EDITORIAL

Mitral Regurgitation — What Is Best for My Patient?

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Mitral regurgitation is common, with 80% of us having some normal valve leakage detectable on echocardiography. Mild regurgitation is well tolerated and rarely leads to overt clinical disease. However, severe regurgitation overloads the left ventricle as blood is pumped both backward across the mitral valve and forward to the systemic circulation. Over time, volume overload results in ventricular dilatation and eventual contractile dysfunction. In addition, increased left atrial pressure leads to atrial fibrillation and pulmonary hypertension.[1] If untreated, these physiological changes lead to heart-failure symptoms and reduced survival. Both can be prevented by an intervention to eliminate mitral regurgitation at the onset of symptoms or before any irreversible changes in cardiac function occur.[2,3] Currently, our choices for intervention are surgical mitral-valve repair or replacement, with repair preferred whenever possible because it has a low operative mortality (about 2%), restores normal valve function, and provides excellent long-term outcomes.[4]

The anatomy of the mitral-valve apparatus is complex. Abnormal leaflet closure occurs with primary disease of the leaflets and chords (e.g., with mitral prolapse in degenerative disease) or may be functional because of altered geometry of the left ventricle, papillary muscles, or mitral annulus, as seen with dilated cardiomyopathy or coronary artery disease.[1] In patients with primary leaflet disease and severe regurgitation, adverse outcomes are directly due to the physiological effects of valve dysfunction. Thus, the key element in clinical care is periodic noninvasive monitoring of valve and ventricular function in patients at risk for adverse outcomes in order to ensure optimal surgical timing.

In contrast, adverse outcomes are largely determined by the underlying myocardial disease in patients with functional mitral regurgitation. Thus, clinical management focuses on treatment of the causal disease process, rather than on direct attempts to decrease regurgitant severity, particularly if treatment normalizes ventricular size, shape, and systolic function, allowing better alignment of the mitral-valve apparatus and more complete valve closure. For example, in patients with dilated cardiomyopathy, regurgitant severity often improves substantially with medical therapy or biventricular pacing.[5] Similarly, in patients with coronary artery disease, regurgitation may improve after revascularization.[6] A subgroup of patients with persistent severe functional mitral regurgitation may benefit from a reduction in regurgitant severity, although this approach remains controversial.[7]

In this issue of the *Journal*, Feldman and colleagues[8] report the results of a randomized, prospective trial of a percutaneously inserted mitral-valve clip for the treatment of severe regurgitation. The idea that valve regurgitation might be treated with a nonsurgical approach is exciting, particularly if the new procedure effectively reduces regurgitant severity with a low procedural risk. Ideally, any new procedure would also be at least equivalent to surgical valve repair in terms of safety, valve function, durability, and long-term outcomes.

The mitral-valve clip that was evaluated in this study fulfills some, but not all, of these criteria. As compared with mitral-valve surgery, the mitral clip was associated with a lower rate of complications at 30 days. However, it is disappointing that by 1 year after the procedure, 20% of patients in the percutaneous-treatment group required surgery for mitral-valve dysfunction, as compared with 2% of patients in the surgical group who required repeat surgery. It is of par-

ticular concern that substantial residual regurgitation (grade 2+ or more) was present in 46% of patients in the percutaneous-treatment group, as compared with 17% in the surgical group at 12 months. This modest reduction in regurgitant severity might be associated with favorable short-term and midterm outcomes, but surgical series suggest that residual mitral regurgitation predicts adverse long-term clinical outcomes. This issue is further confused by the inclusion of both patients with primary leaflet disease and those with functional regurgitation; these are different diseases with different clinical outcomes. Despite these concerns, the authors are to be commended for performing a rigorous clinical trial with objective measures of valve and ventricular function, as well as clinical outcomes.

Regardless of whether the mitral clip becomes part of our clinical toolkit, we will face some difficult challenges in clinical decision making as new minimally invasive devices become clinically available during the next few years. The traditional physician-directed approach to patient care has worked well up to now, when only limited treatment options were available. Currently, the cardiologist most often decides when surgical intervention is appropriate and sends the patient on to the cardiac surgeon. Although efficient, this approach breaks down as more options for intervention become available and the choices of watchful waiting, medical therapy, percutaneous intervention, and surgical valve repair or replacement all must be considered. This challenge is particularly acute because valve disease is relatively uncommon, as compared with diseases such as coronary disease or heart failure, so that our guidelines are based on less compelling data and individual physicians have less experience and are less knowledgeable about valve disease.

To ensure that we do what is best for each patient, we propose a patient-centered approach to decision making in adults with valvular heart disease. Instead of the traditional "consensus of one," we need a true consensus of experts with review of each case by a multidisciplinary panel that includes, at a minimum, a nonprocedural valve-disease specialist, an interventional cardiologist, and a cardiac surgeon. The panel's recommendation should be based on documentation of severe valve dysfunction and indications for intervention, a patient-specific procedural risk assessment,[9] expected anatomical and functional results, expected improvement in clinical symptoms and quality of life, potential medication changes (including anticoagulation), long-term outcome data on survival and repeat procedures, and preferences of the patient.

Surgical correction of severe valve dysfunction has provided dramatic improvements in clinical outcomes of adults with valvular heart disease during the past several decades. As we embrace new approaches to mechanical correction of abnormal valve hemodynamics, we need to be sure that we do not sacrifice proven long-term effectiveness for short-term issues, such as convenience, invasiveness, or reversible procedural complications. The goal is to make the patient feel better and live longer.

