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Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation

5-Year Results of EVEREST II

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ABSTRACT

BACKGROUND In EVEREST II (Endovascular Valve Edge-to-Edge Repair Study), treatment of mitral regurgitation (MR) with a novel percutaneous device showed superior safety compared with surgery, but less effective reduction in MR at 1 year.

OBJECTIVES This study sought to evaluate the final 5-year clinical outcomes and durability of percutaneous mitral valve (MV) repair with the MitraClip device compared with conventional MV surgery.

METHODS Patients with grade 3+ or 4+ MR were randomly assigned to percutaneous repair with the device or conventional MV surgery in a 2:1 ratio (178:80). Patients prospectively consented to 5 years of follow-up.

RESULTS At 5 years, the rate of the composite endpoint of freedom from death, surgery, or 3+ or 4+ MR in the as-treated population was 44.2% versus 64.3% in the percutaneous repair and surgical groups, respectively ($p = 0.01$). The difference was driven by increased rates of 3+ to 4+ MR (12.3% vs. 1.8%; $p = 0.02$) and surgery (27.9% vs. 8.9%; $p = 0.003$) with percutaneous repair. After percutaneous repair, 78% of surgeries occurred within the first 6 months. Beyond 6 months, rates of surgery and moderate-to-severe MR were comparable between groups. Five-year mortality rates were 20.8% and 26.8% ($p = 0.4$) for percutaneous repair and surgery, respectively. In multivariable analysis, treatment strategy was not associated with survival.

CONCLUSIONS Patients treated with percutaneous repair more commonly required surgery for residual MR during the first year after treatment, but between 1- and 5-year follow-up, comparably low rates of surgery for MV dysfunction with either percutaneous or surgical therapy endorse the durability of MR reduction with both repair techniques. (EVEREST II Pivotal Study High Risk Registry; NCT00209274) (J Am Coll Cardiol 2015;66:2844–54) © 2015 by the American College of Cardiology Foundation.

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The MitraClip device (Abbott Vascular, Menlo Park, California) was developed as a percutaneous means to reduce mitral regurgitation (MR) by approximating the mitral valve (MV) leaflets. The procedure is modeled after the surgical Alfieri double-orifice technique of MV repair, which has been shown to have durable results when performed in conjunction with an annuloplasty ring for degenerative MR (1,2). We previously reported the results of the randomized EVEREST II (Endovascular Valve Edge-to-Edge Repair Study), in which percutaneous MV repair using this percutaneous approach was compared with conventional surgery (3–5). The primary outcome at 1 year demonstrated that conventional surgery was more effective than percutaneous repair for reducing MR. However, improvements in left ventricular (LV) remodeling and clinical outcomes were similar for both approaches and the percutaneous approach demonstrated a greater level of safety than did surgery (3).

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Several important clinical questions remain unanswered regarding percutaneous MV repair for moderate-to-severe MR. Given the increased prevalence of residual MR and the lack of annuloplasty with this device, the durability of percutaneous repair relative to conventional surgery, and the impact of MV repair technique on long-term survival, symptoms, and LV remodeling, is unknown. We sought to address these questions based on the 5-year, final results of the EVEREST II randomized trial.

METHODS

STUDY DESIGN AND ELIGIBILITY. EVEREST II is a multicenter, randomized, nonblinded trial of the MitraClip system compared with conventional surgery for the treatment of MR with pre-specified 5-year follow-up. Details of the device, study design, and 1-year primary endpoint analysis have been previously reported (3,4). Briefly, 279 patients were enrolled at 37 study centers in North America between September 2005 and November 2008. Eligible patients had moderate-to-severe (3+) or severe (4+) chronic MR and were either symptomatic with left ventricular ejection fraction (LVEF) >25% and LV end-systolic diameter ≤55 mm or asymptomatic with 1 or more of the following: LVEF 25% to 60%, LV end-systolic diameter ≥40 mm, new-onset atrial fibrillation, or pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg at rest or >60 mm Hg with exercise), all according to the 1998/2006 American College of Cardiology/American Heart Association Joint Task Force recommendations for surgical intervention for MR (6,7). Eligible patients had to be candidates for mitral repair or replacement surgery. Anatomic inclusion criteria required that the primary regurgitant jet originated from malcoaptation of the A2 and P2 scallops of the MV. Patients with both functional and degenerative MR were included.

Baseline and follow-up echocardiograms were assessed by an independent echocardiographic core laboratory (University of California, San Francisco).

ABBREVIATIONS AND ACRONYMS

LV = left ventricular

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

MV = mitral valve

NYHA = New York Heart Association

SLDA = single leaflet device attachment

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MR was graded according to American Society of Echocardiography guidelines (8). LV volumes and ejection fraction were measured using the biplane method of disks.

