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Transcatheter Mitral Valve Replacement After Surgical Repair or Replacement: Comprehensive Mid-Term Evaluation of Valve-in-Valve and Valve-in-Ring Implantation from the VIVID Registry

Running Title: *Simonato et al.; Mitral Valve-in-Valve and Valve-in-Ring Procedures*

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Abstract

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 mid-term 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 mmHg and significant residual mitral regurgitation (MR) as ≥ moderate.

Results: A total of 1,079 patients (857 ViV, 222 ViR; mean age 73.5 years ± 12.5; 40.8% male) from 90 centers were included. Median STS-PROM score 8.6%; median clinical follow-up 492 days [IQR 76 – 996 days]; median echocardiographic follow-up for patients that survived 1 year 772.5 days [IQR 510 – 1211.75 days]. Four-year Kaplan-Meier survival rate was 62.5% in ViV vs. 49.5% for ViR ($p<0.001$). Mean gradient across the mitral valve post-procedure was 5.7 ± 2.8 mmHg (≥5mmHg, 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% vs. 3.1%; $p<0.001$) and was associated with lower survival at 4 years (35.1% vs. 61.6%; $p=0.02$). The rates of MVARC-defined device success were low for both procedures (39.4% total; 32.0% ViR vs. 41.3% ViV; $p=0.01$), mostly related to having post-procedural mean gradient ≥5mmHg. 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 (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 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 post-procedural hemodynamics in mitral ViV and ViR should be further explored.

Key Words: transcatheter mitral valve replacement; valve-in-valve; valve-in-ring; elevated gradients; hemodynamics

Non-standard Abbreviations and Acronyms

MV: mitral valve
ViV: valve-in-valve
ViR: valve-in-ring
MS: mitral stenosis
MR: mitral regurgitation
VIVID: Valve-in-Valve International Data
MVR: mitral valve replacement
STS: Society of Thoracic Surgeons
CKD: chronic kidney disease
MVARC: Mitral Valve Academic Research Consortium
PPM: prosthesis-patient mismatch
EOA: effective orifice area
LVOT: left ventricular outflow tract

ID: internal diameter
IQR: interquartile range
LVEF: left ventricular ejection fraction
DM: diabetes mellitus
NYHA: New York Heart Association
PASP: pulmonary artery systolic pressure
OR: odds ratio
HR: hazard ratio
SHR: subhazard ratio
CI: confidence interval

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 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 four years with approximately 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 post-implantation hemodynamics in order to optimize device durability.
- Alternative therapies to mitral valve-in-ring in patients with mitral valve failure after surgical repair should be considered.

Introduction

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 due to tissue degeneration and disease progression and some patients may require reoperation[3–6]. Almost half of patients may be denied an intervention due to high surgical risk[7]. Reoperation by itself is associated with increased surgical risk[8,9], particularly those with heart failure and non-elective 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 post-procedural 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 mid-term clinical, hemodynamic and echocardiographic outcomes after transcatheter mitral ViV and ViR procedures and to evaluate the clinical significance of post-procedure residual MS and MR.

Methods

Data collection

The Valve-in-Valve International Data (VIVID) 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 post-procedure mean gradient ≥ 10 mmHg), 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 (CKD) was defined as estimated glomerular filtration rate ≤ 60 mL/min/1.73 m^2 (i.e. 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 (PPM) was defined as indexed effective orifice area (EOA) ≤ 0.9 cm^2/m^2 for patients with body mass index (BMI) < 30 kg/m^2 and indexed EOA ≤ 0.75 cm^2/m^2 for those with BMI ≥ 30 kg/m^2 [(18)]. Left ventricular outflow tract (LVOT) obstruction was defined as outflow mean gradient ≥ 10 mmHg[16] or cardiogenic shock that was clinically related to that complication as reported by the center. The true internal diameter (ID) 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 ± standard deviation for continuous variables with normal distribution, median [interquartile range, IQR; 25th – 75th percentiles] for non-normally distributed continuous variables and number (percentage) for categorical data. Student's *t* test was used to compare means of normally distributed continuous variables between two groups. The Mann-Whitney U-test was used to compare distributions of non-normally distributed continuous variables between two groups and the Kruskal-Wallis test was used to compare non-normally distributed continuous variables between three 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 (four-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 (LVEF), transcatheter heart valve diameter, male sex, mitral ViR (vs. ViV) and MR vs. 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 mellitus (DM), peripheral vascular disease, chronic kidney disease, cerebrovascular disease, chronic lung disease, baseline New York Heart Association (NYHA) class IV symptoms (vs. others), immediate post-procedural residual mean gradient ≥ 10 mmHg, residual MR ≥ moderate, baseline pulmonary artery systolic pressure (PASP), transseptal access, LVOT obstruction and if the case was performed before or after the 10^{th} mitral ViR/ViV of a center (i.e. 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% confidence interval (CI). The first author and the corresponding author had full access to the data and vouch for its integrity. A two-tailed p-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS 23 (IBM Corporation, Armonk, New York, United States) and Stata 14.1 (StataCorp, College Station, Texas, United States).

