ORIGINAL ARTICLE

# Transcatheter Repair versus Mitral-Valve Surgery for Secondary Mitral Regurgitation

Stephan Baldus, M.D., Torsten Doenst, M.D., Roman Pfister, M.D., Jan Gummert, M.D., Mirjam Kessler, M.D., Peter Boekstegers, M.D., Edith Lubos, M.D., Jörg Schröder, M.D., Holger Thiele, M.D., Thomas Walther, M.D., Malte Kelm, M.D., Jörg Hausleiter, M.D., Ingo Eitel, M.D., Ulrich Fischer-Rasokat, M.D., Alexander Bufe, M.D., Alexander Schmeisser, M.D., Hüseyin Ince, M.D., Philipp Lurz, M.D., Ralph Stephan von Bardeleben, M.D., Christian Hagl, M.D., Thilo Noack, M.D., Sebastian Reith, M.D., Harald Beucher, M.D., Hermann Reichenspurner, M.D., Wolfgang Rottbauer, M.D., P. Christian Schulze, M.D., Wiebke Müller, M.Sc., Julia Frank, M.Sc., Martin Hellmich, Ph.D., Thorsten Wahlers, M.D., and Volker Rudolph, M.D., for the MATTERHORN Investigators*

## ABSTRACT

### BACKGROUND

Current treatment recommendations for patients with heart failure and secondary mitral regurgitation include transcatheter edge-to-edge repair and mitral-valve surgery. Data from randomized trials comparing these therapies are lacking in this patient population.

### METHODS

In this noninferiority trial conducted in Germany, patients with heart failure and secondary mitral regurgitation who continued to have symptoms despite guideline-directed medical therapy were randomly assigned, in a 1:1 ratio, to undergo either transcatheter edge-to-edge repair (intervention group) or surgical mitral-valve repair or replacement (surgery group). The primary efficacy end point was a composite of death, hospitalization for heart failure, mitral-valve reintervention, implantation of an assist device, or stroke within 1 year after the procedure. The primary safety end point was a composite of major adverse events within 30 days after the procedure.

### RESULTS

A total of 210 patients underwent randomization. The mean (±SD) age of the patients was 70.5±7.9 years, 39.9% were women, and the mean left ventricular ejection fraction was 43.0±11.7%. Within 1 year, at least one of the components of the primary efficacy end point occurred in 16 of the 96 patients with available data (16.7%) in the intervention group and in 20 of the 89 with available data (22.5%) in the surgery group (estimated mean difference, −6 percentage points; 95% confidence interval [CI], −17 to 6; P<0.001 for noninferiority). A primary safety end-point event occurred in 15 of the 101 patients with available data (14.9%) in the intervention group and in 51 of the 93 patients with available data (54.8%) in the surgery group (estimated mean difference, −40 percentage points; 95% CI, −51 to −27; P<0.001).

### CONCLUSIONS

Among patients with heart failure and secondary mitral regurgitation, transcatheter edge-to-edge repair was noninferior to mitral-valve surgery with respect to a composite of death, rehospitalization for heart failure, stroke, reintervention, or implantation of an assist device in the left ventricle at 1 year. (Funded by Abbott Vascular; MATTERHORN ClinicalTrials.gov number, NCT02371512.)

The authors' affiliations are listed in the Appendix. Dr. Baldus can be contacted at stephan.baldus@uk-koeln.de or at the Department of Cardiology, Heart Center, University Hospital Cologne, Cologne Cardiovascular Research Center (CCRC), University of Cologne, Germany.

*The MATTERHORN investigators are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on August 31, 2024, at NEJM.org.

DOI: 10.1056/NEJMoa2408739

Isolated secondary mitral regurgitation causes symptoms in patients with heart failure and is associated with increased morbidity and mortality.[1] Prospective nonrandomized studies and registry studies suggest that isolated surgical repair and replacement of the mitral valve in patients with secondary mitral regurgitation is linked to a reduction in symptoms.[2-4]

Transcatheter edge-to-edge therapy has been established as an alternative to surgery. Currently, up to two thirds of all transcatheter edge-to-edge procedures are performed to treat secondary mitral regurgitation.[5,6] Among selected patients with severe secondary mitral regurgitation despite guideline-directed medical therapy, transcatheter edge-to-edge therapy has been shown to decrease symptoms and reduce the risk of death.[7-13]

Surgical repair has been perceived to be a more invasive treatment, and transcatheter intervention potentially less effective; but data from controlled studies to evaluate the accuracy of these perceptions are lacking. Accordingly, guideline recommendations remain inconsistent: the European guidelines recommend transcatheter intervention only for patients not eligible for surgery, whereas U.S. guidelines recommend surgery only in patients with anatomy that is unfavorable for transcatheter intervention.[14,15] Therefore, we conducted the Multicenter Mitral Valve Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin (MATTERHORN) trial to determine whether transcatheter edge-to-edge therapy is noninferior to mitral-valve surgery in patients with secondary mitral regurgitation who are at high surgical risk.

## Methods

### Trial Design and Oversight

MATTERHORN was a multicenter, prospective, randomized, controlled trial with two parallel treatment groups, conducted in Germany. A full list of participating sites, along with details of the contribution of the authors, is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The manuscript was written by the first and last authors, who, along with the third from last author, vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, available (with the statistical analysis plan) at NEJM.org. There were no agreements between the sponsor and the authors or the institutions with respect to confidentiality of the data. The steering committee and an independent data and safety monitoring board consisting of a statistician, a cardiac surgeon, and an interventional cardiologist provided oversight of trial progress, data quality, and patient safety. The procedures set out in this trial, pertaining to the conduct, evaluation, and documentation of this trial, were designed to ensure that all persons involved in the trial abide by Good Clinical Practice guidelines and the ethical principles described in the Declaration of Helsinki. The trial was carried out in keeping with local legal and regulatory requirements and the requirements of the Federal Data Protection Law.

### Patient Selection

Patients were eligible for enrollment if they had clinically significant secondary mitral regurgitation, which was defined by meeting at least two of the following criteria: effective regurgitant orifice area of at least 20 $mm^2$, biplane vena contracta width of more than 8 mm, a regurgitant volume of at least 30 ml, a regurgitant fraction of at least 50%, or at least two hospitalizations for acute heart failure during the 12 months before enrollment. Additional criteria included a left ventricular ejection fraction of at least 20%, New York Heart Association class II or higher heart failure despite guideline-directed therapy, and eligibility for both transcatheter edge-to-edge repair or mitral-valve surgery as determined by the local heart team. Patients with additional severe valvular disease and patients who had undergone coronary revascularization or cardiac resynchronization therapy within 1 month before enrollment were excluded. A complete list of the inclusion and exclusion criteria is provided in the Supplementary Appendix.

