JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 83, NO. 4, 2024

PUBLISHED BY ELSEVIER

Transcatheter Edge-to-Edge Repair in COAPT-Ineligible Patients With Functional Mitral Regurgitation

Adnan K. Chhatriwalla, MD,[a] David J. Cohen, MD, MSc,[b,c] Sreekanth Vemulapalli, MD,[d] Andrew Vekstein, MD,[d] Chetan P. Huded, MD, MSc,[a] Dianne Gallup, MS,[d] Andrzej S. Kosinski, PhD,[d] Leo Brothers, MPH,[d] JoAnn Lindenfeld, MD,[e] Gregg W. Stone, MD,[f] Paul Sorajja, MD[g]

ABSTRACT

BACKGROUND Mitral valve transcatheter edge-to-edge repair (MTEER) was approved in the United States for treatment of functional mitral regurgitation (FMR) based on results from the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial.

OBJECTIVES The authors sought to analyze outcomes of MTEER in FMR patients who would have been excluded from COAPT.

METHODS MTEER procedures performed for FMR in the TVT (Transcatheter Valve Therapy) Registry between January 1, 2013, and April 30, 2020, were categorized as "trial-ineligible" if any of the following were present: cardiogenic shock, inotropic support, left ventricular ejection fraction <20%, left ventricular end-systolic dimension >7 cm, home oxygen use, or severe tricuspid regurgitation. Trial-ineligible and trial-eligible groups were compared through 1 year using multivariable models. The primary endpoint was 1-year death or heart failure hospitalization (HFH).

RESULTS Of 6,675 patients who underwent MTEER for FMR, 3,721 (55.7%) were trial-eligible and 2,954 (44.3%) were trial-ineligible. Trial-ineligible patients had lower rates of technical procedural success (86.9% vs 92.6%; $P < 0.001$) and more frequent in-hospital complications (11.8% vs 5.7%; $P < 0.001$) compared with trial-eligible patients. A clinically meaningful improvement in health status at 30 days was observed in 78.9% and 77.0% of patients in the trial-ineligible and trial-eligible groups, respectively. There was a higher risk of 1-year death or HFH (HR: 1.73; 95% CI: 1.57-1.91; $P < 0.001$) in trial-ineligible patients.

CONCLUSIONS Among patients who underwent MTEER for FMR in the TVT Registry, nearly one-half would have been ineligible for the COAPT trial. Health status improvement at 30 days was similar in COAPT-ineligible and COAPT-eligible patients, but trial-ineligible patients had higher 1-year rates of death or HFH. (J Am Coll Cardiol 2024;83:488-499)

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From the [a]Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City, Kansas City, Missouri, USA; [b]Cardiovascular Research Foundation, New York, New York, USA; [c]St Francis Hospital and Heart Center, Roslyn, New York, USA; [d]Duke University and Duke Clinical Research Institute, Durham, North Carolina, USA; [e]Vanderbilt University Medical Center, Nashville, Tennessee, USA; [f]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA; and the [g]Valve Science Center, Minneapolis Heart Institute Foundation, Abbott Northwestern Hospital, Minneapolis, Minnesota, USA.

Justin Ezekowitz, MB, BCh, served as Guest Associate Editor for this paper. Javed Butler, MD, MPH, MBA, served as Guest Editor-in-Chief of this paper.

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 28, 2023; revised manuscript received October 6, 2023, accepted October 6, 2023.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2023.11.012

The development of functional mitral regurgitation (FMR) in patients with heart failure (HF) portends a poor prognosis.[1,2] The benefits of transcatheter mitral valve edge-to-edge repair (MTEER) in selected HF patients with severe FMR were demonstrated in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial.[3] Significant reductions in both HF hospitalization (HFH) and mortality as well as improvements in health status were observed in patients with FMR who underwent MTEER with MitraClip (Abbott Cardiovascular) in patients who remained symptomatic on maximally tolerated doses of guideline-directed medical therapy (GDMT). As a result, MTEER was approved in the United States in 2019 for the treatment of HF patients with moderate-to-severe or severe FMR. However, there were significant exclusions for patient enrollment in COAPT, leading to uncertainty regarding clinical benefit for patients with advanced HF features that were ineligible for enrollment. COAPT trial exclusions included cardiogenic shock, inotropic support, left ventricular (LV) ejection fraction (LVEF) <20%, severe LV dilatation (LV end-systolic dimension [LVESD] >7 cm), severe pulmonary hypertension (pulmonary artery systolic pressure [PASP] >70 mm Hg), home oxygen use, and severe tricuspid regurgitation (TR). It is important to understand whether MTEER provides a clinical benefit in such patients given the large number of FMR patients who do not fit COAPT criteria but who remain symptomatic despite GDMT.[4]

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Accordingly, the aim of the present study was to analyze patient outcomes following MTEER in patients with FMR with or without COAPT clinical trial exclusions, using data from the STS/ACC TVT Registry (Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry).

METHODS

DATA SOURCE AND STUDY POPULATION. The STS/ACC TVT Registry is a voluntary U.S. multicenter reporting system for structural heart procedures, jointly sponsored by STS and ACC; data submission to the registry is a required by the Center for Medicare & Medicaid Services (CMS) for reimbursement of commercial MTEER procedures performed in the United States.[5] Demographic, clinical, procedural, and institutional data are collected and entered into a secure centralized database. Automatic system validation, reporting of data completeness, random auditing of participating centers, and education and training of data site managers are performed regularly to promote quality assurance. Data from adult patients undergoing a first MTEER procedure for FMR or mixed mitral valve disease with a component of FMR between January 1, 2013, and April 30, 2020, were collected from the TVT Registry for this study. Patients with degenerative mitral regurgitation (MR), prior mitral valve surgical repair or transcatheter mitral valve intervention, and patients with endocarditis or post-inflammatory MR were excluded from this analysis.

TRIAL ELIGIBILITY DEFINITION. Patients who underwent MTEER procedures for FMR were categorized as "trial-ineligible" based on COAPT trial inclusion and exclusion criteria[3] if any of the following criteria were present at the time of their index procedure: cardiogenic shock, inotropic support, LVEF <20%, LVESD >7 cm, home oxygen use, or severe TR; the remaining patients were categorized as "trial eligible." Patients who met any of these criteria were categorized as "trial-ineligible" even if they had missing data with respect to other criteria, whereas patients who did not meet any of these criteria and had missing data with respect to these criteria were excluded from this analysis.

