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# 2-Year Outcomes of Transcatheter Mitral Valve Replacement in Patients With Annular Calcification, Rings, and Bioprostheses

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## ABSTRACT

**BACKGROUND** The MITRAL (Mitral Implantation of Transcatheter Valves) trial is the first prospective study for valve-in-mitral annular calcification (ViMAC), mitral valve-in-ring (MViR), and mitral valve-in-valve (MViV) using balloon-expandable aortic transcatheter heart valves. Procedural outcomes beyond 1 year are not well described.

**OBJECTIVES** This study evaluated 2-year outcomes in ViMAC, MViR, and MViV in the MITRAL trial.

**METHODS** This multicenter prospective study enrolled patients with severe MAC, prior failed mitral annuloplasty ring repair, or prior failed bioprosthetic MV replacement who were at high surgical risk at 13 U.S. sites.

**RESULTS** Between February 1, 2015, and December 31, 2017, 91 patients were enrolled (31 with ViMAC, 30 with MViR, and 30 with MViV). In the ViMAC group, 2-year all-cause mortality was 39.3%, 66.7% were New York Heart Association (NYHA) functional class I-II, and mean MV gradient was 5.6 ± 2.0 mm Hg. In the MViR group, 2-year all-cause mortality was 50%, 65% were NYHA functional class I-II, and mean MV gradient was 6.5 ± 2.7 mm Hg. In the MViV group, 2-year all-cause mortality was 6.7%, 85% were NYHA functional class I-II, and mean MV gradient was 6.9 ± 2.4 mm Hg. At 2 years, all patients had ≤mild mitral regurgitation and survivors in all 3 arms showed sustained improvement in Kansas City Cardiomyopathy Questionnaire scores compared to baseline.

**CONCLUSIONS** Use of balloon-expandable aortic transcatheter heart valves in selected patients with severe MAC, failed annuloplasty ring, and bioprosthetic MV dysfunction is associated with improvements in symptoms, quality of life, and stable prosthesis function at 2-year follow-up. Between 1 and 2 years, the MViR group experienced higher mortality rates than the MViV and ViMAC groups. (J Am Coll Cardiol 2022;80:2171–2183) © 2022 by the American College of Cardiology Foundation.

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**ABBREVIATIONS AND ACRONYMS**

**KCCQ** = Kansas City Cardiomyopathy Questionnaire

**LVOT** = left ventricular outflow tract

**MAC** = mitral annular calcification

**MV** = mitral valve

**MR** = mitral regurgitation

**MViR** = mitral valve-in-ring

**MViV** = mitral valve-in-valve

**NYHA** = New York Heart Association

**STS** = Society for Thoracic Surgeons

**TMVR** = transcatheter mitral valve replacement

**ViMAC** = valve-in-mitral annular calcification

A large proportion of patients presenting with severe mitral valve (MV) disease are considered high risk for conventional mitral surgery and stand to benefit from less invasive alternatives.[1] Use of balloon-expandable aortic transcatheter valves for treatment of severe MV disease was first described a decade ago in case series, with subsequent larger registries reporting 30-day and 1-year outcomes more recently.[2-5] Outcomes beyond 1 year following transcatheter mitral valve replacement (TMVR) are not well described. The MITRAL (Mitral Implantation of Transcatheter Valves) trial is the first prospective study of balloon-expandable aortic transcatheter valve insertion for treatment of patients with severe mitral annular calcification (MAC), failed annuloplasty ring, and failed bioprosthetic valves. In the 1-year outcomes of the MITRAL trial, excellent 1-year survival (97%) was demonstrated in mitral valve-in-valve (MViV),[6] whereas considerably lower 1-year survival was observed in patients undergoing mitral valve-in-ring (MViR) (77%)[7] and valve-in-mitral annular calcification (ViMAC) (65%).[8] Recently, results of a nonrandomized global prospective study of a dedicated transapical self-expanding transcatheter MV showed sustained reduction in mitral regurgitation (MR) and heart failure hospitalizations, and improvement in symptoms at 2 years of follow-up in patients with native noncalcified MV disease.[9] The aim of this study was to examine the 2-year clinical outcomes following TMVR in patients enrolled in the MITRAL trial.

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## METHODS

This study was conducted following ethical principles according to the Declaration of Helsinki as well as U.S. Food and Drug Administration guidelines (Code of Federal Regulations Title 21, Part 812), and Good Clinical Practices recommended by the International Organization for Standardization (ISO 14155:2011). The study was approved by the Mayo Clinic Institutional Review Board and the respective participating Institutional Review Boards. All patients provided written informed consent.

**STUDY DESIGN AND PATIENTS.** The MITRAL trial early feasibility study is a physician-initiated, prospective multicenter clinical trial (investigational device exemption G140136; NCT02370511) designed to evaluate the safety and feasibility of TMVR using SAPIEN XT and SAPIEN 3 valves (Edwards Lifesciences) with 3 treatment arms: 1) native MV disease with MAC, treated with ViMAC (n = 31); 2) failed MV annuloplasty ring, treated with MViR (n = 30); and 3) failed surgical bioprosthesis, treated with MViV (n = 30). Inclusion criteria included patients with severe mitral stenosis or severe MR and New York Heart Association (NYHA) functional class II or more symptoms who were at high surgical risk after Heart Team evaluation. Complete study methods and inclusion/exclusion criteria have been previously published.[6-8] Echocardiographic and computed tomography studies were analyzed by independent core laboratories, clinical events were adjudicated by an independent clinical events committee, and safety monitored by a Data and Safety Monitoring Board.

**OUTCOMES.** The primary performance endpoint of this analysis was absence of MR grade 2+ or higher and mean MV gradient ≥10 mm Hg at 2 years. Secondary safety endpoint was all-cause mortality at 2 years. Other study endpoints are defined in Supplemental Appendix 1. Quality-of-life endpoints of interest for this analysis were NYHA functional class, Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, and 6-minute walk distance at 2 years. Additional key clinical outcomes of interest included need for MV reintervention, incidence of prosthetic valve thrombosis, and endocarditis.

**STATISTICAL ANALYSIS.** Continuous variables were summarized as median (IQR) and categorical variables presented as frequencies and percentages.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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**TABLE 1 2-Year Clinical Outcomes in ViMAC Arm**

| | 30 Days (n = 30)[a] | 1 Year (n = 29)[b] | 2 Years (n = 28)[c] | Event Rates (per 100 Person-Years) |
|---|---|---|---|---|
| All-cause mortality | 5/30 (16.7) | 10/29 (34.5) | 11/28 (39.3) | 26.6 (13.3-47.7) |
| Cardiovascular | 4/30 (13.3) | 6/29 (20.7) | 6/28 (21.4) | 14.5 (5.3-31.6) |
| Noncardiovascular | 1/30 (3.3) | 4/29 (13.8) | 5/28 (17.9) | 12.1 (3.9-28.3) |
| Device success | 17/30 (56.7) | NA | NA | NA |
| Procedural success | 16/30 (53.3) | NA | NA | NA |
| Primary performance endpoint in survivors at 1 year | 22/25 (88.0) | 18/18 (100.0) | NA | NA |
| Stroke | 2/30 (6.7) | 2/29 (6.9) | 3/28 (10.7) | 7.3 (1.5-21.2) |
| Ischemic | 2/30 (6.7) | 2/29 (6.9) | 3/28 (10.7) | |
| Hemorrhagic | 0/30 (0.0) | 0/29 (0.0) | 0/28 (0.0) | |
| Myocardial infarction requiring revascularization | 0/30 (0.0) | 0/29 (0.0) | 0/28 (0.0) | 0.0 (0.0-8.9) |
| Mitral valve reintervention after index procedure (MViV)[d] | 2/30 (6.7) | 4/29 (13.8) | 4/28 (14.3) | 9.7 (2.6-24.8) |
| Septostomy closed | 4/15 (26.7) | 5/15 (33.3) | 5/14 (35.7) | 21.7 (7.1-50.7) |
| Acute kidney injury requiring hemodialysis | 5/30 (16.7) | 5/29 (17.2) | 5/28 (17.9) | 14.5 (5.3-31.6) |
| Blood transfusion | 16/30 (53.3) | 17/29 (58.6) | 16/28 (57.1)[c] | 75.1 (51.0-106.5) |
| Major vascular complication | 1/30 (3.3) | 1/29 (3.4) | 1/28 (3.5) | 2.4 (0.1-13.5) |
| New permanent pacemaker requirement | 5/30 (16.7) | 5/29 (17.2) | 5/28 (17.9) | 9.7 (2.6-24.8) |
| New onset atrial fibrillation | 5/30 (16.7) | 5/29 (17.2) | 6/28 (21.4) | 16.9 (6.8-34.9) |
| New hospitalization for heart failure | 4/30 (13.3) | 11/29 (37.9) | 11/28 (39.3) | 36.3 (20.3-59.9) |
| Device embolization or migration | 0/30 (0.0) | 0/29 (0.0) | 0/28 (0.0) | 0.0 (0.0-8.9) |
| Hemolytic anemia[e] | 3/30 (10.0) | 5/29 (17.2) | 5/28 (17.9) | 12.1 (3.9-28.3) |
| Valve thrombosis | 0/30 (0.0) | 1/29 (3.4) | 2/28 (7.1) | 4.8 (0.6-17.5) |
| Endocarditis | 0/30 (0.0) | 0/29 (0.0) | 0/28 (0.0) | 0 (0.0-8.9) |
| New York Heart Association functional class | | | | |
| I | 6/25 (24) | 7/18 (38.9)[f] | 2/15 (13.3)[g] | NA |
| II | 9/25 (36) | 8/18 (44.4) | 8/15 (53.4) | |
| III | 8/25 (32) | 3/18 (16.7) | 5/15 (33.3) | |
| IV | 2/25 (8) | 0/18 (0.0) | 0/15 (0.0) | |

