

ORIGINAL RESEARCH

STRUCTURAL

Combined Impact of Residual Mitral Regurgitation and Gradient After Mitral Valve Transcatheter Edge-to-Edge Repair



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ABSTRACT

BACKGROUND Reducing mitral regurgitation (MR) during mitral transcatheter edge-to-edge repair (M-TEER) may come at the cost of increased mitral valve gradient (MVG). The combined impact of residual MR and MVG on clinical outcomes after M-TEER is unknown.

OBJECTIVES This study sought to evaluate the impact of postprocedure MR and MVG on clinical outcomes after M-TEER.

METHODS EXPANDED is a pooled, patient-level cohort of the EXPAND (A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices) and EXPAND G4 studies, which were designed to evaluate real-world safety and effectiveness of the third- and fourth-generation MitraClip TEER Systems. Subjects were categorized by echocardiographic core laboratory (ECL) assessments into 4 groups according to 30-day MR grade and mean MVG: 1) MR $\leq 1+$ /MVG < 5 mm Hg; 2) MR $\leq 1+$ /MVG ≥ 5 mm Hg; 3) MR $\geq 2+$ /MVG < 5 mm Hg; and 4) MR $\geq 2+$ /MVG ≥ 5 mm Hg.

RESULTS A total of 1,723 subjects had evaluable echocardiograms at 30 days: 72% had MR $\leq 1+$ /MVG < 5 mm Hg, 18% had MR $\leq 1+$ /MVG ≥ 5 mm Hg, 7% had MR $\geq 2+$ /MVG < 5 mm Hg, and 3% had MR $\geq 2+$ /MVG ≥ 5 mm Hg. MR $\leq 1+$ was sustained through 1 year in 93% of patients who achieved 30-day MR $\leq 1+$. MVG decreased from 30 days to 1 year in subjects with MVG ≥ 5 mm Hg (6.7 ± 4.0 to 5.5 ± 2.5 mm Hg MR $\leq 1+$ /MVG ≥ 5 mm Hg and 6.5 ± 1.5 to 5.5 ± 1.7 mm Hg MR $\geq 2+$ /MVG ≥ 5 mm Hg). One-year rates of all-cause mortality and heart failure hospitalization were lower for subjects who achieved MR $\leq 1+$ at 30 days, regardless of MVG.

CONCLUSIONS Reduction of MR to mild or less after M-TEER with the latest-generation MitraClip systems was associated with clinical benefit regardless of MVG. (JACC Cardiovasc Interv. 2024;17:2530-2540) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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Mitral transcatheter edge-to-edge repair (M-TEER) with the MitraClip system (Abbott) is an established therapy for prohibitive surgical risk patients with primary mitral regurgitation (PMR) and/or patients with secondary mitral regurgitation (SMR) despite guideline-directed medical therapy.^{1,2} The M-TEER mechanism of action yields a reduction in mitral valve area (MVA). Accordingly, operators must often balance MR reduction with the degree of iatrogenic mitral stenosis. Intra-procedural assessment of mitral stenosis is variable due to dynamic factors such as heart rate, rhythm, and loading conditions under general anesthesia that may change postprocedurally. Static factors such as left atrial compliance, left ventricular (LV) end-diastolic pressure, and valvular pathologies are important limitations in assessing mitral stenosis.^{3,4} Measurement of mitral valve gradients (MVGs) is the most practical method to assess stenosis due to ease of use and reproducibility compared with planimetry and/or pressure half time-based valve area.^{4,5}

The traditional cutoff defining mitral stenosis has been a mean MVG of ≥ 5 mm Hg.^{6,7} This cutoff was established in a younger population with rheumatic mitral stenosis. However, the prognostic value of this threshold in M-TEER is unclear. There is interest in understanding the balance between MR reduction and residual gradients after M-TEER.⁸⁻¹² While some propose lower gradient cutoffs for elderly populations undergoing M-TEER for fear of harm due to mitral stenosis, others have shown no significant harm of minimally elevated gradients ≥ 5 mm Hg.^{11,12} However, these investigations have been smaller in size and/or without considering the impact of concomitant moderate (2+) or more residual MR. Moreover, the relationship between residual MVG and clinical outcomes may be influenced by the degree of residual MR. Therefore, we explored the associations between MR reduction, residual MVG, and the rates of clinical outcomes in patients undergoing M-TEER as part of a large, prospective, echocardiographic core lab (ECL)-adjudicated study.

METHODS

STUDY DESIGN. EXPANDED (A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices) is a pooled, patient-level cohort of subjects from the EXPAND and EXPAND G4 studies, which are global, real-world studies conducted to evaluate the safety and effectiveness of the MitraClip NTR/XTR System (EXPAND, N = 1,041) and MitraClip G4 System (EXPAND G4, N = 1,164). From 2018 to

2022, 2205 subjects with PMR or SMR were enrolled at 91 centers in the United States, Europe, Canada, Israel, Saudi Arabia, and Japan. Subjects met the inclusion criteria according to the associated protocols and in alignment with regional indications-for-use. Follow-up visits occurred at discharge, 30 days, and 1 year after the M-TEER procedure. Transthoracic and transesophageal echocardiography at baseline and follow-up visits were evaluated by ECL. These studies comply with the latest good clinical practice standards of the Declaration of Helsinki and approved by local ethics committees and applicable competent authorities of participating countries. Study details were described previously.¹³⁻¹⁵

ECHOCARDIOGRAPHIC AND CLINICAL END-POINTS.

Two ECLs were used for this study. MR severity and etiology were assessed by MedStar Health Research Institute (Washington, DC, USA) following the American Society of Echocardiography standards for ECLs.¹⁶ MVG and LV parameters were assessed by the Medical Research Development S.L. (Madrid, Spain) for EXPAND and by MedStar Health Research Institute for EXPAND G4. Mean MVG was measured from continuous wave Doppler of the mitral inflow in diastole by tracing the forward flow contour on 3 consecutive beats, whenever available (5 consecutive beats if the patient was in atrial fibrillation). MVA was measured using the continuity equation in EXPAND and pressure half-time in EXPAND G4.

