioprosthetic tissue valves and native valves that were surgically repaired are prone to failure over time because of tissue degeneration and disease progression, and some patients may require reoperation.[3–6] Almost half of patients may be denied an intervention because of high surgical risk.[7] Reoperation by itself is associated with increased surgical risk,[8,9] particularly in those with heart failure and nonelective operations.[8]

The use of transcatheter heart valves in failed bioprosthetic surgical valves (valve-in-valve [ViV]) and annuloplasty rings (valve-in-ring [ViR]) is a less invasive alternative approach to conventional surgical reoperation for high-risk patients only.[10–13] However, the current literature is limited by small number of patients and/or short follow-up. In addition, there is paucity of data on the prognostic significance of postprocedural hemodynamics; in particular, the impact of significant residual mitral stenosis (MS) and mitral regurgitation (MR) after these procedures is uncertain. Our objectives were to perform a large-scale analysis examining midterm clinical, hemodynamic, and echocardiographic outcomes after transcatheter mitral ViV and ViR procedures and to evaluate the clinical significance of postprocedure residual MS and MR.

METHODS

Data Collection

The Valve-in-Valve International Data Registry is a multicenter collaboration and has been previously described in detail.[14] Cases were performed between March 2006 and March 2020 in 90 centers worldwide. Anonymized data were collected through the use of a centralized and secure electronic case report form. All included patients provided informed consent for a ViV or ViR procedure. Cases were included in the Registry after local institutional review board approval. Inconsistencies and missing information in the dataset were resolved through direct contact with the participating investigators by the Registry team. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the board of the Institute of Valvular Research at registry@valveinvalve.org.

Definitions

The primary endpoint of this analysis was patient survival and the main secondary endpoints were significant residual MS (defined as immediate postprocedure mean gradient ≥10 mm Hg), significant residual MR (defined as regurgitation ≥ moderate), and rate of repeat MV replacement ([MVR] either transcatheter or surgical). The mechanism of bioprosthetic valve failure was defined according to European Association of Echocardiography and American Society of Echocardiography criteria.[15] The presence of at least moderate MR and MS was defined as mixed failure. Surgical risk was estimated by the Society of Thoracic Surgeons (STS) MVR score. Chronic kidney disease was defined as estimated glomerular filtration rate ≤60 mL/min·1.73 m^2 (ie, stage III and above). Clinical endpoints are reported according to the Mitral Valve Academic Research Consortium (MVARC) definitions (Expanded Methods).[16] Body surface area was calculated with the Mosteller formula.[17] Severe prosthesis-patient mismatch was defined as indexed effective orifice area ≤0.9 cm^2/m^2 for patients with body mass index <30 kg/m^2 and indexed effective orifice area ≤0.75 cm^2/m^2 for those with body mass index ≥30 kg/m^2.[18] Left ventricular outflow tract (LVOT) obstruction was defined as outflow mean gradient ≥10 mm Hg[16] or cardiogenic shock that was clinically related to that complication as reported by the center. The true internal diameter for each model and size of surgical valve/ring was derived from previously published tables, when available.[19] Malposition was reported by the principal operator and defined as inadequate final position of the transcatheter heart valve for any cause, according to MVARC definitions.

Statistical Analysis

Results are presented as mean±SD for continuous variables with normal distribution, median (interquartile range [IQR]; 25th–75th percentiles) for nonnormally distributed continuous variables and number (percentage) for categorical data. Student's *t* test was used to compare means of normally distributed continuous variables between 2 groups. The Mann–Whitney U-test was used to compare distributions of nonnormally distributed continuous variables between 2 groups and the Kruskal–Wallis test was used to compare nonnormally distributed continuous variables between 3 or more groups. χ^2 and Fisher's exact tests were used to compare proportions of categorical variables, as appropriate. Time-to-event curves were truncated at the last point with ≥10% of patients at risk for the primary endpoint (4-year follow-up).

Logistic regression was utilized to establish independent correlates of significant residual MS and significant residual MR. Cox regression was utilized to establish independent correlates of survival. Given the competing risk of mortality in the evaluation of repeat MVR, a Fine and Gray cause specific subdistribution hazards model was used.[20] The following variables were included in univariable models for significant residual MR and MS: body mass index, age, label size, true internal diameter, baseline MV area, baseline mean mitral gradient, baseline left ventricular ejection fraction, transcatheter heart valve diameter, male sex, mitral ViR (versus ViV), and MR versus MS as the mechanism of failure. In addition to the aforementioned variables, the following were also included in the survival and repeat MVR models: diabetes, peripheral vascular disease, chronic kidney disease, cerebrovascular disease, chronic lung disease, baseline New York Heart Association (NYHA) class IV symptoms (versus others), immediate postprocedural residual mean gradient ≥10 mm Hg, residual MR ≥ moderate, baseline pulmonary artery systolic pressure, transseptal access, and LVOT obstruction, as well as if the case was performed before or after the tenth mitral ViR/ViV of a center (ie, median number of cases performed per center). The proportional hazards assumption was tested for each covariate of the Cox regression and for the final model. A center effect was included in the Cox proportional hazards model in the form of a shared frailty variable. Variables with a *P* value <0.1 in the univariable model were considered for inclusion in the multivariable model, with consideration also given to collinearity and overfitting. Odds ratio (OR), hazard ratio (HR), and subhazard ratio (SHR) are reported for binary logistic, Cox and Fine and Gray models, respectively, with the associated 95% CI. The first author and the corresponding author had full access to the data and vouch for its integrity. A 2-tailed *P* value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS 23 (IBM Corporation, Armonk, NY) and Stata 14.1 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics

A total of 1079 patients were included: 857 mitral ViV and 222 mitral ViR (Figure I in the Data Supplement). Average age was 73.5±12.5 years, 40.8% of patients were male, and median STS score was 8.6% (IQR, 5.4%–14.1%). As shown in Table 1, mitral ViR patients were younger and more commonly male compared with mitral ViV patients. At baseline, mitral ViR patients had lower ejection fraction, and the proportion of failure by pure MR was significantly higher than in ViV patients. Mitral ViR patients were more frequently in NYHA III/IV than mitral ViV patients (94.9% versus 89.5%, respectively; *P*=0.02). Incomplete rings were present in 9.4% of ViR patients. Table I in the Data Supplement includes detailed information on failed surgical valve and ring models and their characteristics.

Out of 1079 patients, 314 patients (29.1%) underwent their operation between the years of 2006 to 2013, 390 patients (36.1%) between 2014 and 2016, and 375 patients (34.8%) between 2017 and 2020. Baseline and procedural details stratified by procedural year are presented in Tables II and III in the Data Supplement. While the proportion of ViV and ViR cases was not significantly different across the years, there was a significant and progressive decrease in the median STS score (Figure 1). There was also a significant increase in the proportion of transseptal access in more recent years (15.6% in 2006–2013, 30.7% in 2014–2016, and 62.7% in 2017–2020; *P*<0.001). The trend of rates of LVOT obstruction throughout the years (1.6% in 2006–2013, 2.8% in 2014–2016, 3.2% in 2017–2020) was not statistically significant (*P*=0.39). There were also decreases in the rate of major bleeding and acute kidney injury in more recent procedures. Finally, patients in the 2006 to 2013 cohort had a trend toward lower survival (*P*=0.05; Figure II in the Data Supplement).

Procedural Characteristics and Outcomes

Patients were most frequently treated with SAPIEN 3 (Edwards Lifesciences, Irvine, CA; n=446; 41.8%). The most frequent access routes were transapical (n=625; 61.6%) and transseptal (n=375; 36.9%). ViV patients were treated with larger transcatheter heart valves and a lower rate of transseptal access than ViR patients. In terms of procedural complications, ViR patients had higher rates of malposition (7.0% versus 2.4% ViV; *P*=0.001), increased need for second transcatheter valve implantation (10.1% versus 2.8% ViV; *P*<0.001), and higher rates of LVOT obstruction (5.9% versus 1.8% ViV; *P*=0.001).

Clinical Outcomes and Survival

As shown in Table 2, MVARC-defined technical success was higher in ViV than in ViR (93.5% versus 82.0%; *P*<0.001). The rates of MVARC-defined device success were low for both procedures (39.4% total; 32.0% ViR versus 41.3% ViV; *P*=0.01). Immediate postprocedural mean gradient ≥5 mm Hg was the most common cause of device failure (present in 95.9% of unsuccessful ViV cases and 88.4% of unsuccessful ViR cases). Causes of absent procedural success are detailed in Table IV in the Data Supplement. With a modified definition of device failure requiring an immediate postprocedural mean gradient ≥10 mm Hg (instead of ≥5 mm Hg), ViR still had lower rates of device success (63.1% versus 84.0% ViV; *P*<0.001). Finally, when excluding the hemodynamic component of the success definition (ie, residual stenosis or regurgitation), success in mitral ViV was 92.5% and in mitral ViR was 81.5% (*P*<0.001). Almost all included patients were discharged on antiplatelets or anticoagulants (96.2%) after the procedure. The rate of anticoagulation was 71.9% and was not significantly different between mitral ViV and ViR (70.8% versus 76.6%; *P*=0.15).