Values are n/N (%) or median (IQR). [a]1 withdrew consent at 8 days after transatrial ViMAC. [b]1 withdrew consent at day 187 after transatrial ViMAC. [c]1 withdrew consent at day 651 after transseptal ViMAC. [d]1 transseptal MViV and 1 transatrial ViMAC. [e]3 at 30 days, 1 treated with MViV, and 2 spontaneously resolved but required transfusion. Two additional hemolysis after 30 days: 1 treated with paravalvular leak closure and 1 conservatively. [f]Ten died, 2 withdrew consent, 1 missing value (1 patient alive at 1 year did not have a 1-year follow-up visit). [g]Eleven died, 3 withdrew consent, 2 missing value (2 patients alive at 2 years missed the 2-year follow-up visit).

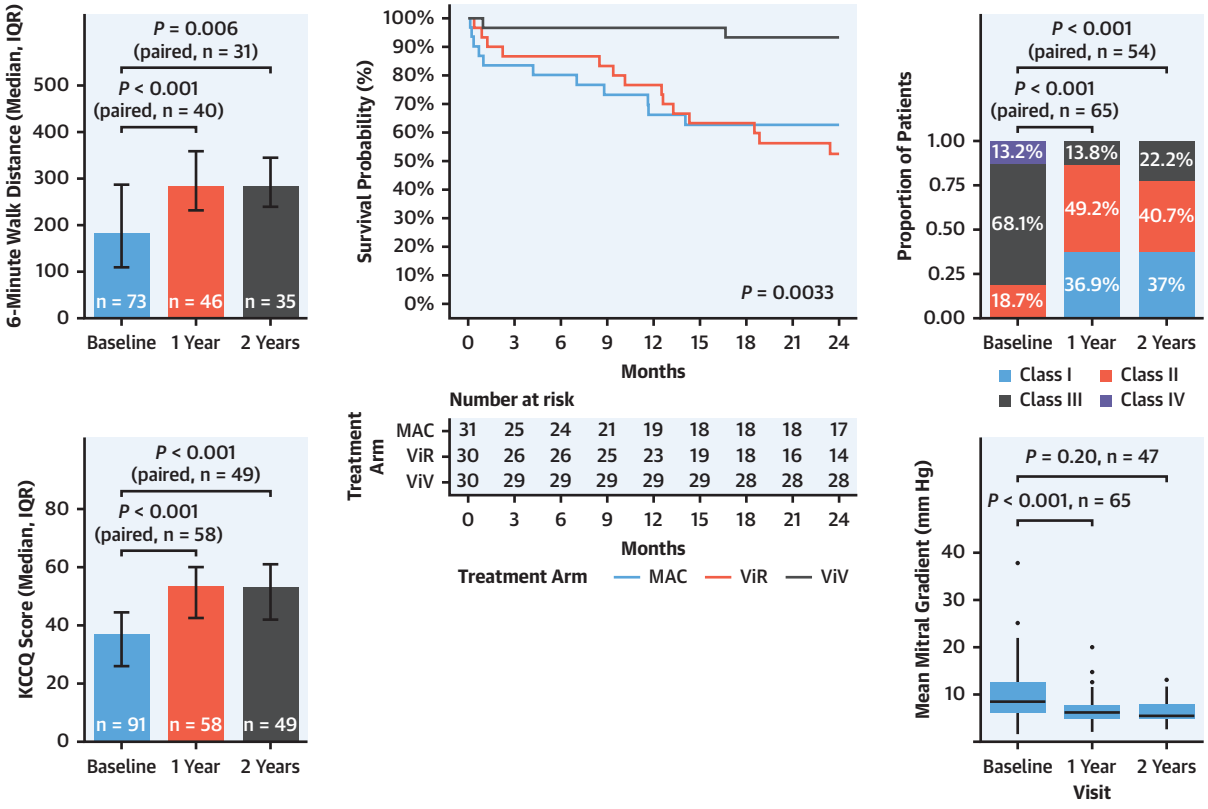
MViV = mitral valve-in-valve; NA = not applicable; ViMAC = valve-in-mitral annular calcification.

Chi-square or Fisher exact test were used to compare discrete groups and Kruskal-Wallis 1-way analysis of variance on ranks was used to compare continuous variables between groups. For comparisons between time points, a Wilcoxon test was used, and comparisons included only patients with values available at both time points. Crude incidence rates were calculated as the number of events over the total person-years. The 95% CIs were calculated assuming a Poisson distribution. A Kaplan-Meier curve was generated for all-cause mortality and treatment arms were compared using the log-rank test. Cox proportional hazards multivariable regression analysis was performed to determine predictors of 2-year all-cause mortality incorporating 3 variables: treatment arm; Society for Thoracic Surgeons (STS) score; and home oxygen use. All *P* values were 2-sided, and values $<0.05$ were considered statistically significant. All analyses were conduction using R (version 4.0.3, R Foundation for Statistical Computing).

## RESULTS

Baseline characteristics of patients enrolled in the 3 arms have been previously published. Briefly, patient characteristics for the ViMAC group included age 75 ± 8 years, 71% female, diabetes in 39%, home oxygen therapy in 23%, median left ventricular ejection fraction 63% (IQR: 55%-67%), median baseline neo-left ventricular outflow tract (LVOT) area 160 $mm^2$ (IQR: 70-240 $mm^2$), and STS score 8.6% ± 8.2%. Patient characteristics for the MViR group included age 72 ± 9 years, 37% female, diabetes in 30%, home oxygen use in 13%, median left ventricular ejection fraction 47% (IRQ: 33%-56%), median baseline neo-LVOT area 440 $mm^2$ (IQR: 330-570 $mm^2$), and STS score 8.7 ± 4.7%. Patient characteristics for the MViV group included age 76 ± 10 years, 63% female, diabetes in 20%, home oxygen use in 10%, median left ventricular ejection fraction 56% (IQR: 49%-65%), median baseline neo-LVOT

**CENTRAL ILLUSTRATION** **2-Year Outcomes of Balloon Expandable Transcatheter Mitral Valve Replacement in the MITRAL Trial**