The study complied with the Declaration of Helsinki regarding investigation in humans and was conducted under an Investigational Device Exemption in the United States and Canada. The study was approved by the institutional review boards at participating sites. Written informed consent for 5 years of follow-up was obtained from all patients before randomization.

The trial was designed by the sponsor, Abbott Vascular, in collaboration with the investigators. The 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.

STUDY PROCEDURE AND DEVICE. The percutaneous procedure was performed with the patient under general anesthesia using transesophageal echocardiography and fluoroscopic guidance in the cardiac catheterization laboratory, as previously described (3,9–11). Deployment of a second MitraClip device was permitted if the first did not result in an adequate reduction in MR. If residual MR ≥3+ was determined to be clinically unacceptable, the patient could undergo either a second procedure to place the second device or elective MV surgery. Patients were treated with aspirin, 325 mg daily, for 6 months and clopidogrel, 75 mg daily, for 30 days.

ENDPOINTS. We compared treatment groups using the following endpoints through 5 years within the all-treated cohort: 1) freedom from death, surgery for MV dysfunction, and 3+ and 4+ MR; 2) freedom from death; 3) freedom from surgery for MV dysfunction; and 4) freedom from death and surgery for MV dysfunction. Additional pre-specified analyses include change in LV dimensions and volumes, New York Heart Association (NYHA) classification of heart failure (12), and 36-item short-form health survey quality-of-life score (13). Clinical and echocardiographic follow-up were mandated annually for 5 years. All components of the primary safety and effectiveness endpoints were adjudicated by members of an independent clinical events committee or the core echocardiographic laboratory.

STATISTICAL ANALYSIS. Comparisons were designed and powered with pre-specified effectiveness and safety margins. Surgery was expected to result in more complete MR reduction; however, percutaneous treatment was anticipated to have significantly lower procedural risk. Comparisons were performed within the all-treated cohort, which excludes patients who were randomized but not treated, to avoid bias toward the null. Results from the intention-to-treat cohort are presented in Online Table 1.

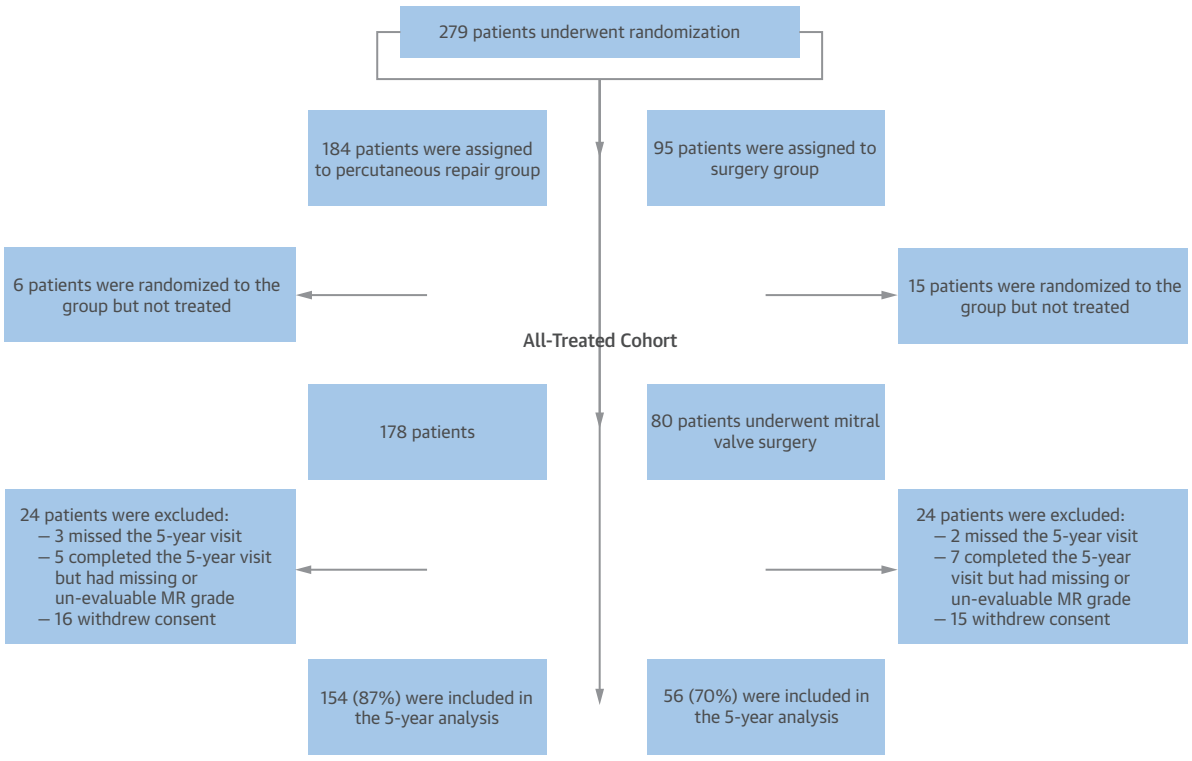
The Student *t* test was used for analyses of continuous variables and Fisher exact test for categorical variables. Because "freedom from 3+ and 4+" is not amenable to time-to-event analyses, we also used Fisher exact test to compare the primary endpoint, its components, and other binary variables. Time-to-event curves were constructed using Kaplan-Meier estimates, which were compared using the log-rank test. To study the effect of risk factors on 5-year mortality, Cox proportional-hazards regression was performed. To evaluate for heterogeneity of the treatment effect on the composite effectiveness endpoint at 5 years, we performed tests for interaction with treatment using the following post-hoc subgroups: sex, age <70 versus ≥70 years, MR etiology (degenerative vs. functional), and LVEF (<60% vs. ≥60%). No adjustments were made for multiple testing. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

