ORIGINAL ARTICLE

Transcatheter Valve Repair in Heart Failure with Moderate to Severe Mitral Regurgitation

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ABSTRACT

BACKGROUND

Whether transcatheter mitral-valve repair improves outcomes in patients with heart failure and functional mitral regurgitation is uncertain.

METHODS

We conducted a randomized, controlled trial involving patients with heart failure and moderate to severe functional mitral regurgitation from 30 sites in nine countries. The patients were assigned in a 1:1 ratio to either transcatheter mitral-valve repair and guideline-recommended medical therapy (device group) or medical therapy alone (control group). The three primary end points were the rate of the composite of first or recurrent hospitalization for heart failure or cardiovascular death during 24 months; the rate of first or recurrent hospitalization for heart failure during 24 months; and the change from baseline to 12 months in the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS; scores range from 0 to 100, with higher scores indicating better health status).

RESULTS

A total of 505 patients underwent randomization: 250 were assigned to the device group and 255 to the control group. At 24 months, the rate of first or recurrent hospitalization for heart failure or cardiovascular death was 37.0 events per 100 patient-years in the device group and 58.9 events per 100 patient-years in the control group (rate ratio, 0.64; 95% confidence interval [CI], 0.48 to 0.85; P=0.002). The rate of first or recurrent hospitalization for heart failure was 26.9 events per 100 patient-years in the device group and 46.6 events per 100 patient-years in the control group (rate ratio, 0.59; 95% CI, 0.42 to 0.82; P=0.002). The KCCQ-OS score increased by a mean (±SD) of 21.6±26.9 points in the device group and 8.0±24.5 points in the control group (mean difference, 10.9 points; 95% CI, 6.8 to 15.0; P<0.001). Device-specific safety events occurred in 4 patients (1.6%).

CONCLUSIONS

Among patients with heart failure with moderate to severe functional mitral regurgitation who received medical therapy, the addition of transcatheter mitral-valve repair led to a lower rate of first or recurrent hospitalization for heart failure or cardiovascular death and a lower rate of first or recurrent hospitalization for heart failure at 24 months and better health status at 12 months than medical therapy alone. (Funded by Abbott Laboratories; RESHAPE-HF2 ClinicalTrials.gov number, NCT02444338.)

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Functional mitral regurgitation is common among patients with heart failure and is associated with a poor prognosis.[1,2] Despite guideline-recommended medical therapy and cardiac-resynchronization therapy, many patients with functional mitral regurgitation remain symptomatic.[3] Surgery is usually not recommended unless another surgical intervention, such as coronary-artery bypass grafting or aortic-valve replacement, is indicated.[4,5] For patients who are not surgical candidates, current international heart-failure guidelines suggest that transcatheter edge-to-edge repair for functional mitral regurgitation should be considered, but they do not make strong recommendations[6,7] because of conflicting evidence of benefit. The MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial showed that percutaneous repair did not lead to a lower rate of death from any cause or hospitalization for heart failure or a lower rate of death from any cause at 1 year and 2 years than medical therapy alone.[8,9] In contrast, the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial showed that transcatheter mitral-valve repair led to not only a lower rate of hospitalization for heart failure but also a lower rate of death from any cause than medical therapy alone during 24 months of follow-up.[10] Several hypotheses have been proposed to explain these discordant results, including differences in the severity of heart failure, medical treatment, and the mechanisms underlying functional mitral regurgitation.[11,12]

The MITRA-FR and COAPT trials involved patients with predominantly severe functional mitral regurgitation, which is usually defined by guidelines as a regurgitant volume of greater than 60 ml, a regurgitant fraction of greater than 50%, and a mean effective regurgitant orifice area larger than 0.40 cm^2. The mean effective regurgitant orifice area in these trial populations were 0.31 cm^2 and 0.40 cm^2.[11,12] A clinical-practice registry showed that 44% of patients undergoing transcatheter mitral-valve repair had only moderate mitral regurgitation.[13] Worldwide, more than 150,000 patients have undergone transcatheter mitral-valve repair, but conclusive evidence of efficacy based on the results of randomized trials is limited, especially for patients with moderate or moderate-to-severe functional mitral regurgitation.[14,15] Accordingly, we conducted a randomized trial to provide further evidence regarding the safety and effectiveness of transcatheter mitral-valve repair in patients with symptomatic heart failure and functional mitral regurgitation.

Methods

Trial Design and Oversight

RESHAPE-HF2 (Randomized Investigation of the MitraClip Device in Heart Failure: Second Trial in Patients with Clinically Significant Functional Mitral Regurgitation) is a prospective, multicenter, investigator-initiated randomized trial involving patients with symptomatic heart failure and moderate to severe functional mitral regurgitation (despite receiving guideline-directed medical therapy) in whom isolated mitral-valve surgery was not recommended.[16-18] The trial was supported by an unrestricted grant from Abbott Laboratories (the financial sponsor) to the University Medical Center Göttingen (the legal sponsor). The trial protocol (available with the full text of this article at NEJM.org) was designed by the principal investigators and representatives from Abbott Laboratories and approved by the institutional review board or ethics committee at each participating site. All the patients provided written informed consent.

