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ORIGINAL RESEARCH

Using Transmitral Pressure Gradients and Residual Mitral Regurgitation to Optimize Outcome After Transcatheter Edge-to-Edge Repair

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ABSTRACT

BACKGROUND Although reducing mitral regurgitation (MR) after mitral transcatheter edge-to-edge repair (M-TEER) improves outcomes, the impact of increased transmitral mean pressure gradient (TMPG) remains controversial.

OBJECTIVES This study aimed to evaluate the clinical significance of MR reduction and TMPG elevation in patients with functional mitral regurgitation (FMR) after M-TEER.

METHODS A total of 2,360 FMR patients were evaluated using postdischarge echocardiography after M-TEER. The relationship between TMPG and outcomes was assessed using spline analysis and group-based comparisons. Based on residual MR severity and TMPG, patients were categorized into 5 groups to assess the prognostic impact of postprocedural hemodynamics: MR ≤ mild and TMPG <5 mm Hg (n = 1,702), MR ≤ mild and TMPG ≥5 to <10 mm Hg (n = 164), moderate MR and TMPG <5 mm Hg (n = 361), moderate MR and TMPG ≥5 to <10 mm Hg (n = 71), and MR > moderate or TMPG 10 mm Hg (n = 62). The primary endpoint was all-cause death or heart failure hospitalization.

RESULTS The 2-year primary endpoint event rates increased progressively with higher TMPG, from 25.0% at 1 mm Hg to 47.0% at 6 mm Hg. In multivariable analysis, TMPG per 1 mm Hg increment was independently associated with the primary endpoint (HR: 1.10; 95% CI: 1.02-1.17; $P = 0.008$). Using MR ≤ mild as the reference, moderate MR was not linked to higher risk, whereas MR > moderate remained a significant predictor of primary endpoint. The patients with MR ≤ mild and TMPG <5 mm Hg had the lowest incidence of the primary endpoint among the 5 groups (28.4%, 39.0%, 33.0%, 43.7%, 48.4%; $P < 0.001$). However, event risk was not significantly different between patients with moderate MR and TMPG <5 mm Hg and those with MR ≤ mild and TMPG <5 mm Hg (HR: 1.13; 95% CI: 0.92-1.41; $P = 0.24$). Failure to achieve MR ≤ mild and TMPG <5 mm Hg was associated with larger left atrial volume index, greater effective regurgitation orifice area, elevated baseline TMPG, and old-generation G2 device use.

CONCLUSIONS In patients with FMR, elevated TMPG was consistently associated with higher risks of the primary endpoint. Mild or moderate residual MR with low TMPG was associated with more favorable prognosis, suggesting that balancing MR reduction and TMPG may help refine risk stratification after M-TEER. (Japanese Registry study of valvular heart diseases treatment and prognosis; UMIN000023653) (JACC. 2025;86:1684-1700) © 2025 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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Mitral valve transcatheter edge-to-edge repair (M-TEER) has been developed as a less invasive catheter-based treatment for patients with mitral regurgitation (MR).[1] Two major randomized controlled trials (RCTs) investigating patients with functional mitral regurgitation (FMR) have demonstrated that M-TEER reduces the risk of cardiovascular (CV) mortality and heart failure (HF) hospitalization compared with optimal medical therapy alone.[2,3] The reduction of MR after M-TEER and its association with improved prognosis in FMR patients has been well-established in numerous previous studies.[4-6]

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Given the rationale of edge-to-edge leaflet approximation, the M-TEER may potentially lead to a risk of mitral stenosis. Large-scale data from the STS/TVT (Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy) Registry have shown that, in patients with degenerative mitral regurgitation (DMR), elevated transmitral pressure gradient (TMPG) in addition to residual MR is strongly associated with adverse prognosis.[7] Although a combination of MR reduction without an increase in TMPG has been considered ideal, it remains inconclusive whether the postprocedural TMPG is associated with outcomes in patients with FMR. A few studies have suggested that TMPG elevation could be a marker of poor prognosis for FMR.[8,9] In contrast, recent analyses, including a subanalysis from the RCT, show conflicting results regarding its prognostic significance.[10-13] Moreover, the residual MR itself could be contributing to the increase in TMPG after M-TEER. Investigating this gap of evidence is important to refine the patient selection of M-TEER and to improve their clinical practice. Therefore, we used large-scale multicenter data from Japan to examine the impact of residual MR and TMPG after M-TEER on the clinical outcomes in patients with FMR.

ABBREVIATIONS AND ACRONYMS

FMR = functional mitral regurgitation

LAVI = left atrium volume index

MR = mitral regurgitation

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

TMPG = transmitral mean pressure gradient

METHODS

STUDY POPULATION. The OCEAN (Optimized CathEter vAlvular iNtervention)-Mitral registry is an ongoing, prospective, investigator-initiated, multicenter registry from Japan that evaluates the safety and efficacy of M-TEER in patients with MR.[6,14] The data comprised 3,764 patients with symptomatic MR who underwent M-TEER between April 2018 and June 2023. Of the patients included in this study, 2,635 were classified as having FMR. Patients were excluded if the MitraClip was not implanted because of deployment failure or unacceptable increased TMPG (n = 15), if any additional mitral valve intervention was performed before discharge (n = 24), or if data on MR and/or TMPG at discharge were missing (n = 236). A total of 2,360 patients remained, comprising the initial study population. To align with DMR data from the STS/TVT Registry,[7] patients were also categorized into 5 groups based on postdischarge

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

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CENTRAL ILLUSTRATION Clinical Impact of Transmitral Pressure Gradients and Residual Mitral Regurgitation

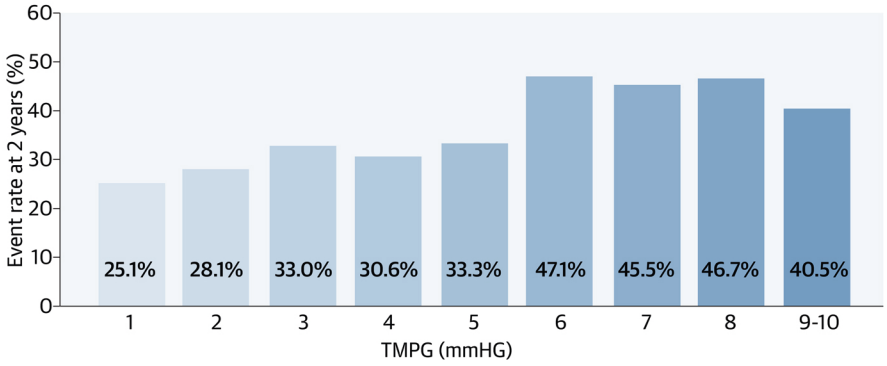
Does post trans-mitral mean pressure gradient (TMPG) impact long term outcomes in functional mitral regurgitation (FMR) after mitral-transcatheter edge-to-edge repair (M-TEER)?

2360 patients with FMR undergoing M-TEER from the OCEAN-Mitral registry (2018-20230)

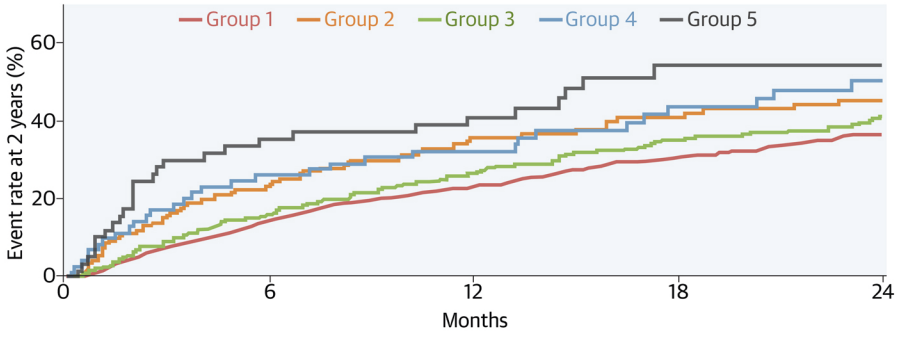
Group 1	Group 2	Group 3	Group 4	Group 5
Mild MR or less/ TMPG <5 mmHg	Mild MR or less/ TMPG ≥5 to <10 mmHg	Moderate MR/ TMPG <5 mmHg	Moderate MR/ TMPG ≥5 to <10 mmHg	Unsuccessful

Primary endpoint:
2-year all-cause death or heart failure hospitalization

All-cause death or heart failure hospitalization at 2 years (%) satisfied by TMPG per 1 mmHg increments



All-cause death or heart failure hospitalization at 2 years (%) satisfied by 5 groups based on residual MR and TMPG



Group 1 → ✓ Best outcome → ↓ MR and avoid TMPG ↑

Higher TMPG after M-TEER is associated with worse outcomes, regardless of MR severity.