Results

Baseline characteristics

A total of 1,079 patients were included: 857 mitral ViV and 222 mitral ViR (Supplemental Figure I). 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% vs. 89.5%, respectively; p = 0.02). Incomplete rings were present in 9.4% of ViR patients. Supplemental Table I includes detailed information on failed surgical valve and ring models and their characteristics.

Out of 1,079 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 Supplemental Table II and Supplemental Table III. 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 (2006-2013 1.6%; 2014-2016 2.8%; 2017-2020 3.2%) 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 2006-2013 cohort had a trend towards lower survival (p = 0.05) (Supplemental Figure II).

Procedural characteristics and outcomes

Patients were most frequently treated with SAPIEN 3 (Edwards Lifesciences, Irvine, CA, United States) (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% vs. 2.4% ViV; p = 0.001), need for second transcatheter valve implantation (10.1% vs. 2.8% ViV; p < 0.001), and LVOT obstruction (5.9% vs. 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 (93.8% vs. 82.0%; p < 0.001). The rates of MVARC-defined device success were low for both procedures (39.4% total; 32.0% ViR vs. 41.3% ViV; p = 0.01). Immediate post-procedural mean gradient ≥ 5 mmHg 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 Supplemental Table IV. With a modified definition of device failure requiring an immediate post-procedural mean gradient ≥ 10 mmHg (instead of ≥ 5 mmHg), ViR still had lower rates of device success (63.1% vs. 84.0% ViV; p < 0.001). Finally, when excluding the hemodynamic component of the success definition (i.e. 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 anti-platelets or anti-coagulants (96.2%) after the procedure. The rate of anticoagulation was 71.9%, and was not significantly different between mitral ViV and ViR (70.8% vs. 76.6%; p = 0.15).

Median absolute follow-up was 492 days [IQR 76 – 996 days] and was similar in the ViV and ViR groups (519 days [IQR 95.5 – 1007 days] vs. 426 days [IQR 40.8 – 895 days], 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 four years (62.5% ViV vs. 49.7% ViR, p = 0.002). Patients at high risk for repeat open-heart surgery (STS score ≥ 8%) also had significantly worse survival at four years (Figure 2B). There was no significant survival difference between patients with transseptal access versus those with other accesses (Supplemental Figure III). There were no significant 4-year survival differences between mitral ViR patients with semi-rigid rings and those with rigid/flexible rings (51.1% vs. 47.3%, respectively; $p = 0.79$), and also no differences between those with complete and incomplete rings (49.5% vs. 56.1%, respectively; $p = 0.93$). Rates of technical success (81.9% semi-rigid vs. 82.7% rigid/flexible; $p = 0.89$) and device success (29.4% semi-rigid vs. 40.4% rigid/flexible; $p = 0.14$) were similar between ring types. The overall rate of repeat MVR at four years was 2.7% (18 events: 13 open heart surgery, 5 transcatheter), with a higher rate in ViR (5.9% vs. 1.9% ViV; $p < 0.001$). There was no difference in the 4-year rate of repeat MVR for patients with immediate post-procedural mean gradient ≥ 5 mmHg (3.8% vs. 1.6% others; $p = 0.64$), but the unadjusted 4-year rate of repeat MVR was higher in patients with immediate post-procedural mean gradient ≥ 10 mmHg (13.4% vs. 2% others; $p < 0.001$).

Echocardiographic follow-up

An immediate post-procedural mean gradient ≥ 5 mmHg 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 post-procedural mean gradient ≥ 10 mmHg) was present in 12.0% of ViR and 8.2% of ViV patients ($p = 0.09$). Post-implant significant residual MR was also more common after ViR than ViV (16.6% vs. 3.1%; $p < 0.001$). Significant residual MR was associated with lower survival at four years in unadjusted analysis (35.1% vs. 61.6% no residual MR; $p = 0.02$) (Figure 1C). No such association was found for significant residual MS (66.1% vs. 60.5% immediate post-procedural mean gradient < 10 mmHg; $p = 0.89$) (Figure 1D). Severe post-procedural PPM was present in 24.5% of cases, with no association to four-year survival (72.7% vs. 60.5% no/moderate PPM; p

= 0.13), four-year repeat MVR (1.3% vs. 2.4% no/moderate PPM; $p = 0.83$) and post-procedural NYHA III/IV functional class (19.4% vs. 17.9%; $p = 0.76$).