### Randomization and Procedures

Patients were randomly assigned, in a 1:1 ratio, to undergo transcatheter edge-to-edge repair (intervention group) or surgical mitral-valve repair or replacement (surgery group). At each site, central, automated randomization was performed with the use of permuted blocks of varying length and was stratified according to trial site into blocks of four and six (Fig. S1 in the Supplementary Appendix). Procedures were performed according to local best practice. Investigators were

selected by the steering committee on the basis of their experience in interventional cardiology or transcatheter mitral-valve repair and mitral-valve surgery. All transcatheter procedures were performed with the use of the latest available iteration of the MitraClip device (Abbott Vascular). For mitral-valve surgery, surgical access and technique, including concomitant ablation procedures or tricuspid-valve surgery, were left to the discretion of the surgeon. Periprocedural management was performed according to local standards. Patients were evaluated at baseline, at hospital discharge, and 1 month and 1 year after the procedure. A standardized transesophageal echocardiographic examination was performed before the procedure, and a standardized transthoracic echocardiographic examination was performed before the procedure, before discharge, and at 12 months after the procedure (details regarding the transthoracic echocardiography protocol are provided in the Supplementary Appendix). All echocardiographic images were analyzed by a central echocardiographic core laboratory at the University of Mainz.

#### END POINTS

The primary efficacy end point was a composite of death from any cause, hospitalization for heart failure, mitral-valve reintervention, implantation of an assist device in the left ventricle, or stroke within 1 year after the procedure. Recurrence of mitral regurgitation grade 3+ (moderate-to-severe disease) or 4+ (severe disease) was a key secondary end point. Additional secondary end points included the change from baseline to 12 months in the 6-minute walk distance, New York Heart Association functional class, and the score on the Minnesota Living with Heart Failure Questionnaire. The primary safety end point was a composite of the following major adverse events within 30 days after the procedure: death (from any cause or from cardiovascular causes), myocardial infarction, major bleeding, stroke or transient ischemic attack, rehospitalization (from any or from cardiovascular causes), reintervention or nonelective cardiovascular surgery, renal failure (need for renal replacement therapy), deep wound infection, mechanical ventilation for more than 48 hours, gastrointestinal complication requiring surgery, new-onset atrial fibrillation, septicemia, or endocarditis. A complete list of secondary end points and detailed definitions are provided in the Supplementary Methods section in the Supplementary Appendix.

#### STATISTICAL ANALYSIS

For the primary end point, we assumed an average incidence of 35%. We estimated that a total of 210 patients would provide the trial with 80% power, accounting for a 5% dropout rate and stratification according to trial site. The upper boundary of the 90% confidence interval of the estimated mean between-group difference had to be below 17.5 percentage points to meet the criterion for noninferiority (see the Supplementary Appendix for additional details). The percentage of patients with freedom from a primary end-point event was compared between the treatment groups with the use of multiple logistic-regression analysis, with treatment group as the only predictor variable. The analysis was performed on a complete-case basis, assuming that data were missing completely at random; however, multiple imputation was used for sensitivity analyses, assuming that data were missing at random. Missing values were addressed with the use of multiple imputation with the Markov chain Monte Carlo method, which was based on a fully conditional specification method, and the corresponding regression results were pooled (see the Supplementary Appendix for further details). The distribution of time to event was described with the use of Kaplan–Meier curves and compared between groups with the use of a log-rank test and multiple Cox regression analysis.

The percentage of patients with a recurrence of mitral regurgitation grade 3+ or 4+ within 12 months after the procedure was evaluated (with a noninferiority margin of 17.5 percentage points) in accordance with a fixed sequence of hypothesis testing as long as noninferiority of the primary end point was shown. The change in the 6-minute walk distance was compared between treatment groups by multiple linear regression with a noninferiority boundary of 50 m, at a two-sided level of 5%, also in accordance with a fixed sequence of hypotheses. The complete sequence testing scheme is shown in the Statistical Methods section in the Supplementary Appendix. The combined safety end point was compared between treatment groups with the use of Fisher's exact test, with the two-sided 95% confidence interval calculated according to

**Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population). ***

| Characteristic | Intervention Group (N=104)† | Surgery Group (N=104)† | Total (N=208)† |
|---|---|---|---|
| **Clinical** | | | |
| Mean age — yr | 70.2±8.1 | 70.9±7.8 | 70.5±7.9 |
| Female sex — no. (%) | 38 (36.5) | 45 (43.3) | 83 (39.9) |
| Mean body-mass index‡ | 27.8±5.1 | 27.7±5.6 | 27.8±5.4 |
| Diabetes — no./total no. (%) | 28/103 (27.2) | 25/103 (24.3) | 53/206 (25.7) |
| Hypertension — no./total no. (%) | 85/103 (82.5) | 86/103 (83.5) | 171/206 (83.0) |
| Coronary artery disease — no./total no. (%) | 48/103 (46.6) | 42/103 (40.8) | 90/206 (43.7) |
| Previous coronary artery bypass — no./total no. (%) | 4/103 (3.9) | 3/103 (2.9) | 7/206 (3.4) |
| History of atrial fibrillation — no./total no. (%) | 57/103 (55.3) | 48/103 (46.6) | 105/206 (51.0) |
| Peripheral vascular disease — no./total no. (%) | 7/103 (6.8) | 6/103 (5.8) | 13/206 (6.3) |
| Stroke — no./total no. (%) | 6/103 (5.8) | 7/103 (6.8) | 13/206 (6.3) |
| Chronic obstructive pulmonary disease — no./total no. (%) | 21/103 (20.4) | 14/103 (13.6) | 35/206 (17.0) |
| Chronic kidney disease — no./total no. (%) | 37/103 (35.9) | 36/103 (35.0) | 73/206 (35.4) |
| Mean creatinine clearance — ml/min | 57.4±20.8 | 56.3±21.5 | 56.9±21.1 |
| Mean hemoglobin level — g/dl | 13.0±1.9 | 12.9±1.9 | 13.0±1.9 |
| Median STS-PROM score (IQR) — %§ | 1.9 (0.9–3.3) | 2.2 (1.4–4.1) | 2.0 (1.1–3.7) |
| Median EuroSCORE II (IQR) — %¶ | 3.0 (1.6–4.5) | 3.0 (1.8–4.2) | 3.0 (1.7–4.3) |
| **Heart failure–related characteristics** | | | |
| NYHA class — no./total no. (%) | | | |
| I | 1/102 (1.0) | 0/101 (0.0) | 1/203 (0.5) |
| II | 17/102 (16.7) | 11/101 (10.9) | 28/203 (13.8) |
| III | 79/102 (77.5) | 83/101 (82.2) | 162/203 (79.8) |
| IV | 5/102 (4.9) | 7/101 (6.9) | 12/203 (5.9) |
| Median 6-minute walk distance (IQR) — meters | 339 (229–389) | 349 (258–414) | 347(240–400) |
| Median Minnesota Living with Heart Failure Questionnaire score (IQR) — points‖ | 37 (23–49) | 39.5 (21–52) | 38 (22–52) |
| Hospitalization for heart failure within previous year — no./total no. (%) | 86/103 (83.5) | 84/102 (82.4) | 170/205 (82.9) |
| Previous cardiac resynchronization therapy — no./total no. (%) | 16/103 (15.5) | 11/103 (10.7) | 27/206 (13.1) |
| ACE inhibitor, ARB, or ARNI at discharge — no./total no. (%)** | 83/102 (81.4) | 55/95 (57.9) | 138/197 (70.1) |
| Beta-blocker at discharge — no./total no. (%)** | 86/102 (84.3) | 79/95 (83.2) | 165/197 (83.8) |
| Mineralocorticoid receptor antagonist at discharge — no./total no. (%)** | 32/102 (31.4) | 20/95 (21.1) | 52/197 (26.4) |
| Dual heart failure medication at discharge — no./total no. (%)** | 46/102 (45.1) | 46/95 (48.4) | 92/197 (46.7) |
| Triple heart failure medication at discharge — no./total no. (%)** | 28/102 (27.5) | 10/95 (10.5) | 38/197 (19.3) |
| **Echocardiographic core laboratory analyses** | | | |
| Mitral regurgitation grade 3+ or higher — no./total no. (%) | 99/102 (97.1) | 92/97 (94.8) | 191/199 (96.0) |
| Median effective regurgitant orifice area (IQR) — $cm^2$ | 0.22 (0.17–0.28) | 0.23 (0.16–0.28) | 0.22 (0.17–0.28) |
| Main mechanism of mitral regurgitation — no./total no. (%) | | | |
| Annular dilatation | 52/100 (52.0) | 50/92 (54.3) | 102/192 (53.1) |
| Ventricular tethering | 48/100 (48.0) | 42/92 (45.7) | 90/192 (46.9) |

**Table 1. (Continued.)**

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, ARB angiotensin receptor blocker, ARNI angiotensin receptor neprilysin inhibitor, IQR interquartile range, and NYHA New York Heart Association.
† Complete data were available for 71 to 104 patients in the group undergoing transcatheter edge-to-edge repair (intervention group) and for 68 to 104 patients undergoing surgery (surgery group). Missing data, in addition to those noted in the body of the table and in other footnotes, are as follows: for age, 2 patients (1.9%) in the intervention group and 3 (2.9%) in the surgery group; for creatinine clearance, 5 (4.8%) and 6 (5.8%), respectively; for hemoglobin level, 3 (2.9%) and 5 (4.8%); for 6-minute walk distance, 17 (16.3%) and 26 (25.0%); and for effective regurgitant orifice area, 18 (17.3%) and 28 (26.9%).
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 1 patient (1.0%) in each group.
§ The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score for mitral-valve repair ranges from 0 to 100%, with higher scores indicating a greater risk of death within 30 days after the procedure. Data were missing for 12 patients (11.5%) in the intervention group and 14 (13.5%) in the surgery group.
¶ The European System for Cardiac Operative Risk Evaluation (EuroSCORE) II scores range from 0 to 100%, with higher scores indicating a greater risk of in-hospital death. Data were missing for 8 patients (7.7%) in the intervention group and 12 (11.5%) in the surgery group.
‖ The Minnesota Living with Heart Failure Questionnaire scores range from 0 to 105, with higher scores indicating a lower quality of life. Data were missing for 3 patients (2.9%) in the intervention group and 10 (9.6%) in the surgery group.
** These categories show the percentage of patients taking these medications at discharge from the index hospital stay for the procedure.

Newcombe's method 10. The primary analysis was performed in the intention-to-treat population. The 95% confidence intervals are given for all end points. Interim analyses of the primary safety end point were performed after 70 patients and after 140 patients completed the 30-day follow-up, as specified in the charter of the data and safety monitoring board. A more detailed description of the statistical analyses is provided in the Supplementary Appendix.

## RESULTS

### PATIENTS

From February 2015 through December 2022, a total of 210 patients underwent randomization. Two patients withdrew their consent after randomization and requested the deletion of their data. Thus, 104 patients were allocated to the intervention group and 104 patients to the surgery group. In the intervention group, 102 patients underwent the assigned intervention, 1 of whom crossed over to the surgical group because of an intraprocedural tendinous chord rupture; 2 additional patients withdrew consent. In the surgery group, 94 patients underwent the assigned surgery: 1 patient underwent a transcatheter intervention, 1 patient was lost to follow-up, and 8 patients withdrew consent (Fig. S2).

Baseline characteristics appeared to be balanced between the two treatment groups (Table 1). The mean (±SD) age of the patients was 70.5±7.9 years, and 39.9% were women. The median Society of Thoracic Surgeons Predicted Risk of Mortality score (range of scores, 0 to 100%, with higher scores indicating a greater risk of death within 30 days after the procedure) was 2.0 (interquartile range, 1.1 to 3.7), the median European System for Cardiac Operative Risk Evaluation II score (range of scores, 0 to 100%, with higher scores indicating a greater risk of in-hospital death) was 3.0 (interquartile range, 1.7 to 4.3), and 13.1% of the patients had received previous cardiac resynchronization therapy. The mean left ventricular ejection fraction was 43.0±11.7%. Mitral regurgitation grade 3+ or higher was present in 191 patients (96.0%), and grade 4+ in 76 patients (38.2%); the median effective regurgitant orifice area was 0.22 $cm^2$ (interquartile range, 0.17 to 0.28); and the mean regurgitant fraction was 57.0±21.0% (Table 1 and Table S1). At hospital discharge, the percentage of patients receiving a renin–angiotensin–aldosterone system inhibitor and the percentage receiving triple heart-failure therapy were higher in the intervention group than in the surgery group (Table 1). The representativeness of the study population is shown in the Supplementary Appendix.

