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Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation

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ABSTRACT

BACKGROUND

In patients who have chronic heart failure with reduced left ventricular ejection fraction, severe secondary mitral-valve regurgitation is associated with a poor prognosis. Whether percutaneous mitral-valve repair improves clinical outcomes in this patient population is unknown.

METHODS

We randomly assigned patients who had severe secondary mitral regurgitation (defined as an effective regurgitant orifice area of >20 mm^2 or a regurgitant volume of >30 ml per beat), a left ventricular ejection fraction between 15 and 40%, and symptomatic heart failure, in a 1:1 ratio, to undergo percutaneous mitral-valve repair in addition to receiving medical therapy (intervention group; 152 patients) or to receive medical therapy alone (control group; 152 patients). The primary efficacy outcome was a composite of death from any cause or unplanned hospitalization for heart failure at 12 months.

RESULTS

At 12 months, the rate of the primary outcome was 54.6% (83 of 152 patients) in the intervention group and 51.3% (78 of 152 patients) in the control group (odds ratio, 1.16; 95% confidence interval [CI], 0.73 to 1.84; P=0.53). The rate of death from any cause was 24.3% (37 of 152 patients) in the intervention group and 22.4% (34 of 152 patients) in the control group (hazard ratio, 1.11; 95% CI, 0.69 to 1.77). The rate of unplanned hospitalization for heart failure was 48.7% (74 of 152 patients) in the intervention group and 47.4% (72 of 152 patients) in the control group (hazard ratio, 1.13; 95% CI, 0.81 to 1.56).

CONCLUSIONS

Among patients with severe secondary mitral regurgitation, the rate of death or unplanned hospitalization for heart failure at 1 year did not differ significantly between patients who underwent percutaneous mitral-valve repair in addition to receiving medical therapy and those who received medical therapy alone. (Funded by the French Ministry of Health and Research National Program and Abbott Vascular; MITRA-FR ClinicalTrials.gov number, NCT01920698.)

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*A list of investigators in the MITRA-FR trial is provided in the Supplementary Appendix, available at NEJM.org.

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In patients with secondary mitral regurgitation, previously referred to as functional mitral regurgitation, the mitral-valve leaflets and chordae are structurally normal, and mitral regurgitation results from alterations in left ventricular geometry and function. Severe secondary mitral regurgitation is a predictor of poor clinical outcomes in patients with heart failure and reduced left ventricular ejection fraction.[1-4] However, whether mitral regurgitation in this patient population is merely the consequence of left ventricular dysfunction and dilation and a marker of severity or whether it contributes to a poor prognosis remains unclear.[2,4-7]

Prospective registry studies suggest that percutaneous mitral-valve repair can reduce symptoms and improve functional capacity and quality of life in patients with secondary mitral regurgitation.[8-12] However, a beneficial effect on hard clinical outcomes when percutaneous mitral-valve repair is added to medical treatment has not been proved. American and European guidelines are in agreement that there is a low level of evidence to support procedures (surgical or percutaneous) to correct mitral regurgitation in patients with secondary mitral regurgitation, and they recommend that multicenter, randomized clinical trials be conducted in this patient population.[13-15] We designed the randomized MITRA-FR trial (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) to evaluate the clinical efficacy and safety of percutaneous mitral-valve repair in addition to medical treatment in patients with heart failure and severe secondary mitral regurgitation.

Methods

Trial Design and Oversight

MITRA-FR was a multicenter, randomized, open-label, controlled phase 3 trial that was conducted in France. The trial was approved by a central ethics committee and the French National Agency for Medicines and Health Products Safety and was conducted in accordance with the provisions of the Declaration of Helsinki.