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echocardiographic findings. For residual MR severity: MR ≤ mild, moderate MR, and MR > moderate. For postprocedural TMPG: <5 and ≥5 mm Hg. Because there were no patients with TMPG >10 mm Hg in this cohort, we used a practical upper limit of 10 mm Hg for TMPG categorization. Patients were further categorized into 5 groups: 1) MR ≤ mild and TMPG <5 mm Hg; 2) MR ≤ mild and TMPG ≥5 to <10 mm Hg; 3) moderate MR and TMPG <5 mm Hg; 4) moderate MR and TMPG ≥5 to <10 mm Hg; and 5) MR > moderate or TMPG 10 mm Hg (unsuccessful). This study was registered with the University Hospital Medical Information Network Clinical Trials Registry, as accepted by the International Committee of Medical Journal Editors (UMIN000023653). All study participants provided informed consent, and the study protocol was approved by the Institutional Review Board of each institution. The study was conducted following the provisions of the Declaration of Helsinki and the guidelines for epidemiological studies issued by the Ministry of Health, Labour, and Welfare of Japan.

DATA COLLECTION AND ECHOCARDIOGRAPHIC EVALUATION. Clinical information of baseline characteristics, laboratory data, echocardiographic findings, and procedural variables were collected for all patients. Clinical follow-up was performed annually after M-TEER, including at baseline and discharge or 1 month. During each visit, patients were assessed for any occurrences of HF hospitalization following M-TEER. If patients were unable to attend a hospital visit, clinical information, such as death or HF hospitalization details, was gathered through phone interviews with the patients, their family members, or relatives. The severity of MR and TMPG was determined based on qualitative and quantitative criteria according to the American Society of Echocardiography guidelines.[15] The preprocedural and postprocedural MR severity was classified as none/trivial, mild, moderate, moderate to severe, or severe. The TMPG was measured using continuous Doppler waveform analysis of the mitral diastolic inflow, as outlined in the guidelines. In patients with atrial fibrillation, the average value was calculated from 3 to 5 consecutive beats.

DETAILED M-TEER PROCEDURE. The MitraClip (Abbott Vascular), a commercially available M-TEER device in Japan, was used during this study period. Initially, only the Generation 2 (G2) system was available in Japan, which corresponds solely to the MitraClip NT device. The G3 system was not introduced in Japan; instead, the next generation device was the MitraClip G4 system, launched in September 2020. The G4 system offers 4 size options—NT, NTW, XT, and XTW—designed to accommodate a range of mitral valve morphologies. The detailed M-TEER procedure has been previously reported.[6,14] Acceptable MR reduction after mitral valve clipping was defined as a postprocedural MR ≤ moderate using perioperative TEE findings. The acute procedural success of M-TEER was determined to maintain procedural safety without life-threatening complications and adequate MR reduction ≤ moderate MR at discharge, based on a previous formula and our data.[1]

CLINICAL OUTCOMES AND ENDPOINT. Patients with FMR were categorized into ventricular functional mitral regurgitation (VFMR) and atrial functional mitral regurgitation (AFMR), with the definition of AFMR based on previous consensus documents.[16] The primary endpoint of this study was the 2-year incidence of all-cause death and HF hospitalization after M-TEER. CV death, all-cause death, and HF hospitalization were also evaluated. The CV death and HF hospitalization was assessed using the Mitral Valve Academic Research Consortium criteria.[17] Clinical outcomes were evaluated for the overall FMR population as well as separately for each subtype, VFMR and AFMR. The primary objective was to evaluate the prognostic value of TMPG as a continuous variable after M-TEER. Cumulative event rates of the primary endpoint were calculated for each 1-mm Hg increment of TMPG. Subsequently, secondary analyses were performed, including evaluation of the combined impact of MR grade and TMPG, as well as assessments across 5 prespecified subgroups.

CENTRAL ILLUSTRATION Continued

(A) Study flowchart. (B) Kaplan-Meier analysis of primary endpoint as all-cause death or heart failure hospitalization between the 5 groups. (C) Bar graph showing the 2-year event rates of all-cause death or heart failure hospitalization according to transmitral mean pressure gradient (TMPG) values at each 1-mm Hg increment. (D) Bar graph comparing primary endpoints among the 5 groups. Patients were stratified into 5 groups based on postprocedural outcomes: 1) mitral regurgitation (MR) ≤ mild and TMPG <5 mm Hg; 2) MR ≤ mild and TMPG ≥5 to <10 mm Hg; 3) moderate MR and TMPG <5 mm Hg; 4) moderate MR and TMPG ≥5 to <10 mm Hg; and 5) unsuccessful procedure. M-TEER = mitral valve transcatheter edge-to-edge repair.

STATISTICAL ANALYSIS. Data were expressed as mean ± SD or median (Q1-Q3) for continuous variables and as frequency (percentage) for categorical variables unless otherwise specified. Group comparisons were performed using the chi-square test for categorical variables and either the Student's *t*-test or the Mann-Whitney *U* test for continuous variables, depending on their distribution. Statistical significance was set at $P < 0.05$, with 95% CIs reported where appropriate. The cumulative incidences were generated using the Kaplan-Meier method for the primary endpoint, and other outcomes were assessed via the log-rank test. Restricted cubic spline Cox regression analysis was used as the primary analysis to assess the continuous relationship between TMPG and clinical outcomes, with analysis performed for each 1-mm Hg increment from 1 to 10 mm Hg. Univariable Cox regression analysis was performed to estimate HRs for the clinical outcomes. HRs were derived from a model adjusted for age, gender, left ventricle (LV) volume, and clinical variables with $P < 0.05$ in univariable analysis. Given the complexity of the multivariable analysis, 2 complementary models were constructed. In Model 1, a multivariable Cox regression was performed to evaluate the independent association of MR severity (≤ mild as reference, moderate, and > moderate) and TMPG (per 1-mm Hg increase) with clinical outcomes, adjusting for baseline clinical characteristics and variables with a univariable *P* value <0.05. In Model 2, we conducted a categorical analysis based on 5 predefined groups combining MR severity and TMPG levels. To estimate the ORs associated with achieving MR ≤ mild and TMPG <5 mm Hg, multivariable models adjusted for confounding factors with $P < 0.05$ in univariable analysis were also investigated. The interaction between various factors and the primary endpoint was evaluated using a forest plot, which examined the occurrence of the primary endpoint across different patient subgroups with varying baseline characteristics. Based on the inclusion criteria from previous RCTs,[2,3] COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation)-like and RESHAPE-HF2 (Randomized Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation)-like cohorts were created. Due to missing data in the registry for certain measurement items, the inclusion criteria do not exactly match and were therefore modified. The modified criteria are presented in Supplemental Table 1. All statistical analyses were performed using IBM SPSS software version 22 (IBM Corp) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS AND PROCEDURAL OUTCOMES. The overall cohort comprised 2,360 patients with functional MR, including 1,889 patients (80.0%) with VFMR and 471 patients (20.0%) with AFMR. Based on postprocedural residual MR severity and TMPG levels, patients were categorized into 5 prespecified combined strata: 1,702 patients (72.1%) achieved MR ≤ mild and TMPG <5 mm Hg, 164 patients (6.9%) had MR ≤ mild and TMPG ≥5 to <10 mm Hg, 361 patients (15.3%) had moderate MR and TMPG <5 mm Hg, 71 patients (3.0%) had moderate MR and TMPG ≥5 to <10 mm Hg, and 62 patients (2.6%) had MR > moderate or TMPG 10 mm Hg (**Central Illustration**). The patient characteristics, laboratory parameters, medical therapy, echocardiographic findings, and procedural outcomes are summarized in **Tables 1 and 2**. Significant differences were observed among groups concerning male gender, body surface area (BSA), baseline comorbidities, laboratory data, medical therapy, and echocardiographic data. The prevalence of G2 device usage was lowest in MR ≤ mild and TMPG <5 mm Hg (38%) compared with others.