**Eleid MF, et al. J Am Coll Cardiol. 2022;80(23):2171-2183.**

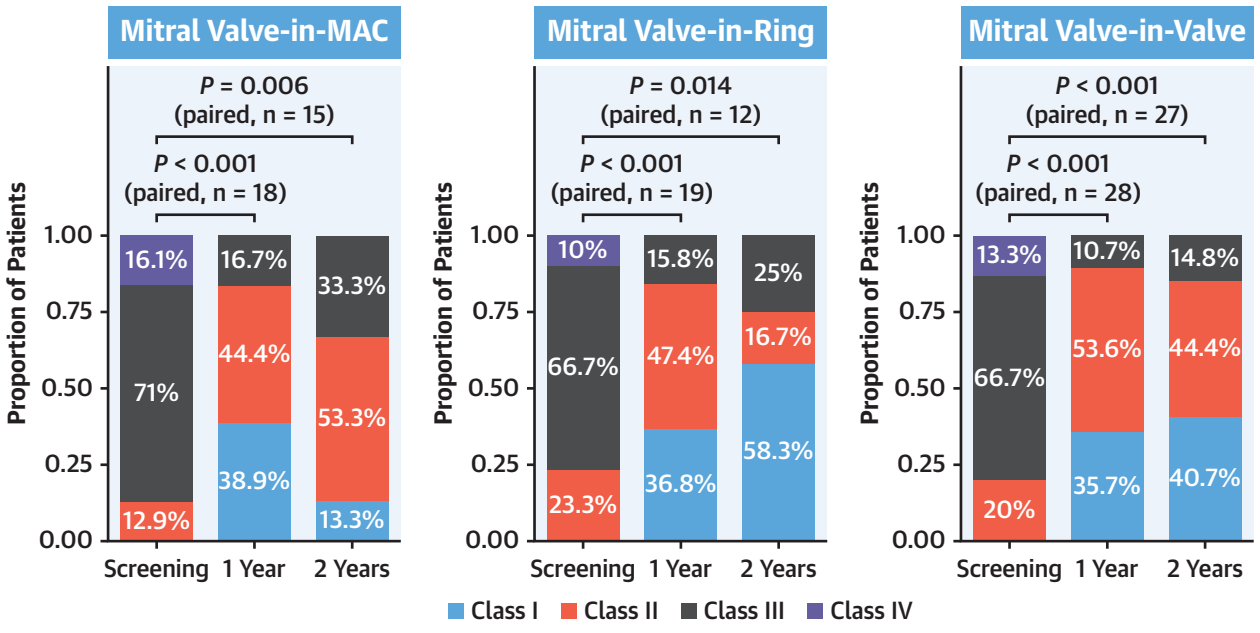
**(Left)** Significant improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) and 6-minute walk were observed at 2 years compared to baseline on pooled analysis. **(Center)** Estimated survival at 2 years in the mitral valve-in-valve (ViV) group (93.3%; 95% CI: 84.2%-100%) was superior to that of the valve-in-mitral annular calcification (MAC) (62.8%; 95% CI: 47.5%-82.9%) and mitral valve-in-ring (ViR) groups (52.5%; 95% CI: 37.2%-74.2%). **(Right)** Significant improvement in New York Heart Association class was observed at 2 years compared to baseline. Mean mitral gradient showed persistent improvement at 2 years compared to baseline. MITRAL = Mitral Implantation of Transcatheter Valves.

area 330 mm$^2$ (IQR: 250-420 mm$^2$), and STS score 10.2% ± 6.5%.

**ViMAC ARM.** Clinical outcomesTwo-year clinical outcomes are listed in Table 1 and the Central Illustration. Fifteen patients with ViMAC underwent surgical transatrial implantation, 1 underwent transapical implantation, and 15 underwent transseptal implantation. Follow-up was 79% (15 of 19 patients) complete. Mortality occurred in 11 of 28 patients (39.3%) of which 6 of 28 (21.4%) were cardiovascular in etiology. Between 1 and 2 years of follow-up, 1 death occurred that was non cardiovascular in etiology. The incidence of stroke was 10.7% at 2 years. Between 1 and 2 years, there was 1 additional case of prosthetic valve thrombosis making the total 2-year incidence 7.1% (2 of 28 patients). No cases of endocarditis were observed at 2 years. No hospitalizations for heart failure occurred between 1 and 2 years of follow-up.

**Quality of life at 2 years.** NYHA functional class continued to show improvement at 2 years compared to baseline, with 66.7% of patients in NYHA functional class I or II (Table 1, Figure 1) as did the KCCQ (median: baseline: 34 [IQR: 26-44]; 1 year: 53 [IQR: 47-64], 2 years: 51 [IQR: 42.25-56.75]) (Figure 2). Similar 2-year outcomes were observed in the transseptal versus transatrial access groups. A trend toward improvement in 6-minute walk distance was observed at 2 years in the ViMAC arm (median: baseline: 140 m [IQR: 85-228 m]; 1 year: 260 m [IQR: 219.75-305.25 m]; 2 years: 270 m [IQR: 225-335 m]). A significant improvement in 6-minute walk distance

**FIGURE 1** **NYHA Functional Class at 2 Years**




Significant improvement in New York Heart Association (NYHA) class was observed at 2 years on paired analysis compared to baseline in the valve-in-mitral annular calcification (MAC) group ($P = 0.006$), mitral valve-in-ring group ($P = 0.014$), and mitral valve-in-valve group ($P < 0.001$).

was demonstrated when all 3 arms were pooled (Figure 3).

**Transcatheter heart valve prosthesis function at 2 years.** Overall similar echocardiographic results were observed at 2 years compared to 1 year (Table 2). The median of the mean MV gradient was 5.6 mm Hg (IQR: 4.1-7.2 mm Hg) with estimated pulmonary artery systolic pressure of 41.5 mm Hg (IQR: 33.3-44.0 mm Hg). Total MR was none to trace in 69% and mild in 31%. At 2 years 87% of patients were taking systemic oral anticoagulation that was unchanged compared to 1-year follow-up ($P = 0.51$) (Supplemental Appendix 2).

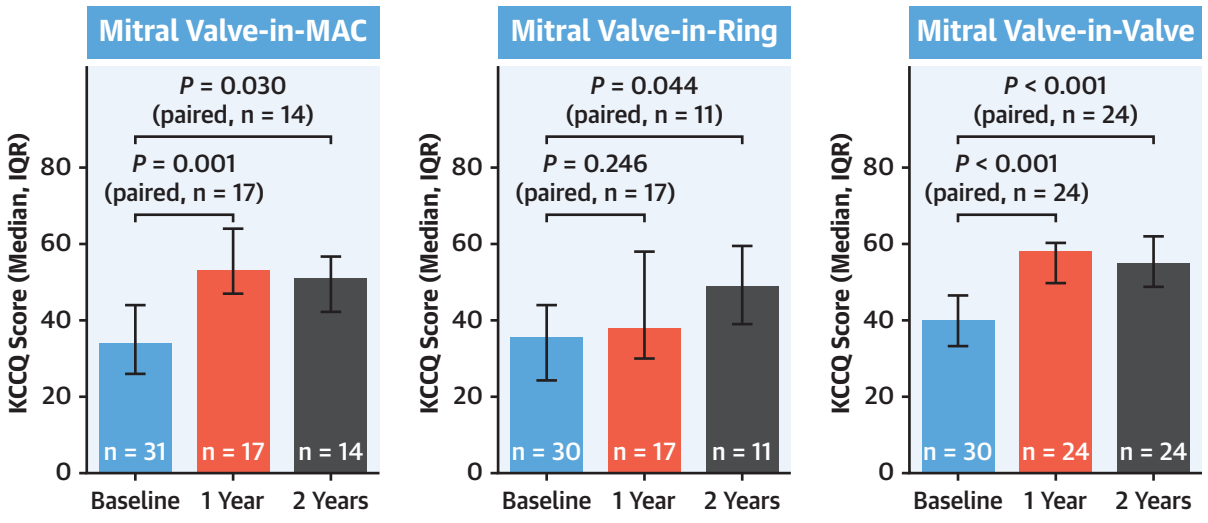
**MVIR ARM 2-YEAR OUTCOMES. Clinical outcomes.** Two-year clinical outcomes are listed in Table 3. Follow-up was 77% (13 of 17 patients) complete. Mortality occurred in 13 of 30 patients (43.3%), of which 5 of 30 (17%) were cardiovascular in etiology. Between 1 and 2 years of follow-up, 6 deaths occurred, 3 (50%) of which were cardiovascular and the remainder were noncardiovascular. Of the 3 cardiovascular deaths, 1 was determined to be device-related after adjudication by the clinical events committee who concluded the development of severe transcatheter heart valve prosthetic stenosis with mean gradient of 20 mm Hg and LVOT obstruction with peak gradient of 62 mm Hg; 1 was sudden death in a patient who had developed LVOT obstruction post-TMVR and end-stage renal disease requiring dialysis, which was determined to be procedure-related; and the last patient experienced sudden death of unknown cause in the setting of chronic left ventricular systolic dysfunction with most recent ejection fraction 28%.