OUTCOMES. The primary endpoint for the analysis was the composite of all-cause death or HFH at 1-year follow-up. Secondary endpoints included in-hospital technical procedural success (defined as the achievement of moderate or less residual MR without in-hospital death, valve reintervention or open-heart surgery), in-hospital procedural complications (major or life-threatening bleeding, myocardial infarction, stroke, single-leaflet device attachment, device embolization, delivery system component embolization, device thrombosis, other device-related events, conversion to open heart surgery, mortality, perforation, major vascular access complication, unplanned vascular surgery or intervention, transseptal complications, complete device detachment, or mitral leaflet or subvalvular injury). Additional secondary endpoints included hospital length of stay, MR severity at 30 days, change in health status at 30 days (as assessed by the Kansas City Cardiomyopathy Questionnaire overall summary score [KCCQ-OS]), poor composite outcome (death, HFH, or a <10-point improvement in KCCQ-OS at 30 days), and the individual endpoints of all-cause death and HFH at 1 year.

ABBREVIATIONS AND ACRONYMS

FMR = functional mitral regurgitation

GDMT = guideline-directed medical therapy

HF = heart failure

HFH = heart failure hospitalization

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score

LV = left ventricular

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic dimension

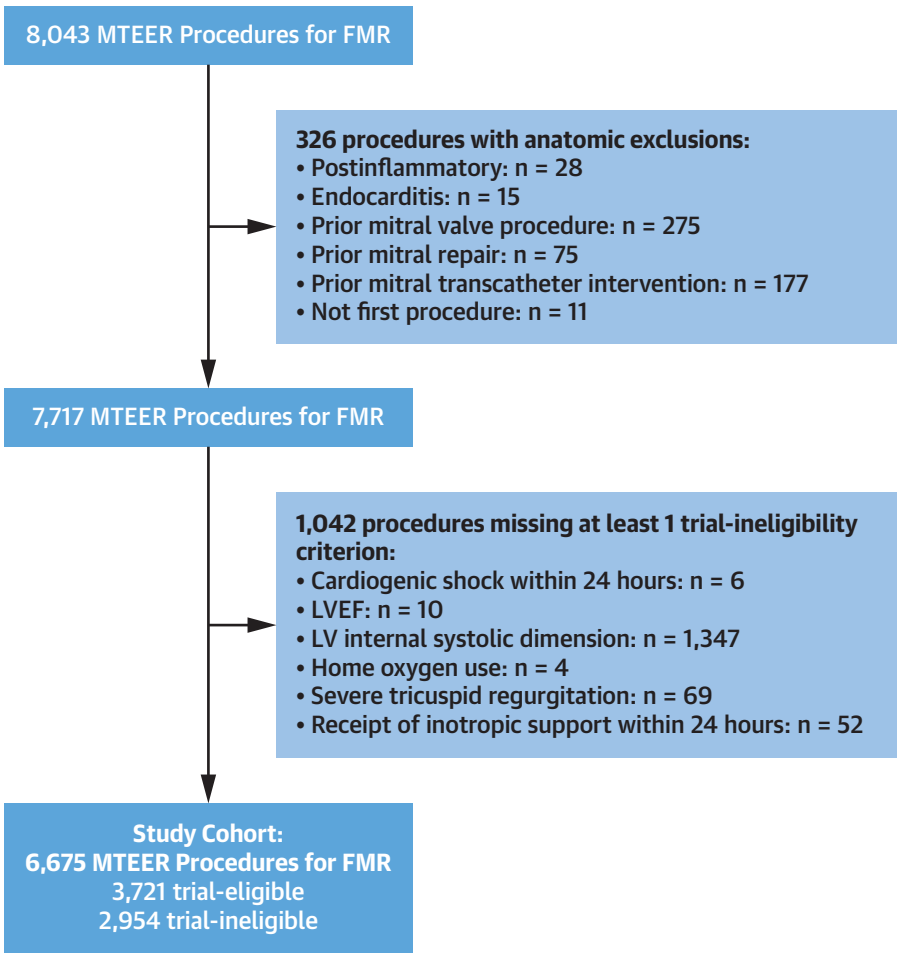
MR = mitral regurgitation

MTEER = mitral valve transcatheter edge-to to-edge repair

PASP = pulmonary artery systolic pressure

TR = tricuspid regurgitation

FIGURE 1 Study Cohort

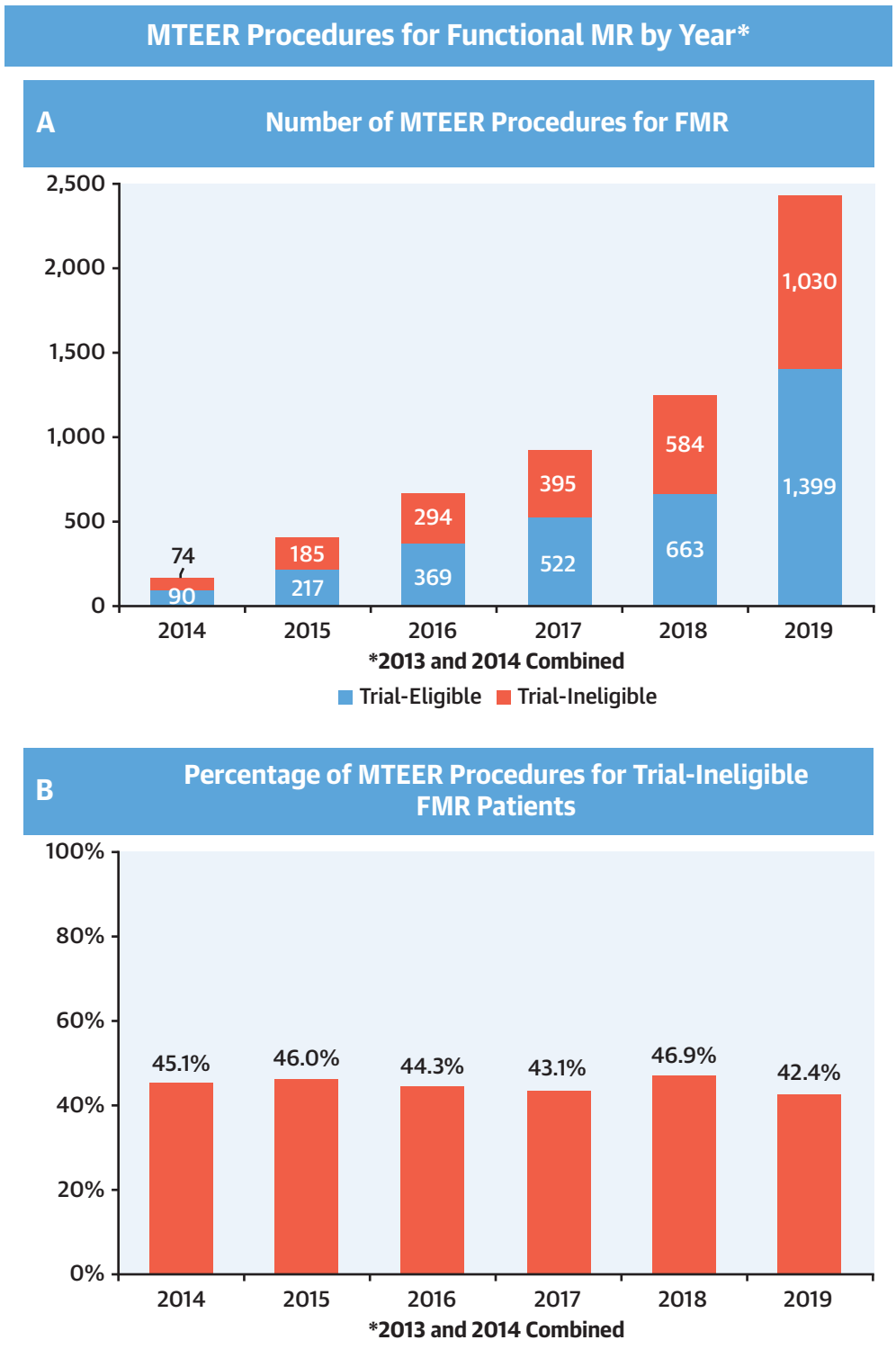


Consort diagram depicting the patient population for this study. Of 8,043 first transcatheter mitral valve edge-to-edge repair (MTEER) procedures for functional mitral regurgitation (FMR) collected by the STS/TVT (Society of Thoracic Surgeons/Transcatheter Valve Therapy) Registry between January 1, 2013, and April 30, 2020, 326 were excluded for anatomical reasons, and 1,042 were excluded because of missing data with respect to trial eligibility criteria. Of the remaining 6,675 procedures, 2,954 were in patients who met trial-ineligibility criteria and 3,721 met no trial-ineligibility criteria. LV = left ventricular; LVEF = left ventricular ejection fraction.

STATISTICAL ANALYSIS. Patient characteristics were compared between trial-ineligible and trial-eligible groups using standardized differences. Unadjusted in-hospital outcomes following MTEER were analyzed with chi-square or Fisher exact tests, as appropriate, without adjusting for clustering of patients within hospital. Multivariable analysis was used to adjust for the following covariates: age, sex, hypertension, diabetes mellitus, previous valve surgery, previous coronary artery bypass surgery, atrial fibrillation or flutter, previous myocardial infarction, prior stroke, peripheral arterial disease, prior percutaneous coronary intervention, current smoking within 1 year, chronic lung disease, frailty, NYHA functional class III or IV HF status (not included in any models involving KCCQ measures), baseline MR severity grade, and discharge medications (or admission medications for patients who did not survive to discharge, for 1-year models only), and baseline KCCQ (only for models involving change in KCCQ).

