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ORIGINAL INVESTIGATIONS

3-Year Outcomes of Transcatheter Mitral Valve Repair in Patients With Heart Failure

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ABSTRACT

BACKGROUND In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial, transcatheter mitral valve repair (TMVr) resulted in fewer heart failure hospitalizations (HFHs) and lower mortality at 24 months in patients with heart failure (HF) with mitral regurgitation (MR) secondary to left ventricular dysfunction compared with guideline-directed medical therapy (GDMT) alone.

OBJECTIVES This study determined if these benefits persisted to 36 months and if control subjects who were allowed to cross over at 24 months derived similar benefit.

METHODS This study randomized 614 patients with HF with moderate-to-severe or severe secondary MR, who remained symptomatic despite maximally tolerated GDMT, to TMVr plus GDMT versus GDMT alone. The primary effectiveness endpoint was all HFHs through 24-month follow-up. Patients have now been followed for 36 months.

RESULTS The annualized rates of HFHs per patient-year were 35.5% with TMVr and 68.8% with GDMT alone (hazard ratio [HR]: 0.49; 95% confidence interval [CI]: 0.37 to 0.63; $p < 0.001$; number needed to treat (NNT) = 3.0; 95% CI: 2.4 to 4.0). Mortality occurred in 42.8% of the device group versus 55.5% of control group (HR: 0.67; 95% CI: 0.52 to 0.85; $p = 0.001$; NNT = 7.9; 95% CI: 4.6 to 26.1). Patients who underwent TMVr also had sustained 3-year improvements in MR severity, quality-of-life measures, and functional capacity. Among 58 patients assigned to GDMT alone who crossed over and were treated with TMVr, the subsequent composite rate of mortality or HFH was reduced compared with those who continued on GDMT alone (adjusted HR: 0.43; 95% CI: 0.24 to 0.78; $p = 0.006$).

CONCLUSIONS Among patients with HF and moderate-to-severe or severe secondary MR who remained symptomatic despite GDMT, TMVr was safe, provided a durable reduction in MR, reduced the rate of HFH, and improved survival, quality of life, and functional capacity compared with GDMT alone through 36 months. Surviving patients who crossed over to device treatment had a prognosis comparable to those originally assigned to transcatheter therapy. (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation [COAPT]; NCT01626079) (J Am Coll Cardiol 2021;77:1029–40) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

CI = confidence interval

EROA = effective regurgitant orifice area

GDMT = guideline-directed medical therapy

HF = heart failure

HFH = heart failure hospitalization

HR = hazard ratio

ITT = intention to treat

KCCQ = Kansas City Cardiomyopathy Questionnaire

LV = left ventricle

MR = mitral regurgitation

NNT = number needed to treat

NYHA = New York Heart Association

QoL = quality of life

TMVr = transcatheter mitral valve repair

Secondary mitral regurgitation (MR) in patients with heart failure (HF) and left ventricular (LV) dysfunction has been shown to be associated with increased mortality and HF hospitalizations (HFHs) and decreased quality of life (QOL) (1,2). In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial, patients with HF with moderate-to-severe or severe secondary MR who remained symptomatic, despite maximally tolerated doses of guideline-directed medical therapy (GDMT) and cardiac resynchronization therapy when indicated, were randomized to transcatheter mitral valve repair (TMVr) with the MitraClip device (Abbott, Santa Clara, California) plus GDMT versus continued GDMT alone. TMVr was shown to be safe and resulted in lower rates of HFH and all-cause mortality, as well as improved QOL and functional capacity at 24 months compared with GDMT alone (3–5). Whether these improvements are sustained with longer-term follow-up is unknown. This is especially important to ascertain because of the poor prognosis of these patients. In addition, in the COAPT trial, surviving patients assigned to GDMT alone were, by protocol, allowed to crossover after 24 months and undergo TMVr with the MitraClip. The present report describes the intention-to-treat results at 36 months from the COAPT trial and a detailed analysis of the outcomes in patients who underwent GDMT alone, who later received transcatheter therapy.

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METHODS

STUDY DESIGN AND PATIENTS. The COAPT trial design was published previously (3,4). In brief, the COAPT trial was a randomized, parallel-controlled, open-label multicenter trial that evaluated the safety and effectiveness of TMVr with the MitraClip device (Abbott) in patients with HF with moderate-to-severe (3+) or severe (4+) MR who remained symptomatic (New York Heart Association [NYHA] functional classes II, III, or ambulatory IV) despite maximally tolerated GDMT. Eligible patients had ischemic or nonischemic cardiomyopathy, with LV ejection fractions between 20% and 50% and LV end-systolic diameter ≤70 mm. Additional inclusion and exclusion criteria were reported (3,4). Patients were randomly assigned in a 1:1 ratio to receive GDMT alone or GDMT with implantation of the MitraClip. For patients randomized to GDMT alone, crossover to TMVr was allowed per protocol (with no charge for the device) after the primary endpoint of 24 months was reached.

PROCEDURES. The MitraClip procedure has been described previously (3). Briefly, the procedure is performed under general anesthesia using fluoroscopic and echocardiographic guidance. Femoral venous access is obtained, and a steerable guide catheter is advanced across the interatrial septum. The MitraClip device is opened in the left atrium and advanced across the mitral valve into the ventricle, then pulled back to grasp the leaflets. If placement of 1 device does not result in sufficient reduction in MR, additional devices may be placed. All patients (device and control groups) were treated with maximally tolerated doses of GDMT before enrollment, and major changes in the baseline regimen were not permitted, except for intolerable side effects or strong medical justification.