We randomly assigned 279 patients from 37 sites between September 2005 and November 2008 in a 2:1 ratio to percutaneous (n = 184) or surgical (n = 95) treatment of MR. Of these patients, 6 and 15 patients in the device and surgery arms, respectively, were randomized but not treated, resulting in 178 and 80 patients in each arm comprising the all-treated cohort that serves as the basis of this analysis. Final 5-year follow-up was completed on November 11, 2013. Twenty-four patients in each arm were excluded from this analysis as detailed in **Figure 1**. The 5-year analysis of the all-treated cohort therefore included 154 (87%) and 56 (70%) patients in the device and surgical arms, respectively. Baseline clinical characteristics were well-balanced across treatment groups (**Table 1**). Ninety patients (50.6%) were treated with a single MitraClip device and 68 patients (38.2%) received 2 devices during the index procedure. The study device was not deployed in the remaining 20 (11.2%) patients.

As previously reported, single leaflet device detachment (SLDA) was observed in 9 patients within the first year of follow-up (3). One additional patient experienced late SLDA approximately 14 months after the percutaneous repair. All patients with SLDA subsequently underwent MV surgery (5 replacement, 5 repair). There were no cases of device embolization through 5-year follow-up. A single case of mitral

FIGURE 1 Study Flow: All-Treated Group



Data are shown for patients in the all-treated cohort evaluated for the 5-year efficacy endpoint. Because the primary endpoint required echocardiographic assessment of mitral regurgitation (MR), patients with missing MR grade at 5-year follow-up were excluded from the analysis.

stenosis, defined as an MV area <1.5 cm^2, was observed after the index procedure before discharge; the patient subsequently underwent MV replacement surgery. There were no additional reports of mitral stenosis through 5 years.

COMPARATIVE EFFECTIVENESS THROUGH 5 YEARS. Freedom from death, surgery for MV dysfunction, and 3+ and 4+ MR occurred at 5 years in 44.2% of patients receiving percutaneous repair and in 64.3% of those receiving surgery ($p = 0.01$) (Table 2). There was no significant difference in mortality between surgery and percutaneous repair at 5 years (20.8% vs. 26.8%; $p = 0.36$) (Table 2); however, surgery or reoperation was more frequent with percutaneous repair (27.9% vs. 8.9%; $p = 0.003$) as was 3+ or 4+ MR (12.3% vs. 1.8%; $p = 0.02$) (Table 2). Clinical outcomes within the intention-to-treat cohort are shown in Online Table 1.

At 5 years, freedom from death and surgery for MV dysfunction was 60.6% with the device versus 73.3% in the surgery group ($p = 0.03$) (Central Illustration). An early hazard for surgery for MV dysfunction was observed after percutaneous repair; specifically, 78% of surgeries (33 of 43) occurred by 6-month follow-up. Beyond 6 months through 5 years, there was no difference in the rate of freedom from surgery for MV dysfunction (77.7% with percutaneous repair vs. 76.2% with surgery; $p = 0.77$) (Central Illustration).

Survivors in both groups demonstrated significant reduction in MR from baseline to 12 months (paired $p < 0.001$ for both groups) and from baseline to 5 years (paired $p < 0.001$ for both groups), demonstrating the durability of MV repair with both the surgical and the percutaneous approaches. As previously reported, surgery proved to be more effective at 12 months because fewer patients had 3+ or 4+ MR after surgery than after percutaneous repair (0% vs. 17.9%; $p = 0.004$). This difference remained at 5-year follow-up (2.5% vs. 18.8%; $p = 0.01$) (Figure 2A).

