ORIGINAL ARTICLE

Five-Year Follow-up after Transcatheter Repair of Secondary Mitral Regurgitation

Gregg W. Stone, M.D., William T. Abraham, M.D., JoAnn Lindenfeld, M.D., Saibal Kar, M.D., Paul A. Grayburn, M.D., D. Scott Lim, M.D., Jacob M. Mishell, M.D., Brian Whisenant, M.D., Michael Rinaldi, M.D., Samir R. Kapadia, M.D., Vivek Rajagopal, M.D., Ian J. Sarembock, M.B., Ch.B., M.D., Andreas Brieke, M.D., Steven O. Marx, M.D., David J. Cohen, M.D., Federico M. Asch, M.D., and Michael J. Mack, M.D., for the COAPT Investigators

ABSTRACT

BACKGROUND

Data from a 5-year follow-up of outcomes after transcatheter edge-to-edge repair of severe mitral regurgitation, as compared with outcomes after maximal doses of guideline-directed medical therapy alone, in patients with heart failure are now available.

METHODS

We randomly assigned 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 to undergo transcatheter edge-to-edge repair plus receive medical therapy (device group) or to receive medical therapy alone (control group) at 78 sites in the United States and Canada. The primary effectiveness end point was all hospitalizations for heart failure through 2 years of follow-up. The annualized rate of all hospitalizations for heart failure, all-cause mortality, the risk of death or hospitalization for heart failure, and safety, among other outcomes, were assessed through 5 years.

RESULTS

Of the 614 patients enrolled in the trial, 302 were assigned to the device group and 312 to the control group. The annualized rate of hospitalization for heart failure through 5 years was 33.1% per year in the device group and 57.2% per year in the control group (hazard ratio, 0.53; 95% confidence interval [CI], 0.41 to 0.68). All-cause mortality through 5 years was 57.3% in the device group and 67.2% in the control group (hazard ratio, 0.72; 95% CI, 0.58 to 0.89). Death or hospitalization for heart failure within 5 years occurred in 73.6% of the patients in the device group and in 91.5% of those in the control group (hazard ratio, 0.53; 95% CI, 0.44 to 0.64). Device-specific safety events within 5 years occurred in 4 of 293 treated patients (1.4%), with all the events occurring within 30 days after the procedure.

CONCLUSIONS

Among patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite guideline-directed medical therapy, transcatheter edge-to-edge repair of the mitral valve was safe and led to a lower rate of hospitalization for heart failure and lower all-cause mortality through 5 years of follow-up than medical therapy alone. (Funded by Abbott; COAPT ClinicalTrials.gov number, NCT01626079.)

The authors' affiliations are listed in the Appendix. Dr. Stone can be contacted at gregg.stone@mountsinai.org or at Mount Sinai Medical Center, 1 Gustave L. Levy Pl., New York, NY 10029.

This article was published on March 5, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2300213

Ischemic and nonischemic cardiomyopathy of the left ventricle results in chamber dilatation with apical and lateral dislocation of the papillary muscles. This process impairs coaptation of the mitral leaflets during systole and results in secondary mitral regurgitation.[1] The development of severe mitral regurgitation in patients with left ventricular dysfunction portends a poor prognosis, with an increased rate of hospitalization for heart failure and reduced survival.[2,3] Transcatheter edge-to-edge repair of the mitral valve reapproximates the mitral leaflets and reduces mitral regurgitation.[4] In the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial, transcatheter edge-to-edge repair was safe and improved 2-year outcomes in patients with heart failure and secondary mitral regurgitation who had remained symptomatic despite the use of maximal doses of guideline-directed medical therapy.[5] Whether these benefits would be sustained over long-term follow-up has been unclear. Here, we describe the final 5-year outcomes of the COAPT trial.

Methods

Trial Design

We conducted a multicenter, randomized, parallel-controlled, open-label trial to evaluate transcatheter edge-to-edge repair with the MitraClip (Abbott) in patients with symptomatic heart failure and moderate-to-severe or severe mitral regurgitation. The design and principal results of the COAPT trial, along with information about the trial organization and participating investigators, institutions, and research organizations, have been published previously.[5,6]

The trial was funded by Abbott (the sponsor). The protocol (available with the full text of this article at NEJM.org) and statistical analysis plan were designed by the principal investigators and the sponsor and were consistent with the Mitral Valve Academic Research Consortium guidelines.[7,8] The trial was approved by the institutional review board at each center, and all the patients provided written informed consent. The sponsor participated in the site selection and in the management and analysis of the data. The first and last authors had unrestricted access to the data and prepared the manuscript. The first and last authors attest to the accuracy and completeness of the data and vouch for the fidelity of the trial to the protocol.

Enrollment, Randomization, and Follow-up

The complete enrollment criteria for the trial have been reported previously.[5,6] In brief, eligible patients had ischemic or nonischemic cardiomyopathy with a left ventricular ejection fraction of 20 to 50%, had moderate-to-severe (3+) or severe (4+) secondary mitral regurgitation that was confirmed at an echocardiographic core laboratory before enrollment, and remained symptomatic (New York Heart Association [NYHA] class II, III, or IVa [ambulatory]) despite the use of stable maximal doses of guideline-directed medical therapy. Before enrollment, patients had undergone coronary revascularization and cardiac resynchronization therapy or had received an implantable cardiac defibrillator if indicated according to societal guidelines.[9] The principal exclusion criteria were a left ventricular end-systolic dimension of more than 7 cm, severe pulmonary hypertension, and moderate or severe symptomatic right ventricular failure. A centralized eligibility committee confirmed that the patient met all the enrollment criteria (including the use of maximal doses of guideline-directed medical therapy) before randomization.