Table 1. Baseline Clinical and Echocardiographic Characteristics of the 2 Groups

	Total (n=1079)	Mitral valve-in-ring (n=222)	Mitral valve-in-valve (n=857)	*P* value
Clinical features				
Male	40.8%	50.9%	38.2%	0.001
Age, y	73.5±12.5	71.2±12.8	74.1±12.4	0.002
Height, cm	165.5±9.7	168.0±9.3	164.9±9.8	<0.001
Weight, kg	70.1±16.7	73.8±17.2	69.1±16.4	<0.001
Body mass index, kg/m2	25.5±5.3	26.1±5.6	25.3±5.2	0.07
New York Heart Association class				0.05
I	0.5%	0.0%	0.6%	
II	9.0%	5.1%	10.0%	
III	59.3%	65.6%	57.7%	
IV	31.3%	29.3%	31.8%	
Time to index surgery, y	9.2 (5.8– 12.8)	6.8 (3.2–10.4)	9.8 (6.5–13.1)	<0.001
Mechanism of failure				<0.001
Regurgitation	15.4%	35.6%	10.2%	
Stenosis	27.6%	15.3%	30.7%	
Mixed	57.1%	49.1%	59.1%	
Label size, mm	28.4±2.1	28.9±2.5	28.2±2.0	<0.001
True internal diameter, mm	25.3±2.6	28.2±2.8	24.7±2.1	<0.001
Diabetes	22.5%	27.6%	21.2%	0.04
Peripheral vascular disease	13.8%	16.1%	13.2%	0.27
Chronic kidney disease	53.4%	62.5%	50.9%	0.003
Atrial fibrillation	49.9%	40.8%	52.3%	0.006
Cerebrovascular disease	15.8%	12.1%	16.7%	0.10
Chronic lung disease	26.9%	29.6%	26.2%	0.32
Permanent pacemaker	26.9%	39.7%	23.6%	<0.001
STS replacement score, %	8.6 (5.4–14.1)	7.4 (4.6–13.0)	9.0 (5.6–14.3)	0.006
Baseline echocardiographic data				
Left ventricular ejection fraction, %	53.2±12.7	45.1±14.8	55.2±11.3	<0.001
Pulmonary artery systolic pressure, mm Hg	59.0±17.8	56.8±17.7	59.5±17.8	0.08
Mitral valve area, cm^2	1.50±0.91	1.87±1.09	1.41±0.83	<0.001
Maximum gradient, mm Hg	22.6±9.9	17.4±11.1	23.8±9.2	<0.001
Mean gradient, mm Hg	10.7±5.9	7.8±5.0	11.4±5.9	<0.001
Mitral regurgitation				<0.001
None/trace	13.5%	6.8%	15.2%	
Mild	13.7%	8.2%	15.1%	
Moderate	12.5%	12.3%	12.6%	
Moderate to Severe	17.4%	25.0%	15.3%	
Severe	43.0%	47.7%	41.7%	

Median absolute follow-up was 492 days (IQR, 76–996) and was similar in the ViV and ViR groups (519 days [IQR, 95.5–1007] versus 426 days (IQR, 40.8–895), respectively; *P*=0.11). Figure 2A shows the Kaplan-Meier survival estimates according to procedure type. Thirty-day mortality was 6.5% in the ViV group and 8.6% in the ViR group (*P*=0.29), while 1-year survival was 86.2% in the ViV group and 76.8% in ViR group (*P*=0.004). In unadjusted analysis, compared with ViV, patients undergoing ViR had significantly lower survival at 4 years (62.5% ViV versus 49.7% ViR; *P*=0.002). Patients at high risk for repeat open-heart surgery (STS score ≥8%) also had significantly worse survival at 4 years (Figure 2B). There was no significant survival difference between patients with transseptal access versus those with other accesses (Figure III in the Data

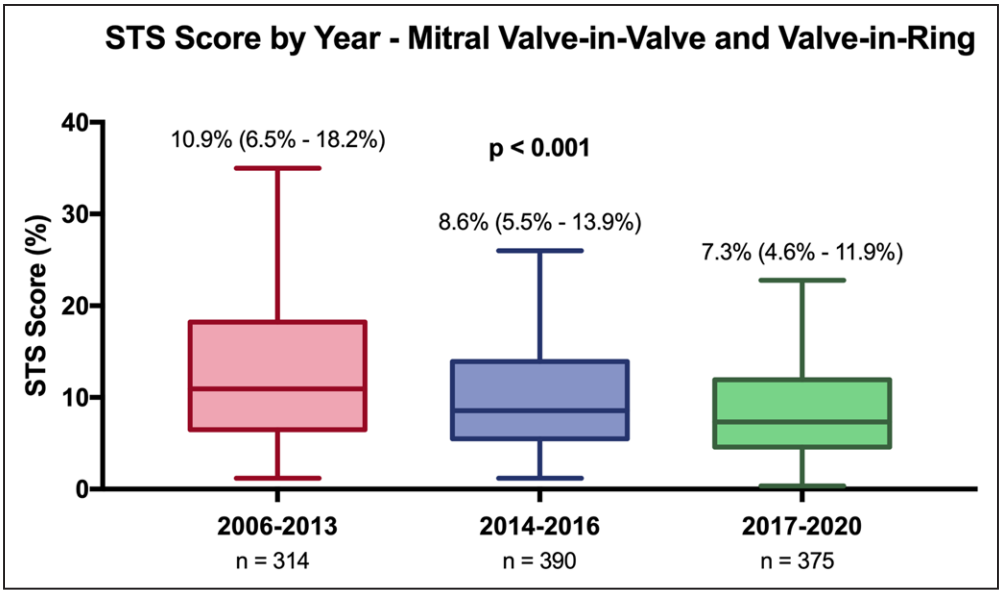

Figure 1. Median Society of Thoracic Surgeons (STS) score across time.
There was a significant decrease in median STS score across the different time periods, indicating a tendency toward the selection of lower risk patients. Numbers represent median and interquartile range.

Supplement). There were no significant 4-year survival differences between mitral ViR patients with semirigid rings and those with rigid/flexible rings (51.1% versus 47.3%, respectively; *P*=0.79), and also no differences between those with complete and incomplete rings (49.5% versus 56.1%, respectively; *P*=0.93). Rates of technical success (81.9% semirigid versus 82.7% rigid/flexible; *P*=0.89) and device success (29.4% semirigid versus 40.4% rigid/flexible; *P*=0.14) were similar between ring types. The overall rate of repeat MVR at 4 years was 2.7% (18 events: 13 open heart surgery, 5 transcatheter), with a higher rate in ViR (5.9% versus 1.9% ViV; *P*<0.001). There was no difference in the 4-year rate of repeat MVR for patients with immediate postprocedural mean gradient ≥5 mm Hg (3.8% versus 1.6% others; *P*=0.64), but the unadjusted 4-year rate of repeat MVR was higher in patients with immediate postprocedural mean gradient ≥10 mm Hg (13.4% versus 2% others; *P*<0.001).

Echocardiographic Follow-Up

An immediate postprocedural mean gradient ≥5 mm Hg was present in 61.4% of all patients, including 67.5% of ViR and 59.9% of ViV patients (*P*=0.05). Significant residual MS (immediate postprocedural mean gradient ≥10 mm Hg) was present in 12.0% of ViR and 8.2% of ViV patients (*P*=0.09). Postimplant significant residual MR was also more common after ViR than ViV (16.6% versus 3.1%; *P*<0.001). Significant residual MR was associated with lower survival at 4 years in unadjusted analysis (35.1% versus 61.6% no residual MR; *P*=0.02; Figure 1C). No such association was found for significant residual MS (66.1% versus 60.5% immediate postprocedural mean gradient <10 mm Hg; *P*=0.89; Figure 1D). Severe postprocedural prosthesis–patient mismatch was present in 24.5% of cases, with no association to 4-year survival (72.7% versus 60.5% no/moderate prosthesis-patient mismatch; *P*=0.13), 4-year repeat MVR (1.3% versus 2.4% no/moderate prosthesis-patient mismatch; *P*=0.83), and/or postprocedural NYHA III/IV functional class (19.4% versus 17.9%; *P*=0.76).

