JACC: CARDIOVASCULAR INTERVENTIONS VOL. 16, NO. 21, 2023

NEW RESEARCH PAPER

STRUCTURAL

1-Year Outcomes With Fourth-Generation Mitral Valve Transcatheter Edge-to-Edge Repair From the EXPAND G4 Study

Ralph Stephan von Bardeleben, MD,[a] Paul Mahoney, MD,[b] M. Andrew Morse, MD,[c] Matthew J. Price, MD,[d] Paolo Denti, MD,[e] Francesco Maisano, MD,[e] Jason H. Rogers, MD,[f] Michael Rinaldi, MD,[g] Federico De Marco, MD,[h] William Rollefson, MD,[i] Bassem Chehab, MD,[j] Mathew Williams, MD,[k] Guillaume Leurent, MD,[l] Federico M. Asch, MD,[m] Evelio Rodriguez, MD[c]

ABSTRACT

BACKGROUND The fourth-generation mitral transcatheter edge-to-edge repair (M-TEER) device introduced an improved clip deployment sequence, independent leaflet grasping, and 2 wider clip sizes to tailor the treatment of patients with mitral regurgitation (MR) for a broad range of anatomies. The 30-day safety and effectiveness of the fourth-generation M-TEER device were previously demonstrated.

OBJECTIVES The aim of this study was to evaluate 1-year outcomes in a contemporary, real-world cohort of subjects treated with the MitraClip G4 system.

METHODS EXPAND G4 is an ongoing prospective, multicenter, international, single-arm study that enrolled subjects with primary and secondary MR. One-year outcomes included MR severity (echocardiographic core laboratory assessed), heart failure hospitalization, all-cause mortality, functional capacity (NYHA functional class), and quality of life (Kansas City Cardiomyopathy Questionnaire).

RESULTS A total of 1,164 subjects underwent M-TEER from 2020 to 2022. At 1 year, there was a durable reduction in MR to mild or less in 92.6% and to none or trace in 44.2% ($P < 0.0001$ vs baseline). Few subjects had major adverse events through 1 year (<2% for myocardial infarction, surgical reintervention, or single-leaflet device attachment). The 1-year Kaplan-Meier estimates for all-cause mortality and heart failure hospitalization were 12.3% and 16.9%. Significant improvements in functional capacity (NYHA functional class I or II in 82%; $P < 0.0001$ vs baseline) and quality of life (18.5-point Kansas City Cardiomyopathy Questionnaire overall summary score improvement; $P < 0.0001$) were observed.

CONCLUSIONS M-TEER with the fourth-generation M-TEER device was safe and effective at 1 year, with durable reductions in MR severity to ≤1+ in more than 90% of patients and concomitant improvements in functional status and quality of life. (J Am Coll Cardiol Intv 2023;16:2600-2610) © 2023 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the [a]Department of Cardiology, University Medical Center of Mainz, Mainz, Germany; [b]University of Pittsburgh Medical Center Heart and Vascular Institute, Pittsburgh, Pennsylvania, USA; [c]Ascension Saint Thomas, Nashville, Tennessee, USA; [d]Division of Cardiovascular Diseases, Scripps Clinic, La Jolla, California, USA; [e]San Raffaele University Hospital, Milan, Italy; [f]University of California Davis Medical Center, Sacramento, California, USA; [g]Sanger Heart and Vascular Institute of Cardiothoracic Surgery, Charlotte, North Carolina, USA; [h]Centro Cardiologico Monzino IRCCS, Milan, Italy; [i]Arkansas Heart Hospital, Little Rock, Arkansas, USA; [j]Ascension Via Christi, Wichita, Kansas, USA; [k]Heart Valve Center, New York University Langone Health, New York, New York, USA; [l]Centre Hospitalier Universitaire de Rennes, Rennes, France; and the [m]Cardiovascular Core Laboratories, MedStar Health Research Institute, Washington, District of Columbia, USA.

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.

Manuscript received August 15, 2023; revised manuscript received September 26, 2023, accepted September 26, 2023.

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2023.09.029

The MitraClip system (Abbott) is the first mitral valve (MV) transcatheter edge-to-edge repair (M-TEER) therapy commercially available in the United States and Europe for the treatment of patients with primary (degenerative) mitral regurgitation (PMR) and secondary (functional) mitral regurgitation (SMR).[1] Over the past 20 years, the MitraClip therapy has demonstrated efficacy and safety in numerous clinical studies, with more than 200,000 patients treated worldwide.[2-10] Since the approval of the MitraClip therapy, other M-TEER devices have become commercially available.[11,12]

Each design iteration of the MitraClip system has led to improved ease of use, better clinical outcomes, and increased patient suitability with minimal risks.[13] The safety and effectiveness of early-generation M-TEER devices were demonstrated in historical trials and registries such as the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II trial,[3] TRAMI (Transcatheter Mitral Valve Interventions) registry,[14] COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial,[5] and TCVT (Transcatheter Valve Treatment Sentinel Pilot Registry).[15] In the third-generation M-TEER device, a more precise and predictable delivery system and longer clip arms (XTR) improved ease of use, allowed the treatment of broader anatomies, and demonstrated improved outcomes in the real-world EXPAND study[13] over first-generation devices.

The current fourth-generation M-TEER device, the MitraClip G4 system, introduced independent and controlled gripper actuation, an improved clip deployment system, and 2 additional wider (6-mm) clip sizes with 9-mm (NTW) and 12-mm (XTW) arm lengths. With 4 available clip sizes, treatment can be tailored to a broad range of valve anatomies, including those that were not originally considered suitable for M-TEER.[16]

The EXPAND G4 study was designed to confirm the safety and effectiveness of the MitraClip G4 system in a contemporary, real-world setting for subjects with PMR or SMR. A previous report of 30-day outcomes demonstrated low all-cause mortality (1.3%), significant mitral regurgitation (MR) reduction (91% MR ≤1+), and improvements in functional status and quality of life.[17] Longer term outcomes with the fourth-generation M-TEER device have not been reported. Here, we provide a 1-year update of outcomes among the 1,164 subjects in EXPAND G4, the largest echocardiography core laboratory (ECL)-assessed study to date of fourth-generation M-TEER.

METHODS

STUDY DESIGN AND SUBJECT COHORT. EXPAND G4 is an ongoing prospective, multicenter, single-arm, postmarket observational study to evaluate the safety and performance of the MitraClip G4 system in subjects with PMR or SMR. Inclusion and exclusion criteria were minimal to reflect real-world use of the study device. This study enrolled 1,164 subjects from 60 centers in the United States, Canada, Europe, and Japan, divided into 2 phases. In phase I, 101 U.S. subjects were followed through 30 days to assess early experience with the fourth-generation M-TEER device. In phase II, 1,063 subjects were followed at discharge, 30 days, and annually through 5 years. Centers were required to have experience in interventional cardiology and/or the MitraClip procedure, with approximately one-half of all centers having performed >300 MitraClip procedures before enrollment. Additional details of the study were previously described.[17] At the time of the present analysis, all available data through the 1-year follow-up were reported on the basis of data extracted on June 21, 2023.