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

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Percutaneous Repair or Surgery for Mitral Regurgitation

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ABSTRACT

BACKGROUND

Mitral-valve repair can be accomplished with an investigational procedure that involves the percutaneous implantation of a clip that grasps and approximates the edges of the mitral leaflets at the origin of the regurgitant jet.

METHODS

We randomly assigned 279 patients with moderately severe or severe (grade 3+ or 4+) mitral regurgitation in a 2:1 ratio to undergo either percutaneous repair or conventional surgery for repair or replacement of the mitral valve. The primary composite end point for efficacy was freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation at 12 months. The primary safety end point was a composite of major adverse events within 30 days.

RESULTS

At 12 months, the rates of the primary end point for efficacy were 55% in the percutaneous-repair group and 73% in the surgery group ($P=0.007$). The respective rates of the components of the primary end point were as follows: death, 6% in each group; surgery for mitral-valve dysfunction, 20% versus 2%; and grade 3+ or 4+ mitral regurgitation, 21% versus 20%. Major adverse events occurred in 15% of patients in the percutaneous-repair group and 48% of patients in the surgery group at 30 days ($P<0.001$). At 12 months, both groups had improved left ventricular size, New York Heart Association functional class, and quality-of-life measures, as compared with baseline.

CONCLUSIONS

Although percutaneous repair was less effective at reducing mitral regurgitation than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes. (Funded by Abbott Vascular; EVEREST II ClinicalTrials.gov number, NCT00209274.)

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Severe mitral regurgitation is associated with progressive left ventricular dysfunction and congestive heart failure.[1] Without intervention, symptomatic patients have an annual rate of death of 5% or more.[1-3] Medical management alleviates symptoms but does not alter the progression of the disease.[2] Current guidelines recommend surgery for moderate-to-severe (grade 3+) or severe (4+) mitral regurgitation in patients with symptoms or evidence of left ventricular dysfunction.[4-6]

One surgical approach for mitral-valve repair involves approximation of the mitral leaflets with suture to create a double orifice.[7-9] This procedure has been described for treatment of degenerative mitral regurgitation and is usually performed with an annuloplasty ring. Selected patients who have been treated with this technique as a standalone procedure have had successful results lasting up to 12 years.[10]

A method for percutaneous double-orifice repair has been developed with the use of a mechanical device that is delivered into the left atrium through transseptal access. The device (MitraClip, Abbott Vascular) grasps and approximates the leaflets.[11,12] Mitral repair with this device in 107 patients showed significant reduction in the severity of mitral regurgitation.[13,14]

We designed the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II), a randomized comparison of percutaneous mitral repair and mitral-valve surgery, to evaluate the efficacy and safety of percutaneous mitral-valve repair, as compared with conventional surgical repair or replacement.[15]

Methods

Patients

From September 2005 through November 2008, we recruited patients at 37 study centers in the United States and Canada. All eligible patients had grade 3+ or 4+ chronic mitral regurgitation. Patients who were symptomatic were required to have a left ventricular ejection fraction (LVEF) of more than 25% and a left ventricular end-systolic diameter of 55 mm or less. Those who were asymptomatic were required to have at least one of the following: an LVEF of 25 to 60%, a left ventricular end-systolic diameter of 40 mm to 55 mm, new atrial fibrillation, or pulmonary hypertension.[4-6] Eligible patients were candidates for mitral-valve repair or replacement surgery. According to the anatomical inclusion criteria, the primary regurgitant jet originated from malcoaptation of the middle scallops of the anterior and posterior leaflets. Full inclusion and exclusion criteria have been reported previously.[15]

An animation showing the placement of a mitral-valve clip is available at NEJM.org

Figure 1 (facing page). Percutaneous Repair of a Mitral Valve.

In patients with mitral regurgitation resulting from incomplete leaflet coaptation (Panels A and B), percutaneous mitral-valve repair is performed by means of femoral venous and transseptal access to the left atrium to steer the device toward the origin of the regurgitant jet (Panel C). A mitral clip is passed through the mitral orifice from the left atrium to the left ventricle and pulled back to grasp the leaflet edges (Panels D and E). If reduction of the mitral regurgitation is satisfactory, the device can be locked and then released (Panel F). A double orifice is created in conjunction with reduction in mitral regurgitation (Panels G and H).

Study Design

The study was conducted in the United States and Canada in compliance with the provisions of the Declaration of Helsinki for human investigation under an investigational device exemption. The study was approved by the institutional review board at each study center. Written informed consent was obtained from all patients.

Study sites were required to have experience with percutaneous interventions, transseptal punctures, and mitral-valve surgery, along with a strong multidisciplinary clinical team. All echocardiograms were assessed by an independent core laboratory (University of California, San Francisco). Mitral regurgitation was graded according to the American Society of Echocardiography guidelines with the use of quantitative criteria (regurgitant volume, regurgitant fraction, and effective regurgitant orifice area) and qualitative criteria (color Doppler and pulmonary venous flow).[16-18] If two regurgitant jets were present, both measurements were incorporated.