Clinical outcomes included NYHA functional class, Kansas City Cardiomyopathy Questionnaire Overall Summary score, all-cause mortality, heart failure hospitalization (HFH), and site-reported major adverse events (MAEs) through 1 year. MAEs through 30 days in the EXPAND study were adjudicated by an independent clinical evaluations committee. Single-leaflet device attachment (SLDA) events were assessed by the ECL (MedStar).

ANALYSIS POPULATION. Patients who received ≥ 1 clip and survived to 30 days were categorized into 4 subgroups according to the 30-day MR severity and mean MVG (hereafter referred to as MVG): 1) MR $\leq 1+$ and MVG < 5 mm Hg; 2) MR $\leq 1+$ and MVG ≥ 5 mm Hg; 3) MR $\geq 2+$ and MVG < 5 mm Hg; and 4) MR $\geq 2+$ and MVG ≥ 5 mm Hg.

STATISTICAL ANALYSIS. This was a post hoc analysis. Categorical variables are reported as percentages of available data per subgroup and were compared

ABBREVIATIONS AND ACRONYMS

| | |
|---------------|--|
| ECL | = echocardiographic core laboratory |
| HFH | = heart failure hospitalization |
| LV | = left ventricular |
| M-TEER | = mitral transcatheter edge-to-edge repair |
| MAE | = major adverse event(s) |
| MR | = mitral regurgitation |
| MV | = mitral valve |
| MVA | = mitral valve area |
| MVG | = mitral valve gradient |
| PMR | = primary mitral regurgitation |
| SLDA | = single-leaflet device attachment |
| SMR | = secondary mitral regurgitation |
| TEER | = transcatheter edge-to-edge repair |

using the Fisher exact test or chi-square test. Bowker's test was used for paired nominal data. Continuous variables are reported as mean \pm SD unless otherwise specified and were compared using analysis of variance or Kruskal-Wallis test for nonparametric data. Student's *t*-test was used for paired continuous data. One-year MAE and device-related complications were reported in subjects who had MAEs or did not withdraw prior to the lower limit of the visit window. A landmark analysis was used to calculate all-cause mortality and annualized rates of HFH starting at the 30-day echocardiogram (when subgroups were defined) to 1 year. The Kaplan-Meier method was used to estimate 1-year all-cause mortality with 95% CIs and *P* values from log-rank tests not corrected for multiple comparisons were reported between subgroups. Patients were censored at their last known event-free date. The annualized 1-year HFH rates per patient-year were compared using Poisson regression. Patients with HFH events prior to 30-day echocardiogram were excluded from HFH analysis (*n* = 76). *P* values of 2-sided alpha <0.05 were considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

STUDY POPULATION. Of the 2,205 subjects who underwent an M-TEER procedure, 2,006 (91%) completed a 30-day follow-up visit (**Central Illustration**). At 30 days, 90% (*n* = 1,664 of 1,847 with evaluable 30-day MR) of subjects had MR $\leq 1+$. A 30-day MVG <5 mm Hg was present in 79% (*n* = 1,368 of 1,736 with evaluable 30-day MVG), an MVG ≥ 5 to <8 mm Hg in 17.9% (*n* = 310 of 1,736), and an MVG ≥ 8 mm Hg in 3.4% (*n* = 58 of 1,736). Of the 1,723 subjects who had both an evaluable MR grade and MVG from the 30-day echocardiogram, 1,241 (72%) had MR $\leq 1+$ and MVG <5 mm Hg, 308 (18%) had MR $\leq 1+$ and MVG ≥ 5 mm Hg, 116 (7%) had MR $\geq 2+$ and MVG <5 mm Hg, and 58 (3%) had MR $\geq 2+$ and MVG ≥ 5 mm Hg (**Central Illustration**).

BASELINE CHARACTERISTICS. Baseline characteristics are detailed in **Table 1**. Subjects with 30-day MVG ≥ 5 mm Hg were more often female, regardless of MR, and more frequently had a prior mitral valve (MV) procedure, especially in the MR $\geq 2+$ subgroup. Subjects with 30-day MR $\geq 2+$, regardless of MVG, were more commonly treated for PMR. Baseline LV ejection fractions were higher with elevated MVG and residual MR. The baseline MVG was higher and the MVA smaller in subjects with a 30-day MVG ≥ 5 mm Hg, regardless of MR.

PROCEDURAL OUTCOMES. Subjects with 30-day residual MR $\geq 2+$ had longer device times. The number of clips implanted were similar between subgroups (**Figure 1, Table 2**) The median length of stay in the hospital for U.S subjects was 1 day following the TEER procedure (**Table 2**).

ECHOCARDIOGRAPHIC OUTCOMES. The 30-day MR grade was sustained through 1 year in all subgroups (**Figure 2**). Subjects with 30-day MR $\leq 1+$ had sustained MR $\leq 1+$ (93%; *n* = 753 of 806 MR $\leq 1+$ /MVG <5, *n* = 172 of 185 MR $\leq 1+$ /MVG ≥ 5) at 1 year, regardless of MVG. Of subjects with 30-day 2+ MR that had 1-year MR improvement, 10 subjects had additional M-TEER procedures or surgical replacements, and half were of SMR etiology. MR severity through follow-up in all subjects is shown in **Supplemental Figure 1**.