Hospices Civils de Lyon, a public academic institution, assumed overall responsibility for the trial. A steering committee designed the trial protocol (available with the full text of this article at NEJM.org), and an independent data and safety monitoring board oversaw the safety of the trial. The Clinical Investigation Center of Lyon, an academic research organization within Hospices Civils de Lyon (INSERM 1407), conducted and coordinated the trial and also collected the trial data. All the analyses were performed by the statistical department at Hospices Civils de Lyon. The first and last authors wrote the first draft of the manuscript. The steering committee reviewed the manuscript and made the decision to submit it for publication. The authors vouch for the completeness and accuracy of the data and the analyses and for the fidelity of the trial to the protocol.

Primary funding was provided by the French Ministry of Health and Research National Program. Abbott Vascular, the manufacturer of the trial device, provided the devices as well as support for investigators' meetings; they also proctored the procedures for implantation of the device. Details of the role of Abbott Vascular in the trial are provided in the Supplementary Appendix, available at NEJM.org. Neither Abbott Vascular nor any other commercial entity had a role in the design of the trial; the selection of participating trial centers; the monitoring or oversight of the centers; the enrollment or care of the patients; the collection, storage, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

Patients and Randomization

From December 2013 through March 2017, we recruited patients at 37 trial centers in France. Centers were required to have experience with percutaneous interventions and were to have performed at least five implantation procedures of the trial device before being selected as a trial site.

Eligible patients had severe secondary mitral regurgitation with a regurgitant volume of greater than 30 ml per beat or an effective regurgitant orifice area of greater than 20 mm^2 as assessed by echocardiography, in accordance with the 2012 guidelines of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery.[14,16] Patients were also required to have a left ventricular ejection fraction between 15% and 40% and to have chronic heart failure symptoms (assessed as New York Heart Association [NYHA] functional class II, III, or IV).

Patients were excluded if they were considered to be candidates for mitral-valve surgery, as determined by local multidisciplinary teams of

specialists who reviewed each patient (additional details are provided in the Supplementary Appendix). Before randomization, all the patients underwent a prospective screening protocol that included one transthoracic echocardiogram and one transesophageal echocardiogram. All the echocardiograms were reviewed at an independent central laboratory in accordance with European Association of Echocardiography guidelines.[17,18] Patients were excluded if they did not meet core laboratory criteria (as described in the Supplementary Appendix, which also includes a complete list of the trial inclusion and exclusion criteria).

Written informed consent was obtained from all the patients before the initiation of trial procedures. Patients were then randomly assigned, in a 1:1 ratio, to either percutaneous mitral-valve repair plus medical therapy or medical therapy alone. Randomization was performed in permuted blocks, with stratification according to trial center. All eligible patients received medical treatment for chronic heart failure with reduced left ventricular ejection fraction according to the European guidelines that were current at the time of the trial.[13,19]

PERCUTANEOUS-REPAIR PROCEDURE

The device used in this trial was the MitraClip (Abbott Vascular). This device received the European Certificate of Conformity (known as the CE mark) in March 2008. The implantation procedure has been reported previously[7,18] and is described in the Supplementary Appendix. The procedure had to be performed within 21 days after a patient was randomly assigned to the intervention group. All implantation procedures were performed with proctoring from Abbott Vascular. Technical success with respect to device implantation was defined according to the consensus document from the Mitral Valve Academic Research Consortium[20] (additional details are provided in the Supplementary Appendix).

OUTCOMES

The primary efficacy outcome was a composite of death from any cause or unplanned hospitalization for heart failure at 12 months after randomization.[18] The prespecified secondary outcomes were individual components of the primary outcome at 12 months, death from cardiovascular causes, and survival free from major adverse cardiovascular events (a composite of death, stroke, myocardial infarction, or unplanned hospitalization for heart failure). Prespecified serious adverse events included ischemic or hemorrhagic stroke, myocardial infarction, the need for renal-replacement therapy, periprocedural complications, and bleeding events at 1 year after randomization. An independent events validation committee, whose members were unaware of the treatment assignments, adjudicated all the clinical outcomes.

