



Expanding the Spectrum of TEER Suitability: Evidence From the EXPAND G4 Post Approval Study

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NEW RESEARCH PAPER

STRUCTURAL

Expanding the Spectrum of TEER Suitability

Evidence From the EXPAND G4 Post Approval Study



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ABSTRACT

BACKGROUND Anatomical and clinical criteria to define mitral transcatheter edge-to-edge repair (TEER) “unsuitability” have been proposed on the basis of a Heart Valve Collaboratory consensus opinion from physician experience with early-generation TEER devices but lacked an evidence-based approach.

OBJECTIVES The aim of this study was to explore the spectrum of TEER suitability using echocardiographic and clinical outcomes from the EXPAND G4 real-world postapproval study.

METHODS EXPAND G4 is a global, prospective, multicenter, single-arm study that enrolled 1,164 subjects with mitral regurgitation (MR) treated with the MitraClip G4 System. Three groups were defined using the Heart Valve Collaboratory TEER unsuitability criteria: 1) risk of stenosis (RoS); 2) risk of inadequate MR reduction (RoIR); and 3) subjects with baseline moderate or less MR (MMR). A TEER-suitable (TS) group was defined by the absence of these characteristics. Endpoints included independent core laboratory-assessed echocardiographic characteristics, procedural outcomes, MR reduction, NYHA functional class, Kansas City Cardiomyopathy Questionnaire score, and major adverse events through 30 days.

RESULTS Subjects in the RoS (n = 56), RoIR (n = 54), MMR (n = 326), and TS (n = 303) groups had high 30-day MR reduction rates ($\leq 1+$: RoS 97%, MMR 93%, and TS 91%; $\leq 2+$: RoIR 94%). Thirty-day improvements in functional capacity (NYHA functional class I or II at 30 days vs baseline: RoS 94% vs 29%, RoIR 88% vs 30%, MMR 79% vs 26%, and TS 83% vs 33%) and quality of life (change in Kansas City Cardiomyopathy Questionnaire score: RoS $+27 \pm 26$, RoIR $+16 \pm 26$, MMR $+19 \pm 26$, and TS $+19 \pm 24$) were safely achieved in all groups, with low major adverse events ($<3\%$) and all-cause mortality (RoS 1.8%, RoIR 0%, MMR 1.5%, and TS 1.3%).

CONCLUSIONS Patients previously deemed TEER unsuitable can be safely and effectively treated with the mitral TEER fourth-generation device. (J Am Coll Cardiol Intv 2023;16:1474-1485) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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Trascatheter edge-to-edge repair (TEER) is approved for the treatment of patients with symptomatic mitral regurgitation (MR),¹ which is the leading heart valve disease and is associated with high morbidity and mortality.²⁻⁴ The MitraClip system (Abbott Vascular) is a widely adopted mitral TEER (M-TEER) therapy commercially approved in Europe (2008) and the United States (2013) for patients with primary MR at high surgical risk, on the basis of the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) I, EVEREST II, EVEREST High Risk Registry, and EVEREST II REALISM (Real World Expanded Multicenter Study of the MitraClip® System) studies,⁵⁻¹⁰ and patients with secondary MR (SMR), who remain symptomatic despite guideline-directed medical therapy, with nonexcessive left ventricular enlargement, right ventricular dysfunction, or pulmonary hypertension, on the basis of the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial results.¹¹ Over the past decade, TEER has evolved with improved clinical outcomes associated with greater MR reduction ($\leq 2+$ adequate) compared with historical trials.¹² A broader range of patients might be successfully treated thanks to recent TEER advancements, including more precise and predictable delivery, independent leaflet grasping, clip retrievability, wider and longer clip sizes, and improvements in adjunctive imaging capabilities.¹³ To properly guide physicians on patient selection, particularly for complex mitral valve (MV) anatomies, there is a need to define anatomical characteristics that deem patients suitable for TEER.

Recently, a Heart Valve Collaboratory (HVC) consensus document¹⁴ proposed criteria defining anatomies and patient characteristics unsuitable (“red light” category) for TEER to identify patients more appropriate for transcatheter MV replacement. Four groups of patients likely unsuitable for M-TEER were identified: 1) patients at risk for resulting MV stenosis following TEER; 2) patients for whom inadequate reduction of MR would be expected; 3) patients in whom the procedure should not be performed because of anatomical, imaging, or

technical reasons; and 4) patients for whom TEER would be futile because of cardiac or noncardiac comorbidities.¹⁴ However, the HVC consensus document lacked an evidence-based approach and relied only on physician experience with earlier generation TEER devices. Although the consensus document acknowledges that these subjects are not absolutely contraindicated for TEER, contemporary clinical evidence to define anatomical and patient characteristics for TEER suitability is essential to the clinical success of the procedure.

We hypothesized that historical, consensus-based criteria for TEER unsuitability may not be applicable in current clinical practice. Therefore, we assessed the safety and effectiveness of M-TEER in a contemporary cohort of patients grouped according to the HVC consensus suitability criteria and treated with the M-TEER fourth-generation device from the prospective, postmarket EXPAND G4 study.

METHODS

STUDY DESIGN. EXPAND G4 (NCT04177394) is a prospective, international, multicenter, single-arm, postmarket observational study that enrolled 1,164 subjects with MR treated with the M-TEER fourth-generation device at 60 centers in the United States, Canada, Europe, the Middle East, and Japan.¹⁵ This study complies with latest good clinical practice standards of the Declaration of Helsinki and was approved by local ethics committees and applicable competent authorities of participating countries. Centers were required to have experience in interventional cardiology and/or the MitraClip procedure; approximately one-half of all centers performed >300 MitraClip procedures before enrollment. The primary effectiveness endpoint was MR reduction to $\leq 2+$ at 30 days. The primary safety endpoint was the occurrence of major adverse events (MAEs), defined as a composite of all-cause mortality, nonelective cardiovascular surgery

ABBREVIATIONS AND ACRONYMS

APS	= acute procedural success
ASE	= American Society of Echocardiography
ECL	= echocardiography core laboratory
HVC	= Heart Valve Collaboratory
KCCQ	= Kansas City Cardiomyopathy Questionnaire
MAE	= major adverse event(s)
MI	= myocardial infarction
MMR	= moderate or less mitral regurgitation
MR	= mitral regurgitation
M-TEER	= mitral transcatheter edge-to-edge repair
MV	= mitral valve
MVA	= mitral valve area
QoL	= quality of life
RoIR	= risk of inadequate mitral regurgitation reduction
RoS	= risk of stenosis
SMR	= secondary mitral regurgitation
TEER	= transcatheter edge-to-edge repair
TS	= transcatheter edge-to-edge repair suitable

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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](#).

for device-related complications, stroke, and myocardial infarction (MI) at 30 days. Additional outcomes from baseline through 30 days post-procedure were collected: 1) acute procedural success (APS), defined as survival to discharge without MV replacement and MR reduction to $\leq 2+$; 2) functional capacity assessed by NYHA functional class; and 3) quality of life (QoL) assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ).