An independent data and safety monitoring committee evaluated patient safety during the trial. Representatives from the Clinical Trials Unit of University Medical Center Göttingen coordinated the trial and collected the data. The first, second, and ninth authors had unrestricted access to the data and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by the first, second, and fifth authors. All statistical analyses were performed by the second and ninth authors. Earlier versions of the manuscript were reviewed and edited by all the authors.

Patients, Randomization, and Follow-up

Eligible patients had symptoms and signs of heart failure despite guideline-recommended therapy, grade 3+ or 4+ functional mitral regurgitation,[19] and a left ventricular ejection fraction of 20 to 50% (initially, left ventricular ejection fraction was 15 to 35% for patients with New York Heart As-

sociation [NYHA] functional class II heart failure and 15 to 45% for patients with NYHA functional class III or IV heart failure) and were required to have, within 90 days before enrollment, either a hospitalization for heart failure or an elevated plasma natriuretic peptide concentration (a B-type natriuretic peptide [BNP] level of ≥300 pg per milliliter or an N-terminal pro–BNP [NT-proBNP] level of ≥1000 pg per milliliter). Patients for whom mitral-valve surgery was recommended were not eligible. Other exclusion criteria were degenerative mitral-valve disease and any of the following procedures performed within 90 days before enrollment: percutaneous coronary intervention, cardiovascular surgery, or atrial fibrillation ablation. The severity of functional mitral regurgitation was defined according to the criteria of European Association of Echocardiography.[20] The complete list of inclusion and exclusion criteria is shown in Table S1 in the Supplementary Appendix, available at NEJM.org.

All the patients at each site were evaluated by a heart team consisting of a heart-failure specialist, an interventional cardiologist, an echocardiographer, and a cardiothoracic surgeon. Both transthoracic and transesophageal echocardiography were required to determine patient eligibility. Patients were considered for randomization only if their heart failure was considered to be sufficiently managed (as assessed by an investigator) and site investigators and staff at the echocardiography core laboratory had confirmed their eligibility.

Patients were randomly assigned in a 1:1 ratio to undergo transcatheter mitral-valve repair and receive medical therapy (device group) or to receive medical therapy alone (control group). Medical therapy was based on guideline recommendations directed by evidence from clinical trials. Patients in the device group were scheduled to undergo transcatheter mitral-valve repair with the MitraClip device implantation within 14 days after randomization. Randomization was based on permuted blocks and was stratified according to trial site and cause of heart failure (ischemic or nonischemic). Details about the procedure have been published previously (Table S2).[21,22] Follow-up visits were conducted at discharge (device group only), at 30, 180, and 365 days, and then yearly. An electronic data-capture system was used to populate case-report forms. All the patients were followed up by a heart-failure specialist (Table S3).

TRIAL OUTCOMES

There were three primary end points: the rate of the composite of first or recurrent hospitalization for heart failure or death from cardiovascular causes during 24 months, the rate of first or recurrent hospitalization for heart failure during 24 months, and the change from baseline to 12 months in the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS; scores range from 0 to 100, with higher scores indicating better health status). Secondary end points included mitral regurgitation of grade 2+ or worse at 12 months, change from baseline to 12 months in the 6-minute walk distance, death from any cause during the entire trial period, the rate of recurrent hospitalization for any cause during 24 months, and NYHA functional class I or II heart failure at 12 months. Left ventricular volumes and severity of mitral regurgitation were assessed at an independent echocardiographic core laboratory. A complete list of trial end points is provided in Table S4.

STATISTICAL ANALYSIS

Assuming an annual incidence of death from cardiovascular causes of 12.5%, an annual incidence of death from noncardiovascular causes of 5.5%, and an annual incidence of hospitalization for heart failure of 60 events per 100 patient-years of follow-up in the control group and a follow-up period of 24 months, we originally estimated that a sample of 420 patients would provide the trial with 80% power to reject the null hypothesis of no effect under the assumption of a hazard ratio of 0.75 at a two-sided significance level of 5%.[16] In 2018, a blinded sample-size review based on noncomparative data was carried out and shared with the steering committee and the legal and financial sponsors; because blinded reviews generally do not inflate the type I error rate, no alpha adjustment was made.[23] After the blinded sample-size review, we decided to follow the patients for more than 24 months and enroll at least 650 patients to maintain 80% power to reject the null hypothesis at a hazard ratio of 0.70. In the aftermath of the coronavirus disease 2019 pandemic, recruitment was lower than anticipated, and ethics committees in several countries would not agree to reporting and adjudication of events after 24 months because of the wording of the original informed-consent form.