Echocardiographic follow-up of more than one year (median time 772.5 days [IQR 510 – 1211.75 days]) was available for 446 patients (70.0% of those alive at one 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 one year of echocardiographic follow-up were included in the analysis (Supplemental Figure IV). The rates of significant residual MS were higher in patients with baseline stenosis and smaller true ID (Supplemental Figure V), but at the same time patients with small valves (true ID ≤ 23 mm) did not have a significant increase in their gradients in follow-up (Supplemental Figure VI). There was a trend for a greater rate of NYHA III/IV symptoms when the immediate post-procedural residual mean gradient was ≥ 10 mmHg (26.1% vs. 17.8% others; $p = 0.09$), but no difference was found when the immediate post-procedural residual mean gradient was ≥ 5 mmHg (17.8% vs. 19.9% others; $p = 0.48$). As shown in Figure 4, there were significant post-procedural 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 ≥ moderate MR 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 (Supplemental Figure VII). 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; Supplemental Figure VIII). Independent predictors for significant residual MS were small device true ID, 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). Supplemental Table V 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) four-year survival was low after both procedures, and was especially notable after ViR (49.7% survival within four 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% vs. 61.6% other patients); 4) both ViV and ViR were commonly associated with residual stenosis (immediate post-procedural mean gradient ≥ 5mmHg in 61% of cases and ≥ 10mmHg 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% vs. 60.5% other patients); 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; 6) there were significant shifts toward treating lower risk patients and increasingly utilizing 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 over 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 to 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 predictors of all-cause mortality, our study is in agreement with prior 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], in our evaluation we show 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 four years and that approximately half of these patients have died within that time frame. While the 37.5% four-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 1,627 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 to the surgical study[8]. To date no head-to-head randomized comparison of transcatheter ViV/ViR vs. 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 to 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 for transseptal access in transcatheter mitral ViV and ViR procedures, both at 30 days[12] and at one 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 non-circular rings, including more residual MR and device under-expansion[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 systole that may lead to reduced anchoring[28]. The need for a second heart valve adds to procedure complexity, 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 due 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 results obtained by the procedure. Nonetheless, in multivariable analysis, ViR was associated with substantially greater mortality than ViV procedures.

Post-procedural mitral regurgitation and stenosis after ViV and ViR procedures

The consequences of post-procedural MR and MS after ViV and ViR procedures have not been previously explored in depth. Suboptimal post procedure hemodynamics are known to influence clinical outcomes in other mitral interventions, such as MitraClip (Abbott Vascular, Menlo Park, CA, United States)[31]. Residual stenosis with mean gradients ≥ 5 mmHg is very common after ViV and ViR. This finding, revealed in our study, is reflected by relatively low rates of MVARC-defined device success. However, immediate post-procedural mean gradients 5 to 9.9 mmHg were not associated with worse clinical outcomes, such as four-year survival, four-year repeat MVR and NYHA functional class. Although significant residual MS (≥ 10 mmHg) was not associated with increased four-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 mmHg may be a more appropriate cut-off for success in mitral ViV and ViR procedures. Mean gradient between 5 mmHg and 9.9 mmHg 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. Post-implant 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.

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, being treated with conventional surgery or medical management instead. Second, it was a retrospective and non-randomized study without core-lab evaluation. Echocardiographic follow-up for 30% of patients confirmed alive at one 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 2-3% (Supplemental Table VI). 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 (e.g. 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 rates, lower survival and higher rates of post-procedural 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 in order to prolong device durability and patient symptom-free survival after ViV and ViR procedures.

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Supplemental Material

Expanded Methods

Supplemental Figures I-VIII

Supplemental Tables I-VI

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Table 1. Baseline clinical and echocardiographic characteristics of the two groups.

	Total (n = 1,079)	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, years	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%	5.1%	10.0%	
III	59.3%	65.6%	57.7%	
IV	31.3%	29.3%	31.8%	
Time to index surgery, years	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 mellitus	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, mmHg	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, mmHg	22.6 ± 9.9	17.4 ± 11.1	23.8 ± 9.2	< 0.001

Mean gradient, mmHg	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%	

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Table 2. Procedural outcomes of the two groups.

	Total (n = 1,079)	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
Pre-inflation	19.0%	24.0%	17.8%	0.05
Post-inflation	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 mmHg	61.4%	67.5%	59.9%	0.05
Mean gradient ≥ 10 mmHg	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 anti-platelet alone	12.7%	10.8%	13.2%	