Any covariates that had <2% missingness were imputed to the mode for categorical variables and median for continuous variables. No singular variable had >2% missingness. To address missingness of 30-day and 1-year outcomes, inverse probability weighting based on the predicted probability of missing data was used in the adjusted analyses.[6] For

FIGURE 2 Procedural Volumes of MTEER for FMR



We evaluated 6,675 MTEER performed for FMR between January 1, 2013, and April 30, 2020, as captured by the STS/TVT Registry. Over this time frame, MTEER procedures for FMR steadily increased (A), whereas the proportion of such procedures performed for patients meeting trial-ineligibility criteria was relatively constant (B). Abbreviations as in Figure 1.

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TABLE 1 Baseline Characteristics

	Trial-Ineligible (n = 2,954)	Trial-Eligible (n = 3,721)	Standardized Difference
Trial-ineligible criteria			0.4218
Cardiogenic shock within 24 h	241/2,950 (8.2)	0/3,721 (0.0)	—
LVEF <20%	578/2,926 (19.8)	0/3,721 (0.0)	—
LV internal systolic dimension >7 cm	187/2,543 (7.4)	0/3,721 (0.0)	—
Home oxygen use	920/2,954 (31.1)	0/3,721 (0.0)	—
Severe tricuspid regurgitation	1,262/2,938 (43.0)	0/3,721 (0.0)	—
Receipt of inotropic support within 24 h	698/2,941 (23.7)	0/3,721 (0.0)	—
Demographics			
Age, y			−0.1005
n	2,954	3,721	
Mean ± SD	74.5 ± 10.9	73.4 ± 11.4	
Median (Q1-Q3)	75 (67-82)	76 (68-83)	
Male	1,660/2,954 (56.2)	2,160/3,721 (58.0)	−0.0375
History and risk factors			
STS-PROM for MV repair			0.3862
n	2,954	3,721	
Median (Q1-Q3)	6.3 (3.4-11.8)	4.6 (2.5-8.0)	
Hypertension	2,516/2,954 (85.2)	3,261/3,721 (87.6)	−0.0720
Diabetes	1,113/2,952 (37.7)	1,330/3,718 (35.8)	0.0401
Previous valve surgery[a]	260/2,949 (8.8)	339/3,712 (9.1)	−0.0111
Prior CABG	886/2,946 (30.1)	1,238/3,716 (33.3)	−0.0697
Atrial fibrillation/flutter	1,932/2,951 (65.5)	2,157/3,713 (58.1)	0.1522
Prior MI	1,197/2,952 (40.5)	1,525/3,711 (41.1)	−0.0111
Prior stroke	372/2,952 (12.6)	422/3,719 (11.3)	0.0386
Prior PAD	567/2,952 (19.2)	746/3,716 (20.1)	−0.0219
Current or recent smoker	355/2,950 (12.0)	342/3,717 (9.2)	0.0921
Chronic lung disease	1,382/2,928 (47.2)	1,243/3,691 (33.7)	0.2782
Frailty	1,523/2,954 (51.6)	1,817/3,721 (48.8)	0.0545
NYHA functional class III or IV status	2,660/2,936 (90.6)	3,103/3,697 (83.9)	0.2010
Mixed mitral valve regurgitation	1,404/2,954 (47.5)	1,841/3,721 (49.5)	−0.0390
Prior HFH within 1 year	1,978/2,669 (74.1)	2,054/3,283 (62.6)	0.2501
Baseline MR grade less than severe	140/2,937 (4.8)	262/3,703 (7.1)	−0.0979
Mitral stenosis	122/2,883 (4.2)	142/3,621 (3.9)	0.0157
LVEF, %			−0.3166
n	2,926	3,721	
Mean ± SD	35.2 ± 16.4	40.0 ± 14.1	
Median (Q1-Q3)	33 (20-48)	38 (28-53)	
MV mean gradient, mm Hg			0.0374
n	1,939	2,399	
Mean ± SD	3.5 ± 6.3	3.3 ± 5.7	
Median (Q1-Q3)	2.0 (2.0-3.0)	2.0 (1.0-3.0)	
Baseline KCCQ			0.7149
n	1,409	2,000	
Mean ± SD	34.6 ± 23.0	43.7 ± 24.0	
Median (Q1-Q3)	30.7 (16.2-50.0)	41.7 (25.5-60.9)	
Medications			
ACE inhibitor or ARB	1,287/2,882 (44.7)	1,885/3,700 (50.9)	−0.1262
Beta-blockers	2,176/2,882 (75.5)	3,051/3,700 (82.5)	−0.1714
Mineralocorticoid receptor antagonists	692/2,882 (24.0)	774/3,700 (20.9)	0.0741