ECHOCARDIOGRAPHIC EVALUATION. An independent echocardiography core laboratory (ECL) assessed all echocardiograms at baseline, discharge, and 30 days, according to the American Society of Echocardiography (ASE) guidelines and standards for ECLs.¹⁶ Assessments included MR severity, left ventricular dimensions and volumes, MV area (MVA) and gradient measured from transthoracic echocardiograms, MR etiology, coaptation depth and length, flail gap and width, effective regurgitant orifice area (proximal isovelocity surface area method), grasping area anatomy, and position and quantity of regurgitant jet(s) measured from transesophageal echocardiograms. Although MR severity was assessed from transthoracic echocardiograms by the ECL at baseline and 30 days, patient inclusion in EXPAND G4 was based on site-reported MR severity considering clinical findings, transesophageal and transthoracic echocardiographic findings, and the dynamic nature of MR. MV anatomy was assessed from transesophageal echocardiograms by the ECL and included the presence of mitral annular and/or leaflet calcification, significant cleft or scallop, bileaflet flail and/or prolapse, severely degenerative leaflets or wide flail gaps (>10 mm) or widths (>15 mm), and minimal excess leaflet tissue for restoration of the coaptation zone (coaptation length <2 mm). Missing or inadequate echocardiograms were not assessed by the ECL. [Supplemental Table 1](#) shows additional details of ECL assessments.

ANALYSIS POPULATION. To assess TEER suitability, 4 subgroups, from 1,164 patients in EXPAND G4 were defined in a post hoc analysis to match 3 of the HVC consensus document's unsuitability groups (risk FOR MV stenosis, inadequate MR reduction, and futility in performing TEER)¹⁴ and 1 group considered TEER suitable (TS) on the basis of clinical evidence from EXPAND G4. Baseline anatomical (ECL assessed) and patient characteristics described in the HVC consensus document that were also available in EXPAND G4 were used to define 4 exclusive subgroups ([Supplemental Figure 1](#)).

Group 1 included TS subjects, defined on the basis of the absence of all available unsuitability criteria in

the HVC consensus document¹⁴; subjects had baseline MR severity $\geq 3+$ and none of the following: secondary jet, severe mitral annular calcification, severe leaflet calcification, significant cleft or scallop, MVA <3.5 cm², prior annuloplasty, Barlow's disease, bileaflet prolapse or flail, severe degenerative leaflets with large gaps, and minimal leaflet tissue.

Subjects in group 2, with risk of stenosis (RoS), were defined on the basis of MV anatomical characteristics and prior procedures associated with a higher likelihood of mitral stenosis after TEER in the HVC consensus document¹⁴; subjects had baseline MR severity $\geq 3+$ and at least 1 of the following: severe mitral annular calcification, severe leaflet calcification, prior mitral annuloplasty, or baseline MVA <3.5 cm².

Subjects in group 3, with risk of inadequate MR reduction (RoIR), were defined on the basis of anatomical complexities associated with an unsuccessful TEER procedure and inadequate MR reduction in the HVC consensus document¹⁴; subjects had baseline MR severity $\geq 3+$ and at least 1 of the following: Barlow's disease, bileaflet flail or prolapse, significant secondary jet, severe leaflet degeneration with large gaps, minimal leaflet tissue, or significant cleft or scallop.

Last, subjects in group 4, with baseline moderate or less MR (MMR), were considered futile to treat in the HVC consensus document¹⁴ and had baseline MR severity $<3+$.

STATISTICAL ANALYSIS. All analyses were performed on subjects with attempted procedures. Categorical variables are reported as percentages of available data per subgroup and were compared using the Fisher exact 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 Student's *t*-test. KCCQ score paired changes from baseline to follow-up visits were assessed using analysis of covariance, adjusting for baseline differences. Subjects withdrawn before 30-day visits were not included in outcomes analyses. Statistical significance was considered at $P < 0.05$ (2-sided); nominal *P* values are presented. All analyses were exploratory and performed using SAS version 9.4 (SAS Institute).

RESULTS

STUDY POPULATION. In total, 1,164 consecutive subjects were enrolled in EXPAND G4 between March 3, 2021, and February 4, 2022, and subsequently underwent procedures; 1,141 subjects (98.0%) were

TABLE 1 Study Population: Baseline Characteristics

	TEER Suitability Groups ^a			
	TS (n = 303)	RoS (n = 56)	RoIR (n = 54)	MMR (n = 326)
Age, y	76.4 ± 10.0 (303)	79.8 ± 8.5 (56) ^b	80.4 ± 6.6 (54) ^b	77.0 ± 8.6 (326)
Sex at birth (male)	57.1 (173/303)	42.9 (24/56) ^b	44.4 (24/54)	54.0 (176/326)
BMI, kg/m ²	25.3 ± 5.3 (303)	27.3 ± 6.6 (56) ^b	23.0 ± 3.5 (54) ^b	26.8 ± 6.1 (326) ^b
STS replacement score, %	8.0 ± 7.7 (160)	9.4 ± 6.5 (36)	6.8 ± 5.9 (28)	8.1 ± 6.1 (171)
STS repair score, %	6.0 ± 7.0 (192)	9.0 ± 8.3 (38) ^b	4.6 ± 4.9 (34)	6.4 ± 6.5 (212)
Cardiac arrhythmia	65.3 (196/300)	48.2 (27/56) ^b	61.1 (33/54)	73.5 (238/324) ^b
Renal failure	32.0 (96/300)	21.4 (12/56)	11.1 (6/54) ^b	28.3 (91/322)
Diabetes	27.3 (82/300)	28.6 (16/56)	13.0 (7/54) ^b	29.3 (95/324)
Prior HFH within 1 y	48.3 (138/286)	45.1 (23/51)	26.9 (14/52)	42.1 (127/302)
Prior MI	22.6 (67/297)	17.9 (10/56)	11.1 (6/54)	19.4 (61/315)
Etiology (PMR)	32.2 (97/301)	52.9 (27/51) ^b	96.3 (52/54) ^b	28.0 (80/286)
MVA, cm ²	5.8 ± 1.5 (303)	4.2 ± 1.5 (37) ^b	5.2 ± 1.0 (29) ^b	5.1 ± 1.5 (179) ^b
EROA, cm ²	0.34 ± 0.12 (234)	0.38 ± 0.15 (40)	0.338 ± 0.15 (31)	0.18 ± 0.07 (144) ^b
LVEF, %	44.6 ± 15.9 (203)	52.4 ± 16.0 (36) ^b	62.0 ± 8.3 (39) ^b	46.6 ± 15.4 (192)
LVESV, mL	87.2 ± 50.1 (204)	62.5 ± 38.6 (36) ^b	45.7 ± 20.8 (39) ^b	77.9 ± 57.6 (192)
LVEDV, mL	149.8 ± 57.7 (203)	124.1 ± 47.3 (37) ^b	116.1 ± 40.6 (41) ^b	133.7 ± 66.1 (196) ^b
MV gradient, mm Hg	3.5 ± 2.5 (227)	3.3 ± 1.6 (45) ^b	2.54 ± 1.23 (38)	2.22 ± 1.16 (235) ^b