OUTCOMES. The primary effectiveness endpoint was all HFH through 24 months (including recurrent events for patients with >1 event), measured at the time when the last patient enrolled reached 12-month follow-up. The primary safety endpoint was the 12-month freedom from device-related complications, defined as a composite of single leaflet

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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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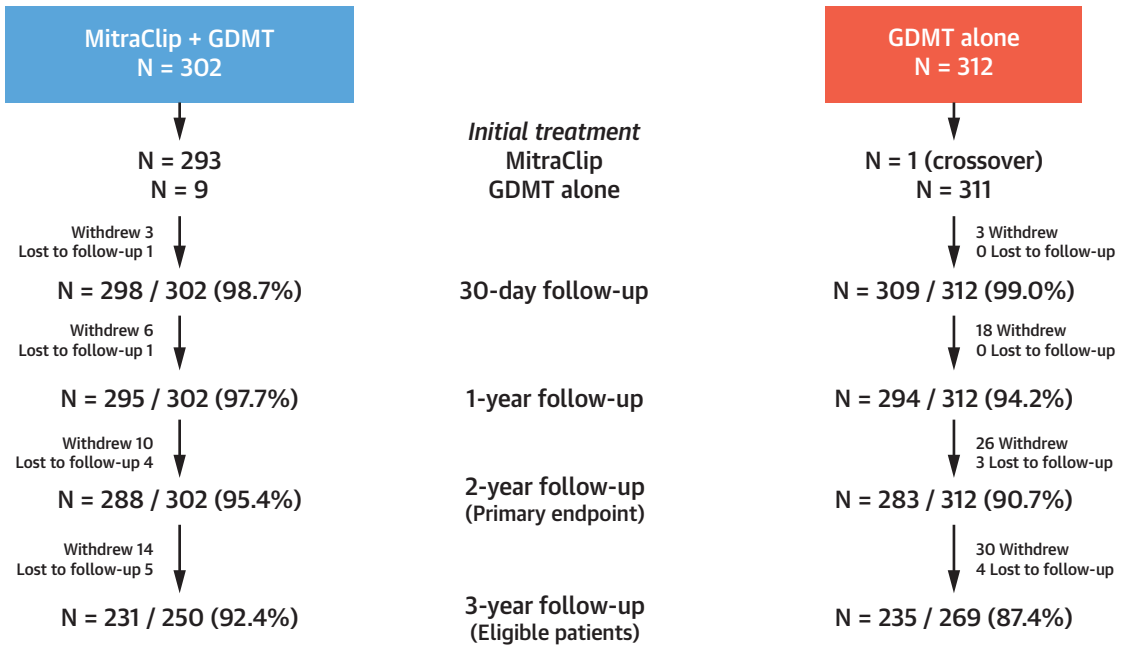
FIGURE 1 CONSORT Diagram of Patient Flow in the COAPT Trial



The primary endpoint was assessed at 24-month duration of follow-up, with all patients having a minimum of 12 months of follow-up. At the present data extraction, 519 of 614 patients reached the 36-month follow-up window, with all patients having a minimum of 24 months of follow-up. All follow-up rates are presented for the intention-to-treat population. COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; GDMT = guideline-directed medical therapy.

device attachment or embolization, endocarditis or mitral stenosis requiring surgery, LV assist device implantation, heart transplantation, or any device-related complication that required nonelective cardiovascular surgery. Transthoracic echocardiography, QOL assessments using the Kansas City Cardiomyopathy Questionnaire (KCCQ), and functional capacity assessments by 6-min walk distance (6MWD) were performed at regular intervals (3,4). Follow-up is ongoing annually through 5 years. Clinical events were adjudicated by an independent committee after review of original source documents (Cardiovascular Research Foundation, New York, New York). All echocardiograms were read at an independent echocardiographic core laboratory (Medstar, Washington, DC). At the time of the present analysis, all patients reached 2-year follow-up, and all available data through 3-year follow-up were reported based on data extraction on August 2, 2019.

STATISTICAL ANALYSIS. Assumptions and power analysis for the primary and secondary endpoints have been previously detailed (3,4). The primary effectiveness endpoint of all HFHs through follow-up was analyzed using a joint frailty model to account for the competing risk of death. The primary safety endpoint was tested using the asymptotic Z statistic against a pre-specified objective performance goal of 88%, with the event-free rate estimated using the Kaplan-Meier method and the SEs estimated using the Greenwood method. All effectiveness analyses were performed from the time of randomization in the intention-to-treat (ITT) population (defined as all subjects in their allocated groups, regardless of treatment received). The primary safety endpoint was analyzed in the safety analysis population, consisting of all device group patients in whom a MitraClip procedure was attempted.

Event rates were estimated using the Kaplan-Meier method. For time-to-first event analyses, hazard ratios (HRs) with confidence intervals (CIs) were determined, and event rates were compared with Cox regression. Time-adjusted multivariable Cox proportional hazards regression was performed to evaluate the composite outcome of death or HFH among patients in the GDMT alone group who crossed over and were treated with TMVr. For this model, patients who received GDMT and who were treated with TMVr

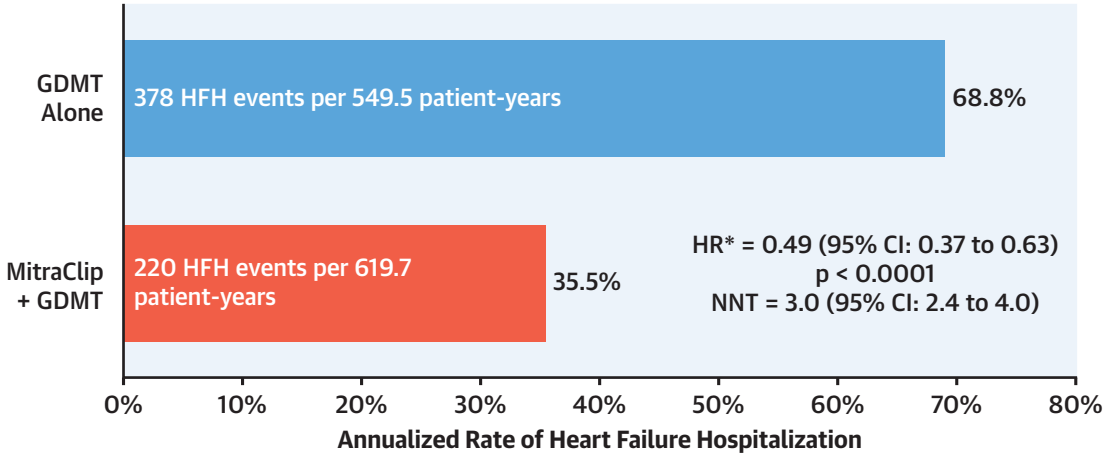
TABLE 1 Clinical Outcomes in the Randomized Groups