CLINICAL OUTCOMES OF POSTPROCEDURAL TMPG AND SUBGROUP ASSESSMENTS. The TMPG values at each 1-mm Hg increment and corresponding event rates are illustrated in the **Central Illustration**, showing progressive increases from 25% at 1 mm Hg to 47% at 6 mm Hg. The histogram of postprocedural TMPG and restricted cubic spline analysis are shown in **Figure 1**. In addition, for both VFMR and AFMR, histograms of postprocedural TMPG values and bar graphs showing the relationship between TMPG and the primary endpoint have been added (**Figure 2**). The spline curve demonstrates the elevated risk of the primary endpoint with increasing TMPG values. The Kaplan-Meier curves for the primary endpoint are compared across the 5 groups at 2-year event rates (28.4%, 39.0%, 33.0%, 43.7%, and 48.4%; $P < 0.001$) in the **Central Illustration**. Additionally, a comparison across the 5 groups was performed for each endpoint, including all-cause death, CV death, and HF hospitalization, as shown in **Figure 3**. In **Figure 4**, the incidence of the primary endpoint is presented for each group, based on the etiology of FMR. VFMR patients had 2-year primary endpoint rates of 29.8%, 43.0%, 33.6%, 41.5%, and 46.0% across the 5 groups, respectively ($P = 0.002$), while AFMR patients

TABLE 1 Baseline Clinical Characteristics According to Residual MR and Transmitral Mean Pressure Gradient

	n	All Patients (N = 2,360)	MR ≤ Mild TMPG <5 mm Hg (n = 1,702)	MR ≤ Mild TMPG ≥5 to <10 mm Hg (n = 164)	MR = Moderate TMPG <5 mm Hg (n = 361)	MR = Moderate TMPG ≥5 to <10 mm Hg (n = 71)	MR > Moderate or TMPG 10 mm Hg (n = 62)	*P* Value
Clinical data								
Age, y	2,360	77.0 ± 9.5	76.9 ± 9.5	79.5 ± 9.2	76.4 ± 9.9	76.3 ± 9.5	78.3 ± 7.9	0.006
Male	2,360	1,401 (59.4)	1,035 (60.8)	74 (45.1)	218 (60.4)	36 (50.7)	38 (61.3)	0.001
Body surface area, m^2	2,360	1.53 ± 0.2	1.54 ± 0.2	1.48 ± 0.2	1.52 ± 0.2	1.49 ± 0.2	1.50 ± 0.2	0.003
NYHA functional class III or IV	2,360	1,522 (64.5)	1,105 (64.9)	105 (64.0)	221 (61.2)	47 (66.2)	44 (71.0)	0.55
CFS ≥4	2,360	1,205 (51.1)	843 (49.5)	98 (59.8)	196 (54.3)	38 (53.5)	30 (48.4)	0.08
STS score for mitral valve replacement	2,211	11.2 ± 8.2	10.7 ± 7.9	12.7 ± 8.0	11.5 ± 9.0	13.8 ± 10.0	13.9 ± 10.1	<0.001
Previous HF hospitalization	2,360	1,851 (78.4)	1,346 (79.1)	118 (72.0)	281 (77.8)	56 (78.9)	50 (80.6)	0.02
Comorbidity								
Hypertension	2,360	1,473 (62.4)	1,049 (61.6)	118 (72.0)	221 (61.2)	43 (60.6)	42 (67.7)	0.10
Diabetes mellitus	2,360	740 (31.4)	558 (32.8)	53 (32.3)	95 (26.3)	15 (21.1)	19 (30.6)	0.05
Atrial fibrillation	2,360	1,502 (63.6)	1,074 (63.1)	91 (55.5)	249 (69.0)	45 (63.4)	43 (69.4)	0.04
Coronary artery disease	2,360	976 (41.4)	733 (43.1)	65 (39.6)	132 (36.6)	23 (32.4)	23 (37.1)	0.08
Chronic kidney disease	2,360	2,078 (88.1)	1,494 (87.8)	149 (90.9)	313 (86.7)	66 (93.0)	56 (90.3)	0.42
Dialysis	2,360	166 (7.0)	106 (6.2)	27 (16.5)	23 (6.4)	5 (7.0)	5 (8.1)	<0.001
Stroke/transient ischemic attack	2,360	261 (11.1)	191 (11.2)	18 (11.0)	42 (11.6)	6 (8.5)	4 (6.5)	0.81
Chronic obstructive pulmonary disease	2,360	198 (8.4)	133 (7.8)	15 (9.1)	38 (10.5)	7 (9.9)	5 (8.1)	0.52
Cardiac rhythm device implant								0.005
Pacemaker	2,360	187 (7.9)	125 (7.3)	25 (15.2)	23 (6.4)	8 (11.3)	6 (9.7)	
ICD	2,360	144 (6.1)	115 (6.8)	4 (2.4)	21 (5.8)	2 (2.8)	2 (3.2)	
CRT-P	2,360	42 (1.8)	28 (1.6)	1 (0.6)	9 (2.5)	2 (2.8)	2 (3.2)	
CRT-D	2,360	279 (11.8)	202 (11.9)	10 (6.1)	49 (13.6)	6 (8.5)	12 (19.4)	
Blood examination								
Hemoglobin, g/dL	2,360	11.7 ± 1.9	11.8 ± 1.9	11.0 ± 1.6	11.8 ± 1.8	11.0 ± 1.8	11.6 ± 1.6	<0.001
BNP, pg/mL	1,737	425 (213-814)	414 (203-784)	404 (222-812)	447 (232.4-1,058)	494 (263-1,122)	542 (284-755)	0.20
NT-proBNP	1,249	3,146 (1,534-6,417)	3,117 (1,550-6,428)	3,599 (1,450-8,846)	3,307 (1,570-6,030)	2,915 (1,380-6,534)	2,725 (2,096-4,799)	0.89
eGFR, mL/min/1.73 m^2	2,347	37.6 ± 19.4	37.9 ± 19.1	33.2 ± 20.1	38.5 ± 20.0	36.1 ± 20.7	36.2 ± 17.8	0.04
Medications on admission								
ACEIs/ARBs/ARNI	2,360	1,544 (65.4)	1,114 (65.5)	106 (64.6)	248 (68.7)	43 (60.6)	33 (53.2)	0.16
β-blocker	2,335	1,894 (80.3)	1,391 (81.7)	115 (70.1)	280 (77.6)	55 (77.5)	53 (85.5)	0.001
SGLT2 inhibitors	2,360	606 (25.7)	474 (27.8)	23 (14.0)	86 (23.8)	8 (11.3)	15 (24.2)	*P* < 0.001
MRAs	2,352	1,379 (58.4)	1,027 (60.3)	64 (39.0)	221 (61.2)	34 (47.9)	33 (53.2)	*P* < 0.001
Diuretics	2,360	1,948 (82.5)	1,412 (83.0)	126 (76.8)	301 (83.4)	58 (81.7)	51 (82.3)	0.39

Values are n, mean ± SD, n (%), or median (Q1-Q3).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; BNP = B-type natriuretic peptide; CFS = Clinical Frailty Scale; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT2 = sodium-glucose cotransporter-2; STS = Society of Thoracic Surgeons; TMPG = transmitral mean pressure gradient.

(n = 471) demonstrated corresponding rates of 22.7%, 30.0%, 30.4%, 50.0%, and 58.3% ($P < 0.001$). For MR severity analysis in Supplemental Figures 1A to 1C, no significant differences were observed between MR ≤ mild and moderate MR in the overall cohort ($P = 0.06$) and VFMR patients ($P = 0.20$), while AFMR patients demonstrated a significant difference between these groups ($P = 0.04$). For TMPG analysis in Supplemental Figures 1D to 1F, patients with TMPG ≥5 mm Hg had significantly worse outcomes compared with those with TMPG <5 mm Hg across all groups: overall cohort ($P < 0.001$), ventricular FMR ($P = 0.005$), and atrial FMR ($P = 0.02$).

THE PREDICTIVE RISK FACTORS OF NON-MR ≤MILD AND TMPG ≤5 MM HG. The multivariable analysis identified the predictive risk factors for not achieving MR ≤ mild and TMPG ≤5 mm Hg after M-TEER (Table 3). The independent risk factors for not achieving MR ≤ mild and TMPG ≤5 mm Hg were left atrium volume index (LAVI) per 10-mL/m^2 increment (OR: 1.00; 95% CI: 1.00-1.01; $P = 0.003$), effective regurgitant orifice area per 0.1-cm^2 increment (OR: 1.11; 95% CI: 1.04-1.20; $P = 0.003$), preprocedural TMPG per 1-mm Hg increment (OR: 1.50; 95% CI: 1.33-1.70; $P < 0.001$), and G2 device usage (OR: 1.27; 95% CI: 1.03-1.58; $P = 0.03$).

