ORIGINAL ARTICLE

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

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ABSTRACT

BACKGROUND

Among patients with heart failure who have mitral regurgitation due to left ventricular dysfunction, the prognosis is poor. Transcatheter mitral-valve repair may improve their clinical outcomes.

METHODS

At 78 sites in the United States and Canada, we enrolled patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy. Patients were randomly assigned to transcatheter mitral-valve repair plus medical therapy (device group) or medical therapy alone (control group). The primary effectiveness end point was all hospitalizations for heart failure within 24 months of follow-up. The primary safety end point was freedom from device-related complications at 12 months; the rate for this end point was compared with a prespecified objective performance goal of 88.0%.

RESULTS

Of the 614 patients who were enrolled in the trial, 302 were assigned to the device group and 312 to the control group. The annualized rate of all hospitalizations for heart failure within 24 months was 35.8% per patient-year in the device group as compared with 67.9% per patient-year in the control group (hazard ratio, 0.53; 95% confidence interval [CI], 0.40 to 0.70; P<0.001). The rate of freedom from device-related complications at 12 months was 96.6% (lower 95% confidence limit, 94.8%; P<0.001 for comparison with the performance goal). Death from any cause within 24 months occurred in 29.1% of the patients in the device group as compared with 46.1% in the control group (hazard ratio, 0.62; 95% CI, 0.46 to 0.82; P<0.001).

CONCLUSIONS

Among patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy, transcatheter mitral-valve repair resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 months of follow-up than medical therapy alone. The rate of freedom from device-related complications exceeded a prespecified safety threshold. (Funded by Abbott; COAPT ClinicalTrials.gov number, NCT01626079.)

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*A list of investigators, institutions, and research organizations participating in the COAPT trial is provided in the Supplementary Appendix, available at NEJM.org.

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In patients with heart failure and left ventricular dilatation, mitral regurgitation may develop as a result of the geometric dislocation of the papillary muscles and chordae tendineae, impairing coaptation of the mitral leaflets.[1] Such secondary (functional) mitral regurgitation increases the severity of volume overload and has been strongly associated with decreased quality of life, an increased rate of hospitalization for heart failure, and shortened survival.[2,3] Guideline-directed medical therapy and cardiac resynchronization therapy may provide symptomatic relief, improve left ventricular function, and in some patients, lessen the severity of mitral regurgitation.[4] However, whether the correction of secondary mitral regurgitation improves the prognosis among patients with heart failure is unknown. Although mitral-valve surgery is curative for primary (degenerative) mitral regurgitation, neither surgical repair nor surgical replacement of the mitral valve has been shown to lower the rate of hospitalization or death associated with secondary mitral regurgitation, and both procedures confer a substantial risk of complications.[4-6] Thus, most patients with heart failure and secondary mitral regurgitation are treated conservatively,[7] and this high-risk group has few therapeutic alternatives.

Reduction of the severity of mitral regurgitation may be accomplished percutaneously by approximation of the anterior and posterior mitral leaflets, a procedure that leads to formation of a double-orifice valve.[8,9] In the randomized Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II, transcatheter mitral-leaflet approximation with the MitraClip device (Abbott) was safer than surgical mitral-valve repair but was not as effective in reducing the severity of mitral regurgitation.[8] However, device-based and surgical mitral-valve repair were associated with similar outcomes in the small subgroup of patients with secondary mitral regurgitation.[8] We therefore conducted a randomized trial to evaluate the safety and effectiveness of transcatheter mitral-leaflet approximation in patients with heart failure and secondary mitral regurgitation who remained symptomatic despite the use of guideline-directed medical therapy.

Methods

Trial Design

Details about the design of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial have been published previously.[10] In brief, the COAPT trial was a multicenter, randomized, controlled, parallel-group, open-label trial of transcatheter mitral-valve repair with the MitraClip device in symptomatic patients with heart failure and moderate-to-severe or severe mitral regurgitation. Details about the organization of the trial and a list of participating centers are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The trial was sponsored by Abbott. The protocol, available at NEJM.org, was designed by the principal investigators and the sponsor in accordance with the principles delineated by the Mitral Valve Academic Research Consortium.[4,11] The protocol was approved by the investigational review board at each participating center, and all the patients provided written informed consent. The sponsor participated in site selection and management and in data analysis. The principal investigators had unrestricted access to the data, wrote the manuscript, and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

Enrollment, Randomization, and Follow-up

Eligible patients had ischemic or nonischemic cardiomyopathy with a left ventricular ejection fraction of 20 to 50%, had moderate-to-severe (grade 3+) or severe (grade 4+) secondary mitral regurgitation that was confirmed at an echocardiographic core laboratory before enrollment, and remained symptomatic (New York Heart Association [NYHA] functional class II, III, or IVa [ambulatory]) despite the use of stable maximal doses of guideline-directed medical therapy and cardiac resynchronization therapy (if appropriate), which were administered in accordance with guidelines of professional societies. A complete list of enrollment criteria is provided in Table S1 in the Supplementary Appendix.[5,6,12] At each site, patients were assessed by a heart team that consisted of a heart-failure specialist, an interventional cardiologist, and a cardiothoracic surgeon with expertise in mitral-valve disease. The interventional cardiologist confirmed that the patient was anatomically eligible for device implantation, and the cardiothoracic surgeon determined that mitral-valve surgery was not appropriate. A central eligibility committee confirmed that the patient met all the enrollment criteria (including use of maximal doses of guideline-directed medical therapy),

confirmed that mitral-valve surgery would not be performed, and categorized the patient's risk of surgery-related complications or death, with high risk defined as a Society of Thoracic Surgeons (STS) score for the risk of death within 30 days after mitral-valve replacement of 8% or higher (on a scale of 0.4 to 98.1%, with higher percentages indicating greater risk) or the presence of features that portend an extremely high risk of operative stroke or death.