Eligible patients were randomly assigned in a 1:1 ratio to undergo transcatheter edge-to-edge repair with the MitraClip plus receive guideline-directed medical therapy (device group) or to receive guideline-directed medical therapy alone (control group). Randomization was stratified according to cause of cardiomyopathy and trial site with the use of random block sizes of two, four, and six. The trial device and procedures have been described previously.[5,6] Clinical and echocardiographic follow-up were performed at 30 days, 6 months, 1 year, 18 months, and 2, 3, 4, and 5 years. Six-minute walk testing and quality-of-life and cost-effectiveness assessments were performed through 2 years of follow-up only; these results have been reported.[5,10,11] After the 2-year visit, crossover treatment with transcatheter edge-to-edge repair was permitted in patients in the control group who still met all the original enrollment criteria.

End Points

The primary effectiveness end point was all hospitalizations for heart failure (including recurrent events) through 2 years after randomization, assessed when the last enrolled patient reached 1 year of follow-up. The primary end point was reported as an annualized rate. The primary safety end point was freedom from device-related complications at 12 months. Additional prespecified end points for which data were collected through 5 years of follow-up are listed in the Supplementary Appendix, available at NEJM.org. The present analysis reports the 5-year results from this trial, including clinical effectiveness and safety outcomes, symptomatic status, and echocardiographic variables (left ventricular function and dimensions and severity of mitral regurgitation).

An independent committee adjudicated clinical outcomes according to prespecified definitions[5,6] after the review of original source documents. An independent echocardiographic core laboratory assessed the severity of mitral regurgitation and ventricular volumes and function according to American Society of Echocardiography criteria at baseline and follow-up.[5,6,12,13]

STATISTICAL ANALYSIS

The 2-year primary effectiveness end point of all hospitalizations for heart failure was analyzed with the use of a joint frailty model to account for correlated events and the competing risk of death.[5,6,14] The 1-year primary safety outcome was tested for noninferiority against an objective performance goal.[5,6] Statistical significance was met for both primary end points and for ten prespecified powered secondary outcomes.[5]

Effectiveness analyses were performed in the intention-to-treat population, which included all the patients according to their assigned randomization group regardless of the actual treatment received. Patients who received a left ventricular assist device (LVAD) or underwent heart transplantation after randomization remained in the trial and did not have their data censored. The between-group difference in the cumulative incidence of all hospitalizations for heart failure through 5 years was assessed with the joint frailty model. Safety end points through 5 years were assessed in patients in the device group in whom MitraClip implantation had been attempted. For other end points, time-to-first-event rates were estimated with the use of Kaplan–Meier analysis and were compared with Cox regression. Relative rates are described with hazard ratios and 95% confidence intervals. The 95% confidence intervals have not been adjusted for multiplicity, and therefore inferences drawn from these intervals should not be used for hypothesis testing. For the principal analyses, missing data were not replaced, and complete case data are presented. In a sensitivity analysis, multiple imputation was used to account for missing follow-up data. All the statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND TREATMENTS

Between December 27, 2012, and June 23, 2017, a total of 614 patients underwent randomization at 78 centers in the United States and Canada; 302 patients were assigned to the device group, and 312 to the control group (Fig. S1 in the Supplementary Appendix). The characteristics of the patients at baseline appeared to be well-matched between the two groups (Table S1). The representativeness of the trial population is described in Tables S2 and S3.

Transcatheter edge-to-edge repair was attempted in 293 of 302 patients (97.0%) in the device group; one or more clips were implanted in 287 of 302 patients (95.0%), with a mean (±SD) number of clips per patient of 1.7±0.7 (range, 1 to 4). Among the 260 patients in whom echocardiography was performed at the time of discharge, the severity of mitral regurgitation at discharge 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%).

Medication use during follow-up appeared to be similar in the two groups, except for inhibitors of the renin–angiotensin axis, which were used more frequently in the device group than in the control group (Table S4). Major medication changes during 5 years of follow-up were infrequent in both groups, and the average daily dose of all medications seemed to be similar in the two groups throughout follow-up (Tables S5 and S6). Only three patients, all in the device group, were treated with sodium–glucose cotransporter 2 inhibitors during the trial, all within the last year of follow-up.

EFFECTIVENESS END POINTS

Five-year follow-up was completed in 270 patients (89.4%) in the device group and in 264 patients (84.6%) in the control group. Effectiveness outcomes are shown in Table 1 and Figure 1.

Table 1. Effectiveness End Points through the 5-Year Follow-up.*

End Point	Device Group (N=302)	Control Group (N=312)	Hazard Ratio (95% CI)
	no. of patients with event (Kaplan–Meier estimate of event rate, %)		
Death from any cause	162 (57.3)	189 (67.2)	0.72 (0.58–0.89)
Cardiovascular cause	128 (49.0)	151 (58.4)	0.71 (0.56–0.90)
Related to heart failure	68 (30.9)	96 (43.2)	0.59 (0.43–0.80)
Not related to heart failure	60 (26.2)	55 (26.7)	0.93 (0.64–1.34)
Noncardiovascular cause	34 (16.3)	38 (21.4)	0.75 (0.47–1.19)
Hospitalization for any cause	251 (88.3)	270 (94.9)	0.75 (0.63–0.89)
Cardiovascular cause	203 (77.0)	236 (89.2)	0.64 (0.53–0.77)
Related to heart failure	151 (61.0)	208 (83.0)	0.49 (0.40–0.61)
Not related to heart failure	116 (51.0)	106 (52.1)	0.98 (0.75–1.27)
Noncardiovascular cause	168 (66.6)	166 (70.5)	0.89 (0.72–1.11)
Death or hospitalization for heart failure	213 (73.6)	266 (91.5)	0.53 (0.44–0.64)
Death from cardiovascular cause or hospitalization for heart failure	193 (70.2)	246 (88.7)	0.53 (0.44–0.64)
Unplanned mitral-valve intervention or surgery	11 (4.5)	75 (52.0)	0.09 (0.05–0.17)
Transcatheter edge-to-edge repair	10 (4.2)	67 (48.7)†	0.09 (0.05–0.18)
Mitral-valve surgery	1 (0.4)	9 (4.3)	0.10 (0.01–0.82)
Mitral-valve replacement	1 (0.4)‡	5 (1.7)	0.20 (0.02–1.75)
PCI or CABG	17 (8.9)	13 (6.1)	1.12 (0.54–2.31)
PCI	17 (8.9)	11 (5.4)	1.31 (0.61–2.81)
CABG	0	2 (0.7)	—
Myocardial infarction	22 (10.1)	26 (14.4)	0.72 (0.41–1.28)
New-onset permanent atrial fibrillation	23 (9.3)	23 (12.6)	0.91 (0.51–1.62)
Stroke	24 (12.0)	18 (8.7)	1.14 (0.62–2.11)
New cardiac resynchronization therapy	8 (3.2)	11 (6.3)	0.66 (0.26–1.64)
New pacemaker	10 (5.0)	10 (5.5)	0.84 (0.35–2.02)
LVAD implantation or heart transplantation§	19 (9.5)	27 (12.4)	0.59 (0.33–1.07)
LVAD implantation	13 (6.5)	19 (8.5)	0.58 (0.29–1.18)
Heart transplantation	9 (4.7)	12 (6.5)	0.62 (0.26–1.48)