The EXPAND G4 study complies with the latest standards of good clinical practice in the Declaration of Helsinki and was approved by the local or central ethics committees and the applicable competent authorities of the countries involved, depending on national requirements. All subjects provided written informed consent. The study is registered at ClinicalTrials.gov (NCT04177394).

ECHOCARDIOGRAPHIC ASSESSMENTS. All echocardiograms were evaluated by a single independent ECL, according to the American Society of Echocardiography standards for ECLs.[18] ECL assessments were performed on transthoracic and transesophageal echocardiograms at baseline, discharge, 30 days, and 1 year. Echocardiographic outcomes included MR severity grade, MV gradients, left ventricular (LV) volumes, LV ejection fraction (LVEF), and forward stroke volume. A subgroup of patients with complex MV anatomy was defined by ECL assessment of baseline MR ≥ 3+ and at least 1 of the following characteristics observed on the baseline transesophageal echocardiogram: 1) primary MR jet outside the A2-P2 coaptation zone; 2) presence of a secondary jet; 3) a wide MR jet requiring multiple NT clips to correct; 4) MV area <4 cm^2; 5) mitral annular

ABBREVIATIONS AND ACRONYMS

ECL = echocardiography core laboratory

GDMT = guideline-directed medical therapy

HFH = heart failure hospitalization

KCCQ = Kansas City Cardiomyopathy Questionnaire

LV = left ventricular

LVEF = left ventricular ejection fraction

MAE = major adverse event(s)

MR = mitral regurgitation

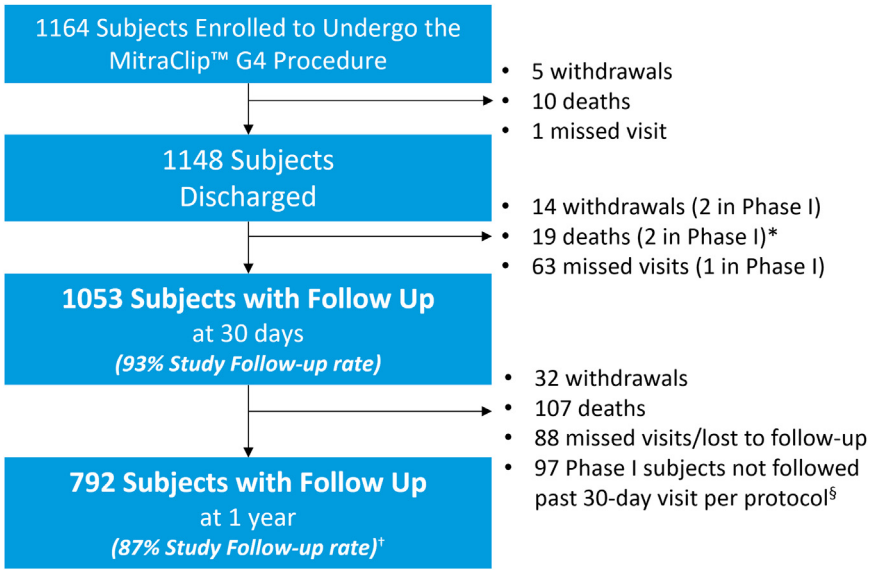
M-TEER = mitral valve transcatheter edge-to-edge repair

MV = mitral valve

PMR = primary (degenerative) mitral regurgitation

SMR = secondary (functional) mitral regurgitation

FIGURE 1 Study Population



Subject enrollment, follow-up visits, and events at discharge, 30 days, and 1 year within the visit windows (1 year window, −30 to +90 days) are shown. *1 patient completed a 30-day visit but died before discharge. †The 1-year follow-up rate was based on the 1,063 phase II subjects who were followed through 5 years. §1 phase I subject died after the 30-day visit.

or leaflet calcification; 6) minimal leaflet tissue (coaptation length <2 mm); 7) severely degenerative leaflets or wide flail gaps (>10 mm) or widths (>15 mm); 8) the presence of a significant cleft or scallop; and 9) bileaflet flail or prolapse.

CLINICAL OUTCOMES. Clinical outcomes included all-cause mortality, heart failure hospitalization (HFH), and the composite of all-cause mortality or HFH through 1 year. Additional clinical evaluations included: 1) functional status assessed using the NYHA functional classification; and 2) quality of life assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score.

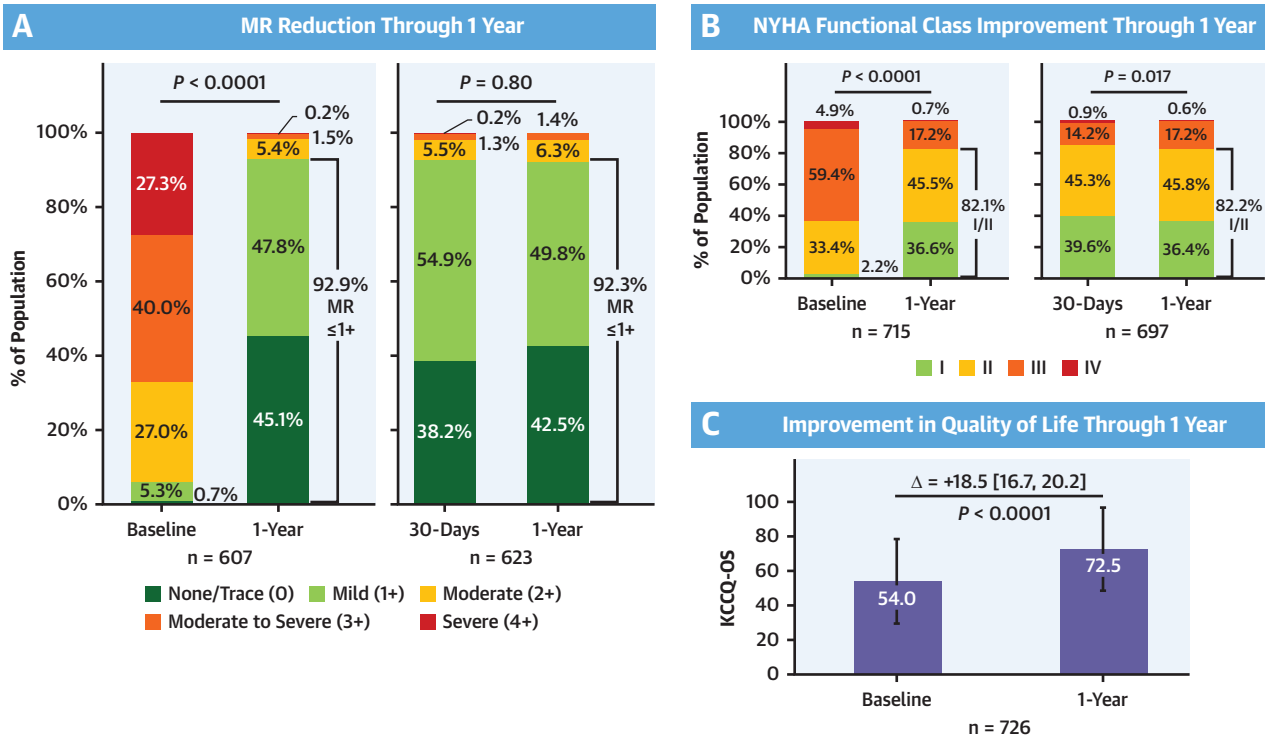
SAFETY OUTCOMES. Safety outcomes included major adverse events (MAE) reported by the site, including mortality, myocardial infarction, stroke, and MV surgical reintervention through 1 year. Leaflet adverse events through 1 year were assessed by the ECL and included single-leaflet device attachment events, leaflet damage, and chordal entrapment.