Additional prespecified secondary outcomes included the change in left ventricular ejection fraction and in the end-diastolic and end-systolic diameters and volumes of the left ventricle; the severity of mitral regurgitation (semiquantitative grade of 0+ [none or trace], 1+ [mild], 2+ [mild to moderate], 3+ [moderate to severe], or 4+ [severe]; regurgitant volume; and effective regurgitant orifice area); NYHA heart failure class; walking distance in the 6-minute walk test; brain natriuretic peptide levels; and quality-of-life scores on the European Quality of Life 5–Dimensions scale[21] at 12 months. Definitions of all the trial outcomes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The rate of death or unplanned hospitalization for heart failure at 12 months in patients with severe secondary mitral regurgitation has been reported to be as high as 50%.[10] In addition, data from the Pilot European Sentinel Registry involving patients with severe secondary mitral regurgitation who underwent percutaneous mitral-valve repair indicated that the rate of death or unplanned hospitalization for heart failure at 12 months was approximately 33%.[12] We calculated that 144 patients would need to be enrolled in each trial group to provide 80% power to show a rate of the primary outcome that was 17 percentage points lower in the intervention group than in the control group (50% vs. 33%), using a chi-square test at a two-sided alpha level of 0.05 and assuming a 10% rate of loss to follow-up.[18]

All the analyses were performed according to the intention-to-treat principle. For the primary efficacy analysis, an unconditional logistic-regression model was fitted to estimate the odds ratio associated with the treatment effect, with adjustment for the randomization stratification factor (trial center). The two-sided 95% Wald confidence interval of the treatment effect was computed. The between-group difference was tested with the use of the Wald chi-square test. Kaplan–Meier sur-

vival curves were constructed for each group and were compared with the use of the log-rank test.

Prespecified subgroup analyses of the primary outcome were performed in the intention-to-treat population to test for an interaction between trial group and the subgroup variable. A per-protocol analysis of the primary outcome was also performed. This analysis excluded all patients who had a protocol deviation and all patients in the intervention group in whom the device was not implanted; the analysis also excluded all events that occurred during the first 21 days after randomization.

A two-sided P value of less than 0.05 was considered to indicate statistical significance. P values for the secondary outcomes are not reported because no adjustment was made for multiplicity. Because a substantial amount of data on echocardiography, functional status, and quality of life were missing at 12 months, the results for these variables are reported only descriptively. All the statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

PATIENTS

A total of 452 patients provided written informed consent and underwent the screening protocol; 145 patients were excluded during the screening process (Fig. 1, and Table S1 in the Supplementary Appendix). Thus, 307 patients with secondary mitral regurgitation underwent randomization: 152 patients were randomly assigned to undergo percutaneous mitral-valve repair in addition to receiving medical therapy (intervention group), and 155 to receive medical therapy alone (control group). Three patients were excluded from the control group after randomization owing to issues with informed consent, which resulted in the inclusion of 152 patients in the control group. The demographic and clinical characteristics of the two groups were similar at baseline, with the exception of a history of myocardial infarction, which was more common in the intervention group (Table 1). Medical therapy at baseline was also similar in the two groups (Table S2 in the Supplementary Appendix).

PROCEDURAL RESULTS

The percutaneous mitral-valve repair procedure was performed a median of 14 days (interquartile range, 9 to 18) after randomization. Among the 152 patients in the intervention group, 14 (9.2%) had no study device implanted: implantation was not attempted in 8 patients, and the device implantation failed in 6 patients (details are provided in Table S3 in the Supplementary Appendix). Thus, implantation was attempted in 144 patients, and technical success with device implantation was achieved in 138 of these patients (95.8%). Among these 138 patients, 63 (45.7%) had one device implanted, 62 (44.9%) had two devices implanted, and 13 (9.4%) had three or more devices implanted. A total of 21 of the 144 patients (14.6%) in whom implantation was attempted had periprocedural complications (Table 2).