Enrolled patients were randomly assigned, in a 1:1 ratio, to undergo transcatheter mitral-valve repair, to be performed within 14 days after randomization, and receive guideline-directed medical therapy (device group) or to receive guideline-directed medical therapy alone (control group). Randomization was stratified according to trial site and cause of cardiomyopathy (ischemic or nonischemic) and was performed with random block sizes of 2, 4, or 6. Details about the trial device and implantation procedure have been published previously and are provided in the Supplementary Appendix.[8-10] Details about the trial assessments are shown in Table S2 in the Supplementary Appendix. Clinical follow-up, which is ongoing, was to be performed at 1 week and at 1, 6, 12, 18, and 24 months after the implantation procedure in the device group and after a visit with the site heart-failure specialist in the control group (either of which would occur within 14 days after randomization) and then annually through 5 years. Follow-up assessments include periodic echocardiography, 6-minute walk tests (with longer distances indicating more preserved functional capacity and a 10% relative change from the baseline value indicating a minimally significant difference), and assessments of quality-of-life measures, including the NYHA functional class and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score (on a scale of 0 to 100, with higher scores indicating better quality of life and a difference of 5 points indicating a minimally significant difference). Assessment for the primary effectiveness end point was to be performed through 2 years, with a minimum of 1 year of follow-up in all patients. Crossover was not to be permitted before 2 years of follow-up.

END POINTS

The definitions of the primary and secondary end points for hypothesis testing are provided in Tables S3 and S4 in the Supplementary Appendix. The primary effectiveness end point was all hospitalizations for heart failure within 24 months of follow-up, including recurrent events in patients with more than one event. The primary safety end point was freedom from device-related complications at 12 months. A device-related complication was defined as any occurrence of single-leaflet device attachment, embolization of the device, endocarditis that led to surgery, mitral stenosis (as confirmed by the echocardiographic core laboratory) that led to mitral-valve surgery, implantation of a left ventricular assist device, heart transplantation, or any other device-related event that led to nonelective cardiovascular surgery. Adverse events were adjudicated by an independent events committee with the use of source documents. Ventricular volumes and function, the severity of stenosis, and the severity of mitral regurgitation (with grade 0 indicating none, 1+ mild, 2+ moderate, 3+ moderate-to-severe, and 4+ severe) were assessed at the independent echocardiographic core laboratory.[13,14]

STATISTICAL ANALYSIS

Details about the event-rate assumptions and power analyses have been published previously.[10] Analysis of the primary effectiveness end point of all hospitalizations for heart failure was performed with a joint frailty model to account for correlated events and the competing risk of death.[15] Assuming an annualized rate of all hospitalizations for heart failure of 42.0% per patient-year in the device group and 60.0% per patient-year in the control group, a 12-month mortality of 22.0% and 27.0%, respectively, and a 12-month attrition rate of 7.5%, we calculated that a sample of 610 patients would provide the trial with 80% power, at a one-sided alpha level of 0.05, to show the superiority of device-based treatment over medical therapy alone with regard to the annualized rate of all hospitalizations for heart failure within 24 months. Hazard ratios and two-sided 95% confidence intervals were also calculated with the joint frailty model. Analysis of the primary safety end point of freedom from device-related complications was performed with the asymptotic z test; the event-free rate was estimated with the Kaplan–Meier method and the standard error was estimated with the Greenwood method.[16] We calculated that a sample of 305 patients in the device group would provide the trial with more than 95% power, at a one-sided alpha level of 0.05, to show that the rate of freedom from device-related complications at 12 months was higher than