STATISTICAL ANALYSIS. Categorical variables were compared using the Fisher exact test, and the Bowker test was applied for paired nominal data. Continuous variables were compared using Student's *t*-test. The Kaplan-Meier method was used to estimate all-cause mortality, HFH, and the composite of all-cause mortality or HFH at 1 year with 95% CIs and *P* values from log-rank tests between subjects with PMR and those with SMR. Patients were censored at their last known event-free date. MAE and device-related complications were reported in subjects who had adverse events or did not withdraw from the study prior to the lower limit of the visit window. Changes in KCCQ overall summary score and LV volumes from baseline to later intervals were tested using a paired Student's *t*-test. All analyses were performed on the attempted-procedure population, and missing data were excluded. Outcomes by MR etiology were evaluated by categorizing subjects with PMR or mixed mechanisms (hereafter referred to as PMR) and those with SMR. *P* values of 2-sided alpha <0.05 were considered to indicate statistical significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

STUDY POPULATION AND FOLLOW-UP. A total of 1,164 subjects were enrolled and underwent attempted MitraClip G4 procedures in the EXPAND G4 study from January 21, 2020, to February 4, 2022. The 1-year follow-up rate was 87%. Details of the study population are shown in Figure 1.

CENTRAL ILLUSTRATION **1-Year Outcomes of the EXPAND G4 Study With the MitraClip G4 System**



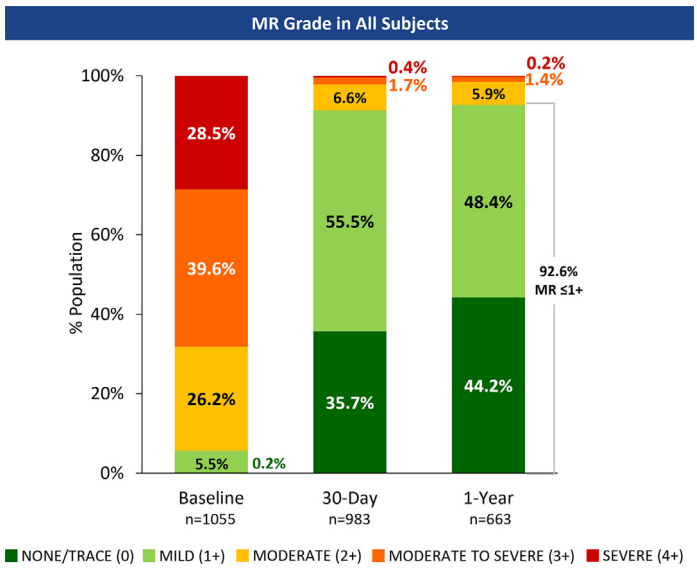
von Bardeleben RS, et al. J Am Coll Cardiol Intv. 2023;16(21):2600-2610.

The EXPAND G4 study was conducted to assess the safety and effectiveness of the fourth-generation mitral transcatheter edge-to-edge repair device in a contemporary, real-world setting. EXPAND G4 showed significant echocardiography core laboratory-assessed mitral regurgitation (MR) reduction to ≤1+ from baseline to 1 year, with sustained reduction from 30 days to 1 year in a paired analysis (A). Through 1 year, there were significant improvements in NYHA functional class to functional class I or II (B) and quality of life assessed using the Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS) score (C).

Baseline characteristics were previously presented (Supplemental Table 1).[17] The cohort included 43.0% of subjects with PMR and 8.1% of subjects with baseline tricuspid regurgitation severity ≥3+. Supplemental Table 2 summarizes the baseline characteristics of subjects stratified by type of clip implanted. Baseline characteristics of subjects who did not complete 1-year follow-up visits are listed in Supplemental Table 3. These characteristics reflect the patients who died prior to 1 year (Supplemental Table 4). Guideline-directed medical therapy (GDMT) use in subjects with SMR is summarized in Supplemental Table 5.

ECHOCARDIOGRAPHIC OUTCOMES. MR reduction. At 1 year, 92.9% of subjects achieved mild or less (≤1+) MR, and 45.1% achieved none or trace (0+) MR ($P < 0.0001$ vs baseline) in a paired analysis (n = 607) from baseline to 1 year. The rate of MR ≤1+ did not change significantly between 30 days and 1 year ($P = 0.80$; n = 623) (**Central Illustration A**). Differences in the number of subjects between the paired analyses can be attributed to nonevaluable or missing transthoracic echocardiographic images. An unpaired analysis of MR reduction showed similar outcomes, with 92.6% of all subjects achieving MR ≤ 1+ at 1 year (**Figure 2**). Among subjects with PMR, 90.1% demonstrated MR ≤ 1+ at 30 days and 88.8% achieved MR ≤1+ at 1 year (**Figure 3A**), with a similar, significant reduction in MR ($P < 0.0001$) that was sustained from 30 days to 1 year ($P = 0.29$) in a paired analysis (**Figure 3B**). For subjects with SMR, 93.1% demonstrated MR ≤ 1+ at 30 days and 95.3% achieved MR ≤1+ at 1 year (**Figure 3C**), with a similar, significant reduction in MR ($P < 0.0001$) that was sustained from 30 days to 1 year ($P = 1.00$) in a paired analysis (**Figure 3D**). In subjects with complex MV anatomies, MR reduction to ≤1+ was achieved in 90.3% at 1 year

FIGURE 2 MR Reduction in All Subjects



Mitral regurgitation (MR) severity, assessed by the echocardiography core laboratory, is shown in all subjects at baseline, 30 days, and 1 year.

(Figure 4A), with similar changes in a paired analyses ($P < 0.0001$), and sustained from 30 days to 1 year ($P = 0.75$) (Figure 4B). MR reduction by baseline MR grade is reported in Supplemental Table 6. MR reduction at 1 year to ≤1+ was achieved in 96.5% and 91.2% of subjects with ECL-assessed baseline MR severity of ≤2+ and ≥3+, respectively.