* Some patients had more than one hospitalization event. The 95% confidence intervals have not been adjusted for multiplicity, so inferences drawn from these intervals should not be used for hypothesis testing. CABG denotes coronary-artery bypass graft surgery, and PCI percutaneous coronary intervention.

† The rate of transcatheter edge-to-edge repair in the control group shown here is a Kaplan–Meier estimate and thus differs from the binary crossover rate shown in the Supplementary Appendix.

‡ Mitral-valve replacement was performed in one patient on day 141 after randomization (day 135 after transcatheter edge-to-edge repair). This patient had site-assessed mild mitral regurgitation and mitral stenosis with a mitral valve area of 2.9 cm^2 that was determined on the basis of echocardiographic core laboratory analysis as not meeting the prespecified core laboratory criterion for severe mitral stenosis (<1.5 cm^2).

§ Some patients were treated with both a left ventricular assist device (LVAD) and heart transplantation.

One or more hospitalizations for heart failure during follow-up occurred in 151 patients (50.0%) in the device group and in 208 patients (66.7%) in the control group. The total number of hospitalizations for heart failure within 5 years was 314 in the device group and 447 in the control group. The annualized rate of hospitalization for heart failure was 33.1% per year in the device

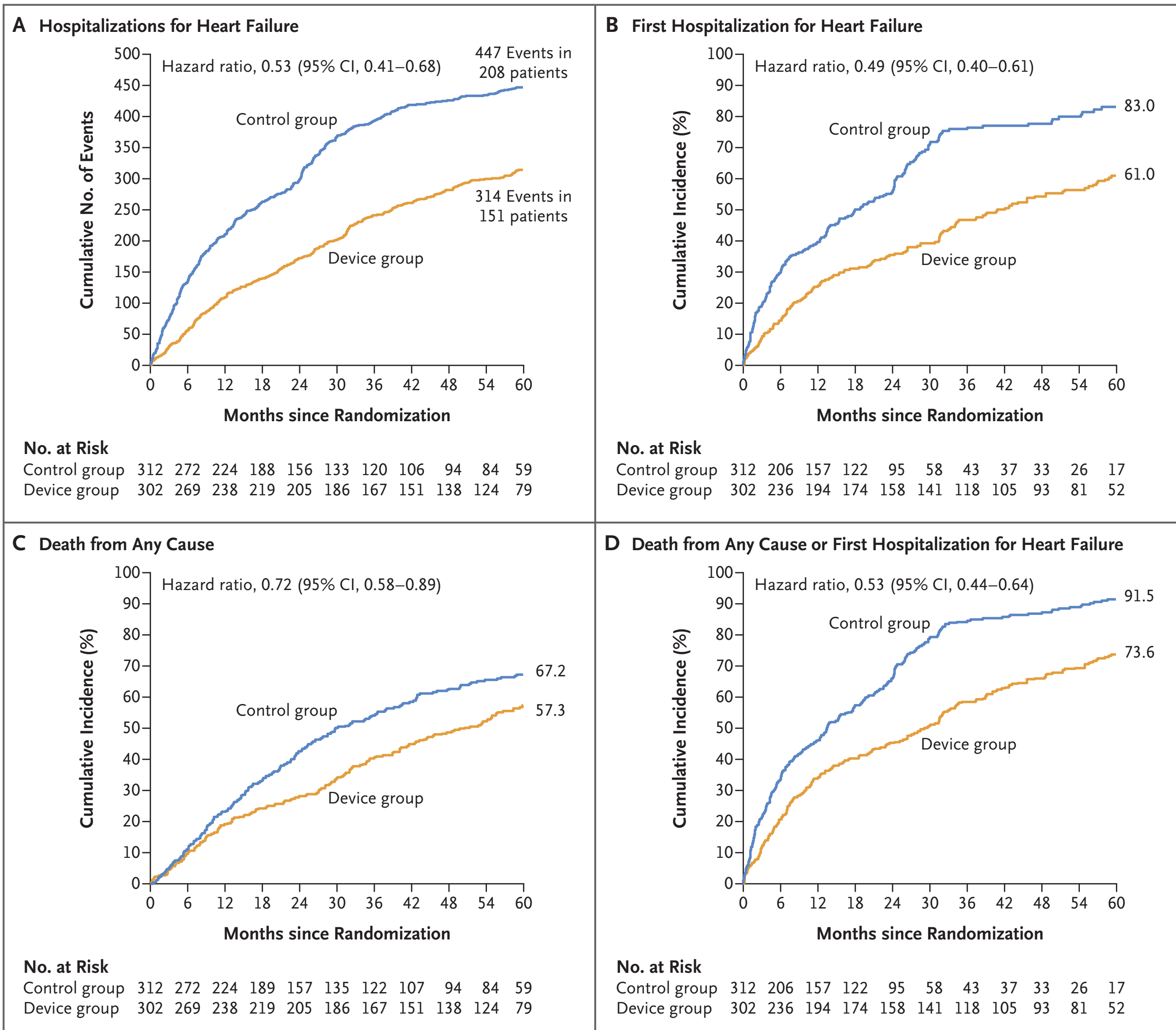