The incidence of stroke was 3.3% at 2 years. There were no cases of prosthetic valve thrombosis and no cases of endocarditis observed at 2 years. Rehospitalization for heart failure occurred in 27% of patients at 2 years of follow-up, which was 10% higher than the first year (3 additional patients were hospitalized for heart failure between year 1 and year 2).

**Quality of life at 2 years.** The NYHA functional class continued to show improvement at 2 years compared to baseline, with 75% of patients in NYHA functional class I or II (Table 3, Figure 1). The KCCQ scores showed persistent improvement at 2 years on paired analysis compared to baseline (median: baseline: 35.5 [IQR: 24.25-44]; 1 year: 38 [IQR: 30-58]; 2 years: 49 [IQR: 39-59.5]) (Figure 2). The 6-minute walk tests showed a trend toward sustained improvement at 2 years (median: baseline: 195 m [IQR: 110-318 m]; 1 year: 279 m [IQR: 242.5-344 m]; 2 years: 303 m [IQR: 233-352.5 m]) (Figure 3).

**Transcatheter heart valve prosthesis function at 2 years.** Overall similar echocardiographic results

**FIGURE 2 KCCQ Results at 2 Years**




Significant improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) measures of quality life were observed at 2 years on paired analysis compared to baseline in the valve-in-mitral annular calcification (MAC) group ($P = 0.03$), mitral valve-in-ring group ($P = 0.044$), and mitral valve-in-valve group ($P < 0.001$). **Bar heights and error bars** correspond to median (IQR).

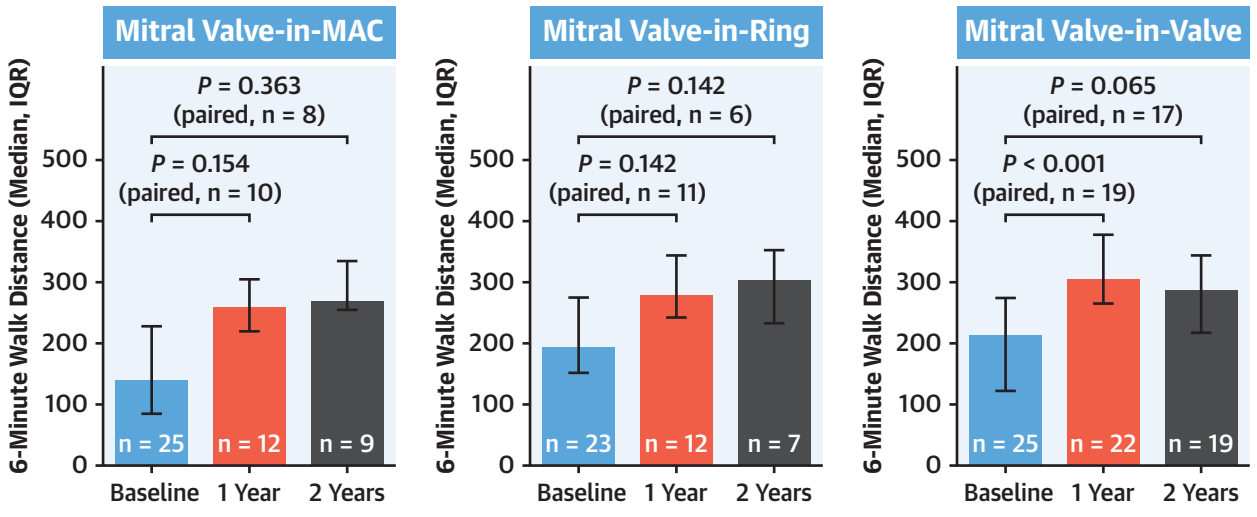
were observed at 2 years compared to 1 year (Table 4). The median of the mean MV gradient was 5.2 mm Hg (IQR: 4.5-8.3 mm Hg) with estimated pulmonary artery systolic pressure of 31.0 mm Hg (IQR: 26.0-41.8 mm Hg). Total MR was none to trace in 67% of patients and mild in 33%. In the 6 patients who died between 1 and 2 years, the average MV mean gradient at 1-year echocardiogram after excluding the 1 patient who developed prosthetic stenosis was 5.5 mm Hg. Of patients who died between 1 and 2 years, average left ventricular ejection fraction was 30.0% ± 5.3%, 2 patients had significant LVOT obstruction (peak LVOT gradient was 42 mm Hg in one and 68 mm Hg in another). No patients had more than mild MR. At 2 years, 100% of patients were taking systemic oral anticoagulation that was unchanged compared to 1-year follow-up ($P = 0.40$).

**MVIV ARM 2-YEAR OUTCOMES. Clinical outcomes.** Two-year clinical outcomes are listed in Table 5. Follow-up was 100% (28 of 28 patients) complete. Mortality occurred in 2 of 30 patients (6.7%), of which 1 of 30 (3.3%) was cardiovascular in etiology. Between 1 and 2 years of follow-up, 1 death occurred that was cardiovascular in etiology. The incidence of stroke was 6.7% at 2 years. There were no cases of valve thrombosis and no cases of endocarditis observed at 2 years. No hospitalization for heart failure occurred between years 1 and 2 of follow-up.

**Quality of life at 2 years.** The NYHA functional class continued to show improvement at 2 years compared to baseline, with 85% of patients in NYHA functional class I or II (Table 5, Figure 1). The KCCQ scores continued to show improvement at 2 years compared to baseline (median: baseline: 40 [IQR: 33.25-46.5]; 1 year: 58 [IQR: 49.75-60.25]; 2 years: 55 [IQR: 48.75-62]) (Figure 2). Compared to 1 year, there were sustained improvements in NYHA functional class and KCCQ score on paired analysis. The 6-minute walk tests showed significant improvement compared to baseline and sustained improvement compared to 1 year on paired analysis (median: baseline: 213 m [IQR: 122-274 m]; 1 year: 305 m [IQR: 265-377.5 m]; 2 years: 287 m [IQR: 217.5-343.5 m]) (Figure 3).

**Transcatheter heart valve prosthesis function at 2 years.** Overall similar echocardiographic results were observed at 2 years compared to 1 year (Table 6). The median of the mean MV gradient was 5.5 mm Hg (IQR: 5.1-8.8 mm Hg) with estimated pulmonary artery systolic pressure of 37.0 mm Hg (30.0-51.0 mm Hg). Total MR was none to trace in 96% of patients and mild in 4.2%. At 2 years, 61% of patients were taking systemic oral anticoagulation that was unchanged compared to 1-year follow-up ($P = 0.92$). Compared to other groups, fewer patients in the MViV group were taking anticoagulation at 2 years (61% vs 87% and 100% in ViMAC and MviR groups, respectively; $P = 0.01$). There was a trend toward differences in direct oral anticoagulant versus warfarin therapy compared among groups (29% direct oral anticoagulant and 71% warfarin in MViV group compared to 0%

**FIGURE 3** 6-Minute Walk Distance at 2 Years




Nonsignificant trends toward improvement in 6-minute walk distance were observed in all 3 groups in paired analysis at 2 years of follow-up. **Bar heights and error bars** correspond to median (IQR). MAC = mitral annular calcification.

and 100% in ViMAC and 21% and 79% in the MViR groups; $P = 0.109$) (Supplemental Appendix 2).

**COMPARATIVE SURVIVAL AT 2 YEARS.** Median duration of follow-up was 2.0 years (IQR: 1.1-2.0 years). Two-year probability of survival in the ViMAC, MViR, and MViV arms are shown in **Figure 4**. Estimated survival at 2 years in the MViV group (93.3%; 95% CI: 84.2%-100%) was superior to that of the ViMAC (62.8%; 95% CI: 47.5%-82.9%) and MViR groups (52.5%; 95% CI: 37.2%-74.2%) ($P = 0.003$) (**Central Illustration**). In multivariable analysis incorporating treatment arm, STS score, and home oxygen use, the only significant predictor of 2-year mortality was the MViV arm, which had a protective effect (HR: 0.12; 95% CI: 0.03-0.56; $P = 0.007$).