Values are mean ± SD (n) or % (n/N), where N is the number of subjects with available baseline characteristics. ^aTEER suitability groups were defined per the Heart Valve Collaboratory consensus document¹⁴; 425 patients were not categorized per TEER-suitable definitions, because of nonevaluable or missing data by echocardiography core laboratory. ^bBaseline characteristics with significant differences between the TS group and the RoS, RoIR, or MMR group (*P* < 0.05).

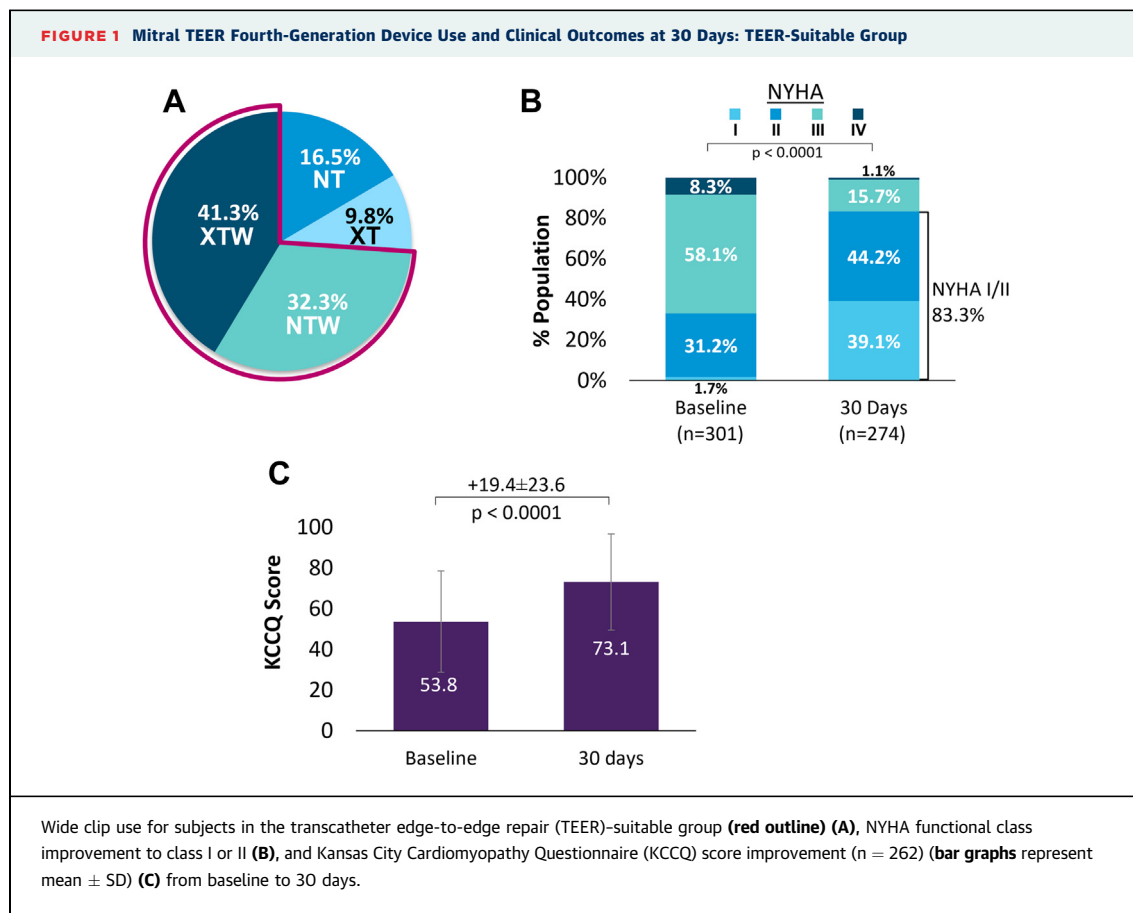
BMI = body mass index; EROA = effective regurgitant orifice area; HFH = heart failure hospitalization; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MI = myocardial infarction; MMR = baseline moderate or less mitral regurgitation; MV = mitral valve; MVA = mitral valve area; PMR = primary mitral regurgitation; RoIR = risk of inadequate mitral regurgitation reduction; RoS = risk of stenosis; STS = Society of Thoracic Surgeons; TEER = transcatheter edge-to-edge repair; TS = transcatheter edge-to-edge repair-suitable.

discharged with at least 1 clip implanted. Thirty-day follow-up was complete in 91% of subjects (Supplemental Figure 2), which is expected in a real-world study because of deaths, withdrawals, and loss to follow-up. A total of 303 subjects (26.0%) were categorized as TS, 56 (4.8%) as RoS, 54 (4.6%) as RoIR, and 326 (28.0%) as MMR. A total of 425 subjects (36.5%) could not be categorized into a TS group, because of nonevaluable or missing echocardiographic data (Table 1) from any 1 of the criteria described in the “Methods” section.

BASILINE CHARACTERISTICS. Baseline characteristics stratified by TEER suitability subgroups are shown in Table 1. The average ages in the TS, RoS, RoIR, and MMR groups were 76.4 ± 10.0, 79.8 ± 8.5, 80.4 ± 6.6, and 77.0 ± 8.6 years, and the proportions of male subjects were 57.1%, 42.9%, 44.4%, and 54.0%. Cardiac arrhythmia, renal dysfunction, and diabetes mellitus were frequently present. Heart failure hospitalizations within 1 year before the procedure were reported in 48.3%, 45.1%, 26.9%, and 42.1% of subjects in the TS, RoS, RoIR, and MMR groups.