TABLE 2 Baseline Echocardiographic Findings and Procedural Characteristics and Outcomes of M-TEER: Comparison Between the 5 Groups Categorized Residual MR Severity and Post-TMPG Values

	n	All Patients (N = 2,360)	MR ≤ Mild TMPG <5 mm Hg (n = 1,702)	MR ≤ Mild TMPG ≥5 to <10 mm Hg (n = 164)	MR = Moderate TMPG <5 mm Hg (n = 361)	MR = Moderate TMPG ≥5 to <10 mm Hg (n = 71)	MR > Moderate or TMPG 10 mm Hg (n = 62)	*P* Value
Transthoracic echocardiography								
LV EDD, mm	2,360	59.3 ± 10.2	59.1 ± 10.2	55.3 ± 8.6	61.6 ± 10.9	58.4 ± 7.6	62.6 ± 9.6	<0.001
LV ESD, mm	2,359	48.4 ± 12.7	48.5 ± 12.6	43.6 ± 11.6	50.3 ± 13.6	45.3 ± 10.8	51.0 ± 11.5	<0.001
LV EDV, mL	2,277	161.4 ± 73.4	160.5 ± 73.1	142.6 ± 61.9	172.9 ± 79.3	158.9 ± 63.9	170.3 ± 74.8	<0.001
LV ESV, mL	2,360	107.9 ± 64.4	108.5 ± 64.5	90.1 ± 53.0	114.4 ± 68.6	96.1 ± 55.8	111.4 ± 64.1	0.001
LV EF, %	2,360	38.6 ± 14.1	37.9 ± 13.9	42.4 ± 14.9	38.8 ± 14.2	44.0 ± 14.0	40.6 ± 14.7	<0.001
Left atrial diameter, mm	2,347	50.3 ± 9.9	49.5 ± 9.4	48.2 ± 8.3	52.8 ± 10.8	54.5 ± 11.3	56.9 ± 13.1	<0.001
LAVI, mL/m^2	2,269	88.9 ± 55.1	83.6 ± 49.0	81.2 ± 48.2	105.3 ± 63.5	109.3 ± 62.7	135.5 ± 102.1	<0.001
Etiology of FMR								<0.001
Ischemic VFMR	2,360	719 (30.5)	554 (32.5)	43 (26.2)	92 (25.5)	14 (19.7)	16 (25.8)	
Nonischemic VFMR	2,360	1,170 (49.6)	826 (48.5)	71 (43.3)	200 (55.4)	39 (54.9)	34 (54.8)	
AFMR	2,360	471 (20.0)	322 (18.9)	50 (30.5)	69 (19.1)	18 (25.4)	12 (19.4)	
MR grade	2,360							<0.001
Moderate		367 (15.6)	300 (17.6)	28 (17.1)	34 (9.4)	2 (2.8)	367 (15.6)	
Moderate-severe		744 (31.5)	587 (34.5)	50 (30.5)	89 (24.7)	12 (16.9)	6 (9.7)	
Severe		1,249 (52.9)	815 (47.9)	86 (52.4)	238 (65.9)	57 (80.3)	53 (85.5)	
Vena contracta, mm	1,700	6.9 ± 3.5	6.8 ± 3.4	6.4 ± 3.8	7.6 ± 3.6	7.1 ± 3.5	7.9 ± 4.1	0.001
EROA, cm^2	2,114	0.34 ± 0.16	0.33 ± 0.15	0.32 ± 0.13	0.39 ± 0.18	0.38 ± 0.15	0.34 ± 0.16	<0.001
Regurgitant volume, mL	2,182	50.5 ± 27.9	48.8 ± 29.2	50.1 ± 21.3	54.6 ± 22.9	57.7 ± 23.6	65.7 ± 31.0	<0.001
TMPG, mm Hg	2,192	1.7 ± 0.9	1.6 ± 0.8	2.0 ± 1.0	1.8 ± 0.9	2.6 ± 1.0	2.2 ± 1.3	<0.001
TRPG, mm Hg	2,292	33.6 ± 13.3	33.1 ± 13.3	34.1 ± 13.0	34.7 ± 13.0	37.9 ± 13.5	34.8 ± 11.4	0.01
Estimated PASP, mm Hg	2,002	40.4 ± 15.0	39.8 ± 15.1	40.1 ± 13.9	42.1 ± 15.0	44.9 ± 14.6	41.7 ± 13.6	0.01
TAPSE, mm	1,945	15.8 ± 4.6	15.7 ± 4.7	16.6 ± 4.4	15.8 ± 4.4	16.0 ± 4.7	15.3 ± 5.3	0.30
Transesophageal echocardiography								
Coaptation length <2 mm	1,453	289 (12.2)	221 (13.0)	19 (11.6)	39 (10.8)	5 (7.0)	5 (8.1)	0.90
Tenting height ≥11 mm	1,847	280 (11.9)	199 (11.7)	11 (6.7)	55 (15.2)	4 (5.6)	11 (17.7)	0.01
Posterior leaflet length <10 mm	2,183	635 (26.9)	447 (26.3)	64 (39.0)	82 (22.7)	20 (28.2)	22 (35.5)	0.001
MAC	2,360	342 (14.5)	242 (14.2)	27 (16.5)	50 (13.9)	12 (16.9)	11 (17.7)	0.81
PVF pattern	2,020							0.06
S>D		221 (9.4)	162 (9.5)	19 (11.6)	34 (9.4)	3 (4.2)	3 (4.8)	
S<D		932 (39.5)	700 (41.1)	59 (36.0)	125 (34.6)	26 (36.6)	22 (35.5)	
Systolic R		867 (36.7)	595 (35.0)	62 (37.8)	148 (41.0)	31 (43.7)	31 (50.0)	
MVA, cm^2		5.2 ± 1.6	5.2 ± 1.6	4.4 ± 1.4	5.6 ± 1.8	4.6 ± 1.3	5.5 ± 1.6	<0.001

Continued on the next page

INDEPENDENT PROGNOSTIC SIGNIFICANCE OF RESIDUAL MR AND TMPG. The results of Cox regression multivariable analysis were shown in Table 4. TMPG per 1-mm Hg increment was independently associated with the primary endpoint (HR: 1.10; 95% CI: 1.02-1.17; $P = 0.008$). MR ≤ mild as reference, the outcomes were not significantly different between ≤ mild and moderate residual MR (HR: 1.04; 95% CI: 0.66-1.62; $P = 0.88$), but were significantly worse in patients with > moderate residual MR (HR: 3.36; 95% CI: 1.13-9.98; $P = 0.03$). Analysis of 5 groups (Model 2) revealed that patients with moderate MR and TMPG <5 mm Hg showed similar outcomes to those with ≤ mild MR and TMPG <5 mm Hg (HR: 1.13; 95% CI: 0.92-1.41; $P = 0.24$), while all groups with TMPG ≥5 mm Hg or > moderate MR had significantly worse outcomes. In the VFMR subgroup (80% of cohort), TMPG per 1 mm Hg remained a significant predictor (HR: 1.10; 95% CI: 1.01-1.18; $P = 0.02$). Comparing MR ≤mild and TMPG <5 mm Hg and other groups, the interaction related to the primary endpoint was assessed using a forest plot, which evaluated the occurrence of the primary endpoint across different patient groups with varying backgrounds (Figure 5).

DISCUSSION

This is the largest study of patients with FMR undergoing M-TEER that has been reported to date. The main findings of this study were as follows: 1) postprocedural TMPG elevation was consistently

TABLE 2 Continued

	n	All Patients (N = 2,360)	MR ≤ Mild TMPG <5 mm Hg (n = 1,702)	MR ≤ Mild TMPG ≥5 to <10 mm Hg (n = 164)	MR = Moderate TMPG <5 mm Hg (n = 361)	MR = Moderate TMPG ≥5 to <10 mm Hg (n = 71)	MR > Moderate or TMPG 10 mm Hg (n = 62)	*P* Value
Procedural characteristics and outcomes								
Procedural time, min	2,205	88.8 ± 45.0	83.9 ± 40.2	91.1 ± 45.8	102.0 ± 49.7	103.9 ± 56.9	121.6 ± 78.7	<0.001
Device generation	2,360							0.15
G2 (NT)		932 (39.5)	648 (38.1)	76 (46.3)	150 (41.6)	29 (40.8)	29 (46.8)	
G4		1,428 (60.5)	1,054 (61.9)	88 (53.7)	211 (58.4)	42 (59.2)	33 (53.2)	
Number of implanted clips								<0.001
1		1,785 (75.6)	1,332 (78.3)	115 (70.1)	261 (72.3)	45 (63.4)	32 (51.6)	
2		551 (23.3)	362 (21.3)	48 (29.3)	90 (24.9)	25 (35.2)	26 (41.9)	
3		24 (1.0)	8 (0.5)	1 (0.6)	10 (2.8)	1 (1.4)	4 (6.5)	
First clip type	2,360				n			0.001
NT (G2)		932 (39.5)	648 (38.1)	76 (46.3)	150 (41.6)	29 (40.8)	29 (46.8)	
NT (G4)		258 (10.9)	185 (10.9)	27 (16.5)	31 (8.6)	10 (14.1)	5 (8.1)	
NTW		673 (28.5)	504 (29.6)	43 (26.2)	88 (24.4)	25 (35.2)	13 (21.0)	
XT		42 (1.8)	26 (1.5)	2 (1.2)	13 (3.6)	0 (0.0)	1 (1.6)	
XTW		455 (19.3)	339 (19.9)	16 (9.8)	79 (21.9)	7 (9.9)	14 (22.6)	
Residual MR grade	2,360							<0.001
None/mild		1,868 (78.2)	1,702 (100)	164 (100)	0 (0.0)	0 (0.0)	2 (3.2)	
Moderate		433 (18.3)	0 (0.0)	0 (0.0)	361 (100.0)	71 (100.0)	1 (1.6)	
Moderate to severe		37 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	37 (59.7)	
Severe		22 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (35.5)	
TMPG, mm Hg	2,360	2.9 ± 1.5	2.5 ± 1.0	5.9 ± 1.1	2.6 ± 1.0	6.1 ± 1.1	3.7 ± 2.1	<0.001
TMPG ≥5 mm Hg	2,360	248 (10.5)	1 (0.1)	164 (100.0)	0 (0.0)	71 (100.0)	12 (19.4)	<0.001
SLDA or leaflet tear	2,360	18 (0.8)	7 (0.4)	0 (0.0)	4 (1.1)	1 (1.4)	6 (9.7)	<0.001

Values are n, mean ± SD, n (%), or median (Q1-Q3).