Echocardiographic follow-up of more than 1 year (median time, 772.5 days [IQR 510 – 1211.75]) was available for 446 patients (70.0% of those alive at 1 year). Both mitral ViV and ViR were associated with immediate significant increases in mitral valve area that remained stable during follow-up (Figure 3A). Mitral ViV and ViR procedures immediately reduced mean gradients (Figure 3B). There was, however, a slight but statistically significant increase in mean MV gradients during the follow-up period after ViV (*P*<0.001), but none after ViR (*P*=0.20; Figure 3B). Similar results were obtained when only patients with more than 1 year of echocardiographic follow-up were included in the analysis (Figure IV in the Data Supplement). The rates of significant residual MS were higher in patients with baseline stenosis and smaller true internal diameter (Figure V in the Data Supplement), but at the same time patients with small valves (true internal diameter ≤23 mm) did not have a significant increase in their gradients in follow-up (Figure VI in the Data Supplement). There was a trend for a greater rate of NYHA III/IV symptoms when the immediate postprocedural residual mean gradient was ≥10 mm Hg (26.1% versus 17.8% others; *P*=0.09), but no difference was found when the immediate postprocedural residual mean

Table 2. Procedural Outcomes of the 2 Groups

	Total (n=1079)	Mitral valve-in-ring (n=222)	Mitral valve-in-valve (n=857)	*P* value
Transcatheter heart valve diameter, mm	27.1±2.0	26.7±2.0	27.1±2.0	0.01
Access				0.002
Transapical	61.6%	50.7%	64.4%	
Transseptal	36.9%	46.4%	34.5%	
Right thoracotomy	1.0%	1.9%	0.7%	
Other	0.5%	0.9%	0.4%	
General anesthesia	97.4%	96.4%	97.6%	0.36
Transesophageal echocardiography	97.3%	98.0%	97.1%	0.50
Preinflation	19.0%	24.0%	17.8%	0.05
Postinflation	12.4%	28.8%	8.4%	<0.001
Vascular complications				0.06
Minor	2.3%	1.4%	2.5%	
Major	2.7%	0.5%	3.2%	
Major bleeding complication	8.0%	4.7%	8.8%	0.05
Acute kidney injury	9.6%	13.0%	8.8%	0.07
Success and components				
Technical success*	91.1%	82.0%	93.5%	<0.001
Device success†	39.4%	32.0%	41.3%	0.01
Modified device success‡	79.7%	63.1%	84.0%	<0.001
Device success without hemodynamics criteria§	90.3%	81.5%	92.5%	<0.001
Malposition/embolization/migration	3.3%	7.0%	2.4%	0.001
Second transcatheter heart valve needed	4.3%	10.1%	2.8%	<0.001
Mean gradient ≥5 mm Hg	61.4%	67.5%	59.9%	0.05
Mean gradient ≥10 mm Hg	8.9%	12.0%	8.2%	0.09
Mitral regurgitation ≥moderate	5.8%	16.6%	3.1%	<0.001
Major stroke	1.2%	0.5%	1.4%	0.27
Left ventricular outflow tract obstruction	2.6%	5.9%	1.8%	0.001
Procedural mortality	1.8%	0.5%	2.1%	0.10
30-day mortality	7.0%	8.6%	6.5%	0.29
Discharge medications				0.01
Single antiplatelet alone	12.7%	10.8%	13.2%	
Single antiplatelet and anticoagulation	38.2%	46.8%	36.1%	
Double antiplatelet	11.4%	10.1%	11.8%	
Double antiplatelet and anticoagulation	2.8%	5.1%	2.2%	
Warfarin/coumadin alone	26.8%	19.6%	28.6%	
Novel oral anticoagulants alone	4.2%	5.1%	3.9%	
Other	0.1%	0.6%	0.0%	
None	3.8%	1.9%	4.2%	
Immediate postprocedural echocardiographic data				
Left ventricular ejection fraction, %	52.1±12.8	45.2±15.4	53.8±11.4	<0.001
Mitral valve area, cm^2	2.04±0.74	2.13±0.74	2.01±0.74	0.17
Severe patient–prosthesis mismatch	24.5%	26.9%	23.8%	0.54
Maximum gradient, mm Hg	12.6±5.6	12.1±5.6	12.7±5.6	0.24
Mean gradient, mm Hg	5.7±2.8	6.0±2.8	5.6±2.7	0.08
Mitral regurgitation				<0.001

(*Continued*)

Table 2. Continued

	Total (n=1079)	Mitral valve-in-ring (n=222)	Mitral valve-in-valve (n=857)	*P* value
None/trace	71.7%	50.7%	77.0%	
Mild	22.5%	32.7%	19.9%	
Moderate	5.0%	12.8%	2.9%	
Moderate to Severe	0.5%	2.4%	0.0%	
Severe	0.4%	1.4%	0.1%	

*Technical success: absence of procedural mortality, and successful access, delivery and retrieval of the device delivery system, successful deployment and correct positioning of the first intended device, and freedom from emergency surgery or reintervention related to the device or access procedure.

†Device success: absence of procedural mortality or stroke, proper placement and positioning of the device, freedom from unplanned surgical or interventional procedures related to the device or access procedure, continued intended safety and performance of the device, including no evidence of structural or functional failure, no specific device-related technical failure issues, and complications and reduction of mitral regurgitation to either optimal or acceptable levels without significant mitral stenosis (ie, postprocedure effective regurgitant orifice area is ≥1.5 cm^2 with a transmitral gradient <5 mm Hg), and with no greater than mild (>1) paravalvular MR (and without associated hemolysis).

‡≥10 mm Hg considered as a cut-off.

§Only the components of device success not related to hemodynamics (ie, procedural death, malposition/embolization/migration, second transcatheter heart valve, left ventricular outflow tract obstruction, and stroke) considered.

gradient was ≥5 mm Hg (17.8% versus 19.9% others; *P*=0.48). As shown in Figure 4, there were significant postprocedural decreases in MR severity after both ViV and ViR procedures. The distribution of MR severity remained stable during follow-up after ViR procedures. In contrast, the proportion of cases with MR severity of moderate or more increased over time in the ViV group.

Multivariable Analyses

In a Cox regression model, mitral ViR as compared with ViV was independently associated with mortality (HR, 1.52; 95% CI, 1.03–2.25; *P*=0.04; Figure 5). The 4-year adjusted survival was 66.7% for mitral ViV and 53.8% for mitral ViR (Figure VII in the Data Supplement). In addition, both significant residual MS (SHR, 4.67; 95% CI, 1.74–12.56; *P*=0.002) and significant residual MR (SHR, 7.88; 95% CI, 2.88–21.53; *P*<0.001) were independent predictors of the need for repeat MVR (Figure 5; Figure VIII in the Data Supplement). Independent predictors for significant residual MS were small device true internal diameter, young age, and a larger body mass index (Figure 5). Finally, the only independent predictor of significant residual MR was a ViR procedure (OR, 7.90; 95% CI, 4.01–15.56; *P*<0.001; Figure 5). Table V in the Data Supplement contains further details on the univariable and multivariable models.

DISCUSSION

ViV and ViR procedures are increasingly performed to treat failing mitral valves after open heart surgery. The current analysis is the largest and most comprehensive evaluation of mitral ViV and ViR procedures to date with the longest follow-up reported. This is also the first analysis to extensively detail echocardiographic findings at ≥1 year. The major findings include: (1) transcatheter heart valve implantation in failed surgical mitral valves has acceptable safety and clinical outcomes over the medium-term in a selected group of high-risk patients; (2) 4-year survival was low after both procedures, and was especially notable after ViR (49.7% survival within 4 years for patients with an average age of 71 years), which was also associated with a higher rate of significant residual MR and LVOT obstruction; (3) significant residual MR was associated with lower 4-year survival (35.1% versus 61.6% other patients); (4) both ViV and ViR were commonly associated with residual stenosis (immediate postprocedural mean gradient ≥5 mm Hg in 61% of cases and ≥10 mm Hg in 9% of cases), which was associated with need for repeat MVR and a trend toward worse heart failure symptoms, but not 4-year survival (66.1% versus 60.5% other patients); and (5) the severity of MS and MR increased in ViV procedures, but not in ViR, with a significant loss of echocardiographic follow-up. It is apparent that the durability of these mitral procedures should be further explored, as other major findings were a significant shift towards treating lower risk patients, and an increasing utilization of transseptal access over time.