MR etiology assessments from transesophageal echocardiograms were adequate and available for 692 subjects from all groups (n = 301 [99.3%] TS, n = 51 [91.1%] RoS, n = 54 [100%] RoIR, and n = 286 [87.7%] MMR). In the TS group, 32.2% of subjects had primary MR compared with 52.9%, 96.3%, and 28.0% in the RoS, RoIR, and MMR groups. Mean MV gradients varied slightly, at 3.5 ± 2.5, 3.3 ± 1.6, 2.5 ± 1.2, and 2.2 ± 1.2 mm Hg in the TS, RoS, RoIR, and MMR groups. The mean MVA in the RoS group (4.2 ± 1.5 cm²) was numerically smaller in than the TS (5.8 ± 1.5 cm²), RoIR (5.2 ± 1.0 cm²), and MMR (5.1 ± 1.5 cm²) groups. The left ventricular ejection fraction was numerically higher in the RoS and RoIR groups (52.4% ± 16.0% and 62.0% ± 8.3%) compared with the TS (44.6% ± 15.9%) and MMR groups (46.6% ± 15.4%). Baseline echocardiographic characteristics (ECL assessed) of the TEER suitability subgroups are summarized in Table 1. A breakdown of subjects in the RoS group is shown in Supplemental Table 2.

TS GROUP. Procedural outcomes. In the TS group, 73.6% of the subjects were treated with wide clips (41.3% XTW, 32.3% NTW) (Figure 1A). The median procedure time was 80 minutes, and device time



(time from placement of the steerable guiding catheter across the interatrial septum to time of clip delivery system retraction into the guide catheter) was 36 minutes. The median number of clips implanted per patient was 1.0 (Table 2). The implantation success rate was 99.0%, and APS was 96.9%.

Echocardiographic and clinical outcomes at 30 days. At baseline, 59.1% and 40.9% of subjects in the TS group had MR severity of 3+ and 4+, respectively. MR reduction to ≤1+ and ≤2+ 30 days postprocedure was achieved in 90.8% and 99.6% of subjects (Central Illustration). Functional capacity significantly improved, with 83.3% of subjects in NYHA functional class I or II 30 days postprocedure vs 32.9% at baseline ($P < 0.0001$) (Figure 1B). The mean KCCQ score increased by 19.4 ± 23.6 points from baseline to 30 days ($P < 0.0001$) (Figure 1C). The MAE rate at 30 days was 3.0%, with a 1.3% mortality rate, a 1.3% reintervention rate, a 0.3% MI rate, and a 0.3% stroke rate (Table 2).

RoS GROUP. Procedural outcomes. In the RoS group, wide clips were used in 75.8% of subjects (33.9% XTW, 41.9% NTW) (Figure 2A). The median

procedure and device times were 75 and 32 minutes. The median number of clips implanted per patient was 1.0 (Table 2). The implantation success rate was 98.2%, with an APS of 98.2%, similar to the TS group ($P = 0.50$).

Echocardiographic and clinical outcomes at 30 days. At baseline, 50.0% of the RoS group had MR severity of 3+ and 50.0% had MR severity of 4+. At 30 days, MR decreased significantly, with 97.4% of subjects achieving MR ≤ 1+ ($P < 0.0001$) (Central Illustration). The mean postprocedural MV gradient increased slightly from baseline (3.3 ± 1.6 mm Hg) to 30 days (4.5 ± 1.6 mm Hg). Functional capacity significantly improved, with 94.0% of subjects categorized in NYHA functional class I/II at 30 days compared with 28.6% at baseline ($P < 0.0001$) (Figure 2B). QoL significantly improved (KCCQ score $+27.1 \pm 26.1$ points; $P < 0.0001$) 30 days postprocedure (Figure 2C). The MAE rate through 30 days was 1.8%, with a mortality rate of 1.8% and no stroke, MI, or need for reintervention (Central Illustration). All 30-day outcomes in the RoS group were similar to those in the TS group (MR ≤ 2+, $P = 0.30$; NYHA

TABLE 2 Procedural Outcomes

	TS Group (n = 303)	RoS Group (n = 56)	RoIR Group (n = 54)	MMR Group (n = 326)
Implantation rate, %	99.0 (300/303)	98.2 (55/56)	96.3 (52/54)	97.9 (319/326)
APS, % ^a	96.9 (286/295)	98.2 (55/56)	94.4 (51/54)	96.6 (313/324)
Device time, min	36 (20.5-55.5)	32 (24.0-53.0)	44 (25.0-62.0)	32 (20.0-50.0)
Procedure time, min	80 (59.0-105.0)	76 (55.0-103.5)	75 (55.0-106.0)	75 (57.0-101.0)
Clip rate (n)	1.0 (1.0-2.0)	1.0 (1.0-1.0) ^b	2.0 (1.0-2.0)	1.0 (1.0-2.0) ^b
Length of hospital stay, d	4.0 (1.0-9.0)	3.5 (1.0-7.5)	2.0 (1.0-2.0)	1.0 (1.0-2.0)
30-day MAE ^c	3.0 (9/302)	1.8 (1/56)	0.0 (0/54)	2.2 (7/325)
All-cause death	1.3 (4/302)	1.8 (1/56)	0.0 (0/54)	1.5 (5/325)
MI	0.3 (1/302)	0.0 (0/56)	0.0 (0/54)	0.0 (0/325)
Stroke	0.3 (1/302)	0.0 (0/56)	0.0 (0/54)	0.3 (1/325)
Reintervention	1.3 (4/302)	0.0 (0/56)	0.0 (0/54)	0.6 (2/325)

Values are % (n/N) or median (IQR). ^aAPS was defined as survival to discharge without mitral valve replacement surgery and with MR reduction to $\leq 2+$ at discharge or 30 days when discharge echocardiogram was unavailable. Patients with evaluable MR severity assessed by the echocardiography core laboratory at discharge or 30-day follow-up visits were assessed. ^bClip rate was significantly smaller in the RoS ($P = 0.02$) and MMR ($P = 0.04$) groups compared with the TS group. All other procedural outcomes and 30-day MAE in the RoS, RoIR, and MMR groups were similar to the TS group. ^cMAE were evaluated for patients with completed follow-up visits through 30 days.