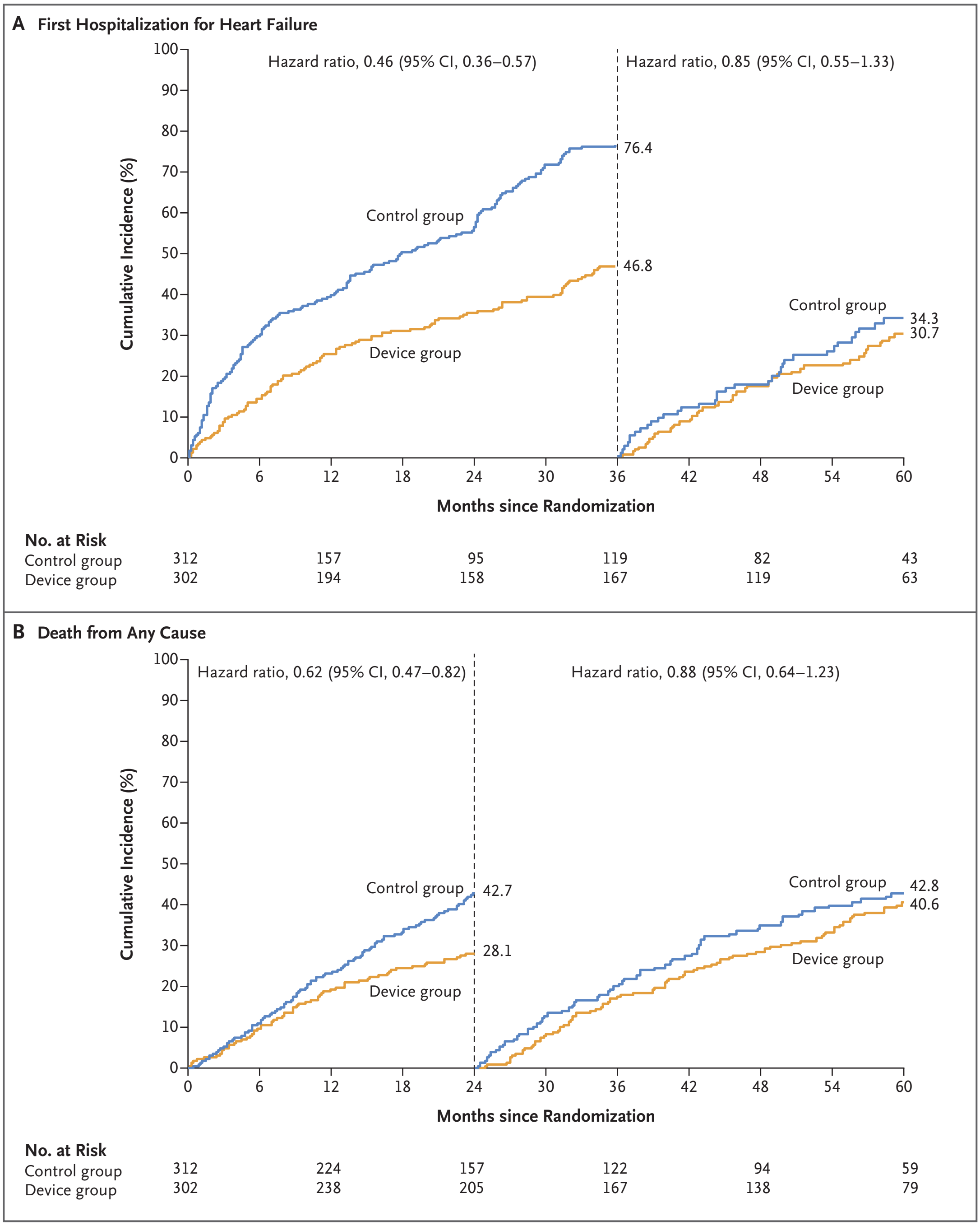


Figure 1. Event Curves for Hospitalizations for Heart Failure and Death from Any Cause.

Kaplan–Meier time-to-event curves are shown for patients with heart failure and moderate-to-severe or severe mitral regurgitation who had been randomly assigned to undergo transcatheter edge-to-edge repair plus receive guideline-directed medical therapy (device group) or to receive guideline-directed medical therapy alone (control group). The proportional-hazards assumption was not violated, as determined on the basis of visual inspection of the graph in Panel A and on the basis of the Kolmogorov-type supremum test in Panels B, C, and D. For a patient to be included in the number at risk at each time point in the Kaplan–Meier plots, valid follow-up data at each exact day had to be available, and patients who died or had an earlier event were removed from the number at risk. In contrast, qualifying follow-up for the Consolidated Standards of Reporting Trials (CONSORT) diagram included a window around each time point, and patients who died were included in each subsequent window (see the Supplementary Appendix). The 95% confidence intervals (CIs) have not been adjusted for multiplicity, so inferences drawn from these intervals should not be used for hypothesis testing.

group and 57.2% per year in the control group (hazard ratio, 0.53; 95% confidence interval [CI], 0.41 to 0.68).