Values are n/N (%) unless otherwise indicated. [a]Prior surgical or transcatheter aortic, tricuspid, or pulmonic valve procedure.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; HFH = heart failure hospitalization; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MR = mitral regurgitation; MV = mitral valve; PAD = peripheral arterial disease; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

primary and secondary endpoints, we used a non-parsimonious logistic regression model including the trial-eligible/ineligible covariate as well as covariates listed in the preceding text to predict the likelihood of a patient not missing the outcome. Adjusted analyses were then performed utilizing logistic regression (30-day outcomes) and survival analysis (1-year outcomes) to assess the relationship between trial ineligibility and each endpoint, incorporating inverse proportional propensity weighting and adjusting for all covariates, while accounting for clustering of patients in hospitals within the generalized estimating equations framework. One-year HFH models utilized the same methodology while also accounting for the competing risk of death using cause-specific hazards.[7] For the in-hospital outcomes, logistic regression with no weighting was used while accounting for clustering of patients in hospitals within the generalized estimating equations framework adjusting for aforementioned covariates for the adjusted models and no adjustment for these covariates for unadjusted models. A landmark analysis was performed to determine whether there was a difference between trial ineligible and trial eligible in discharge to 1-year death or HFH after adjusting for preidentified covariates as well as technical success.[8] Thirty-day change in KCCQ, as a continuous variable, was analyzed utilizing a generalized linear model with normal errors, adjusting for baseline KCCQ while accounting for clustering of patients in hospitals within the generalized estimating equations framework. Only participants in sites with >50% completeness in change in 30-day overall KCCQ were utilized (n = 3,409), as has been done previously.[9] All analyses were done at the Duke Clinical Research Institute using SAS v.9.4 software (SAS Institute). This study was approved by the Duke University Institutional Review Board and the STS/TVT Registry Institutional Review Board activities are approved by Advarra.

RESULTS

Data from 6,675 patients who underwent a first MTEER procedure for FMR were available for analysis. Of these, 2,954 (44.3%) were COAPT trial-ineligible patients and 3,721 (55.7%) were trial-eligible patients (Figure 1). The number of cases performed for FMR per year increased steadily over time; however, there was no difference over time in the proportion of procedures performed annually for trial-eligible vs trial-ineligible patients (Figure 2). Baseline patient characteristics of trial-ineligible and trial-eligible patients are shown in Table 1. The most common reasons for trial-ineligibility were severe TR (43.0%) and home oxygen use (31.1%). Trial-ineligible patients were more likely to have atrial fibrillation or flutter, chronic lung disease, and NYHA functional class III or IV status at baseline. Trial-ineligible patients were less likely to be treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers but were more likely to be treated with mineralocorticoid receptor antagonists than trial-eligible patients (Table 1).

TABLE 2 In-Hospital Outcomes Following MTEER

	Trial-Ineligible (n = 2,954)	Trial-Eligible (n = 3,721)	*P* Value[a]
In-hospital technical success	2,556/2,941 (86.9)	3,431/3,707 (92.6)	<0.001
Survival	2,810/2,954 (95.1)	3,689/3,721 (99.1)	<0.001
Moderate or less residual MR	2,750/2,947 (93.3)	3,513/3,717 (94.5)	0.04
Freedom from open heart surgery	2,934/2,947 (99.6)	3,697/3,711 (99.6)	0.68
Freedom from other cardiac surgery	2,869/2,954 (97.1)	3,673/3,721 (98.7)	<0.001
Freedom from valve reintervention	2,933/2,954 (99.3)	3,702/3,721 (99.5)	0.29
Length of stay, d			<0.001
Mean ± SD	7.9 ± 13.4	4.0 ± 7.3	
Median (Q1-Q3)	3.0 (1.0-10.0)	1.0 (1.0-3.0)	
Any in-hospital complication	347/,2948 (11.8)	213/3,711 (5.7)	<0.001
In-hospital mortality	144/2,954 (4.9)	32/3,721 (0.9)	<0.001
Major or life-threatening bleeding	142/2,954 (4.8)	72/3,720 (1.9)	<0.001
Myocardial infarction[b]	2/2,954 (0.1)	3/3,721 (0.1)	1.00
Stroke	30/2,954 (1.0)	11/3,721 (0.3)	<0.001
Single-leaflet device attachment	28/2,954 (0.9)	42/3,721 (1.1)	0.47
Device embolization[b]	2/2,954 (0.1)	3/3,721 (0.1)	1.00
Delivery system component embolization[b]	0/2,954 (0.0)	1/3,721 (0.03)	1.00
Device thrombosis[b]	0/2,954 (0.0)	1/3,721 (0.03)	1.00
Other device-related events	14/2,954 (0.5)	22/3,721 (0.6)	0.52
Perforation	21/2,954 (0.7)	20/3,721 (0.5)	0.37
Major vascular access complication	23/2,954 (0.8)	14/3,721 (0.4)	0.03
Unplanned vascular surgery or intervention	25/2,954 (0.8)	13/3,721 (0.3)	0.007
Trans-septal complication	29/2,954 (1.0)	7/3,721 (0.2)	<0.001
Complete device detachment[b]	4/2,954 (0.1)	6/3,721 (0.2)	1.00
Mitral leaflet or subvalvular injury	17/2,954 (0.6)	25/3,721 (0.7)	0.62

Values are n/N (%) unless otherwise indicated. [a]*P* values from chi-square test unless otherwise indicated. [b]*P* value from Fisher exact test.