APS = acute procedural success; MR = mitral regurgitation; other abbreviations as in Table 1.

functional class I or II, $P = 0.05$; KCCQ score, $P = 0.30$; and MAE, $P > 0.60$) (Table 2).

RoIR GROUP. Procedural outcomes. In the RoIR group, the XTW clip was used more frequently (50.7%) than the NTW (13.4%) or the NT and XT (35.8%) clips (Figure 3A). The median procedure and device times were 75 and 44 minutes. The median number of clips implanted per patient was 2.0 (Table 2). The implantation success rate was 96.3%, with an APS of 94.4%, similar to the TS group ($P = 0.20$).

Echocardiographic and clinical outcomes at 30 days. At baseline, 51.9% and 48.1% of patients had MR severity of 3+ and 4+, which was significantly reduced to $\leq 1+$ in 75.0% and $\leq 2+$ in 92.5% of subjects at 30 days ($P < 0.0001$) (Central Illustration); the proportion of subjects with MR $\leq 2+$ at 30 days was lower than in the TS group ($P = 0.01$). Functional capacity improved significantly, with 88.0% of subjects categorized in NYHA functional class I or II at 30 days ($P < 0.0001$) (Figure 3B) compared with 29.6% at baseline. The mean KCCQ score significantly increased at 30 days by 16.2 ± 25.5 points ($P < 0.0001$) compared with baseline (Figure 3C). No MAE were observed through 30 days (Central Illustration). Thirty-day NYHA functional class I or II ($P = 0.40$), KCCQ score ($P = 0.70$), and MAE rate ($P > 0.40$) were similar to those in the TS group (Table 2).

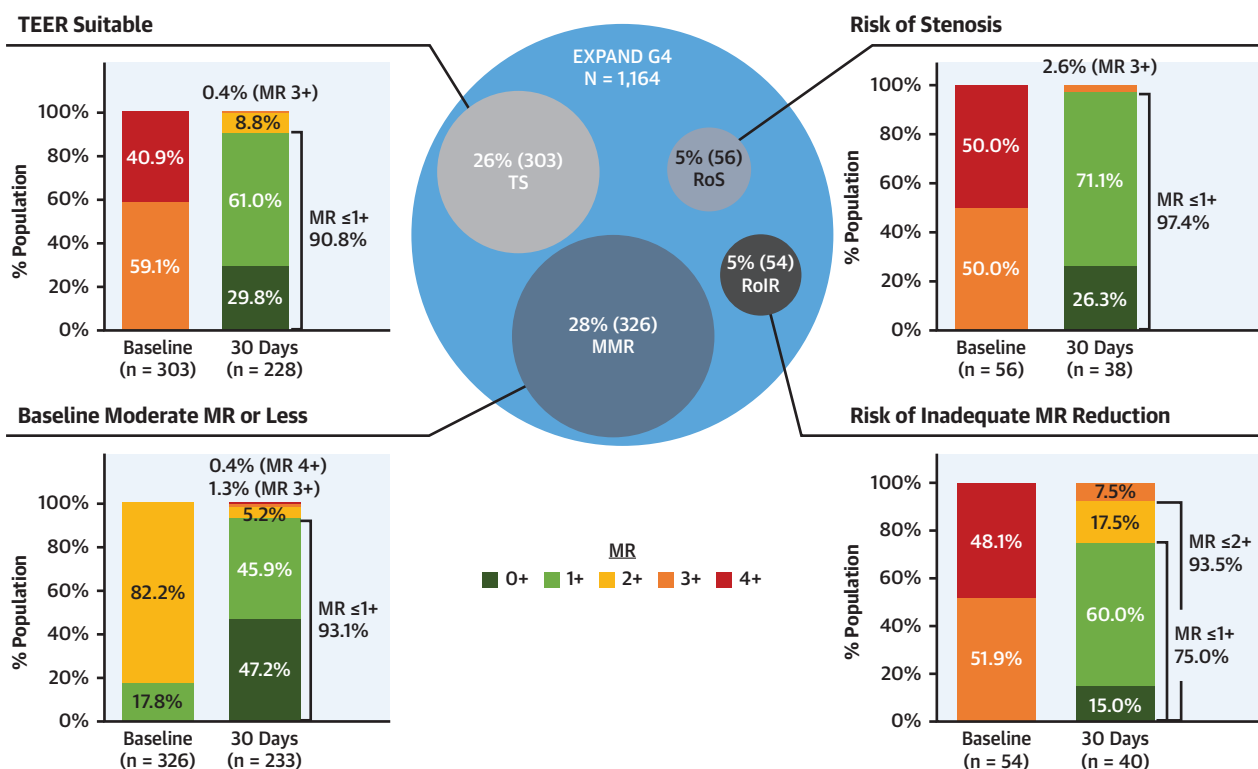
BASELINE MMR GROUP. Procedural outcomes. In the MMR group, 76.5% were treated with wide clips (Figure 4A). The XTW clip (41.2%) was used more

frequently compared with the NTW clip (35.3%). The median procedure and device times were 75 and 32 minutes. The median number of clips implanted per patient was 1.0 (Table 2), with an implantation success rate of 97.9% and APS of 96.6%, similar to the TS group ($P = 0.30$).

Echocardiographic and clinical outcomes at 30 days. Within the MMR group, all subjects had baseline MR severity $< 3+$. At 30 days, MR severity decreased significantly to $\leq 1+$ in 93.1% of subjects, with 47.2% achieving no or trace MR ($P < 0.0001$) (Central Illustration). Although 82.2% of MMR subjects had baseline MR of 2+, only 5.2% of subjects had 2+ MR at 30 days. Functional capacity significantly improved after M-TEER, with 79.3% of subjects in NYHA functional class I or II at 30 days compared with 26.4% at baseline ($P < 0.0001$) (Figure 4B). QoL significantly improved, with an increase in KCCQ score of 19.3 ± 25.9 points from baseline to 30 days postprocedure ($P < 0.0001$). Although MMR subjects had lower KCCQ scores at baseline and 30 days compared with those in the TS group ($P = 0.004$), the paired improvement was similar ($P = 1.00$) (Figure 4C). Of the 72% of MMR subjects with SMR etiology, there was no clinically significant change in medication use from baseline to 30 days (Supplemental Table 3). The MAE rate at 30 days was 2.2%, with 1.5% mortality, 0.3% stroke, and 0.6% reintervention rates (Central Illustration). Thirty-day MR $\leq 2+$ ($P = 0.40$), NYHA functional class I or II ($P = 0.20$), and MAE ($P > 0.50$) rates were similar to those in the TS group (Table 2).