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Device Group (N=302)	Control Group (N=312)
Clinical		
Age — yr	71.7±11.8	72.8±10.5
Male sex — no. (%)	201 (66.6)	192 (61.5)
Diabetes — no. (%)	106 (35.1)	123 (39.4)
Hypertension — no. (%)	243 (80.5)	251 (80.4)
Hypercholesterolemia — no. (%)	166 (55.0)	163 (52.2)
Previous myocardial infarction — no. (%)	156 (51.7)	160 (51.3)
Previous percutaneous coronary intervention — no. (%)	130 (43.0)	153 (49.0)
Previous coronary-artery bypass grafting — no. (%)	121 (40.1)	126 (40.4)
Previous stroke or transient ischemic attack — no. (%)	56 (18.5)	49 (15.7)
Peripheral vascular disease — no. (%)	52 (17.2)	57 (18.3)
Chronic obstructive pulmonary disease — no. (%)	71 (23.5)	72 (23.1)
History of atrial fibrillation or flutter — no. (%)	173 (57.3)	166 (53.2)
Body-mass index†	27.0±5.8	27.1±5.9
Creatinine clearance		
Mean — ml/min‡	50.9±28.5	47.8±25.0
≤60 ml/min — no./total no. (%)	214/299 (71.6)	227/302 (75.2)
Anemia — no./total no. (%)§	180/301 (59.8)	192/306 (62.7)
STS risk score¶		
Mean — %	7.8±5.5	8.5±6.2
≥8% — no. (%)	126 (41.7)	136 (43.6)
Risk of surgery-related complications or death — no./total no (%)‖		
High	205/299 (68.6)	218/312 (69.9)
Not high	94/299 (31.4)	94/312 (30.1)
Related to heart failure		
Cause of cardiomyopathy — no. (%)		
Ischemic	184 (60.9)	189 (60.6)
Nonischemic	118 (39.1)	123 (39.4)
NYHA class — no./total no. (%)		
I	1/302 (0.3)	0/311 (0)
II	129/302 (42.7)	110/311 (35.4)
III	154/302 (51.0)	168/311 (54.0)
IVa, ambulatory	18/302 (6.0)	33/311 (10.6)
Hospitalization for heart failure within previous 1 yr — no. (%)	176 (58.3)	175 (56.1)
Previous cardiac resynchronization therapy — no. (%)	115 (38.1)	109 (34.9)
Previous implantation of defibrillator — no. (%)	91 (30.1)	101 (32.4)
B-type natriuretic peptide level — pg/ml	1014.8±1086.0	1017.1±1212.8
N-terminal pro–B-type natriuretic peptide level — pg/ml	5174.3±6566.6	5943.9±8437.6
Assessed at the echocardiographic core laboratory		
Severity of mitral regurgitation — no./total no. (%)		
Moderate-to-severe, grade 3+	148/302 (49.0)	172/311 (55.3)
Severe, grade 4+	154/302 (51.0)	139/311 (44.7)
Effective regurgitant orifice area — cm^2	0.41±0.15	0.40±0.15
Left ventricular end-systolic dimension — cm	5.3±0.9	5.3±0.9

Table 1. (Continued.)

Characteristic	Device Group (N=302)	Control Group (N=312)
Left ventricular end-diastolic dimension — cm	6.2±0.7	6.2±0.8
Left ventricular end-systolic volume — ml	135.5±56.1	134.3±60.3
Left ventricular end-diastolic volume — ml	194.4±69.2	191.0±72.9
Left ventricular ejection fraction		
Mean — %	31.3±9.1	31.3±9.6
≤40% — no./total no. (%)	231/281 (82.2)	241/294 (82.0)
Right ventricular systolic pressure — mm Hg	44.0±13.4 (253)	44.6±14.0 (275)

* Plus–minus values are means ±SD. Data on B-type natriuretic peptide level were available for 208 patients in the device group and 209 patients in the control group; N-terminal pro–B-type natriuretic peptide level, 74 and 85, respectively; effective regurgitant orifice area, 289 and 302; left ventricular end-systolic dimension, 301 and 306; left ventricular end-diastolic dimension, 301 and 307; left ventricular end-systolic volume, end-diastolic volume, and ejection fraction, 281 and 294; and right ventricular systolic pressure, 253 and 275. There were no significant differences between the trial groups with regard to baseline characteristics. NYHA denotes New York Heart Association.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The mean creatinine clearance was calculated with the Cockcroft–Gault equation.
§ In accordance with World Health Organization criteria, anemia was defined as a hemoglobin level at initial presentation of less than 13 g per deciliter in men and less than 12 g per deciliter in women.
¶ Society of Thoracic Surgeons (STS) scores for the risk of death within 30 days after mitral-valve replacement range from 0.4 to 98.1%, with higher percentages indicating greater risk.
‖ Risk of surgery-related complications or death was determined by the central eligibility committee. High risk was defined as an STS score for the risk of death within 30 days after mitral-valve replacement of 8% or higher or the presence of features that portend an extremely high risk of operative stroke or death.

a prespecified objective performance goal of 88.0% (see the Supplementary Appendix). If the hypotheses for both primary end points were met, then analyses of 10 secondary end points that the trial was powered to assess were to be performed in a prespecified hierarchical order to control for multiple comparisons (Table S3 in the Supplementary Appendix).[10]

All effectiveness analyses were performed from the time of randomization in the intention-to-treat population. The primary safety analysis was performed in the safety population, which consisted of all patients in the device group in whom device implantation was attempted. Sensitivity analyses were performed in the per-protocol and as-treated populations. Detailed descriptions of these populations are provided in the Supplementary Appendix.