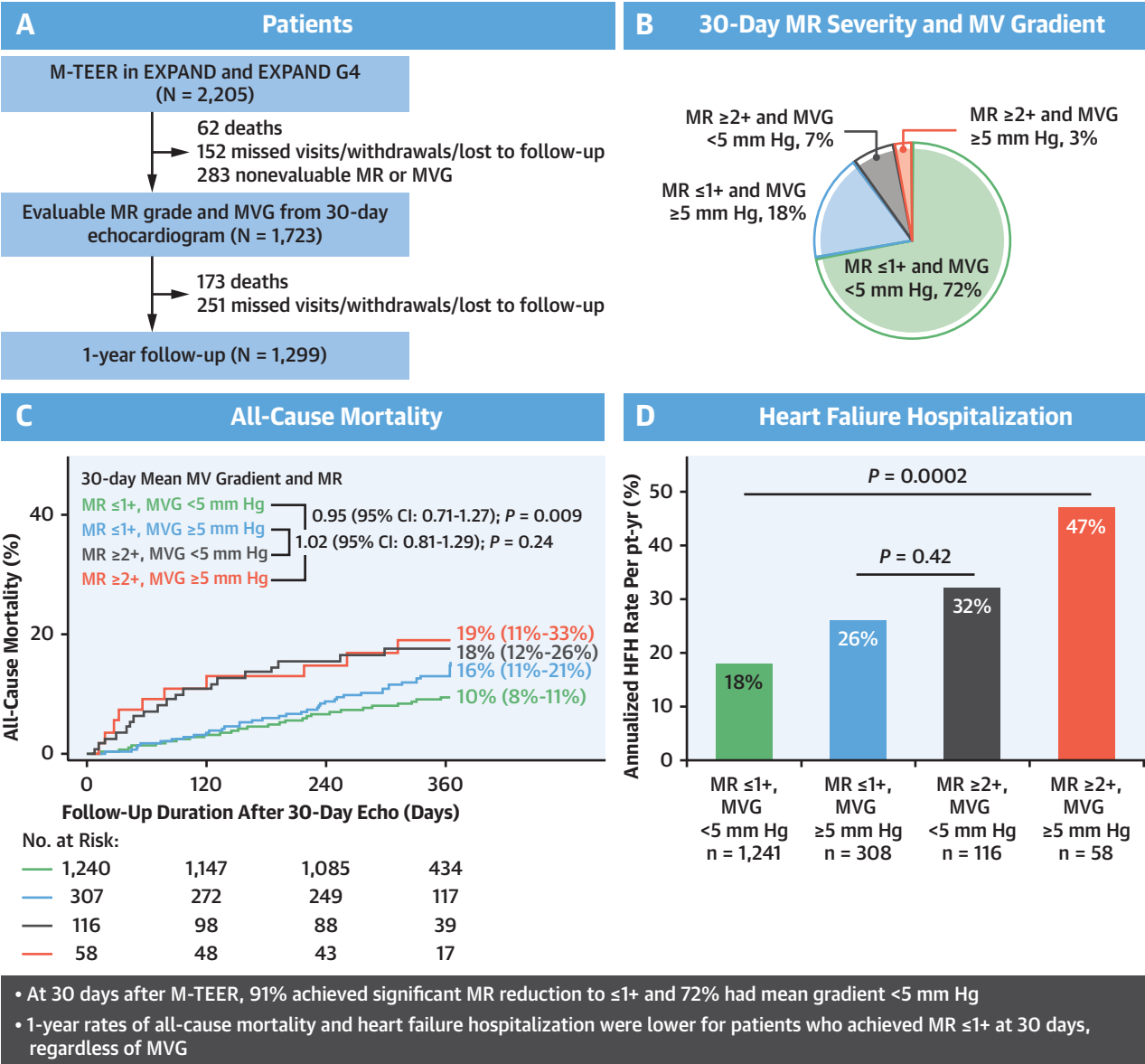
Directional changes in paired ECL-assessed MVG at 30 days and 1 year varied among groups (**Figure 3**). Subjects with MVG <5 mm Hg experienced a small increase in MVG from 30 days to 1 year (MR $\leq 1+$ /MVG <5: 2.9 \pm 1.0 mm Hg to 3.2 \pm 1.9 mm Hg; *P* < 0.0001; MR $\geq 2+$ /MVG <5: 3.0 \pm 0.9 mm Hg to 3.1 \pm 1.5 mm Hg; *P* = 0.34). Subjects with 30-day MVG ≥ 5 mm Hg experienced a significant decrease in MVG at 1 year (MR $\leq 1+$ /MVG ≥ 5 : 6.7 \pm 4.0 mm Hg to 5.5 \pm 2.5 mm Hg; *P* = 0.0003; MR $\geq 2+$ /MVG ≥ 5 : 6.5 \pm 1.5 mm Hg to 5.5 \pm 1.7 mm Hg; *P* = 0.02). This MVG decrease coincided with slight decreases in heart rate (**Supplemental Table 1**). Site-reported mean MVG fluctuated slightly immediately postprocedure to discharge and 30 days for all groups (**Supplemental Table 2**).

CLINICAL OUTCOMES. All-cause mortality and HFH. Subjects with MR $\leq 1+$ had lower 1-year all-cause mortality rates than subjects with MR $\geq 2+$, regardless of MVG (**Central Illustration**). All-cause mortality was significantly lower in the MR $\leq 1+$ /MVG <5 group (10% [95% CI: 8%-11%]) compared with the MR $\geq 2+$ /MVG ≥ 5 group (19% [95% CI: 11%-33%]) (*P* = 0.009). Subjects in the MR $\leq 1+$ /MVG ≥ 5 group had a lower all-cause mortality rate (16% [95% CI: 11%-21%]) than the MR $\geq 2+$ /MVG <5 group (18% [95% CI: 12%-26%]), albeit not significant (*P* = 0.24).

The annualized HFH rate trended upward with increased MR grade followed by elevated MVG (**Central Illustration**). Annualized HFH rate was significantly lower in the MR $\leq 1+$ /MVG <5 group (18%, 172 events per 954.1 patient-years) compared with the MR $\geq 2+$ /MVG ≥ 5 (47%, 17 events per 36.4 patient-years) (*P* = 0.0002). Subjects in the MR $\leq 1+$ /MVG ≥ 5 had a lower HFH rate (26%, 57 events per 217.4 patient-years) than the MR $\geq 2+$ /MVG <5 (32%,

CENTRAL ILLUSTRATION Impact of Postprocedure MR and MVG After M-TEER

EXPANDED: Impact of Postprocedure MR and MVG on Clinical Outcomes After M-TEER, N = 1,723



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(A) In echocardiography core lab-assessed outcomes from the EXPANDED studies, 1723 subjects had an evaluable mitral regurgitation (MR) and mitral valve gradient (MVG) at 30 days. (B) A total of 91% of subjects achieved significant MR reduction to ≤1+ and 72% had a mean MVG <5 mm Hg at 30 days. Subjects with 30-day MR ≤1+ had numerically lower (C) all-cause mortality and (D) annualized heart failure hospitalization rates than MR ≥2+ (P = NS), regardless of MVG. One-year all-cause mortality rates after the 30-day echocardiography reported as Kaplan Meier-estimates (95% CI) with log-rank P values between subgroups. EXPAND = A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices; M-TEER = mitral transcatheter edge-to-edge repair.