At the time of discharge from the hospital, assessments of the severity of mitral regurgitation were available for 123 patients in the intervention group. Of these patients, 117 (95.1%) had a reduction in mitral regurgitation of at least one grade; 113 patients (91.9%) had reduction of mitral regurgitation to 2+ (mild to moderate) or lower, and 93 patients (75.6%) had reduction to 0+ (none or trace) to 1+ (mild) (Fig. S1 in the Supplementary Appendix).

EFFICACY OUTCOMES AND ADVERSE EVENTS

In the intention-to-treat analysis, the composite primary outcome of death from any cause or unplanned hospitalization for heart failure at 12 months occurred in 83 patients (54.6%) in the intervention group and in 78 patients (51.3%) in the control group (odds ratio, 1.16; 95% confidence interval [CI], 0.73 to 1.84; P=0.53) (Table 3 and Fig. 2). At 12 months, a total of 37 deaths (24.3%) had occurred in the intervention group and 34 (22.4%) in the control group (hazard ratio in the intervention group, 1.11; 95% CI, 0.69 to 1.77). A total of 74 patients (48.7%) in the intervention group had an unplanned hospitalization for heart failure, as compared with 72 patients (47.4%) in the control group (hazard ratio, 1.13; 95% CI, 0.81 to 1.56) (Fig. S2 in the Supplementary Appendix). All the other major cardiovascular events that occurred are summarized in Table 3. The results of the per-protocol analysis were consistent with those of the intention-to-treat analysis (Table S4 in the Supplementary Appendix). The mortality rate at 30 days was 3.3% (5 patients) in the intervention group and 2.6% (4 patients) in the control group.

The incidence of prespecified serious adverse events is presented in Table 2. The rates of