In the intervention group, transcatheter edge-to-edge repair was successful and resulted in a mitral regurgitation grade of 2+ or lower in 96.1% of the patients at 1 year; 48.5% of patients received one device and 40.6% received two devices. Detailed information on the devices is presented in Figure S3. In the surgery group, mitral-valve surgery resulted in a mitral regurgitation grade of 2+ or lower in 98.6% of the patients at 1 year: 72.0% underwent mitral-valve repair and 28.0% underwent mitral-valve replacement. Further details regarding surgical techniques and the distribution of treatment across trial sites are provided in Tables S2 and S3, respectively.

**Table 2. Primary and Secondary End Points (Intention-to-Treat Population).***

| End Point | Intervention Group N=104 | Surgery Group N=104 | Mean Difference (95% CI)† | Regression Coefficient $\beta$ (95% CI) |
|---|---|---|---|---|
| **Primary** | | | | |
| Efficacy — no./total no. (%)‡ | 16/96 (16.7) | 20/89 (22.5) | −6 (−17 to 6) | |
| Death from any cause — no./total no. (%) | 8/96 (8.3) | 9/87 (10.3) | −2 (−11 to 7) | |
| Rehospitalization for congestive heart failure — no./total no. (%) | 3/101 (3.0) | 7/101 (6.9) | −4 (−11 to 3) | |
| Mitral-valve reintervention — no./total no. (%) | 5/101 (5.0) | 2/101 (2.0) | 3 (−3 to 9) | |
| Implantation of assist device implantation in left ventricle — no./total no. (%) | 2/101 (2.0) | 4/101 (4.0) | −2 (−8 to 4) | |
| Stroke — no./total no. (%) | 1/101 (1.0) | 4/101 (4.0) | −3 (−9 to 2) | |
| Safety — no./total no. (%)§ | 15/101 (14.9) | 51/93 (54.8) | −40 (−51 to −27) | |
| **Secondary** | | | | |
| Safety — no./total no. (%)¶ | 35/96 (36.5) | 70/93 (75.3) | −39 (−51 to −25) | |
| Recurrence of grade 3 or 4 mitral regurgitation — no./total no. (%) | 7/79 (8.9) | 1/65 (1.5) | 7 (0 to 14) | |
| Death from any cause — no./total no. (%)‖ | 8/99 (8.1) | 10/89 (11.2) | 0.61 (0.24 to 1.57)** | |
| Median change in Minnesota Living with Heart Failure Questionnaire score from baseline to 1 year (IQR) — points | −10 (−20 to 0) | −5 (−19 to 4) | | −3.70 (−10.52 to 3.11) |
| Median in-hospital stay after intervention (IQR) — days | 4 (3 to 6) | 12 (9 to 17) | | −7.88 (−10.64 to −5.11) |
| Median length of ICU stay after intervention (IQR) — days | 1 (0 to 2) | 3 (2 to 7) | | −2.95 (−5.40 to −0.50) |

* Data for the Minnesota Living with Heart Failure Questionnaire score were missing for 35 patients (33.7%) in the intervention group and 45 patients (43.3%) in the surgery group; data for in-hospital stay and for length of stay in the intensive care unit (ICU) after intervention were missing for 2 patients (1.9%) and 9 patients (8.7%), respectively.

† The mean difference is calculated as the percentage in the intervention group minus the percentage in the surgery group, expressed as percentage points. The 95% confidence intervals have not been adjusted for multiplicity and should not be used to reject or not reject the null hypothesis of a treatment effect.

‡ The primary efficacy end point was a composite of death from any cause, hospitalization for heart failure, mitral-valve reintervention, implantation of an assist device in the left ventricle, or stroke at 1-year follow-up.

§ The primary safety end point was a composite of the following major adverse events within 30 days after the intervention: death (from any cause or from cardiovascular causes), myocardial infarction, major bleeding, stroke or transient ischemic attack, rehospitalization (from any cause or from cardiovascular causes), reintervention or nonelective cardiovascular surgery, renal failure (need for renal-replacement therapy), deep wound infection, mechanical ventilation for more than 48 hours, gastrointestinal complication requiring surgery, new-onset atrial fibrillation, septicemia, or endocarditis.

¶ The secondary safety end point was a composite of the major adverse events within 365 (±30) days after the intervention.

‖ Data for death from any cause as a secondary end point were not censored at 365 (±30) days.

** This value is a hazard ratio (95% CI), rather than a difference.

### PRIMARY END POINT

In the intervention group, 8 patients were excluded from the primary analysis: 2 patients withdrew before undergoing the procedure, 2 were lost to follow-up (without a primary endpoint event) before reaching the 1-year follow-up (defined as 365±30 days), and 4 underwent follow-up before reaching 335 days (without an event). In the surgery group, 15 patients were excluded from the primary analysis: 9 patients withdrew before undergoing the procedure, 1 withdrew before the 30-day follow-up (without an event), 2 withdrew before the 1-year follow-up (without an event), and 3 underwent follow-up before reaching 335 days (without an event). Therefore, a total of 96 patients (92.3%) in the intervention group and 89 (85.6%) in the surgery group had data available at the 1-year follow-up. The median follow-up time was 370 days (interquartile range, 366 to 374) in the intervention group and 368

days (interquartile range, 364 to 372) in the surgery group. Within 1 year after the procedure, 16 patients (16.7%) in the intervention group and 20 patients (22.5%) in the surgery group had a primary efficacy end-point event (estimated mean difference, −6 percentage points; 95% confidence interval [CI], −17 to 6; P<0.001 for noninferiority) (Table 2 and Fig. S4). The relative risk ratio was 0.74 (95% CI, 0.41 to 1.34). The Kaplan–Meier estimate was 16.9% in the intervention group and 22.7% in the surgery group (P=0.30 by log-rank test) (Fig. 1). Results of a subgroup analysis and a stacked probability plot of the components of the primary end point are provided in Figures S5 and S6, respectively.

A total of 101 patients in the intervention group and 93 in the surgery group had data available at 30 days after the procedure. A primary safety end-point event occurred in 15 patients (14.9%) in the intervention group and in 51 patients (54.8%) in the surgery group (estimated mean difference, −40 percentage points; 95% CI, −51 to −27; P<0.001) (Table 2).