TABLE 1 Baseline Characteristics by 30-Day MR and MVG

| | 30-d MR ≤1+ | | 30-d MR ≥2+ | | P Value |
|------------------------------------|--------------------------|------------------------|------------------------|-----------------------|---------|
| | MVG <5 mm Hg (n = 1,241) | MVG ≥5 mm Hg (n = 308) | MVG <5 mm Hg (n = 116) | MVG ≥5 mm Hg (n = 58) | |
| Age, y | 78 ± 9 | 76 ± 11 | 79 ± 10 | 78 ± 11 | 0.07 |
| Female | 41.1 (510/1,241) | 56.2 (173/308) | 41.4 (48/116) | 51.7 (30/58) | <0.0001 |
| BMI, kg/m ² | 25.8 ± 5.4 (1,240) | 27.2 ± 6.1 (308) | 24.2 ± 4.3 (116) | 24.7 ± 5.4 (58) | <0.0001 |
| STS replacement, % | 7.3 ± 5.8 (734) | 8.0 ± 6.8 (191) | 7.0 ± 4.7 (72) | 7.7 ± 4.8 (38) | 0.75 |
| STS repair, % | 5.7 ± 5.8 (823) | 6.6 ± 7.6 (216) | 5.2 ± 4.6 (83) | 5.6 ± 4.8 (42) | 0.63 |
| Atrial fibrillation | 57.6 (712/1,236) | 57.3 (176/307) | 61.2 (71/116) | 63.2 (36/57) | 0.76 |
| Diabetes | 24.9 (307/1,233) | 29.3 (90/307) | 20.2 (23/114) | 17.2 (10/58) | 0.10 |
| Renal failure | 31.3 (386/1,234) | 29.5 (91/308) | 24.3 (28/115) | 21.1 (12/57) | 0.18 |
| Prior mitral valve procedure | 3.5 (44/1,241) | 5.8 (18/308) | 2.6 (3/116) | 15.5 (9/58) | 0.0008 |
| Prior aortic valve procedure | 7.0 (87/1,241) | 14.9 (46/308) | 6.0 (7/116) | 10.3 (6/58) | <0.0001 |
| PMR etiology | 43.9 (460/1,047) | 48.4 (119/246) | 54.0 (54/100) | 59.1 (26/44) | 0.05 |
| EROA, cm ² | 0.3 ± 0.2 (727) | 0.3 ± 0.2 (169) | 0.4 ± 0.2 (74) | 0.4 ± 0.2 (36) | <0.0001 |
| Mitral valve area, cm ² | 4.6 ± 1.6 (760) | 4.4 ± 1.5 (184) | 4.9 ± 1.7 (75) | 4.2 ± 1.1 (37) | 0.03 |
| Mean MVG, mm Hg | 2.1 ± 1.1 (839) | 3.3 ± 1.6 (223) | 2.4 ± 1.3 (77) | 3.5 ± 1.6 (42) | <0.0001 |
| LVEF, % | 49.4 ± 16.0 (862) | 52.5 ± 15.2 (217) | 53.0 ± 16.5 (89) | 58.4 ± 13.3 (41) | 0.0001 |
| LVEDD, cm | 5.5 ± 1.0 (1,059) | 5.3 ± 0.8 (273) | 5.7 ± 0.9 (98) | 5.4 ± 0.9 (51) | 0.0005 |
| LVESD, cm | 4.2 ± 1.2 (1,019) | 3.9 ± 1.1 (267) | 4.2 ± 1.3 (92) | 3.9 ± 1.2 (51) | <0.0001 |
| LVEDVi, mL/m ² | 79.4 ± 35.2 (864) | 70.5 ± 26.8 (221) | 83.2 ± 28.4 (89) | 75.8 ± 39.1 (41) | 0.0008 |
| LVESVi, mL/m ² | 43.4 ± 31.0 (864) | 36.0 ± 24.4 (217) | 42.2 ± 27.2 (90) | 34.4 ± 32.5 (41) | 0.004 |

Values are mean ± SD, %, (n/N), or mean ± SD (n).
 BMI = body mass index; EROA = effective regurgitant orifice area; LVEDD = left ventricular end-diastolic diameter; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESVi = left ventricular end-systolic volume index; MVG = mitral valve gradient; MR = mitral regurgitation; PMR = primary mitral regurgitation; STS = Society of Thoracic Surgeons.

24 events per 75.2 patient-years), albeit not significant ($P = 0.42$).
Functional capacity and quality of life.
 All subjects had significant improvements in NYHA

functional class (Figure 4). In the MR ≤1+/MVG <5 group, 83% (n = 739 of 890) were categorized as NYHA functional class I or II at 1 year compared with 30% (n = 267 of 890) at baseline ($P < 0.0001$). In the