Single anti-platelet and anti-coagulation	38.2%	46.8%	36.1%	
Double anti-platelet	11.4%	10.1%	11.8%	
Double anti-platelet and anti-coagulation	2.8%	5.1%	2.2%	
Warfarin/coumadin alone	26.8%	19.6%	28.6%	
Novel oral anti-coagulants alone	4.2%	5.1%	3.9%	
Other	0.1%	0.6%	0.0%	
None	3.8%	1.9%	4.2%	
Immediate post-procedural echocardiographic data				
Left ventricular ejection fraction, %	52.1 ± 12.8	45.2 ± 15.4	53.8 ± 11.4	< 0.001
Mitral valve area, cm2	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, mmHg	12.6 ± 5.6	12.1 ± 5.6	12.7 ± 5.6	0.24
Mean gradient, mmHg	5.7 ± 2.8	6.0 ± 2.8	5.6 ± 2.7	0.08
Mitral regurgitation				< 0.001
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, and 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, and proper placement and positioning of the device, and freedom from unplanned surgical or interventional procedures related to the device or access procedure, and 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 (i.e., post-procedure effective regurgitant orifice area is ≥ 1.5 cm2 with a trans-mitral gradient < 5 mm Hg), and with no greater than mild (1+) paravalvular MR (and without associated hemolysis). ‡Considering ≥ 10 mmHg as a cut-off. §Considering only the components of device success not related to hemodynamics, i.e. procedural death, malposition/embolization/migration, second transcatheter heart valve, left ventricular outflow tract obstruction and stroke.

Figure Legends

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

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

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.

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: Mitral regurgitation.