CENTRAL ILLUSTRATION 30-Day Clinical Outcomes From EXPAND G4

Efficacy of TEER Among Patients With Challenging Anatomies or Moderate MR in the EXPAND G4 Registry



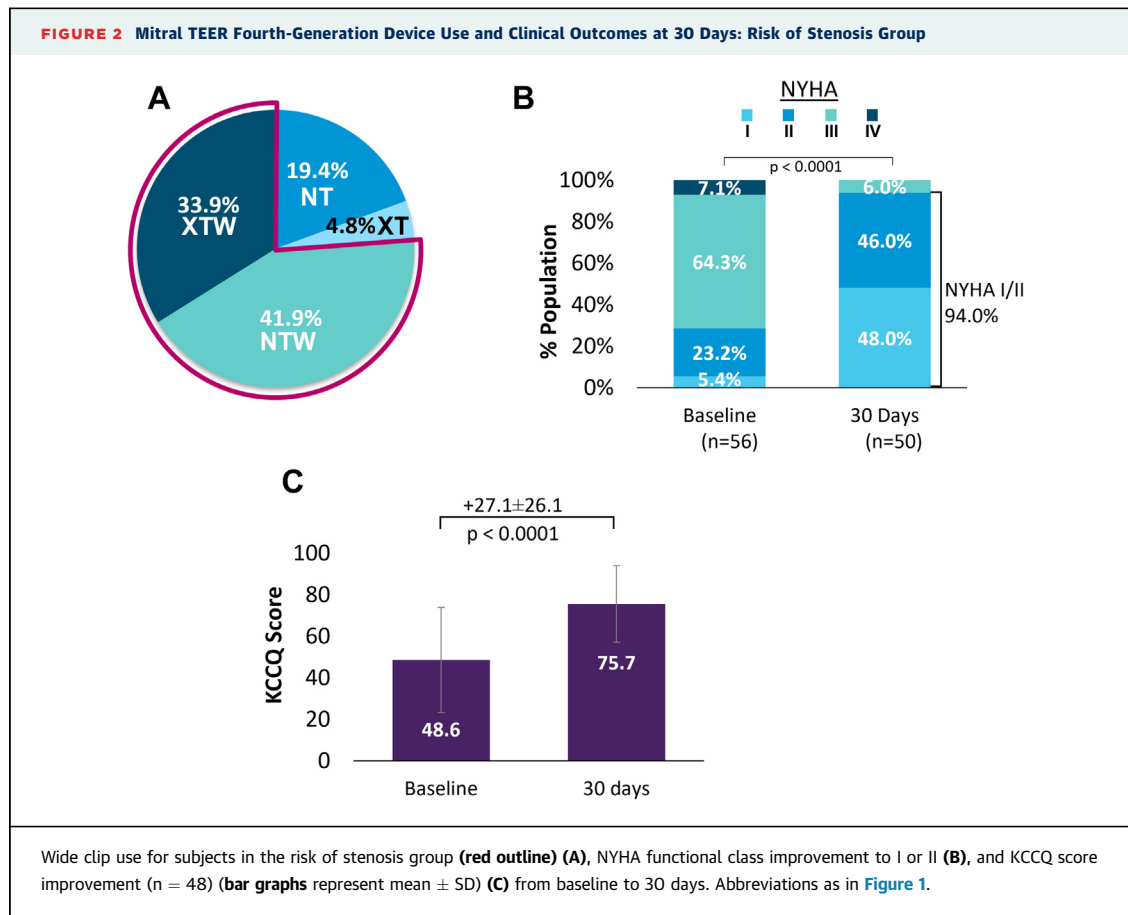
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Real-world outcomes from EXPAND G4 show patients treated with the mitral transcatheter edge-to-edge repair (M-TEER) fourth-generation device in previously proposed transcatheter edge-to-edge repair (TEER)-unsuitable groups (risk of stenosis [RoS], risk of inadequate mitral regurgitation reduction [RoIR], and baseline moderate or less mitral regurgitation [MMR]) and a TEER-suitable (TS) group. In the RoS group, MV gradient increased slightly within clinically acceptable thresholds (3.3 ± 1.6 mm Hg at baseline vs 4.5 ± 1.6 mm Hg at 30 days) and similar outcomes to the TS group. In the RoIR group, 30-day NYHA functional class I or II, KCCQ score, and MAE were similar to those in the TS group, and MR ≤2+ was lower than in the TS group but above clinically acceptable thresholds. In the MMR group, outcomes were similar to those in the TS group. Subjects in all groups (TS, RoS, RoIR, and MMR) had clinically significant MR reduction to ≤1+ (75%–97% of subjects) and low MAE rates through 30 days, including mortality rates <2%, demonstrating the feasibility, safety, and effectiveness of TEER in broader patient populations. Of the 1,164 patients enrolled in EXPAND G4, 739 with evaluable echocardiograms were included in this analysis. MR = mitral regurgitation.

DISCUSSION

A recent HVC consensus document¹⁴ proposed criteria for M-TEER unsuitability on the basis of a physician committee's opinion and clinical experience from previous generation devices. However, this consensus was not informed by contemporary clinical evidence with latest generation devices. To address this knowledge gap, we assessed the clinical and echocardiographic outcomes of subjects treated with the fourth-generation M-TEER system in the real-