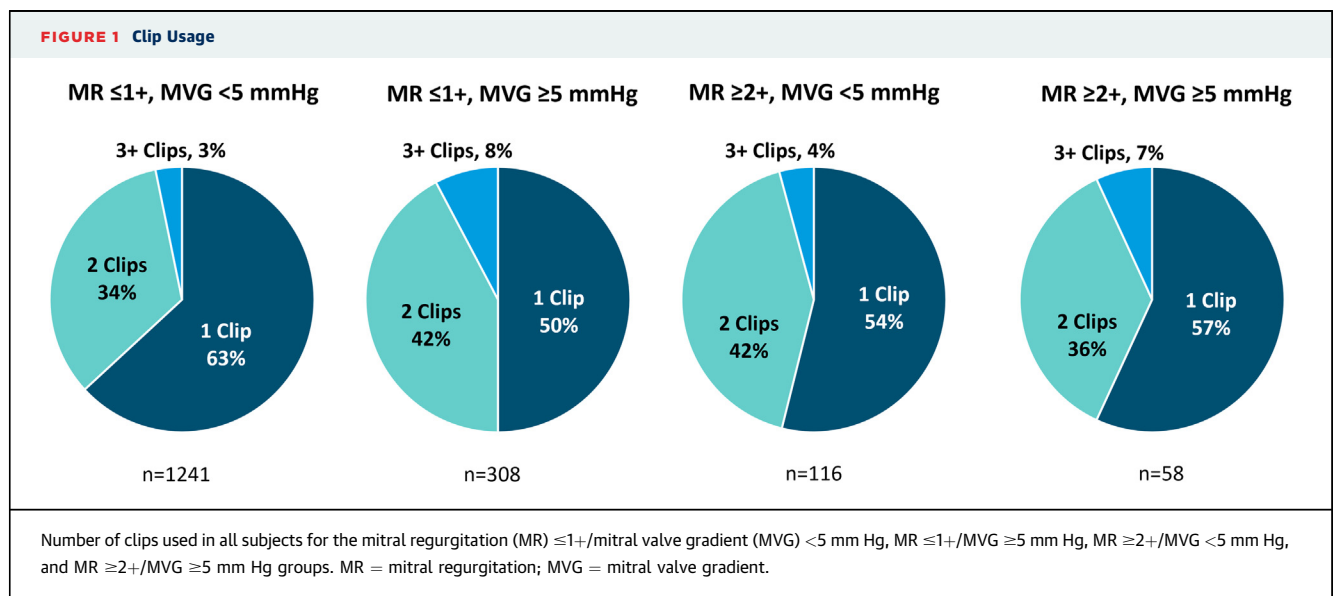


TABLE 2 Procedural Characteristics

| | 30-d MR $\leq 1+$ | | 30-d MR $\geq 2+$ | |
|--|-----------------------------|------------------------------|---------------------------|-----------------------------|
| | MVG < 5 mm Hg (n = 1,241) | MVG ≥ 5 mm Hg (n = 308) | MVG < 5 mm Hg (n = 116) | MVG ≥ 5 mm Hg (n = 58) |
| Procedure time, min | 82 \pm 40 | 91 \pm 46 | 100 \pm 54 | 93 \pm 102 |
| Device time, min | 46 \pm 33 | 51 \pm 40 | 59 \pm 44 | 60 \pm 47 |
| Clips/subject | 1.4 \pm 0.6 | 1.5 \pm 0.6 | 1.6 \pm 0.7 | 1.5 \pm 0.6 |
| Length of stay in hospital for index procedure (U.S. subjects only), d | 1 (1-2) (544) | 1 (1-2) (189) | 1 (1-3) (60) | 1 (1-2) (38) |

Values are mean \pm SD or median (Q1-Q3) (n).
 Abbreviations as in Table 1.

MR $\leq 1+$ /MVG ≥ 5 and MR $\geq 2+$ /MVG < 5 groups, 79% (n = 159 of 201 MR $\leq 1+$ /MVG ≥ 5 , n = 55 of 70 MR $\geq 2+$ /MVG < 5) were categorized as NYHA functional class I or II at 1 year compared with 34% (n = 69 of 201) and 30% (n = 21 of 70) at baseline, respectively (P < 0.0001). Similarly, 75% (n = 24 of 32) of subjects in the MR $\geq 2+$ /MVG ≥ 5 were in NYHA functional class I or II at 1 year compared with 22% (n = 7 of 32) at baseline (P = 0.003).

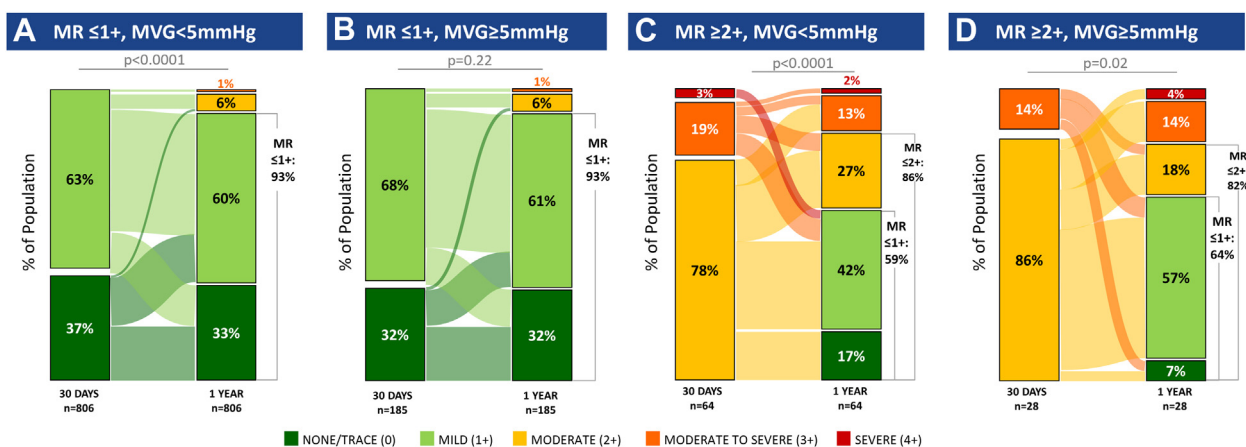
Subjects in all groups had significant improvements in Kansas City Cardiomyopathy Questionnaire Overall Summary score (Figure 5). In the MR $\leq 1+$ /MVG < 5 group, there was a +21 \pm 25-point increase at 1 year (P < 0.0001). In the MR $\leq 1+$ /MVG ≥ 5 , MR $\geq 2+$ /MVG < 5 , and MR $\geq 2+$ /MVG ≥ 5 groups, there were increases of +15 \pm 25 (P < 0.0001), +15 \pm 27 (P < 0.0001), and +14 \pm 25 (P = 0.005) points from baseline to 1 year.

SAFETY OUTCOMES. One-year MAEs are shown in Table 3. Stroke and myocardial infarction rates were <1.8% for all groups. MV replacement occurred in 8.6% (n = 5 of 58) of subjects in the MR $\geq 2+$ /MVG ≥ 5 group; residual severe MR with an SLDA was identified in 4 of these subjects. SLDA events were 0.7% in the MR $\leq 1+$ /MVG < 5 mm Hg (n = 8 of 1,222) and 0.6% in the MR $\leq 1+$ /MVG ≥ 5 mm Hg (n = 2 of 301) groups and were numerically higher in the MR $\geq 2+$ /MVG < 5 mm Hg (4.4% [n = 5 of 114]) and MR $\geq 2+$ /MVG ≥ 5 mm Hg (6.9% [n = 4 of 58]) groups.