Accordingly, recruitment was closed in October 2023, with a planned final follow-up visit in April 2024. On February 6, 2024, the steering committee, the members of which were unaware of the trial-group assignments, decided to revert to the originally planned primary end point — the rate of first or recurrent hospitalization for heart failure or death from cardiovascular causes during 24 months of follow-up — and to complement it with two additional primary end points: the rate of first or recurrent hospitalization for heart failure during 24 months and the change from baseline to 12 months in the KCCQ-OS score.

Statistical analyses were performed according to the intention-to-treat principle and included all the patients who had undergone randomization. The primary and secondary end points were analyzed by means of the Hochberg procedure.[24] All end points that were based on recurrent events were analyzed with Lin–Wei–Yang–Ying (LWYY) models. In these analyses, trial discontinuation was handled as an independent censoring event, and the actual time in the trial was included in the LWYY analyses. Sensitivity analyses were conducted in the form of shared random-effects models that included the event of interest and competing events. Analyses of continuous outcomes, including the changes from baseline to 12 months in the KCCQ-OS score, the 6-minute walk distance, and echocardiographic variables, were performed with linear mixed models for repeated measures with gaussian distribution and included all available data with no imputation. Although the mixed models for repeated measures approach is robust with regard to missing data to some extent, sensitivity analyses were performed with the use of reference-based multiple imputation. Subgroup analyses of the first primary end point were conducted with the use of 13 baseline characteristics. The respective baseline characteristic and its interaction with treatment were included in the LWYY regression model described above. Further details are provided in the statistical analysis plan, available with the protocol. Statistical analyses were performed with the use of R software, version 4.3.1.

RESULTS

PATIENTS

From March 2015 through October 2023, a total of 621 patients underwent screening, of whom 505 were enrolled at 30 sites in nine countries. A total of 250 patients were randomly assigned to the device group and 255 to the control group (Fig. S1). The baseline characteristics of the patients are shown in Table 1 and Table S5. Among the trial patients, the mean (±SD) age was 70±10 years, 20% were women, 35% had nonischemic cardiomyopathy, and 29% had cardiac-resynchronization therapy devices. The median left ventricular ejection fraction was 31% (interquartile range, 25 to 37), the median left ventricular end-diastolic volume was 205 ml (interquartile range, 157 to 250), the median effective regurgitant orifice area was 0.23 cm^2 (interquartile range, 0.20 to 0.29), and the median regurgitant volume was 36 ml (interquartile range, 29 to 43). The median KCCQ-OS score was 43 points (interquartile range, 26 to 63). Medical therapy at baseline appeared to be similar in the two trial groups. The representativeness of the trial population is shown in Table S6.

PROCEDURES

Of 250 participants assigned to the device group, 248 (99.2%) had transcatheter mitral-valve repair attempted. The MitraClip device was deployed in 244 patients (98.4%), and echocardiographic data at the end of the procedure were available for 243 patients (97.2%). The severity grade of mitral regurgitation was 1+ or lower in 181 patients (74.5%), 2+ in 43 patients (17.7%), 3+ in 10 patients (4.1%), and 4+ in 9 patients (3.7%). Procedures were performed within 14 days after randomization in 220 patients, within 15 to 30 days in 21 patients, and after 30 days in 7 patients. The median procedure time was 117 minutes (interquartile range, 70 to 150). The median fluoroscopy time was 22 minutes (interquartile range, 12 to 34).

EFFICACY END POINTS

The mean duration of follow-up was 18.8±8.2 months. At 24 months, the rate of first or recurrent hospitalization for heart failure or death from cardiovascular causes was 37.0 events per 100 patient-years (a total of 151 events) in the device group and 58.9 events per 100 patient-years (a total of 225 events) in the control group (rate ratio, 0.64; 95% confidence interval [CI], 0.48 to 0.85; P=0.002). The rate of first or recurrent hospitalization for heart failure during 24 months was 26.9 events per 100 patient-

Table 1. Baseline Demographic and Clinical Characteristics of the Patients with Heart Failure and Moderate-to-Severe Functional Mitral Regurgitation.*

