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4-Year Results of a Randomized Controlled Trial of Percutaneous Repair Versus Surgery for Mitral Regurgitation

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Objectives This study sought to evaluate 4-year outcomes of percutaneous repair versus surgery for mitral regurgitation.

Background Transcatheter therapies are being developed to treat valvular heart disease. In the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II trial, treatment of mitral valve regurgitation (MR) with a novel percutaneous device was compared with surgery and showed superior safety, but less reduction in MR at 1 year overall. We report the 4-year outcomes from the EVEREST II trial.

Methods Patients with grade 3+ or 4+ MR were randomly assigned to percutaneous repair with the MitraClip (Abbott, Menlo Park, California) device or conventional mitral valve surgery in a 2:1 ratio (184:95). Patients prospectively consented to 5 years of follow-up.

Results At 4 years, the rate of the composite endpoint of freedom from death, surgery, or 3+ or 4+ MR in the intention-to-treat population was 39.8% versus 53.4% in the percutaneous repair group and surgical groups, respectively ($p = 0.070$). Rates of death were 17.4% versus 17.8% ($p = 0.914$), and 3+ or 4+ MR was present in 21.7% versus 24.7% ($p = 0.745$) at 4 years of follow-up, respectively. Surgery for mitral valve dysfunction, however, occurred in 20.4% versus 2.2% ($p < 0.001$) at 1 year and 24.8% versus 5.5% ($p < 0.001$) at 4 years.

Conclusions Patients treated with percutaneous repair of the mitral valve more commonly required surgery to treat residual MR; however, after the first year of follow-up, there were few surgeries required after either percutaneous or surgical treatment and no difference in the prevalence of moderate-severe and severe MR or mortality at 4 years. (Endovascular Valve Edge-to-Edge Repair Study [EVEREST II]; NCT00209274) (J Am Coll Cardiol 2013;62:317–28)

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Abbreviations and Acronyms

LVEF = left ventricular ejection fraction

LVIDd = left ventricular internal diameter diastolic

MR = mitral regurgitation

NYHA = New York Heart Association

Surgical treatment of mitral regurgitation (MR) is recommended for patients who are symptomatic from 3+ or 4+ MR or have evidence of left ventricular dysfunction or enlargement to avoid progressive deterioration in cardiac function (1–3). The durability of surgical mitral valve repair has been studied in several single-center series (4,5). Although mitral valve regurgitation may recur within the first 6 months after surgical repair, the grade of MR as ascertained by routine clinical echocardiography generally remains stable beyond the first year of follow-up (5).

A novel percutaneous device has been developed to reduce MR by approximating the 2 leaflets of the valve (MitraClip, Abbott, Menlo Park, California). This is the first percutaneous device for MR to be compared in a randomized trial to conventional mitral valve surgery. Percutaneous treatment of MR with the MitraClip device is currently allowed under CE Mark in Europe and is investigational in the United States and parts of Asia.

The EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II randomized trial compared treatment with the MitraClip device to treatment with surgery for MR (6,7). At 1 year, rates of death were similar, but the rate and degree of MR was higher with the percutaneous approach compared with surgery. Major adverse events at 30 days were lower overall for percutaneously treated subjects, and certain patient groups, such as the elderly and subjects lacking intrinsic leaflet pathology (e.g., with functional MR), experienced effectiveness of the percutaneous treatment that was comparable to surgery at 1 year in exploratory analysis.

The EVEREST II randomized trial pre-specified mandatory clinical and echocardiographic follow-up at 1-year intervals for 5 years in both study arms, and echocardiographic images were reviewed and adjudicated by a central core laboratory. All randomized subjects reached eligibility for 4-year follow-up at the time of this report. We sought to compare the clinical and echocardiographic durability of percutaneous treatment with surgical treatment of mitral valve regurgitation at 4 years among patients enrolled in the EVEREST II randomized trial.

Methods

Patients. The EVEREST II trial is a prospective, multicenter, randomized, nonblinded evaluation of the MitraClip

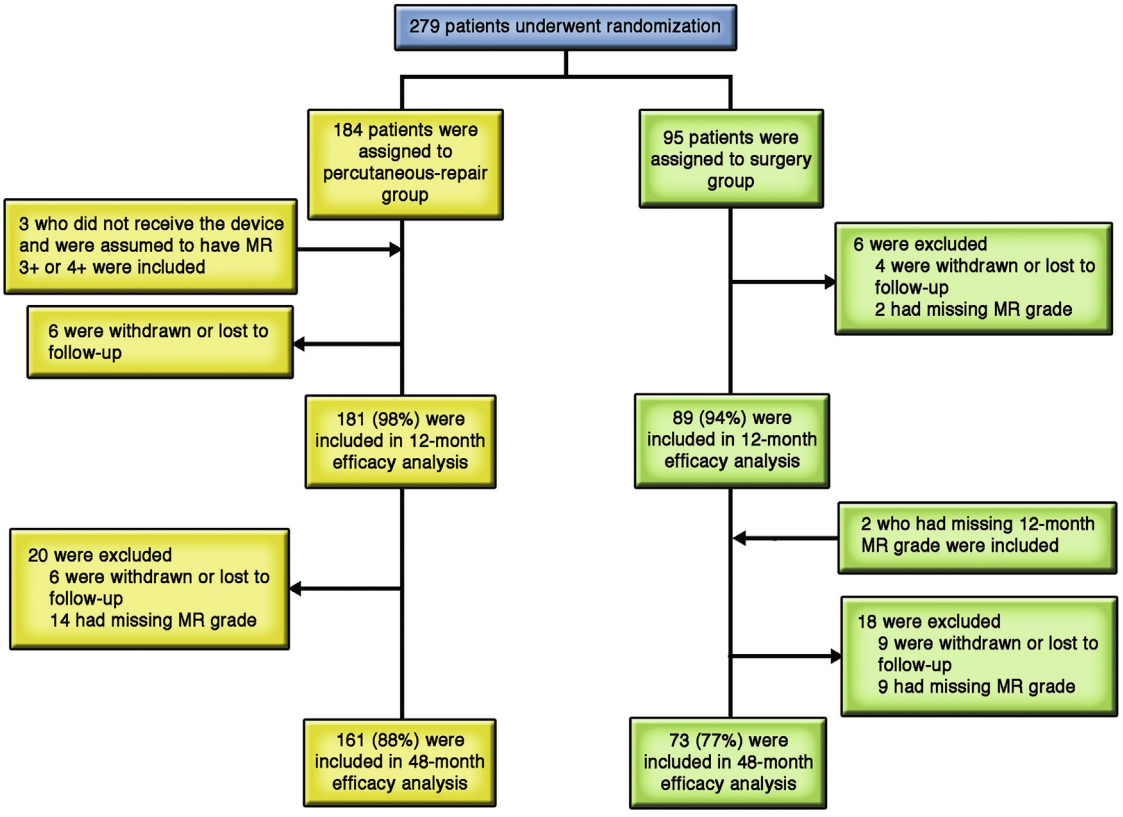


Figure 1 Enrollment and Follow-Up in the Intention-to-Treat Group

MR = mitral valve regurgitation.