MR = mitral regurgitation; MTEER = mitral valve edge edge-to to-edge repair.

IN-HOSPITAL RESULTS. Compared with trial-eligible patients, trial-ineligible patients had lower rates of technical procedural success in unadjusted (86.9% vs 92.6%; $P < 0.001$) and adjusted (OR: 0.56; 95% CI: 0.47-0.66; $P < 0.001$) analyses. Residual MR severity of moderate or less was achieved slightly less frequently in trial ineligible patients (93.3% vs 94.5%; $P = 0.04$); however, no difference was observed after adjustment (OR: 0.86; 95% CI: 0.69-1.06; $P = 0.16$). In-hospital complications were more frequent in trial-ineligible patients, both in unadjusted (11.8% vs 5.7%; $P < 0.001$) and adjusted (adjusted OR: 2.22;

TABLE 3 30-Day Outcomes in Trial-Ineligible and Trial-Eligible Patients

	Unadjusted			Adjusted		
	Trial-Ineligible (n = 2,954)	Trial-Eligible (n = 3,721)	*P* Value	OR (95% CI)	Risk Difference (95% CI)	*P* Value
Poor outcome[a]	337/1,089 (30.9)	539/1,623 (33.2)	0.20	1.03 (0.87 to 1.23)		0.72
MR > moderate	269/2,947 (9.1)	277/3,718 (7.5)	0.02	1.17 (0.97 to 1.42)		0.10
Lack of 10-point improvement in KCCQ-OS from baseline	272/1,055 (25.8)	486/1,594 (30.5)	0.005	0.93 (0.76 to 1.13)		0.45
KCCQ-OS, 30-d change						
n	1,055	1,594				
Mean ± SD	28.0 ± 27.5	24.9 ± 26.2	0.013		1.48 (−0.28 to 3.24)	0.10

Values are n/N (%) unless otherwise indicated. [a]30-day poor outcome = 30-day death or HFH or lack of 10-point improvement in 30-day KCCQ-OS from baseline. Analysis restricted to sites with >50% completeness of change in 30-day overall KCCQ-OS.

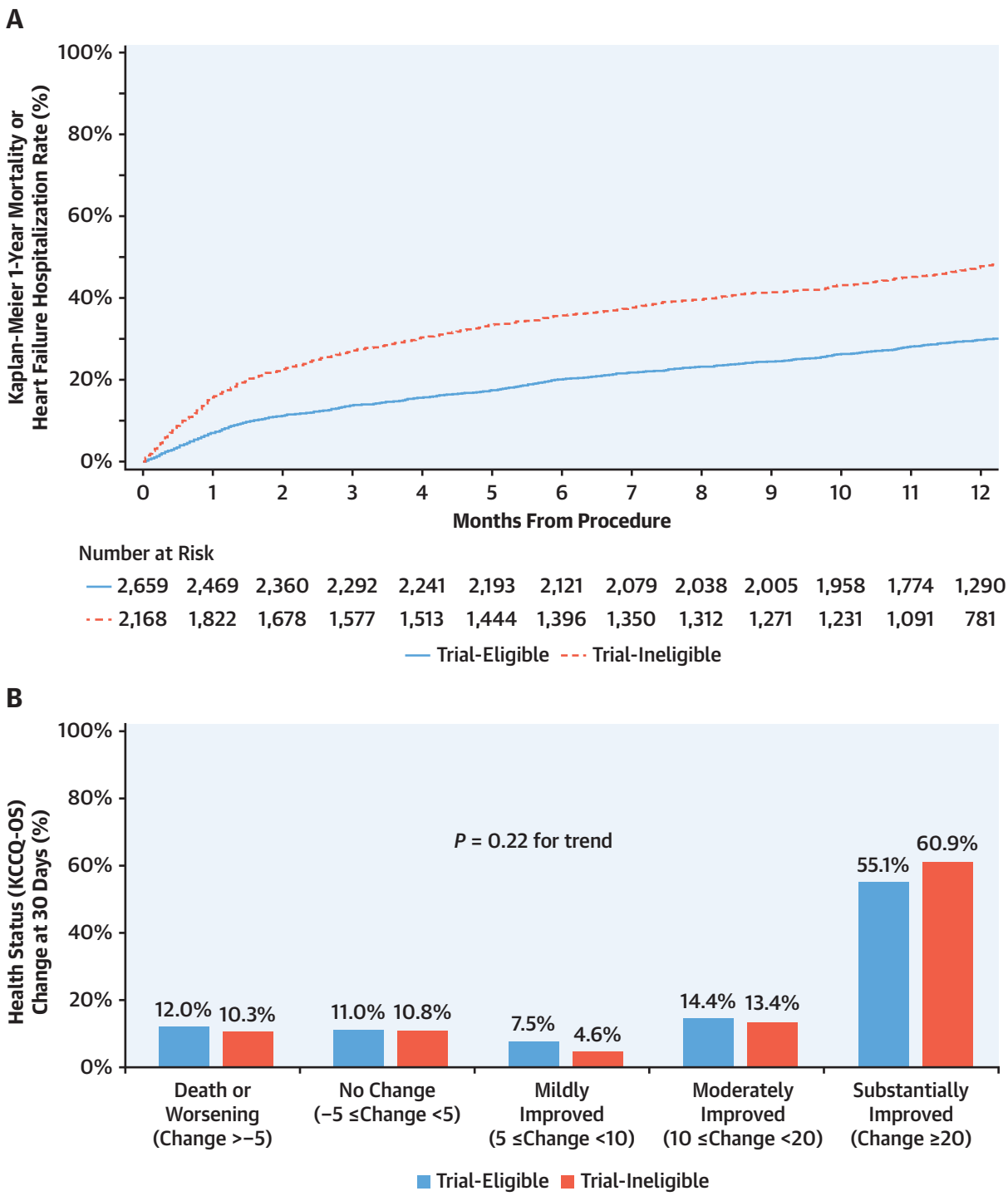
Abbreviations as in Table 1.

95% CI: 1.83-2.7; $P < 0.001$) analyses (Table 2). Specifically, in-hospital mortality (4.9% vs 0.9%; $P < 0.001$), major or life-threatening bleeding (4.8% vs 1.9%; $P < 0.001$), major access site complications (0.8% vs 0.4%; $P = 0.03$), unplanned vascular interventions (0.8% vs 0.3%; $P = 0.01$), stroke (1.0% vs 0.3%; $P < 0.001$), and transseptal complications (1.0% vs 0.2%; $P < 0.001$) occurred more frequently in trial-ineligible patients. Hospital length of stay was also significantly higher in trial-ineligible patients (7.9 vs 4.0 days; $P < 0.001$; adjusted OR: 1.78; 95% CI: 1.61-1.95; $P < 0.001$).