Characteristic	Device Group (N=250)	Control Group (N=255)
Age — yr	70.0±10.4	69.4±10.7
Male sex — no. (%)	195 (78.0)	211 (82.8)
Diabetes — no. (%)	91 (36.4)	85 (33.3)
Hypertension — no. (%)	141 (56.4)	127 (49.8)
Previous myocardial infarction — no. (%)	144 (57.6)	135 (52.9)
Previous PCI — no. (%)	118 (47.2)	125 (49.0)
Previous CABG — no. (%)	69 (27.6)	64 (25.1)
Previous stroke or TIA — no. (%)	29 (11.6)	30 (11.8)
Peripheral vascular disease — no. (%)	38 (15.2)	27 (10.6)
History of atrial fibrillation or flutter — no. (%)	118 (47.2)	125 (49.0)
Body-mass index†	27.0±4.3	26.7±4.3
Nonischemic cause of cardiomyopathy — no. (%)	88 (35.2)	88 (34.5)
NYHA functional class — no. (%)		
II	59 (23.6)	65 (25.5)
III	150 (60.0)	153 (60.0)
IV	41 (16.4)	36 (14.1)
Hospitalization for heart failure within previous year — no. (%)	165 (66.0)	168 (65.9)
Systolic blood pressure — mm Hg	112±16	113±16
Median NT-proBNP level (IQR) — pg/ml‡	2651 (1630–4918)	2816 (1306–5496)
Median BNP level (IQR) — pg/ml§	556 (312–1018)	406 (231–874)
Median 6-minute walk distance (IQR) — m	300 (220–382)	310 (200–378)
Estimated glomerular filtration rate — ml/min/1.72 cm^2	54.9±19.0	56.7±23.3
Median KCCQ-OS score (IQR) — points¶	42.2 (28.3–62.0)	44.3 (25.8–64.2)
Median left ventricular ejection fraction (IQR) — %	32 (26–37)	31 (25–37)
Median left ventricular end-diastolic volume (IQR) — ml	200 (153–249)	206 (158–250)
Severity of mitral regurgitation — no. (%)		
Grade 3+	141 (56.4)	141 (55.3)
Grade 4+	109 (43.6)	114 (44.7)
Median effective regurgitant orifice area (IQR) — cm^2	0.23 (0.20–0.30)	0.23 (0.19–0.29)
Median regurgitant volume (IQR) — ml	35.4 (28.9–43.9)	35.6 (28.2–42.5)

* Plus–minus values are means ±SD. CABG denotes coronary-artery bypass graft, IQR interquartile range, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TIA transient ischemic attack.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Data on N-terminal pro–B-type natriuretic peptide (NT-proBNP) level were available for 384 patients (191 in the device group and 193 in the control group).
§ Data on B-type natriuretic peptide (BNP) level were available for 123 patients (61 in the device group and 62 in the control group).
¶ Scores on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) range from 0 to 100, with higher scores indicating better health status.

years (a total of 110 events) in the device group and 46.6 events per 100 patient-years (a total of 178 events) in the control group (rate ratio, 0.59; 95% CI, 0.42 to 0.82; P=0.002).

The mean change from baseline to 12 months in the KCCQ-OS score was 21.6±26.9 points in the device group and 8.0±24.5 points in the control group (least-squares mean difference, 10.9 points;

Table 2. Primary and Secondary End Points.*

End Point	Device Group (N=250)	Control Group (N=255)	Difference (95% CI)†	P Value‡
Primary End Points§				
Rate of the composite of first or recurrent hospitalization for heart failure or death from cardiovascular causes during 24 mo per 100 patient-yr (no. of events/total no. of patient-yr)	37.0 (151/408.6)	58.9 (225/381.9)	0.64 (0.48–0.85)	0.002¶
Rate of first or recurrent hospitalization for heart failure during 24 mo per 100 patient-yr (no. of events/total no. of patient-yr)	26.9 (110/408.6)	46.6 (178/381.9)	0.59 (0.42–0.82)	0.002¶
Mean change from baseline to 12 mo in the KCCQ-OS score — points	21.6±26.9	8.0±24.5	10.9 (6.8–15.0)‖	<0.001¶
Secondary end points				
Mitral regurgitation grade ≤2+ at 12 mo — no./total no. (%)	132/146 (90.4)	43/119 (36.1)**	21.3 (10.7–45.8)††	<0.001¶
Mean change in 6-min walk distance from baseline to 12 mo — m	34.0±105.9	5.1±97.6	20.5 (0.3–40.7)‖	0.05‡‡
Rate of death from any cause during the complete follow-up per 100 patient-yr (no. of events/total no. of patient-yr)	17.0 (142/836.7)	18.6 (142/765.2)	0.90 (0.71–1.13)	0.37‡‡
Rate of recurrent hospitalization for any cause during 24 mo per 100 patient-yr (no. of events/total no. of patient-yr)	48.7 (199/408.6)	61.0 (233/381.9)	0.82 (0.63–1.07)	0.15‡‡
NYHA functional class I or II heart failure at 12 mo — no./total no. (%)§§	140/188 (74.5)	96/164 (58.5)	2.35 (1.48–3.77)††	<0.001¶

* Plus–minus values are means ±SD.
† The difference in treatment effect is given as a rate ratio unless otherwise noted.
‡ Unadjusted P values are presented, but they were tested for significance according to the thresholds as defined by the Hochberg procedure.
§ The three primary end points were tested at a two-sided significance level of 5%. After the results for all three were found to be statistically significant, the Hochberg procedure was also applied to the secondary end points at a two-sided significance level of 5%.
¶ The finding was statistically significant according to the Hochberg procedure.
‖ The difference in treatment effect is given as the difference in least-squares means, as estimated with linear mixed models for repeated measures with gaussian distribution.
** Of these 43 patients, 15 had undergone transcatheter mitral-valve repair.
†† The difference in treatment effect is given as an odds ratio.
‡‡ The finding was not significant according to the Hochberg procedure.
§§ At 12 months, 33 patients in the control group and 27 patients in the device group had died.