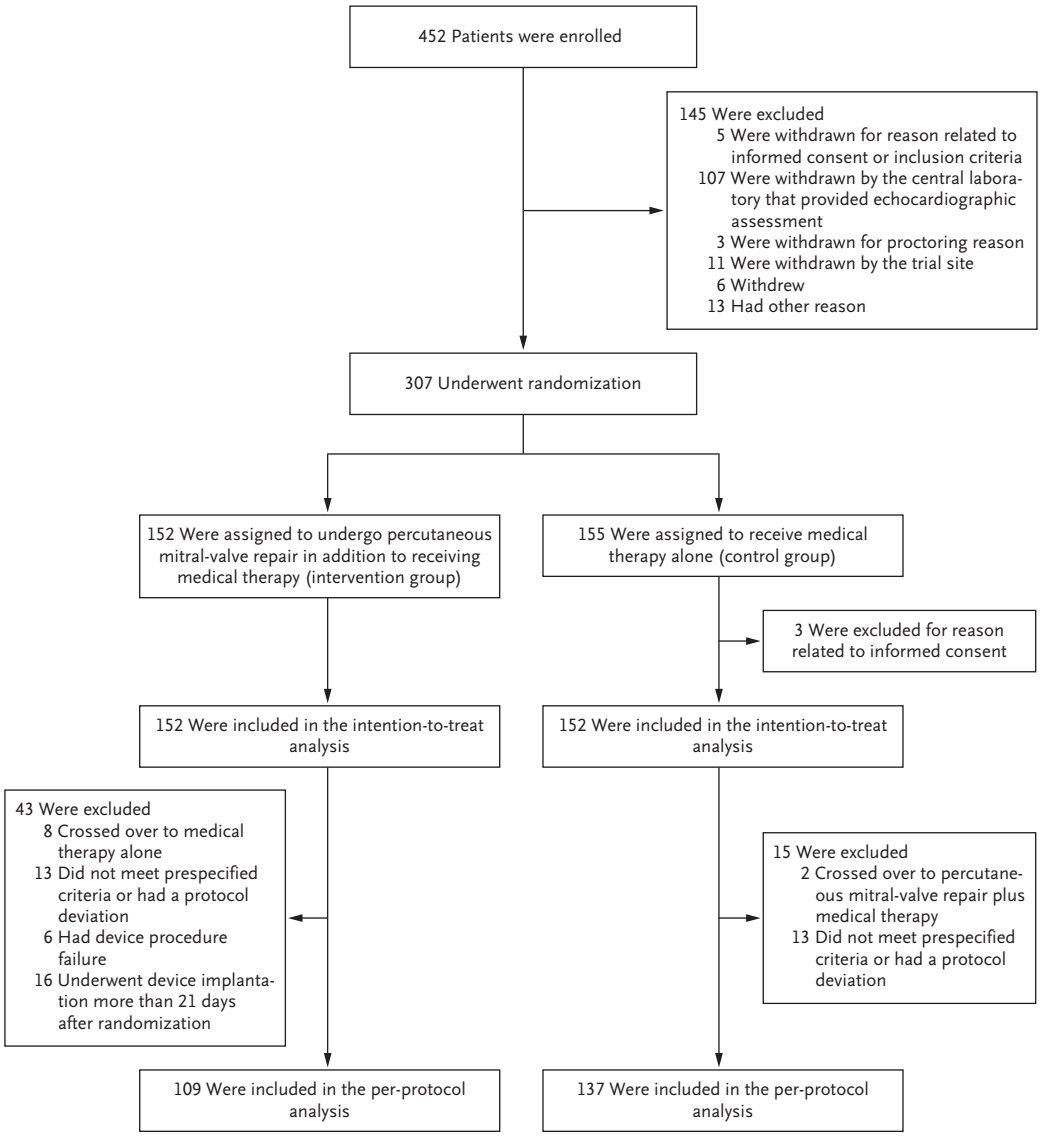

Figure 1. Enrollment, Randomization, and Follow-up.

Additional details regarding the reasons for patient exclusion from the trial before randomization are provided in Table S1 in the Supplementary Appendix. Of the 3 patients excluded after randomization for reasons related to informed consent, 1 withdrew from the trial and specifically asked for his data to be deleted; 1 was under legal protection (which was not known to the investigator) and the legal representative did not sign the consent form; and 1 signed the consent form but did not provide his name or date of signature and the consent form was therefore classified as invalid by the trial sponsor. Of the 13 patients in the control group who were excluded from the per-protocol analysis because they did not meet prespecified criteria or had a protocol deviation, 11 had not had a minimum of one hospitalization for heart failure within 12 months before randomization, 1 had undergone coronary angioplasty within 1 month before randomization, and 1 had received renal-replacement therapy. Of the 13 patients in the intervention group who were excluded from the per-protocol analysis because they did not meet prespecified criteria or had a protocol deviation, 12 had not had a minimum of one hospitalization for heart failure within 12 months before randomization and 1 had initiated cardiac resynchronization therapy within 3 months before randomization.

ischemic or hemorrhagic stroke, renal-replacement therapy, and severe hemorrhage were higher in the intervention group than in the control group. A full list of serious adverse events is provided in Table S5 in the Supplementary Appendix.

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

Characteristic	Intervention Group (N=152)	Control Group (N=152)
Age — yr	70.1±10.1	70.6±9.9
Age >75 yr — no. (%)	51 (33.6)	59 (38.8)
Male sex — no. (%)	120 (78.9)	107 (70.4)
Medical and surgical history – no./total no. (%)		
Ischemic cardiomyopathy	95/152 (62.5)	85/151 (56.3)
Nonischemic cardiomyopathy	57/152 (37.5)	66/151 (43.7)
Previous myocardial infarction	75/152 (49.3)	52/152 (34.2)
Previous coronary revascularization	71/152 (46.7)	64/151 (42.4)
Atrial fibrillation	49/142 (34.5)	48/147 (32.7)
Diabetes	50/152 (32.9)	39/152 (25.7)
Renal insufficiency	22/152 (14.5)	19/152 (12.5)
NYHA class — no. (%)		
II	56 (36.8)	44 (28.9)
III	82 (53.9)	96 (63.2)
IV	14 (9.2)	12 (7.9)
Systolic blood pressure — mm Hg	109±16	108±18
Heart rate — beats/min	73±13	72±13
Median EuroSCORE II (IQR)†	6.6 (3.5–11.9)	5.9 (3.4–10.4)
Left ventricular ejection fraction — %	33.3±6.5	32.9±6.7
Left ventricular end-diastolic volume — ml/m^2	136.2±37.4	134.5±33.1
Effective regurgitant orifice area — mm^2	31±10	31±11
Regurgitant volume — ml	45±13	45±14
Median NT-proBNP (IQR) — ng/liter‡	3407 (1948–6790)	3292 (1937–6343)
Median brain natriuretic peptide (IQR) — ng/liter‡	765 (417–1281)	835 (496–1258)
Glomerular filtration rate — ml/min	48.8±19.7	50.2±20.1