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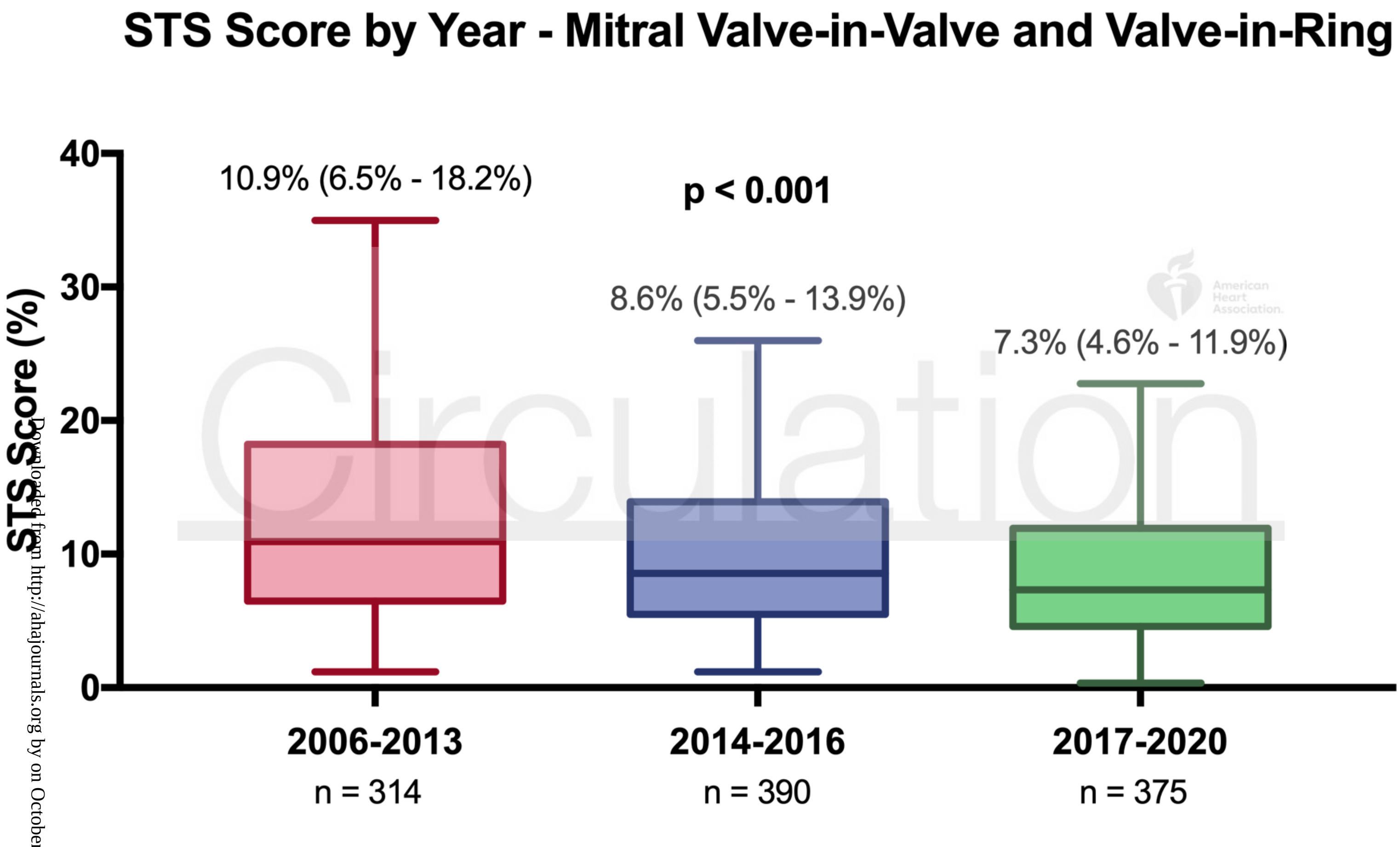
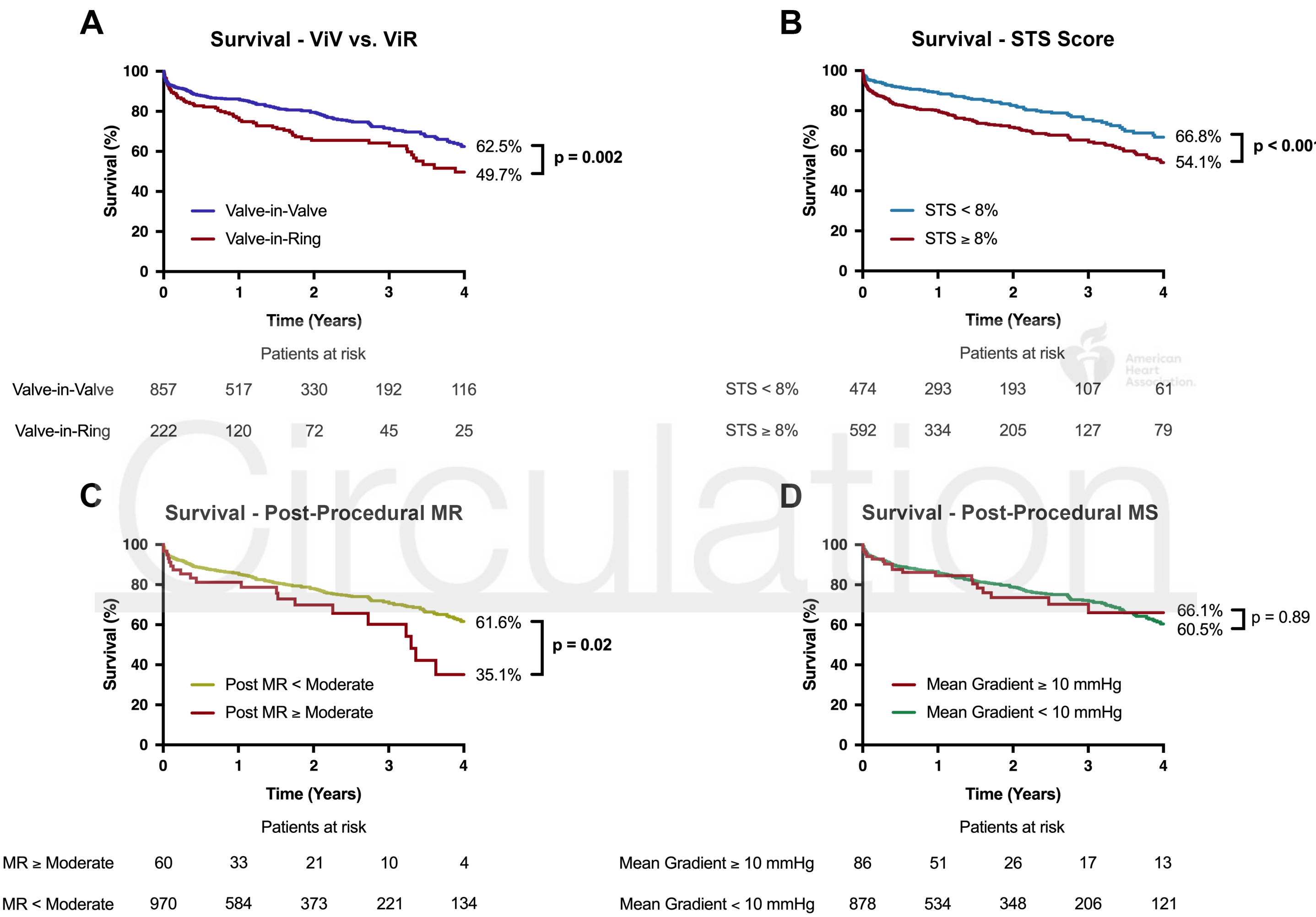
Figure 5. Multivariable models for mortality, repeat mitral valve replacement, residual mean gradient ≥ 10 mmHg and residual mitral regurgitation ≥ moderate. PASP: pulmonary artery systolic pressure; NYHA: New York Heart Association; MR: mitral regurgitation; HR: hazard ratio; SHR: subhazard ratio; OR: odds ratio; CI: confidence interval.