Despite increased MR reduction with surgery, NYHA functional class III/IV symptoms were more frequently experienced at 12 months with surgery compared with percutaneous repair (7.5% vs. 1.0%; $p = 0.03$) (Figure 2B). At 5 years, a nonsignificant

TABLE 1 Baseline Characteristics: All-Treated Cohort

	Percutaneous Repair	Surgery
Age, yrs	67.0 ± 12.7 (178)	64.7 ± 12.6 (80)
Female	36.5 (65/178)	33.8 (27/80)
Comorbidities		
Congestive heart failure	90.4 (161/178)	80.0 (64/80)
Atrial fibrillation	32.9 (56/170)	38.7 (29/75)
Coronary artery disease	46.9 (83/177)	43.8 (35/80)
Myocardial infarction	21.5 (38/177)	21.5 (17/79)
Coronary artery bypass graft	20.8 (37/178)	16.3 (13/80)
Previous percutaneous intervention	23.7 (42/177)	16.3 (13/80)
Hypercholesterolemia	60.2 (106/176)	68.4 (54/79)
Hypertension	72.5 (129/178)	82.5 (66/80)
Diabetes mellitus	7.9 (14/178)	8.8 (7/80)
COPD	15.3 (27/177)	13.8 (11/80)
LVEF, %	59.9 ± 10.1 (176)	61.3 ± 10.7 (80)
NYHA functional class		
I	9.6 (17/178)	17.5 (14/80)
II	40.4 (72/178)	32.5 (26/80)
III	43.8 (78/178)	45.0 (36/80)
IV	6.2 (11/178)	5.0 (4/80)
MR severity		
0: none	0.0 (0/178)	0.0 (0/80)
1+: mild	0.0 (0/178)	0.0 (0/80)
1+ to 2+: mild to moderate	0.0 (0/178)	1.3 (1/80)
2+: moderate	3.9 (7/178)	6.3 (5/80)
3+: moderate to severe	71.9 (128/178)	70.0 (56/80)
4+: severe	24.2 (43/178)	22.5 (18/80)
Regurgitant volume, ml/beat	42.3 ± 23.4 (169)	46.5 ± 26.7 (73)
Regurgitant orifice area, cm^2	0.55 ± 0.36 (166)	0.60 ± 0.36 (73)
MR etiology		
Functional	27.0 (48/178)	22.5 (18/80)
Degenerative	73.0 (130/178)	77.5 (62/80)
Degenerative with anterior/bileaflet flail/prolapse	32.6 (58/178)	27.5 (22/80)
Degenerative with posterior flail/prolapse	37.6 (67/178)	47.5 (38/80)
Degenerative with neither flail nor prolapse	2.8 (5/178)	2.5 (2/80)

Values are mean ± SD (N) or % (n/N).
COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association.

reversal of this trend was observed such that 8.6% of percutaneous repair patients and 2.5% of surgery patients were classified as having NYHA functional class III or IV symptoms (p = 0.19).

LV REMODELING. As previously reported, significant improvements in LV dimensions were observed after both percutaneous and surgical management of MR at 1- and 4-year follow-up (3,5). LV end-diastolic volume continued to improve between 1 and 5 years after percutaneous MV repair (Table 3). A small increase in LV internal diastolic diameter was observed late after both percutaneous repair and surgery, and LV internal diastolic diameter was significantly smaller at 1 and 5 years with surgery compared with percutaneous repair (Table 3). LVEF decreased slightly beyond 1 year after percutaneous MV repair, but the overall decrement in LV systolic function was comparable between arms and largely attributable to greater reduction in LV end-diastolic versus end-systolic volumes.

Systolic septal-lateral annular dimension was equivalent at baseline, but smaller at 5 years after surgery compared with device. Importantly, systolic septal-lateral annular dimension remained unchanged from baseline to 1 year and from 1 to 5 years among device-treated patients despite the lack of annuloplasty. After surgery, systolic septal-lateral annular dimension decreased significantly from baseline to 1-year follow-up but then increased beyond 1 year. Diastolic septal-lateral annular dimension improved by 1 year but remained stable thereafter in both treatment arms.