AFMR = atrial functional mitral regurgitation; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; EROA = effective regurgitant orifice area; ESD = end-systolic diameter; ESV = end-systolic volume; FMR = functional mitral regurgitation; LAVI = left atrial volume index; LV = left ventricular; MAC = mitral annular calcification; MVA = mitral valve area; OS = optimal success; PVF = pulmonary venous flow; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid regurgitation pressure gradient; VFMR = ventricular functional mitral regurgitation.

associated with worse long-term outcomes, with this finding confirmed across analytical approaches including spline analysis and multivariable Cox regression; 2) when using MR ≤ mild as the reference, multivariate analysis demonstrated that moderate residual MR was not associated with an increased risk of the primary endpoint, whereas > moderate MR remained significantly associated with adverse outcomes; and 3) in the 5-group stratification by residual MR and TMPG, MR ≤ mild and TMPG <5 mm Hg was associated with the lowest event rates. Multivariate analysis using this group as the reference showed that moderate MR with TMPG <5 mm Hg was associated with a similar risk of the primary endpoint.

The primary goal of M-TEER is to reduce MR; however, an associated concern is the increase in TMPG caused by a reduction of mitral valve area (MVA). Therefore, considering both parameters as a potential dual target (MR-TMPG) and clarifying their prognostic implications is important. Some studies have reported that postprocedural TMPG elevation is associated with worse outcomes,[18] particularly in patients with DMR, [7,10,13] while its impact on FMR remains controversial.[8,9,12] Recent data suggest that TMPG elevation may not be a significant risk factor,[19,20] and a recent RCT found no association between TMPG and prognosis.[11] However, this RCT excluded patients with small MVA, potentially underestimating the impact of TMPG elevation. Previous studies reported that residual MR was consistently associated with adverse outcomes, while TMPG alone did not emerge as an independent prognostic factor after adjustment.[19,20] Given these uncertainties, we conducted a large-scale analysis of 2,360 FMR patients after M-TEER. In this study, an elevated TMPG was identified as an independent adverse prognostic factor in patients with FMR, with each 1-mm Hg increase in TMPG associated with primary endpoint. Our spline analysis consistently supported the association between increased TMPG and worse outcomes. This finding was also consistent in the VFMR subgroup, which comprised 80% of our cohort. In contrast, in the AFMR subgroup, elevated TMPG showed only a trend toward worse outcomes in multivariate analysis. Due to the relatively small

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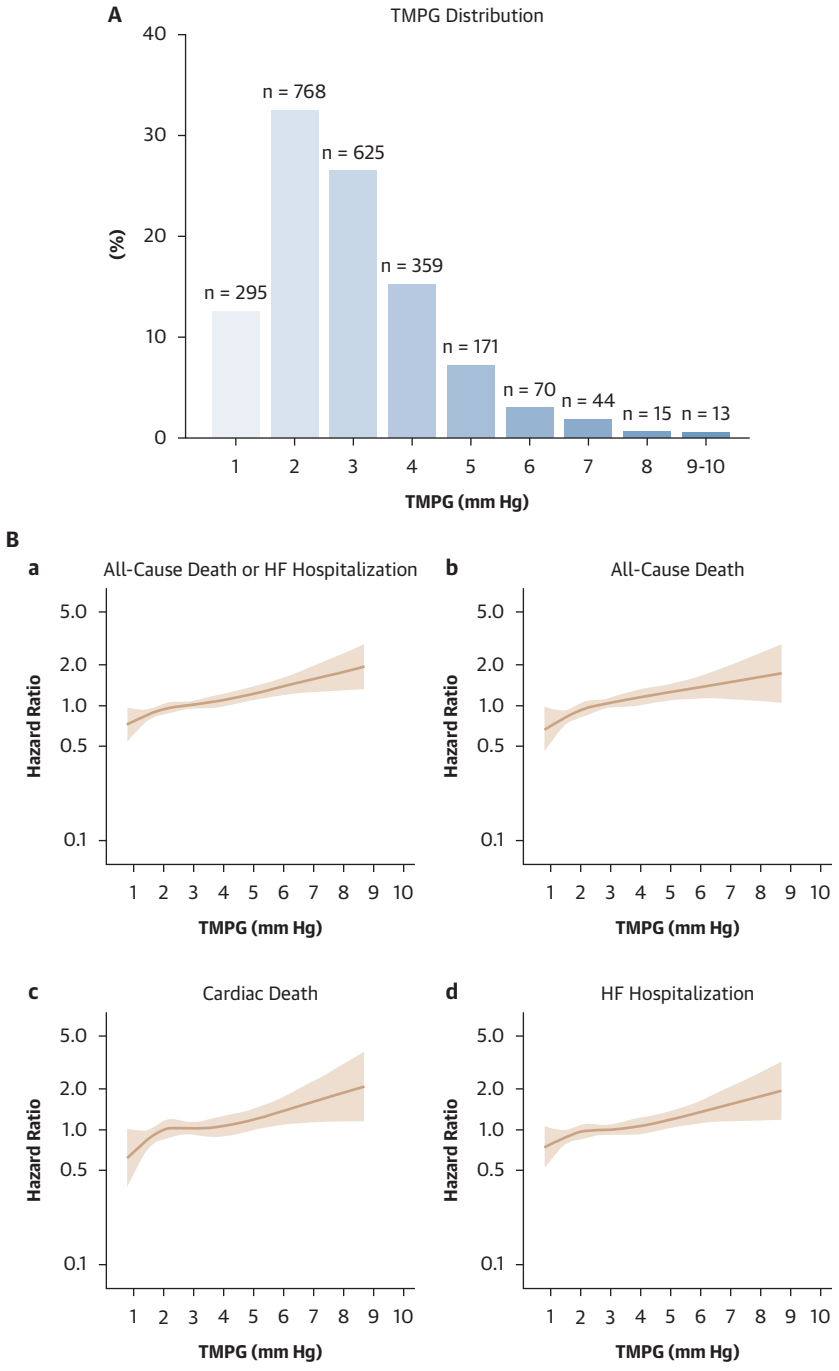
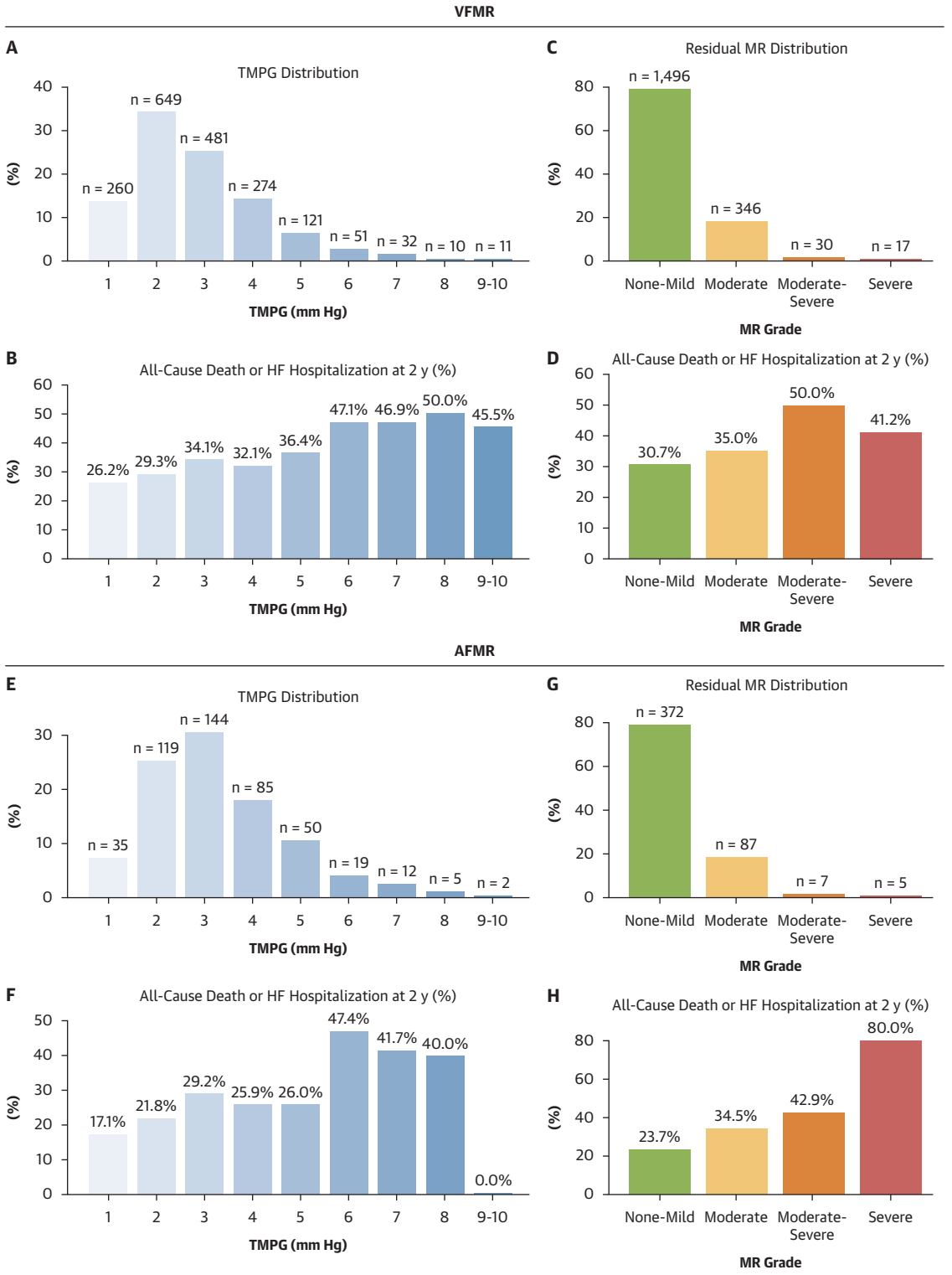
FIGURE 1 **Distribution of TMPG Values and Cubic Spline Curves of HRs for Clinical Outcomes Based on TMPG Values**