	TMVr + GDMT (n = 302)	GDMT Alone (n = 312)	Hazard Ratio or Difference (95% CI)	p Value
All heart failure hospitalizations at 36 months*	220/619.7 (35.5)	378/549.5 (68.8)	0.49 (0.37–0.63)†	<0.0001†
Freedom from device-related complications at 36 months,‡ %	91.3 ± 2.1	–	–	0.055§
Mitral regurgitation grade of ≤2+				
At 24 months	161/162 (99.4)	57/124 (46.0)	–	<0.0001
At 36 months	85/86 (98.8)	39/49 (79.6)	–	0.0002
Death from any cause at 36 months‖	112 (42.8)	150 (55.5)	0.67 (0.52–0.85)	0.001
Death or heart failure hospitalization at 36 months‖	161 (58.8)	244 (88.1)	0.48 (0.39–0.59)	<0.0001
Change in KCCQ score from baseline to 24 months, points	7.8 ± 2.3	−12.1 ± 2.3	20.0 (13.7–26.2)	<0.0001
Change in 6-min walk distance from baseline to 24 months, m	−55.0 ± 10.8	−93.5 ± 10.9	38.5 (8.3–68.7)	0.01
All hospitalizations for any cause at 36 months*	636/619.7 (102.6)	791/549.5 (143.9)	0.72 (0.57–0.90)†	0.003†
NYHA functional class I or II				
At 24 months	122/206 (59.2)	81/206 (39.3)	–	<0.0001
At 36 months	72/147 (49.0)	45/149 (30.2)	–	0.001

Values are n/N (%) or mean ± SD, unless otherwise indicated. *Number of events/total number of patient-100 years (annualized rate). †Based on joint frailty model. ‡Kaplan-Meier estimated event rate (lower limit of 1-sided 95% confidence interval [CI]). §Compared with an 88.0% performance goal. ‖Rates are Kaplan-Meier estimated event rate (no. of events).
GDMT = guideline-directed medical therapy; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; TMVr = transcatheter mitral valve repair.

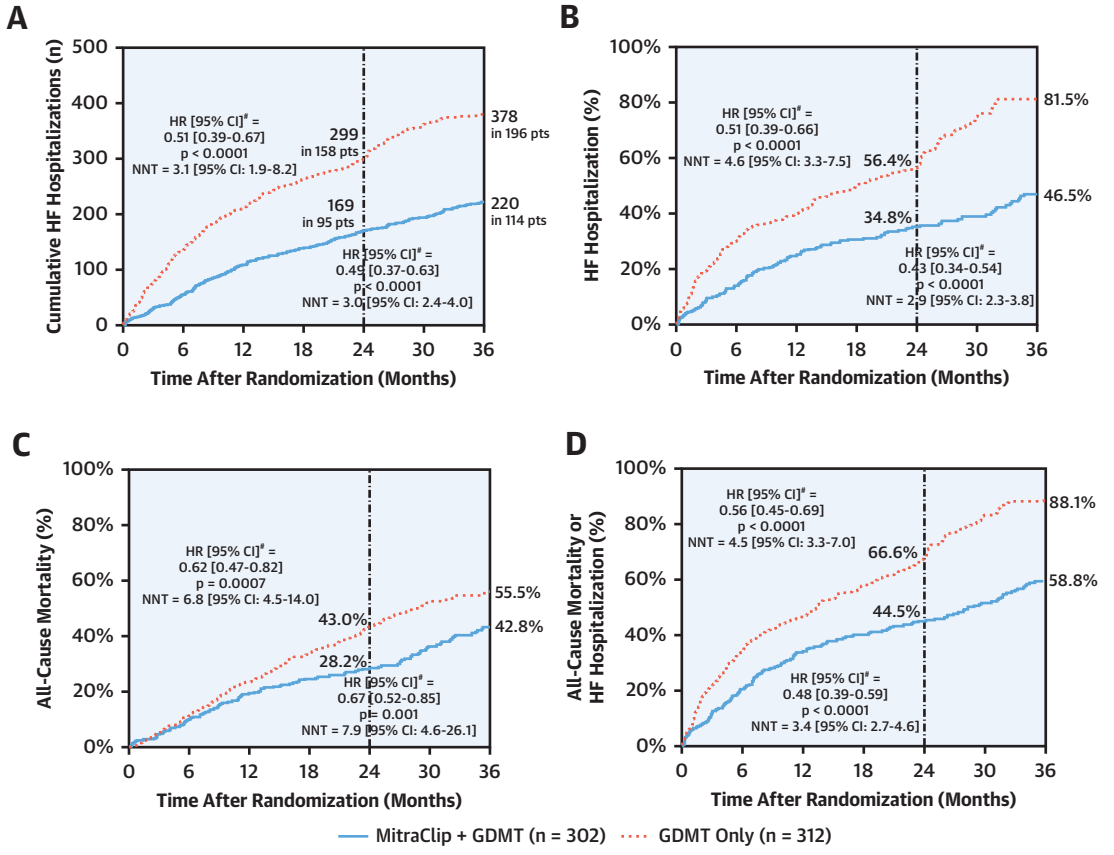
were censored at time of crossover. Variables were entered into the model at the 0.2 significance level and removed at the 0.1 level. Variables were eligible for inclusion in the multivariable model–building process if the variable was present for 90% of the subjects in the analyses and had the higher level of significance if highly correlated with another variable. Covariates entered in the final model were baseline brain natriuretic protein, history of anemia, serum creatinine, use of renin-angiotensin-aldosterone system blockers, use of beta-blockers, use of vasodilators (hydralazine or nitrates), effective regurgitant orifice area (EROA), sex, previous percutaneous coronary intervention and/or coronary artery bypass graft, Society of Thoracic Surgeons replacement score, LV end-diastolic volume, LV ejection fraction, renal disease, 6MWD, previous stroke, systolic blood pressure, tricuspid regurgitation grade, and treatment with MitraClip as a time-varying covariate. Categorical variables were compared with the Fisher exact test. Continuous variables were compared with Student's *t*-tests or the Wilcoxon rank-sum test for non-normally distributed data. Analysis of covariance was used to compare

FIGURE 2 Annualized Rates of HFH Through 3-Year Follow-Up in the Intention-to-Treat Population



The annualized rate is calculated as the total number of heart failure hospitalization (HFH) events divided by total follow-up years. *Analysis was performed with the joint frailty model. Additional results of the model are provided in Supplemental Table 4. CI = confidence interval; HR = hazard ratio; NNT = number needed to treat; other abbreviation as in Figure 1.