Death from any cause through 5 years occurred in 162 patients (57.3%) in the device group and in 189 patients (67.2%) in the control group (hazard ratio, 0.72; 95% CI, 0.58 to 0.89). The results regarding hospitalization for any cause, for cardiovascular causes, and for heart failure through 5 years are shown in Table 1. Death or hospitalization for heart failure through 5 years occurred in 213 patients (73.6%) in the device



group and in 266 patients (91.5%) in the control group (hazard ratio, 0.53; 95% CI, 0.44 to 0.64). These results appeared to be similar after multiple imputation (Tables S7 and S8).

In post hoc analyses, the differences in the rate of hospitalizations for heart failure and in mortality diverged until 3 years and 2 years, respectively; thereafter, these event rates appeared to be similar in the two groups (Fig. 2). The lower risks of death, hospitalization for heart failure, and the composite of death or hospitalization for heart failure with transcatheter edge-to-edge repair also seemed to be consistent across numerous subgroups in post hoc analyses (Fig. 3 and Figs. S2 and S3).

The 5-year rates of myocardial infarction, re-

Figure 2 (facing page). Landmark Analyses for Hospitalization for Heart failure and Death from Any Cause.
Results of the time-to-event analysis of the first hospitalization for heart failure (Panel A) are shown between 0 and 3 years and between 3 and 5 years. Results of the time-to-event analysis of death from any cause (Panel B) are shown between 0 and 2 years and between 2 and 5 years. The timings for the landmark periods were chosen to show the periods during which the event curves between the groups were diverging (before the landmark) and were not diverging (after the landmark). The proportional-hazards assumption was not violated either before or after the landmark period in either analysis on the basis of the Kolmogorov-type supremum test. For a patient to be included in the number at risk at each time point in the Kaplan–Meier plots, valid follow-up at each exact day had to be available, and patients who died or had an earlier event were removed from the number at risk. The one exception was that at the beginning of the 3-year landmark period in the analysis of time to the first hospitalization for heart failure, all the patients who were alive were included in the numbers at risk, regardless of whether a previous hospitalization for heart failure had occurred. In contrast, qualifying follow-up for the CONSORT diagram included a window around each time point, and patients who died were included in each subsequent window (see the Supplementary Appendix). The 95% confidence intervals have not been adjusted for multiplicity, and therefore inferences drawn from these intervals should not be used for hypothesis testing.

vascularization, atrial fibrillation, stroke, cardiac resynchronization therapy or pacemaker implantation, and LVAD or heart transplantation seemed to be similar in the two groups (Table 1 and Fig. S4). Patients in the device group appeared to be more likely than those in the control group to be in NYHA functional class I or II throughout the 5-year follow-up (Fig. S5). By 5 years, patients in the device group had a mean number of 1123.5±664.8 days alive and out of the hospital, as compared with 894.8±655.1 days among patients in the control group (Table S9).

SAFETY END POINTS

Freedom from device-related complications through 5 years was 89.2%; device-specific safety events occurred in 4 patients (1.4%), with all the events occurring within 30 days after the procedure (Table 2). Unplanned transcatheter and surgical mitral-valve procedures were performed in 11 patients in the device group and in 75 patients in the control group (Table 1). Severe mitral stenosis (valve area of <1.5 cm^2, as assessed at the echocardiographic core laboratory) within 5 years was observed in 23 patients (7.6%) in the device group and in no patients in the control group; no patient underwent surgery or intervention for severe mitral stenosis. Two patients (0.7%) in the device group and no patients in the control group received an intervention for an atrial septal defect within the 5-year follow-up. A complete listing of all the safety events from the trial appears in Tables S10 and S11.

ECHOCARDIOGRAPHIC RESULTS

Mitral regurgitation seemed to be less severe in patients in the device group than in those in the control group during the 5-year follow-up (Fig. S6). Left ventricular chamber size and function, forward stroke volume and cardiac output, and right ventricular systolic pressure seemed to be similar in the two groups during follow-up. The mean mitral-valve gradient appeared to be higher and the mitral-valve orifice area smaller in patients in the device group than in those in the control group (Table S12).

CROSSOVER ANALYSIS

In post hoc analyses, we found that mitral transcatheter edge-to-edge repair was performed in 67 of 312 patients (21.5%) in the control group, including in 5 patients before 2 years and in 62 patients after 2 years, the latter representing 44.9% of the 138 patients who were eligible for mitral valve repair at that time (Fig. S7). The median time after randomization to crossover was 26.2 months (interquartile range, 24.5 to 29.5), and the median follow-up after crossover was 29.9 months (interquartile range, 13.0 to 35.6). Among 66 patients in the control group who underwent transcatheter edge-to-edge repair, 1 (2%) had NYHA class IV symptoms at baseline, as compared with 32 of the 245 patients (13.1%) in this group who did not undergo the procedure (data on NYHA class were not available for 1 patient who underwent the procedure). Patients in the control group who underwent transcatheter edge-to-edge repair had lower mean natriuretic peptide levels than those who did not undergo the procedure (Table S13). Among the 126 patients in the control group surviving to 2 years in whom echocardiography was performed, the mitral regurgitation was not severe (2+ or less) in 59 (46.8%).