Survival Analysis

Until recently, the mitral ViV and ViR reports in the literature were limited to single center or small multicenter studies, mainly reporting 30-day and 1-year outcomes.[13,21–24] A small study with 91 patients from a single center reported 35.7% 2-year mortality.[25] The largest cohort to date with more than 30 days follow-up (463 mitral ViV and ViR patients) showed that 1-year mortality was significantly higher in mitral ViR patients at 30.6%, compared with 14% in mitral ViV patients.[10] These results are similar to our own 1-year mortality findings of 23.2% and 13.8%, respectively. In terms of

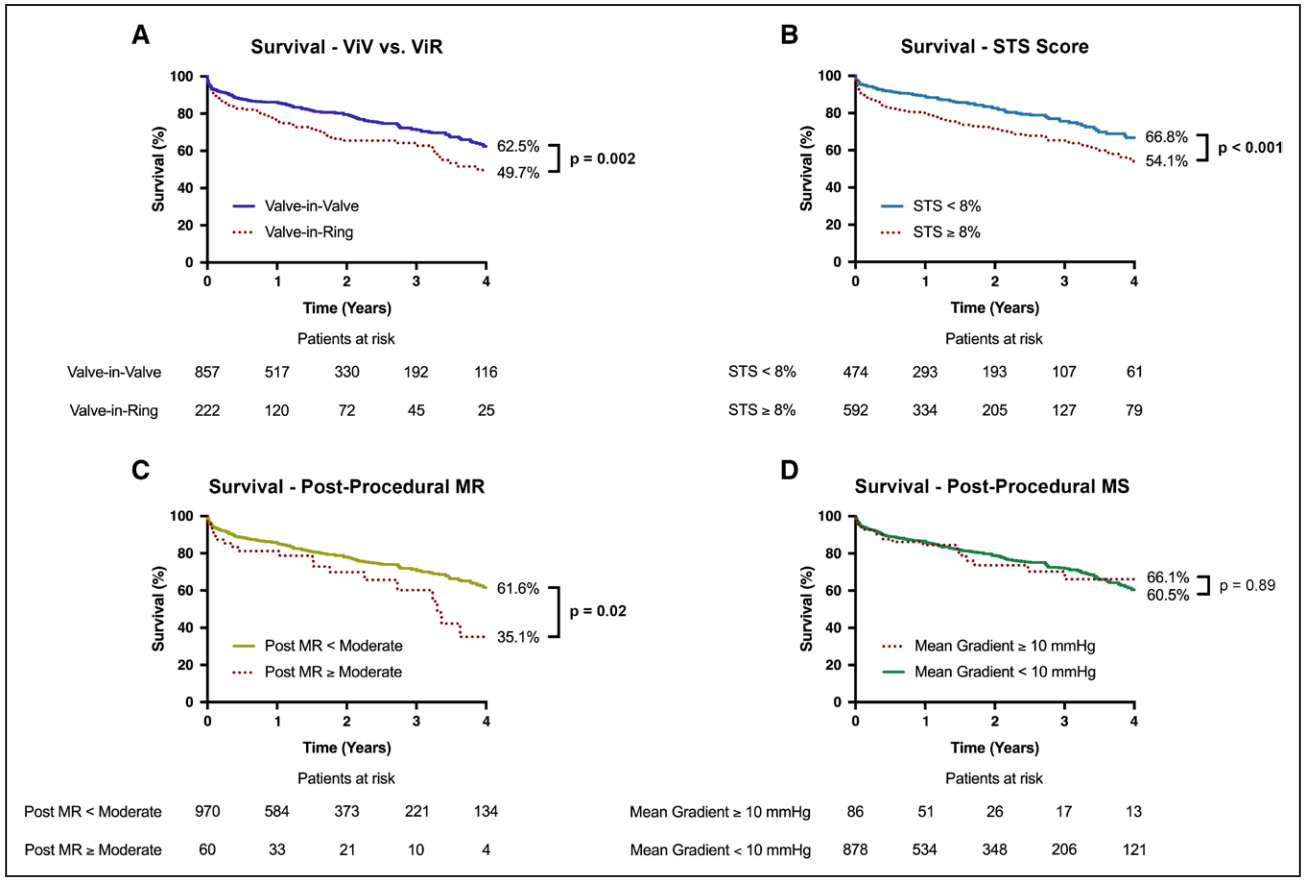

Figure 2. Kaplan-Meier survival curves in different patient subgroups.
A, ViV vs ViR. **B**, STS MVR score <8% vs ≥8%. **C**, Postprocedural MR ≥ moderate vs < moderate. **D**, Immediate postprocedural mean mitral gradient ≥10 mm Hg vs <10 mm Hg. ViR patients, those with STS score ≥ 8% and postprocedural MR ≥ moderate had lower survival at 4 years. No difference in 4-year survival was found for those with mean gradients ≥10 mm Hg. MR indicates mitral regurgitation; MS, mitral stenosis; STS, Society of Thoracic Surgeons; ViR, valve-in-ring; and ViV, valve-in-valve.

predictors of all-cause mortality, our study is in agreement with previous analyses showing the association of mitral ViR and chronic lung disease with clinical outcomes.[10] While that study chose to include STS score in multivariable analyses,[10] our evaluation shows the predictive importance of individual components of this score, including age, chronic kidney disease, baseline functional class, and others that are not included in this score, such as baseline pulmonary hypertension.

The present large-scale study demonstrates that the worse survival in mitral ViR patients persists at 4 years and that approximately half of these patients have died within that time frame. While the 37.5% 4-year mortality of mitral ViV patients is also of concern, the markedly decreased survival after mitral ViR procedures emphasizes the need for alternative therapies geared toward patients with failed surgical ring annuloplasty, including surgical reoperation.[26] It also highlights the need for improved patient selection. Comparison of mitral ViV and ViR results with surgical reoperation outcomes is challenging, given the dissimilarity in risk profile in patients referred for transcatheter strategy, in comparison to those having redo open heart surgery. One study with 1627 Medicare beneficiaries undergoing mitral valve reoperation reports 3-year survival of 68.1%.[8] Our results were comparable, with 3-year survival of 64.2% and 71.6% for mitral ViR and ViV patients, respectively. Although this surgical registry did not report STS scores, these naturally represented a cohort who were deemed operable. This is consistent with higher baseline comorbidity rates in our population of chronic kidney disease, peripheral vascular disease and history of cerebrovascular disease compared with the surgical study.[8] To date no head-to-head randomized comparison of transcatheter ViV/ViR versus surgical reoperation has been performed, and therefore objective contrasting is limited.

In our study, we identified a significant decrease in the risk scores of included patients, demonstrating that operators became progressively more comfortable in offering ViV and ViR to lower risk individuals. Additionally, we also saw an increase in the rates of transseptal access over time. While transapical access has been previously associated with worse outcomes in aortic procedures, we did not identify a survival difference in the current cohort. Our study confirms the findings of other studies that have not identified a survival advantage

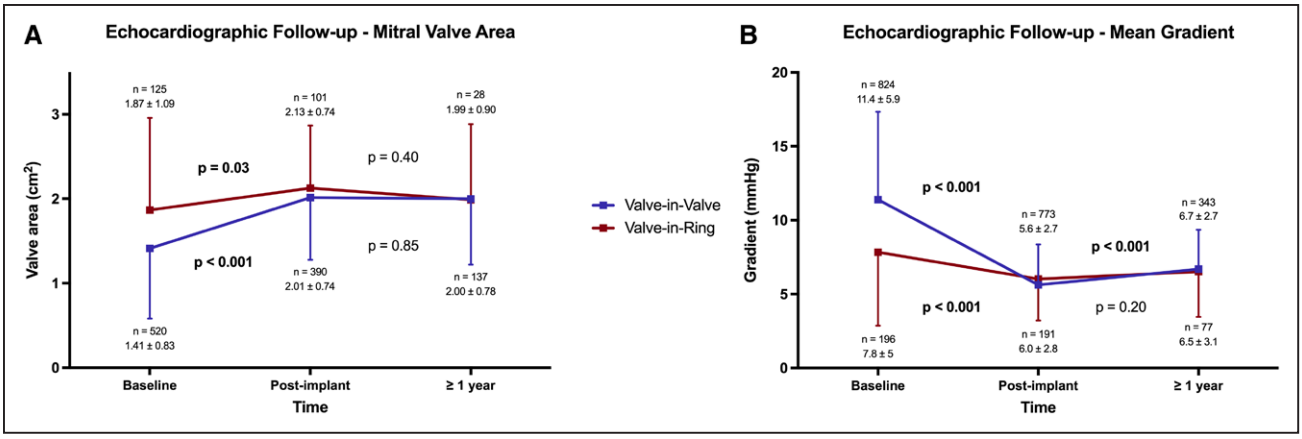

Figure 3. Echocardiographic findings at baseline and during follow-up after mitral ViV and ViR.
A, Mean mitral valve area. **B**, Mean mitral valve gradient. A slight increase in mean gradient occurred in mitral ViV patients. ViR indicates valve-in-ring; and ViV, valve-in-valve.

for transseptal access in transcatheter mitral ViV and ViR procedures, both at 30 days[12] and at 1 year.[10] Even though procedural invasiveness is reduced with transseptal access, it is likely that survival differences would be more closely related to patient characteristics and not as much to procedural aspects, especially considering that transapical access is performed for several years by experienced operators for this indication.