CENTRAL ILLUSTRATION **Outcomes Through 3-Year Follow-Up in the Intention-to-Treat Population**



Mack, M.J. et al. J Am Coll Cardiol. 2021;77(8):1029–40.

(A) Number of cumulative heart failure hospitalizations. **(B)** Time to first heart failure hospitalization. **(C)** Time to all-cause mortality. **(D)** Time to all-cause mortality or heart failure hospitalization.

mean changes in continuous outcome measures from baseline to follow-up between the 2 groups. For superiority, a 2-sided p value <0.05 was considered statistically significant. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

ORGANIZATION, APPROVALS, AND ROLE OF THE FUNDING SOURCE. The protocol was designed by the principal investigators and sponsor in concert with the U.S. Food and Drug Administration. The study was approved by the investigational review board or ethics committee at each participating center, and all patients provided informed, written consent. The trial was sponsored by Abbott, which participated in the design of the protocol, site selection and management, and data analysis. The principal investigators (M.J.M. and G.W.S.) had unrestricted data access, prepared the manuscript, controlled the decision for its submission, and vouch for the integrity of the trial. The sponsor had the right to a nonbinding review of this paper before its submission.

RESULTS

PATIENTS AND FOLLOW-UP. From December 27, 2012 through June 23, 2017, a total of 614 patients were enrolled, with 302 patients randomly assigned to TMVr plus GDMT and 312 to GDMT alone. The baseline characteristics of the study population have been previously described and are listed in Supplemental Table 1. Mean age was 72.0 ± 11.2 years, 36.0% were women, and 36.5% had previously undergone cardiac resynchronization therapy. The etiology of LV dysfunction was ischemic cardiomyopathy in 60.7% and nonischemic

TABLE 2 Device-Related Complications in the Safety Analysis Population

	Through 30 Days	Through 12 Months	Through 24 Months	Through 36 Months
Overall rate	4 (1.4)	9 (3.3)	13 (5.2)	18 (8.7)
Device-related complications	4 (1.4)	4 (1.4)	4 (1.4)	4 (1.4)
Single leaflet device attachment	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)
Device embolization	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Endocarditis requiring surgery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mitral stenosis requiring surgery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any device-related complication requiring nonelective cardiovascular surgery	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Progressive heart failure	0 (0.0)	5 (2.0)	9 (3.8)	14 (7.4)
Left ventricular assist device implant	0 (0.0)	3 (1.2)	6 (2.6)	10 (5.4)
Heart transplantation	0 (0.0)	2 (0.8)	3 (1.3)	5 (2.6)

Values are n (%). The safety population (n = 293) consisted of those patients in whom a MitraClip procedure was attempted. Therefore, the left ventricular assist device and heart transplantation rates here vary slightly from those in Table 3, which were analyzed in the intention-to-treat population.

cardiomyopathy in 39.3%. Thirty-six month outcomes were available in 231 of 250 (92.4%) eligible patients in the TMVr group and in 235 of 269 (87.4%) patients in the GDMT alone group (Figure 1).

CLINICAL OUTCOMES. Clinical outcomes for the primary effectiveness, safety endpoints, and major secondary endpoints are listed in Table 1. Through 36 months, the annualized rates of HFH in the ITT population were 35.5% per patient-year with TMVr plus GDMT and 68.8% per patient-year with GDMT alone (HR: 0.49; 95% CI: 0.37 to 0.63; $p < 0.0001$) (Figure 2). The number needed-to-treat (NNT) with TMVr to prevent 1 hospitalization within 36 months was 3.0 (95% CI: 2.4 to 4.0). This was compared with the findings at 24 months of 31.5% HFHs per patient-

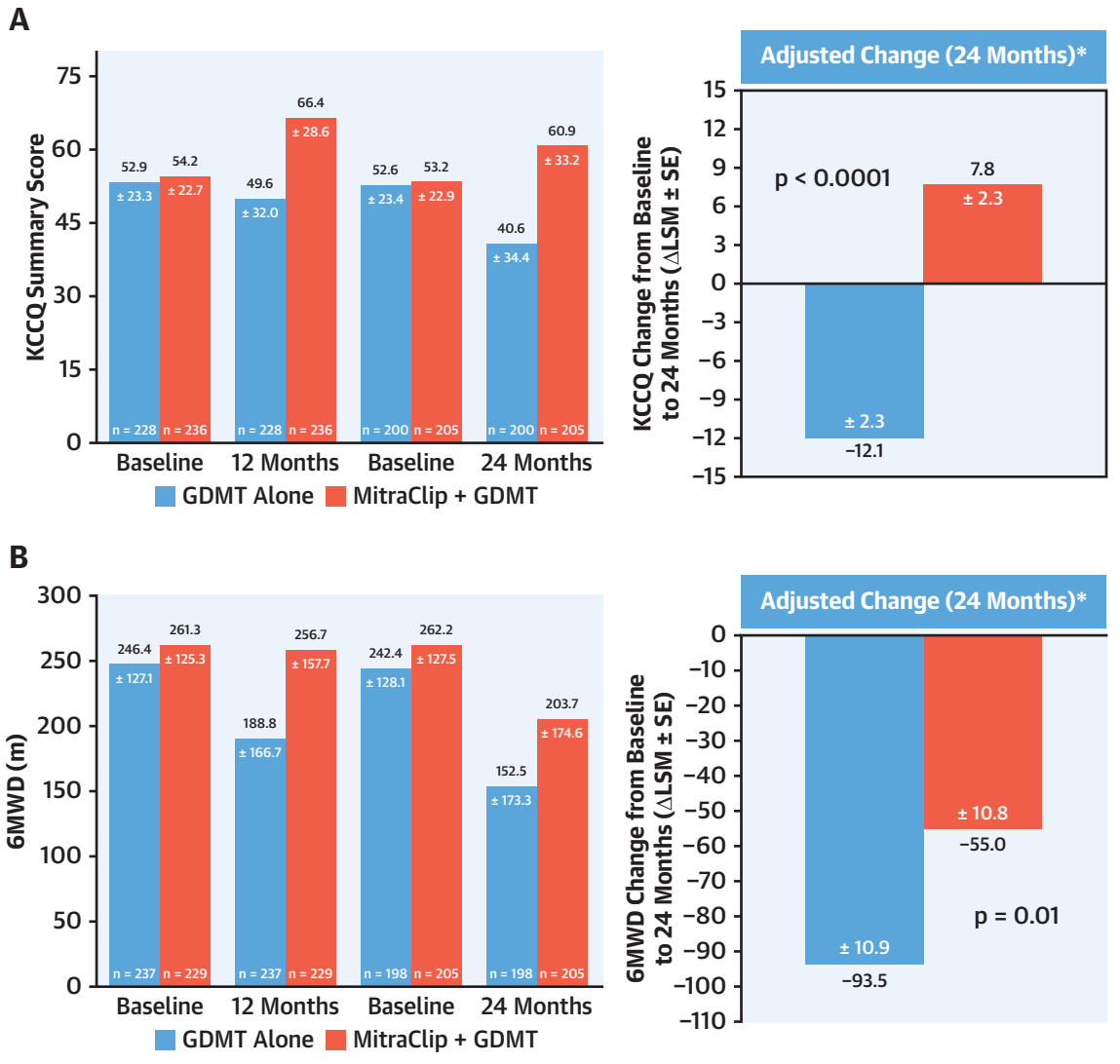
TABLE 3 Adverse Events Through 36-Month Follow-Up in the Randomized Groups