## DISCUSSION

The primary findings of this 2-year follow-up analysis of the prospective early feasibility MITRAL trial outcomes in patients undergoing ViMAC, MViR, and MViV are as follows: 1) quality of life measures including NYHA functional class and KCCQ score showed sustained improvements at 2 years compared to 1 year in all 3 arms; 2) echocardiographic analysis showed stable TMVR prosthetic valve function at 2 years with low transvalvular gradients and low rates of MR; 3) very low rates of transcatheter heart valve thrombosis and endocarditis were observed at 2 years; 4) survival at 2 years was excellent in the MViV group, whereas 2-year survival was lower in the MViR and ViMAC groups, with higher mortality noted in the MViR group between 1 and 2 years; and 5) improvement in 6-minute walk distance was sustained at 2 years.

The present study shares similarities with the recently published 2-year outcomes of the self-expanding transapical Tendyne (Abbott) transcatheter valve delivery system.[9] Baseline patient demographics were comparable with age 75 ± 8 years and STS score of 7.8%, and 2-year all-cause mortality was 39%, which was analogous to that seen in the ViMAC and MViR arms in the MITRAL trial. Despite the high 2-year mortality, heart failure hospitalization fell from 1.30 events per year preprocedure to 0.51 per year in the 2 years post-TMVR ($P < 0.0001$), and 82% of patients were NYHA functional class I or II. The study was limited because a large number of patients were lost to follow-up and there was lack of echocardiographic follow-up in >50% of patients at 2 years. However, the study did show TMVR can achieve effective correction of MV disease with stable prosthesis function at 2 years. Concerns raised from the analysis were a relatively high in-hospital mortality of 5.5% and high 2-year mortality, leading to questions about the high comorbidity burden of this population and the need for better patient selection. Similar conclusions can be made for the ViMAC and MViR groups in the MITRAL trial regarding comorbidity burden that led to a high 2-year mortality. Additionally, LVOT obstruction was identified as a major factor leading to early mortality in these 2

**TABLE 2 Echocardiographic Characteristics at 2 Years in ViMAC Arm**

| | 30 Days (n = 25) | 1 Year (n = 18)[a] | 2 Years (n = 13)[b] | *P* Value (n) | |
|---|---|---|---|---|---|
| | | | | 1-Year vs 2-Year | Baseline vs 2-Year |
| Ejection fraction (visual), % | 55.5 (50.7-66.2) | 65.3 (60.8-69.9) | 65.0 (60.0-67.0) | 0.10 (13) | 0.97 (13) |
| Stroke volume, mL | 65.3 (46.3-76.2) | 89.2 (62.8-94.5) | 62.5 (55.0-85.0)[c] | 0.44 (6) | 0.56 (6) |
| Cardiac output, L/min | 5.1 (3.8-6.0) | 5.1 (4.5-7.4) | 4.6 (3.7-6.8)[c] | 1.00 (6) | 0.84 (6) |
| Mean MVG, mm Hg | 6.0 (5.2-7.8) | 6.1 (5.6-7.1) | 5.6 (4.1-7.2) | 0.62 (12) | 0.001 (12) |
| Pulmonary artery systolic pressure, mm Hg | 50.5 (41.6-69.9) | 39.3 (35.0-48.3) | 41.5 (33.3-44.0)[d] | 0.74 (8) | 0.38 (7) |
| Peak LVOT gradient | 7.2 (4.8-11.6) | 5.3 (3.5-8.4) | 4.5 (3.8-5.7) | 0.91 (12) | 0.76 (11) |
| Mean LVOT gradient | 3.5 (2.7-6.1) | 3.1 (2.2-4.9) | 2.6 (2.1-3.5) | 0.45 (12) | 0.64 (11) |
| Severity of total mitral regurgitation[e] | | | | 0.35 (13) | 0.005 (13) |
| None to trace | 17/25 (68.0) | 10/18 (55.6) | 9/13 (69.0) | | |
| 1 (+) | 6/25 (24.0) | 8/18 (44.4) | 4/13 (31.0) | | |
| 2 (+) | 1/25 (4.0) | 0/18 (0.0) | 0/13 (0.0) | | |
| ≥3 (+) | 1/25 (4.0) | 0/18 (0.0) | 0/13 (0.0) | | |
| Severity of paravalvular mitral regurgitation[e] | | | | 0.35 (13) | NA |
| None to trace | 20/25 (80.0) | 16/18 (88.9) | 10/13 (77.0) | | |
| 1 (+) | 3/25 (12.0) | 2/18 (11.1) | 3/13 (23.0) | | |
| 2 (+) | 1/25 (4.0) | 0/18 (0.0) | 0/13 (0.0) | | |
| ≥3 (+) | 1/25 (4.0) | 0/18 (0.0) | 0/13 (0.0) | | |
| RV dysfunction | | | | 0.85 (13) | 0.34 (13) |
| Normal | 16/25 (64.0) | 12/18 (66.7) | 10/13 (76.9) | | |
| Mild | 5/25 (20.0) | 6/18 (33.3) | 2/13 (15.4) | | |
| Moderate | 3/25 (12.0) | 0/18 (0.0) | 0/13 (0.0) | | |
| Severe | 1/25 (4.0) | 0/18 (0.0) | 1/13 (7.7) | | |

Values are median (IQR) or n/N (%), unless otherwise indicated. [a]10 died (1 of them had echo at 1-year visit prior to death at day 350); 1 withdrew consent 187 days after transcatheter mitral valve replacement; and 2 subjects alive at 1 year did not have 1-year follow-up visit. [b]11 died; 3 withdrew consent; and 3 alive at 2 years missed 2-year follow-up echocardiogram. [c]5 missing value. [d]3 missing value. [e]1 missing mitral regurgitation severity.

LVOT = left ventricular outflow tract; MVG = mitral valve gradient; RV = right ventricular; other abbreviations as in Table 1.

groups, and important mitigation strategies to reduce incidence of LVOT obstruction (eg, preemptive alcohol septal ablation and anterior mitral leaflet laceration) have been developed[10,11] and are now routinely used in the MITRAL II pivotal trial (NCT04408430).

**SUSTAINED QUALITY OF LIFE IMPROVEMENT AT 2 YEARS.** A key finding from this study is that symptom burden as assessed by NYHA functional class as well as KCCQ score improved at 1 year and showed sustained improvement at 2 years of follow-up on paired analysis compared to baseline in all 3 groups of patients undergoing balloon-expandable mitral valve implantation. Quality of life is among the most important measures to patients experiencing dyspnea who wish to be more active. There was a trend toward improvement in 6-minute walk distance in all 3 groups at 2 years compared to baseline and may have been limited by reduced sample size for paired analysis at 2 years. Supporting this hypothesis, a pooled analysis of all 3 groups demonstrated a significant improvement in 6-minute walk at 2 years compared to baseline. These data provide reassurance that the MV disease in these populations is a prominent contributor to dyspnea and heart failure symptoms, and that despite the large burden of comorbidities, treatment with balloon-expandable transcatheter valves in the mitral position is effective at relieving symptoms attributable to MV disease at 2 years of follow-up.