Specific Technical Challenges of Mitral ViR

There are several explanations for the worse outcomes after transcatheter ViR procedures. First, annuloplasty rings have many different shapes, not all of which are amenable to circular deformation.[27] Currently available transcatheter valves were all designed for use in the aortic valve, which is more circular in shape. The mismatch in the shape of the annulus and the transcatheter valve creates a greater likelihood for formation of gaps and consequently worse hemodynamics, particularly in rigid and noncircular rings, including more residual MR and device underexpansion.[12] This is less a concern with ViV, in that failed tissue valve rings are circular and more closely conform to the newly implanted valves. Second, mitral ViR is more prone to procedural complications than ViV. Malposition and need for a second transcatheter valve were significantly more common with ViR in our study. Transcatheter heart valves in the mitral position are subjected to higher closing pressures from the left ventricle during

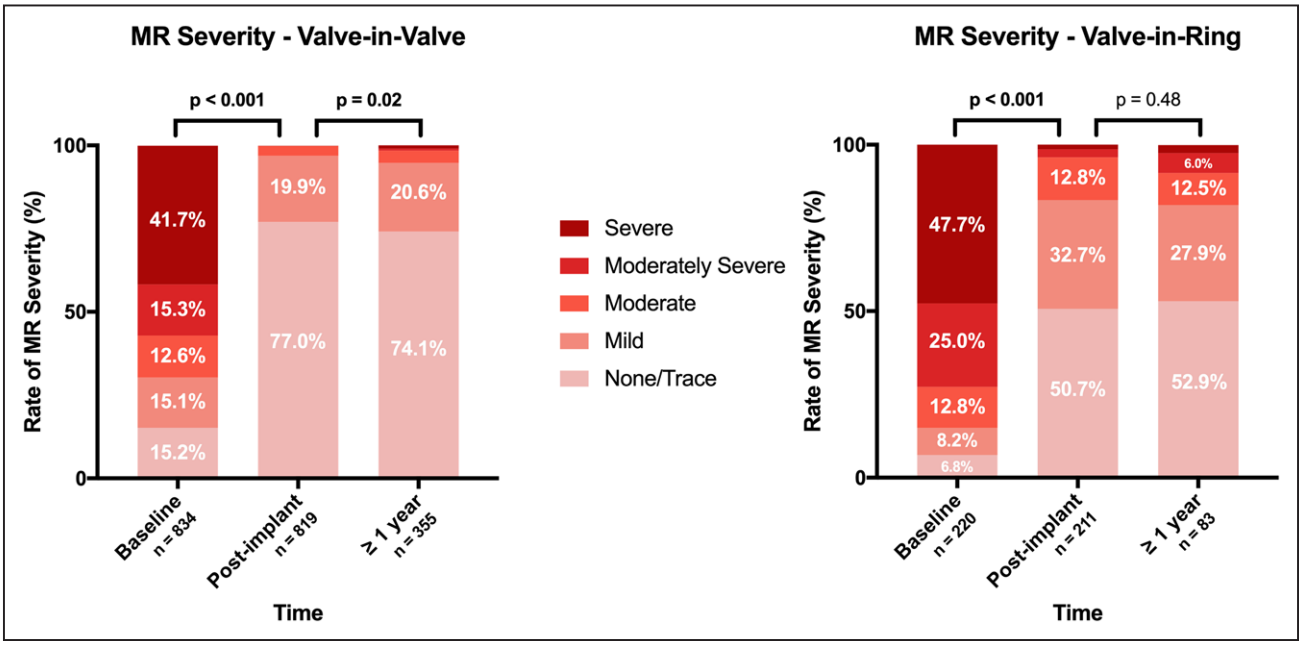

Figure 4. Echocardiographic follow-up of mitral regurgitation in mitral ViV and ViR patients.
Significant immediate decreases in mitral regurgitation severity occurred in both the ViV and ViR groups. The distribution of mitral regurgitation severity in ViR remained stable during follow-up, but there was a significant increase in the proportion of moderate and above mitral regurgitation in the ViV group. MR indicates mitral regurgitation; ViR, valve-in-ring; and ViV, valve-in-valve.

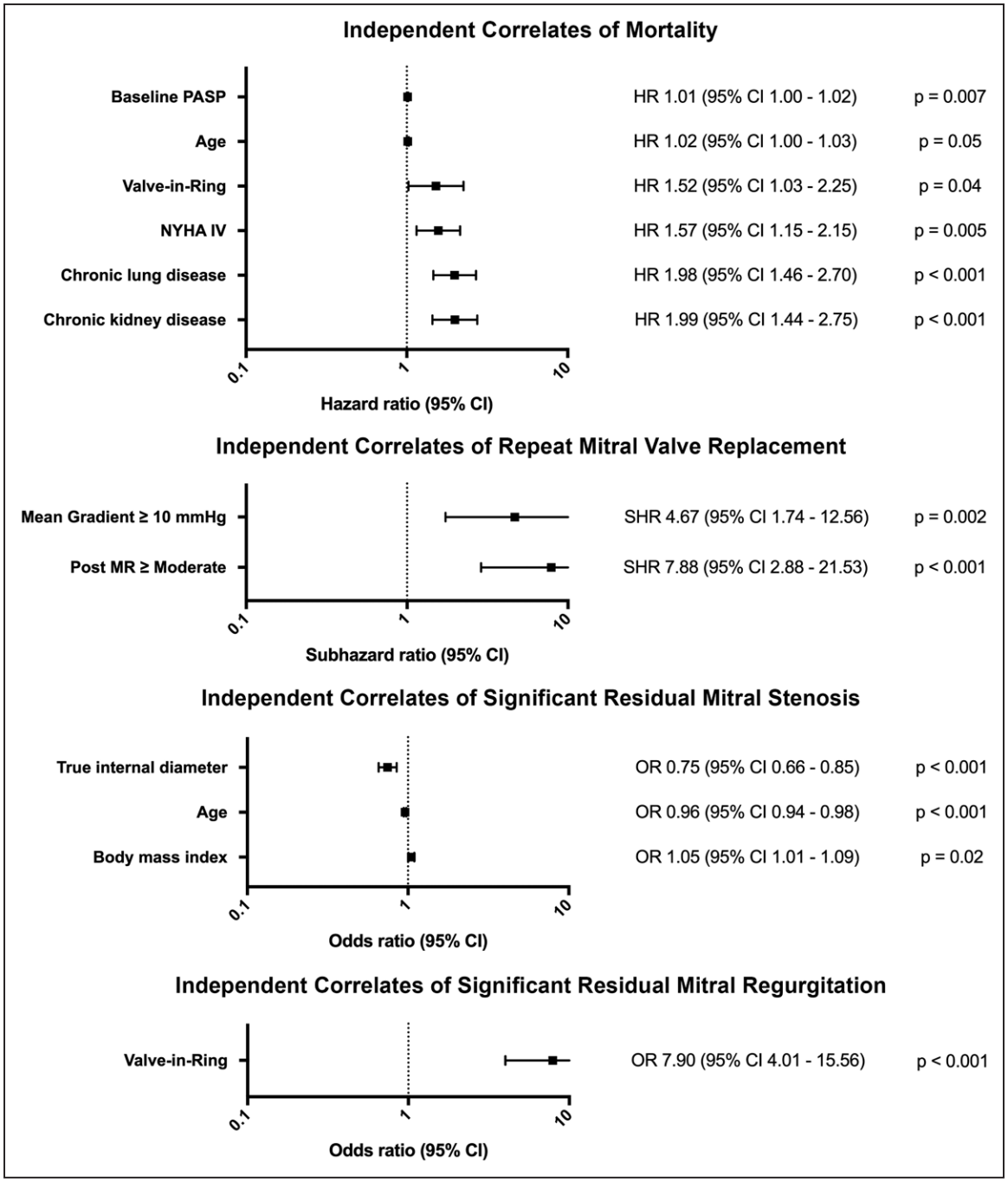

Figure 5. Multivariable models for mortality, repeat mitral valve replacement, residual mean gradient ≥10 mm Hg and residual mitral regurgitation ≥ moderate.