System in the treatment of MR. The MitraClip device, procedure, study design, and 1-year primary endpoint analysis have been previously described (6,7). From September 2005 through November 2008, 279 patients were recruited at 37 study centers in North America. Patients were eligible for the EVEREST II trial if they had grade 3+ or 4+ chronic MR, were symptomatic with a left ventricular ejection fraction (LVEF) of more than 25%, and a left ventricular end-systolic diameter of 55 mm or less; or if asymptomatic, had at least 1 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. All eligible patients were candidates for mitral valve repair or replacement surgery and cardiopulmonary bypass. Patients underwent transthoracic and transesophageal echocardiography to quantify mitral valve regurgitation and to judge morphologic suitability for MitraClip implantation. Pertinent exclusion criteria were a baseline mitral valve area <4.0 cm^2, presence of severe leaflet or annular calcification, flail width ≥ 15 mm, flail gap ≥ 10 mm, and in patients with functional etiology, a coaptation depth >11 mm below the annulus or a coaptation length <2 mm. Before randomization, all patients provided written informed consent for 5 years of follow-up. The study protocol was reviewed and approved by the institutional review board of each participating site.

Procedure. The MitraClip system is a catheter-based device designed to approximate the mitral valve leaflets while the heart is beating. The procedure is performed in the cardiac catheterization laboratory with echocardiographic and fluoroscopic guidance while the patient is under general anesthesia. The MitraClip System includes a MitraClip device, a steerable guide catheter and a MitraClip delivery system. The MitraClip device is a polyester-covered mechanical device with 2 arms that are opened and closed by control mechanisms on the delivery catheter. The tip of the outer guide catheter is delivered to the left atrium through a transseptal approach over a guidewire and dilator. The MitraClip delivery system is advanced through the guide catheter into the left atrium and positioned so that the device is orthogonal to the plane of the mitral valve annulus and at the origin of the regurgitant jet. After adequacy of the grasp is assessed, the reduction of MR is confirmed, and the diastolic transmitral gradients are assessed with the use of transthoracic echocardiography, the MitraClip device is deployed. If reduction in MR is inadequate with 1 device the device may be removed or a second device placed. 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.

Statistical analysis. The trial primary effectiveness endpoint was freedom from death, surgery for mitral valve dysfunction, and 3+ and 4+ MR at 12 months (determined by an echocardiographic core laboratory; Dr. Foster, University of California, San Francisco), designed to compare the percutaneous treatment to surgery and demonstrate effectiveness within a pre-specified margin of difference, and for safety, a composite of major adverse events within 30 days, to demonstrate improvement by a pre-specified margin. Results of analyses on this endpoint for the intention-to-treat analysis set (entire randomized cohort) and per-protocol cohort (subset of randomized cohort with discharge MR $\leq 2+$) have been previously reported (7).

The endpoints to be compared between randomized treatment groups here include the following endpoints evaluated through 4 years (48 months) after randomized procedure: 1) freedom from death, surgery for mitral valve dysfunction, and 3+ and 4+ MR at 48 months; 2) freedom from surgery for mitral valve dysfunction; and 3) freedom

Table 1 Baseline Characteristics

Characteristic*	Percutaneous Repair Group (n = 184)	Surgical Group (n = 95)
Age, yrs, mean ± SD (n)	67.3 ± 12.8 (184)	65.7 ± 12.9 (95)
Sex		
Male	62.5% (115/184)	66.3% (63/95)
Female	37.5% (69/184)	33.7% (32/95)
Comorbidities		
Congestive heart failure	90.8% (167/184)	77.9% (74/95)
Atrial fibrillation	33.7% (59/175)	39.3% (35/89)
Coronary artery disease	47.0% (86/183)	46.3% (44/95)
Prior myocardial infarction	21.9% (40/183)	21.3% (20/94)
Previous CABG	20.7% (38/184)	18.9% (18/95)
Previous percutaneous intervention	24.0% (44/183)	15.8% (15/95)
Hypercholesterolemia	61.0% (111/182)	62.8% (59/94)
Hypertension	72.3% (133/184)	78.9% (75/95)
Diabetes mellitus	7.6% (14/184)	10.5% (10/95)
Chronic pulmonary disease	14.8% (27/183)	14.8% (14/95)
LVEF, %	60.0 ± 10.1 (182)	60.6 ± 11.0 (95)
NYHA functional class, % (n/N)		
I	9.2% (17/184)	20.0% (19/95)
II	39.7% (73/184)	32.6% (31/95)
III	44.6% (82/184)	43.2% (41/95)
IV	6.5% (12/184)	4.2% (4/95)
MR, % (n/N)		
1+ to 2+, mild-to-moderate	0.0% (0/184)	1.1% (1/95)
2+, moderate	4.3% (8/184)	6.3% (6/95)
3+, moderate-to-severe	70.7% (130/184)	70.5% (67/95)
4+, severe	25.0% (46/184)	22.1% (21/95)
Regurgitant volume, ml/beat	42.0 ± 23.3 (174)	45.2 ± 26.6 (88)
Regurgitant orifice area, cm^2	0.56 ± 0.38 (171)	0.59 ± 0.35 (87)
MR etiology, % (n/N)		
Functional	26.6% (49/184)	27.4% (26/95)
Degenerative		
With anterior or bileaflet flail, or prolapse	31.5% (58/184)	26.3% (25/95)
With posterior flail or prolapse	39.1% (72/184)	44.2% (42/95)
With neither flail nor prolapse	2.7% (5/184)	2.1% (2/95)

*Continuous variables are mean ± SD.