	TMVr + GDMT (n = 302)	GDMT alone (n = 312)	HR (95% CI)	p Value
Death from any cause	112 (42.8)	150 (55.5)	0.67 (0.52–0.85)	0.001
Cardiovascular cause	88 (36.0)	121 (47.4)	0.65 (0.49–0.85)	0.002
Related to heart failure	45 (21.6)	77 (34.7)	0.51 (0.35–0.74)	0.0004
Not related to heart failure	43 (18.4)	44 (19.8)	0.88 (0.58–1.34)	0.55
Non-cardiovascular cause	24 (10.6)	29 (15.5)	0.74 (0.43–1.27)	0.27
Hospitalization for any cause	216 (77.7)	258 (93.3)	0.70 (0.58–0.84)	0.0001
Cardiovascular cause	165 (64.6)	223 (86.7)	0.58 (0.48–0.72)	<0.0001
Related to heart failure	114 (46.5)	196 (81.5)	0.43 (0.34–0.54)	<0.0001
Not related to heart failure	92 (40.8)	89 (40.6)	0.98 (0.73–1.31)	0.87
Non-cardiovascular cause	143 (56.9)	147 (62.3)	0.89 (0.71–1.12)	0.31
Death or heart failure hospitalization	162 (59.0)	246 (88.0)	0.48 (0.39–0.59)	<0.0001
Death from cardiovascular cause or heart failure hospitalization	145 (54.6)	227 (85.1)	0.47 (0.38–0.58)	<0.0001
Unplanned mitral valve intervention	10 (3.8)	65 (49.2)	0.10 (0.05–0.20)	<0.0001
Transcatheter mitral valve repair	9 (3.5)	58 (47.1)	0.10 (0.05–0.20)	<0.0001
Mitral valve surgery	1 (0.4)	8 (3.3)	0.12 (0.02–0.97)	0.047
PCI or CABG	9 (4.0)	12 (4.9)	0.70 (0.29–1.66)	0.42
PCI	9 (4.0)	10 (4.3)	0.83 (0.34–2.05)	0.69
CABG	0 (0.0)	2 (0.7)	–	–
Stroke	16 (7.7)	18 (9.8)	0.80 (0.41–1.57)	0.51
Myocardial infarction	17 (7.7)	23 (13.3)	0.65 (0.35–1.23)	0.19
New CRT implantation	8 (3.4)	8 (3.1)	0.96 (0.36–2.56)	0.93
LVAD implant or heart transplantation	14 (7.3)	25 (11.4)	0.49 (0.25–0.94)	0.03
LVAD implantation	10 (5.4)	18 (8.6)	0.48 (0.22–1.04)	0.06
Heart transplantation	5 (2.6)	10 (4.9)	0.45 (0.15–1.30)	0.14

Values are n (%) unless otherwise indicated.

CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; LVAD = left ventricular assist device; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

FIGURE 3 Quality-of-Life and Functional Capacity Through 2-Year Follow-Up in the Intention-to-Treat Population



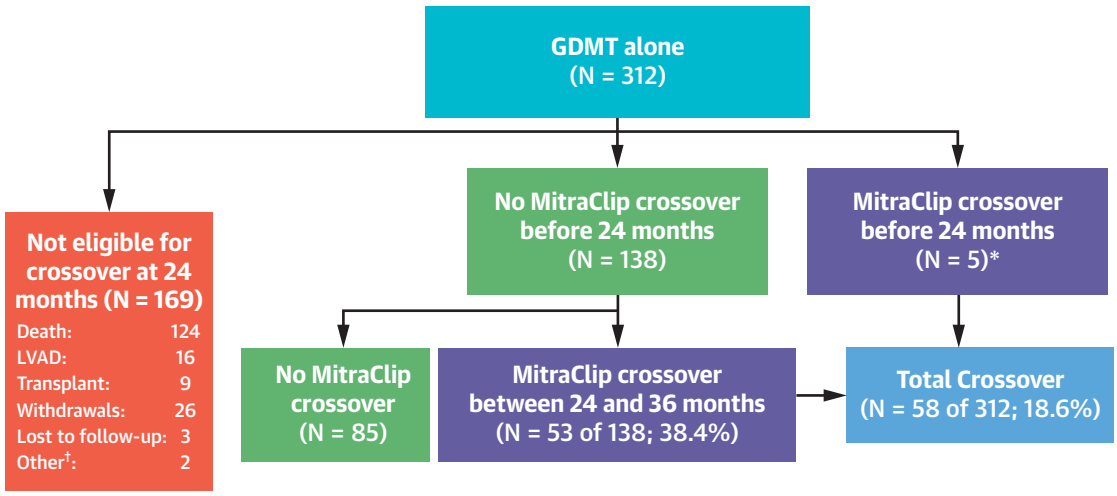
(A) Change in Kansas City Cardiomyopathy Score (KCCQ) from baseline to 12 and 24 months. **(B)** Change in 6-min walk distance (6MWD) from baseline to 12 and 24 months. For the KCCQ analysis, as specified in the protocol, patients with an adjudicated heart failure death were assigned a KCCQ score of 0 at 24 months. For the 6MWD analysis, as specified in the protocol, patients with an adjudicated heart failure death or unable to walk due to cardiac reasons were assigned a 6MWD of 0 at 24 months. *Analysis of covariance model with baseline KCCQ or 6MWD and treatment effect as covariates. Other abbreviation as in Figure 1.