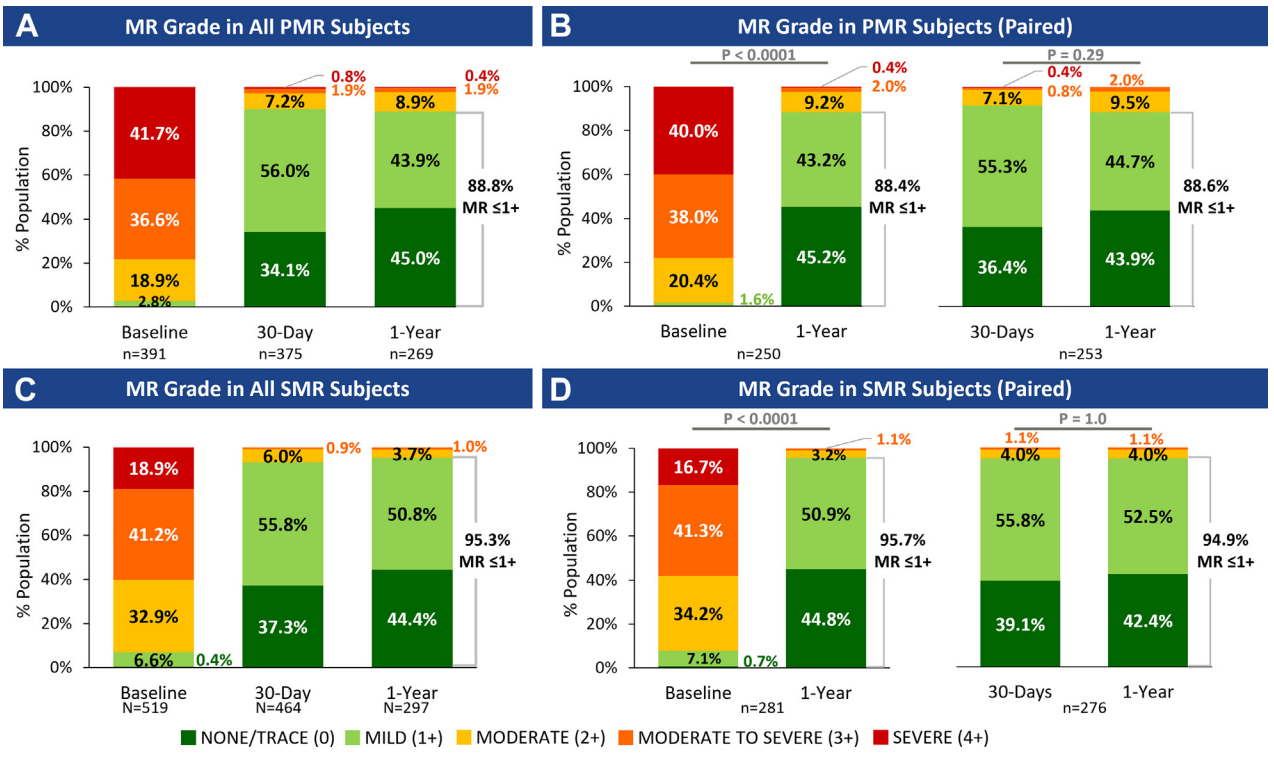
MV gradients and reverse LV remodeling. The mean MV gradient was 2.5 ± 1.3 mm Hg at baseline and increased slightly to 3.8 ± 1.9 mm Hg at 30 days, with no clinically significant change (without stenosis) from 30 days to 1 year (Figure 5A) and similar trends in a paired analysis (Figure 5B). LV end-diastolic volume was significantly reduced at 1 year, from 140.4 ± 62.3 mL at baseline to 125.0 ± 59.6 mL at 1 year (paired $P < 0.0001$) (Figure 6A). The mean LV end-systolic volume decreased from 78.1 ± 54.1 mL at baseline to 71.8 ± 53.9 mL at 1 year but was not significant (paired $P = 0.47$) (Figure 6B). A decrease in LVEF was observed at discharge (43.4% ± 17.0% vs 48.3% ± 16.2% at baseline) but nearly recovered by 1 year (47.1% ± 15.7%) (paired $P < 0.0001$) (Figure 6C). Forward stroke volume increased from 52.1 ± 18.0 mL at baseline to 55.5 ± 16.9 mL at 1 year (paired $P = 0.02$) (Figure 6D). Variability in LV volumes and LVEF from the full cohort reflect differences in LV parameters between subjects with SMR, who had large LV volumes and lower LVEF, and subjects with PMR (Supplemental Figure 1). Both etiologies had similar trends in LV remodeling postprocedure.

CLINICAL OUTCOMES. All-cause mortality and HFH. Kaplan-Meier 1-year estimates for all-cause mortality, HFH, and the composite outcome of all-cause mortality or HFH for the overall cohort and by MR etiology are shown in Figure 7. One-year estimated all-cause mortality rates were 12.3% (95% CI: 10.5%-14.5%) for the full cohort, 8.4% (95% CI: 6.0%-11.6%) in subjects with PMR, and 14.2% (95% CI: 11.4%-17.6%) in subjects with SMR. One-year HFH rates were 16.9% (95% CI: 14.7%-19.4%) for the full cohort, 10.4% (95% CI: 7.7%-13.9%) in subjects with PMR, and 20.8% (95% CI: 17.4%-24.7%) in subjects with SMR. The composite outcome of all-cause mortality or HFH at 1 year was 24.0% (95% CI: 21.6%-26.7%) for the full cohort, 16.7% (95% CI: 13.3%-20.7%) in subjects with PMR, and 28.2% (95% CI: 24.4%-32.3%) in subjects with SMR.

Functional capacity and quality of life. NYHA functional class significantly improved, with 82.1% of subjects categorized in class I or II at 1 year ($P < 0.0001$ vs baseline), which was clinically sustained from 30 days with 91% improving in NYHA class or remaining in class I/II (Central Illustration B) and similar to paired outcomes, albeit statistically different from 30 days to 1 year ($P = 0.017$) (Supplemental Figure 2). There was a significant improvement in quality of life, with a mean improvement in KCCQ overall summary score of 18.5 ± 24.5 points (95% CI: 16.7-20.2 points; $P < 0.0001$) at 1 year (Central Illustration C).

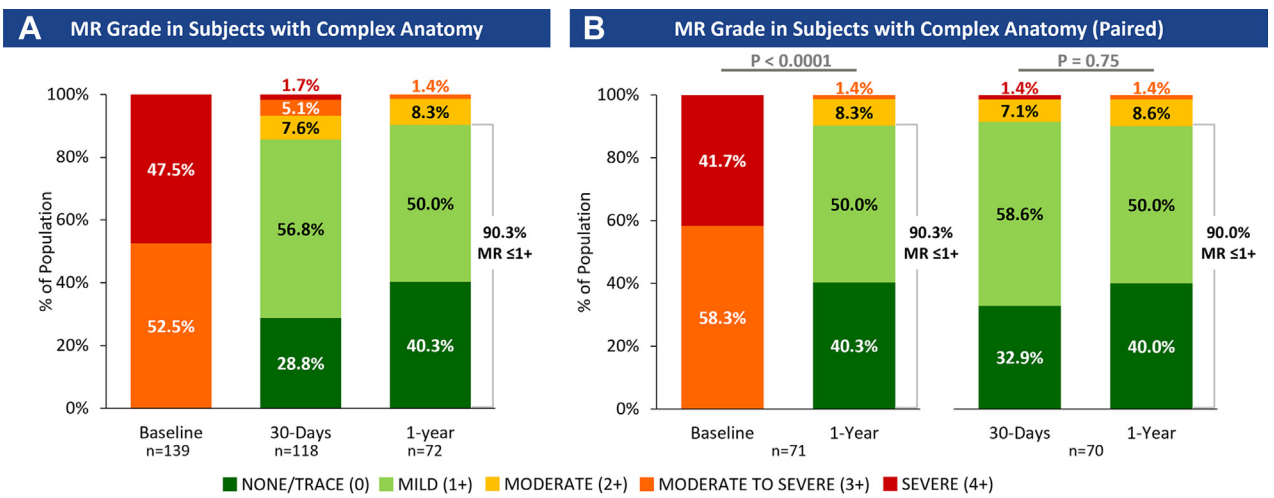
SAFETY OUTCOMES. MAE rates at 1 year are presented in Table 1. At 1 year, 1.2% of subjects had experienced a myocardial infarction and 1.8% had experienced a stroke. A total of 1.9% of subjects required MV surgical reintervention because of recurrence of severe MR or unsuccessful M-TEER procedures. The early incidence of surgical reintervention was reported previously.[17] Single-leaflet device attachment events were reported in 17 subjects (1.6%) at 1 year. Three of these subjects died within 1 year following the initial procedure, with 1 death due to cardiovascular reasons; 5 subjects underwent additional MitraClip procedures after discharge and within 1 year. Leaflet damage and chordal entrapment were both observed at a rate of 0.2% at 1 year. Overall, 128 subjects died after the procedure and within 1 year (Kaplan-Meier estimate 12.3%), with 10 deaths (0.8%) occurring in the hospital; cardiovascular death occurred in 81 of these patients.