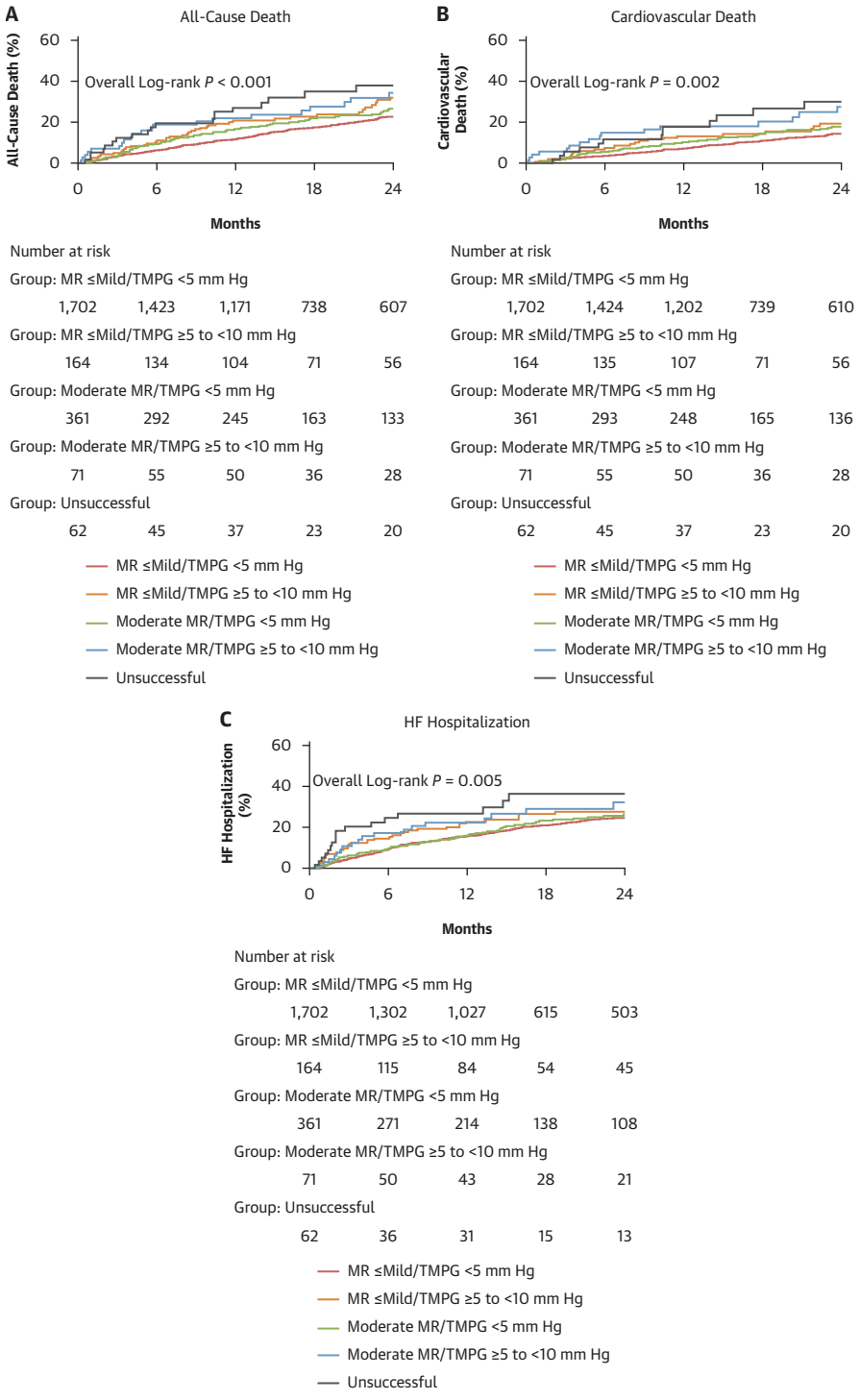
(A) Histogram showing the distribution of postprocedural transmitral mean pressure gradient (TMPG) values. (B) Cubic spline curves of HRs for clinical outcomes based on TMPG values. Primary endpoint (a), all-cause death (b), cardiovascular death (c), and heart failure (HF) Hospitalization (d).

FIGURE 2 **Distribution and Cumulative Event Rates of the Primary Endpoint According to TMPG and MR Grading**



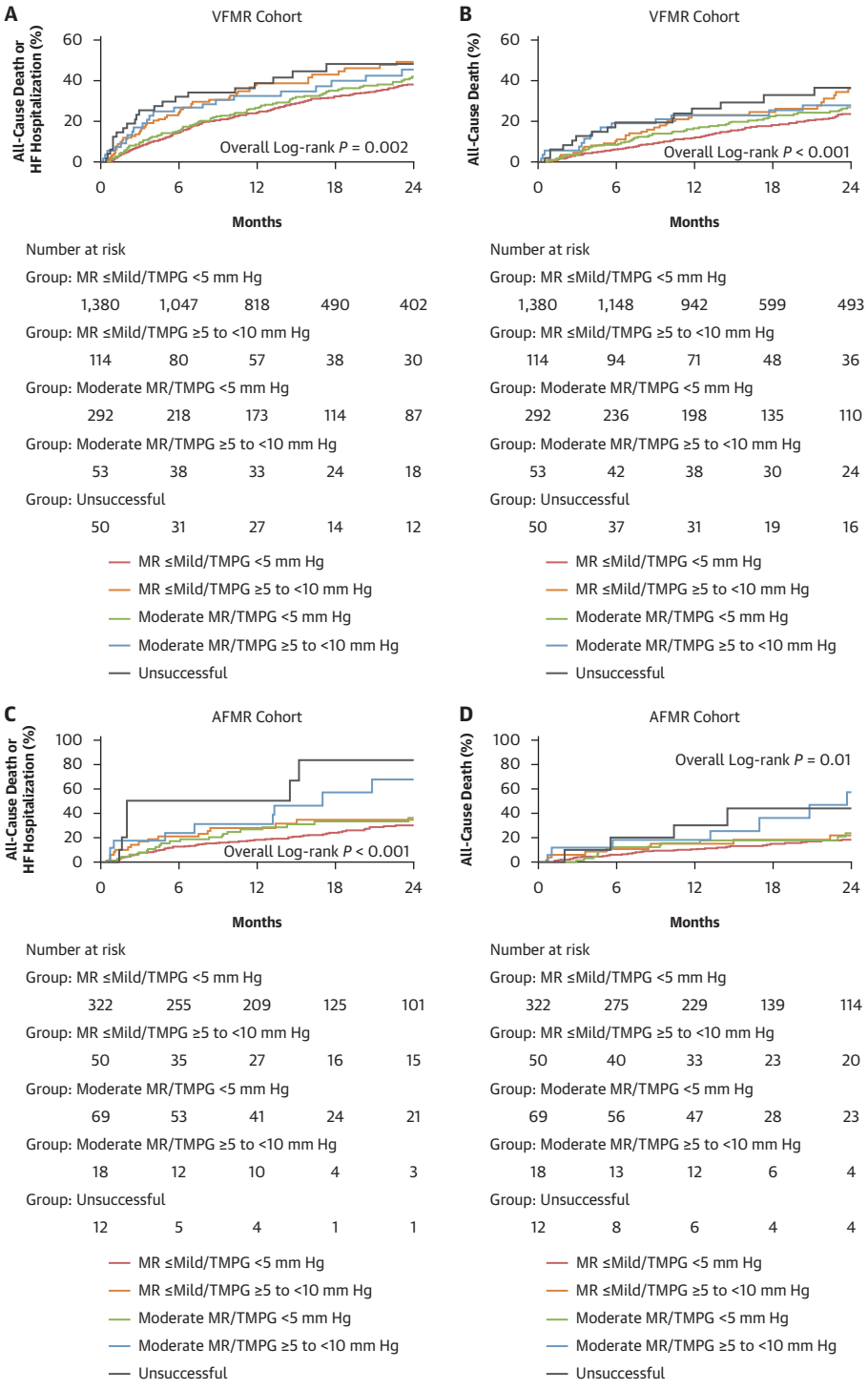
(Left) The patients with ventricular functional mitral regurgitation (VFMR). Distribution of TMPG grades in VFMR population (A). Bar graph showing the cumulative incidence of the primary endpoint according to TMPG values (B). Histogram showing the distribution of mitral regurgitation (MR) grades (none-mild, moderate, moderate to severe, severe). (C) Bar graph showing the cumulative incidence of the primary endpoint according to MR grading (D). (Right) The right side panel the patients with atrial functional mitral regurgitation (AFMR). Distribution of TMPG grades in VFMR population (E). Bar graph showing the cumulative incidence of the primary endpoint according to TMPG values (F), Histogram showing the distribution of MR grades (none-mild, moderate, moderate to severe, severe) (G). Bar graph showing the cumulative incidence of the primary endpoint according to MR grading (H). Abbreviations as in Figure 1.