30-DAY ECHOCARDIOGRAPHIC AND HEALTH STATUS OUTCOMES. The 30-day endpoint of greater than moderate residual MR was more frequent in the trial-ineligible cohort (9.1% vs 7.5%; $P = 0.02$), but this difference was no longer statistically significant after risk-adjustment (adjusted OR: 1.17; 95% CI: 0.97-1.42; $P = 0.10$) (Table 3). Health status as measured by the KCCQ-OS from baseline to 30 days improved in both trial-ineligible (+28.0 points; $P < 0.001$) and trial-eligible patients, (+24.9 points; $P < 0.001$). In unadjusted analyses, the difference in health status improvement between groups was statistically significant ($P = 0.01$); however, this difference was not statistically significant in adjusted analyses (adjusted absolute difference 1.48 points; 95% CI: −0.28 to 3.24; $P = 0.10$). The categorization of change in health status at 30-days was similar between groups, with 78.9% and 77.0% of trial-ineligible and trial-eligible patients respectively reporting a clinically meaningful improvement (increase in KCCQ-OS ≥5 points) and 60.9% and 55.1% reporting a substantial improvement (increase in KCCQ-OS ≥20 points) (Central Illustration). A poor 30-day composite outcome occurred with similar frequency in the trial-ineligible and trial eligible groups (30.9% vs 33.2%; $P = 0.20$, adjusted OR: 1.03; 95% CI: 0.87-1.23; $P = 0.72$).

1-YEAR OUTCOMES. Based on Kaplan-Meier estimates, there was a higher risk of 1-year death (35.2% vs 18.3%; $P < 0.001$), HFH (20.3% vs 16.0%; $P < 0.001$) and the composite of death or HFH (47.4% vs 29.6%; $P < 0.001$) in the trial-ineligible compared with the trial-eligible population (Table 4). In adjusted analyses, there was a higher risk of 1-year death (HR: 2.07; 95% CI: 1.82-2.36; $P < 0.001$), HFH (HR: 1.26; 95% CI: 1.11-1.44; $P < 0.001$), and death or HFH (HR: 1.73; 95% CI: 1.57-1.91; $P < 0.001$) than in the trial-ineligible population. Cumulative incidence curves depicting 1-year death or HFH and the individual endpoints of 1-year death, and cumulative HFH are depicted in the Central Illustration and in Figure 3. Each clinical trial exclusion criterion was associated with a higher composite rate of death or HFH at 1 year in unadjusted and adjusted analyses, with the highest risk associated with measures of physiological decompensation such as preprocedure cardiogenic shock and inotropic support (Supplemental Table 1). Independent predictors of 1-year death or HFH in trial-ineligible patients following MTEER are shown in Supplemental Table 2. The strongest predictor of the 1-year combined endpoint of death or HFH in trial-ineligible patients was NYHA functional class III or IV symptoms at baseline (adjusted HR: 2.20; 95% CI: 1.70-2.84; $P < 0.001$) (Supplemental Table 2). Moderate or less residual MR following MTEER was associated with a lower risk of death or HFH at 1 year for trial-ineligible patients (adjusted HR: 0.47; 95% CI: 0.36-0.62; $P < 0.001$). However, trial-ineligible patients had a higher adjusted 1-year rate of death or HFH in landmark analyses excluding patients who did not survive until hospital discharge adjusting for technical procedural success (HR: 1.67; 95% CI: 1.51-1.85; $P < 0.001$) or moderate or less residual MR (HR: 1.74; 95% CI: 1.57-1.92; $P < 0.001$).

CENTRAL ILLUSTRATION **Mortality or Heart Failure Hospitalization and Health Status After Mitral Valve Edge-to-Edge Repair for Functional Mitral Regurgitation**



Chhatriwalla AK, et al. J Am Coll Cardiol. 2024;83(4):488-499.

We evaluated 6,675 transcatheter mitral valve edge-to-edge repairs (MTEER) performed for functional mitral regurgitation (FMR) between January 1, 2013, and April 30, 2020, as captured by the STS/TVT (Society of Thoracic Surgeons/Transcatheter Valve Therapy) Registry. Inverse propensity weighting was utilized to adjust for missing data, and competing risk modeling was utilized for heart failure hospitalization (HFH). (A) The primary endpoint of 1-year death or HFH was higher in patients who met trial ineligibility criteria. Health status as measured by the Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OS) was collected at baseline and 30 days after the procedure. (B) At 30 days, health status was significantly higher in both groups, with no significant difference in the magnitude of improvement between the 2 groups.

TABLE 4 1-Year Outcomes (Kaplan-Meier Estimates) in Trial-Ineligible and Trial-Eligible Patients

	Trial-Ineligible (n = 2,954)	Trial-Eligible (n = 3,721)	*P* Value
Mortality or HFH	47.4	29.6	<0.001
Mortality	35.2	18.3	<0.001
HFH	20.3	16.0	<0.001

Values are %.
HFH = heart failure hospitalization.