Percutaneous-Repair Procedure

The MitraClip device is a 4-mm-wide cobalt–chromium implant with two arms that are opened and closed with the use of the delivery-system handle (Fig. 1, and the animation available with the full text of this article at NEJM.org).[13,14] The procedure is performed under general anesthesia with the use of fluoroscopic and transesophageal

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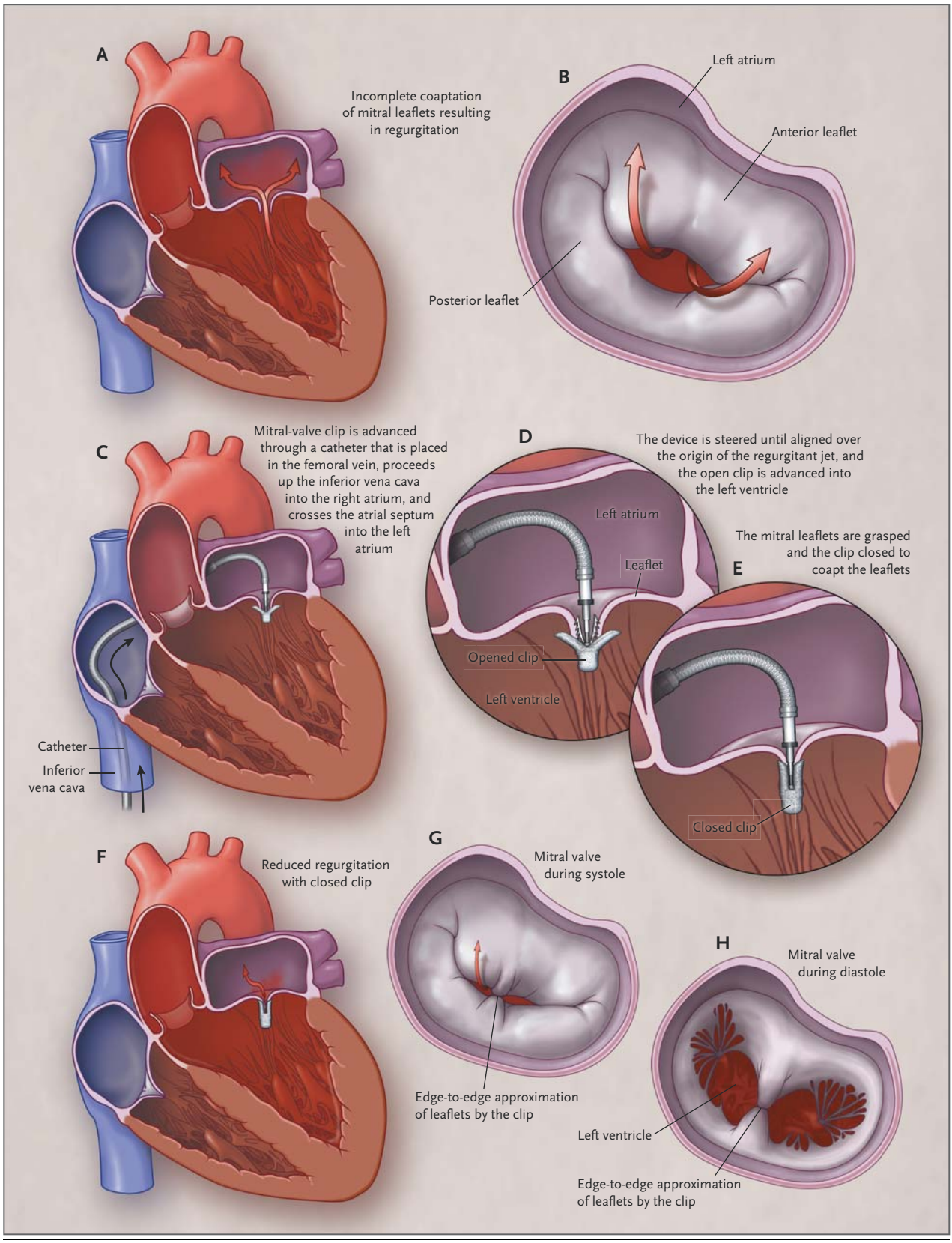

echocardiographic guidance. Atrial transseptal puncture is performed. The device is steered until it is aligned over the origin of the regurgitant jet[18] and advanced into the left ventricle. The mitral leaflets are grasped, and the device is closed to approximate the leaflets. Adequate reduction of mitral regurgitation to a grade of 2+ or less is assessed with the use of echocardiography. If the reduction in mitral regurgitation is inadequate with one device, the device may be removed or a second device placed. Patients with grade 3+ or 4+ mitral regurgitation despite device treatment were referred for elective valve surgery. Patients were treated with heparin during the procedure, with aspirin (at a dose of 325 mg daily) for 6 months and with clopidogrel (at a dose of 75 mg daily) for 30 days after the procedure.

END POINTS

The primary composite end point for efficacy was freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation at 12 months. The primary safety end point was the rate of major adverse events at 30 days, defined as the composite of death, myocardial infarction, reoperation for failed mitral-valve surgery, nonelective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, mechanical ventilation for more than 48 hours, gastrointestinal complication requiring surgery, new-onset permanent atrial fibrillation, septicemia, and transfusion of 2 units or more of blood.

Additional prespecified secondary end points included the change in left ventricular dimensions and volumes, New York Heart Association (NYHA) heart failure class,[19] and quality-of-life scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).[20] Yearly clinical and echocardiographic evaluations are planned for 5 years of follow-up. All end-point components were adjudicated by an independent events committee or core echocardiographic laboratory.