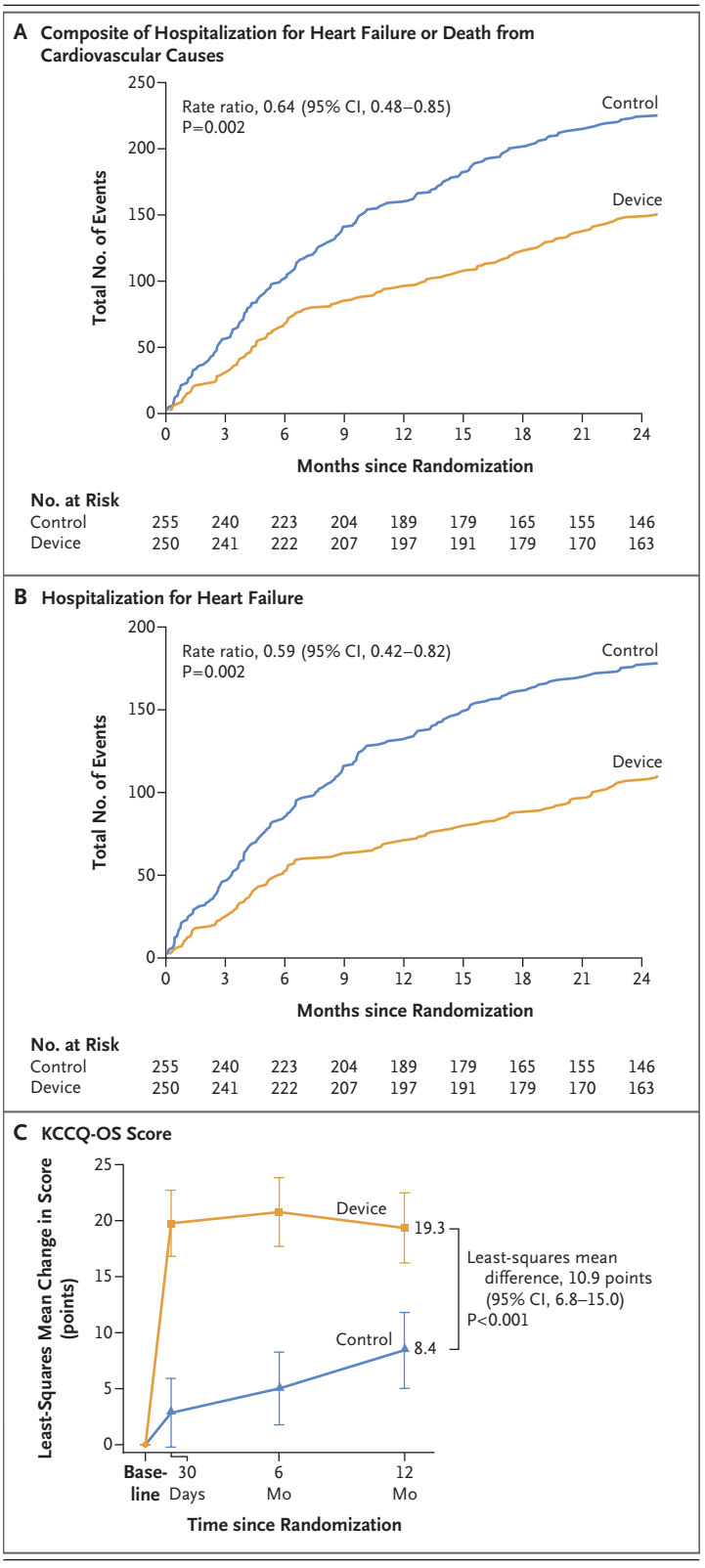
95% CI, 6.8 to 15.0; P<0.001). The results for the primary and secondary end points are shown in Table 2 and Figure 1. The total number of first or recurrent hospitalizations for any cause during 24 months was 199 in the device group and 233 in the control group (rate ratio, 0.82; 95% CI, 0.63 to 1.07). During the entire duration of follow-up (38.1±18.1 months), 142 deaths occurred in the device group (annualized rate [the number of events divided by the total number of patient-years], 17.0%) and 142 deaths occurred in the control group (annualized rate, 18.6%), for a hazard ratio of 0.90 (95% CI, 0.71 to 1.13). A total of 140 of 188 patients (74.5%) in the device group and 96 of 164 (58.5%) in the control group had NYHA functional class I or II heart failure at 12 months (P<0.001). The mean change in 6-minute walk distance from baseline to 12 months was 34.0±105.9 m in the device group and 5.1±97.6 m in the control group (least-squares mean difference, 20.5 m; 95% CI, 0.3 to 40.7; P=0.047; not significant according to the Hochberg procedure). A total of 132 of 146 patients (90.4%) in the device group and 43 of 119 patients (36.1%) in the control group had a mitral regurgitation severity grade of 2+ or lower at 12 months (P<0.001). The results of the subgroup analyses are shown in Figure 2.