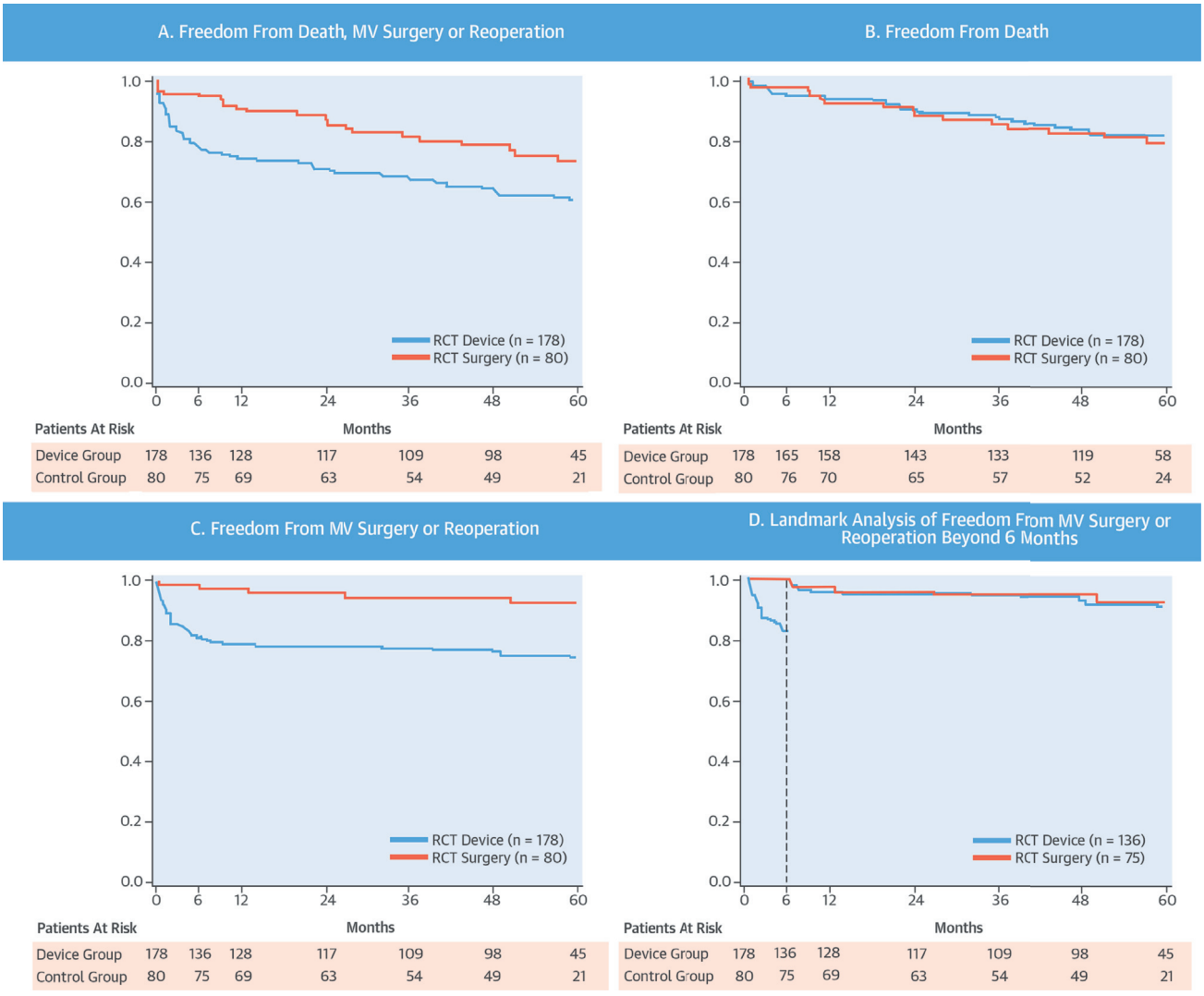
At 1 year, treatment effect heterogeneity was observed in age and etiology of MR subgroups, with a trend suggesting heterogeneity based on LVEF as well (3,5). In relation to freedom from death, surgery for MV dysfunction, and 3+ and 4+ MR at 5 years, significant subgroup interactions persisted between patients who were ≥70 and <70 years of age, such that surgery performed better than percutaneous repair in younger patients (interaction p = 0.005) (Table 4). Similar to what was seen at 1 year, surgery was superior to percutaneous repair in patients with degenerative MR at 5 years (interaction p = 0.02); efficacy, however, was comparable across groups in those with functional MR. Additionally, a significant

TABLE 2 All-Treated Cohort: Efficacy Endpoint and Components at 5 Years*

	5 Years			5 Years if Event-Free at 1 Year		
	Percutaneous Repair (n = 154)	Surgery (n = 56)	p Value	Percutaneous Repair (n = 87)	Surgery (n = 48)	p Value
Freedom from death, MV surgery, or reoperation, and 3+ or 4+ MR	44.2 (68)	64.3 (36)	0.01	69.0 (60)	75.0 (36)	0.55
Death	20.8 (32)	26.8 (15)	0.36	16.1 (14)	16.7 (8)	>0.99
MV surgery or reoperation	27.9 (43)	8.9 (5)	0.003	5.7 (5)	6.3 (3)	>0.99
3+ or 4+ MR	12.3 (19)	1.8 (1)	0.02	11.5 (10)	2.1 (1)	0.10

Values are % (n). *Includes patients that completed the 5-year visit and had MR grade available or died or had MV surgery before withdrawal from the study.
MR = mitral regurgitation; MV = mitral valve.