STUDY OVERSIGHT

The study was designed by the sponsor, Abbott Vascular, in collaboration with the investigators. The study protocol is available at NEJM.org. Harvard Clinical Research Institute was contracted by Abbott Vascular to perform data management, analysis, and clinical-event adjudication. The first and last authors wrote the first draft of the manuscript, and the authors vouch for the integrity of the analysis. The study publications committee, consisting of academic authors and investigators, made the decision to submit the manuscript for publication.

STATISTICAL ANALYSIS

We performed all analyses according to the intention-to-treat principle. A total of 21 randomized patients who did not receive treatment in either study group and did not undergo subsequent assessment of mitral regurgitation were considered to maintain the same grade of mitral regurgitation as the grade at baseline for the efficacy analysis. Any valve surgery that was performed after percutaneous repair was considered as a component of the composite primary end point. We also performed two additional analyses that were prespecified in the protocol. In the first analysis, we rated patients with insufficient reduction of in-hospital mitral regurgitation after percutaneous repair who received successful mitral-valve surgery as having had a successful outcome (comparison of strategies). In the second analysis, we compared the subgroup of patients who had grade 2+ or less mitral regurgitation at the time of hospital discharge, according to study group (per protocol).

We also analyzed the primary safety end point according to the intention-to-treat principle, with the exclusion of five patients who withdrew from the study before 30 days. Sensitivity analysis with the use of multiple imputation for missing efficacy and safety data provided similar results to those presented here.

Comparisons with efficacy and safety margins were prespecified in the protocol to achieve a power of 80% for 279 randomized patients, as described previously.[15] These sample-size calculations were based on the expectation that surgery would be more effective in reducing the grade of mitral regurgitation and that percutaneous therapy would have a lower risk.[15,16] The specified margin of reduced efficacy of percutaneous therapy, as compared with surgical therapy, was a reduction of 25% for the comparison of strategies and a reduction of 31% for the per-protocol analysis. The specified margin of improved safety for percutaneous therapy was 2% for the intention-to-treat analysis. We calculated one-sided continuity-corrected confidence intervals (95% intervals for efficacy and 97.5% intervals for safety, as specified in the protocol) and P values with the Farring-

ton–Manning test to compare treatment differences with the efficacy and safety margins.[21] The continuity-corrected one-sample z-test of proportions had consistent results.

We used Fisher's exact test to compare other binary variables and Student's t-test for continuous variables. A modified ridit analysis was used to compare the ordinal categorical variables of mitral-regurgitation grade and NYHA functional class.

Although no formal subgroup analyses were prespecified, we performed limited tests for interaction with treatment on the efficacy and safety end points in the intention-to-treat population to evaluate whether consistent treatment differences were present in which plausible variation might exist with respect to age (<70 vs. ≥70 years), sex, functional versus degenerative mitral regurgitation, and LVEF (<60% vs. ≥60%). No formal adjustment was made for multiple testing, since the primary focus of this analysis was to assess consistency across subgroups. All statistical analyses were performed with the use of SAS for Windows software, version 9.1 or higher.

RESULTS

PATIENTS

We randomly assigned 279 patients in a 2-to-1 ratio to undergo either percutaneous repair (184 patients) or mitral-valve surgery (95 patients) of mitral regurgitation (Fig. 2). A total of 21 patients who underwent randomization withdrew consent for treatment (3% in the percutaneous-repair group and 16% in the surgery group) (Fig. 1 in the Supplementary Appendix, available at NEJM.org). Of 258 treated patients, 243 (94%) complied with the protocol for the 12-month follow-up. Baseline characteristics were similar in the two study groups, with the exception of a history of congestive heart failure, which was more common in the percutaneous-repair group (Table 1). (Characteristics of the per-protocol cohort are listed in Table 1 in the Supplementary Appendix.)

PROCEDURAL RESULTS

Of 178 patients who were treated in the percutaneous-repair group, 41 (23%) had grade 3+ or 4+ mitral regurgitation on assessment before hospital discharge and were referred for surgery. Of these 41 patients, 28 underwent subsequent mitral-valve surgery (15 repair and 13 replacement procedures). In the surgery group, all 80 treated patients had mitral regurgitation of grade 2+ or less before hospital discharge. Among these patients, mitral-valve replacement was performed in 11 patients (14%) and repair in 69 patients (86%), including 38 patients (55%) who underwent leaflet resection and annuloplasty, 16 patients (23%) who underwent annuloplasty alone, 14 patients (20%) who underwent complex leaflet or chordal repair with annuloplasty, and 1 patient (1%) who underwent an unspecified method of leaflet repair. In the intention-to-treat analysis, patients who were assigned to the surgery group but did not undergo surgery were considered to have had a treatment failure.

EFFICACY END POINT

In the intention-to-treat analysis, the rates of death and mitral regurgitation of grade 3+ or 4+ at 12 months were similar in the two study groups, whereas surgery for mitral-valve dysfunction was more common in the percutaneous-repair group. The rate of surgery for mitral-valve dysfunction was 20% in the percutaneous-repair group, as compared with a rate of 2.2% for repeated mitral-valve surgery in the surgery group (Table 2). Overall, the rates of the primary efficacy end point (a composite of freedom from death, from surgery for valve dysfunction, and from grade 3+ or 4+ mitral regurgitation at 12 months) were 55% in the percutaneous-repair group and 73% in the surgery group ($P=0.007$). In the analysis comparing treatment strategies, in which patients who had unsuccessful percutaneous reduction of mitral regurgitation before hospital discharge were referred for elective mitral-valve surgery, the rates of the primary end point were 67% in the percutaneous-repair group and 73% in the surgery group ($P=0.42$; comparison to margin of reduced efficacy of –25%, $P<0.001$) (Table 2 in the Supplementary Appendix).