SAFETY

Adverse events are shown in Table 3. Among the patients assigned to the device group, periproce-

Figure 1. Number of Primary End-Point Events and Change in KCCQ-OS Score.

Panel A shows the total number of events in the composite of first or recurrent hospitalization for heart failure or death from cardiovascular causes over a period of 24 months. Panel B shows the total number of first or recurrent hospitalizations for heart failure over a period of 24 months. Panel C shows the least-squares mean change from baseline over a period of 12 months in the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) for quality of life (scores range from 0 to 100, with higher scores indicating better health status). I bars indicate 95% confidence intervals.



dural adverse events were reported in four (1.6%). These events included two cases of hematoma, one case of pericardial effusion, and one case of right atrial perforation that led to thoracotomy after completion of the device implantation.

DISCUSSION

In the RESHAPE-HF2 trial, which involved patients with moderate to severe functional mitral regurgitation who remained symptomatic despite medical therapy, transcatheter mitral-valve repair led to a lower rate of first or recurrent hospitalization for heart failure or death from cardiovascular causes during 24 months, as well as a lower rate of first or recurrent hospitalization for heart failure during 24 months and a greater increase from baseline to 12 months in the KCCQ-OS score, than medical therapy alone. These results appeared to be consistent across most subgroups.

Previous studies of transcatheter mitral-valve repair in patients with functional mitral regurgitation mainly involved patients with severe mitral regurgitation and provided conflicting results.[8,10] The extent of left ventricular damage and severity of mitral-valve regurgitation have been proposed as important determinants of benefit from transcatheter mitral-valve repair.[25,26] The mean effective regurgitant orifice area was smaller among the patients in our trial (0.25 cm^2) than among those in the COAPT trial (0.40 cm^2) and the MITRA-FR trial (0.31 cm^2); at baseline, 14% of the patients in our trial had an effective regurgitant orifice area larger than 0.40 cm^2 and 23% had an effective regurgitant orifice area smaller than 0.20 cm^2. However, there was no

Subgroup	Device	Control	Rate Ratio for Hospitalization for Heart Failure or Death from Cardiovascular Causes (95% CI)
	no. of patients (annualized rate [no. of events/ total no. of patient-yr])		
Sex			
Male	195 (37.7 [120/318])	211 (58.2 [185/318])	0.66 (0.47–0.92)
Female	55 (34.4 [31/90])	44 (64.5 [40/62])	0.56 (0.30–1.03)
Age			
≥70 yr	140 (39.6 [90/227])	143 (64.7 [130/201])	0.63 (0.42–0.94)
<70 yr	110 (33.9 [61/180])	112 (53.1 [95/179])	0.64 (0.42–0.97)
Body-mass index			
≥30	52 (29.4 [25/85])	49 (59.2 [42/71])	0.49 (0.27–0.91)
<30	197 (39.4 [126/320])	203 (59.8 [183/306])	0.68 (0.48–0.94)
LVEF			
≥30%	151 (34.5 [82/249])	137 (44.5 [89/200])	0.79 (0.53–1.18)
<30%	99 (41.1 [65/158])	118 (75.6 [136/180])	0.55 (0.36–0.85)
Cause of heart failure			
Nonischemic	88 (39.0 [55/141])	88 (77.8 [98/126])	0.51 (0.33–0.79)
Ischemic	162 (36.1 [96/266])	167 (50.0 [127/254])	0.74 (0.50–1.09)
Estimated GFR			
≥50 ml/min/1.73 m^2	143 (30.7 [73/238])	149 (43.5 [104/239])	0.72 (0.45–1.13)
<50 ml/min/1.73 m^2	103 (44.8 [74/165])	103 (88.2 [120/136])	0.52 (0.36–0.75)
BNP or NT-proBNP			
≥Median	124 (49.5 [98/198])	121 (76.4 [123/161])	0.68 (0.47–0.99)
<Median	122 (25.6 [52/203])	129 (46.2 [97/210])	0.54 (0.34–0.87)
Previous cardiac-resynchronization			
Yes	77 (34.1 [43/126])	68 (72.9 [70/96])	0.49 (0.31–0.77)
No	172 (38.4 [108/281])	187 (54.6 [155/284])	0.71 (0.50–1.03)
Severity of mitral regurgitation			
Severe, grade 4+	109 (35.7 [61/171])	114 (75.2 [118/157])	0.48 (0.32–0.72)
Moderate to severe, grade 3+	141 (38.1 [90/236])	141 (48.0 [107/223])	0.81 (0.54–1.23)
NYHA functional class			
III or IV	191 (37.9 [121/319])	189 (70.3 [185/263])	0.56 (0.41–0.76)
I or II	59 (34.1 [30/88])	65 (34.8 [40/115])	0.91 (0.42–1.98)
Left ventricular end-diastolic volume			
High, >227 ml	80 (37.0 [50/135])	88 (74.8 [98/131])	0.49 (0.30–0.80)
Medium, >170 to 227 ml	83 (46.0 [63/137])	85 (63.1 [77/122])	0.78 (0.48–1.25)
Low, ≤170 ml	87 (28.1 [38/135])	82 (39.4 [50/127])	0.70 (0.40–1.23)
Effective regurgitant orifice area			
High, >0.27 cm^2	84 (42.3 [58/137])	75 (89.0 [89/100])	0.51 (0.32–0.82)
Medium, >0.21 to 0.27 cm^2	75 (40.2 [47/117])	84 (47.3 [61/129])	0.81 (0.46–1.44)
Low, ≤0.21 cm^2	76 (30.2 [39/129])	84 (47.4 [64/135])	0.66 (0.39–1.12)
Hospitalization for heart failure within 12 mo before randomization			
Yes	165 (36.7 [99/270])	168 (71.0 [179/252])	0.53 (0.37–0.75)
No	85 (38.0 [52/137])	87 (35.9 [46/128])	1.05 (0.62–1.79)