Transcatheter edge-to-edge repair reduced mitral regurgitation in patients in the control

Subgroup	Device Group	Control Group	Hazard Ratio (95% CI)
	no. of patients with event/total no. of patients (Kaplan–Meier estimate of event rate, %)		
All patients	213/302 (73.6)	266/312 (91.5)	0.53 (0.44–0.64)
Median age			
≥74 yr	118/157 (78.1)	136/160 (93.9)	0.57 (0.44–0.74)
<74 yr	95/145 (68.6)	130/152 (89.1)	0.49 (0.38–0.64)
Sex			
Female	64/101 (66.6)	94/120 (83.7)	0.60 (0.43–0.82)
Male	149/201 (77.0)	172/192 (96.2)	0.47 (0.38–0.59)
Cause of cardiomyopathy			
Ischemic	135/184 (76.1)	159/189 (92.4)	0.53 (0.42–0.67)
Nonischemic	78/118 (69.6)	107/123 (90.2)	0.54 (0.40–0.72)
Previous cardiac resynchronization therapy			
Yes	84/115 (74.9)	96/109 (93.0)	0.56 (0.41–0.75)
No	129/187 (72.9)	170/203 (90.6)	0.52 (0.41–0.66)
Hospitalization for heart failure within previous yr			
Yes	143/204 (73.7)	175/203 (92.5)	0.52 (0.41–0.65)
No	70/98 (73.4)	91/109 (89.0)	0.57 (0.42–0.78)
Baseline NYHA class			
I or II	92/130 (72.8)	92/110 (88.2)	0.55 (0.41–0.74)
III	108/154 (74.5)	143/168 (92.2)	0.56 (0.44–0.73)
IV	13/18 (72.2)	30/33 (100)	0.48 (0.25–0.94)
STS replacement score			
≥8%	96/126 (80.7)	115/136 (94.8)	0.56 (0.42–0.74)
<8%	117/176 (68.7)	151/176 (89.2)	0.51 (0.40–0.66)
Surgical risk status			
High	154/205 (79.3)	183/218 (91.1)	0.59 (0.47–0.73)
Not high	56/94 (60.8)	83/94 (92.0)	0.41 (0.29–0.58)
Baseline grade of mitral regurgitation			
3+	97/148 (69.0)	143/172 (89.1)	0.51 (0.39–0.66)
4+	116/154 (78.0)	122/139 (94.4)	0.54 (0.42–0.70)
Baseline left ventricular ejection fraction			
≥30%	102/150 (70.8)	125/151 (88.9)	0.54 (0.41–0.70)
<30%	94/131 (75.3)	128/143 (95.6)	0.45 (0.34–0.59)
>40%	34/50 (72.0)	42/53 (92.0)	0.49 (0.31–0.79)
≤40%	162/231 (73.0)	211/241 (92.1)	0.50 (0.40–0.61)
Median baseline left ventricular end-diastolic volume			
≥181 ml	102/141 (75.6)	130/147 (93.1)	0.53 (0.40–0.69)
<181 ml	94/140 (69.9)	123/147 (91.1)	0.47 (0.36–0.62)

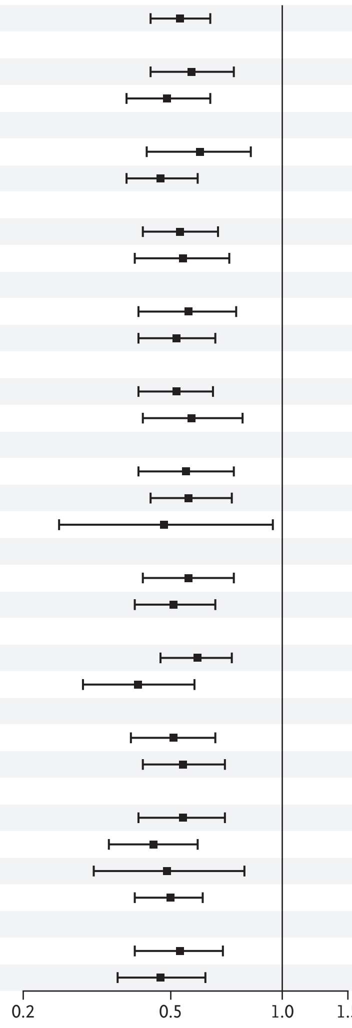


Figure 3. Post Hoc Subgroup Analyses for the 5-Year End Point of Death from Any Cause or First Hospitalization for Heart Failure.
Shown are post hoc Kaplan–Meier estimates of the 5-year event rate. Kaplan–Meier estimated rates may vary substantially from values calculated from the numerator divided by the denominator. In the analysis regarding the Society for Thoracic Surgeons (STS) replacement score, the subgroups were defined according to a risk of death at 30 days of 8%. Surgical risk status was determined by the mitral-valve surgeons on the central eligibility committee. Eligible patients had moderate-to-severe (3+) or severe (4+) secondary mitral regurgitation that was confirmed at an echocardiographic core laboratory before enrollment. The median left ventricular ejection fraction was 30%. The 95% confidence intervals have not been adjusted for multiplicity, and therefore inferences drawn from these intervals should not be used for hypothesis testing. NYHA denotes New York Heart Association.

group after crossover treatment (Fig. S8), to an extent similar to that in patients who had initially been randomly assigned to the device group (Fig. S9). Device treatment in patients in the control group was an independent predictor of freedom from subsequent death or hospitalization for heart failure in this group (hazard ratio, 0.53; 95% CI, 0.36 to 0.78) (Table S14). Event rates after transcatheter edge-to-edge repair among patients in the control group appeared to

Table 2. Primary Safety End Points among 293 Patients in the Device Group through the 5-Year Follow-up.*

Event	Time after Index Procedure					
	30 Days	12 Mo	24 Mo	36 Mo	48 Mo	60 Mo
	no. of patients with event (Kaplan–Meier estimate of event rate, %)					
Any safety event	4 (1.4)	9 (3.3)†	13 (5.2)	20 (8.8)	22 (10.1)	23 (10.8)
Device-specific event	4 (1.4)	4 (1.4)	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)	2 (0.7)	2 (0.7)
Device embolization	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Endocarditis leading to surgery	0	0	0	0	0	0
Mitral stenosis leading to surgery‡	0	0	0	0	0	0
Any device-related complication leading to nonelective cardiovascular surgery	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Progressive heart failure unrelated to device complications	0	5 (2.0)	9 (3.8)	16 (7.5)§	18 (8.8)§	19 (9.5)§
LVAD implantation	0	3 (1.2)	6 (2.6)	11 (5.1)	12 (5.8)	13 (6.5)
Heart transplantation	0	2 (0.8)	3 (1.3)	7 (3.4)	9 (4.7)	9 (4.7)

* The population for the safety analysis was limited to the 293 patients in whom a transcatheter edge-to-edge repair was attempted.
† Any safety event at 12 months was the prespecified primary safety outcome.
‡ Mitral stenosis was defined as a mitral-valve area of less than 1.5 cm according to the criteria of the echocardiographic core laboratory.
§ Some patients were treated with both an LVAD and heart transplantation.

be similar to those among patients who had originally been assigned to the device group (Fig. S10). No device-specific safety events occurred during follow-up among the 67 patients in the control group who crossed over and were treated with a MitraClip.