DISCUSSION

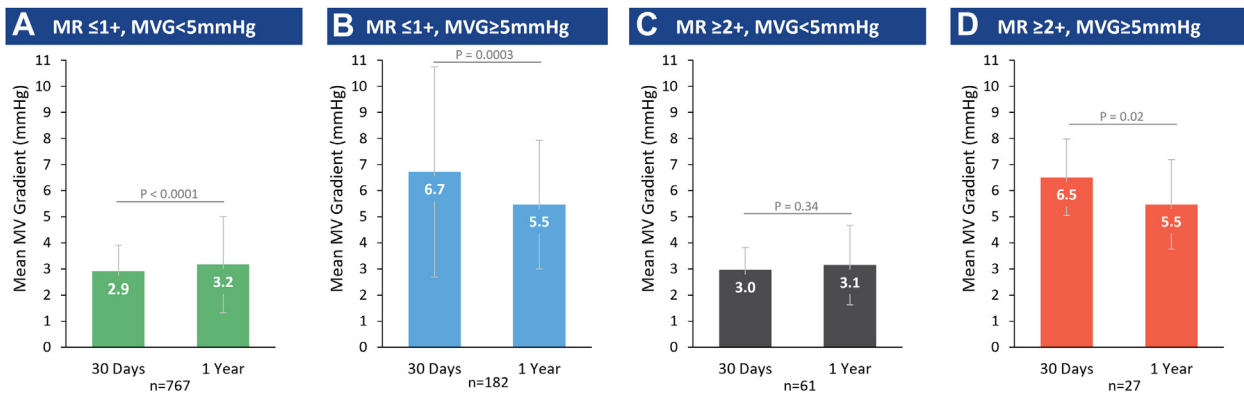
The major findings of this analysis of a large prospective registry of contemporary M-TEER are that: 1) 90% of patients undergoing the procedure with the third or fourth-generation MitraClip system achieved

FIGURE 2 Echocardiography Core Lab-Assessed MR Reduction



Sankey diagrams of echocardiography core lab-assessed MR severity from 30-day to 1-year echocardiography for subjects with 30-day (A) MR $\leq 1+$ /MVG < 5 mm Hg, (B) MR $\leq 1+$ /MVG ≥ 5 mm Hg, (C) MR $\geq 2+$ /MVG < 5 mm Hg, and (D) MR $\geq 2+$ /MVG ≥ 5 mm Hg. Abbreviations as in Figure 1.

FIGURE 3 Echocardiography Core Lab-Assessed Mean Mitral Valve Gradient



Paired change in echocardiography core lab-assessed mean MVG from 30-day to 1-year echocardiography for subjects with 30-day (A) MR ≤1+/MVG <5 mm Hg, (B) MR ≤1+/MVG ≥5 mm Hg, (C) MR ≥2+/MVG <5 mm Hg, and (D) MR ≥2+/MVG ≥5 mm Hg. Values represented as mean ± SD. Abbreviations as in Figures 1 and 2.

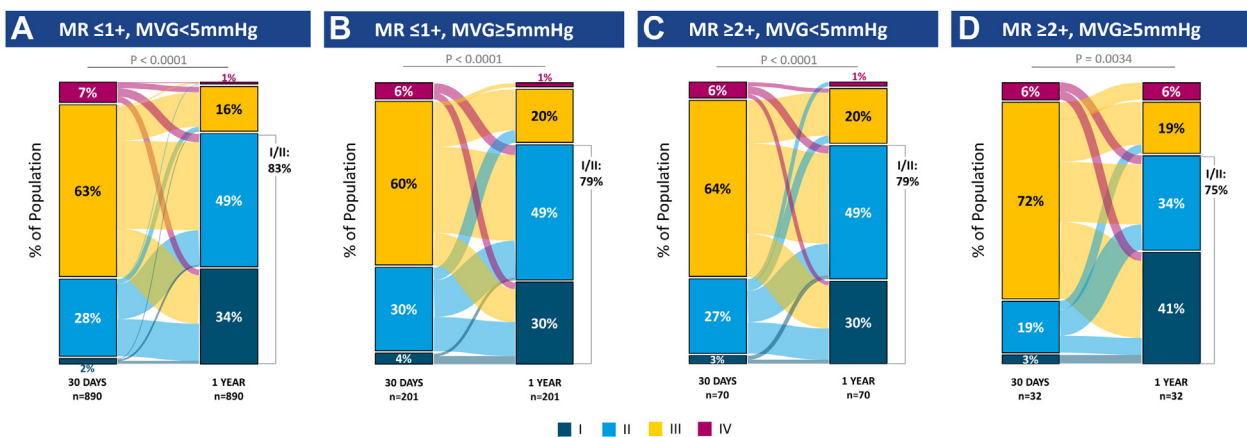
a final MR grade of ≤1+, which was sustained through 1-year follow-up; and 2) those patients with MR grade ≤1+ had the lowest 1-year mortality and HFH rates irrespective of residual gradient.

TARGETING post-M-TEER GRADE OF ≤1+. Traditionally, the goal of M-TEER therapy has been to implant a single device and reduce MR to ≤2+. However, this goal was set in the early days of M-TEER when implantation techniques and intra-procedural imaging were in their infancy. Furthermore, the approved M-TEER population was elderly