FIGURE 3 Kaplan-Meier Analysis of All-Cause Death and Cardiovascular Death and HF Hospitalization Between the 5 Groups of FMR



Incidence of all-cause death (A), cardiovascular death (B), and HF hospitalization (C) at 2 years after mitral valve transcatheter edge-to-edge repair across the 5 groups. Patients were stratified into 5 groups based on postprocedural outcomes: 1) MR ≤ mild with TMPG <5 mm Hg (red); 2) MR ≤ mild with TMPG ≥5 to <10 mm Hg (orange); 3) moderate MR with TMPG <5 mm Hg (green); 4) moderate MR with TMPG ≥5 to <10 mm Hg (blue); and 5) unsuccessful procedure (black). Abbreviations as in Figures 1 and 2.

FIGURE 4 Kaplan-Meier analysis of Primary Endpoint and All-Cause Death Between the 5 Groups of VFMR and AFMR



The incidence of all-cause death or HF hospitalization (A) and all-cause death (B) at 2 years after mitral valve transcatheter edge-to-edge repair across the 5 groups in VFMR cohort. The incidence of all-cause death or HF hospitalization (C) and all-cause death (D) at 2 years after mitral valve transcatheter edge-to-edge repair across the 5 groups in AFMR cohort. Abbreviations as in Figures 1 and 2.

TABLE 3 Risk Factors for Non-MR ≤ Mild and TMPG <5 mm Hg Following M-TEER

	Univariate Model		Multivariable Model	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Predictive risk factors				
Age, y	0.99 (0.99-1.01)	0.39	0.99 (0.97-1.00)	0.11
Male	0.81 (0.67-0.97)	0.02	0.99 (0.74-1.32)	0.93
Body surface area, m^2	0.45 (0.28-0.72)	<0.001	0.63 (0.28-1.41)	0.26
NYHA functional class III or IV	0.93 (0.78-1.13)	0.48		
CFS ≥4	1.25 (1.04-1.49)	0.02	0.96 (0.77-1.20)	0.71
Hypertension	1.13 (0.94-1.36)	0.21		
Atrial fibrillation	1.09 (0.90-1.31)	0.38		
Coronary artery disease	0.69 (0.57-0.85)	<0.001	0.91 (0.72-1.14)	0.39
Chronic kidney disease	1.10 (0.83-1.46)	0.51		
Dialysis	1.51 (1.09-2.10)	0.01	1.23 (0.82-1.84)	0.32
Hemoglobin (per 1.0-g/dL increase)	0.91 (0.87-0.96)	<0.001	0.95 (0.89-1.01)	0.08
High BNP or NT-proBNP, pg/mL	1.03 (0.86-1.23)	0.72		
eGFR, mL/min/1.73 m^2	0.99 (0.99-1.00)	0.18		
β-blocker	0.72 (0.58-0.90)	<0.001	0.79 (0.61-1.03)	0.08
LV EDV, mL	1.01 (0.99-1.02)	0.37	1.01 (0.99-1.01)	0.11
LV ESV, mL	1.00 (0.99-1.01)	0.43	0.99 (0.98-1.00)	0.19
LV EF (per 10% increase)	1.14 (1.06-1.21)	<0.001	1.08 (0.91-1.28)	0.38
LAVI, mL/m^2 (per 10-mL/m^2 increase)	1.06 (1.04-1.08)	<0.001	1.00 (1.00-1.01)	0.003
AFMR	1.25 (1.01-1.56)	0.04	0.77 (0.51-1.16)	0.21
EROA, cm^2 (per 0.1-cm^2 increase)	1.20 (1.13-1.27)	<0.001	1.11 (1.04-1.20)	0.003
Regurgitant volume, mL[a]	1.01 (1.01-1.01)	<0.001		
Pre TMPG, mm Hg	1.57 (1.41-1.74)	<0.001	1.50 (1.33-1.70)	<0.001
TRPG, mm Hg	1.01 (1.00-1.02)	<0.001	1.01 (0.99-1.01)	0.21
Coaptation length <2 mm	0.97 (0.90-1.04)	0.38		
Tenting height ≥11 mm	1.00 (0.97-1.03)	0.97		
Posterior leaflet length <10 mm	1.01 (0.98-1.04)	0.45		
MAC	1.08 (0.84-1.39)	0.54		
MVA, cm^2	0.98 (0.93-1.04)	0.58		
Device generation G2 (for G4 usage)	1.24 (1.03-1.48)	0.02	1.27 (1.03-1.58)	0.03

[a]Not included in the multivariable analysis.
Abbreviations as in Tables 1 and 2.

sample size and low event rate in AFMR patients, the statistical power was limited, and definitive conclusions regarding the prognostic impact of TMPG in this population cannot be drawn.

Although TMPG ≥5 mm Hg has been commonly used as a cutoff, this threshold was not originally established for patients undergoing M-TEER.[12,21,22] The appropriate cutoff for TMPG should consider various factors such as body size, preprocedural MVA, and heart rate.[23,24] The appropriateness of using a TMPG cutoff of 5 mm Hg remains under discussion, while stratification by residual MR and TMPG effectively differentiated prognosis. Patients with MR ≤ mild and TMPG <5 mm Hg had the lowest incidence of the primary endpoint in this study. These findings were obtained using the same evaluation criteria as those adopted in the large-scale STS/TVT Registry for DMR,[7] were consistently associated with better prognosis across various subgroup analyses, including patients with smaller preprocedural MVA, and those meeting COAPT- and RESHAPE-like cohort criteria. The multivariate analysis showed that moderate residual MR with TMPG <5 mm Hg had a similar risk to ≤ mild MR, while more severe MR was associated with worse prognosis. These findings suggest that ≤ mild to moderate residual MR with low TMPG may be acceptable from a prognostic standpoint. These observations suggest that consideration of both MR reduction and TMPG management—the concept of a dual target—may inform procedural decision-making, particularly in balancing the degree of MR reduction against the risk of elevated TMPG. However, prospective studies are needed to establish optimal strategies and to confirm whether this approach improves patient outcomes.

Notably, the use of the older G2 device was identified as a risk factor for not achieving MR ≤ mild and

TABLE 4 Cox Regression Analysis for the Association Between Primary Endpoint and Clinical Findings