CENTRAL ILLUSTRATION **5-Year Clinical Outcomes: Percutaneous Repair and Surgery for Mitral Regurgitation**



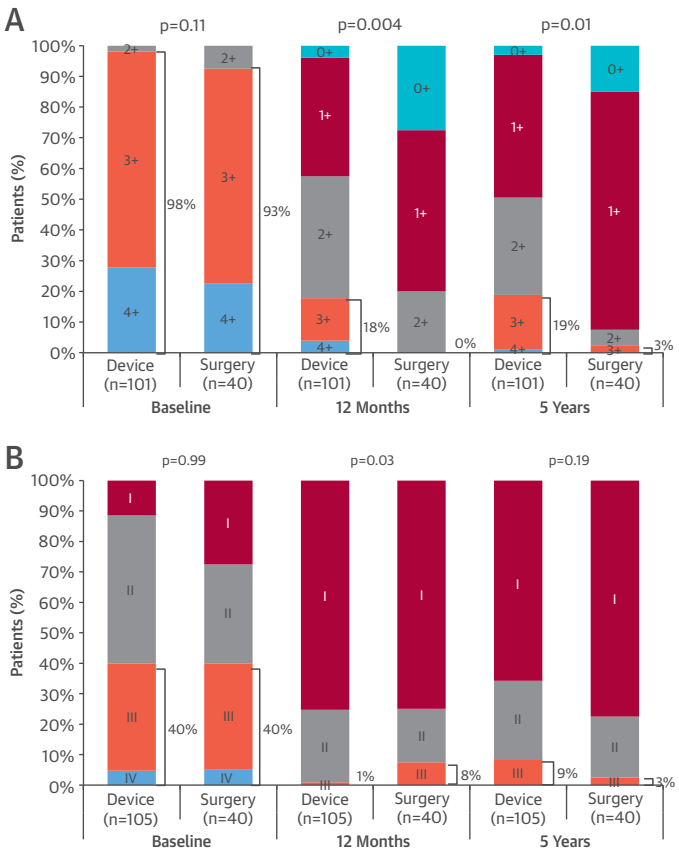
Feldman, T. et al. J Am Coll Cardiol. 2015; 66(25):2844–54.

Kaplan-Meier curves depict **(A)** freedom from the composite of death, mitral valve (MV) surgery, or reoperation, **(B)** freedom from death, **(C)** freedom from MV surgery or reoperation, and **(D)** landmark analysis of freedom from MV surgery or reoperation beyond 6 months after percutaneous repair or surgery. Although patients undergoing percutaneous repair more commonly required surgery for residual mitral regurgitation during the first year after treatment, comparably low rates of surgery for MV dysfunction with either percutaneous or surgical therapy were seen between 1- and 5-year follow-up. RCT = randomized clinical trial.

interaction with LVEF was observed with superior results seen with surgery in those with LVEF ≥60% (interaction p = 0.04).

PREDICTORS OF 5-YEAR MORTALITY. Within pooled analyses of the entire all-treated population, univariable logistic regression identified several predictors of 5-year mortality (Table 5). Predictors consisted largely of established clinical risk factors and comorbid conditions including older age; diabetes; hypertension; moderate-to-severe renal disease; chronic obstructive pulmonary disease; established coronary artery, peripheral artery, or cerebrovascular disease; low LVEF; atrial fibrillation; prior myocardial infarction; and prior cardiac surgery. Functional MR etiology and higher NYHA functional class portended worse 5-year survival. Treatment strategy (percutaneous repair or surgery) did not

FIGURE 2 Severity of MR and Heart Failure Symptoms Post-Treatment



For patients who survived to 5 years and had pertinent data reported at each time point, comparisons are seen for **(A)** echocardiographic severity of MR in 101 and 40 patients in the device and surgery arms, respectively, and **(B)** New York Heart Association functional class in 105 and 40 patients in the device and surgery arms, respectively. MR = mitral regurgitation.

impact 5-year survival in this population. Multivariable analyses identified functional MR, chronic obstructive pulmonary disease, older age, diabetes, and peripheral artery disease as independent predictors of 5-year mortality (Table 5).