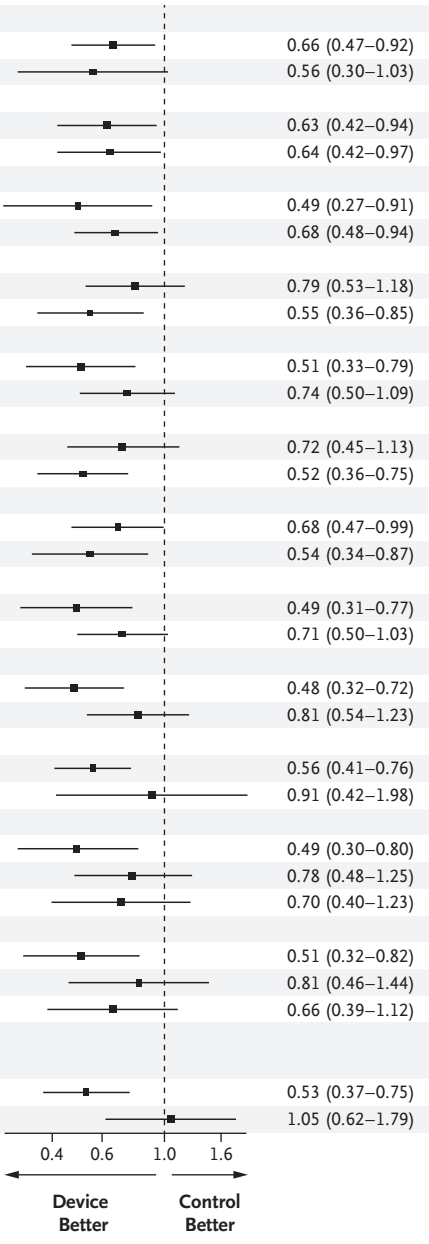


Figure 2. Subgroup Analysis of the Composite of First or Recurrent Hospitalization for Heart Failure or Death from Cardiovascular Causes.

The annualized rate (expressed as a percentage) is the number of events divided by the total number of patient-years. The body-mass index is the weight in kilograms divided by the square of the height in meters. BNP denotes B-type natriuretic peptide level, LVEF left ventricular ejection fraction, NT-proBNP N-terminal pro–BNP, and NYHA New York Heart Association.

Table 3. Adverse Events of Interest during 24 Months in the Intention-to-Treat Population.*

Event	Device Group (N=250)	Control Group (N=255)	Hazard or Rate Ratio (95% CI)†	P Value
	no. of patients with event (estimate of event rate)			
Death from any cause‡	51 (22.3)	67 (29.6)	0.73 (0.51–1.05)	0.09
Death from cardiovascular causes§	41 (17.8)	47 (20.4)	0.84 (0.55–1.28)	0.43
Death from noncardiovascular causes§	10 (4.5)	20 (9.3)	0.46 (0.22–0.99)	0.04
Unplanned MitraClip implantation¶	8 (2.0)	25 (6.5)	0.32 (0.14–0.70)	0.004
All unplanned transcatheter mitral-valve repair¶	8 (2.0)‖	38 (10.0)**	0.21 (0.10–0.44)	<0.001
Mitral-valve surgery††	1 (0.004)	2 (0.008)	0.51 (0.05–5.58)	0.57
PCI§	6 (0.026)	8 (0.034)	0.74 (0.26–2.12)	0.57
CABG	0	0	—	—
Stroke§	5 (0.022)	2 (0.008)	2.5 (0.48–12.9)	0.25
Myocardial infarction¶	3 (0.007)	3 (0.008)	1.02 (0.14–7.52)	0.99
LVAD implantation††	1 (0.008)	2 (0.02)	0.5 (0.05–5.49)	0.56
Heart transplantation	1	0	—	—
Implantation of ICD or CRT-D§	7 (1.8)	7 (1.7)	0.96 (0.35–2.66)	0.93