In the per-protocol analysis of data from treated patients with successful in-hospital results, the rates of the primary end point were 72% in the percutaneous-repair group and 88% in the surgery group ($P=0.02$). The between-group difference in the one-sided lower limit of the 95% confidence interval (–25%) was greater than the prespecified margin of –31% ($P=0.001$). The margins of reduced efficacy and increased safety were prespecified in order to compare the actual study results with the expectation that surgical treatment would be more effective but that percutaneous treatment would be safer.

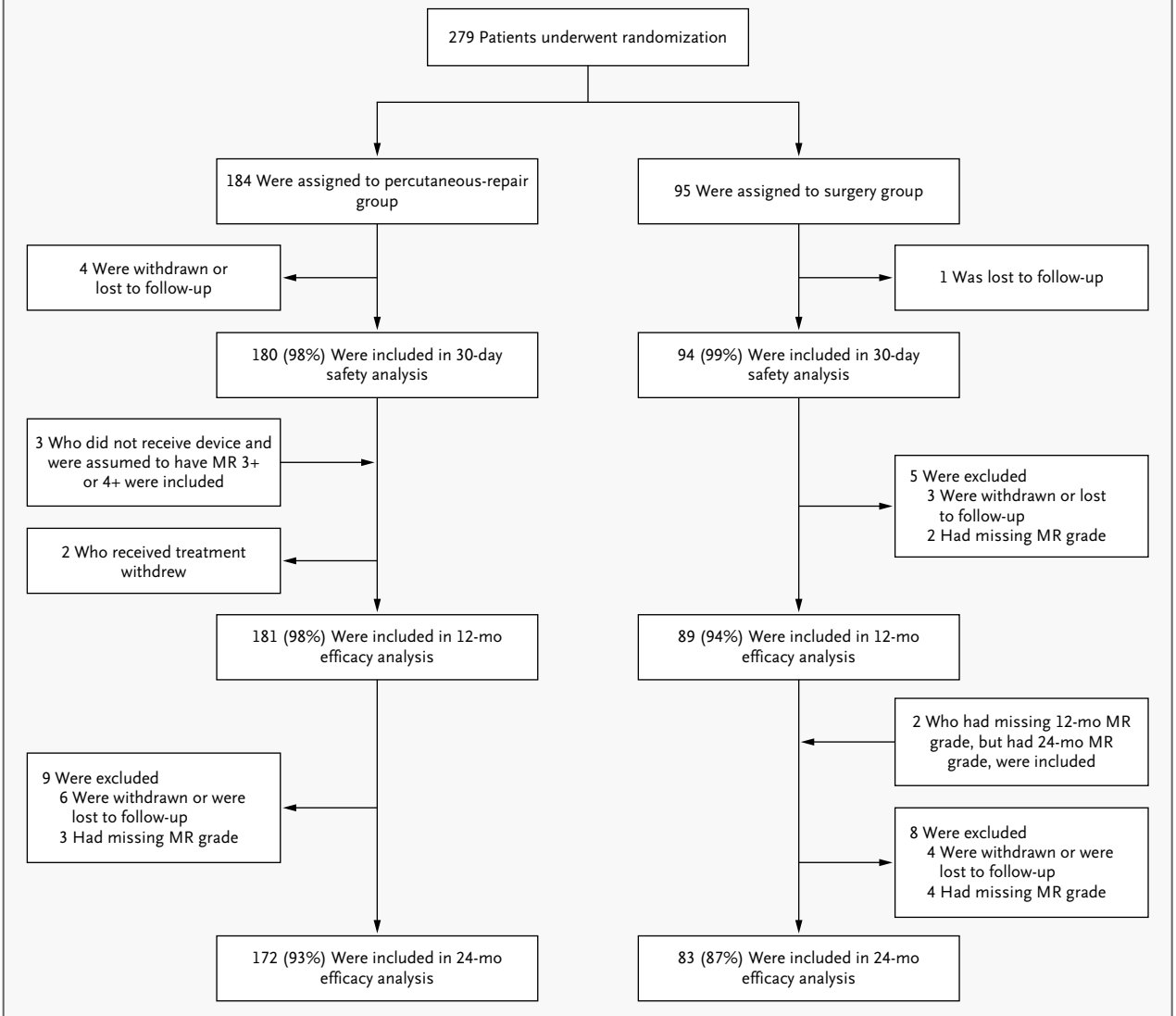

Figure 2. Enrollment and Follow-up in the Intention-to-Treat Group.

Data are shown for patients who were available for analysis at 30 days (safety analysis) and at both 12 months and 24 months (efficacy analysis). Since the efficacy end point required echocardiographic assessment of mitral regurgitation (MR), patients who did not undergo implantation of a device, but were known to be alive, were presumed to have retained their baseline grade of mitral regurgitation and thus are included among patients in whom treatment failed.

In the intention-to-treat analysis at 2 years, the rate of death (11%) was the same in the two study groups. In the percutaneous-repair group, as compared with the surgery group, the respective rates of surgery for valve dysfunction were 22% and 4%, and the proportions of patients with grade 3+ or 4+ mitral regurgitation at 24 months were 20% and 22%. Overall, the proportions of patients with the primary end point (i.e., the absence of these events) were 52% in the percutaneous-repair group and 66% in the surgery group (P=0.04).