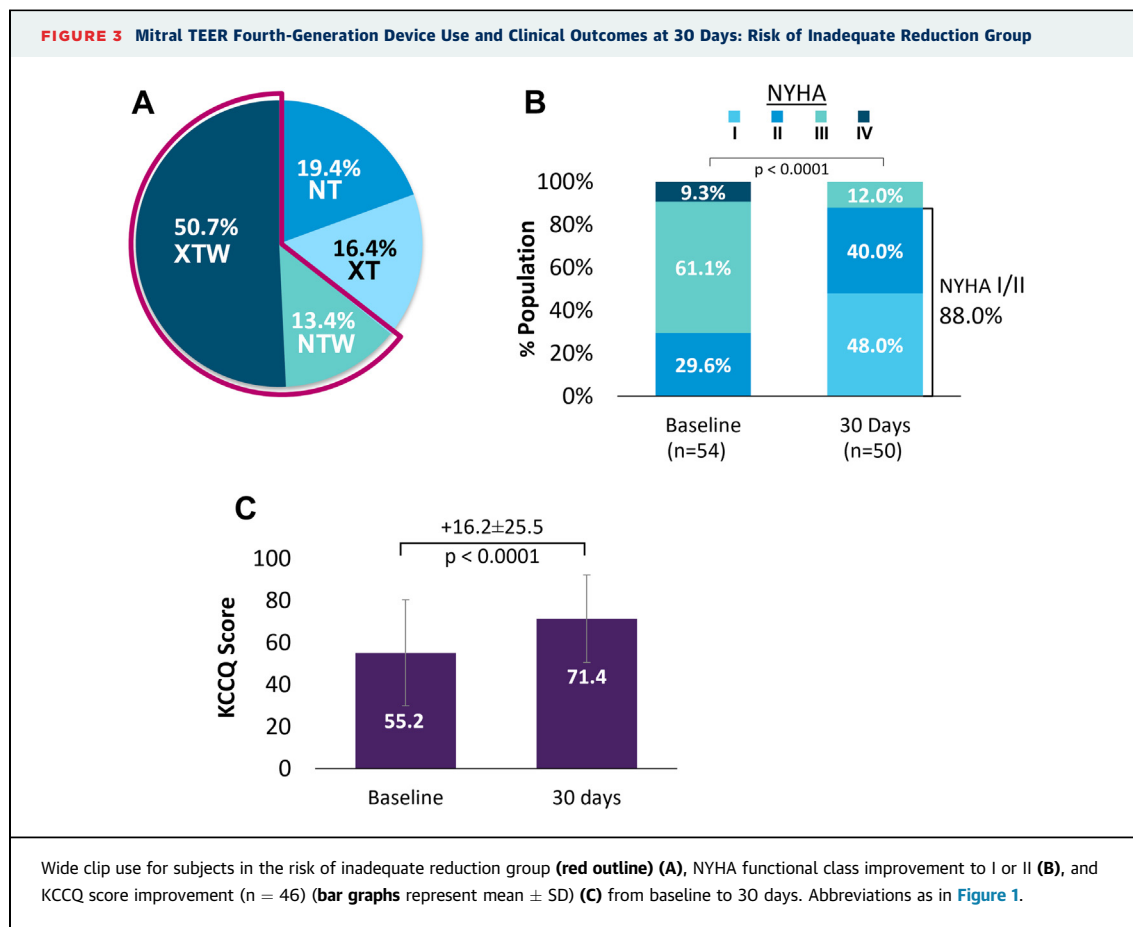
world EXPAND G4 study who were deemed unsuitable according to the HVC consensus document. Our findings suggest that subjects previously deemed unsuitable for M-TEER because of RoS, RoIR because of MV complexity, or baseline MMR had significant MR reductions, improved functional capacity and QoL, and low 30-day MAE rates, broadly similar to those among patients deemed suitable for M-TEER. This evidence-driven assessment demonstrates the feasibility, safety, and effectiveness of TEER across a broad range of patients and underscores the need to



reconsider the TEER suitability criteria using contemporary device technology and implantation techniques.

Although the anatomical exclusion criteria from historic trials (EVEREST II and COAPT) were reflected in the HVC consensus document, there has been limited clinical evidence reported with latest generation technology to support contemporary TEER unsuitability criteria. Our findings provide evidence that treatment of patients with broader MV anatomies with TEER, described in subgroup definitions, is feasible with improvements in device technology, advances in imaging techniques, and increasing operator experience. Our analysis showed that subjects deemed unsuitable by HVC criteria had high implantation success (96%-99%) and APS (>94%) with rapid device times (~32-44 minutes). These subjects achieved significant 30-day improvements in functional capacity (NYHA functional class I or II in 79%-94% at 30 days vs 26%-33% at baseline) and QoL (increases in KCCQ score of +16 to +27 points from

baseline to 30 days) while maintaining safe outcomes. Thirty-day MR reduction to ≤1+ was achieved in >91% of subjects in the TS, RoS, and MMR groups. In the RoIR group, though fewer subjects achieved MR ≤1+ (75.0%), 92.5% of subjects achieved MR ≤2+ at 30 days, demonstrating clinically acceptable MR reduction in a large majority of patients without any MAE occurrences. Encouragingly, these data suggest that TEER can be applied successfully to more complex anatomies when performed by experienced operators and centers. Although the number of patients excluded from TEER by experienced operators is unknown, all patients included in EXPAND G4 were selected for treatment by experienced heart teams with a solid understanding of the TEER procedure. Therefore these patients are not representative of every patient with MR in clinical practice. Although these outcomes may not be achievable at less experienced centers, referral to high-volume centers for complex anatomies should be considered when reasonable. Assessing TEER suitability is a process



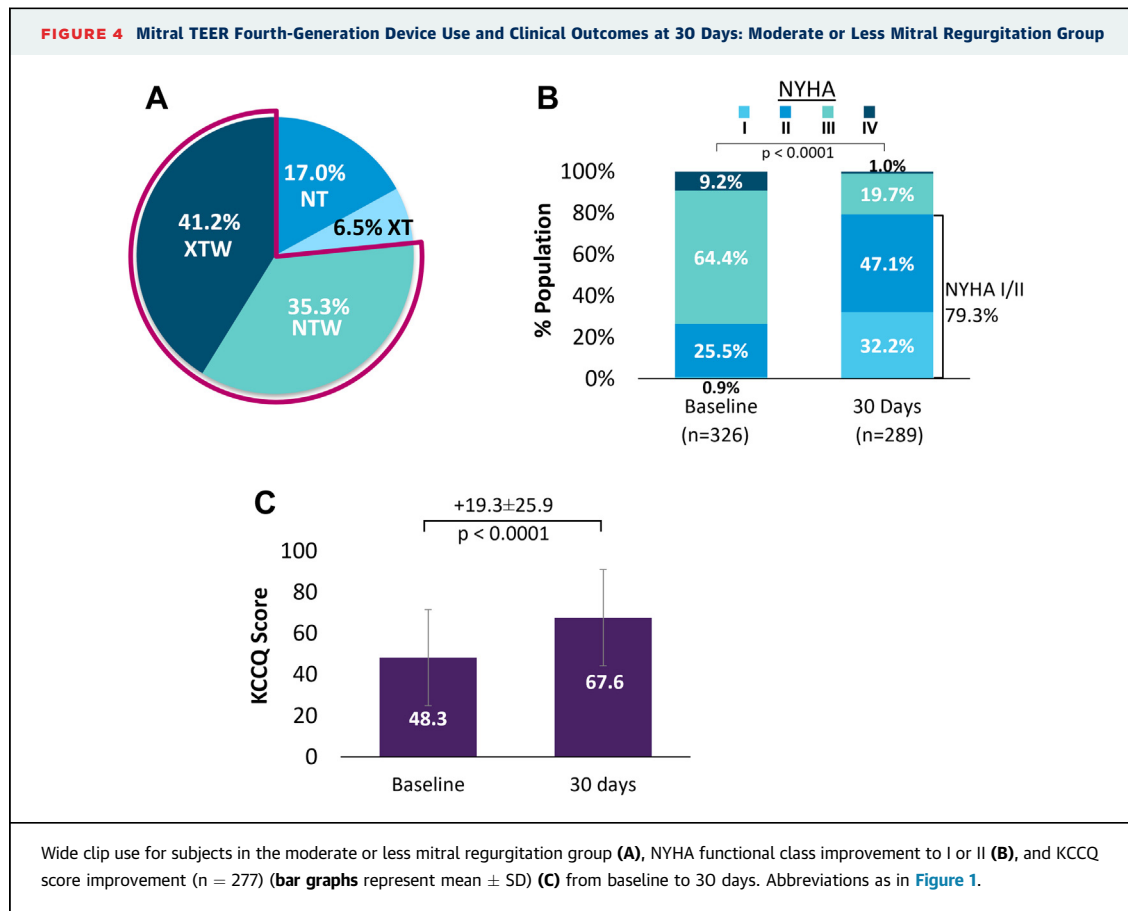
that involves evaluation of patient clinical factors, anatomical leaflet graspability, imaging clarity, and thoughtful assessment of baseline and predicted residual valve area. A limitation of this study is the number of patients with nonevaluable echocardiographic assessments by the ECL who could not be included in this analysis. One-year through 5-year follow-up is actively being collected in EXPAND G4. These early outcomes demonstrate that many patients previously thought to be “unsuitable” can be successfully and safely treated.