For analyses of time to first event, event rates were compared with a Cox regression model. Categorical variables were compared with Fisher's exact test. Continuous variables were compared with t tests or the Wilcoxon rank–sum test for nonnormally distributed data. An analysis of covariance model was used to compare mean changes in continuous variables from baseline to follow-up between groups. A sensitivity analysis with multiple imputation was performed to account for missing data.[17] For the analysis of superiority, a two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND TREATMENTS

From December 27, 2012, through June 23, 2017, a total of 614 patients at 78 centers in the United States and Canada were enrolled in the trial; 302 were randomly assigned to the device group and 312 to the control group (Fig. S2 in the Supplementary Appendix). The baseline characteristics of the patients in the two trial groups were well matched (Table 1). Among all the patients, the mean (±SD) age was 72.2±11.2 years, 36.0% were women, and 36.5% had received previous cardiac resynchronization therapy. The cause of cardiomyopathy was ischemic in 60.7% of the patients and nonischemic in 39.3%. The mean left ventricular ejection fraction was 31.3±9.3%, and the mitral regurgitation grade was 3+ in 52.2% of the patients and 4+ in 47.8%. The mean STS score for the risk of death within 30 days after mitral-valve replacement was 8.2±5.9%. The central eligibility committee determined that 69.2% of the

patients were at high risk for surgery-related complications or death and 30.8% were not.

Device implantation was attempted in 293 of the 302 patients (97.0%) in the device group, with 1 or more clips implanted in 287 patients (98.0% of the 293 patients in whom implantation was attempted; 95.0% of all 302 patients in the device group) and a mean of 1.7±0.7 clips implanted per patient (range, 1 to 4) (Table S5 in the Supplementary Appendix). Among the 260 patients in whom echocardiography was performed at the time of discharge, the mitral regurgitation grade was 1+ or lower in 214 patients (82.3%), 2+ in 33 patients (12.7%), 3+ in 9 patients (3.5%), and 4+ in 4 patients (1.5%). In the device group, the 30-day rates of death and stroke were 2.3% and 0.7%, respectively, and no patients underwent mitral-valve surgery. Details about medication use are provided in Tables S6 and S7 in the Supplementary Appendix. Major changes in medications during follow-up were infrequent in the two trial groups.

PRIMARY AND SECONDARY END POINTS

Data collection for this analysis ended on August 3, 2018, when the last enrolled patient had completed 1 year of follow-up. A total of 97.7% of the patients in the device group and 94.2% in the control group had data available for 1 year of follow-up; the median follow-up was 22.7 months (interquartile range, 12.4 to 24.0) and 16.5 months (interquartile range, 10.1 to 24.0), respectively (Fig. S2 in the Supplementary Appendix). The results for the primary and secondary end points that the trial was powered to assess are shown in Table 2, and in Tables S8 through S18 in the Supplementary Appendix. One or more hospitalizations for heart failure occurred during follow-up in 92 of the patients in the device group and in 151 in the control group. The total number of hospitalizations for heart failure within 24 months was 160 in the device group and 283 in the control group (Fig. 1A). The annualized rate of all hospitalizations for heart failure was 35.8% per patient-year in the device group as compared with 67.9% per patient-year in the control group (hazard ratio, 0.53; 95% confidence interval [CI], 0.40 to 0.70; P<0.001). The number needed to treat to prevent 1 hospitalization for heart failure within 24 months was 3.1 (95% CI, 1.9 to 7.9). The rate of freedom from device-related complications at 12 months was 96.6% (lower 95% confidence limit, 94.8%), a rate that exceeded the objective performance goal of 88.0% for the primary safety end point (P<0.001) (Fig. 1B). The results of analyses performed in the per-protocol and as-treated populations were similar to the results of the primary effectiveness and safety analyses (Table S9 in the Supplementary Appendix).

Hypothesis testing was positive for the 10 prespecified secondary end points that the trial was powered to assess. All-cause mortality within 24 months was significantly lower with device-based treatment than with medical therapy alone (29.1% vs. 46.1%; hazard ratio, 0.62; 95% CI, 0.46 to 0.82; P<0.001) (Fig. 1C). The number needed to treat to save one life within 24 months was 5.9 (95% CI, 3.9 to 11.7). In addition, quality of life (as assessed by the KCCQ and by determination of the NYHA functional class) was significantly better, functional capacity (as measured by the 6-minute walk test) was more preserved, and mitral regurgitation and left ventricular remodeling (as measured by mitral regurgitation grade and left ventricular end-diastolic volume) were less severe with device-based treatment than with medical therapy alone. The results for the primary and secondary end points were consistent after accounting for missing data with multiple imputation (Table S10 in the Supplementary Appendix).

ADDITIONAL OUTCOME MEASURES

Data on adverse events are shown in Table 3, and in Table S19 and Figures S3 through S6 in the Supplementary Appendix. The 24-month risk of the composite of death from any cause or hospitalization for heart failure was significantly lower in the device group than in the control group, as was the 24-month risk of hospitalization for any cause. The lower rate of hospitalization for heart failure in the device group was robust after adjustment for differences between the trial groups in medications used for heart failure at baseline (hazard ratio, 0.55; 95% CI, 0.42 to 0.73; P<0.001), as was the lower mortality (hazard ratio, 0.65; 95% CI, 0.49 to 0.86; P=0.003). The rate of implantation of a left ventricular assist device or heart transplantation during follow-up was lower in the device group than the control group. The lower rates of hospitalization for heart failure, death, and the composite of death or hospitalization for heart failure in the device group were consistent across all the examined subgroups (Fig. 2, and Figs. S5 and S6 in the Supplementary Appendix). There were no significant interactions