* Plus–minus values are means ±SD. There were no significant differences between the two groups in the characteristics listed, with the exception of previous myocardial infarction (P=0.01). IQR denotes interquartile range, and NYHA New York Heart Association.

† Scores on the European System for Cardiac Operative Risk Evaluation (EuroSCORE II) are calculated by means of a logistic-regression equation and range from 0 to 100%, with higher scores indicating greater risk. The EuroSCORE interactive calculator can be found at www.euroscore.org/calc.html.

‡ N-terminal pro–brain natriuretic peptide (NT-proBNP) was measured in 75 of the 152 patients in the intervention group and in 72 of the 152 patients in the control group, and brain natriuretic peptide was measured in 66 and 60 patients, respectively. All the measurements were obtained locally.

OTHER OUTCOMES

A large amount of follow-up data on echocardiographic outcomes, functional status, natriuretic peptide levels, and quality-of-life outcomes at 1 year were missing. As a consequence, the results are subject to substantial selection bias, and no formal statistical analyses are reported. However, at least 48 patients in the intervention group in whom technical success of device implantation was achieved were confirmed to have mitral regurgitation of grade 2+ or higher at 1 year. The results, which are based on the available data, are provided in Table S6 and Figure S3 in the Supplementary Appendix. Fewer data were missing for NYHA class, and an analysis with imputed results for missing data was performed; these results are shown in Figure S4 in the Supplementary Appendix.

Table 2. Periprocedural Complications and Prespecified Serious Adverse Events (Intention-to-Treat Population).*

Variable	Intervention Group (N=152)	Control Group (N=152)
Periprocedural complications during device implantation — no./total no. (%)†	21/144 (14.6)	NA
Device-implantation failure	6/144 (4.2)‡	NA
Hemorrhage resulting in transfusion or vascular complication resulting in surgical intervention	5/144 (3.5)	NA
Atrial septum lesion or atrial septal defect	4/144 (2.8)	NA
Cardiogenic shock resulting in intravenous inotropic support	4/144 (2.8)	NA
Cardiac embolism, including gas embolism and stroke	2/144 (1.4)	NA
Tamponade	2/144 (1.4)	NA
Urgent conversion to heart surgery	0	NA
Prespecified serious adverse events at 1 year — no. (%)		
All serious adverse events	125 (82.2)	121 (79.6)
Heart transplantation or mechanical cardiac assistance	6 (3.9)	9 (5.9)
Ischemic or hemorrhagic stroke§	7 (4.6)	1 (0.7)
Myocardial infarction	0	2 (1.3)
Need for renal-replacement therapy	5 (3.3)	1 (0.7)
Severe hemorrhage ¶	11 (7.2)	6 (3.9)
Infections	28 (18.4)	27 (17.8)

* No P values are reported because no adjustment was made for multiple testing. NA denotes not applicable.
† The denominator of 144 represents the number of patients in whom device implantation was attempted.
‡ Among the six patients, the trial device was not implanted in three patients owing to the inability of the operator to grasp the mitral-valve leaflets during implantation, two patients had cardiac tamponade that occurred during transseptal puncture, and one patient had cardiogenic shock during the procedure, which resulted in the procedure being aborted.
§ One patient in the intervention group had a hemorrhagic stroke; the remaining patients had an ischemic stroke.
¶ Severe hemorrhage was defined as bleeding that was categorized as type 2 or higher, according to the modified Bleeding Academic Research Consortium (BARC) bleeding scale,[20] which ranges from type 0 (no bleeding) to type 5b (definite fatal bleeding), with type 2 indicating any overt, actionable sign of bleeding.