In the as-treated population, a primary efficacy end-point event occurred in 13 patients of 94 with available data (13.8%) in the intervention group and in 23 patients of 91 with available data (25.3%) in the surgery group (relative risk ratio, 0.55; 95% CI, 0.30 to 1.01); a primary safety end-point event was observed in 12 of 99 patients with available data (12.1%) and in 54 of 95 patients with available data (56.8%), respectively. The per-protocol analyses appeared to have similar results. Multiple imputation of missing values supported the results of the primary efficacy end-point analysis (estimated mean difference, −12 percentage points; 95% CI, −24 to 1).

#### SECONDARY END POINTS

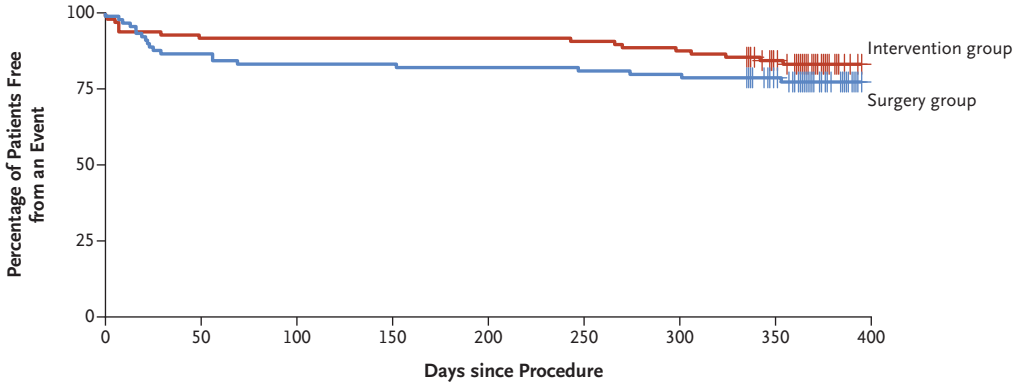
Recurrence of grade 3+ or 4+ mitral regurgitation at 1 year, defined as recurrence within 365 (±30) days after the procedure, was observed in 7 of 79 patients with available data (8.9%) in the intervention group and in 1 of 65 patients with available data (1.5%) in the surgery group (estimated mean difference, 7 percentage points; 95% CI, 0 to 14; P=0.02 for noninferiority). An analysis that included multiple imputation of missing values supported the results of the secondary efficacy end-point analysis (estimated mean difference, −7 percentage points; 95% CI, −19 to 5). The severity of mitral regurgitation at baseline and at 1-year follow-up is shown in Figure 2.

Data on the change in the 6-minute walk distance from baseline to 1 year were available for 90 patients; the median change in distance was 31 m (interquartile range, −56 to 85) in the intervention group and 32 m (interquartile range, −51 to 80) in the surgery group. The linear regression model adjusted for site and 6-minute walk distance at baseline yielded a regression coefficient of 5.22 (95% CI, −42.39 to 52.82), with the surgery group as the reference group ($R^2$=0.318). This confidence interval remains above −50 m, thereby meeting the criterion for noninferiority. Multiple imputation of missing values confirmed the results of the change in 6-minute walk distance, with a regression coefficient of 6.97 (95% CI, −29.81 to 43.75). At baseline, 84 patients (82.4%) in the intervention group and 90 patients (89.1%) in the surgery group had New York Heart Association functional class III or IV heart failure; at 1 year, 17 patients (23.3%) and 12 patients (18.2%), respectively, had New York Heart Association functional class III or IV heart failure (Fig. 2). The median change in the Minnesota Living with Heart Failure Questionnaire (range of scores, 0 to 105, with higher scores indicating a lower quality of life) at 1 year was −10 (interquartile range, −20 to 0) in the intervention group and −5 (interquartile range, −19 to 4) in the surgical group (Table 2). The median length of stay in the hospital and the median length of stay in the intensive care unit are shown in Table 2. Data on echocardiographic variables of atrial and ventricular reverse remodeling are shown in Table S1.

#### SAFETY AND ADVERSE EVENTS

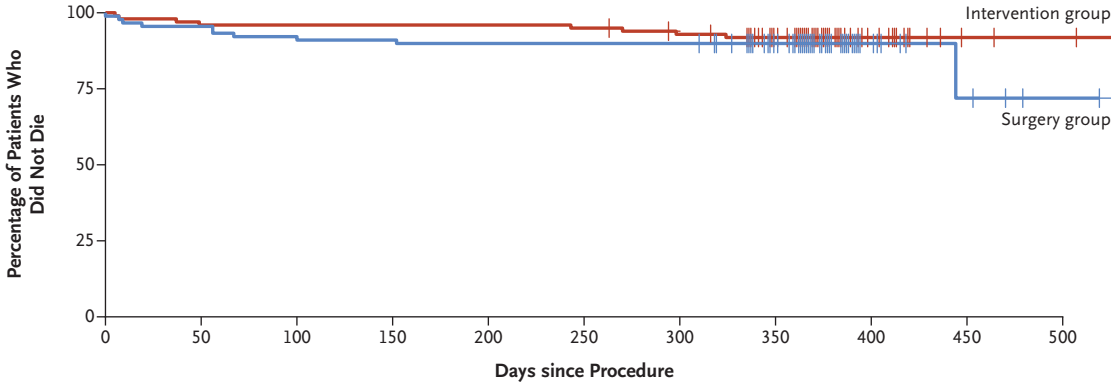
The secondary safety end point, which was a composite of major adverse events within 365 (±30) days after the procedure, occurred in 35 of the 96 patients with available data (36.5%) in the intervention group and in 70 patients of the 93 with available data (75.3%) in the surgery group (estimated mean difference, −39 percentage points; 95% CI, −51 to −25) (Table 2 and Table S4). In the intervention group, intraprocedural partial detachment of the clip occurred in 1 patient and chordae rupture in 2 patients. One patient underwent immediate valve-replacement surgery, and a second patient underwent nonimmediate surgical-valve replacement before discharge. In the surgery group,