**DISCORDANT 2-YEAR SURVIVAL IN MViV COMPARED TO OTHER GROUPS.** Severe MAC represents a culmination of advanced cardiovascular disease processes, and patients with severe MAC will inevitably have multiple comorbidities including left ventricular diastolic dysfunction and hypertrophy and chronic kidney disease.[12] In some cases, severe MAC is a result of mediastinal irradiation, which carries many disabling comorbidities including restrictive cardiomyopathy and restrictive lung disease. This high burden of comorbidities may lead to high rates of noncardiovascular mortality in the first year even after an initially successful TMVR procedure.[13] Interestingly, the only additional death in the ViMAC group occurring between 1 and 2 years of follow-up was noncardiovascular in etiology. Völzke et al[14] showed on multivariable analyses that MAC was significantly associated with all-cause mortality

**TABLE 3 2-Year Clinical Outcomes in MViR Arm**

| | 30 Days (n = 30) | 1 Year (n = 30) | 2 Years (n = 28)[a] | Event Rates (per 100 Person-Years) |
|---|---|---|---|---|
| All-cause mortality | 2/30 (6.7) | 7/30 (23.3) | 14/28 (50) | 32.3 (17.6-54.2) |
| Cardiovascular | 2/30 (6.7) | 2/30 (6.7) | 6/28 (21.43) | 13.8 (5.1-30.1) |
| Noncardiovascular | 0/30 (0.0) | 5/30 (16.7) | 8/28 (26.65) | 16.1 (6.5, 33.3) |
| Device success | 22/30 (73.3) | NA | NA | NA |
| Procedural success | 22/30 (73.3) | NA | NA | NA |
| Primary performance endpoint in survivors at 1 year | 24/28 (85.7)[b] | 17/19 (89.5)[c] | NA | NA |
| Stroke | 1/30 (3.3) | 1/30 (3.3) | 1/28 (3.6) | 2.3 (0.1-12.8) |
| Ischemic | 0/30 (0.0) | 0/30 (0.0) | 0/28 (0.0) | |
| Hemorrhagic[d] | 1/30 (3.3) | 1/30 (3.3) | 1/28 (3.6) | |
| Myocardial infarction requiring revascularization | 0/30 (0.0) | 0/30 (0.0) | 0/28 (0.0) | 0 (0.0-8.5) |
| Mitral valve reintervention after index procedure[e] | 2/30 (6.7) | 3/30 (10.0) | 3/28 (10.7) | 11.5 (3.7-26.9) |
| Septostomy closed[f] | 5/30 (16.7) | 7/30 (23.3) | 7/28 (25) | 16.1 (6.5-33.3) |
| Acute kidney injury requiring hemodialysis | 3/30 (10.0) | 4/30 (13.3) | 5/28 (17.9) | 9.2 (2.5-23.6) |
| Patients who received blood transfusion | 9/30 (30.0) | 12/30 (40.0) | 12/28 (42.9) | 46.1 (28.2-71.2) |
| Major vascular complication[g] | 2/30 (6.7) | 2/30 (6.7) | 2/28 (7.1) | 4.6 (0.6-16.7) |
| New permanent pacemaker requirement | 0/30 (0.0) | 0/30 (0.0) | 0/28 (0.0) | 0 (0.0-8.5) |
| New onset atrial fibrillation[h] | 1/30 (3.3) | 1/30 (3.3) | 1/28 (3.6) | 2.3 (0.1-12.8) |
| New hospitalization for heart failure | 0 (0.0) | 5/30 (16.7) | 8/28 (28.6) | 23.1 (11.1-42.4) |
| Device embolization or migration | 1/30 (3.3) | 1/30 (3.3) | 1/28 (3.6) | 2.3 (0.1-12.8) |
| Hemolytic anemia[i] | 1/30 (3.3) | 3/30 (10.0) | 3/28 (10.7) | 9.2 (2.5-23.6) |
| Valve thrombosis | 0/30 (0.0) | 0/30 (0.0) | 0/28 (0.0) | 0 (0.0-8.5) |
| Endocarditis | 0/30 (0.0) | 0/30 (0.0) | 0/28 (0.0) | 0 (0.0-8.5) |
| NYHA functional class | | | | |
| I | 9/28 (32.1) | 7/19 (36.8)[j] | 7/12 (58.3)[k] | NA |
| II | 12/28 (42.9) | 9/19 (47.4) | 2/12 (16.7) | |
| III | 7/28 (25.0) | 3/19 (15.8) | 3/12 (25.0) | |
| IV | 0/28 (0.0) | 0/19 (0.0) | 0/12 (0.0) | |

Values are n/N (%) or median (IQR). [a]2 lost to follow-up. [b]2 died within 30 days. [c]7 died and 4 alive at 1 year missed 1-year echocardiogram. [d]Spontaneous bleed in previously undiagnosed pre-existing brain tumor. [e]1 PVL closure attempt followed by surgical mitral valve replacement and 1 transseptal MViV plus PVL closure within 30 days. 1 PVL closure between 30 days and 1 year. [f]4 during index procedure, 1 between discharge and 30-day follow-up, and 2 between 30 days and 1 year. [g]Retroperitoneal bleed during index hospitalization. [h]Post-open heart surgery in a patient who underwent conventional surgical mitral valve replacement because of a PVL. This patient withdrew consent 38 days after transcatheter mitral valve replacement. [i]1 prior to discharge treated with PVL closure attempt followed by surgical mitral valve replacement. 1 more after 30 days treated conservatively. [j]7 died; 1 lost to follow-up; and 3 alive at 1 year did not have NYHA functional class. [k]13 died; 2 lost to follow-up; and 3 alive at 2 years did not have NYHA functional class.

MViR = mitral valve-in-ring; NYHA = New York Heart Association; PVL = paravalvular leak; other abbreviations as in Tables 1 and 2.

(HR: 2.47; 95% CI: 1.72-3.53; $P < 0.001$) and cardiovascular mortality (HR: 3.08; 95% CI: 1.72-5.49; $P < 0.001$). Similarly Ramaraj et al[15] studied patients with any echocardiographic evidence for MAC and showed that MAC was independently associated with all-cause mortality (OR: 2.50; 95% CI: 1.81-3.45; $P < 0.001$). The patients in the ViMAC cohort of the MITRAL trial, despite having relief of functionally severe MV disease, have extensive MAC and thus might predictably have poor 2-year outcomes.

On the other hand, in the MViR group, another 20% of patients (n = 6) enrolled died between 1 and 2 years, of which 50% were cardiovascular in etiology. Similarly high mortality has been demonstrated in MViR in the Valve in Valve International Database, with observed 50% mortality at 4 years.[4] The MViR population also represents a population with poor natural history outcomes, with reduced left ventricular ejection fraction, high prevalence of renal failure and atrial fibrillation, and prior coronary artery bypass grafting.[7] These baseline characteristics, as well as MR being the primary etiology of the dysfunction in this cohort, suggest the presence of ventricular functional disease that remains severe despite surgical MV repair, which may ultimately drive the 2-year outcomes. This observation also raises awareness of the need for better patient selection for surgical MV repair, including consideration of MVR as an alternative in appropriate cases of severe secondary MR.

The most important cardiovascular predictor of mortality observed in the global mitral ViMAC registry was LVOT obstruction.[13] Improvements in imaging-based procedural planning through careful assessment of MAC burden[16] and LVOT virtual valve modeling[17] may lead to reduction in procedural risk through minimizing risk of valve migration and postimplant neo-LVOT obstruction. Additionally,