FIGURE 3 MR Reduction by Etiology



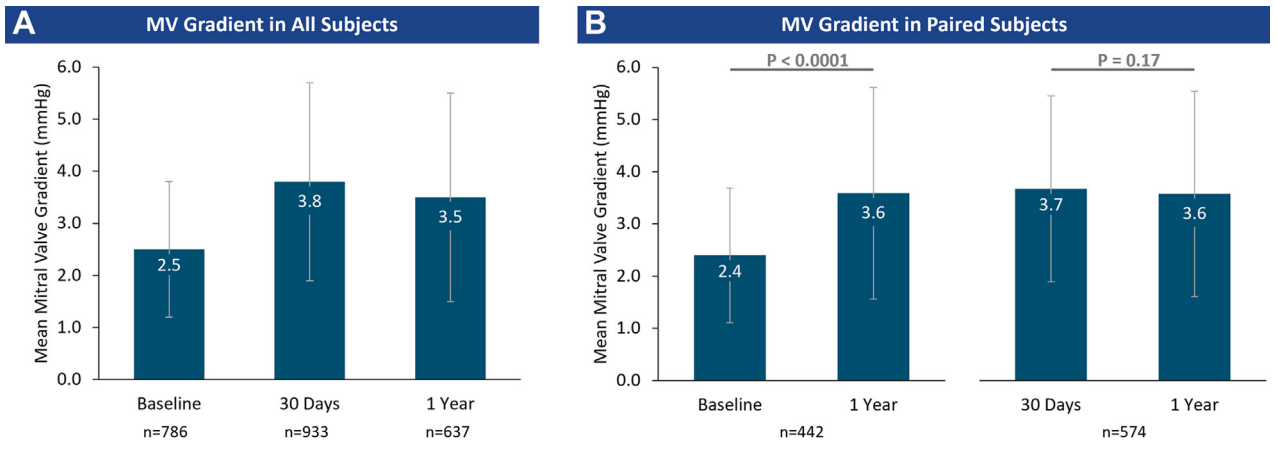
Echocardiography core laboratory–assessed mitral regurgitation (MR) grade in (A) all subjects with primary MR (PMR), (B) paired subjects with PMR, (C) all subjects with secondary MR (SMR), and (D) paired subjects with SMR. Paired subjects are shown from baseline to 1 year and from 30 days to 1 year.

FIGURE 4 MR Reduction in Subjects with Complex Anatomies



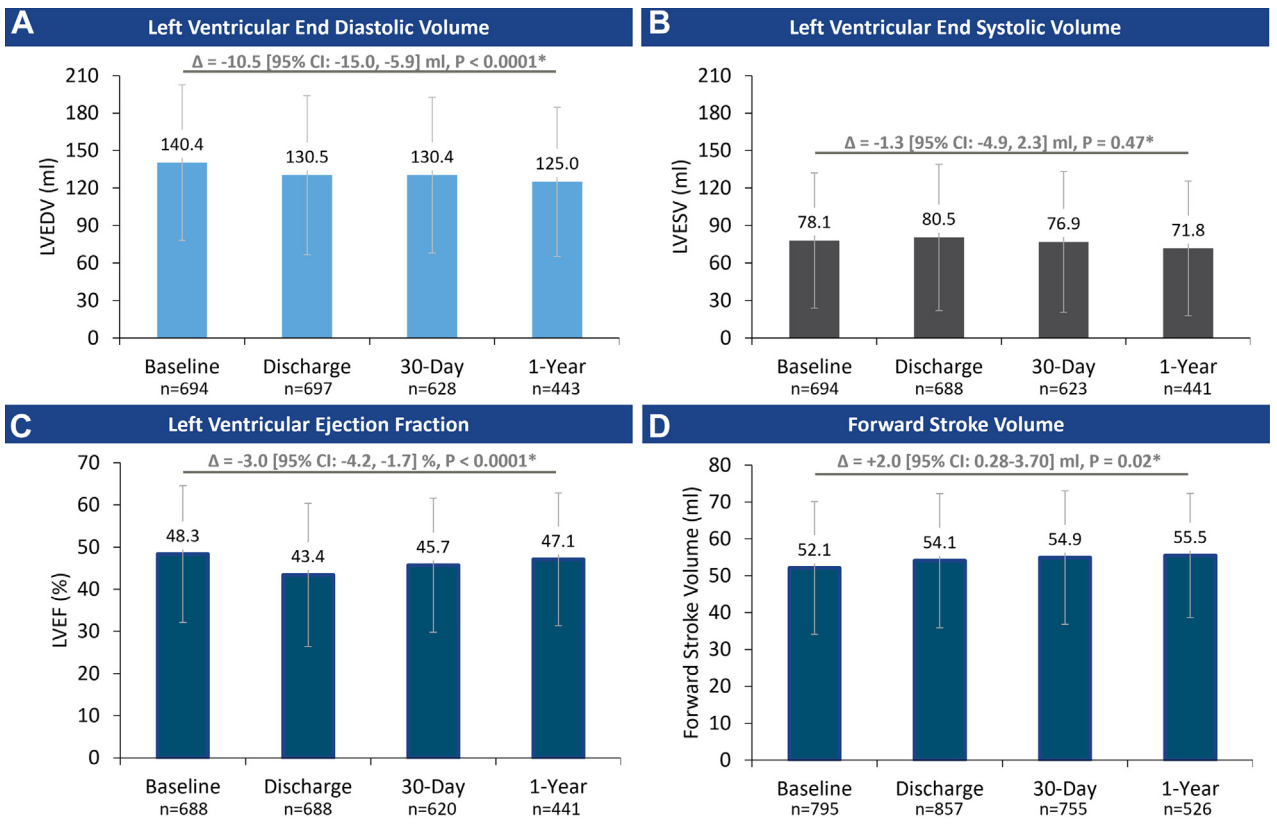
Echocardiography core laboratory–assessed mitral regurgitation (MR) grade through 1 year are shown for subjects with baseline MR ≥3+ and any of the following complexities: primary jet outside A2-P2, presence of >1 significant MR jet, presence of an extremely wide MR jet, small mitral valve area (<4 cm^2), mitral annular or leaflet calcification, presence of minimal leaflet tissue (coaptation length < 2mm), presence of severe leaflet degeneration or wide flail gaps (>10 mm) or widths (>15 mm), presence of significant cleft or scallop, or bileaflet flail or prolapse. MR is shown for (A) subjects with complex anatomy and (B) paired subjects with complex anatomy between baseline and 1 year and between 30 days and 1 year.