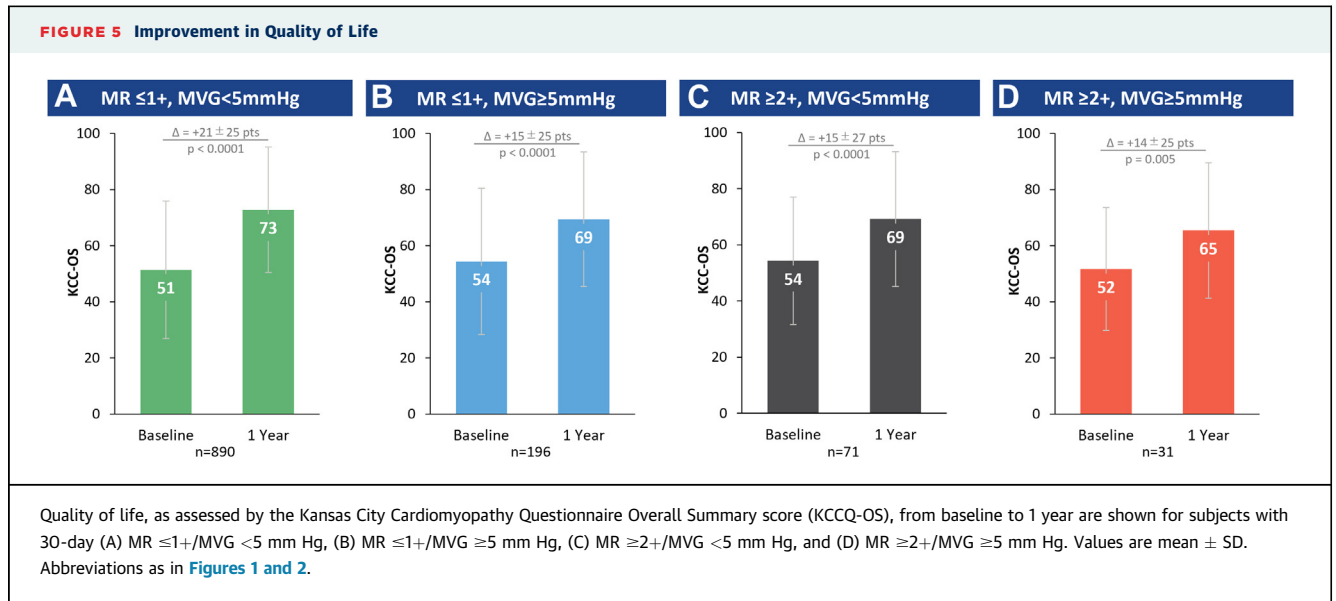
and comorbid where MR 2+ was satisfactory.¹⁷ With evolution of the implant system, improvements in imaging, and increasing clinical and technical experience, we have seen improvement in our ability to achieve lower MR grade for PMR and SMR. From 2005 to 2015, rates of MR ≤1+ ranged from 49% to 55%.^{1,17-20} However, recent studies have reported MR ≤1+ in 89% to 93%, including data from the present investigation.¹³⁻¹⁵

Many now appreciate that 2+ MR might be considered a successful procedure but in some patients may lead to more recurrent MR, worsened

FIGURE 4 Change in Functional Capacity from Baseline to 1-Year Follow-Up



Sankey diagrams of NYHA functional class from baseline to the 1-year follow-up visit for subjects with 30-day (A) MR ≤1+/MVG <5 mm Hg, (B) MR ≤1+/MVG ≥5 mm Hg, (C) MR ≥2+/MVG <5 mm Hg, and (D) MR ≥2+/MVG ≥5 mm Hg. Abbreviations as in Figure 1.



functional class, and increased long-term mortality/HFH.⁹ While some patients with residual MR had improvements in MR at 1 year, this was attributed to additional MV reintervention or the dynamic nature of SMR. If clinical and anatomic parameters allow, implanters should consider targeting a final MR grade of ≤1+. The magnitude of MR reduction is important for better short- and long-term outcomes, as it may increase the durability of M-TEER in PMR and improve favorable hemodynamics and remodeling in SMR.^{21,22} In this analysis, of those with 30-day MR ≤1+, 93% had sustained MR ≤1+ at 1 year, irrespective of the residual gradient, and exhibited better 1-year survival and HFH compared with those with higher residual MR (≥2+), consistent with contemporary investigations.

CLINICAL DATA EVALUATING ROLE OF ELEVATED GRADIENTS POST-M-TEER. Targeting a post-procedure MR grade of 1+ should be the treatment goal for patients with suitable anatomies, lower gradients, and larger MVAs. A total of 72% of this study cohort had this phenotype with a 30-day MR ≤1+ and MVG <5 mm Hg. Nearly all patients had sustained MR reduction at 1 year in a matched analysis and low 1-year mortality and HFH rates. A more challenging scenario arises when patients have significant MR but slightly higher baseline gradients and/or smaller MVAs. In these scenarios, more clips may be needed to reduce MR to ≤1+ at the expense of a modest elevation in MVG. To date, outcomes in patients with elevated MVG after M-TEER are mixed and likely related to variable residual MR with higher gradients, a broad

TABLE 3 AEs Through 1 Year

| | 30-d MR ≤1+ | | 30-d MR ≥2+ | |
|----------------------------------|-----------------------------|---------------------------|---------------------------|--------------------------|
| | MVG <5 mm Hg (n = 1,222) | MVG ≥5 mm Hg (n = 301) | MVG <5 mm Hg (n = 114) | MVG ≥5 mm Hg (n = 58) |
| All-cause mortality ^a | 10 (8-11) | 16 (11-21) | 18 (12-26) | 19 (11-33) |
| Stroke | 1.1 (14) | 1.3 (4) | 1.7 (2) | 0.0 (0) |
| Myocardial infarction | 1.4 (17) | 1.3 (4) | 0.9 (1) | 1.7 (1) |
| Mitral valve replacement | 0.7 (9) | 2.3 (7) | 0.9 (1) | 8.6 (5) |
| SLDA | 0.7 (8) | 0.6 (2) | 4.3 (5) | 6.9 (4) |

Values are % (95% CI) or % (n). Subjects terminated from the study prior to the lower limit of the 1-year visit window without any reported AEs were excluded from the denominator. ^aKaplan-Meier estimate of all-cause mortality after the 30-day echocardiography visit.
 AE = adverse event(s); SLDA = single leaflet device attachment; other abbreviations as in Table 1.

range of gradient categories, evaluation of gradients during abnormal loading conditions (eg, under general anesthesia or immediately postprocedure), and/or inconsistent and clinically unreasonable definitions of elevated gradients post-M-TEER.

Recent guideline and consortium statements recommend avoiding post-M-TEER gradients >5 mm Hg.^{6,7} This recommendation is based on younger, healthier patients with rheumatic heart disease and/or those with postsurgical repair. Though postsurgical patients with PMR and elevated gradients are at risk of adverse clinical outcomes,^{23,24,25} surgical repair involves more valvular manipulation than M-TEER. In surgical repair of PMR, patients are younger, redundant leaflets can be resected, chordal repair can immobilize leaflet segments, and almost all receive an annuloplasty ring or band, which immobilizes the annulus. In surgical repair of SMR, patients often receive an undersized annuloplasty ring. These anatomic and physiologic changes in the setting of elevated gradients in younger patients may contribute to less favorable outcomes in surgery.²⁵ Contrastingly, an M-TEER procedure achieves edge-to-edge approximation with only partial acute and long-term annular reduction with preserved annular motion. This impact on the mitral apparatus function postsurgical repair vs M-TEER may explain the differing outcomes with elevated gradients treated via two differing repair approaches.