CABG = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; MR = mitral regurgitation.

JACC Vol. 62, No. 4, 2013
July 23, 2013:317–28

from death. Analysis of annual outcomes was pre-specified, albeit with no adjustment for multiple testing, or plan to compare with the original pre-specified differences compared at the primary endpoint time. All of the analyses included here, therefore, should be considered secondary.

The rate of clinical success and its components at 48 months is compared between treatments using the chi-square continuity corrected test. In addition, Kaplan-Meier curves of freedom from surgery and freedom from death are presented for each treatment, with treatment comparisons performed using the log-rank test. Patients not experiencing the endpoint before 48 months are censored at 48 months or last known follow-up, whichever is earlier.

The analysis is performed on an intent-to-treat basis (all randomized patients). Randomized patients who did not receive treatment in either arm (n = 21) and did not have subsequent MR assessment were considered to maintain the same grade of MR as baseline for the effectiveness analysis. Analysis of the subset of patients with available 4-year data was also performed (Online Appendix). Randomized patients with grade 3+ or 4+ MR after the assigned percutaneous procedure were referred for elective valve surgery and were analyzed according to the randomized treatment arm.

Treatment comparison on demographic binary variables was performed using Fisher's exact test, and on demographic continuous variables, was performed using the Student *t* test. Changes from baseline on echocardiographic assessment were compared among patients who completed both the baseline and follow-up echocardiographic assessment. A modified ridit analysis was used to compare the ordinal categorical variables of MR grade and New York Heart Association (NYHA) functional class (8,9).

To evaluate for heterogeneity of the treatment effect on the composite effectiveness endpoint at 4 years, we performed limited tests for interaction with treatment on those groups where heterogeneity was observed on the 12-month primary endpoint: age ≥70 years and functional versus degenerative MR. Degenerative MR was defined as the presence of leaflet pathology (either anterior, or posterior or both), and functional MR was defined as the absence of leaflet pathology.

All statistical analyses were performed using PC SAS for Windows version 9.1 or higher (SAS Institute, Cary, North Carolina).

Role of the funding source. The trial was designed by the sponsor, Abbott Vascular, in collaboration with the investigators. Harvard Clinical Research Institute was contracted by Abbott Vascular to perform data management, analysis, and clinical events adjudication. All authors had access to all data. The trial's publication committee had final responsibility to submit the manuscript for publication.

Results

Patients. Disposition of patients in the intention-to-treat group is presented in Figure 1. A total of 279 patients

Table 2 Echocardiographic Indices of Mitral Valve Area at 4 Years

Measure	Baseline		48 Months		48 Months–Baseline			
	Percutaneous	Surgery	Percutaneous	Surgery	Percutaneous	Surgery	Difference (95% CI)	p Value
MV area by planimetry, cm^2								
Mean ± SD (n)	6.10 ± 1.50 (171)	6.37 ± 1.73 (89)	3.14 ± 0.87 (77)	3.87 ± 0.95 (29)	−3.14 ± 1.33 (76)	−2.75 ± 1.55 (27)	−0.39 (−1.01, 0.23)	0.213
MV area by pressure half-time, cm^2								
Mean ± SD (n)	4.24 ± 1.06 (179)	4.32 ± 0.96 (91)	2.82 ± 0.82 (96)	3.03 ± 1.00 (45)	−1.38 ± 1.22 (94)	−1.12 ± 1.00 (44)	−0.26 [−0.68, 0.16]	0.222
Mean MV gradient, mm Hg								
Mean ± SD (n)	1.82 ± 0.78 (179)	1.86 ± 1.12 (92)	3.06 ± 1.39 (96)	3.10 ± 1.52 (45)	1.32 ± 1.27 (94)	0.94 ± 1.74 (44)	0.38 (−0.14, 0.90)	0.199

CI = confidence interval; MV = mitral valve.

Table 3 Effectiveness Endpoint and Components at 4 Years

	1 Year			4 Years		
	Percutaneous Repair	Surgical	p Value	Percutaneous Repair	Surgical	p Value
Freedom from death, MV surgery or reoperation, and MR 3+ or 4+	55.2% (100/181)	73.0% (65/89)	0.007	39.8% (64/161)	53.4% (39/73)	0.070
Death	6.1% (11/181)	5.6% (5/89)	1.000	17.4% (28/161)	17.8% (13/73)	0.914
MV surgery or reoperation	20.4% (37/181)	2.2% (2/89)	<0.001	24.8% (40/161)	5.5% (4/73)	<0.001
MR 3+ or 4+ at follow-up	21.0% (38/181)	20.2% (18/89)	1.000	21.7% (35/161)	24.7% (18/73)	0.745

MV = mitral valve; MR = mitral regurgitation.

were randomly assigned in a 2:1 ratio to undergo either percutaneous mitral valve repair (184 patients) or mitral valve surgery (95 patients). Twenty-one patients (6 randomized to the percutaneous repair arm and 15 to surgery) withdrew consent and did not undergo treatment per their randomized assignment. The last patient was