Table 2. Primary and Secondary End Points.*

End Point	Device Group (N=302)	Control Group (N=312)	Hazard Ratio (95% CI)	P Value†
Primary				
Effectiveness: all hospitalizations for heart failure within 24 mo — no. of events/total no. of patient-yr (annualized rate)	160/446.5 (35.8)	283/416.8 (67.9)	0.53 (0.40 to 0.70)‡	<0.001§
Safety: freedom from device-related complications at 12 mo — Kaplan–Meier estimate of event-free rate (lower 95% confidence limit)	96.6 (94.8)	—	—	<0.001 for comparison with goal of 88.0%¶
Secondary, listed in hierarchical order				
Mitral regurgitation grade of 2+ or lower at 12 mo — no./total no. (%)‖	199/210 (94.8)	82/175 (46.9)	—	<0.001**
Death from any cause at 12 mo — no. of events (Kaplan–Meier estimate of event rate)	57 (19.1)	70 (23.2)	0.81 (0.57 to 1.15)††	<0.001 for noninferiority‡‡
Death or hospitalization for heart failure within 24 mo	—	—	—	<0.001§§
Change in KCCQ score from baseline to 12 mo — points¶¶	12.5±1.8	−3.6±1.9	16.1 (11.0 to 21.2)‖‖	<0.001***
Change in distance on 6-min walk test from baseline to 12 mo — m†††	−2.2±9.1	−60.2±9.0	57.9 (32.7 to 83.1)‖‖	<0.001***
All hospitalizations for any cause within 24 mo — no. of events/total no. of patient-yr (annualized rate)	474/446.5 (106.2)	610/416.8 (146.4)	0.76 (0.60 to 0.96)	0.02§
NYHA functional class of I or II at 12 mo — no./total no. (%)	171/237 (72.2)	115/232 (49.6)	—	<0.001**
Change in left ventricular end-diastolic volume from baseline to 12 mo — ml	−3.7±5.1	17.1±5.1	−20.8 (−34.9 to −6.6)‖‖	0.004***
Death from any cause within 24 mo — no. of events (Kaplan–Meier estimate of event rate)	80 (29.1)	121 (46.1)	0.62 (0.46 to 0.82)	<0.001‡‡‡
Freedom from death from any cause, stroke, myocardial infarction, and nonelective cardiovascular surgery for a device-related complication at 30 days — % (lower 95% confidence limit)	96.9 (94.7)	—	—	<0.001 for comparison with goal of 80.0%**

* Plus–minus values are least-squares means ±SE. All analyses were performed in the intention-to-treat population, except for the analyses of the two freedom-from-event end points, which were performed in the safety population (293 patients). CI denotes confidence interval.
† P values are for superiority unless otherwise noted.
‡ When the hazard ratio was calculated at a one-sided alpha level of 0.05, the upper 95% confidence limit was 0.66.
§ The analysis was performed with the joint frailty model, which accounted for the competing risk of death.
¶ The analysis was performed with the asymptotic z test. Of the 293 patients in the safety population, 9 had an event.
‖ A mitral regurgitation grade of 2+ or lower indicates the presence of no, mild, or moderate mitral regurgitation.
** The analysis was performed with Fisher's exact test.
†† When the hazard ratio was calculated at a one-sided alpha level of 0.05, the upper 95% confidence limit was 1.09.
‡‡ The analysis was performed with a Cox regression model, with treatment effect as a covariate and with a noninferiority margin of 1.5.
§§ The analysis was performed with the Finkelstein–Schoenfeld method with win ratios. (Details are provided in Table S12 in the Supplementary Appendix.)
¶¶ Kansas City Cardiomyopathy Questionnaire (KCCQ) scores range from 0 to 100, with higher scores indicating better quality of life and a difference of 5 points indicating a minimally significant difference.
‖‖ The value is a difference rather than a hazard ratio.
*** The analysis was performed with an analysis of covariance model, with baseline score and treatment effect as covariates.
††† The minimally significant difference in the distance on the 6-minute walk test is a 10% relative change from the baseline value.
‡‡‡ The analysis was performed with a Cox regression model, with treatment effect as a covariate.