**A Primary End-Point Event**



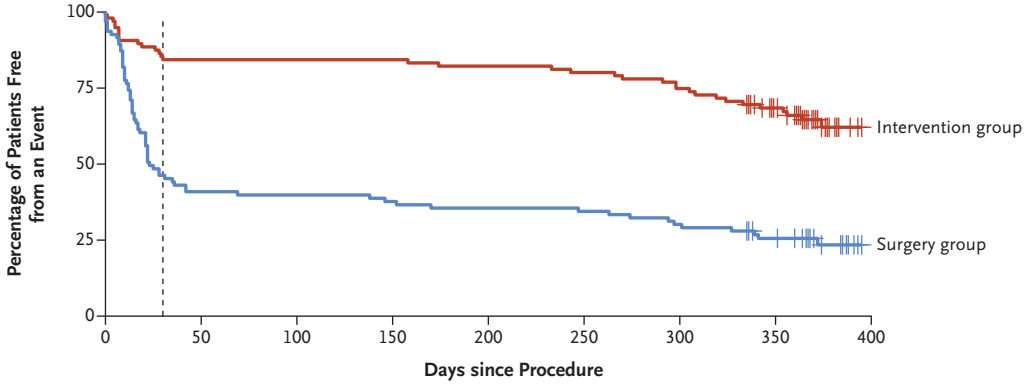

| No. at Risk (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Intervention group | 96 (100) | 88 (92) | 88 (92) | 88 (92) | 88 (92) | 87 (91) | 84 (88) | 71 (74) | 0 (0) |
| Surgery group | 89 (100) | 77 (87) | 74 (83) | 74 (83) | 73 (82) | 72 (81) | 71 (80) | 58 (65) | 0 (0) |

**B Death from Any Cause**




| No. at Risk (%) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Intervention group | 99 (100) | 95 (96) | 95 (96) | 95 (96) | 95 (96) | 94 (95) | 90 (91) | 77 (78) | 15 (15) | 3 (3) | 2 (2) |
| Surgery group | 89 (100) | 85 (96) | 82 (92) | 81 (91) | 80 (90) | 80 (90) | 80 (90) | 63 (71) | 10 (11) | 4 (4) | 1 (1) |

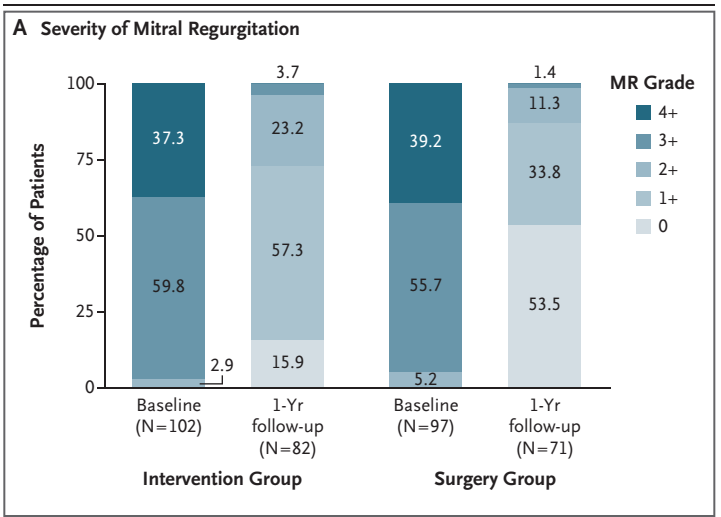
**C Major Adverse Event**




| No. at Risk (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Intervention group | 95 (100) | 80 (84) | 80 (84) | 80 (84) | 78 (82) | 76 (80) | 71 (75) | 57 (60) | 0 (0) |
| Surgery group | 93 (100) | 38 (41) | 37 (40) | 35 (38) | 33 (35) | 32 (34) | 28 (30) | 21 (23) | 0 (0) |

**Figure 1 (facing page). Freedom from Primary Efficacy and Safety End-Point Events and from Death.**

The primary end point was a composite of death from any cause, hospitalization for heart failure, mitral-valve reintervention, implantation of an assist device, or stroke within 1 year. The primary safety end point was a composite of major adverse events. Panel A shows the cumulative percentage of patients who were free from a primary end-point event among patients with secondary mitral regurgitation who underwent transcatheter edge-to-edge repair (intervention group) and among patients who underwent surgery (surgery group). Panel B shows the freedom from death from any cause in the two groups. Panel C shows the percentage of patients in the two groups who did not have a primary safety end-point event at 30 days after the procedure (dashed line) and over the entire trial period.



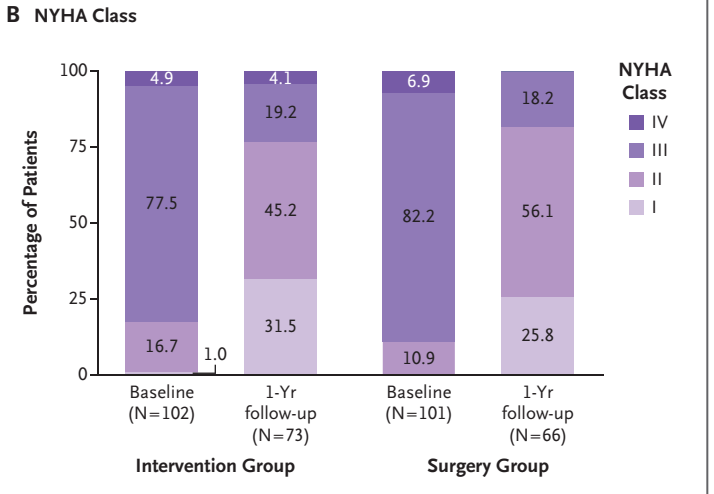




**Figure 2. Mitral Regurgitation Severity Grade and New York Heart Association Functional Class.**

Panel A shows the relative frequency of mitral regurgitation (MR) severity grades in patients undergoing transcatheter edge-to-edge repair (intervention group) and in patients undergoing surgery (surgery group) at baseline and at 1 year after the procedure. Grade 0 indicates no mitral regurgitation, grade 1+ mild mitral regurgitation, grade 2+ moderate mitral regurgitation, grade 3+ moderate-to-severe mitral regurgitation, and grade 4+ severe mitral regurgitation. Panel B shows the distribution of New York Heart Association (NYHA) functional class for patients in the intervention group and for those in the surgery group at baseline and at 1 year after the procedure. A higher class indicates more severe symptoms.

8 patients underwent reinterventions, two of which were mitral-valve replacements before discharge; three surgeries were related to thoracic bleeding and four to deep wound infection.