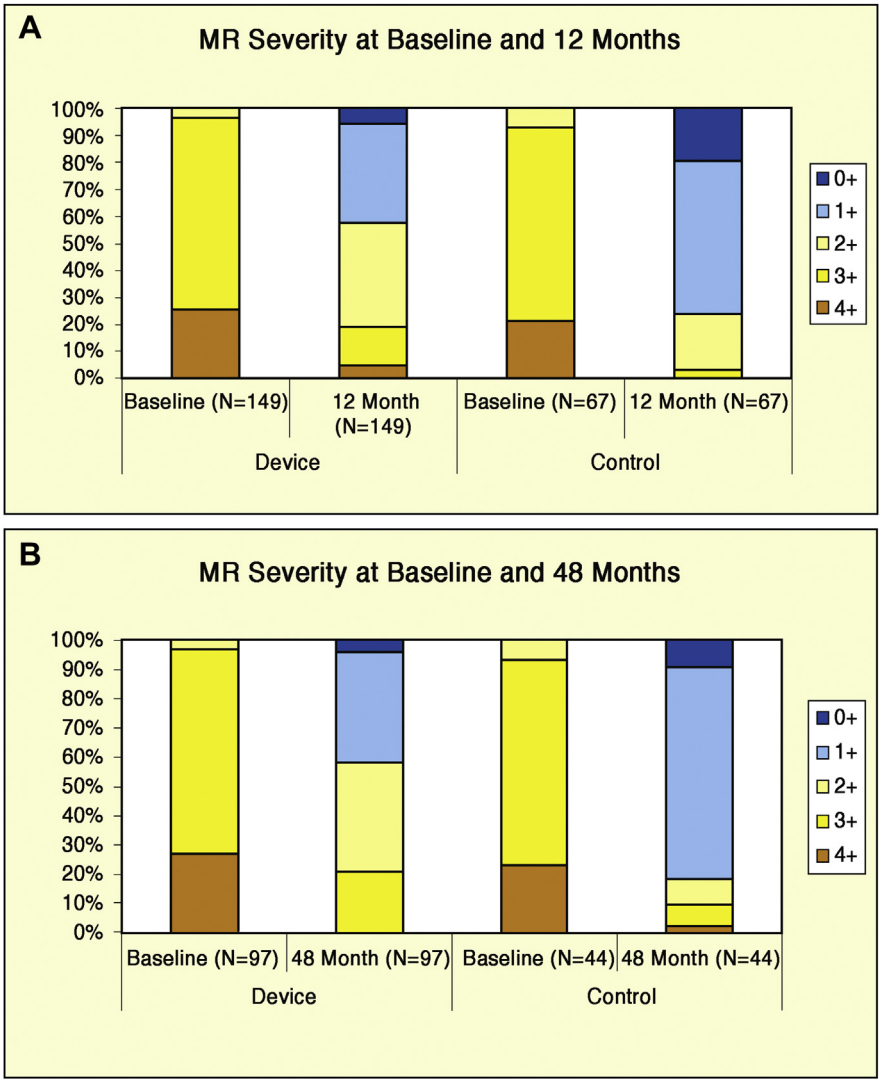
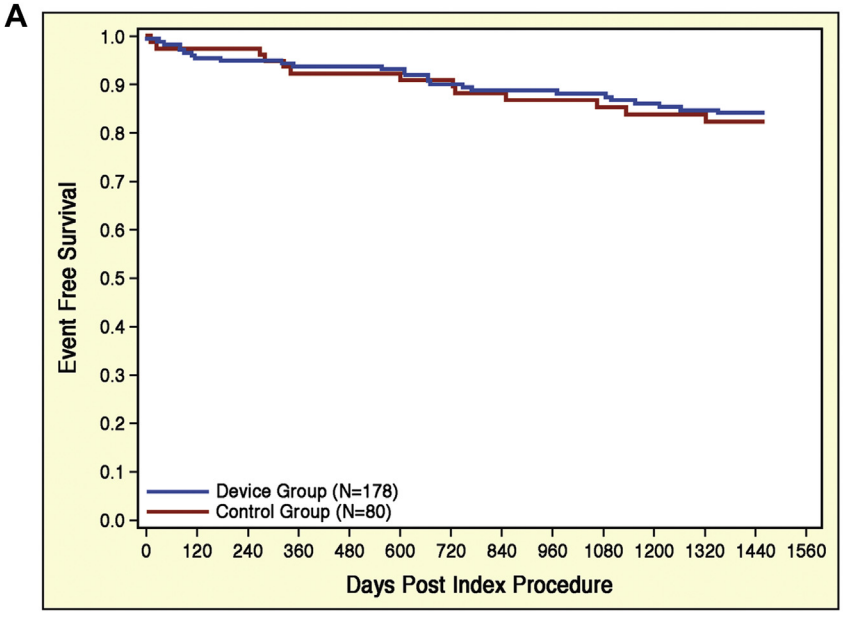


Figure 2 MR Severity by Echocardiography at Baseline, 1-Year, and 4-Year Follow-Up

(A) Mitral valve regurgitation (MR) severity at baseline and 12 months. **(B)** MR severity at baseline and 48 months. Results are matched for each timepoint, and comparisons are presented for patients who had both baseline mitral valve regurgitation (MR) and the given follow-up MR. Mitral regurgitation severity: **dark blue** indicates 0+; **turquoise** indicates 1+; **light yellow** indicates 2+; **dark yellow** indicates 3+; and **orange** indicates 4+.

enrolled and randomized on September 17, 2008, and the last patient was treated on November 11, 2008. The last 4-year follow-up visit was completed on May 9, 2012. Four-year clinical follow-up was complete in 88% in the device group and 77% in the surgical group. The baseline characteristics of patients in the 2 groups, shown in Table 1, were generally well balanced with the exception of a history of congestive heart failure, which was more common in the percutaneous-repair group. Ninety patients (50.6%) were treated with 1 MitraClip device and 68 patients (38.2%) received 2 devices during the index procedure.

Device safety. As previously reported (7), within the first 12 months, 9 patients were noted to have attachment of the device to a single (rather than both) mitral valve leaflet. After 12 months, 1 additional patient was noted to have attachment of the device to a single leaflet. There were no embolizations of any devices observed and all patients with attachment of the device to a single leaflet were treated with mitral valve surgery (5 replacement, 5 repair). There was no difference in the mean change in mitral valve area by pressure-half time or planimetry, nor in the mean change in mitral valve gradient from baseline to 4 years (Table 2). At 4 years, there was 1 (0.6%) case of mitral stenosis (defined as mitral valve area <1.5 cm^2) in a subject with device implanted. At discharge, this patient's mitral valve area and mean gradient were 1.5 cm^2 and 14.5 mm Hg,