MAJOR ADVERSE EVENTS

In the intention-to-treat analysis, the rates of major adverse events at 30 days after the procedure were 15% in the percutaneous-repair group and 48% in the surgery group (Table 2), for an absolute difference between the percutaneous-repair group and the surgery group of –33% with a one-sided upper limit of the 97.5% confidence interval of –21%, which was lower than the –2% margin of increased safety (P<0.001). With the exclusion of the need for transfusion, the rate of major adverse

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Percutaneous Repair (N=184)	Surgery (N=95)	P Value
Age			
Mean — yr	67.3±12.8	65.7±12.9	0.32
>75 yr — no. (%)	55 (30)	26 (27)	0.68
Male sex — no. (%)	115 (62)	63 (66)	0.60
Coexisting condition — no./total no. (%)			
Congestive heart failure	167/184 (91)	74/95 (78)	0.005
Coronary artery disease	86/183 (47)	44/95 (46)	0.99
Previous myocardial infarction	40/183 (22)	20/94 (21)	0.99
Atrial fibrillation	59/175 (34)	35/89 (39)	0.42
Diabetes	14/184 (8)	10/95 (11)	0.50
Chronic obstructive pulmonary disease	27/183 (15)	14/95 (15)	0.99
Previous coronary-artery bypass grafting	38/184 (21)	18/95 (19)	0.87
Previous percutaneous intervention	44/183 (24)	15/95 (16)	0.12
Left ventricular ejection fraction — %	60.0±10.1	60.6±11.0	0.65
New York Heart Association functional class — no. (%)			0.16
I	17 (9)	19 (20)	
II	73 (40)	31 (33)	
III	82 (45)	41 (43)	
IV	12 (7)	4 (4)	
Severity of mitral regurgitation — no. (%)			0.38
1+ to 2+ (mild to moderate)	0	1 (1)	
2+ (moderate)	8 (4)	6 (6)	
3+ (moderate to severe)	130 (71)	67 (71)	
4+ (severe)	46 (25)	21 (22)	
Regurgitant volume — ml/beat	42.0±23.3	45.2±26.6	0.31
Regurgitant orifice area — cm^2	0.56±0.38	0.59±0.35	0.55
Cause of mitral regurgitation — no. (%)			0.81
Functional	49 (27)	26 (27)	
Degenerative			
With anterior or bileaflet flail or prolapse	58 (32)	25 (26)	
With posterior flail or prolapse	72 (39)	42 (44)	
With no flail and no prolapse	5 (3)	2 (2)	

* Plus–minus values are means ±SD.

events at 30 days was lower in the percutaneous-repair group than in the surgery group (5% vs. 10%, P=0.23), although the difference was not significant. The rates of major adverse events in the per-protocol analysis are provided in Table 3 in the Supplementary Appendix.

Among 41 patients with mitral regurgitation of grade 3+ or 4+ after percutaneous repair, the rate of major adverse events was 34% at 30 days, including postsurgical events that included two deaths, one of which occurred after a stroke.

During 12 months of follow-up, 37 of 178 patients (21%) in the percutaneous-repair group subsequently underwent mitral-valve surgery. The reasons for surgery were no percutaneous implantation of a device (17 patients), mitral regurgita-

Table 2. Primary Efficacy End Point at 12 Months and Major Adverse Events at 30 Days in the Intention-to-Treat Population.*

Event	Percutaneous Repair	Surgery	P Value
	no. (%)		
Primary efficacy end point			
Freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation†	100 (55)	65 (73)	0.007
Death	11 (6)	5 (6)	1.00
Surgery for mitral-valve dysfunction‡	37 (20)	2 (2)	<0.001
Grade 3+ or 4+ mitral regurgitation	38 (21)	18 (20)	1.00
Major adverse event at 30 days§			
Any major adverse event	27 (15)	45 (48)	<0.001¶
Any major adverse event excluding transfusion	9 (5)	9 (10)	0.23
Death	2 (1)	2 (2)	0.89
Myocardial infarction	0	0	NA
Reoperation for failed surgical repair or replacement	0	1 (1)	0.74
Urgent or emergency cardiovascular surgery for adverse event	4 (2)	4 (4)	0.57
Major stroke	2 (1)‖	2 (2)	0.89
Renal failure	1 (<1)	0	1.00
Deep wound infection	0	0	NA
Mechanical ventilation for >48 hr	0	4 (4)	0.02
Gastrointestinal complication requiring surgery	2 (1)	0	0.78
New onset of permanent atrial fibrillation	2 (1)	0	0.78
Septicemia	0	0	NA
Transfusion of ≥2 units of blood	24 (13)	42 (45)	<0.001

* The 12-month efficacy analysis included 181 patients in the percutaneous-repair group and 89 patients in the surgery group. The 30-day safety analysis included 180 patients in the percutaneous-repair group and 94 in the surgery group (for details, see Fig. 1). NA denotes not applicable.
† Rates of the components of the composite primary end point do not total the rates of the composite because patients could have more than one event.
‡ This component is the rate of the first mitral-valve surgery in the percutaneous-repair group and the rate of reoperation for mitral-valve dysfunction in the surgery group.
§ Patients could have more than one adverse event at 30 days.
¶ This P value was calculated to test for the increased superiority of percutaneous repair, as compared with surgery, by a prespecified safety margin of –2%.
‖ One stroke occurred in a patient who underwent randomization but was not treated.

tion of grade 3+ or 4+ after device implantation before hospital discharge (5), mitral regurgitation of grade 3+ or 4+ after attachment of a device to a single leaflet (9), mitral regurgitation of grade 3+ or 4+ after discharge despite dual-leaflet attachment (3), and symptoms (3). In 7 cases, leaflet or chordae tears were noted during surgery. No device embolization occurred. No substantial mitral stenosis was observed. Site-reported serious adverse events at 12 months are listed in Table 4 in the Supplementary Appendix.