HR indicates hazard ratio; MR, mitral regurgitation; NYHA, New York Heart Association; OR, odds ratio; PASP, pulmonary artery systolic pressure; and SHR, subhazard ratio.

systole that may lead to reduced anchoring.[28] The need for a second heart valve adds to procedure complexity and cost, and its suboptimal expansion may be associated with complications such as thrombosis or early degeneration. Another major complication that is much more common in ViR than ViV is LVOT obstruction. This complication is potentially life-threatening but may be predicted and prevented by one of several technical approaches.[29,30] The possibility of selection bias attributable to exclusion of patients with small neo-LVOT from mitral ViV and ViR procedures from the current cohort should be noted. Third, intrinsic characteristics of the ViR patient population at baseline, including worse left ventricular function and greater comorbidities than in patients undergoing ViV procedures, may also limit the potential benefits obtained by the procedure. Nonetheless, in multivariable analysis, ViR was associated with substantially greater mortality than ViV procedures.

Postprocedural Mitral Regurgitation and Stenosis After ViV and ViR Procedures

The consequences of postprocedural MR and MS after ViV and ViR procedures have not been previously explored in depth. Suboptimal postprocedure hemodynamics are known to influence clinical outcomes in other mitral interventions, such as MitraClip (Abbott Vascular, Menlo Park, CA).[31] Residual stenosis with mean gradients ≥5 mm Hg is common after ViV and ViR. This finding, revealed in our study, is reflected by relatively low rates of MVARC-defined device success. However, immediate postprocedural mean gradients 5 to 9.9 mm Hg were not associated with worse clinical outcomes, such as 4-year survival, 4-year repeat MVR, and NYHA functional class. Although significant residual MS (≥10 mm Hg) was not associated with increased 4-year mortality in our cohort, it was an independent predictor of the need for MVR, and a trend toward more severe heart failure symptoms. Therefore, 10 mm Hg may be a more appropriate cut-off for success in mitral ViV and ViR procedures. Mean gradient between 5 and 9.9 mm Hg after these procedures might be acceptable in selected patients. Strategies to reduce residual stenosis may include a more ventricular device position and, in selected cases, fracturing the bioprosthetic valve ring.[32,33] However, high pressure dilatation has limited value in mitral ViR and is potentially associated with several safety concerns. Postimplant significant residual MR was also associated with the later need for repeat MVR. The fact that there was a slight worsening in valve hemodynamics over follow-up (higher gradients and more significant regurgitation) is concerning. Longer follow-up is warranted to further evaluate the durability of implanted transcatheter valves after mitral ViV and ViR procedures.

Study Limitations

Our study has important limitations that should be taken into account. First, our study did not have a control arm of other possible alternative treatments for failed mitral valves or rings, such as repeat surgical MVR or repair. We have also not collected data on cases with failed surgical valves or rings that did not undergo ViV or ViR and were instead treated with medications alone. Second, it was a retrospective and nonrandomized study without core laboratory evaluation. Echocardiographic follow-up for 30% of patients confirmed alive at 1 year is missing from longer follow-up. As with many other retrospective and industry-independent studies, our study has some degree of missing data, although this issue is quite limited (commonly 2% to 3%; Table VI in the Data Supplement). Our data regarding MR does not differentiate between transvalvular and paravalvular MR. We have not systematically collected data on hemolysis or leaflet thrombosis. Small increases in gradients during follow-up may represent stroke volume improvement. However, we did not collect the additional echocardiographic parameters needed to evaluate this possibility. Although the case number is high, the included procedures are spread over 90 centers and a long period of time (14 years). Transapical access was utilized in the majority of cases. While we did not identify a survival difference, transapical access may add to procedural morbidity and is less commonly utilized nowadays. In addition, multiple device types have been included in the current analysis, as performed in real world practice, and our ability to examine clinical outcomes of several devices that are rarely utilized is limited. We have not systematically collected data on procedures to treat or prevent LVOT obstruction. We have also not collected LVOT gradients in patients not reported to have an LVOT obstruction per MVARC definition. The reasons for second valve implantation were not available in our database. Finally, while the currently available follow-up is the longest reported to date, longer-term follow-up (eg, 8–10 years) is required to assess late outcomes of ViV and ViR.

Conclusions

Mitral ViV has acceptable safety and clinical outcomes in a select group of high-risk patients. Mitral ViR may need further evaluation, as it is associated to lower success and survival rates, and higher rates of postprocedural MR. Significant residual MS and/or MR were not infrequent after mitral ViV and ViR procedures and were both associated with a need for repeat valve replacement. Strategies should be explored to prevent residual MR and MS, aiming to prolong device durability and patient symptom-free survival after ViV and ViR procedures.

ARTICLE INFORMATION

Received May 29, 2020; accepted August 12, 2020.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.120.049088.

Authors

Matheus Simonato, MD; Brian Whisenant, MD; Henrique Barbosa Ribeiro, MD; John G. Webb, MD; Ran Kornowski, MD; Mayra Guerrero, MD; Harindra Wijeysundera, MD; Lars Søndergaard, MD; Ole De Backer, MD; Pedro Villablanca, MD; Charanjit Rihal, MD; Mackram Eleid, MD; Jörg Kempfert, MD; Axel Unbehaun, MD; Magdalena Erlebach, MD; Filip Casselman, MD; Matti Adam, MD; Matteo Montorfano, MD; Marco Ancona, MD; Francesco Saia, MD; Timm Ubben, MD; Felix Meincke, MD; Massimo Napodano, MD; Pablo Codner, MD; Joachim Schofer, MD; Marc Pelletier, MD; Anson Cheung, MD; Mony Shuvy, MD; José Honório Palma, MD; Diego Felipe Gaia, MD; Alison Duncan, MD; David Hildick-Smith, MD; Verena Veulemans, MD; Jan-Malte Sinning, MD; Yaron Arbel, MD; Luca Testa, MD; Arend de Weger, MD; Helene Eltchaninoff, MD; Thibault Hemery, MD; Uri Landes, MD; Didier Tchetche, MD; Nicolas Dumonteil, MD; Josep Rodés-Cabau, MD; Won-Keun Kim, MD; Konstantinos Spargias, MD; Panagiota Kourkoveli, MD; Ori Ben-Yehuda, MD; Rui Campante Teles, MD; Marco Barbanti, MD; Claudia Fiorina, MD; Arun Thukkani, MD; G. Burkhard Mackensen, MD; Noah Jones, MD; Patrizia Presbitero,

MD; Anna Sonia Petronio, MD; Abdelhakim Allali, MD; Didier Champagnac, MD; Sabine Bleiziffer, MD; Tanja Rudolph, MD; Alessandro Iadanza, MD; Stefano Salizzoni, MD; Marco Agrifoglio, MD; Luis Nombela-Franco, MD; Nikolaos Bonaros, MD; Malek Kass, MD; Giuseppe Bruschi, MD; Nicolas Amabile, MD; Adnan Chhatriwalla, MD; Antonio Messina, MD; Sameer A. Hirji, MD, MPH; Martin Andreas, MD; Robert Welsh, MD; Wolfgang Schoels, MD; Farrel Hellig, MD; Stephan Windecker, MD; Stefan Stortecky, MD; Francesco Maisano, MD; Gregg W. Stone, MD; Danny Dvir, MD

Correspondence

Danny Dvir, MD, Jesselson Integrated Heart Center, Shaare Zedek Medical Centre, Hebrew University, 12 Shmuel Bait St, PO Box 3235, Jerusalem, 9103102, Israel. Email danny.dvir@gmail.com