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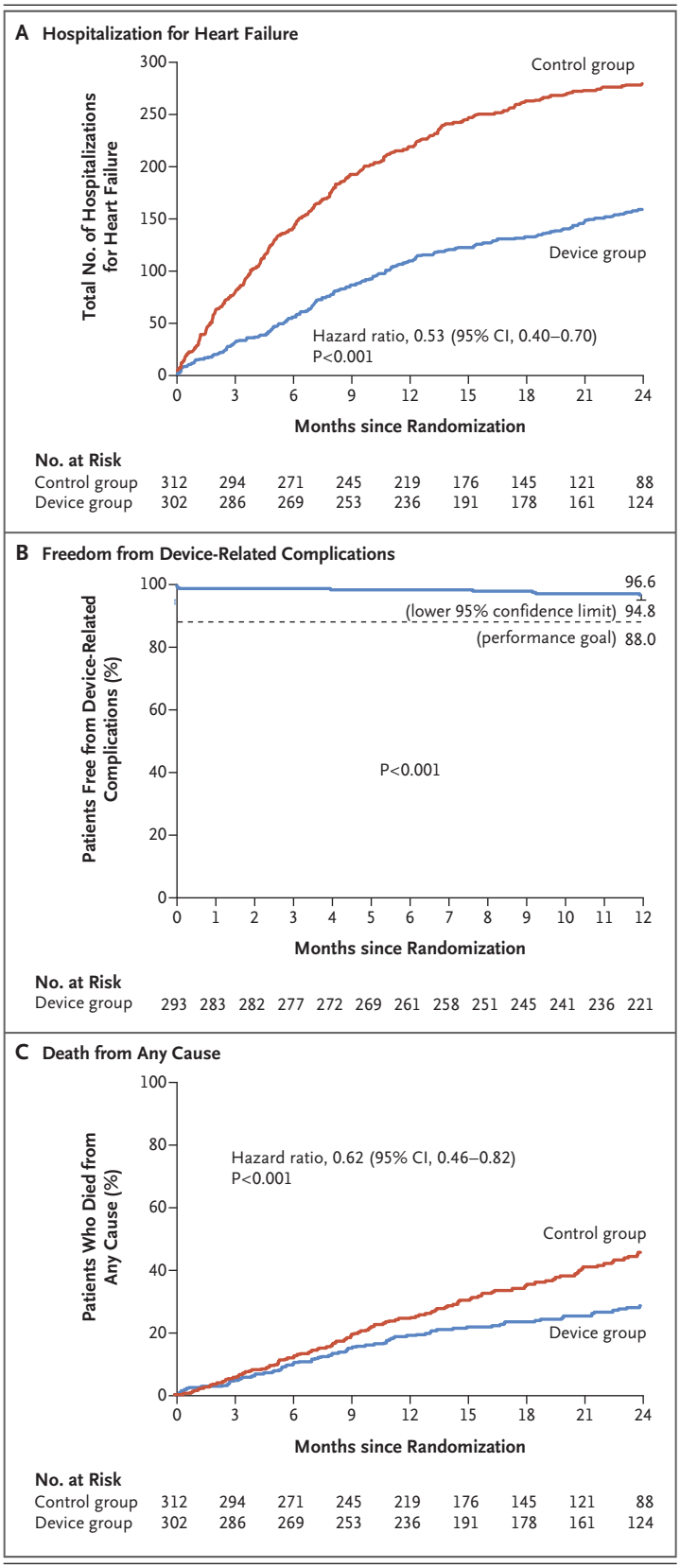

Figure 1. Primary Effectiveness and Safety End Points and Death.

Panel A shows the cumulative incidence of the primary effectiveness end point of all hospitalizations for heart failure within 24 months of follow-up among patients who underwent transcatheter mitral-valve repair and received guideline-directed medical therapy (device group) and among those who received guideline-directed medical therapy alone (control group). The data shown here do not account for the competing risk of death, which was considered in the joint frailty model. A total of 160 hospitalizations for heart failure occurred in 92 patients in the device group, and a total of 283 hospitalizations for heart failure occurred in 151 patients in the control group. Panel B shows the rate of the primary safety end point of freedom from device-related complications at 12 months among the 293 patients in whom device implantation was attempted, as compared with an objective performance goal. Panel C shows time-to-event curves for all-cause mortality in the device group and the control group.

between the trial group and these events according to age, sex, the severity of mitral regurgitation, left ventricular function or volume, the cause of cardiomyopathy, or the risk of surgery-related complications or death at baseline.

DISCUSSION

The COAPT trial evaluated the safety and effectiveness of transcatheter mitral-valve repair in patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy. In this trial, device-based treatment resulted in a significantly lower rate of hospitalization for heart failure, lower mortality, and better quality of life and functional capacity within 24 months of follow-up than medical therapy alone. In addition, the rate of freedom from device-related complications with transcatheter mitral-valve repair exceeded a prespecified objective performance goal. The benefits were consistent across numerous subgroups, including patients who had ischemic and nonischemic cardiomyopathy and those who were and were not at high risk for surgery-related complications or death, and the benefits were independent of the mitral regurgitation grade and left ventricular volume and function at baseline.

The MitraClip device used in this trial was approved by the Food and Drug Administration in 2013 for the treatment of primary mitral re-