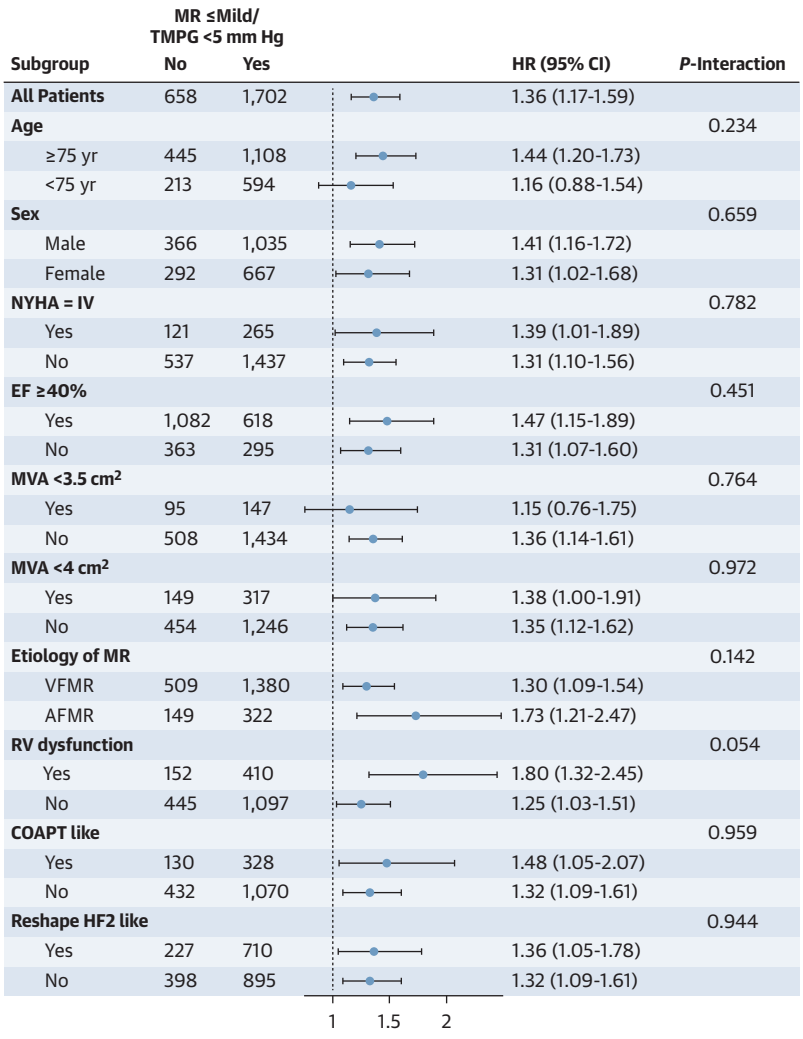
	Univariate Analysis			Multivariate Analysis						
				Model 1				Model 2		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	*P* Interaction	HR	95% CI	*P* Value
FMR[a]										
Model 1										
TMPG, mm Hg	1.11	1.06-1.17	<0.001	1.10	1.02-1.17	0.008	0.58			
MR ≤ mild (reference)										
MR = moderate	1.18	0.99-1.43	0.06	1.04	0.66-1.62	0.88				
MR > moderate	2.13	1.47-3.10	<0.001	3.36	1.13-9.98	0.03				
Model 2										
MR ≤ mild and TMPG <5 mm Hg (reference)										
MR ≤ mild and TMPG ≥5 to <10 mm Hg	1.49	1.15 -1.94	0.003					1.42	1.07-1.90	0.02
MR = moderate and TMPG <5 mm Hg	1.15	0.94-1.42	0.15					1.13	0.92-1.41	0.24
MR = moderate and TMPG ≥5 to <10 mm Hg	1.57	1.09-2.25	0.02					1.54	1.05-2.24	0.03
MR >moderate or TMPG 10 mm Hg	2.14	1.48-3.10	<0.001					2.27	1.50-3.45	<0.001
Ventricular FMR[b]										
Model 1										
TMPG, mm Hg	1.12	1.06-1.17	<0.001	1.10	1.01-1.18	0.02	0.56			
MR ≤ mild (reference)										
MR = moderate	1.12	0.92-1.37	0.27	0.90	0.48-1.34	0.40				
MR > moderate	1.80	1.17-2.76	0.007	1.79	0.51-6.35	0.37				
Model 2										
MR ≤ mild and TMPG <5 mm Hg (reference)										
MR ≤ mild and TMPG ≥5 to <10 mm Hg	1.56	1.16-2.10	0.003					1.53	1.09-2.11	0.01
MR = moderate and TMPG <5 mm Hg	1.18	0.90-1.39	0.32					1.06	0.83-1.35	0.66
MR = moderate and TMPG ≥5 to <10 mm Hg	1.34	0.87-2.06	0.18					1.30	0.83-2.03	0.25
MR > moderate or TMPG 10 mm Hg	1.80	1.18-2.74	0.006					1.85	1.14-3.00	0.01
Atrial FMR[c]										
Model 1										
TMPG, mm Hg	1.16	1.03-1.30	0.01	1.17	0.99-1.38	0.07	0.29			
MR ≤ mild (reference)										
MR = moderate	1.53	1.02-2.33	0.04	3.80	1.05-13.7	0.04				
MR > moderate	4.48	2.07-9.69	<0.001	1.46	0.06-36.3	0.82				
Model 2										
MR ≤ mild and TMPG <5 mm Hg (reference)										
MR ≤ mild and TMPG ≥5 to <10 mm Hg	1.49	0.85-2.59	0.16					1.81	0.96-3.41	0.07
MR = moderate and TMPG <5 mm Hg	1.38	0.85-2.25	0.19					1.83	1.02-3.31	0.04
MR = moderate and TMPG ≥5 to <10 mm Hg	2.74	1.37-5.49	0.004					2.45	1.08-5.56	0.03
MR > moderate or TMPG 10 mm Hg	4.74	2.18-10.3	<0.001					4.51	1.53-13.3	0.006

[a]Adjusting factors: age, male, BSA, NYHA functional class III or IV, CFS ≧4, CKD, dialysis, cardiac rhythm device implant, HFH before M-TEER, hemoglobin, BNP or NT-proBNP over the media, β-blocker, LVEDV, LVESV, LAVi, AFMR, pre-TMPG. [b]Adjusting factors: age, male, BSA, NYHA functional class III or IV, CFS ≧4, CKD, cardiac rhythm device implant, HFH before M-TEER, hemoglobin, BNP or NT-proBNP over the media, β-blocker, ACE/ARB/ARNI, LVEDV, LVESV, LAVi, pre-TMPG, PASP. [c]Adjusting factors: age, male, BSA, NYHA functional class III or IV, CFS ≧4, hemoglobin, BNP or NT-proBNP over the media, LVEDV, LVESV, EROA , LAVi, PASP.

Abbreviations as in Tables 1 and 2.

TMPG <5 mm Hg. This aligns with previous reports and highlights the improvement in clinical outcomes with newer device iterations,[4] and is supported by data from a global registry that included Japanese patients and reported a low single leaflet rate of 1.1% with the newer G4 device, reflecting enhanced safety and treatment efficacy.[25] The preprocedural severity of MR, higher MR volume, and larger LAVI were associated with difficulty in achieving MR reduction, findings that are largely consistent with previous studies and similarly observed in the presented analysis.[26,27] The baseline high hemoglobin value and use of β-blockers showed a trend toward higher incidence of MR ≤ mild and TMPG <5 mm Hg. In terms of TMPG elevation, patients with anemia were more likely to experience postprocedural TMPG elevation, suggesting a relationship with increased blood flow in a high-flow state.[21,25] Interestingly, the use of β-blockers was associated with lower TMPG, which may indicate the effect of β-blockers on

FIGURE 5 Interaction Effects for the Primary Endpoint Across Patient Subgroups



The risk of primary endpoint in each subset between MR ≤ mild and TMPG <5 mm Hg or not. EF = ejection fraction; MVA = mitral valve area; RV = right ventricular; other abbreviations as in Figures 1 and 2.

reducing heart rate. High heart rate was associated with increased TMPG, suggesting a potential role for pharmacological interventions in managing hemodynamics.

STUDY LIMITATIONS. As a registry-based, retrospective analysis, selection bias is inherent. Although multivariable analysis adjusts for numerous potential confounders, unmeasured confounders cannot be entirely excluded. Additionally, echocardiographic assessments were conducted at individual institutions rather than being evaluated by a centralized core laboratory, introducing potential interobserver variability in MR grading and TMPG measurements. Echocardiographic data at discharge were unavailable for 236 patients, including those who experienced in-hospital death. This missing data could have influenced the observed associations and should be considered when interpreting the results. The chosen TMPG cutoff of 5 mm Hg was not completely established, raising uncertainty about its optimal threshold in this population. Furthermore, while the study cohort is large, it consists exclusively of Japanese patients, whose smaller body size compared with Western populations may influence TMPG-related outcomes. The small MVA and mitral annular calcification were not significant factors to

achieving residual MR ≤ mild and TMPG <5 mm Hg in our small anatomy cohort. This could partly explain the discrepancy between our findings and previous reports suggesting that postprocedural TMPG is not prognostically significant. In addition, the cohort was predominantly composed of elderly patients, with a high prevalence of chronic kidney disease (approximately 80%), which may further influence both procedural selection and outcomes. These physiological and clinical characteristics may limit the generalizability of our findings to other populations. Despite these limitations, the study provides valuable insights into the prognostic impact of achieving both MR reduction and TMPG optimization following M-TEER.

CONCLUSIONS

In this large-scale study of 2,360 patients with FMR undergoing M-TEER, we demonstrated that postprocedural TMPG elevation significantly impacts long-term outcomes. Stratification by residual MR severity and TMPG suggested that the prognosis appeared similar between ≤ mild and moderate residual MR when TMPG remained low. These findings indicate that considering both MR reduction and TMPG management as a potential dual target could serve as a useful marker for risk stratification. Prospective studies are needed to confirm these associations and to determine whether this approach represents a procedural mandate.

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APPENDIX For a supplemental figure, statistical analysis plan, and trial protocol, please see the online version of this paper.