FIGURE 5 Mitral Valve Gradient Through 1 Year



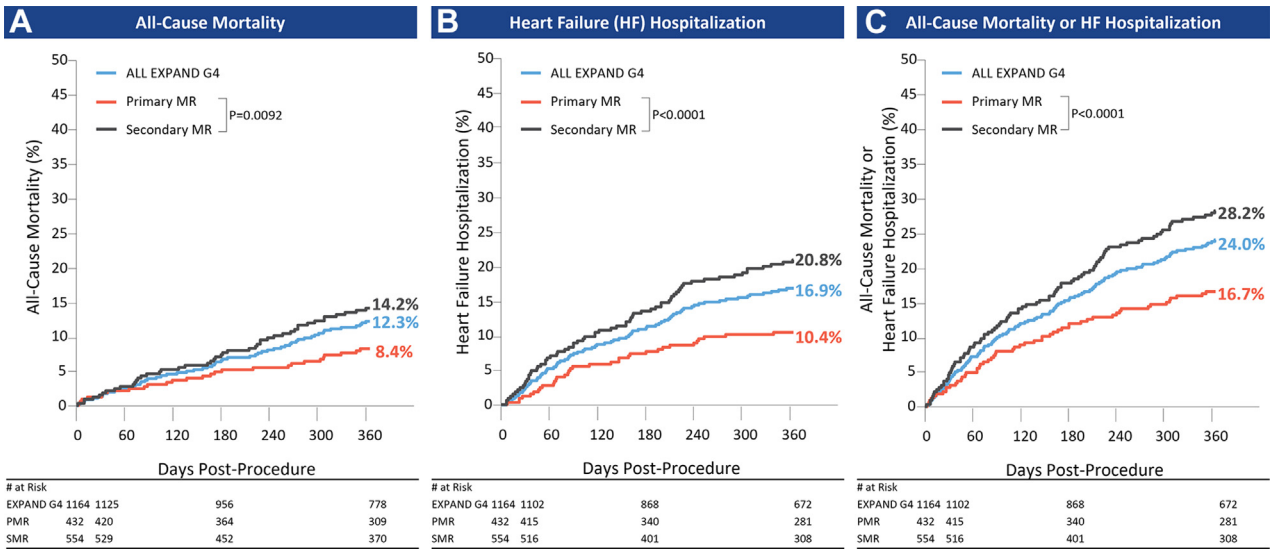
Mean mitral valve (MV) gradient, assessed by the echocardiography core laboratory, in (A) all subjects and (B) in paired subjects from baseline to 1 year and from 30 days to 1 year.

FIGURE 6 LV Remodeling Through 1 Year



Left ventricular (LV) echocardiography core laboratory-assessed measures for all subjects are shown at baseline, discharge, 30 days, and 1 year for (A) LV end-diastolic volume (LVEDV) ($P < 0.0001$; n = 303), (B) LV end-systolic volume (LVESV) ($P = 0.47$; n = 299), (C) LV ejection fraction (LVEF) ($P < 0.0001$; n = 299), and (D) forward stroke volume ($P = 0.02$; n = 388). *Changes in LV metrics are shown from a paired analysis between baseline and 1 year.

FIGURE 7 Kaplan-Meier All-Cause Mortality, HF Hospitalization, and Composite Outcome Through 1 Year



(A) All-cause mortality, (B) heart failure (HF) hospitalization, and (C) the composite outcome of all-cause mortality or HF hospitalization through 1 year in all subjects, subjects with PMR, and subjects with SMR are displayed as Kaplan-Meier time-to-first event curves. Log-rank comparisons between subjects with PMR and those with SMR were significantly different. Abbreviations as in Figures 2 and 3.

DISCUSSION

This study reports the 1-year outcomes of the largest cohort of subjects treated with the fourth-generation M-TEER device with ECL-assessed outcomes. At 1 year, MR severity was reduced to ≤2+ in 98.5% and ≤1+ in 92.6%, with nearly one-half of subjects achieving none or trace MR (44.2%). Rates of 1-year all-cause mortality and HFH were low at 12.3% and 16.9%. Positive outcomes in MR reduction were accompanied by LV reverse remodeling, improved quality of life, and improved NYHA functional class. These outcomes continue to support the long-term safety, effectiveness, and durability of the fourth-generation M-TEER device in the treatment of PMR and SMR.

MR reduction to ≤2+ has been the standard for M-TEER with early-generation devices. Historic studies reported high rates of MR ≤2+ in the EVEREST II randomized controlled trial (81.6%),[3] the EVEREST II High Risk Registry and REALISM Continued Access Study High-Risk Arm (83.6%),[10] and the COAPT trial (94.8%).[5] However, MR reduction to ≤1+ was noticeably less in these studies, at 36.9% to 69.1%.[3,5,10] Since these studies, the number of subjects achieving MR reduction to ≤1+ has increased with each design iteration. Improvements are notable even between the 2 most recent device iterations: 1-year MR ≤1+ in 92.6% treated with the fourth-generation M-TEER device (EXPAND G4) and 89.2% treated with the third-generation M-TEER device (EXPAND) (Figure 8A). This improvement in achieving and maintaining MR ≤1+ through 1 year was shown in subjects with PMR (88.8%) and those with SMR (95.3%), as well as in subjects with complex MV anatomies (90.3%) and baseline ECL-assessed MR ≥3+ (91.2%). With achievement of MR ≤1+ in 84% of subjects at 6 months when treated with other M-TEER devices (PASCAL, Edwards Lifesciences)[11] and MR ≤1+ in 92.6% of subjects at 1 year with the MitraClip G4 system, updated expectations of MR reduction following M-TEER may be necessary. These outcomes from EXPAND G4 demonstrate the continuous improvement in M-TEER therapy and the largest 1-year MR reduction to date. Rates of MR ≤1+ in EXPAND G4 were numerically similar to those observed in 2 recent trials of patients undergoing surgical MV repair that observed ECL-assessed MR ≤ 1+ in 90% and 92% of patients alive at 1 year.[19,20]

At 1 year, ECL-assessed MV gradients did not have a clinically significant change compared with post-procedure and were similar to those observed with previous generations of the MitraClip system.[13] Additionally, 30-day outcomes of EXPAND G4 showed that MV gradients were not substantially different by clip size.[17] After treatment with M-TEER,

TABLE 1 1-Year Major Adverse Events and Device-Related Complications (N = 1,140)[a]

Composite of all-cause mortality or heart failure hospitalization	24.0 (21.6-26.7) (253)[b]
Heart failure hospitalization	16.9 (14.7-19.4) (171)[b]
All-cause death	12.3 (10.5-14.5) (128)[b]
Cardiovascular death	5.7 (81)
MI	1.2 (14)
Stroke	1.8 (20)
Mitral valve surgical reintervention	1.9 (23)
SLDA[c]	1.6 (17)
Leaflet damage[c]	0.2 (2)
Chordal entrapment[c]	0.2 (2)