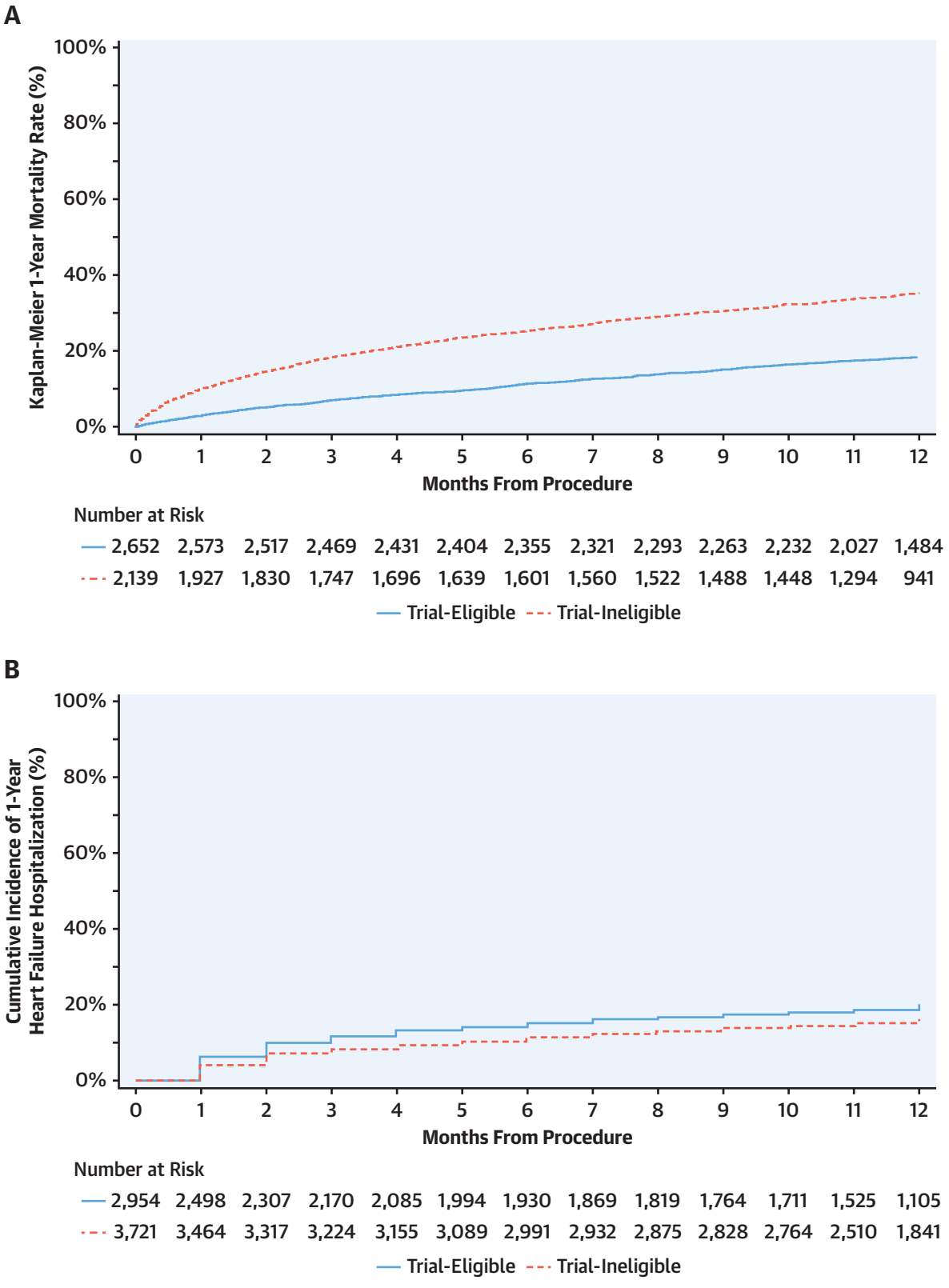
DISCUSSION

The major findings from this study, based on real-world data from the TVT registry, are as follows: First, the number of MTEER procedures performed for FMR in the United States increased steadily between 2013/2014 and 2019, with a notable acceleration after the publication of the COAPT trial in 2018. Second, over this same time period, nearly one-half of all MTEER procedures for FMR were performed in patients with clinical characteristics that would have excluded them from the COAPT trial. Third, although technical procedural success rates were high, they were lower in trial-ineligible (compared to trial-eligible) patients, in whom in-hospital complications including bleeding and mortality were more frequent, and the length of hospitalization was significantly longer. The observed difference in technical procedural success was driven primarily by the difference in in-hospital mortality (rather than the difference in residual MR) between groups. Fourth, although trial-ineligible patients had significant improvements in health status at 30 days (similar to trial-eligible patients), they nonetheless had a higher risk of 1-year death, HFH, and the composite of death or HFH—findings that were consistent after excluding patients who did not survive until hospital discharge. Finally, each clinical trial exclusion criterion (cardiogenic shock, inotropic support, LVEF <20%, LVESD >7 cm, home oxygen use, and severe TR) was independently associated with an increased risk of 1-year death or HFH.

The COAPT trial demonstrated reductions in death and HFH, and improved health status after MTEER in patients with severe FMR who remained symptomatic despite maximally tolerated doses of GDMT.[3] By contrast, no such benefits were observed in the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation).[10] Although several differences exist between the 2 studies, 1 hypothesis for the differing findings is that patients enrolled in MITRA-FR had larger left ventricles and less severe MR at baseline compared with those enrolled in COAPT.[11] In addition, patients with other high-risk features that were excluded from COAPT were not excluded from MITRA-FR, and maximally tolerated doses of GDMT at entry were not required in MITRA-FR. Importantly, although a large proportion of patients in the present analysis were treated with GDMT, the proportion is not as high as in COAPT or in recent HF registries;[12-14] whether this is due to less aggressive therapy or patient intolerance is unknown. As such, it is reasonable to hypothesize that more aggressive medical therapy may have improved outcomes for both trial-ineligible and trial-eligible patients in this study. Furthermore, age is a strong predictor of survival in HF patients based on the MAGGIC (Meta-Analysis Global Group In Chronic Heart Failure) criteria,[15] and the patient population in the present study was somewhat older than in COAPT and MITRA-FR. Given the growing (and aging) population of patients with HF, it is important to understand whether MTEER is beneficial in an even "sicker" patient population than enrolled in COAPT—particularly when other advanced HF therapies (such as cardiac transplantation or LV assist devices) are available for some patients as effective, but higher-risk, alternatives. The present data suggest that MTEER in COAPT trial-ineligible patients does provide substantial symptomatic improvement, although such patients have higher rates of both in-hospital and 1-year mortality and 1-year HFH compared with COAPT trial-eligible patients. These findings are consistent with those from a smaller 3-center European study that reported a 58% rate of death or HFH at 2 years in patients with a single COAPT trial exclusion criterion.[4]

Nevertheless, based on the present data, MTEER may be beneficial in the COAPT trial-ineligible patient population. The majority of surviving COAPT trial-ineligible as well as trial-eligible patients reported a substantial improvement in health status 30 days after MTEER. Moreover, in the COAPT trial, the 1-year the rate of HFH was reduced by ~50% with MTEER plus GDMT compared with GDMT alone.[1] Although cross-study extrapolation is challenging, it is noteworthy that in the present study, the adjusted risk of 1-year HFH (adjusted OR: 1.34) observed with MTEER in COAPT trial-ineligible compared with trial-eligible patients is lower than what might have been expected with medical therapy alone (expected HR: ~2.0). On the other hand, in COAPT, mortality at 1 year was slightly, but nonsignificantly, reduced in MTEER-treated patients compared with GDMT alone.[1] By contrast, higher adjusted 1-year mortality (OR: 2.07) was observed with MTEER in COAPT trial-ineligible compared with trial-eligible patients in

FIGURE 3 Mortality and HFH at 1-Year Following MTEER for FMR



We evaluated 6,675 transcatheter MTEER performed for FMR between January 1, 2013, and April 30, 2020, as captured by the STS/TVT Registry. Inverse propensity weighting was utilized to adjust for missing data, and competing risk modeling was utilized for heart failure hospitalization (HFH). The individual endpoints of 1-year death (A) and cumulative HFH (B) were higher in patients who met trial-ineligibility criteria. Abbreviations as in Figure 1.

this study. Although a control group of patients treated with medical therapy alone is not present in the TVT registry, these data suggest that COAPT trial-ineligible patients with FMR who undergo MTEER may achieve health status benefits similar to the trial-eligible patients as well as improved freedom from HFH. However, MTEER in high-risk trial-ineligible patients appears not to mitigate the impact that the additional qualifying adverse risk features have on mortality—at least at 1 year. In this regard, the mortality benefit of MTEER in COAPT was not realized until 2-year follow-up, and it is thus possible that an improvement in survival may be experienced in COAPT trial-ineligible patients as well.