SUBGROUP ANALYSIS

We assessed the consistency of the results of the primary outcome in 14 subgroups (Fig. S5 in the Supplementary Appendix). There were no significant interactions between trial group and any of the subgroups with respect to the rate of a primary outcome event at 12 months, with the exception of a possible interaction of treatment assignment with serum creatinine level at baseline.

DISCUSSION

The MITRA-FR trial showed that in patients with severe secondary mitral regurgitation, percutaneous mitral-valve repair plus medical treatment did not result in a lower rate of the composite outcome of death from any cause or unplanned hospitalization for heart failure at 12 months than medical treatment alone. This result was consistent across all the subgroups tested, with one possible exception; although a significant interaction with the subgroup defined according to baseline serum creatinine was detected, we believe that this is probably a chance finding.

The MitraClip device evaluated in this trial is increasingly used in many countries, mainly for secondary mitral regurgitation.[9,10,12,22] Previous reports have shown a benefit with percutaneous mitral-valve repair for correction of mitral regurgitation and improvement in functional status and have suggested significant improvements in hard clinical outcomes at 12 months.[10,23] However, these studies were not randomized, controlled trials. For this reason, there is no strong recommendation for percutaneous correction of secondary mitral regurgitation in the current guidelines.[14,15]

Our results regarding technical success in de-

Table 3. Primary Outcome and Secondary Efficacy Outcomes at 12 Months (Intention-to-Treat Population).

Outcome	Intervention Group (N=152)	Control Group (N=152)	Hazard Ratio or Odds Ratio (95% CI)*	P Value†
Composite primary outcome: death from any cause or unplanned hospitalization for heart failure at 12 months — no. (%)	83 (54.6)	78 (51.3)	1.16 (0.73–1.84)	0.53
Secondary outcomes‡				
Death from any cause	37 (24.3)	34 (22.4)	1.11 (0.69–1.77)	
Cardiovascular death	33 (21.7)	31 (20.4)	1.09 (0.67–1.78)	
Unplanned hospitalization for heart failure	74 (48.7)	72 (47.4)	1.13 (0.81–1.56)	
Major adverse cardiovascular events§	86 (56.6)	78 (51.3)	1.22 (0.89–1.66)	

* Hazard ratios were calculated with the use of stratified Cox proportional-hazards models. The primary outcome was calculated with the use of a logistic-regression model and corresponds to an odds ratio. The 95% confidence intervals were not corrected for multiple testing; therefore, these intervals should not be used to infer definitive treatment effects.
† No P values other than that for the primary outcome are reported because no adjustment was made for multiple testing.
‡ The rates of the components of the composite primary outcome do not total the rates of the composite because patients could have more than one event.
§ This category is a composite of death, stroke, myocardial infarction, or unplanned hospitalization for heart failure.