Table 3. Adverse Events within 24 Months in the Intention-to-Treat Population.*

Event	Device Group (N=302)	Control Group (N=312)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (Kaplan–Meier estimate of event rate)			
Death from any cause	80 (29.1)	121 (46.1)	0.62 (0.46–0.82)	<0.001
Cardiovascular cause	61 (23.5)	97 (38.2)	0.59 (0.43–0.81)	0.001
Related to heart failure	28 (12.0)	61 (25.9)	0.43 (0.27–0.67)	<0.001
Not related to heart failure	33 (13.1)	36 (16.6)	0.86 (0.54–1.38)	0.53
Noncardiovascular cause	19 (7.3)	24 (12.7)	0.73 (0.40–1.34)	0.31
Hospitalization for any cause	194 (69.6)	228 (81.8)	0.77 (0.64–0.93)	0.01
Cardiovascular cause	138 (51.9)	180 (66.5)	0.68 (0.54–0.85)	<0.001
Related to heart failure	92 (35.7)	151 (56.7)	0.52 (0.40–0.67)	<0.001
Not related to heart failure	72 (29.4)	72 (31.0)	0.98 (0.71–1.36)	0.92
Noncardiovascular cause	124 (48.2)	128 (52.9)	0.91 (0.71–1.17)	0.47
Death or hospitalization for heart failure	129 (45.7)	191 (67.9)	0.57 (0.45–0.71)	<0.001
Death from cardiovascular cause or hospitalization for heart failure	117 (42.7)	177 (63.6)	0.56 (0.44–0.70)	<0.001
Unplanned mitral-valve intervention	10 (4.0)	15 (9.0)	0.61 (0.27–1.36)	0.23
MitraClip implantation	9 (3.7)	8 (6.6)	0.99 (0.38–2.58)	0.99
Mitral-valve surgery	1 (0.4)	7 (2.5)	0.14 (0.02–1.17)	0.07
PCI or CABG	7 (2.8)	13 (4.3)	0.62 (0.24–1.60)	0.32
PCI	7 (2.8)	11 (3.6)	0.75 (0.28–2.02)	0.57
CABG	0	2 (0.7)	—	—
Stroke	11 (4.4)	11 (5.1)	0.96 (0.42–2.22)	0.93
Myocardial infarction	12 (4.7)	14 (6.5)	0.82 (0.38–1.78)	0.62
New cardiac resynchronization therapy	7 (2.9)	8 (3.3)	0.85 (0.31–2.34)	0.75
LVAD implantation or heart transplantation	9 (4.4)	22 (9.5)	0.37 (0.17–0.81)	0.01
LVAD implantation	6 (3.0)	16 (7.1)	0.34 (0.13–0.87)	0.02
Heart transplantation	3 (1.4)	8 (3.6)	0.35 (0.09–1.32)	0.12

* CABG denotes coronary-artery bypass grafting, LVAD left ventricular assist device, and PCI percutaneous coronary intervention.

gurgitation in patients who are at a prohibitive risk for surgery-related complications or death. Approval was based on uncontrolled registry data that showed symptomatic improvements,[18,19] and in the United States, the device is principally used for this indication.[20] However, outside the United States, the device is more often used to treat secondary mitral regurgitation in patients with heart failure.[21,22] The prognosis among patients with heart failure and secondary mitral regurgitation is very poor; in this trial, approximately two thirds of such patients died or were hospitalized for heart failure within 2 years despite the use of guideline-directed medical therapy. Transcatheter mitral-leaflet approximation led to a decrease in the severity of secondary mitral regurgitation; this is presumably the mechanism behind the improvements in prognosis, quality of life, and functional capacity among patients who received device-based treatment. Of note, the lower rate of hospitalization for heart failure with device-based treatment emerged within 30 days after treatment. The lower mortality predominantly emerged more than 1 year after treatment, a delayed response consistent with long-term benefits from a durable decrease in the severity of left ventricular volume overload.

The clip implantation rate of 98% and the

Subgroup	No. of Patients	Device Group annualized rate (no. of events/ total no. of patient-yr)	Control Group	Hazard Ratio (95% CI)	P Value for Interaction
All patients	614	35.8 (160/446.5)	67.9 (283/416.8)	0.54 (0.41–0.70)	
Age					0.29
≥74 yr	317	37.7 (86/228.0)	61.7 (129/209.2)	0.62 (0.44–0.88)	
<74 yr	297	33.9 (74/218.5)	74.2 (154/207.5)	0.47 (0.31–0.71)	
Sex					0.05
Female	221	44.3 (66/149.0)	58.2 (98/168.4)	0.77 (0.49–1.21)	
Male	393	31.6 (94/297.5)	74.5 (185/248.4)	0.44 (0.32–0.61)	
Cause of cardiomyopathy					0.35
Ischemic	373	30.8 (85/276.0)	66.0 (162/245.6)	0.48 (0.34–0.68)	
Nonischemic	241	44.0 (75/170.5)	70.7 (121/171.1)	0.62 (0.41–0.94)	
Previous cardiac resynchronization therapy					0.62
Yes	224	41.6 (68/163.3)	72.0 (107/148.7)	0.58 (0.38–0.89)	
No	390	32.5 (92/283.2)	65.7 (176/268.1)	0.51 (0.36–0.72)	
Hospitalization for heart failure within previous 1 yr					0.58
Yes	407	38.2 (116/303.8)	69.1 (189/273.7)	0.56 (0.41–0.78)	
No	207	30.8 (44/142.7)	65.7 (94/143.1)	0.48 (0.30–0.76)	
Baseline NYHA class					0.66
I or II	240	31.5 (62/197.1)	53.4 (80/149.9)	0.59 (0.38–0.92)	
III	322	34.6 (78/225.5)	68.9 (158/229.4)	0.52 (0.36–0.75)	
IVa, ambulatory	51	83.4 (20/24.0)	113.0 (40/35.4)	0.77 (0.34–1.75)	
STS risk score					0.70
≥8%	262	39.6 (68/171.7)	80.3 (132/164.4)	0.51 (0.34–0.77)	
<8%	352	33.5 (92/274.8)	59.8 (151/252.4)	0.57 (0.40–0.80)	
Risk of surgery-related complications or death					0.28
High	423	36.5 (106/290.4)	76.3 (215/281.8)	0.49 (0.35–0.68)	
Not high	188	33.1 (51/153.9)	50.4 (68/135.0)	0.67 (0.41–1.08)	
Baseline severity of mitral regurgitation					0.53
Moderate-to-severe, grade 3+	320	27.3 (62/227.0)	58.8 (137/232.9)	0.48 (0.31–0.74)	
Severe, grade 4+	293	44.6 (97/219.5)	80.1 (146/182.4)	0.57 (0.40–0.80)	
Baseline left ventricular ejection fraction					
With median as cutoff					0.96
≥30%	301	29.0 (66/227.7)	60.3 (123/204.0)	0.49 (0.32–0.76)	
<30%	274	40.1 (76/189.6)	82.2 (153/186.1)	0.50 (0.34–0.72)	
With additional cutoff					0.34
>40%	103	32.9 (26/79.0)	51.0 (35/68.6)	0.65 (0.33–1.27)	
≤40%	472	34.3 (116/338.3)	75.0 (241/321.5)	0.47 (0.34–0.64)	
Baseline left ventricular end-diastolic volume					0.44
≥181 ml	288	35.1 (73/207.9)	80.4 (162/201.5)	0.44 (0.31–0.64)	
<181 ml	287	32.9 (69/209.4)	60.4 (114/188.7)	0.56 (0.36–0.85)	