Time Post Index Procedure	Baseline	30 Days	6 Month	12 Month	24 Month	36 Months	48 Months
Device Group							
# At Risk	178	176	165	158	133	133	124
# Censored	0	1	4	9	24	24	28
# Events	0	2	9	11	17	21	26
% Event Free	100%	98.9%	94.9%	93.7%	90.0%	87.5%	84.1%
95% CI	-	(95.6%, 99.7%)	(90.4%, 97.3%)	(88.8%, 96.5%)	(84.2%, 93.8%)	(81.1%, 91.8%)	(77.1%, 89.1%)
Control Group							
# At Risk	80	78	76	70	65	57	52
#Censored	0	0	2	4	7	12	15
# Events	0	2	2	6	8	11	13
% Event Free	100%	97.5%	97.5%	92.3%	89.6%	85.3%	82.3%
95% CI	-	(90.4%, 99.4%)	(90.2%, 99.4%)	(83.5%, 96.5%)	(79.9%, 94.7%)	(74.3%, 91.9%)	(70.%, 89.8%)
log-rank							0.7350

Figure 3 Kaplan-Meier Estimates of Freedom From Death and From Surgery at 4 Years

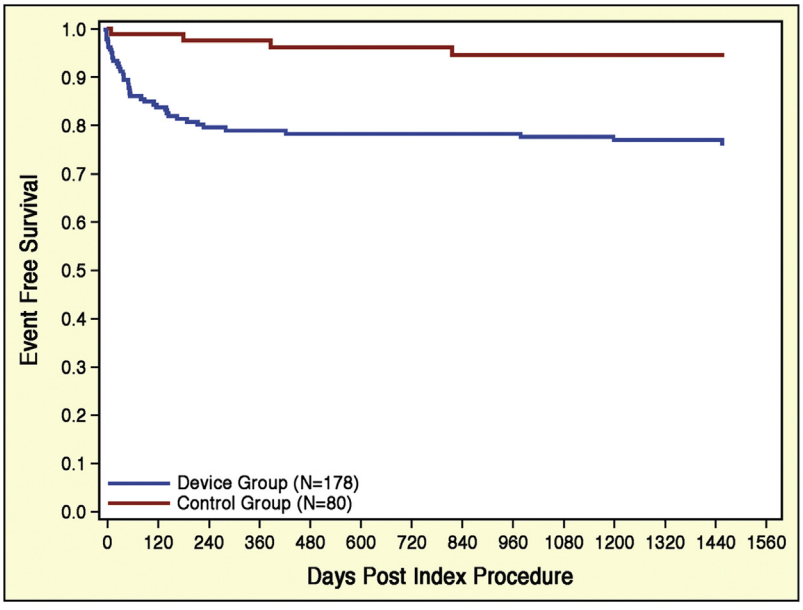
(A) Kaplan-Meier estimates of freedom from death at 4 years.

respectively; and 2.0 cm^2, and 14.7 mm Hg, respectively, at 30-day follow-up. The patient underwent mitral valve replacement surgery for recurrent MR 61 days after the index procedure.

Effectiveness endpoint at 4 years. The overall rate of freedom from death, surgery for mitral valve dysfunction (other than the assigned treatment in the surgical arm), and MR 3+ or 4+ was 39.8% in the percutaneous arm versus 53.4% in the surgical arm (p = 0.070) (Table 3).

Severity of mitral regurgitation. The MR severity as measured by the echocardiography core laboratory is shown for the percutaneous repair and surgical groups in Figure 2. Both groups show an immediate reduction in the number of patients with moderate-to-severe (3+) and severe (4+) MR at discharge. Patients in the surgical group experienced more MR reduction at discharge and throughout 4-year follow-up than percutaneous repair group patients. At 12 months and 4 years, the proportions of patients with 3+ or 4+ MR in the percutaneous repair group were 18.8% (28 of 149) and 20.6% (20 of 97), respectively (4 subjects with 3+ or 4+ MR at year 1 died before year 4; 2 had surgery for MR; and 7 were observed to have had a reduction in MR to

B



Time Post Index Procedure	Baseline	30 Days	6 Month	12 Month	24 Month	36 Months	48 Months
Device Group							
# At Risk	178	164	136	128	117	109	103
# Censored	0	0	9	13	23	30	34
# Events	1	14	33	37	38	39	41
% Event Free	99.4%	92.1%	81.3%	78.9%	78.2%	77.6%	76.1%
95% CI	(96.1%, 99.9%)	(87.1%, 95.3%)	(74.5%, 86.4%)	(71.7%, 84.4%)	(70.7%, 84.0%)	(69.7%, 83.6%)	(68.0%, 82.4%)
Control Group							
# At Risk	80	77	75	69	63	54	49
#Censored	0	2	4	9	14	22	27
# Events	0	1	1	2	3	4	4
% Event Free	100%	98.8%	98.8%	97.4%	96.0%	94.4%	94.4%
95% CI	-	(91.2%, 99.8%)	(91.0%, 99.8%)	(89.5%, 99.4%)	(87.2%, 98.8%)	(84.2%, 98.1%)	(83.4%, 98.2%)
log-rank							0.0006

Figure 3 Continued

(B) Kaplan-Meier estimates of freedom from surgery to treat mitral valve dysfunction at 4 years. In the percutaneous repair arm, any surgery after randomization is considered; in the surgery arm, only reoperation is considered. **Blue lines** indicate device group (n = 178); **red lines** indicate control group (n = 80). CI = confidence interval.

1 or 2+; 7 were not available for follow-up; and 11 new patients had MR 3+). In the surgical group the proportions of patients with 3+ or 4+ MR were 3% (2 of 67) and 9.1% (4 of 44) at 12 months and 4 years, respectively (1 patient had a reduction in MR to 1 or 2+ and 3 new patients had MR 3+). The proportion of patients with 2+ or greater MR at 12 months and 4 years were 57.1% (85 of 149) and 57.7% (56 of 97), respectively, for the percutaneous repair group, and 23.9% (16 of 67) and 18.2% (8 of 44) for the surgical group, respectively.

Second MitraClip procedure. Five patients in the percutaneous repair group underwent a second intervention to place a second MitraClip device through 12 months. In 4 of the 5 second MitraClip interventions, a second MitraClip device was successfully implanted. The patient who did not have a successful second intervention had an additional intervention to place a second MitraClip device between 12 months and 4 years of follow-up.

Four-year mortality. Overall, 82.6% (133 of 161) of patients in the percutaneous repair group and 82.2% (60 of 73) of patients in the surgical group were alive at 48 months (Table 3, Fig. 3A).