At 30 days, 2 of 101 patients with available data (2.0%) in the intervention group and 4 of 93 with available data (4.3%) in the surgery group had died. Rehospitalization for any cause occurred in 7 of 97 patients with available data (7.2%) in the intervention group and in 10 of 86 with available data (11.6%) in the surgery group. Major bleeding as defined by the Valve Academic Research Consortium (VARC) occurred in 3 of 97 patients with available data (3.1%) in the intervention group and in 22 of 90 patients with available data (24.4%) in the surgery group (estimated difference, –21 percentage points; 95% CI, –31 to –12) (Table 3). New-onset atrial fibrillation occurred in 3 of 97 patients with available data (3.1%) in the intervention group and in 25 of 90 patients with available data (27.8%) in the surgery group (estimated difference, –25 percentage points; 95% CI, –35 to –15). Stroke occurred in no patients in the intervention group and in 4 of 90 patients with available data (4.4%) in the surgery group. The percentages of patients who underwent nonelective cardiovascular surgical interventions and who received mechanical ventilation for more than 48 hours are also shown in Table 3.

Overall, among 197 patients in the safety-analysis population (100 in the intervention group and 97 in the surgery group), 303 adverse events occurred in 116 patients; 41 patients (41.0%) in the intervention group and 75 patients (77.3%) in the surgery group had at least one adverse event (Table S5). Serious adverse events occurred in 35 patients (35.0%) in the intervention group and in 64 patients (66.0%) in the surgery group (Table S6).

**Table 3. Adverse Events at 30 Days.***

| Event | Intervention Group | Surgery Group | Difference (95% CI)† |
|---|---|---|---|
| | *no./total no. (%)* | | *percentage points* |
| Death from any cause | 2/101 (2.0) | 4/93 (4.3) | –2 (–9 to 3) |
| Cardiovascular death | 1/101 (1.0) | 3/93 (3.2) | –2 (–8 to 3) |
| Noncardiovascular death | 1/101 (1.0) | 1/93 (1.1) | –0.1 (–5 to 4) |
| Rehospitalizations for any cause | 7/97 (7.2) | 10/86 (11.6) | –4 (–14 to 4) |
| Cardiovascular rehospitalization | 1/97 (1.0) | 5/86 (5.8) | –5 (–12 to 1) |
| Rehospitalization because of congestive heart failure | 1/97 (1.0) | 3/86 (3.5) | –3 (–9 to 3) |
| Reintervention | 5/100 (5.0) | 10/91 (11.0) | –6 (–15 to 2) |
| Major bleeding as defined by VARC | 3/97 (3.1) | 22/90 (24.4) | –21 (–31 to –12) |
| Stroke | 0/97 (0.0) | 4/90 (4.4) | –4 (–11 to 0.2) |
| Nonelective cardiovascular surgery | 1/98 (1.0) | 5/91 (5.5) | –5 (–11 to 1) |
| Mechanical ventilation >48 h | 4/99 (4.0) | 10/92 (10.9) | –7 (–15 to 0.8) |
| New-onset atrial fibrillation | 3/97 (3.1) | 25/90 (27.8) | –25 (–35 to –15) |

* VARC denotes Valve Academic Research Consortium.
† The difference is calculated as the percentage in the intervention group minus the percentage in the surgery group. The 95% confidence intervals, which are calculated with Newcombe's method 10, should not be used to reject or not reject the null hypothesis of a treatment effect.

## DISCUSSION

The multicenter, investigator-initiated, randomized, controlled MATTERHORN trial showed that among patients with heart failure and secondary mitral regurgitation who were at high surgical risk, transcatheter edge-to-edge repair was noninferior to surgical mitral-valve repair or replacement with respect to the primary end point, which was a composite of death, hospitalization for heart failure, reintervention, implantation of an assist device, or stroke at 1 year after the procedure. Multiple prospective registries, single-group studies, and randomized, controlled trials have documented the benefit of mitral-valve repair and replacement for reducing symptoms in patients with secondary mitral regurgitation.[2,5,16] The current trial reinforces this tenet; the median Minnesota Living with Heart Failure Questionnaire score and the New York Heart Association functional class appeared to improve during follow-up. Whether the reduction in symptoms occurred more rapidly in patients assigned to transcatheter edge-to-edge repair than in those assigned to surgery, as seen in other trials,[17,18] was not assessed in MATTERHORN; however, the median length of stay in the intensive care unit and the median length of overall hospital stay were shorter in the intervention group. The intervention group had a 60% lower relative risk of a primary safety end-point event than the surgery group at 30 days, and this decreased risk was sustained throughout the first year of follow-up. This difference was driven mainly by lower percentages of patients in the intervention group than in the surgery group who had major bleeding as defined by VARC and who had new-onset atrial fibrillation.

When we compared the efficacy of the two therapies throughout the first year after the procedure, both procedures appeared to be highly effective. A total of 98.6% of patients in the surgery group had mitral regurgitation of grade 2+ or lower at 1 year of follow-up, which is better than that anticipated on the basis of previously published results for this patient population, in which recurrence of mitral regurgitation of grade 3+ and 4+ at 1 year of follow-up occurred

in 30% or more of the patients.[2] This difference may reflect the low threshold for mitral-valve replacement rather than enforcement of surgical mitral-valve repair in our trial, the technical advances in surgical mitral-valve repair strategies, and the less-advanced left ventricular disease in our trial cohort. A total of 96% of patients in the intervention group had mitral regurgitation of grade 2+ or lower (73% had grade 1+ or lower) at 1 year (Fig. 2). Our results appear to be similar to those from the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation)[7] trial and from contemporary registries with outcome data from patients treated with the newest-generation devices.[19]

Our trial has some important limitations. We enrolled a relatively low-risk group of patients, as evidenced by the lower frequency of overall primary end-point events in our trial than in trials that randomly assigned patients to transcatheter edge-to-edge therapy or medical therapy or trials evaluating surgery for secondary mitral regurgitation that included patients with secondary mitral regurgitation. The participating centers were selected on the basis of their level of experience with both transcatheter edge-to-edge repair procedures and mitral-valve surgeries, and results may not be generalizable to all centers. Masking of the group assignments from patients and investigators was not possible because of the nature of the procedures. However, to minimize bias, standardized echocardiographic protocols were used in the trial, and evaluations were performed at a central echocardiographic core laboratory. In addition, patients were enrolled in the trial over a period of more than 7 years; the latest iterations of the MitraClip and the latest operative advances in surgical repair were not available to the entire cohort. Pharmacotherapies for systolic heart failure were not administered as vigorously as in recent trials, even if that less than half the trial population had a left ventricular ejection fraction below 40%. A total of 18 patients died before the 1-year outcome assessments. In our analyses, we imputed values for these patients, which could have affected the results.