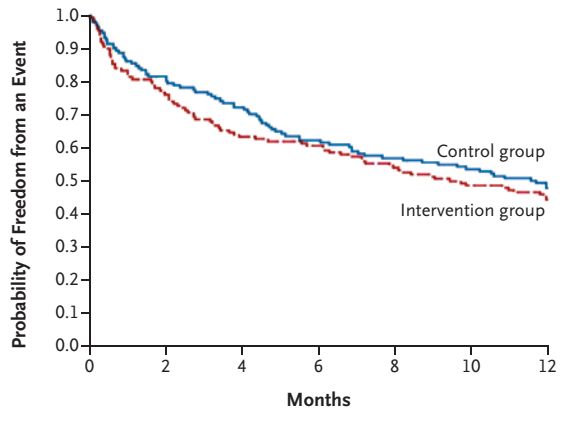

Figure 2. Kaplan–Meier Estimates of Survival without a Primary Outcome Event.
Shown are estimates of the probability of survival without a primary outcome event (death from any cause or unplanned hospitalization for heart failure) in the two trial groups (Kaplan–Meier estimates according to individual trial outcomes are provided in Fig. S2 in the Supplementary Appendix). The number of patients at risk in the intervention group at month 0 was 151 rather than 152 because 1 patient died before randomization, but trial personnel did not become aware of his death until after he was randomly assigned to the intervention group.

vice implantation are similar to those reported in registries,[9,11,22] with 76.4% of the patients in the intervention group having a mitral regurgitation grade of 0+ to 1+ at the time of hospital discharge. Unfortunately, substantial amounts of echocardiographic data were missing at 12 months, so we cannot confirm a durable result of percutaneous repair with respect to the reduction of mitral regurgitation at 1 year for many of the trial participants.

The lack of a clinical benefit of percutaneous mitral-valve repair on the primary outcome suggests that the underlying cardiomyopathy might be the principal driver of subsequent adverse clinical outcomes in patients with secondary mitral regurgitation. In this context, secondary mitral regurgitation may be merely a marker of illness severity and not a direct contributor to the pathophysiology of heart failure.

Another explanation for the lack of clinical benefit that we observed could be the fact that some of the patients who underwent percutaneous mitral-valve repair had incomplete correction of mitral regurgitation. Although echocardiographic data were missing for many of the patients, at least 48 patients in the intervention group had residual mitral regurgitation of grade 2+ or higher at 12 months. Residual mitral regurgitation has been significantly associated with poorer outcomes.[24]

The lack of clinical benefit in our trial might also be related to the severity of illness in our patient population. Given the high rate of the pri-

mary outcome, it is possible that percutaneous mitral-valve repair may have been performed too late in the course of the progression of heart failure. The potential benefit of percutaneous mitral-valve repair might be diminished in patients with more serious illness. However, in the prespecified subgroup analyses, the variables of age older than 75 years, NYHA class III or IV heart failure, and a left ventricular ejection fraction of less than 30% did not show any significant interaction with treatment.

The lack of benefit could also be explained by the good quality of the medical treatment in the control group; the baseline use of heart-failure drugs in the control group was very high, in concordance with the guidelines.[13,19] These heart failure drugs included the new class of angiotensin receptor–neprilysin inhibitor drugs that became available in France during the course of the trial.[25] We do not have systematic information about the rates of the use of individual classes of drugs during the course of the trial.

Our trial has several limitations. First, in 14 patients (9.2%) in the intervention group, either the procedure was not performed or the device implantation failed. However, in the per-protocol analysis in which the data from these patients were excluded, no significant difference in outcomes was seen between the two groups at 12 months. Second, the considerable amount of missing follow-up data for the assessments of echocardiography, functional status, natriuretic peptide, and quality of life is a limitation of the trial. However, a very low number of patients was lost to follow-up for the primary outcome, with 99% of the patients having complete data at 12 months. Third, the trial was powered to detect a substantial effect on the primary outcome (an event rate of 50% in the control group vs. 33% in the intervention group). Therefore, we did not have power to detect a smaller difference between the groups, although the point estimate for the primary outcome does not suggest a trend in favor of percutaneous mitral-valve repair.

In conclusion, in this multicenter, randomized, open-label, controlled trial involving patients with severe secondary mitral regurgitation, the rate of the composite primary outcome of death or unplanned hospitalization for heart failure at 12 months did not differ significantly between the intervention group and the control group.

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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.

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This article is dedicated to the memory of Larry Gotlieb for his help in the early phase of the trial.

APPENDIX

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