Affiliations

The Cardiovascular Research Foundation, New York (M.Simonato, G.W.S., O.B-Y.). Escola Paulista de Medicina – Universidade Federal de São Paulo, São Paulo, Brazil (M.Simonato, J.H.P., D.F.G.). Intermountain Healthcare, Murray, UT (B.W.). Instituto do Coração da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil (H.B.R., J.H.P.). St. Paul's Hospital, Vancouver, Canada (J.G.W., A.Cheung, U.L.). Rabin Medical Center, Petah Tikva, Israel (R.K., P.C.). Mayo Clinic, Rochester, MN (M.G., C.R., M.Eleid). Sunnybrook Hospital, Toronto, Canada (H.W). Rigshospitalet, Copenhagen, Denmark (L.S., O.DB.). Henry Ford Hospital, Detroit, MI (P.V.). Deutsches Herzzentrum Berlin, Berlin, Germany (J.K., A.U.). Deutsches Herzzentrum München, Munich, Germany (M.Erlebach). Onze-Lieve-Vrouwziekenhuis, Aalst, Belgium (F.C.). Uniklinik Köln, Köln, Germany (M.Adam). I.R.C.C.S. Ospedale San Raffaele, Milan, Italy (M.M., M.Ancona). Policlinico Sant'Orsola-Malpighi, Bologna, Italy (F.S.). Asklepios Klinik St. Georg, Hamburg, Germany (T.U., F.Meincke). Università degli Studi di Padova, Padova, Italy (M.N.). Medizinisches Versorgungszentrum, Hamburg, Germany (J.S.). University Hospitals Harrington Heart and Vascular Institute, Cleveland, OH (M.P.). Hadassah Medical Center, Jerusalem, Israel (M.Shuvy). The Royal Brompton Hospital, London, United Kingdom (A.D.). Brighton and Sussex University Hospitals, Brighton, United Kingdom (D.H-S.). Universitätsklinikum Düsseldorf, Düsseldorf, Germany (V.V.). Universitätsklinikum Bonn, Bonn, Germany (J-M.S.). Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel (Y.A.). I.R.C.C.S. Policlinico San Donato, Milan, Italy (L.T.). Leids Universitair Medisch Centrum, Leiden, the Netherlands (A.d.W.). Rouen University Hospital, Rouen, France (H.E., T.H.). Clinique Pasteur, Toulouse, France (D.T., N.D.). Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec City, Canada (J.R-C.). Kerckhoff-Klinik, Bad Nauheim, Germany (W-K.K.). Hygeia Hospital, Athens, Greece (K.S., P.K.). University of California San Diego (O.B-Y.). Hospital de Santa Cruz, Lisboa, Portugal (R.C.T.). Università degli Studi di Catania, Catania, Italy (M.B.). Spedali Civili Brescia, Brescia, Italy (C.F.). Central Maine Healthcare, Lewiston (A.T.). University of Washington, Seattle (G.B.M.). Mount Carmel Health System, Columbus, OH (N.J.). Humanitas, Milan, Italy (P.P.). Università di Pisa, Pisa, Italy (A.S.P.). Segeberger Kliniken, Bad Segeberg, Germany (A.A.). Cardiologie Tonkin, Villeurbanne, France (D.C.). Herz- und Diabeteszentrum Nordrhein-Westfalen, Bad Oeynhausen, Germany (S.B.). Azienda Ospedaliera Universitaria Senese, Siena, Italy (A.I.). Città della Salute e della Scienza - "Molinette" Hospital, Torino, Italy (S.Salizzoni). Centro Cardiologico Monzino, Milan, Italy (M.Agrifoglio). Hospital Clínico San Carlos, Madrid, Spain (L.N-F.). Medizinische Universität Innsbruck, Innsbruck, Austria (N.B.). University of Manitoba, Winnipeg, Canada (M.K.). Ospedale Niguarda Ca' Granda, Milan, Italy (G.B.). Institut Mutualiste Montsouris, Paris, France (N.A.). Saint Luke's Mid America Heart Institute, Kansas City, MO (A.Chhatriwalla). Fondazione Poliambulanza Istituto Ospedaliero, Brescia, Italy (A.M.). Brigham and Women's Hospital, Boston, MA (S.A.H.). Medizinische Universität Wien, Vienna, Austria (M.Andreas). University of Alberta, Edmonton, Canada (R.W.W). Evangelisches Klinikum Niederrhein, Duisburg, Germany (W.S.). Sunninghill Hospital, Johannesburg, South Africa (F.H.). Inselspital, Bern, Switzerland (S.W., S.Stortecky). Universitätsspital Zürich, Zurich, Switzerland (F.Maisano). The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York (G.W.S.).

Sources of Funding

This work was funded by the Institute of Valvular Research, a nonprofit organization.

Disclosures

Dr Whisenant reports consulting for Edwards Lifesciences. Dr Erlebach reports speaking honoraries from Medtronic Inc. Dr Adam reports personal fees from Edwards Lifesciences and Boston Scientific and grants and personal fees from Medtronic Inc. Dr Saia reports personal fees from Abbott Laboratories, Boston Scientific, Edwards Lifesciences and Medtronic Inc. Dr Hildick-Smith reports consulting and advisory board participation for Boston Scientific, Medtronic Inc. and Edwards Lifesciences. Dr Veulemans reports consulting fees, travel expenses, or study honoraria from Medtronic Inc. and/or Edwards Lifesciences and educational training for Medtronic Inc. Dr Spargias reports proctoring and consulting for Edwards Lifesciences. Dr Rudolph reports speaker's honoraria from Edwards Lifesciences. Dr Bonaros reports educational grants from Edwards Lifesciences and LivaNova, speaker's fees from Edwards Lifesciences, LivaNova and Medtronic Inc., and travel grants from Edwards Lifesciences and Medtronic Inc. Dr Chhatriwalla reports proctoring for Edwards Lifesciences and Medtronic Inc, speaker's bureau for Abbott Laboratories, Edwards Lifesciences and Medtronic Inc., and research support from Boston Scientific and Silk Road Medical. Dr Kempfert reports speaker's fees and proctoring for Edwards Lifesciences, Medtronic Inc. and Abbott Laboratories. Dr Kim reports proctor and speaker's fees from Medtronic Inc., Boston Scientific, Abbott Laboratories and Edwards Lifesciences. Dr Jones reports proctoring and consulting for Medtronic Inc. and Edwards Lifesciences, and consulting for Boston Scientific. Dr Petronio reports consulting and research funds from Boston Scientific and Abbott Laboratories and consulting for Medtronic Inc. Dr Dvir is a consultant to Edwards Lifesciences. The other authors report no conflicts.

Supplemental Materials

Data Supplement Figures I–VIII
Data Supplement Tables I–VI

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet.* 2006;368:1005–1011. doi: 10.1016/S0140-6736(06)69208-8
2. Gammie JS, Sheng S, Griffith BP, Peterson ED, Rankin JS, O'Brien SM, Brown JM. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *Ann Thorac Surg.* 2009;87:1431–7; discussion 1437. doi: 10.1016/j.athoracsur.2009.01.064
3. Mohty D, Orszulak TA, Schaff HV, Avierinos JF, Tajik JA, Enriquez-Sarano M. Very long-term survival and durability of mitral valve repair for mitral valve prolapse. *Circulation.* 2001;104(12 Suppl 1):I1–I7. doi: 10.1161/hc37t1.094903
4. Beute TJ, Goehler M, Parker J, Boeve T, Heiser J, Murphy E, Timek T, Willekes CL. Long-term outcomes of mosaic versus perimount mitral replacements: 17-year follow-up of 940 implants. *Ann Thorac Surg.* 2020;110:508–515. doi: 10.1016/j.athoracsur.2019.10.075
5. David TE, Armstrong S, McCrindle BW, Manlhiot C. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. *Circulation.* 2013;127:1485–1492. doi: 10.1161/CIRCULATIONAHA.112.000699
6. Lazam S, Vanoverschelde JL, Tribouilloy C, Grigioni F, Suri RM, Avierinos JF, de Meester C, Barbieri A, Rusinaru D, Russo A, et al; MIDA (Mitral Regurgitation International Database) Investigators. Twenty-year outcome after mitral repair versus replacement for severe degenerative mitral regurgitation: analysis of a large, prospective, multicenter, international registry. *Circulation.* 2017;135:410–422. doi: 10.1161/CIRCULATIONAHA.116.023340
7. Zhuge RQ, Hou XP, Qi XL, Wu YJ, Zhang MZ. Clinical features and treatment options for mitral regurgitation in elderly inpatients. *J Geriatr Cardiol.* 2018;15:428–433. doi: 10.11909/j.issn.1671-5411.2018.06.005
8. Kwedar K, McNeely C, Zajarias A, Markwell S, Vassileva CM. Outcomes of early mitral valve reoperation in the Medicare population. *Ann Thorac Surg.* 2017;104:1516–1521. doi: 10.1016/j.athoracsur.2017.05.001
9. Kilic A, Acker MA, Gleason TG, Sultan I, Vemulapalli S, Thibault D, Ailawadi G, Badhwar V, Thourani V, Kilic A. Clinical outcomes of mitral valve reoperations in the United States: an analysis of The Society of Thoracic Surgeons National Database. *Ann Thorac Surg.* 2019;107:754–759. doi: 10.1016/j.athoracsur.2018.08.083
10. Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Dhoble A, Schofer N, Eschenbach L, Bansal E, Murdoch DJ, Ancona M, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. *Eur Heart J.* 2019;40:441–451. doi: 10.1093/eurheartj/ehy590
11. Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Schofer N, Eschenbach L, Fujita B, Sharma R, Ancona M, Yzeiraj E, et al. Transcatheter mitral valve

replacement for degenerated bioprosthetic valves and failed annuloplasty rings. *J Am Coll Cardiol.* 2017;70:1121–1131. doi: 10.1016/j.jacc.2017.07.714