Among patients with heart failure and secondary mitral regurgitation who were suitable candidates for isolated mitral-valve surgery according to current practice, transcatheter edge-to-edge repair was noninferior to surgery with respect to a composite of death, hospitalization for heart failure, reintervention, implantation of an assist device, or stroke at 1 year after the procedure.

Supported by an unrestricted research grant from Abbott Vascular.

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.

We thank personnel, in particular Claudia Michalik, at the Clinical Trials Center Cologne, University of Cologne, for their management and monitoring of the project.

## APPENDIX

The authors' affiliations are as follows: the Department of Internal Medicine III (S.B., R.P.), the Institute of Medical Statistics and Computational Biology (W.M., J.F., M.H.), and Cardiothoracic Surgery (T. Wahlers), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, the Department of Cardiothoracic Surgery (T.D.) and Cardiology (P.C.S.), Jena University Hospital, Friedrich-Schiller-University of Jena, Jena, Thoracic and Cardiovascular Surgery (J.G.) and General and Interventional Cardiology/Angiology (V.R.), Heart and Diabetes Center NRW, University Hospital of the Ruhr-University Bochum, Medical Faculty OWL, Bad Oeynhausen, the Department of Cardiology, Ulm University Heart Center, Ulm (M. Kessler, W.R.), the Faculty of Health, School of Medicine (P.B.), and Helios Klinikum Krefeld (A.B.), University Witten/Herdecke, Witten, Marienkrankenhaus (E.L.), the Department of Cardiology, University Hospital Eppendorf (E.L.), and the Department of Cardiothoracic Surgery, University Heart and Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf (H.R.), Hamburg, the Department of Internal Medicine I, University Hospital Aachen, RWTH Aachen University, Aachen (J.S.), Cardiac Surgery (T.N.), Heart Center Leipzig at Leipzig University (H.T.), and Leipzig Heart Science (H.T.), Leipzig, the Department of Cardiovascular Surgery, University Hospital Frankfurt and Goethe University Frankfurt, Frankfurt (T. Walther), University Hospital Düsseldorf and CARID (Cardiovascular Research Institute Düsseldorf), Düsseldorf (M. Kelm), Medical Clinic and Polyclinic I (J.H.) and the Department of Cardiac Surgery (C.H.), Ludwig Maximilian University Munich, Munich, Medical Clinic II, University Heart Center Lübeck, and the German Center for Cardiovascular Research (DZHK), Lübeck (I.E.), the Department of Cardiology, Kerckhoff Heart Center, Bad Nauheim (U.F.-R.), Otto-von-Guericke-University Magdeburg, Magdeburg (A.S.), the Department of Cardiology, University Medical Center Rostock, Rostock (H.I.), the Department of Cardiology, University Medical Center Mainz (P.L., R.S.B.), and the German Center for Cardiovascular Research (DZHK) partner site Rhine Main (P.L.), Mainz, St. Franziskus Hospital, Münster (S.R.), and the Department of Cardiology, Helios Klinikum Siegburg, Siegburg (H.B.) — all in Germany.

## REFERENCES


1. Coats AJS, Anker SD, Baumbach A, et al. The management of secondary mitral regurgitation in patients with heart failure: a joint position statement from the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC. Eur Heart J 2021; 42:1254-69.
2. 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.
3. Acker MA, Jessup M, Bolling SF, et al. Mitral valve repair in heart failure: five-year follow-up from the mitral valve replacement stratum of the Acorn randomized trial. J Thorac Cardiovasc Surg 2011; 142(3):569-574, 574.e1.
4. Shah AS, Hannish SA, Milano CA, Glower DD. Isolated mitral valve repair in patients with depressed left ventricular function. Ann Thorac Surg 2005;80: 1309-14.
5. von Bardeleben RS, Mahoney P, Morse MA, et al. 1-Year outcomes with fourth-generation mitral valve transcatheter edge-to-edge repair from the EXPAND G4 study. JACC Cardiovasc Interv 2023;16:2600-10.
6. Rudolph V, von Bardeleben RS, Friede T, et al. Contemporary safety outcomes of mitral edge-to-edge repair in Germany. JACC Cardiovasc Interv 2023;16:2939-41.
7. 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.
8. von Bardeleben RS, Rogers JH, Mahoney P, et al. Real-world outcomes of fourth-generation mitral transcatheter repair: 30-day results from EXPAND G4. JACC Cardiovasc Interv 2023;16:1463-73.
9. Cox ZL, Zalawadiya SK, Simonato M, et al. Guideline-directed medical therapy tolerability in patients with heart failure and mitral regurgitation: the COAPT trial. JACC Heart Fail 2023;11:791-805.
10. Popolo Rubbio A, Testa L, Grasso C, et al. Transcatheter edge-to-edge mitral valve repair in atrial functional mitral regurgitation: insights from the multi-center MITRA-TUNE registry. Int J Cardiol 2022; 349:39-45.
11. Webb JG, Hensey M, Szerlip M, et al. 1-Year outcomes for transcatheter repair in patients with mitral regurgitation from the CLASP study. JACC Cardiovasc Interv 2020;13:2344-57.
12. Kang D-H, Park S-J, Shin S-H, et al. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. Circulation 2019;139:1354-65.
13. Milwidsky A, Mathai SV, Topilsky Y, Jorde UP. Medical therapy for functional mitral regurgitation. Circ Heart Fail 2022; 15(9):e009689.
14. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2022;43:561-632.
15. 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. Circulation 2021; 143(5):e72-e227.
16. Szerlip M, Spargias KS, Makkar R, et al. 2-Year outcomes for transcatheter repair in patients with mitral regurgitation from the CLASP study. JACC Cardiovasc Interv 2021;14:1538-48.
17. Blankenberg S, Seiffert M, Vonthein R, et al. Transcatheter or surgical treatment of aortic-valve stenosis. N Engl J Med 2024;390:1572-83.
18. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695-705.
19. Kar S, von Bardeleben RS, Rottbauer W, et al. Contemporary outcomes following transcatheter edge-to-edge repair: 1-year results from the EXPAND Study. JACC Cardiovasc Interv 2023;16:589-602.