year in the TMVr group and 50.6% HFHs per patient-year in the GDMT alone group (HR: 0.51; 95% CI: 0.39 to 0.67; $p < 0.0001$; NNT = 3.1; 95% CI: 1.9 to 8.2). All-cause mortality within 36 months occurred in 42.8% of the device group versus 55.5% of the control group (HR: 0.67; 95% CI: 0.52 to 0.85; $p = 0.001$; NNT = 7.9; 95% CI: 4.6 to 26.1) (Central Illustration).

Device-related complications within 36 months in the safety analysis population are listed in Tables 1 and 2. Freedom from device-related complications was 91.3% at 36 months compared with 94.8% at 24 months. Only 5 safety events occurred between 24 and 36 months, all due to progressive HF that required heart transplantation or LV assist device implantation.

All outcome events within 36 months are listed in Table 3. Patients treated with TMVr compared with GDMT alone had lower rates of all-cause death, death from HF, all-cause hospitalizations, HFHs, the composite of death or HF, as well as the need for heart

FIGURE 4 MitraClip Crossovers in GDMT-Assigned Patients



Protocol allowed crossover to treatment arm at 24 months (median: 25.5 months). Cross overs included 5 patients before 24 months (*protocol deviation). Reasons for non-crossover included ineligibility and lost to follow-up after 24 months,† as well as patient and care provider choice. LVAD = left ventricular assist device; other abbreviation as in Figure 1.

transplantation or LV assist device. The benefits in terms of improved KCCQ scores and 6MWD previously reported at 12 months persisted through complete 24-month follow-up (Table 1, Figure 3). Finally, TMVr substantially reduced the severity of MR compared with GDMT, with durable effects through 36 months (Table 1, Supplemental Figure 1).

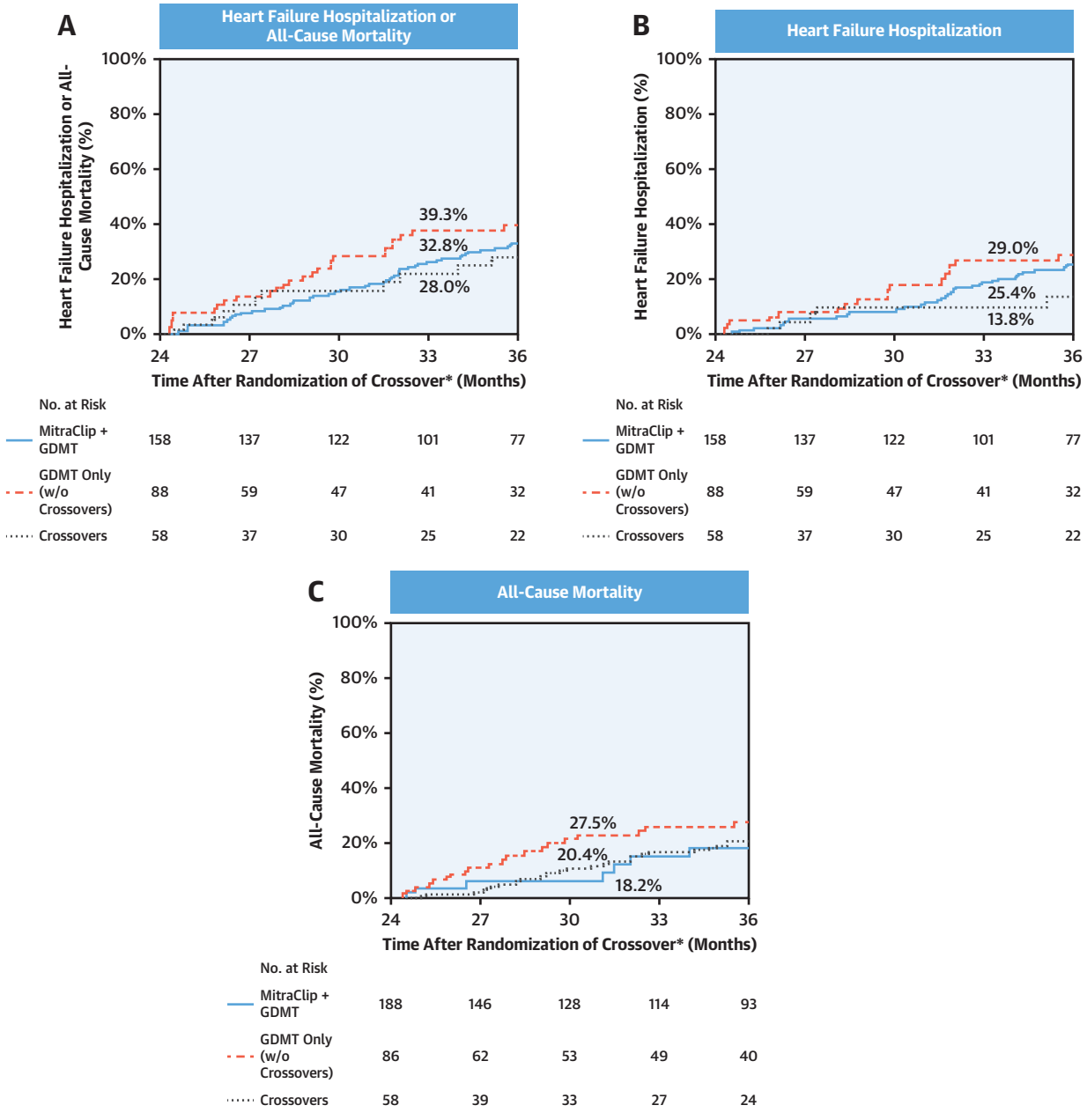
CROSSOVER ANALYSIS. As shown in Figure 4, among the 312 patients assigned to GDMT alone, 138 were eligible for crossover at 2 years, 53 (38.4%) of whom received the MitraClip between 2 and 3 years. An additional 5 patients underwent TMVr before the 2-year protocol eligibility time point for crossover. Thus, 58 total patients (18.6%) of the original GDMT alone control arm were treated with the MitraClip. Median duration from initial randomization to crossover was 25.5 months (range: 0.2 to 32.9 months) with a median (quartile 1 to quartile 3) follow-up after crossover of 7.7 months (quartile 1 to quartile 3: 0 to 43.6 months). In comparison, the median (quartile 1 to quartile 3) follow-up of the overall ITT population was 24.5 months (quartile 1 to quartile 3: 12.1 to 36.1 months). Patients assigned to GDMT alone who were subsequently treated with MitraClip had similar demographic characteristics as those who did not cross over but had less severe HF as evidenced by a lower rate of NYHA functional class IV, lower brain natriuretic protein levels, and better 6MWD (Supplemental Table 2). Details of the MitraClip procedure in GDMT crossover patients compared with those originally assigned to MitraClip treatment are shown in Supplemental Table 3. The MitraClip reduced MR as effectively in patients assigned to GDMT alone who subsequently were treated with MitraClip as in the originally randomized MitraClip plus GDMT patient group (Supplemental Figure 2).