12. Guerrero M, Vemulapalli S, Xiang Q, Wang DD, Eleid M, Cabalka AK, Sandhu G, Salinger M, Russell H, Greenbaum A, et al. Thirty-day outcomes of transcatheter mitral valve replacement for degenerated mitral bioprostheses (valve-in-valve), failed surgical rings (valve-in-ring), and native valve with severe mitral annular calcification (valve-in-mitral annular calcification) in the United States: data from the Society of Thoracic Surgeons/American College of Cardiology/Transcatheter Valve Therapy Registry. *Circ Cardiovasc Interv.* 2020;13:e008425. doi: 10.1161/CIRCINTERVENTIONS.119.008425
13. Eleid MF, Cabalka AK, Williams MR, Whisenant BK, Alli OO, Fam N, Pollak PM, Barrow F, Malouf JF, Nishimura RA, et al. Percutaneous transvenous transseptal transcatheter valve implantation in failed bioprosthetic mitral valves, ring annuloplasty, and severe mitral annular calcification. *J Am Coll Cardiol. Cardiovasc Interv.* 2016;9:1161–1174. doi: 10.1016/j.jcin.2016.02.041
14. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, Barbanti M, Latib A, Schaefer U, Rodés-Cabau J, et al; Valve-in-Valve International Data Registry Investigators. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA.* 2014;312:162–170. doi: 10.1001/jama.2014.7246
15. Zoghbi WA, Chambers JB, Dumesnil JG, Foster E, Gottdiener JS, Grayburn PA, Khandheria BK, Levine RA, Marx GR, Miller FA Jr, et al; American Society of Echocardiography's Guidelines and Standards Committee; Task Force on Prosthetic Valves; American College of Cardiology Cardiovascular Imaging Committee; Cardiac Imaging Committee of the American Heart Association; European Association of Echocardiography; European Society of Cardiology; Japanese Society of Echocardiography; Canadian Society of Echocardiography; American College of Cardiology Foundation; American Heart Association; European Association of Echocardiography; European Society of Cardiology; Japanese Society of Echocardiography; Canadian Society of Echocardiography. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. *J Am Soc Echocardiogr.* 2009;22:975–1014; quiz 1082. doi: 10.1016/j.echo.2009.07.013
16. Stone GW, Adams DH, Abraham WT, Kappetein AP, Généreux P, Vranckx P, Mehran R, Kuck KH, Leon MB, Piazza N, et al; Mitral Valve Academic Research Consortium (MVARC). Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. *Eur Heart J.* 2015;36:1878–1891. doi: 10.1093/eurheartj/ehv333
17. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med.* 1987;317:1098. doi: 10.1056/NEJM198710223171717
18. Lancellotti P, Pibarot P, Chambers J, Edvardsen T, Delgado V, Dulgheru R, Pepi M, Cosyns B, Dweck MR, Garbi M, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Department of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2016;17:589–590. doi: 10.1093/ehjci/jew025
19. Bapat VN, Attia R, Thomas M. Effect of valve design on the stent internal diameter of a bioprosthetic valve: a concept of true internal diameter and its implications for the valve-in-valve procedure. *J Am Coll Cardiol. Cardiovasc Interv.* 2014;7:115–127. doi: 10.1016/j.jcin.2013.10.012
20. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;94:496–509.
21. Ye J, Cheung A, Yamashita M, Wood D, Peng D, Gao M, Thompson CR, Munt B, Moss RR, Blanke P, et al. Transcatheter aortic and mitral valve-in-valve implantation for failed surgical bioprosthetic valves: an 8-year single-center experience. *J Am Coll Cardiol. Cardiovasc Interv.* 2015;8:1735–1744. doi: 10.1016/j.jcin.2015.08.012
22. Seiffert M, Conradi L, Baldus S, Schirmer J, Knap M, Blankenberg S, Reichenspurner H, Treede H. Transcatheter mitral valve-in-valve implantation in patients with degenerated bioprostheses. *J Am Coll Cardiol. Cardiovasc Interv.* 2012;5:341–349. doi: 10.1016/j.jcin.2011.12.008
23. Bouleti C, Fassa AA, Himbert D, Brochet E, Ducrocq G, Nejjari M, Ghodbane W, Depoix JP, Nataf P, Vahanian A. Transfemoral implantation of transcatheter heart valves after deterioration of mitral bioprosthesis or previous ring annuloplasty. *J Am Coll Cardiol. Cardiovasc Interv.* 2015;8:83–91. doi: 10.1016/j.jcin.2014.07.026
24. Urena M, Himbert D, Brochet E, Carrasco JL, Iung B, Nataf P, Vahanian A. Transseptal transcatheter mitral valve replacement using balloon-expandable transcatheter heart valves: a step-by-step approach. *J Am Coll Cardiol. Cardiovasc Interv.* 2017;10:1905–1919. doi: 10.1016/j.jcin.2017.06.069
25. Urena M, Brochet E, Lecomte M, Kerneis C, Carrasco JL, Ghodbane W, Abtan J, Alkhoder S, Raffoul R, Iung B, et al. Clinical and haemodynamic outcomes of balloon-expandable transcatheter mitral valve implantation: a 7-year experience. *Eur Heart J.* 2018;39:2679–2689. doi: 10.1093/eurheartj/ehy271
26. Mehaffey HJ, Hawkins RB, Schubert S, Fonner C, Yarboro LT, Quader M, Speir A, Rich J, Kron IL, Ailawadi G. Contemporary outcomes in reoperative mitral valve surgery. *Heart.* 2018;104:652–656. doi: 10.1136/heartjnl-2017-312047
27. Wan S, Lee AP, Jin CN, Wong RH, Chan HH, Ng CS, Wan IY, Underwood MJ. The choice of mitral annuloplastic ring-beyond "surgeon's preference." *Ann Cardiothorac Surg.* 2015;4:261–265. doi: 10.3978/j.issn.2225-319X.2015.01.05
28. Bapat VV, Khaliel F, Ihleberg L. Delayed migration of sapien valve following a transcatheter mitral valve-in-valve implantation. *Catheter Cardiovasc Interv.* 2014;83:E150–E154. doi: 10.1002/ccd.25076
29. Blanke P, Naoum C, Dvir D, Bapat V, Ong K, Muller D, Cheung A, Ye J, Min JK, Piazza N, et al. Predicting LVOT obstruction in transcatheter mitral valve implantation: concept of the neo-LVOT. *J Am Coll Cardiol. Cardiovasc Imaging.* 2017;10:482–485. doi: 10.1016/j.jcmg.2016.01.005
30. Khan JM, Babaliaros VC, Greenbaum AB, Foerst JR, Yazdani S, McCabe JM, Paone G, Eng MH, Leshnower BG, Gleason PT, et al. Anterior leaflet laceration to prevent ventricular outflow tract obstruction during transcatheter mitral valve replacement. *J Am Coll Cardiol.* 2019;73:2521–2534. doi: 10.1016/j.jacc.2019.02.076
31. Neuss M, Schau T, Isotani A, Pilz M, Schöpp M, Butter C. Elevated mitral valve pressure gradient after MitraClip implantation deteriorates long-term outcome in patients with severe mitral regurgitation and severe heart failure. *J Am Coll Cardiol. Cardiovasc Interv.* 2017;10:931–939. doi: 10.1016/j.jcin.2016.12.280
32. Simonato M, Webb J, Kornowski R, Vahanian A, Frerker C, Nissen H, Bleiziffer S, Duncan A, Rodés-Cabau J, Attizzani GF, et al. Transcatheter replacement of failed bioprosthetic valves: large multicenter assessment of the effect of implantation depth on hemodynamics after aortic valve-in-valve. *Circ Cardiovasc Interv.* 2016;9:e003651.
33. Simonato M, Webb J, Bleiziffer S, Abdel-Wahab M, Wood D, Seiffert M, Schäfer U, Wöhrle J, Jochheim D, Woitek F, et al. Current generation balloon-expandable transcatheter valve positioning strategies during aortic valve-in-valve procedures and clinical outcomes. *J Am Coll Cardiol. Cardiovasc Interv.* 2019;12:1606–1617. doi: 10.1016/j.jcin.2019.05.057