DISCUSSION

In the COAPT trial, which involved patients with heart failure and severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of medical therapy and other indicated treatments, transcatheter edge-to-edge repair led to a lower rate of hospitalization for heart failure and lower all-cause mortality through 5-year follow-up, despite the protocol-permitted crossover treatment of severe mitral regurgitation in patients in the control group after 2 years. Transcatheter edge-to-edge repair improved outcomes across all prespecified subgroups and was associated with consistent reductions in the risks of death and hospitalization for heart failure regardless of patient age, sex, mitral regurgitation severity, left ventricular function and volume, cause of cardiomyopathy, and surgical risk. Symptomatic status (NYHA class) was also improved throughout the 5-year follow-up after transcatheter repair of mitral regurgitation. Treatment with the MitraClip was safe; only 4 patients (1.4%) in the device group had device-specific complications within 5 years (all of which occurred within 30 days after the procedure), and fewer unplanned mitral-valve surgeries and percutaneous interventions during follow-up occurred in the device group than in the control group. Nonetheless, despite the favorable risk–benefit profile of mitral transcatheter edge-to-edge repair, adverse outcomes continued to occur in both groups, such that 73.6% of the patients in the device group and 91.5% of those in the control group either died or were hospitalized for heart failure within 5 years. These findings emphasize the need for further therapies to address the underlying left ventricular dysfunction in this high-risk population.

In the present trial, mitral transcatheter edge-to-edge repair was associated with lower rates of all hospitalizations, hospitalizations for cardiovascular causes, and hospitalizations for heart failure during the 5-year follow-up, although most of this benefit was realized within the first 3 years after randomization. Similarly, transcatheter edge-to-edge repair was associated with lower all-cause mortality, cardiovascular mortality, and heart failure–related mortality at 5 years, predominantly during the first 2 years after randomization. The diminishing treatment effect during late follow-up in this trial was in large part due to the performance of transcatheter edge-to-edge repair in 44.9% of the patients in the control group surviving to 2 years — a crossover procedure that was allowed by the protocol. The prognosis of patients in the control group who underwent such treatment was substantially improved (hazard ratio for subsequent death or hospitalization for heart failure, 0.53), a finding that was similar to that in patients who had originally been assigned to mitral-valve repair. However, nearly half the patients in the control group had died before 2 years (i.e., the threshold for eligibility for crossover as allowed in the protocol). Patients with heart failure who are appropriate candidates for transcatheter edge-to-edge repair need to be identified and considered for treatment as early as possible.

By reducing volume and pressure overload from mitral regurgitation, transcatheter edge-to-edge repair improves symptoms and prognosis in patients with heart failure. Nonetheless, left ventricular cardiomyopathy, the underlying disease in most patients with secondary mitral regurgitation, is not directly affected by mitral-valve repair.[1] As such, cardiovascular and noncardiovascular events continued to occur over time, even after successful transcatheter edge-to-edge repair — a finding that reflects the advanced age and multiple coexisting conditions in this trial population.

The standard of care for patients with heart failure evolved during the COAPT trial.[15,16] The use of angiotensin receptor–neprilysin inhibitors progressively increased during follow-up, more so among patients in the device group than among those in the control group, probably owing to improved hemodynamics after mitral transcatheter edge-to-edge repair. The extent to which the greater use of sacubitril–valsartan during follow-up contributed to the improved outcomes in the device group is uncertain. Sodium–glucose cotransporter 2 inhibitors were used in only three patients during the trial. More frequent use of these agents (and neprilysin inhibitors) may have decreased the pool of patients with refractory symptoms and severe mitral regurgitation who may have been eligible for transcatheter edge-to-edge repair[17,18] but is unlikely to have eliminated the benefits of correction of mitral regurgitation in appropriate patients.

Treatment with the MitraClip was safe, with no device-specific complications occurring after 30 days. Pressure gradients across the mitral valve were higher after transcatheter edge-to-edge repair, but we previously found that such gradients did not impair the prognostic benefits of treatment in this population,[19] and no patient underwent surgery for severe mitral stenosis. Concern has also been expressed that surgical mitral-valve replacement rather than repair is usually required after a failure of transcatheter edge-to-edge repair.[20] However, mitral-valve replacement is preferred when surgery for secondary mitral regurgitation becomes indicated,[21,22] and in the present trial, mitral-valve surgery (including replacement) was performed less frequently in the device group than in the control group during the 5-year follow-up.

The limitations of this trial include the fact that device treatment was unblinded, and withdrawal from the trial by patients during follow-up occurred more frequently in the control group than in the device group. However, the principal results were consistent after multiple imputation to account for missing data. The eligibility requirement for maximal medical therapy at baseline minimized changes in background treatments during follow-up (thus allowing the effects of the device to emerge), and use of an independent clinical-events committee and echocardiographic core laboratory reduced variability in ascertainment. Hospitalizations for heart failure were adjudicated only when strict criteria were met, and the sustained reduction in all-cause mortality during 5 years of follow-up (the end point least prone to bias) provides reassurance regarding the validity of the observations. The reasons why some patients in the control group were not treated with transcatheter edge-to-edge repair as permitted by the protocol after 2 years were not collected. However, 46.8% of the surviving patients in the control group were no longer eligible because the mitral regurgitation at 2 years was no longer severe. The present results reflect treatment with the first-generation MitraClip in all patients; recent enhancements to this device have been introduced that make achievement of mitral regurgitation of 1+ or lower severity more likely,[23] and an alternative device that performs transcatheter edge-to-edge repair[24] has recently been approved by the Food and Drug Administration for the treatment of degenerative mitral regurgitation. Finally, all the enrolled patients were symptomatic despite the use of maximal doses of medical therapy, had moderate-to-severe or severe mitral regurgitation, and a left ventricular ejection fraction of 20 to 50% without marked chamber dilatation or severe right heart involvement. Whether the correction of mitral regurgitation would safely improve outcomes in more or less critically ill patients or in patients with moderate mitral regurgitation is unclear.