* CRT-D denotes cardiac-resynchronization therapy defibrillator, and ICD implantable cardioverter–defibrillator.
† Whenever recurrent event analyses were performed (unplanned MitraClip implantation, all unplanned transcatheter mitral-valve repair, and myocardial infarction), rate ratios are given.
‡ Death from any cause was analyzed by means of Cox regression, with adjustment for country and cause of heart failure. Event rates are given as Kaplan–Meier estimates.
§ Death from cardiovascular causes, death from noncardiovascular causes, PCI, stroke, and implantation of ICD or CRT-D were analyzed by means of Cox regression, with adjustment for country and cause of heart failure. Event rates are given as the cumulative incidence (expressed as a percentage) at 24 months. In these analyses, death was included in the model as a competing event.
¶ The analyses of unplanned MitraClip implantations, all unplanned transcatheter mitral-valve repair, and myocardial infarction included recurrent events and were conducted with the Lin–Wei–Yang–Ying model for recurrent events, with adjustment for country and cause of heart failure. Event rates are given as the annualized rate, defined as the number of events divided by the total number of patient-years and expressed as a percentage.
‖ All eight implantations were performed by month 12 (with seven performed by month 6).
** Of the 38 implantations, 35 were performed by month 12 (with 28 performed by month 6).
†† Mitral-valve surgery and left ventricular assist device (LVAD) implantation were analyzed by means of Cox regression without covariate adjustments. Event rates are given as the cumulative incidence (expressed as a percentage) at 24 months. In the analyses, death was included in the model as a competing event.

apparent heterogeneity in treatment effect in subgroups defined according to key baseline echocardiographic measurements. The findings of the current trial are relevant because untreated functional mitral regurgitation can cause changes in cardiac structure and function that lead to worsening heart failure and an adverse prognosis.[27,28]

Patients with heart failure and functional mitral regurgitation are at high risk for recurrent hospitalizations.[1,29] The relative difference in the rate of first or recurrent hospitalization for heart failure during 24 months between the device group and control group of 41% represents an absolute difference in risk of 19.7 events per 100 patient-years, which translates into a number needed to treat of only 5.1 to prevent one hospitalization for heart failure with transcatheter mitral-valve repair in combination with guideline-directed medical therapy. Also, the reductions in symptoms that were assessed according to NYHA functional class and the KCCQ-OS score at 12 months were greater in the device group than in the control group, and the difference between the groups in the 6-minute walk distance at 12 months was a least-squares mean of 20.5 m in favor of the device group. By 12 months, 90.4% (132 of 146) of the patients assigned to the device group had a reduction in

mitral regurgitation grade to 2+ or lower, as compared with 36% (43 of 119) of those in the control group, of whom 35% (15 of 43) had undergone a mitral-valve procedure. This finding may explain the greater reductions in symptoms and hospitalization rates and improvements in functional capacity and health status that were observed in device group as compared with the control group.

The COAPT trial showed that during 24 months of follow-up, transcatheter mitral-valve repair in combination with medical therapy resulted in a lower rate of death from any cause than medical therapy alone (hazard ratio, 0.62; 95% CI, 0.46 to 0.82),[10] but the MITRA-FR trial did not show a lower rate of death from any cause with transcatheter mitral-valve repair in a similar comparison.[8] In our trial, the rate of death from any cause was also not lower with transcatheter mitral-valve repair than with medical therapy alone, which could be related to a smaller clinical benefit or fewer outcome events, findings consistent with both less severe mitral regurgitation and less advanced heart failure. All-cause mortality at 2 years in the control group of our trial was 29.6% (Table 3), as compared with 46.1% in control group of the COAPT trial, and the rate of recurrent hospitalization in our trial was less than half that observed in the COAPT trial, which suggests that the patients enrolled in our trial had less severe disease.

The trial has several limitations. Although randomization was performed in a blinded manner, the participants, investigators, and echocardiographers were not unaware of subsequent treatments. This situation could have created bias, especially for quality-of-life assessments recorded by patients. Some patients who had been assigned to receive medical therapy alone underwent transcatheter mitral-valve repair, which could have diluted the observed treatment effect. Finally, the trial was not designed to show differences in mortality.

Among patients with heart failure and moderate to severe functional mitral regurgitation who remained symptomatic despite guideline-recommended medical therapy, transcatheter mitral-valve repair in combination with medical therapy led to a lower rate of first or recurrent hospitalization for heart failure or death from cardiovascular causes during 24 months, a lower rate of first or recurrent hospitalization for heart failure during 24 months, and better health status at 12 months than medical therapy alone.

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APPENDIX

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