Surgery for mitral regurgitation. The rates of surgery for valvular dysfunction were 20.4% versus 2.2% at 1 year ($p < 0.001$) and 24.8% versus 5.5%% ($p < 0.001$) overall over 4 years in the percutaneous versus surgical groups, respectively (Table 3, Fig. 3B). In the percutaneous repair group, the majority of mitral valve surgery (20 repair and 17 replacement) occurred before 12 months (Fig. 3B). After 1 year, 3 patients underwent mitral valve surgery; all undergoing repair rather than replacement. In the surgical group, 2 patients underwent reoperation through 12 months (replacement), and 2 patients underwent reoperation (replacement) between 1 and 4 years.

Change in left ventricular dimensions. In both groups, improvements in left ventricular end-diastolic volume, left ventricular internal diameter, diastolic (LVIDd), and left ventricular end-systolic volume were observed at 1 year and were sustained at 4 years (Table 4). Left ventricular dimensions were similar in both groups except for smaller LVIDd in the surgical group compared with the percutaneous repair group at 4 years (4.84 ± 0.67 cm versus 5.25 ± 0.65 cm, $p < 0.001$).

NYHA functional class. Both groups showed an improvement in NYHA functional class from baseline to 12 months, which was sustained at 4 years (Fig. 4). The proportion of patients in NYHA functional class III or IV in the percutaneous repair group decreased from 45.7% at baseline to 2% at 12 months, and remained low (5.7%) at 4 years. The surgical group also showed improvement in NYHA functional class, with the proportion of patients in NYHA functional class III or IV reduced from 44.8% at baseline to 13.4% at 12 months, and to 6.3% at 4 years.

Interaction and subgroup analysis. Tests of interaction on age and etiology, both significant at 12 months, were performed on the 4-year efficacy endpoint. At 4 years, both etiology and age were still significant ($p = 0.023$ and $p = 0.025$, respectively) (Fig. 5). Among 66 patients with

Table 4 Left Ventricular Dimensions by Echocardiography at Baseline and 1-Year and 4-Year Follow-Up

Measure	Device Group	Control Group	Difference (Device-Control) 95% 2-Sided CI	p Value 2-Sided
Baseline				
LVEDV, ml	159.03 ± 37.33 (144)	160.39 ± 46.66 (66)	−1.35 (−13.22 to 10.51)	0.836
LVIDd, cm	5.53 ± 0.64 (148)	5.41 ± 0.70 (67)	0.12 (−0.07 to 0.31)	0.215
LVESV, ml	63.03 ± 23.54 (144)	61.34 ± 27.88 (66)	1.68 (−5.64 to 9.00)	0.651
LVIDs, cm	3.62 ± 0.88 (146)	3.31 ± 0.72 (67)	0.31 (0.07 to 0.55)	0.012
Month 12				
LVEDV, ml	133.71 ± 35.52 (144)	120.19 ± 44.33 (66)	13.51 (2.24 to 24.79)	0.032
LVIDd, cm	5.10 ± 0.67 (148)	4.80 ± 0.69 (67)	0.30 (0.10 to 0.50)	0.003
LVESV, ml	57.54 ± 24.04 (144)	55.74 ± 31.39 (66)	1.80 (−5.98 to 9.58)	0.680
LVIDs, cm	3.53 ± 0.83 (146)	3.29 ± 0.80 (67)	0.23 (−0.01 to 0.47)	0.056
Baseline*				
LVEDV, ml	155.76 ± 33.67 (94)	162.80 ± 50.82 (41)	−7.04 (−21.71 to 7.62)	0.420
LVIDd, cm	5.51 ± 0.59 (94)	5.40 ± 0.76 (43)	0.11 (−0.13 to 0.34)	0.412
LVIDd, cm	5.51 ± 0.59 (94)	5.40 ± 0.76 (43)	0.11 (−0.13 to 0.34)	0.412
LVIDs, cm	3.58 ± 0.83 (94)	3.28 ± 0.70 (43)	0.30 (0.02 to 0.59)	0.039
Month 48				
LVEDV, ml	125.90 ± 33.42 (94)	113.50 ± 41.67 (41)	12.40 (−0.96 to 25.76)	0.069
LVIDd, cm	5.25 ± 0.65 (94)	4.84 ± 0.67 (43)	0.41 (0.17 to 0.65)	<0.001
LVESV, ml	54.46 ± 24.20 (94)	48.93 ± 27.89 (41)	5.52 (−3.87 to 14.91)	0.247
LVIDs, cm	3.56 ± 0.92 (94)	3.28 ± 0.86 (43)	0.27 (−0.06 to 0.60)	0.103

Values are mean ± SD (n). Results are matched for each time point, and comparisons are presented for patients who had echocardiographic left ventricular measures both at baseline and at the given follow-up. *Among subjects with 48-month echocardiographic follow-up.

CI = confidence interval; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVIDd = left ventricular internal diameter diastolic; LVIDs = left ventricular internal diameter systolic.