SEVERITY OF MITRAL REGURGITATION

There was improvement in the severity of mitral regurgitation in the two study groups, with greater reduction in the surgery group (P<0.001) (Table 3). The reduction in the severity of mitral regurgitation to grade 1+ or less in the surgery group at 12 months was more common after valve replacement (8 of 8 patients, 100%) than after valve repair (43 of 59 patients, 73%; P=0.18), with the exclusion of 1 patient who did not undergo surgery and 1 patient who underwent valve replace-

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Table 3. Secondary End Points at 12 Months in the Intention-to-Treat Population.*

End Point	Percutaneous Repair (N=184)			Surgery (N=95)			P Value for Comparison between Study Groups
	No. of Patients	Value	P Value for Comparison between Baseline and 12 Mo	No. of Patients	Value	P Value for Comparison between Baseline and 12 Mo	
Change from baseline in left ventricular measurement							
End-diastolic volume — ml	144	−25.3±28.3	<0.001	66	−40.2±35.9	<0.001	0.004
End-diastolic diameter — cm	148	−0.4±0.5	<0.001	67	−0.6±0.6	<0.001	0.04
End-systolic volume — ml	144	−5.5±14.5	<0.001	66	−5.6±21.0	0.04	0.97
End-systolic diameter — cm	146	−0.1±0.6	0.06	67	−0.0±0.6	0.86	0.38
Ejection fraction — %	144	−2.8±7.2	<0.001	66	−6.8±10.1	<0.001	0.005
Change from baseline in quality-of-life score†							
30 days							
Physical component summary	147	3.1±9.4	<0.001	64	−4.9±13.3	0.004	<0.001
Mental component summary	148	4.4±11.3	<0.001	64	1.8±13.4	0.29	0.14
12 months							
Physical component summary	132	4.4±9.8	<0.001	60	4.4±10.4	0.002	0.98
Mental component summary	133	5.7±9.9	<0.001	60	3.8±10.3	0.006	0.24
Severity of mitral regurgitation at 12 mo — no. (%)	153			69			<0.001
0+ (none)		9 (6)	NA		13 (19)	NA	
1+ (mild)		57 (37)	NA		39 (57)	NA	
1+ to 2+ (mild to moderate)		18 (12)	NA		5 (7)	NA	
2+ (moderate)		41 (27)	NA		9 (13)	NA	
3+ (moderate to severe)		21 (14)	NA		3 (4)	NA	
4+ (severe)		7 (5)	NA		0	NA	

* Plus–minus values are means ±SD. NA denotes not applicable.
† Quality of life was measured with the use of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), with scores ranging from 0 to 100, with higher scores indicating better quality of life.

ment 11 days after an unsuccessful repair procedure.

CHANGE IN LEFT VENTRICULAR DIMENSIONS

In the intention-to-treat analysis at 12 months, left ventricular end-diastolic and end-systolic volumes and dimensions were significantly reduced from baseline in the two study groups. The reduction in the left ventricular end-diastolic volume between baseline and 12 months was greater in the surgery group than in the percutaneous-repair group (P=0.004), but the reduction in LVEF was also greater in the surgery group than in the percutaneous-repair group (P=0.005) (Table 3).

HEART FAILURE AND QUALITY OF LIFE

In the intention-to-treat analysis at 12 months, NYHA functional class III or IV heart failure was present in 2% of patients in the percutaneous-repair group and in 13% of those in the surgery group (P=0.002). Patients' quality of life improved from baseline to 12 months in the two study groups, yet surgery was associated with a transient decrease in the quality of life at 30 days.

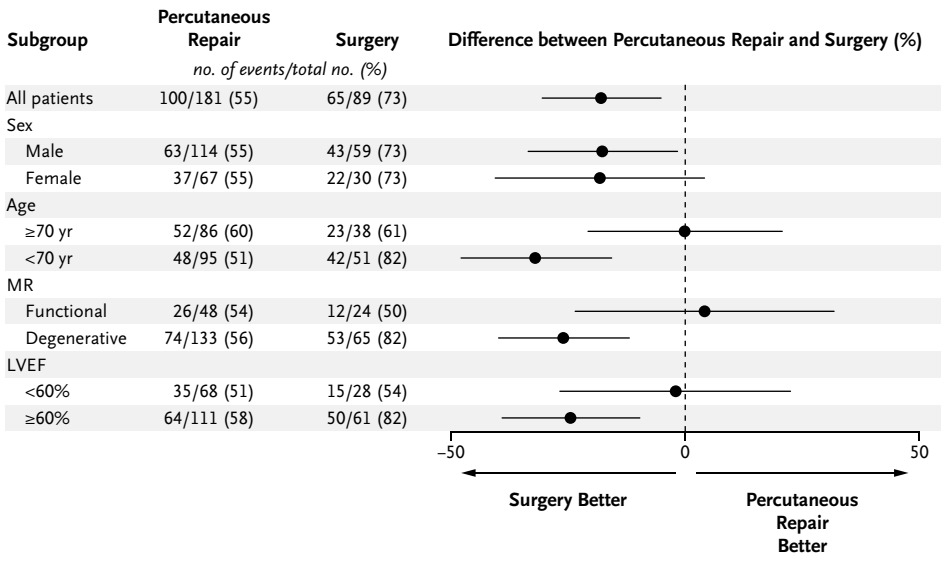

Figure 3. Subgroup Analyses for the Primary End Point at 12 Months.