In a landmark analysis, the rates of HFH and mortality after crossover to TMVr in the GDMT alone group were by inspection lower than that in the patients alive at 24 months. These patients remained in the GDMT alone group without crossover to TMVr for the equivalent follow-up duration of 24 to 36 months and were comparable to the patients who remained alive in the originally assigned TMVr plus GDMT group beyond 24 months (Figure 5). After adjusting for baseline differences between groups and times to crossover, treatment with TMVr in the GDMT alone group compared with continuing on GDMT alone was an independent predictor of freedom from subsequent death or HFH (adjusted HR: 0.43; 95% CI: 0.24to 0.78; p = 0.006) (Table 4).

DISCUSSION

With follow-up through 2 years, the principal findings of the COAPT trial were that in patients with HF and moderate-to-severe or severe secondary MR who remained symptomatic despite GDMT, transcatheter mitral leaflet approximation with the MitraClip device was safe and reduced the rate of HFHs and improved

FIGURE 5 Landmark Analysis of the Outcomes of Patients in the GDMT Alone Group Who Crossed Over to MitraClip Treatment Compared With Those Who Continued to Be Treated With GDMT Alone and Those Who Were Originally Assigned to MitraClip Treatment



(A) Time to all-cause mortality or HFH. **(B)** Time to first HFH. **(C)** Time to all-cause mortality. For display purposes, the outcomes of 58 patients in the GDMT group who received a MitraClip were analyzed from the time of transcatheter mitral valve repair (TMVr) treatment and their subsequent outcomes from the time of cross over landmarked to 24 months. Hazard curves are also shown for 86 patients in the GDMT alone group who did not cross over and the 186 patients in the TMVr plus GDMT group, both landmarked to 24 months. The event rates for patients in the GDMT group who received a MitraClip were, by inspection, lower than those who continued with GDMT alone and approximated those of the patients originally assigned to MitraClip treatment in the equivalent follow-up period between 2 and 3 years after randomization. No statistical comparisons are provided. w/o = without; other abbreviations as in Figures 1 and 2.

TABLE 4 Multivariable Predictors of Death or Heart Failure Hospitalization in the GDMT Alone Group

	Hazard Ratio (95% CI)	p Value
Treatment with MitraClip	0.43 (0.24–0.78)	0.006
BNP (per 250 pg/ml)	1.06 (1.03–1.09)	<0.0001
Vasodilator use (hydralazine or nitrates)	1.91 (1.37–2.66)	0.0001
Systolic blood pressure (per 10 mm Hg)	0.87 (0.80–0.96)	0.004
STS replacement score (per 1 U)	1.04 (1.01–1.07)	0.005
Beta-blocker use	0.57 (0.37–0.88)	0.01
LVEDV (per 50 ml)	1.13 (1.02–1.25)	0.02

The p values were >0.05 for all other covariates entered into the model (see Methods for complete list).

BNP = B-type natriuretic peptide; LVEDV = left ventricular end-diastolic volume; STS denotes Society of Thoracic Surgery.

survival. The present analysis extends these findings, demonstrating that through 36 months, TMVr continued to be safe and provided a durable reduction in MR, which resulted in fewer HFHs and deaths, with improved QOL and greater preservation of functional capacity compared with GDMT alone.

A greater absolute benefit for TMVr compared with GDMT alone in the reduction in the composite of death or HFH was present at 36 months compared with 24 months (i.e., the curves continued to diverge), with correspondingly lower NNT values. The magnitude of treatment benefit with TMVr (e.g., NNT of 4.5 and 3.4 to prevent 1 death or HFH within 2 and 3 years, respectively) was substantially greater than that seen in previous studies of Class I recommended pharmacological therapies (6–9) and cardiac resynchronization therapy (10,11). The absolute reduction of adverse events with TMVr in the COAPT trial (as reflected in the low NNT) was especially notable because all patients were treated with a maximally tolerated GDMT regimen. In contrast, in the recently published VICTORIA (A Study of Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction) trial, the oral soluble guanylate cyclase stimulator vericiguat, compared with placebo on a background of GDMT, reduced cardiovascular death or HFH in patients in NYHA functional classes II to IV from 40.1 events per 100 patient-years to 35.9 events per 100 patient-years, with a NNT of approximately 24 per year (12). Finally, among patients initially assigned to be treated with GDMT alone in the COAPT trial, those who crossed over and were treated with TMVr experienced a lower subsequent rate of HFHs and the composite of death or HFH than those who remained on GDMT alone. The incidence of adverse events was comparable to patients originally assigned to TMVr. These findings demonstrated that patients with HF who received delayed treatment might still benefit from correction of severe MR.