These findings extend those reported from 2 prior studies. In the MitraBridge Registry,[16] approximately two-thirds of patients with advanced HF and FMR who underwent MTEER were free from adverse events at 1 year, and nearly 25% were no longer listed for heart transplantation due to clinical improvement. Similarly, a secondary analysis from the COAPT trial in which patients were categorized based on LV dimensions and MR severity demonstrated that patients with larger LV size and less MR had no improvement in mortality or HFH with MTEER in additional to GDMT; however, benefits in 6-minute walk distance and health status were preserved.[17] Further studies of MTEER in patients with FMR and advanced HF are warranted given the large proportion of trial-ineligible patients treated with MTEER in the United States, as demonstrated in the present study. Ideally, these investigations should be randomized trials with a control group of GDMT alone, similar to COAPT. Complementary studies involving transcatheter mitral valve therapies other than MTEER (such as transcatheter mitral valve replacement) should be considered as well.[18]

STUDY LIMITATIONS. This was a retrospective, observational study, and despite adjustment for various demographic, clinical, and procedural variables, unmeasured factors can confound the results of this analysis. Data in the TVT registry are site-reported, and data regarding echocardiographic parameters such as LVEF, LV size, and MR and TR severity were not adjudicated by a core laboratory. Although data regarding medication use are available in the dataset, the doses of these medications or contraindications to these medications are not known, and determinations regarding optimal GDMT cannot be made. In addition, the use of more novel HF medications such as angiotensin receptor/neprilysin inhibitors and sodium-glucose co-transporter-2 inhibitors was not collected in the Registry. The definition of "trial-ineligible" used in the present analysis does not characterize all of the COAPT exclusion criteria. For example, missing data regarding pulmonary hypertension within the registry precluded an analysis of this variable as it pertains to trial-ineligibility, and data regarding right ventricular function and HF stage are not collected in the TVT Registry. Furthermore, the lack of a control group of trial-ineligible patients treated with medical therapy alone limits direct comparisons of mortality, HFH, and health status attributable to MTEER therapy. Finally, adjustments for multiple comparisons were not made, and due to data missingness, the models for all KCCQ-QS outcomes utilized data only from sites where completeness of change in KCCQ was >50%.

CONCLUSIONS

From this largescale study representative of patients with HF and severe FMR undergoing MTEER with the MitraClip in the United States, patients with FMR and 1 or more COAPT trial exclusion criteria who underwent MTEER had lower rates of technical procedural success and more frequent procedural and in-hospital complications than COAPT trial-eligible patients. Although 30-day health status was comparable in COAPT trial-ineligible and trial-eligible patients, trial-ineligible patients had a greater adjusted risk of 1-year death and HFH. Further studies are warranted to examine the long-term results of MTEER in COAPT trial-ineligible patients, especially in comparison to alternatives such as LV assist devices or heart transplantation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This research was supported by the ACC/STS TVT Registry. The views expressed in this paper represent those of the author(s), and do not necessarily represent the official views of the registry or its associated professional societies identified at CVQuality.ACC.org/NCDR. Dr Chhatriwalla is a proctor for Edwards Lifesciences, and Medtronic Inc; and is on the Speakers Bureau for Abbott Vascular, Edwards Lifesciences, and Medtronic. Dr Cohen receives research grant support and consulting income from Abbott, Edwards Lifesciences, Medtronic, and Boston Scientific. Dr Vemulapalli has grants from Abbott Vascular, Boston Scientific, HeartFlow, American College of Cardiology, Society of Thoracic Surgeons, National Institutes of Health, and Patient Centered Outcomes Research Institute; and serves as a consultant to Boston Scientific, Premiere, Janssen, and Zafgen. Dr Huded has received consulting fees from Boston Scientific; and has received a research grant from Abbott Vascular. Dr Lindenfeld has been a consultant for Abbott, Alleviant, AstraZeneca, Biotronik, Boston Scientific, CVRx, Edwards Lifesciences, Merck, Medtronic, V-wave, Vascular Dynamics, Whiteswell, and Vectorious; and receives research funding from AstraZeneca. Dr Stone has received speaker honoraria from Medtronic, Pulnovo, Abiomed, Amgen, and Boehringer Ingelheim; has served as a consultant to Abbott, Daiichi-Sankyo, CorFlow, Apollo Therapeutics, Cardiomech, Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Miracor, Vectorious, Neovasc, Ancora, Elucid Bio, Occlutech, Impulse Dynamics, Adona Medical, Millennia Biopharma, Oxitope, Cardiac

Success, and HighLife; and has equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter; his daughter is an employee at IQVIA; and his employer, Mount Sinai Hospital, receives research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense Webster, Shockwave, Vascular Dynamics, Pulnovo, and V-wave. Dr Sorajja is a consultant for Abbott Structural, Anteris, Edwards Lifesciences, Evolution Medical, Shifamed, WL Gore, xDot, ValCare, 4C Medical, Medtronic, Boston Scientific, and vDyne.

ADDRESS FOR CORRESPONDENCE: Dr Adnan K. Chhatriwalla, Saint Luke's Mid America Heart Institute, 4330 Wornall Road, Suite 2000, Kansas City, Missouri 64111, USA. E-mail: achhatriwalla@saint-lukes.org. @akcmahi.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

The benefits of MTEER on mortality and heart failure hospitalization are attenuated in patients with FMR with exclusion criteria for participation in the COAPT trial.

TRANSLATIONAL OUTLOOK:

Future studies should evaluate the comparative effectiveness of medical, transcatheter and advanced therapies such as left ventricular assist devices and heart transplantation in patients with FMR and decompensated heart failure.

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KEY WORDS edge-to-edge repair, functional mitral regurgitation, health status, heart failure

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