STS Score by Year - Mitral Valve-in-Valve and Valve-in-Ring
STS Score (%)
40
30
20
10
0
10.9% (6.5% - 18.2%)
p < 0.001
8.6% (5.5% - 13.9%)
7.3% (4.6% - 11.9%)
2006-2013
n = 314
2014-2016
n = 390
2017-2020
n = 375



Patients at risk

	0	1	2	3	4
Valve-in-Valve	857	517	330	192	116
Valve-in-Ring	222	120	72	45	25

Patients at risk

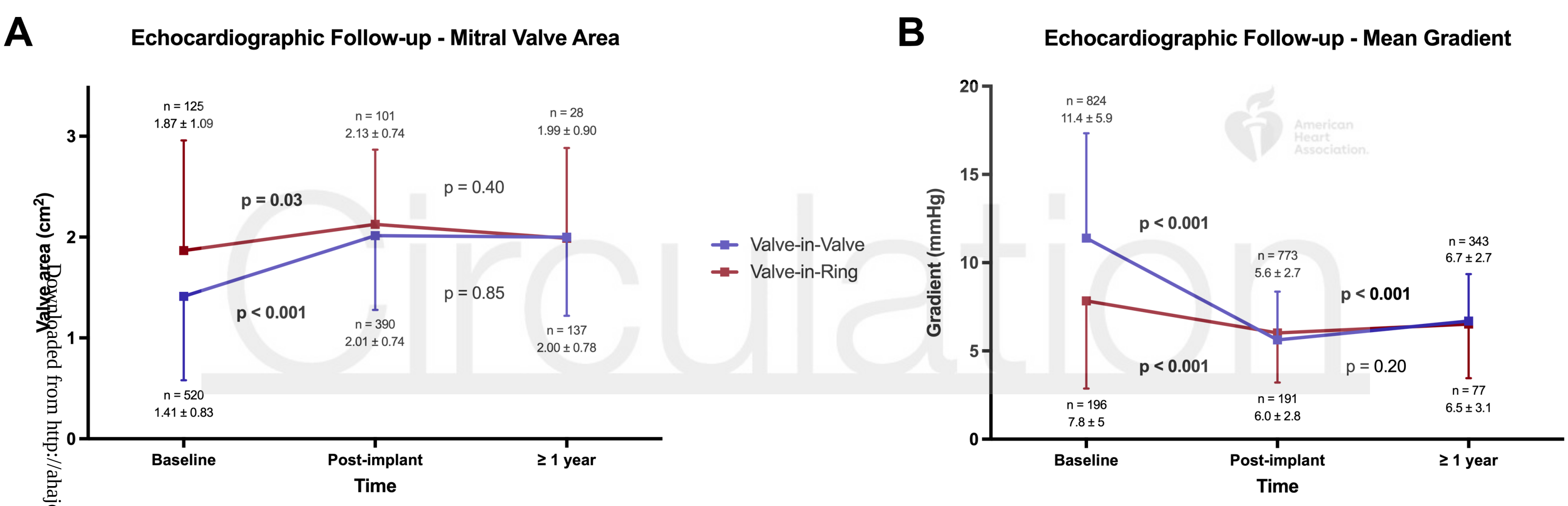
	0	1	2	3	4
STS < 8%	474	293	193	107	61
STS ≥ 8%	592	334	205	127	79