DISCUSSION

The EVEREST II randomized trial evaluated the safety and efficacy of percutaneous MV repair using the MitraClip device relative to standard MV surgery (3,4). The 1-year primary analyses demonstrated that percutaneous MV repair was less effective than surgery in reducing MR but that safety with the device was superior to surgery, that LV dimensions and volumes decreased after both percutaneous repair and surgery, and that both techniques similarly relieve clinical symptoms and improve quality of life (3). Taken together with data from the EVEREST II High Risk Registry, REALISM (Real-world Continued Access registry), and the growing European experience with percutaneous repair (14–16), the short-term safety of this percutaneous approach has been clear as has its efficacy in reducing MR, although to a lesser degree than surgery.

The primary finding of the EVEREST II 5-year follow-up is the durability of MR reduction with this device. Despite early imbalance in rates of 3+ or 4+ MR and of subsequent surgery for MV dysfunction, few patients (n = 10 of 43) experienced worsening MR or surgery after 6-month follow-up. In addition, even when there was more severe residual MR after device placement, there was no difference in long-term survival after percutaneous repair compared with surgery (**Central Illustration**) and no decrement in LV systolic function. Supplementing these observations was the persistent reduction in symptoms and LV dimensions at 5 years. The percutaneous approach proved to be safe during follow-up with only 1 case of late (>1 year) SLDA and no reported episodes of device embolization.

Because intrinsic MV pathology in those with degenerative MR does not respond to medical therapy, degenerative MR patients at prohibitive risk for surgery have no alternative treatment options. The favorable safety profile of this device was believed to be a reasonable option for such patients. Based on the experience to date and the observed superiority of surgery for MR reduction in EVEREST II (3), the U.S. Food and Drug Administration approved the MitraClip device in October 2013 for the reduction of "symptomatic MR ≥3+ due to primary abnormality of the mitral apparatus (degenerative MR) in patients who have been determined to be at prohibitive risk for MV surgery by a heart team" (17). Because this approved device is now used in routine clinical practice, it has become important to describe its long-term safety and efficacy. This report of the final 5-year results of EVEREST II support the durability of MR reduction observed after successful device implantation and resultant symptom alleviation and LV reverse remodeling, endorse the long-term safety of this approach, and refute concerns that greater residual MR after percutaneous repair results in reduced long-term survival.

Our findings suggest that the mechanical reduction of MR with percutaneous repair using this device is durable beyond 6 months. Additionally, because MR was reduced to a lesser extent following percutaneous repair compared with surgery, it is also an important finding that residual low-grade MR