The MitraClip procedure was safe. True device-related complications occurred in only 4 (1.4%) patients at 30 days, as previously described (3). These complications included 2 single leaflet device attachments managed conservatively, 1 device embolization (retrieved percutaneously), and 1 post-procedure nonelective surgery due to unexplained late pericardial bleeding and tamponade (no perforation was found). No device-related complications occurred between 30 days and 3 years. The incidence of MitraClip-treated patients who underwent LV assist device implantation or heart transplantation rose progressively from 0% at 30 days to 7.4% at 3 years. Although these events were formally considered part of the pre-specified safety endpoint as agreed upon with Food and Drug Administration, they likely reflect progression in underlying LV dysfunction rather than MitraClip-related complications per se. In this regard, the 3-year rate of LV assist device or heart transplantation in patients treated with GDMT alone was 11.4%, which was significantly greater than in patients treated with MitraClip plus GDMT.

The findings from the COAPT trial should be interpreted in the context of other studies of patients with HF and secondary MR. In the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial, the primary 1-year outcome of the composite of death or HFH after treatment with the MitraClip device was not improved compared with medical therapy alone (13). A recently published 2-year update showed similar results (14). Numerous hypotheses were put forward in an attempt to explain the discordant results of these 2 trials (15–18). Proposed explanations included differences in sample size, trial endpoints, length of follow-up, definitions, as well as severity of baseline MR, LV volumes, establishment and maintenance of GDMT, degree and durability of MR reduction, and operator experience. Grayburn et al. (19) advanced the concept of proportionate and disproportionate MR to explain the relationship between LV size and MR severity (19–23), roughly expressed as the ratio between the EROA and the LV end-diastolic volume. The greater the severity of MR in relation to the LV size (i.e., the greater the percentage of “disproportionate” or very severe MR), the greater the likelihood that TMVr correction of MR would be effective in improving prognosis compared with GDMT alone. In contrast, the prognosis of patients with HF with relatively less volumetric MR and/or greater LV volumes would be dictated primarily by the severity of the underlying cardiomyopathy, and thus benefit from MR reduction was less likely to occur. In this regard, patients in the COAPT trial had greater degrees of MR

and smaller LVs than the patients in the MITRA-FR trial. Future studies are required to validate this hypothesis. A third trial (RESHAPE-HF [A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation]; NCT01772108) has now randomized 430 of a planned 650 patients and may shed further light as to which patients with HF are most likely to benefit from MR correction.

STUDY LIMITATIONS. Beyond the general limitations of the COAPT trial (3), several considerations relevant to the present study deserve consideration. First, the outcomes of the patients who received GDMT alone and who crossed over and underwent TMVr were improved compared with those who remained on GDMT alone. The favorable outcomes in these patients likely diluted the true impact of MitraClip treatment in the principal ITT analysis. Second, with regard to analysis of outcomes after TMVr treatment in the GDMT alone group, although time-to-first event curves provided a visual representation of trends, because the times to actual crossover varied in individual patients (including 5 patients who underwent TMVr before 24 months), such curves were limited in accurately representing comparable risk periods for the crossover and non-crossover groups. Time-adjusted multivariable analysis is the statistically correct way to compare the outcomes between these groups because it accounts for the exact time periods of risk for each patient before and after crossover, in addition to adjusting for baseline differences between nonrandomized groups. Third, many patients assigned to GDMT alone died before reaching the 2-year eligibility time point for MitraClip treatment, introducing the potential for survivorship bias in the outcomes of crossover patients (i.e., selective treatment of a surviving cohort with a better prognosis). Nonetheless, the relative magnitude of treatment benefit after late crossover in the GDMT alone group appeared to be similar to earlier treatment with the MitraClip in the unselected COAPT-eligible population in the device arm. Fourth, the reasons why some surviving GDMT alone-assigned patients underwent TMVr after 2 years, whereas other did not, are uncertain. Thus, although multivariable analysis was performed to account for the differences in baseline characteristics (and timing) of control subjects who did and did not undergo crossover MitraClip implantation, the role of unmeasured confounders could not be excluded. Finally, additional insights regarding the durability of TMVr treatment in this patient population will be gained from follow-up through 5 years in the COAPT trial.

CONCLUSIONS

Among patients with HF and moderate-to-severe and severe secondary MR who remained symptomatic despite maximally tolerated GDMT, transcatheter mitral leaflet approximation with the MitraClip was safe, provided a durable reduction in MR, reduced the rate of HFHs, and improved survival, QOL, and functional capacity compared with GDMT alone. With extended follow-up through 36 months, there was no loss of effectiveness with MitraClip treatment nor did new safety concerns emerge. In addition, compared with patients who continued treatment with GDMT alone, patients assigned to GDMT alone who crossed over and received a MitraClip experienced fewer subsequent HFHs and deaths, with rates comparable to patients originally treated with the MitraClip. Thus, patients meeting COAPT eligibility criteria might benefit from MitraClip reduction of severe MR even after an extended period of GDMT. This finding notwithstanding, because 67% and 87% of patients managed with GDMT alone died or had a HFH within 2 and 3 years, respectively, COAPT-eligible patients with HF who remain symptomatic after medical therapy optimization should be considered for early MitraClip treatment to improve event-free survival.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with severe secondary MR and HF, transcatheter MitraClip repair reduced the severity of regurgitation and HFHs and improved functional capacity, quality of life, and survival over 3 years, compared with medical therapy without valvular intervention.

TRANSLATIONAL OUTLOOK: Further research is needed to extend the assessment of clinical outcomes beyond 36 months and to assess the impact of TMVr on patients with more or less severe mitral regurgitation, additional comorbidities, and other types of valvular devices.

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