In this trial involving patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of medical therapy, transcatheter edge-to-edge repair of the mitral valve was safe, led to a lower rate of hospitalization for heart failure than medical therapy alone, and prolonged survival during 5 years of follow-up.

Supported by Abbott.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' affiliations are as follows: the Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai (G.W.S.), Columbia University Medical Center (S.O.M.), and the Cardiovascular Research Foundation (D.J.C.), New York, and St. Francis Hospital and Heart Center, Roslyn (D.J.C.) — all in New York; the Departments of Medicine, Physiology, and Cell Biology, Division of Cardiovascular Medicine, and the Davis Heart and Lung Research Institute, Ohio State University, Columbus (W.T.A.), the Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland (S.R.K.), and Lindner Clinical Research Center and the Christ Hospital, Cincinnati (I.J.S.); Advanced Heart Failure, Vanderbilt Heart and Vascular Institute, Nashville (J.A.L.); the Division of Cardiology, HCA Healthcare, Los Angeles (S.K.), and Kaiser Permanente–San Francisco Hospital, San Francisco (J.M.M.); Baylor University Medical Center, Baylor Heart and Vascular Institute, Dallas (P.A.G.), and Baylor Scott and White Heart Hospital Plano, Plano (M.J.M.) — both in Texas; the Division of Cardiology, University of Virginia, Charlottesville (D.S.L.); Intermountain Medical Center, Murray, UT (B.W.); Carolinas Medical Center, Charlotte, NC (M.R.); Piedmont Hospital, Atlanta (V.R.); University of Colorado Hospital, Aurora (A.B.); and MedStar Health Research Institute, Hyattsville, MD (F.M.A.).

REFERENCES

1. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol 2015;65:1231-48.
2. Sannino A, Smith RL II, Schiattarrella GG, Trimarco B, Esposito G, Grayburn PA. Survival and cardiovascular outcomes of patients with secondary mitral regurgitation: a meta-analysis of 53 studies. JAMA Cardiol 2017;2:1130-9.
3. Goliasch G, Bartko PE, Pavo N, et al. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. Eur Heart J 2018;39:39-46.
4. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol 2009;54:686-94.
5. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307-18.
6. Mack MJ, Abraham WT, Lindenfeld J, et al. Cardiovascular outcomes assessment of the MitraClip in patients with heart failure and secondary mitral regurgitation: design and rationale of the COAPT trial. Am Heart J 2018;205:1-11.
7. Stone GW, Vahanian AS, Adams DH, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement. 1. Clinical trial design principles: a consensus document from the Mitral Valve Academic Research Consortium. J Am Coll Cardiol 2015;66:278-307.
8. Stone GW, Adams DH, Abraham WT, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement. 2. Endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. J Am Coll Cardiol 2015;66:308-21.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:776-803.
10. Arnold SV, Stone GW, Jain SS, et al. Prognostic importance of health status versus functional status in heart failure and secondary mitral regurgitation. JACC Heart Fail 2021;9:684-92.
11. Baron SJ, Wang K, Arnold SV, et al. Cost-effectiveness of transcatheter mitral valve repair versus medical therapy in patients with heart failure and secondary mitral regurgitation: results from the COAPT trial. Circulation 2019;140:1881-91.
12. Asch FM, Grayburn PA, Siegel RJ, et al. Echocardiographic outcomes after transcatheter leaflet approximation in patients with secondary mitral regurgitation: the COAPT trial. J Am Coll Cardiol 2019;74:2969-79.
13. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777-802.
14. Rondeau V, Mathoulin-Pelissier S, Jacqmin-Gadda H, Brouste V, Soubeyran P. Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events. Biostatistics 2007;8:708-21.
15. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2022;79(17):e263-e421.
16. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.
17. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.

18. Ahmad Y, Madhavan MV, Stone GW, et al. Sodium-glucose cotransporter 2 inhibitors in patients with heart failure: a systematic review and meta-analysis of randomized trials. Eur Heart J Qual Care Clin Outcomes 2022;8:383-90.
19. Halaby R, Herrmann HC, Gertz ZM, et al. Effect of mitral valve gradient after MitraClip on outcomes in secondary mitral regurgitation: results from the COAPT trial. JACC Cardiovasc Interv 2021;14:879-89.
20. Kaneko T, Hirji S, Zaid S, et al. Mitral valve surgery after transcatheter edge-to-edge repair: mid-term outcomes from the CUTTING-EDGE international registry. JACC Cardiovasc Interv 2021;14:2010-21.
21. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med 2014;370:23-32.
22. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2021;77(4):e25-e197.
23. Orban M, Rottbauer W, Williams M, et al. Transcatheter edge-to-edge repair for secondary mitral regurgitation with third-generation devices in heart failure patients: results from the Global EXPAND Post-Market study. Eur J Heart Fail 2023 January 04 (Epub ahead of print).
24. Lim DS, Smith RL, Gillam LD, et al. Randomized comparison of transcatheter edge-to-edge repair for degenerative mitral regurgitation in prohibitive surgical risk patients. JACC Cardiovasc Interv 2022;15:2523-36.