This prospective study of patients undergoing clinically indicated TEER with the M-TEER fourth-generation device allowed us to explore outcomes across a broad range of anatomies. TS subjects were treated safely and effectively, achieving high rates of MR reduction (91% MR ≤1+) and improvement in functional capacity and QoL with low MAE rates through 30 days postprocedure. Although RoS subjects were classified as having a high RoS according to the HVC consensus document, subjects were

treated more often with wider clips and achieved the highest MR reduction with relatively small changes in the MV gradient to <5 mm Hg postprocedure, generally considered clinically acceptable, highlighting that RoS did not compromise successful TEER treatment. Furthermore, substantial improvements in functional capacity and QoL were achieved in the RoS group, while maintaining low MAE rates.

Similarly, RoIR subjects were safely and effectively treated despite highly complex MV anatomy. Although MR reduction to ≤1+ at 30 days (75.0%) was less than that observed in other groups, the overwhelming proportion of patients achieved MR ≤2+ (92.5%) with substantially improved functional capacity and QoL, similar to that observed in the TS group. Importantly, the procedure was safe in the RoIR group, without any MAE.

Finally, MMR subjects who would be deemed futile to treat by the HVC consensus document were safely and effectively treated. Despite not having severe



baseline MR according to the ECL, most achieved effective MR reduction to $\leq 1+$ at 30 days, with substantial improvements in functional capacity and QoL, while maintaining safe outcomes, similar to recent findings from the EXPAND study.¹² Regarding the inclusion of patients with MR $\leq 2+$ in EXPAND G4, it is important to recognize that subjects were site selected for inclusion on the basis of the heart team assessment of significant MR using clinical findings and transthoracic and transesophageal echocardiographic images. The ECL assessment of MR grade was based on transthoracic echocardiographic images at a single time point in accordance with multiparametric ASE guidelines. Most patients in the MMR group had SMR (71.3%), which is expected as SMR is dynamic in nature and attributed to MR grade assessment variability.¹⁷ These challenges alongside inherent variability in transthoracic and transesophageal echocardiographic MR severity assessments¹⁷ from center to center and region to region further highlight the challenges in quantitatively assessing MR severity

in a real-world setting. Standardized core laboratory-assessed outcomes of the MMR group underscore the importance of a comprehensive MR assessment in patients prior to TEER, and rather than being associated with futility to treat as outlined in the HVC consensus document, TEER in selected patients with moderate MR may provide improvements in functional capacity and QoL. Similarly, subjects in the EXPAND study with MR $< 3+$ were safely treated with TEER with significant MR reduction, alleviation of symptoms, and QoL improvement at 30 days and 1 year.¹² Further study is required to better delineate the patient population with ASE-defined moderate MR that benefits from TEER.

Real-world, contemporary outcomes from EXPAND G4 show that treatment with TEER in patients previously categorized as “TEER unsuitable” in the HVC consensus document is safe and effective. The HVC consensus assertion that TEER-unsuitable patients may be more appropriate for transcatheter MV replacement is an unanswered question that can be

resolved only in the context of a randomized clinical trial, as many “unsuitable” patients may have favorable outcomes with TEER,¹⁸ and the procedural safety of the 2 approaches may differ considerably. Clinical evidence from the contemporary EXPAND G4 study demonstrates the need to redefine and expand the spectrum of TEER suitability with the latest generation of MV TEER devices. Future guidance documents on TEER suitability should be based on real-world, contemporary outcomes from the latest generation devices to identify patients who could benefit from alternative treatments.

CONCLUSIONS

Outcomes from the EXPAND G4 study show that contemporary TEER with the latest M-TEER fourth-generation device safely provides clinically significant MR reduction and improved functional capacity and QoL in patients deemed unsuitable for TEER in an HVC consensus document and traditionally considered to be anatomically unsuitable for the procedure, including those at risk for stenosis and complex anatomies. This data-driven analysis demonstrates the expanding spectrum of TEER suitability on the basis of contemporary outcomes from the latest generation devices.

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PERSPECTIVES

WHAT IS KNOWN? TEER unsuitability criteria for the treatment of MR have been proposed on the basis of a consensus opinion but are not supported by contemporary evidence. EXPAND G4 is a contemporary real-world study of the effectiveness and safety of the MitraClip G4 System.

WHAT IS NEW? Real-world outcomes from EXPAND G4 show that treatment of patients with the M-TEER fourth-generation device in previously proposed TEER-unsuitable groups is feasible and resulted in clinically meaningful MR reduction with high procedural safety.

WHAT IS NEXT? Future TEER suitability guidance documents should be based on contemporary outcomes with latest generation devices.

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

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