Higher gradients in patients undergoing M-TEER must undergo better characterization rather than a binary cutoff. In this study, an elevated gradient is predominantly considered to be an MVG of 5 to 7 mm Hg, in-line with other investigations of moderately elevated gradients post-M-TEER. Patients with higher gradients in this investigation had very few (3%) gradients of ≥ 8 mm Hg. Outcomes highlight that a modestly elevated post-M-TEER gradient (5-7 mm Hg) in the context of MR $\leq 1+$ was associated with 1-year mortality and HFH rates statistically similar to those with lower gradients and similar MR reduction. Though these outcomes may be driven by comorbidities contributing to higher adverse event rates, these results are consistent with other studies. A previous study had consistent observations with a 1-year HFH rate of 10% in those with MR $\leq 1+$ and MVG ≥ 5 mm Hg vs $\sim 30\%$ in those with MR $2+$, irrespective of residual gradient.¹¹ In the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) 25% of SMR patients treated with first-generation M-TEER had an MVG ≥ 5 mm Hg (mean 7.25 mm Hg) and showed similar rates of mortality and HFH compared

with those with lower gradients.¹² Another study stratified PMR patients by postimplantation MVG quartiles (highest quartile 6.0 ± 1.2 mm Hg with $\sim 75\%$ MR $\leq 1+$) and found no differences in 2-year mortality and HFH by quartile and no association of elevated gradients to all-cause mortality/HFH by multivariate analyses.²⁶ These studies continue to support the notion that MR reduction outweighs the hypothesized detrimental effects of mildly elevated gradients of 5 to 7 mm Hg in appropriately selected patients.

However, others have shown conflicting findings with adverse outcomes in those with elevated gradients post-M-TEER. One series ($n = 713$) found that MVG ≥ 5 mm Hg was an independent predictor of mortality and HFH after multivariate adjustment in PMR, but not SMR. However, those PMR patients with elevated gradients had $\leq 1+$ MR in only 49% and 40% at 30 days and 2 years.²⁷ In a multicenter European series ($n = 215$), an elevated MVG (>4.4 mm Hg) in PMR, but not SMR, was associated with adverse outcomes; in the entire cohort, residual MR, though not sustained through follow-up, was predictive of adverse outcomes but not an elevated MVG.⁹ Similarly, a single-center European study ($n = 268$) showed increased adverse event rates in patients with postimplantation MVG ≥ 5 mm Hg.⁸ However, the combined endpoint of death, surgical MV replacement, and LV assist device was lowest in MR $1+$ patients, irrespective of MVG.

GROUPING BASED ON 30-DAY MR AND MVG AND INTRAPROCEDURAL DECISION MAKING. The current investigation evaluates outcomes based on 30-day MVG as this may serve as a better predictor for long-term outcomes than intraprocedural and/or discharge MVG in which patients are under general anesthesia with different loading conditions or are in an abnormal hemodynamic state after extubation. Postoperative transthoracic echocardiograms are often obtained when patients are not fully on outpatient medications. Previous studies showed variation between intraprocedural and discharge measurements; MVG in one series at discharge increased in 36%, decreased in 26%, and remained unchanged in 38% of patients undergoing M-TEER.²⁷ Reductions in follow-up gradients (median 600 days) after surgical repair has also been observed.²⁸ In our investigation, all groups exhibited nonsignificant but numerical elevation in MVG from intraprocedural transesophageal echocardiography to discharge and 30-day transthoracic echocardiograms.

The data presented here suggests prioritization of MR elimination over modest MVG elevation in

carefully selected patients. As MVG can be dynamic from procedure to discharge and beyond due to heart rate, exercise, and imaging, slight elevation of MVG past the traditional 5 mm Hg threshold may be acceptable. Other anatomic and/or hemodynamic markers of stenosis in addition to MR reduction may be better at predicting long-term outcomes; however, interobserver variability should be considered when evaluating potential hemodynamic measures. In this study, 1-year outcomes demonstrate that MR reduction to $\leq 1+$ is associated with improved clinical outcomes, regardless of MVG. Longer-term outcomes are needed to confirm these findings.

STUDY LIMITATIONS. In the EXPANDED studies, a large majority of patients had optimal results with MR $\leq 1+$ and MVG < 5 mm Hg and few patients had elevated MVGs, limiting the sample size of the subgroups. Subject inclusion was determined based on site selection using a heart team assessment of clinically significant MR from clinical findings and echocardiography images and treated by experienced operators from relatively higher-volume centers, and thus may not represent the clinical experience at all centers. In EXPANDED, MVG was assessed by 2 separate ECLs, which may contribute to variability among measurements. However, MVG is known to fluctuate with day-to-day activities and heart rate, and paired analyses were used to capture these changes. MVA was measured differently in the EXPAND vs EXPAND G4 studies with the continuity equation in the EXPAND study and pressure half-time in the EXPAND G4 study.

CONCLUSIONS

This large contemporary, prospective study of patients undergoing M-TEER demonstrated that a high proportion of patients can undergo the procedure with a goal of reducing MR to $\leq 1+$. The most favorable outcomes of reduced mortality and HFH were seen in those that were able to achieve MR grades of $\leq 1+$, suggesting that elimination of MR may be prioritized at the expense of modest elevation of MVG in carefully selected patients. Further studies are needed to evaluate long-term outcomes of patients with modestly increased MVG after TEER.

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PERSPECTIVES

WHAT IS KNOWN? Increased MVG and residual MR after M-TEER are 2 factors independently associated with poorer outcomes in patients treated with earlier TEER device generations.

WHAT IS NEW? An analysis on the combined impact of MVG and residual MR from the 1-year echocardiography core lab-assessed outcomes from the EXPANDED dataset found that reduction of MR to $\leq 1+$ was associated with improvements in functional capacity and decreased risk of death, regardless of gradient.

WHAT IS NEXT? TEER operators should consider the balance of additional clip placement to reduce MR, which may result in a higher MVG but improve functional and clinical outcomes through 1 year.

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KEY WORDS MitraClip, mitral regurgitation, mitral valve gradient, mitral valve repair

APPENDIX For a supplemental figure and tables, please see the online version of this paper.