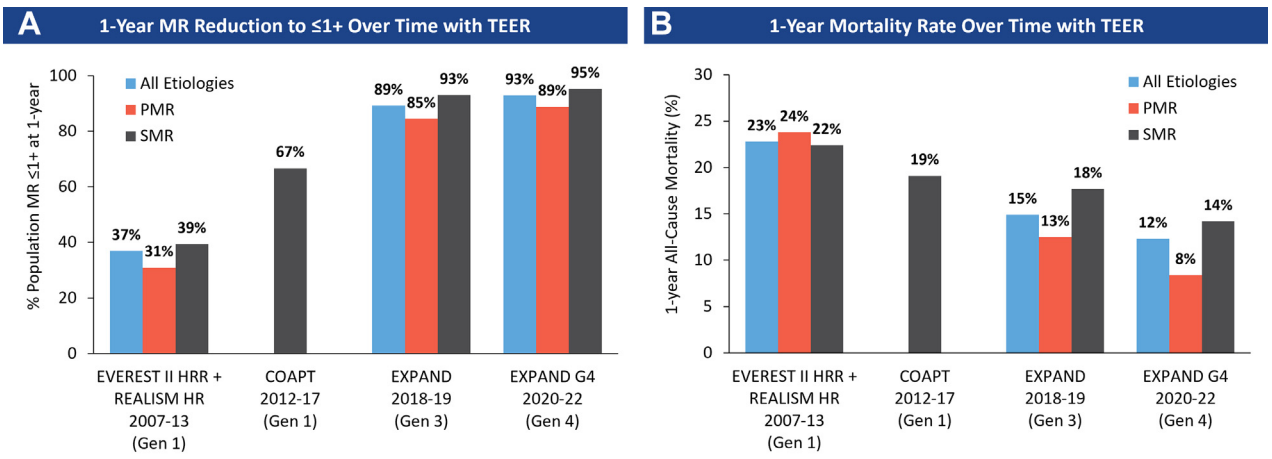
Values are % (95% CI) (N) or % (n). [a]Subjects who withdrew from the study prior to the lower limit of the 1-year visit window without any reported adverse events were excluded from this analysis. [b]1-year estimates using the Kaplan-Meier method. [c]SLDA, leaflet damage, and chordal entrapment events in the EXPAND G4 study were assessed by the echocardiography core laboratory on the basis of procedural and follow-up images.

MI = myocardial infarction; SLDA = single-leaflet device attachment.

there was an acute decrease in LVEF at discharge, which may be attributed to the initial response to increased antegrade flow with consecutive afterload resulting from MR reduction, similar to the LV remodeling that occurs following MV surgery.[21] At 1 year, LV reverse remodeling was observed with reductions in LV end-diastolic volume and LV end-systolic volume as well as recovery of LVEF and an increase in forward stroke volume, consistent with the EXPAND study.[13]

The Kaplan-Meier-estimated 1-year mortality and HFH rates in EXPAND G4 (12.3% and 16.9%, respectively) were lower than in previous studies (Figure 8B). Historical studies reported higher 1-year all-cause mortality with 22.8% in the EVEREST II High Risk Registry and REALISM study,[10] 15.3% in the TVCT registry,[15] 19.8% in TRAMI,[14] 24.3% in MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation),[6] and 19.1% in COAPT.[5] With the third-generation M-TEER device in EXPAND, 1-year all-cause mortality and HFH were 14.9% and 18.9%, respectively.[13] For subjects with PMR and those with SMR in EXPAND G4, mortality was even lower, with 8.4% and 14.2% 1-year mortality rates, respectively, in alignment with real-world 1-year outcomes from the COAPT Post-Approval Study.[22] Several factors may contribute to these improved outcomes, including advances in medical therapy (particularly for heart failure with reduced ejection fraction) in patients with SMR and changes in patient selection. Additionally, reduction in 1-year all-cause mortality in PMR and SMR etiologies may reflect the increased MR reduction resulting from improvements in M-TEER therapy, increased operator experience, and improved imaging technology.

FIGURE 8 Progression of 1-Year Outcomes With MitraClip TEER Therapy



(A) The EXPAND G4 (fourth-generation) study showed greater MR reduction to ≤1+ at 1 year than EXPAND (third generation), COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) (first generation), and EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II High Risk Registry (HRR) and REALISM (first generation) studies, in the full cohort and the PMR-only and SMR-only groups. (B) One-year all-cause mortality in the EXPAND G4 study was lower relative to previous generations. TEER = transcatheter edge-to-edge repair; other abbreviations as in Figures 2 and 3.

A majority of subjects in EXPAND G4 had large improvements in functional class and quality of life. Most subjects were in NYHA functional class I or II at 1 year (82.1%), sustained from the 30-day improvement (84.9%). Substantial quality-of-life improvements were achieved with the fourth-generation M-TEER device, with an 18.5-point improvement in KCCQ overall summary score at 1 year from baseline. These observations further support the durability of patient-oriented outcomes at 1 year after M-TEER therapy in patients with SMR and PMR.

STUDY STRENGTHS AND LIMITATIONS. As a real-world study, EXPAND G4 reports the outcomes of patients as they would be treated in the clinic. With a high 1-year follow-up rate of 87%, assessments of longer term outcomes can be made by following patients through 5 years. Although ECL-assessed MR severity and other echocardiographic measurements were reported using American Society of Echocardiography guidelines, enrollment was based on site-interpreted MR severity using regional echocardiographic guidelines for defining MR and a comprehensive assessment, including local transesophageal echocardiographic assessments that were not evaluated for MR severity by the ECL; therefore, discrepancies between site-interpreted and ECL-assessed MR are expected, especially for subjects with SMR, in whom MR severity is dynamic in nature. The number of patients with ECL-reported MR $\leq 2+$ can also be attributed to worldwide differences in guideline recommendations and indications. Moreover, missing or nonevaluable imaging contributed to fewer assessments by the ECL. However, MR grading assessed by one independent ECL reduces variability and bias and strengthens the reliability of outcomes in EXPAND G4. Although GDMT use may have been less uptitrated in EXPAND G4 relative to previous randomized controlled trials,[5,6] greater use of the modern components of GDMT with increased use of sacubitril/valsartan and combination therapies reflect current guidelines and real-world scenarios.

CONCLUSIONS

Treatment with the fourth-generation M-TEER device resulted in durable 1-year MR reduction to $\leq 1+$ in most patients (93%) and the lowest 1-year rates of all-cause mortality and HFH in an M-TEER study to date. These benefits were accompanied by improved functional capacity and quality of life. In the 1,164 subjects treated in the contemporary, real-world EXPAND G4 study, 1-year ECL outcomes demonstrate the durable safety and effectiveness of the MitraClip G4 system.