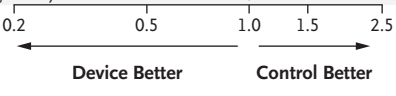

Figure 2. Subgroup Analyses of Hospitalization for Heart Failure within 24 Months.

Shown are annualized estimates of all hospitalizations for heart failure within 24 months of follow-up across subgroups. The median value was used as a cutoff for age (median, 74 years), left ventricular ejection fraction (median, 30%), and left ventricular end-diastolic volume (median, 181 ml). For the additional cutoff for left ventricular ejection fraction, a value of 40% or less indicates the presence of heart failure with reduced ejection fraction and a value of more than 40% the presence of heart failure with preserved ejection fraction, two different diseases associated with different prognoses and treatments. Society of Thoracic Surgeons (STS) scores for the risk of death within 30 days after mitral-valve replacement range from 0.4 to 98.1%, with higher percentages indicating greater risk. The risk of surgery-related complications or death was determined by the central eligibility committee, with high risk defined as an STS score for the risk of death within 30 days after mitral-valve replacement of 8% or higher or the presence of features that portend an extremely high risk of operative stroke or death. NYHA denotes New York Heart Association.

immediate achievement of a mitral regurgitation grade of 2+ or lower in 95% of the patients in the device group in this trial were substantially better than those outcomes among lower-risk patients in the early EVEREST II trial,[8] findings that probably reflect operators' increased experience with implantation and improved echocardiographic guidance. The decrease in the severity of mitral regurgitation that was associated with transcatheter mitral-leaflet approximation was also durable over time. Among surviving patients in the device group, the mitral regurgitation grade at 2 years was 3+ or higher in only 0.9% and was 2+ or higher in only 22.8%. In contrast, a previous randomized trial evaluated the effectiveness of a downsized annuloplasty ring in patients who had secondary ischemic mitral regurgitation of similar severity to that seen in this trial; among surviving patients who were treated with the downsized annuloplasty ring, the mitral regurgitation grade at 2 years was 3+ or higher in 14.0% and was 2+ or higher in 58.8%.[23]

Some limitations of this trial should be noted. First, because the MitraClip device is visible on imaging studies, the investigators were aware of the trial-group assignments. Efforts to mitigate bias included rigorous protocol-specified procedures to standardize guideline-directed medical therapy and the use of an independent events committee and a central echocardiographic core laboratory. The robustness of the lower rate of hospitalization for heart failure and the lower mortality in the device group, coupled with consistent decreases in the severity of mitral regurgitation and improvements in quality of life and functional capacity in that group, supports the validity of the principal findings. Nonetheless, potential bias cannot be completely ruled out. Second, the median follow-up was longer in the device group than in the control group, in part because of the lower mortality in the device group. However, withdrawal from the trial was more frequent in the control group. The principal results were consistent after imputation for missing data. Third, agents that affect the renin–angiotensin axis were by chance used more frequently at baseline in the device group. The principal findings were robust after adjustment for these differences. Fourth, long-term follow-up, which is to be ongoing through 5 years, is necessary to fully characterize the safety and effectiveness of the device. The results of this analysis apply to treatment of secondary mitral regurgitation with mitral-leaflet approximation as tested in this trial; whether other transcatheter-based or surgical approaches would have similar results is uncertain. Finally, all enrolled patients were symptomatic (NYHA class II, III, or IVa [ambulatory]) despite the use of maximal doses of guideline-directed medical therapy (with more than one third of patients having undergone cardiac resynchronization therapy) and had moderate-to-severe or severe mitral regurgitation, a left ventricular ejection fraction of 20 to 50%, and frequent coexisting conditions. Whether the device would have similar benefits in patients who are less or more critically ill or in those with less severe mitral regurgitation is unknown.

In conclusion, among patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy, transcatheter mitral-valve repair resulted in a lower rate of hospitalization for heart failure, lower mortality, and better quality of life and functional capacity within 24 months of follow-up than medical therapy alone, and the prespecified goal for freedom from device-related complications was met.

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APPENDIX

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