**TABLE 4 Echocardiographic Characteristics at 2 Years in MViR Arm**

| | 30 Days (n = 28)[a] | 1 Year (n = 19)[a] | 2 Years (n = 8)[b] | *P* Value (n) | |
|---|---|---|---|---|---|
| | | | | 1-Year vs 2-Year | Baseline vs 2-Year |
| Ejection fraction, % | 48.3 (39.1-52.2) | 40.0 (32.7-57.5) | 41.5 (31.0-62.3) | 0.57 (8) | 0.55 (8) |
| Stroke volume, mL | 68.2 (52.2-95.7) | 75.9 (66.3-85.5) | 59.0 (49.5-83.5)[c] | 0.25 (3) | 0.44 (6) |
| Cardiac output, L/min | 5.0 (3.7-6.9) | 5.0 (3.8-5.4) | 4.5 (4.3-5.2)[c] | 0.50 (3) | 0.84 (6) |
| Mean MVG, mm Hg | 7.6 (5.9-9.1) | 6.0 (4.7-7.3) | 5.6 (4.5-8.6) | 0.95 (8) | 0.55 (8) |
| Pulmonary artery systolic pressure | 44.4 (42.7-56.7)[d] | 37.6 (33.4-52.5)[e] | 32.0 (28.0-46.5) | 0.58 (7) | 0.22 (6) |
| Peak LVOT gradient | 4.6 (2.9-6.7) | 4.3 (2.5-5.2) | 3.9 (2.4-5.6) | 0.38 (8) | 0.15 (8) |
| Mean LVOT gradient | 2.7 (1.6-3.7) | 2.1 (1.4-3.1) | 2.1 (1.2-3.0) | 0.64 (8) | 0.08 (8) |
| Severity of total mitral regurgitation | | | | 1.00 (8) | 0.01 (8) |
| None to trace | 22/28 (77.7) | 11/19 (57.9) | 5/8 (62.5) | | |
| 1 (+) | 6/28 (22.2) | 8/19 (42.1) | 3/8 (37.5) | | |
| 2 (+) | 0/28 (0.0) | 0/19 (0.0) | 0/8 (0.0) | | |
| ≥3 (+) | 0/28 (0.0) | 0/19 (0.0) | 0/8 (0.0) | | |
| Severity of paravalvular mitral regurgitation | | | | 1.00 (8) | NA |
| None to trace | 23/28 (81.5) | 17/19 (89.5) | 7/8 (87.5) | | |
| 1 (+) | 5/28 (18.5) | 2/19 (10.5) | 1/8 (12.5) | | |
| 2 (+) | 0/28 (0.0) | 0/19 (0.0) | 0/8 (0.0) | | |
| ≥3 (+) | 0/28 (0.0) | 0/19 (0.0) | 0/8 (0.0) | | |
| RV dysfunction | | | | 0.12 (8) | 0.20 (8) |
| Normal | 9/27 (33.3) | 5/18 (27.8) | 4/8 (50.0) | | |
| Mild | 13/27 (48.1) | 5/18 (27.8) | 3/8 (37.5) | | |
| Moderate | 5/27 (18.5) | 7/18 (38.8) | 1/8 (12.5) | | |
| Severe | 0/27 (0.0) | 0/18 (0.0) | 0/8 (0.0) | | |

Values are median (IQR) or n/N (%), unless otherwise indicated. [a]7 died, and 4 alive at 1 year but missed the 1-year follow-up echocardiogram. [b]14 died; 2 lost to follow-up; and 6 missed the 2-year follow-up echocardiogram. [c]2 missing values. [d]5 missing values. [e]3 missing values.

Abbreviations as in Tables 1 to 3.

anterior leaflet laceration through electrosurgical techniques[10] is another promising tool serving to reduce risk of LVOT obstruction in patients both ViMAC and MViR groups. In contrast to the ViMAC and MViR groups, patients in the MViV group are at low risk for these complications and experienced excellent 2-year survival with only 1 additional death observed between 1 and 2 years of follow-up. Supporting these observations, the MViV group was the only independent predictor of 2-year survival on multivariable analysis.

**PROSTHESIS DURABILITY AT 2 YEARS.** In all 3 arms of the MITRAL trial, prosthesis function remained largely unchanged between 1 and 2 years. Specifically, no differences were observed on paired analysis in mean MV gradient, MV area, or degree of prosthetic or periprosthetic MR between 1 and 2 years of follow-up. Furthermore, there were no cases of infective endocarditis detected between 1 and 2 years and only 1 case of prosthetic valve thrombosis, occurring in the ViMAC group not associated with MV dysfunction or embolic event. Importantly, based on initial experience with observed risk of prosthetic valve thrombosis with balloon-expandable valve implantation in the mitral position,[2] the majority of patients were prescribed anticoagulation with a vitamin K antagonist indefinitely, which likely was a factor in the low rates of prosthetic valve thrombosis. The optimal adjunctive antiplatelet and antithrombotic therapy is unknown for patients undergoing balloon-expandable aortic valves in the mitral position and prospective studies comparing different regimens are needed to more definitively address this question.

**STUDY LIMITATIONS.** Given the early feasibility design of this study, a small number of patients were enrolled, limiting statistical power. The lack of randomization and control group limit inferences about the effects of MV intervention on survival. Data on the natural history of patients with severe MV disease with severe MAC, prior annuloplasty ring, or bioprosthetic valve who are untreated are unavailable. Patients in this study were carefully selected and results cannot be applied to the general population. Calculation of the prosthetic MV area by transthoracic Doppler echocardiography has several limitations that may contribute to the relatively low observed MV areas reported in serial follow-up.

Survival bias is likely present in the MViR group between 1 and 2 years. Of the 6 patients who died between 1 and 2 years, 2 had severe LVOT obstruction

**TABLE 5 2-Year Clinical Outcomes in MViV Arm**

| | 30 Days (n = 30) | 1 Year (n = 30) | 2 Years (n = 30) | Event Rates (per 100 Person-Years) |
|---|---|---|---|---|
| All-cause mortality | 1/30 (3.3) | 1/30 (3.3) | 2/30 (6.7) | 3.5 (0.4-12.6) |
| Cardiovascular | 0/30 (0.0) | 0/30 (0.0) | 1/30 (3.3) | 1.7 (0.0-9.7) |
| Noncardiovascular | 1/30 (3.3) | 1/30 (3.3) | 1/30 (3.3) | 1.7 (0.0-9.7) |
| Device success | 28/30 (93.3) | NA | NA | |
| Procedural success | 28/30 (93.3) | NA | NA | |
| Primary performance endpoint in survivors at 1 year | 28/29 (96.6) | 24/29 (82.8) | NA | |
| Stroke | 1/30 (3.3) | 2/30 (6.7) | 2/30 (6.7) | 3.5 (0.4-12.6) |
| Ischemic | 0/30 (0.0) | 0/30 (0.0) | 0/30 (0.0) | |
| Hemorrhagic[a] | 1/30 (3.3) | 2/30 (6.7) | 2/30 (6.7) | |
| Myocardial infarction requiring revascularization | 0/30 (0.0) | 0/30 (0.0) | 0/30 (0.0) | 0.0 (0.0-6.4) |
| Mitral valve reintervention after index procedure | 0/30 (0.0) | 0/30 (0.0) | 0/30 (0.0) | 0.0 (0.0-6.4) |
| Septostomy closed[b] | 1/30 (3.3) | 3/30 (10.0) | 3/30 (10.0) | 5.2 (1.1-15.3) |
| Acute kidney injury requiring hemodialysis | 0/30 (0.0) | 0/30 (0.0) | 0/30 (0.0) | 0.0 (0.0-6.4) |
| Blood transfusion patients | 3/30 (10.0) | 6/30 (20.0) | 7/30 (23.3) | 20.9 (10.8-36.5) |
| Major vascular complication[c] | 1/30 (3.3) | 1/30 (3.3) | 1/30 (3.3) | 3.5 (0.4-12.6) |
| New permanent pacemaker requirement | 1/30 (3.3) | 1/30 (3.3) | 1/30 (3.3) | 1.7 (0.0-9.7) |
| New onset atrial fibrillation | 0/30 (0.0) | 0/30 (0.0) | 0/30 (0.0) | 0.0 (0.0-6.4) |
| New hospitalization for heart failure | 1/30 (3.3) | 5/30 (16.7) | 5/30 (16.7) | 17.4 (8.3-32.0) |
| Device embolization or migration | 0/30 (0.0) | 0/30 (0.0) | 0/30 (0.0) | 0.0 (0.0-6.4) |
| Hemolytic anemia | 0/30 (0.0) | 0/30 (0.0) | 0/30 (0.0) | 0.0 (0.0-6.4) |
| Valve thrombosis | 0/30 (0.0) | 0/30 (0.0) | 0/30 (0.0) | 0.0 (0.0-6.4) |
| Endocarditis | 0/30 (0.0) | 0/30 (0.0) | 0/30 (0.0) | 0.0 (0.0-6.4) |
| NYHA functional class | | | | |
| I | 14/29 (48.3) | 10/28 (35.7)[d] | 11/27 (40.7)[e] | NA |
| II | 10/29 (34.5) | 15/28 (53.6) | 12/27 (44.5) | |
| III | 5/29 (17.2) | 3/28 (10.7) | 4/27 (14.8) | |
| IV | 0/29 (0.0) | 0/28 (0.0) | 0/27 (0.0) | |

Values are n/N (%) or median (IQR). [a]1 spontaneous intracranial microhemorrhage found on magnetic resonance imaging done for headache (no focal deficit per neurologist's evaluation). One hemorrhage after a fall. [b]1 during index procedure and 2 between 30-day and 1 year follow-ups. [c]Pulmonary embolism on postoperative day 2. [d]1 subject died, and 1 subject missing NYHA functional class at 1 year. [e]2 died, and 1 missing NYHA functional class at 2 years.