Patients at risk

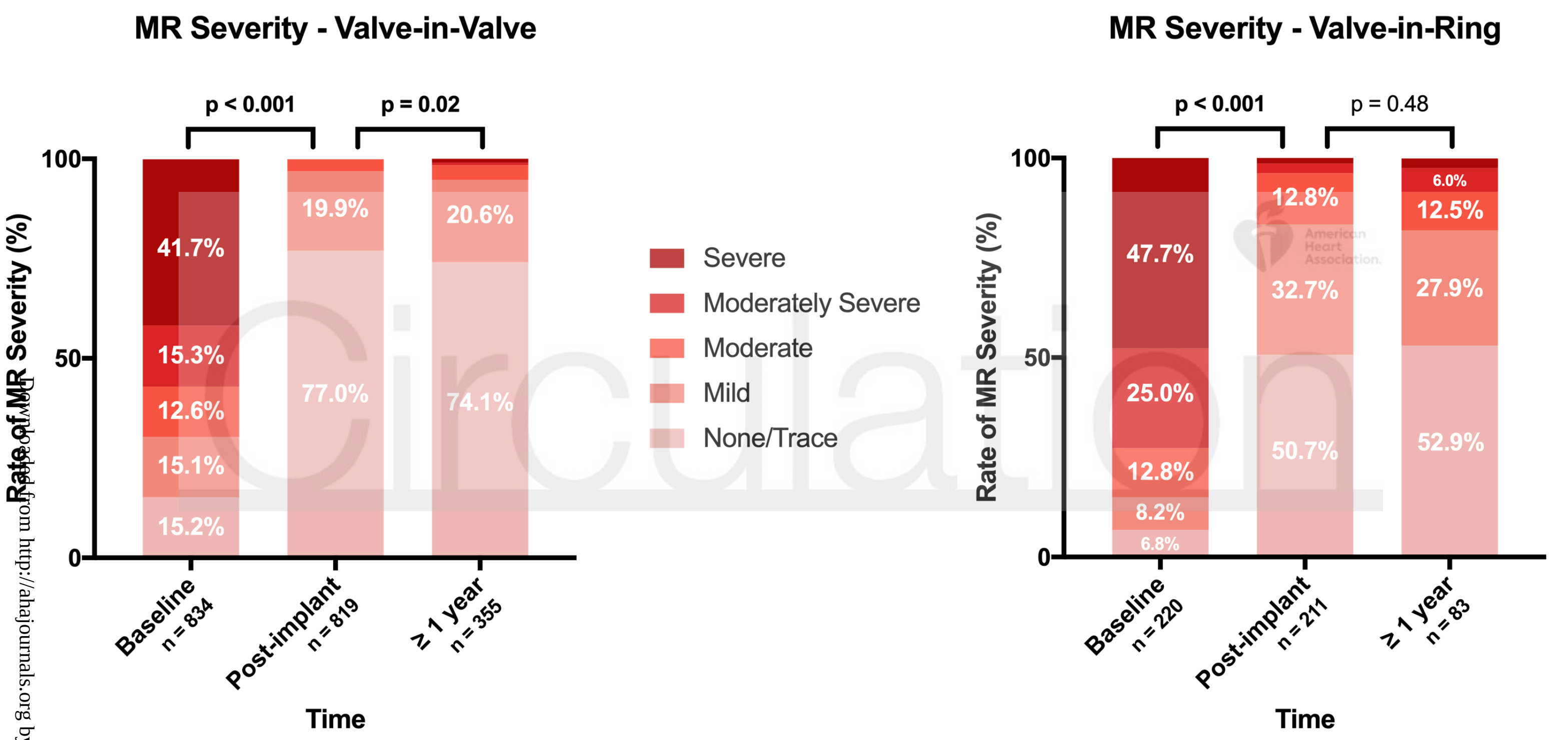
	0	1	2	3	4
Post MR ≥ Moderate	60	33	21	10	4
Post MR < Moderate	970	584	373	221	134

Patients at risk

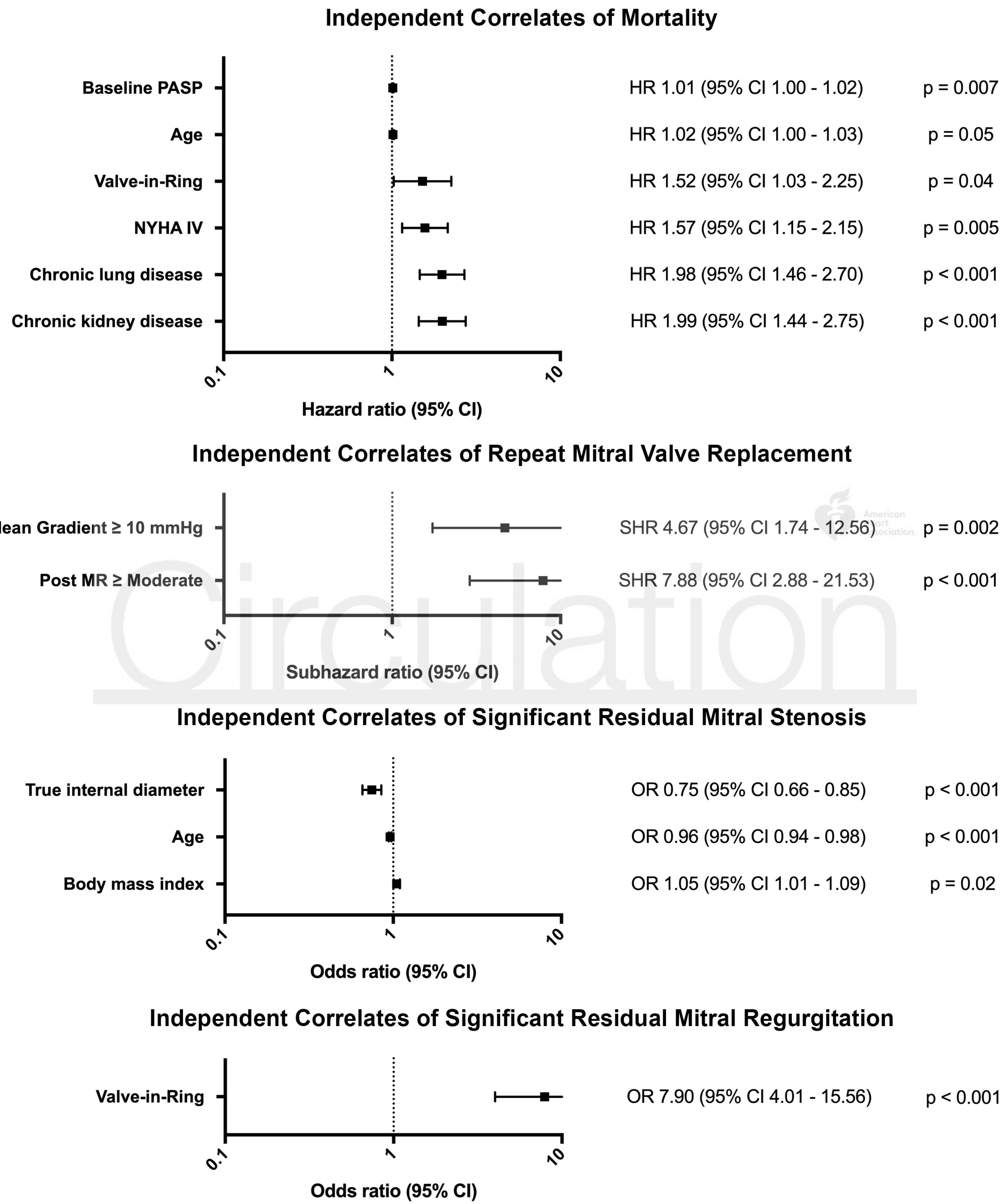
	0	1	2	3	4
Mean Gradient ≥ 10 mmHg	86	51	26	17	13
Mean Gradient < 10 mmHg	878	534	348	206	121