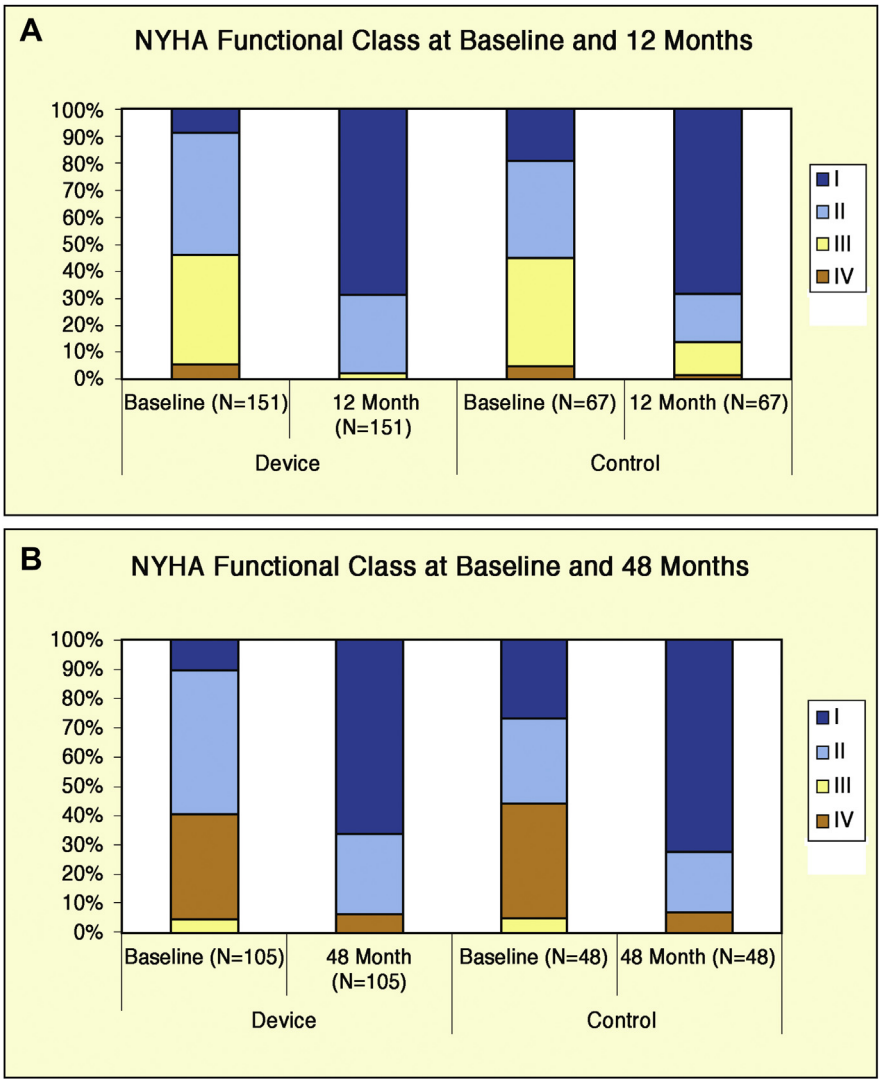


Figure 4 NYHA Functional Class at Baseline and 1-Year and 4-Year Follow-Up

(A) New York Heart Association (NYHA) functional class at baseline and 12 months. **(B)** NYHA functional class at baseline and 48 months. Results are matched for each timepoint, and comparisons are presented for patients who had both baseline mitral valve regurgitation (MR) and the given follow-up MR. **Dark blue** indicates NYHA functional class I; **turquoise** indicates class II; **yellow** indicates class III; and **orange** indicates class IV.

functional MR, the efficacy endpoint rate at 4 years was 34.1% versus 22.7% in the percutaneous repair and surgical groups, respectively ($p = 0.344$). Of subjects with 3+ or 4+ MR at 4 years, functional MR was more prevalent in the surgical arm (9 of 22 subjects) than in the percutaneous arm (8 of 44 subjects).

Discussion

Percutaneous treatment of MR with the MitraClip device was compared with surgery in the EVEREST II randomized trial, and the follow-up of these subjects to 4 years was studied to determine the durability of this procedure to 4 years. Although patients treated with percutaneous therapy achieve less complete reduction in MR at discharge and at 1 years as measured by echocardiography, we found that after year 1, few patients in either treatment arm had recurrent MR or required a repeat mitral valve procedure between years 1 and 4, and mortality rates were not different between the treatment arms at 1 year or 4 years. For the overall trial population, benefits in terms of reduction in NYHA class were sustained and comparable to surgery. Although left ventricular dimensions were reduced with either therapy, the degree of reduction was greater for surgery. In the subset of patients with functional MR, who appeared to have had comparable outcomes with the percutaneous procedure compared with surgery at 1 year, these results were sustained, as measured by freedom from

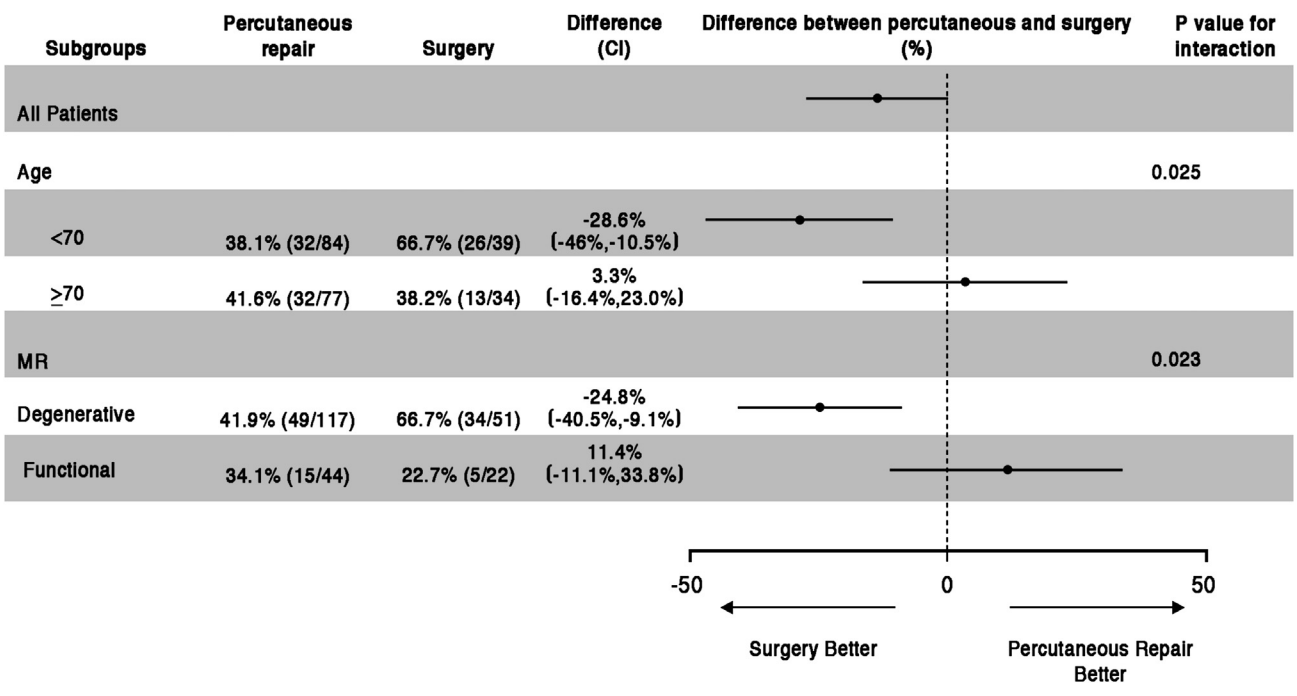


Figure 5 Subgroup Analyses of Efficacy Endpoint at 4 Years

Shown are the differences in rates of the efficacy endpoint (freedom from death, from mitral valve surgery, and from grade 3+ or 4+ mitral regurgitation [MR]) between patients in the percutaneous repair group and patients in the surgery group for all patients and for those in 2 subgroups (age and MR etiology). CI = confidence interval.

death, operation for mitral valve dysfunction, or recurrent MR of grade 3+ or higher.