Abbreviations as in Tables 1 to 3.

evident on 1 year echocardiogram, and 1 patient developed severe prosthetic stenosis of the transcatheter valve that was a contributor to mortality. However, in 4 of the 6 patients there was no evidence of prosthetic stenosis or significant MR at 1 year. Cardiovascular contributor to mortality in these patients may more likely have been the severe underlying LV dysfunction given that 3 of the 6 patients had ejection fraction of 30% or less on 1-year echocardiogram. In contrast, in the ViMAC and MViV groups, only 1 patient died in each group between 1 and 2 years, making it unlikely that survival bias affected the 2-year clinical and echocardiographic outcomes in these groups.

## CONCLUSIONS

Use of balloon-expandable aortic transcatheter heart valves for selected patients with severe MAC, failed annuloplasty ring, and bioprosthetic MV dysfunction is associated with sustained improvements in quality of life and heart failure symptoms at 2 years of follow-up. Transcatheter heart valve prosthesis function remained stable between year 1 and year 2. The 2-year survival estimates were greater in the MViV than in the MViR and VIMAC groups. The MViR group experienced higher mortality rates between 1 and 2 years compared to the MViV and ViMAC groups.

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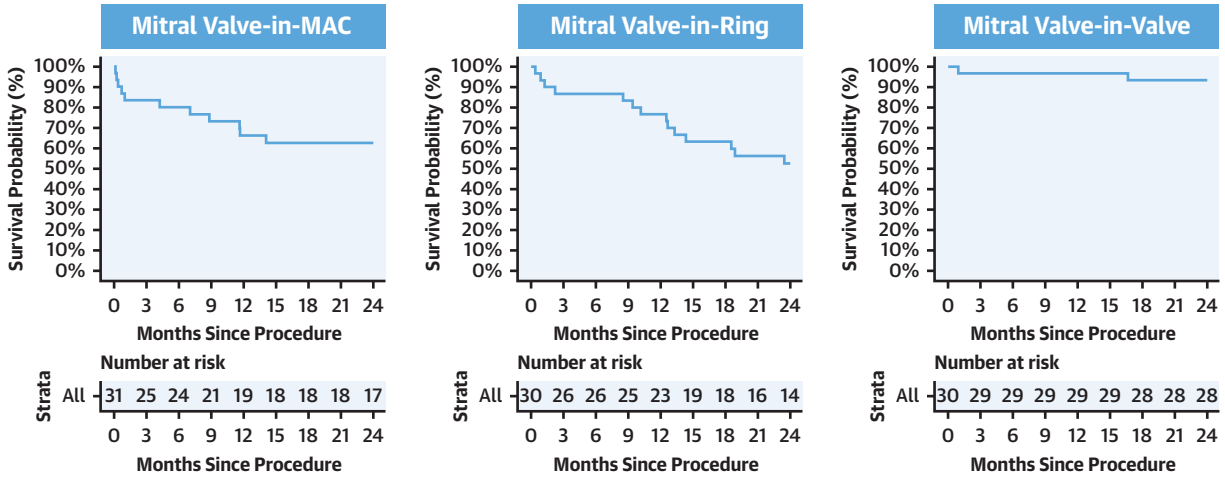
**TABLE 6 Echocardiographic Characteristics at 2 Years in MViV Arm**

| | 30 Days (n = 29)[a] | 1 Year (n = 29)[a] | 2 Years (n = 25)[b] | *P* Value (n) | |
|---|---|---|---|---|---|
| | | | | 1-Year vs 2-Year | Baseline vs 2-Year |
| Ejection fraction, % | 56.6 (47.0-66.2) | 57.7 (45.8-62.3) | 55.0 (44.0-65.0) | 0.74 (26) | 0.45 (25) |
| Stroke volume, mL | 54.0 (45.0-69.0) | 65.6 (52.6-79.3)[c] | 76.0 (61.0-85.0)[d] | 0.10 (9) | 0.67 (13) |
| Cardiac output, L/min | 3.1 (1.7-4.3) | 4.6 (3.7-5.2)[c] | 5.2 (4.3-5.5)[d] | 0.20 (9) | 0.59 (13) |
| Mean MVG, mm Hg | 6.0 (4.7-7.3) | 6.6 (5.5-8.9) | 5.5 (5.1-8.8) | 0.11 (26) | 0.001 (23) |
| Pulmonary artery systolic pressure | 32.2 (27.8-39.0) | 45.3 (35.8-54.8) | 37.0 (30.0-51.0) | 0.50 (23) | 0.62 (23) |
| Peak LVOT gradient | 4.9 (4.0-8.0) | 4.1 (2.6-6.8) | 4.1 (2.9-5.3) | 0.19 (25) | 0.59 (23) |
| Mean LVOT gradient | 2.9 (1.8-4.5) | 2.4 (1.5-3.9) | 2.3 (1.8-3.2) | 0.23 (25) | 0.10 (23) |
| Severity of total mitral regurgitation | | | | 1.00 (26) | <0.001 (24) |
| None to trace | 28/29 (96.6) | 26/29 (89.6) | 24/25 (96.0) | | |
| 1 (+) | 1/29 (3.4) | 3/29 (3.4) | 1/25 (4.0) | | |
| 2 (+) | 0/29 (0.0) | 0/29 (0.0) | 0/25 (0.0) | | |
| ≥3 (+) | 0/29 (0.0) | 0/29 (0.0) | 0/25 (0.0) | | |
| Severity of paravalvular mitral regurgitation | | | | NA | NA |
| None to trace | 29/29 (100.0) | 27/29 (93.1) | 25/25 (100.0) | | |
| 1 (+) | 0/29 (0.0) | 2/29 (6.9) | 0/25 (0.0) | | |
| 2 (+) | 0/29 (0.0) | 0/29 (0.0) | 0/25 (0.0) | | |
| ≥3 (+) | 0/29 (0.0) | 0/29 (0.0) | 0/25 (0.0) | | |
| RV dysfunction | | | | 0.66 (25) | NA |
| Normal | 1/2 (50.0) | 13/29 (44.8) | 14/24 (58.3) | | |
| Mild | | 14/29 (48.3) | 6/24 (25.0) | | |
| Moderate | 1/2 (50.0) | 2/29 (6.9) | 3/24 (12.5) | | |
| Severe | | 0/29 (0.0) | 1/24 (4.2) | | |

Values are median (IQR) or n/N (%), unless otherwise indicated. [a]1 died on postoperative day 29. [b]2 died, and 3 alive at 2 years missed 2-year echo. [c]15 missing values. [d]11 missing values.

Abbreviations as in Tables 1 and 2.

**FIGURE 4 Survival at 2 Years Following Balloon-Expandable ViMAC, MViR, and MViV**




Predicted 2-year all-cause mortality in the valve-in-mitral annular calcification (ViMAC) arm was 39.3%, 47.5% in the mitral valve-in-ring (MViR) arm, and 6.7% in the mitral valve-in-valve (MViV) arm.

Abbott Structural, Baylis Medical, Edwards Lifesciences, and Philips Healthcare; has institutional consulting contracts for which she receives no direct compensation with Abbott Structural, Boston Scientific, Edwards Lifesciences, Medtronic, and Novartis; has stock options with Navigate; and has served as Chief Scientific Officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored trials, for which she has received no direct industry compensation. Dr Guerrero has received institutional research grant support from Edwards Lifesciences; and has served as a consultant for Abbott Structural Heart and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Balloon-expandable aortic transcatheter heart valve prostheses in the mitral position can deliver sustained improvement in symptoms, quality of life, and valve function 2 years of following deployment in selected patients with severe annular calcification, failed annuloplasty rings, or malfunctioning bioprostheses.

### TRANSLATIONAL OUTLOOK:

Longer-term follow-up is needed to assess the durability of balloon-expandable aortic transcatheter heart valves in the mitral position and identify clinical predictors of outcome to guide optimal patient selection.

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**KEY WORDS** annuloplasty ring, mitral annular calcification, mitral bioprosthesis, mitral valve disease, transcatheter mitral valve replacement

**APPENDIX** For additional information about the study endpoints and supplemental tables, please see the online version of this paper.