A
Echocardiographic Follow-up - Mitral Valve Area
Valve area (cm²)
Time
Baseline
Post-implant
≥ 1 year
n = 125
1.87 ± 1.09
n = 101
2.13 ± 0.74
n = 28
1.99 ± 0.90
p = 0.03
p = 0.40
p < 0.001
p = 0.85
n = 520
1.41 ± 0.83
n = 390
2.01 ± 0.74
n = 137
2.00 ± 0.78
Valve-in-Valve
Valve-in-Ring
B
Echocardiographic Follow-up - Mean Gradient
Gradient (mmHg)
Time
Baseline
Post-implant
≥ 1 year
n = 824
11.4 ± 5.9
p < 0.001
n = 773
5.6 ± 2.7
n = 343
6.7 ± 2.7
p < 0.001
p < 0.001
p = 0.20
n = 196
7.8 ± 5
n = 191
6.0 ± 2.8
n = 77
6.5 ± 3.1



MR Severity - Valve-in-Valve
p < 0.001
p = 0.02
100
50
0
Rate of MR Severity (%)
41.7%
15.3%
12.6%
15.1%
15.2%
19.9%
77.0%
20.6%
74.1%
Baseline n = 834
Post-implant n = 819
≥ 1 year n = 355
Time
Severe
Moderately Severe
Moderate
Mild
None/Trace
MR Severity - Valve-in-Ring
p < 0.001
p = 0.48
47.7%
25.0%
12.8%
8.2%
6.8%
12.8%
32.7%
50.7%
6.0%
12.5%
27.9%
52.9%
Baseline n = 220
Post-implant n = 211
≥ 1 year n = 83
Time


Independent Correlates of Mortality
Baseline PASP
Age
Valve-in-Ring
NYHA IV
Chronic lung disease
Chronic kidney disease
HR 1.01 (95% CI 1.00 - 1.02)
HR 1.02 (95% CI 1.00 - 1.03)
HR 1.52 (95% CI 1.03 - 2.25)
HR 1.57 (95% CI 1.15 - 2.15)
HR 1.98 (95% CI 1.46 - 2.70)
HR 1.99 (95% CI 1.44 - 2.75)
p = 0.007
p = 0.05
p = 0.04
p = 0.005
p < 0.001
p < 0.001
0.1
1
10
Hazard ratio (95% CI)
Independent Correlates of Repeat Mitral Valve Replacement
Mean Gradient ≥ 10 mmHg
Post MR ≥ Moderate
SHR 4.67 (95% CI 1.74 - 12.56)
SHR 7.88 (95% CI 2.88 - 21.53)
p = 0.002
p < 0.001
0.1
1
10
Subhazard ratio (95% CI)
Independent Correlates of Significant Residual Mitral Stenosis
True internal diameter
Age
Body mass index
OR 0.75 (95% CI 0.66 - 0.85)
OR 0.96 (95% CI 0.94 - 0.98)
OR 1.05 (95% CI 1.01 - 1.09)
p < 0.001
p < 0.001
p = 0.02
0.1
1
10
Odds ratio (95% CI)
Independent Correlates of Significant Residual Mitral Regurgitation
Valve-in-Ring
OR 7.90 (95% CI 4.01 - 15.56)
p < 0.001
0.1
1
10
Odds ratio (95% CI)