ACKNOWLEDGMENTS The authors thank all sites and study principal investigators who contributed to the EXPAND G4 study, as well as Melody Dong, PhD, Meridith Doyle, PhD, and Joshua Rapkin for their assistance with the analysis.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The EXPAND G4 study (NCT04177394) was funded and sponsored by Abbott. Dr von Bardeleben has performed unpaid trial activities for Abbott, Edwards Lifesciences, Medtronic, and the University of Göttingen (IIT); and serves as an advisory board or Speakers Bureau member for Abbott Cardiovascular, Edwards Lifesciences, Medtronic, and NeoChord. Dr Mahoney is a consultant and proctor for Medtronic, Edwards Lifesciences, and Boston Scientific; is a consultant for Abbott; and has been awarded research grants from Edwards Lifesciences, Medtronic, Abbott, and Boston Scientific. Dr Morse is a consultant for Edwards Lifesciences. Dr Denti has received speaker honoraria from Abbott and Edwards Lifesciences; and has been a consultant to InnovHeart, Artiness and Pi-Cardia. Dr Maisano has received grants and/or institutional research support from Abbott, Medtronic, Edwards Lifesciences, Biotronik, Boston Scientific, New Valve Technology, and Terumo; has received honoraria and consulting fees (personal and institutional) from Abbott, Medtronic, Edwards Lifesciences, Xeltis, and Cardiovalve; has received royalty income and intellectual property rights from Edwards Lifesciences; and is a shareholder (including stock options) in CardioGard, Magenta, SwissVortex, Transseptal Solutions, Occlufit, 4Tech, and Perifect. Dr Rinaldi has been awarded honoraria and/or consulting fees from Abbott, Boston Scientific, and Edwards Lifesciences. Dr De Marco is a consultant and has provided paid expert testimony for Abbott and Boston Scientific. Dr Chehab has received study and consulting grants from Abbott, Edwards Lifesciences, and BioTronics. Dr Price has received consulting fees from Alleviant Medical, Medtronic, Boston Scientific, Abbott, W.L. Gore, Philips Medical, and InnovHeart. Dr Williams has received funding for research from Abbott, Medtronic, Boston Scientific, and Edwards Lifesciences. Dr Leurent has received proctoring, lecture, and consulting fees from Abbott. Dr Rogers has received consulting fees from Abbott and Boston Scientific. Dr Asch's work as an academic core laboratory director is performed through institutional research grants (MedStar Health) with Abbott, Boston Scientific, Medtronic, Edwards Lifesciences, Neovasc, Ancora Heart, LivaNova, MVRx, InnovHeart, Polares Medical, and Aria CV. Dr Rodriguez has been awarded grants and support for research from Abbott, Edwards Lifesciences, Boston Scientific, AtriCure, and CardioMech; and has received honoraria or consulting fees from Abbott, Edwards Lifesciences, Philips, Teleflex, and CardioMech. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Prof Dr Ralph Stephan von Bardeleben, Department of Cardiology, Heart Valve Center, Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Zentrum für Kardiologie, Kardiologie 1, Langenbeckstrasse 1, 55131 Mainz, Germany. E-mail: stephan.von_bardeleben@unimedizin-mainz.de.

PERSPECTIVES

WHAT IS KNOWN? The 30-day outcomes from the EXPAND G4 study demonstrated that treatment with the fourth-generation MitraClip system resulted in acute MR reduction with an excellent safety profile.

WHAT IS NEW? The 1-year outcomes with the MitraClip G4 system in the EXPAND G4 study continue to demonstrate durable MR reduction to ≤1+ in 93% of subjects with low all-cause mortality, HFH, and improved functional status.

WHAT IS NEXT? The durable long-term outcomes support the continued improvement of M-TEER therapy in achieving higher standards in MR reduction and clinical outcomes that should drive future development of M-TEER therapy.

REFERENCES

1. Nishimura RA, Vahanian A, Eleid MF, Mack MJ. Mitral valve disease—current management and future challenges. *Lancet*. 2016;387(10025):1324–1334.

2. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge Repair Study) cohort. *J Am Coll Cardiol*. 2009;54(8):686–694.

3. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364(15):1395–1406.

4. Kar S, Feldman T, Qasim A, et al. Five-year outcomes of transcatheter reduction of significant mitral regurgitation in high-surgical-risk patients. *Heart*. 2019;105(21):1622–1628.

5. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379(24):2307–2318.

6. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379(24):2297–2306.

7. Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol*. 2013;62(12):1052–1061.

8. Grasso C, Capodanno D, Scandura S, et al. One- and twelve-month safety and efficacy outcomes of patients undergoing edge-to-edge percutaneous mitral valve repair (from the GRASP registry). *Am J Cardiol*. 2013;111(10):1482–1487.

9. Sorajja P, Vemulapalli S, Feldman T, et al. Outcomes with transcatheter mitral valve repair in the United States: an STS/ACC TVT Registry report. *J Am Coll Cardiol*. 2017;70(19):2315–2327.

10. Glower DD, Kar S, Trento A, et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. *J Am Coll Cardiol*. 2014;64(2):172–181.

11. Lim DS, Smith RL, Gillam LD, et al. Randomized comparison of transcatheter edge-to-edge repair for degenerative mitral regurgitation in prohibitive surgical risk patients. *J Am Coll Cardiol Intv*. 2022;15(24):2523–2536.

12. Mauri V, Sugiura A, Spieker M, et al. Early outcomes of 2 mitral valve transcatheter leaflet approximation devices: a propensity score-matched multicenter comparison. *J Am Coll Cardiol Intv*. 2022;15(24):2541–2551.

13. Kar S, von Bardeleben RS, Rottbauer W, et al. Contemporary outcomes following transcatheter edge-to-edge repair: 1-year results from the EXPAND study. *J Am Coll Cardiol Intv*. 2023;16(5):589–602.

14. Puls M, Lubos E, Boekstegers P, et al. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German Transcatheter Mitral Valve Interventions registry. *Eur Heart J*. 2016;37(8):703–712.

15. Nickenig G, Estevez-Loureiro R, Franzen O, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. *J Am Coll Cardiol*. 2014;64(9):875–884.

16. Rogers JH, Asch F, Sorajja P, et al. Expanding the spectrum of TEER suitability: evidence from the EXPAND G4 Post Approval Study. *J Am Coll Cardiol Intv*. 2023;16(12):1474–1485.

17. von Bardeleben RS, Rogers JH, Mahoney P, et al. Real-world outcomes of fourth-generation mitral transcatheter repair: 30-day results from EXPAND G4. *J Am Coll Cardiol Intv*. 2023;16(12):1463–1473.

18. Zoghbi WA, Asch FM, Bruce C, et al. Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2019;32:431–475.

19. Gammie JS, Chu MWA, Falk V, et al. Concomitant tricuspid repair in patients with degenerative mitral regurgitation. *N Engl J Med*. 2022;386(4):327–339.

20. Akowuah EF, Maier RH, Hancock HC, et al. Minithoracotomy vs conventional sternotomy for mitral valve repair: a randomized clinical trial. *JAMA*. 2023;329(22):1957–1966.

21. Le Tourneau T, Topilsky Y, Inamo J, et al. Reverse left ventricular remodeling after surgery in primary mitral regurgitation: a volume-related phased process. *Structural Heart*. 2019;3(5):383–390.

22. Goel K, Lindenfeld J, Makkar R, et al. Transcatheter edge-to-edge repair in 5,000 patients with secondary mitral regurgitation: COAPT Post-Approval Study. *J Am Coll Cardiol*. 2023;82(13):1281–1297.

KEY WORDS MitraClip G4, mitral regurgitation, mitral valve repair, TEER, transcatheter edge-to-edge repair

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