Shown are the difference in rates of the primary efficacy end point (freedom from death, from mitral-valve surgery, and from grade 3+ or 4+ mitral regurgitation) between patients in the percutaneous-repair group and those in the surgery group for all randomized patients and those in four post hoc subgroups. In the subgroup for the comparison of the left ventricular ejection fraction (LVEF), data were missing for two patients, including one patient who had mitral regurgitation of more than grade 2+. The horizontal lines indicate 95% confidence intervals.

SUBGROUP ANALYSIS

In an exploratory intention-to-treat analysis that was not prespecified in the study protocol, we assessed the consistency of between-group differences regarding efficacy and safety in four subgroups (Fig. 3). There was significant subgroup interaction between patients who were at least 70 years of age, as compared with those under 70 years of age (P=0.009), and those with functional mitral regurgitation, as compared with degenerative mitral regurgitation (P=0.02), with smaller between-group differences among patients at least 70 years of age and among those with functional mitral regurgitation. No significant interactions with subgroups were identified regarding the rate of major adverse events at 30 days (Fig. 2 in the Supplementary Appendix).

DISCUSSION

In patients with mitral regurgitation, we analyzed the efficacy and safety of percutaneous repair, as compared with conventional surgery, which is the standard of care for substantial mitral regurgitation with symptoms or left ventricular dilatation or dysfunction. We found that although percutaneous treatment was effective at reducing mitral regurgitation, surgical treatment was more effective, as graded by an echocardiographic core laboratory. However, percutaneous treatment was associated with a reduction in the rate of major adverse events at 30 days, as compared with surgery, and with sustained clinical improvement, as measured by quality of life, heart failure status, and left ventricular function. Although percutaneous treatment did not reduce mitral regurgitation below grade 3+ in 23% of patients, among those who had improved mitral regurgitation after the procedure, the improvement remained at 12 and 24 months for a majority. Measures of efficacy remained durable through 24 months of follow-up, and 78% of patients remained free from mitral-valve surgery.

Despite differences in residual mitral regurgitation between the percutaneous-repair group and the surgery group, patients who underwent percutaneous repair had significantly reduced left ventricular end-diastolic volume and dimensions,

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improved NYHA functional class, and improved quality of life at 12 months, as compared with baseline measures. A transient decrease in the physical component of the quality-of-life score in the surgery group at 30 days was probably related to the invasiveness of surgery.

Percutaneous treatment was associated with more frequent additional procedures for treatment of mitral regurgitation than was surgery, but this less invasive option had superior safety, and most patients with residual or recurrent mitral regurgitation underwent subsequent successful mitral-valve surgery. Transfusions comprised the largest single component of the major adverse events at 30 days in our study and have an important effect on late outcomes.[22] Even after the exclusion of transfusion events, the rate of adverse events was lower in the percutaneous-repair group than in the surgery group.

Although the multicenter, randomized design is an important strength of this study, there are several limitations. First, the study was not blinded, and more patients discontinued participation in the surgery group than in the percutaneous-repair group. Second, the use of multiple surgical techniques, including annuloplasty, is usual with surgical mitral-valve repair. The lack of annuloplasty in the percutaneous method may in part explain the increased reduction in mitral regurgitation in the surgery group. An ongoing follow-up report at 5 years is planned to evaluate this question.

We chose a composite primary end point to represent the range of expected adverse events in the two study groups. Because the components are not all equal in severity, each must be weighed both quantitatively and qualitatively for consistency. The protocol specified a wide margin of reduced efficacy between percutaneous and surgical treatments, with the expectation that a less effective therapy could be acceptable if it proved to be safer. Given the complexity of choosing between two different treatments with different safety and efficacy profiles, it is helpful to refer to the actual between-group differences for each event instead of comparing P values that rely on a prespecified definition of an acceptable margin for each composite end point. Because certain characteristics of the patients could influence treatment effects, we examined a limited number of subgroups for interaction. We identified an age of at least 70 years and functional mitral regurgitation as subgroups in which surgery was not superior to percutaneous treatment with regard to efficacy, and there was a similar trend in the subgroup with reduced left ventricular systolic function. These analyses were not prespecified and must be considered exploratory.

In conclusion, we describe results of percutaneous treatment of mitral regurgitation, as compared with conventional surgery, in a randomized, controlled trial that used echocardiographic assessment of mitral regurgitation by a core laboratory. Although percutaneous repair was less effective at reducing mitral regurgitation than surgery before hospital discharge, at 12 and 24 months the rates of reduction in mitral regurgitation were similar, and percutaneous treatment was associated with increased safety, improved left ventricular dimensions, and clinical improvements in NYHA class and quality of life. Longer-term follow-up will provide additional data to better understand percutaneous treatment of mitral regurgitation.

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