Percutaneous treatment of MR with the MitraClip device is currently allowed under CE Mark in Europe and is investigational in the United States. The observation that the results of percutaneous treatment are sustained between 1 and 4 years in this study is of critical importance when considering this novel approach. Although there was an up-front lower procedural success rate with percutaneous therapy in the overall trial population, if the percutaneous approach was initially successful, the results were durable, without evidence of late device complications. It is important to consider that the level of procedure experience both by individual operators and overall as well in the EVEREST II trial represents early experience with this novel device. Ten patients (5%) had single leaflet device attachment in this trial, whereas the rate of single leaflet device attachment in practice now is closer to 1% (10). Furthermore, placement of a second device has become more frequent in use of this device after this trial. Therefore, the acute results of this trial of a novel treatment represent early experience that is already being refined in clinical trials and practice.

Almost all of the MitraClip-treated patients who require an additional procedure do so within the first 6 months after initial treatment (Fig. 3B). After this, the rates of reoperation or additional MitraClip procedures are no different between the 2 treatment groups. Based on prior experience with mitral valve surgical repair, there was a concern that the greater amount of post-procedural residual MR in the MitraClip group would lead to more subsequent cross-over to surgery as time passed, or that lesser degrees of residual MR (2+) would result in later deterioration of the 1-year results. Although there does not appear to be significant change in MR grade ventricular function or dimension in follow-up, longer-term follow-up of the subset of patients with MR 2+ is ongoing.

The stability of the results in MitraClip-treated patients up to 4 years is a key finding of this report, with preserved left ventricular function, and ventricular dimensions in follow-up, and few additional patients having increased MR grade after the first year of follow-up. The finding that some patients with MR3+ at 1 year were measured to have 2+ at 4 years, and vice versa, suggests that there is variability in MR or in the measurement of MR over time. This variability may be explained by changing hemodynamic conditions or by left ventricular or valvular remodeling within individual subjects. While such variability is expected of a categorical endpoint, we sought to minimize this by the use of standardized criteria employed by an echocardiographic core laboratory. The results in the surgical arm showed that mitral regurgitation was not unusual in follow-up, and these rates were somewhat higher than those reported in single-center series. It is likely that this observation results from the presence of an echocardiographic core laboratory as

well as from the trial including relatively older patients with more frequent functional MR than those reported in national databases. While the trial inclusion criteria were broad, it is possible that such patients and their physicians were more likely to seek out a percutaneous option even within the context of a randomized trial.

Current experience outside of the United States has shown that percutaneous therapy for MR tends to be selected for patients with either functional MR, and/or patients with higher than average surgical risk (11). Because of the complex pathophysiological underpinnings of ventricular dysfunction and concurrent coronary artery disease, patients with functional MR represent a treatment challenge where surgical treatment options are more limited than for those with isolated leaflet pathology, and are associated with more residual or recurrent MR. In these patients, the relative benefit of surgery over medical therapy is less clear (1–3). While the EVEREST trial was designed to compare a broad spectrum of patients with MR—including both degenerative and functional etiologies of MR—patients with degenerative MR appeared to derive greater benefit from surgery relative to the percutaneous procedure compared with patients with functional MR, a population with more difficulty avoiding recurrent MR after surgery (12). Moreover, patients with degenerative MR who are at high risk for surgery might be expected to have improvements in clinical status with percutaneous repair even if MR reduction is less complete than would have been surgery.

The findings we describe should be viewed in the context of the study design. We chose to utilize an intention-to-treat comparison, following the standard reporting of comparison of treatment strategies, even though some patients, more commonly in the surgical arm, did not receive the assigned therapy. An analysis of patients as treated has shown consistent results regarding 1-year to 4-year durability of findings, and within the subgroup of subjects with functional MR. While 5-year follow-up was specified in the patient consent, many patients withdrew or were lost to follow-up before the 4-year visit, and this was more common in the surgical arm. To overcome this, we performed analysis of MR grade assuming that the last available MR grade was carried forward. However, results using only available data show a lower rate of MR 3+ or 4+ at 4 years in the surgical arm than in the imputed data, and lower than the percutaneous arm. While the results of the imputed data may be biased toward the null, the results for the available data are likely biased toward follow-up of those with more favorable outcomes. Furthermore, the findings in the subgroup with functional MR, even with a positive test for interaction, should be viewed as exploratory. Given the overall sample size, further categorizing subgroups according to components of the primary endpoint or secondary endpoints is limited by power and multiple testing. Whether these results will be reproducible is the subject of 2 ongoing randomized trials in Europe and the United States, comparing percutaneous treatment with the MitraClip device to surgical therapy in patients with functional MR. Finally, while it is reassuring that there is no associated increase in mortality with a percutaneous strategy despite less effective reduction in mitral regurgitation, the sample size and relatively low mortality rate precludes sufficient power to fully understand the impact of the degree of reduction of mitral regurgitation on long-term survival in operative candidates.

Conclusions

At 4 years, surgery remains the standard of care for treatment of MR among eligible patients. Percutaneous repair is associated with similar mortality and symptomatic improvement but a higher rate of MR requiring repeat procedures, and less improvement in left ventricular dimensions than surgery. Although percutaneous repair of the mitral valve to treat MR was associated with a higher rate of residual MR at 1 year, there was no difference in later occurrence of MR or mitral valve intervention between 1-year and 4-year follow-up. Further studies are necessary in patients with functional MR where percutaneous treatment was most comparable to surgery in terms of late efficacy.

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JACC Vol. 62, No. 4, 2013
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Key Words: mitral regurgitation ■ mitral repair ■ percutaneous valve therapy.

APPENDIX

For a full list of site investigators, please see the online version of this article.