TABLE 3 Left Ventricular Dimensions by Echocardiography*

Measure-Matched Analysis	Percutaneous Repair			Surgery			Difference (Percutaneous Repair-Surgery) (95% CI)	p Value
Baseline								
LVEDV, ml	158.1 ± 35.9 (98)			155.7 ± 44.3 (38)			2.4 (-12.1 to 16.9)	0.74
LVESV, ml	61.3 ± 20.1 (98)			58.3 ± 26.7 (38)			3.1 (-5.3 to 11.4)	0.53
LVIDd, cm	5.5 ± 0.6 (101)			5.5 ± 0.7 (41)			0.1 (-0.2 to 0.3)	0.54
LVIDs, cm	3.6 ± 0.9 (99)			3.4 ± 0.8 (41)			0.2 (-0.1 to 0.5)	0.13
LVEF, %	61.5 ± 7.9 (98)			63.2 ± 10.3 (38)			-1.7 (-4.9 to 1.6)	0.37
SLAD diastolic	3.9 ± 0.6 (80)			3.9 ± 0.5 (8)			0.0 (-0.4 to 0.4)	0.94
SLAD systolic	3.3 ± 0.6 (80)			3.3 ± 0.5 (8)			0.0 (-0.5 to 0.4)	0.92
1 Year		**Change From Baseline to 1 Year**	**p Value for Paired Comparison**		**Change From Baseline to 1 Year**	**p Value for Paired Comparison**		
LVEDV, ml	133.7 ± 32.3 (98)	-24.4 ± 2.7	<0.0001	113.5 ± 38.8 (38)	-42.2 ± 6.0	<0.0001	20.3 (7.3 to 33.2)	0.002
LVESV, ml	56.8 ± 21.3 (98)	-4.5 ± 1.4	0.0017	51.4 ± 26.8 (38)	-6.9 ± 3.2	0.04	5.4 (-3.2 to 14.1)	0.22
LVIDd, cm	5.1 ± 0.6 (101)	-0.4 ± 0.0	<0.0001	4.8 ± 0.8 (41)	-0.7 ± 0.1	<0.0001	0.3 (0.1 to 0.6)	0.02
LVIDs, cm	3.5 ± 0.7 (99)	-0.1 ± 0.1	0.06	3.3 ± 0.8 (41)	-0.1 ± 0.1	0.14	0.2 (-0.1 to 0.5)	0.10
LVEF, %	58.2 ± 8.1 (98)	-3.3 ± 0.7	<0.0001	56.3 ± 9.8 (38)	-6.9 ± 1.6	0.0001	2.0 (-1.3 to 5.2)	0.24
SLAD diastolic	3.8 ± 0.4 (80)	0.0 ± 0.1	0.46	3.2 ± 0.4 (8)	-0.6 ± 0.2	0.01	0.6 (0.3 to 1.0)	<0.001
SLAD systolic	3.3 ± 0.4 (80)	-0.1 ± 0.1	0.02	2.7 ± 0.4 (8)	-0.7 ± 0.2	0.002	0.6 (0.3 to 0.9)	<0.001
5 Year		**Change From 1 to 5 Years**			**Change From 1 to 5 Years**			
NYHA functional class I or II	91.4 (96/105)			97.5 (39/40)				0.19
LVEDV, ml	128.5 ± 32.4 (98)	-5.2 ± 2.3	0.02	112.6 ± 38.8 (38)	-0.9 ± 3.1	0.77	15.9 (3.0 to 28.9)	0.02
LVESV, ml	57.2 ± 23.3 (98)	0.4 ± 1.5	0.78	50.2 ± 27.0 (38)	-1.2 ± 2.1	0.57	7.1 (-2.2 to 16.3)	0.13
LVIDd, cm	5.3 ± 0.7 (101)	0.1 ± 0.0	0.0004	4.9 ± 0.7 (41)	0.1 ± 0.1	0.05	0.3 (0.1 to 0.6)	0.009
LVIDs, cm	3.6 ± 0.9 (99)	0.1 ± 0.1	0.06	3.3 ± 0.9 (41)	0.1 ± 0.1	0.40	0.3 (-0.1 to 0.6)	0.09
LVEF, %	56.4 ± 10.2 (98)	-1.8 ± 0.8	0.03	56.9 ± 9.5 (38)	0.7 ± 1.2	0.59	-0.5 (-4.3 to 3.3)	0.79
SLAD diastolic	3.9 ± 0.5 (80)	0.0 ± 0.1	0.61	3.7 ± 0.4 (8)	0.2 ± 0.1	0.07	0.3 (-0.1 to 0.6)	0.14
SLAD systolic	3.3 ± 0.5 (80)	0.1 ± 0.1	0.08	3.0 ± 0.3 (8)	0.5 ± 0.2	0.02	0.4 (0.0 to 0.7)	0.03

Values are mean ± SD (n) or % (n/N), unless otherwise indicated. *Includes patients with each echocardiographic measure at all time points.

CI = confidence interval; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVIDd = left ventricular internal diameter in diastole; LVIDs = left ventricular internal diameter in diastole; SLAD = septal-lateral annular dimension; other abbreviations as in Table 1.

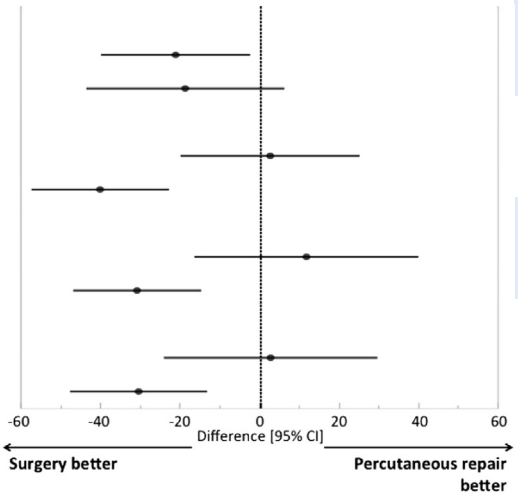
was not associated with either worsening MR or progressive LV dilation. Rather, LV dimensions and volumes and septal-lateral dimensions were comparable following percutaneous repair and surgery at 5 years. Reasons for these favorable results may include tethering of the annulus from the tissue bridge that forms between the anterior and posterior mitral leaflets caused by the device implant, resulting in preserved septal-lateral annular dimension, and overall maintenance of the geometry of the ventricle.

The landmark analysis of this device demonstrated that the clinical failures primarily occurred within the first 6 months, most of which were caused by inadequate MR reduction during the index procedure or early SLDA. Failure to implant a device occurred in 9.5% and SLDA in 6.3% of procedures in this trial. The EVEREST II trial was performed early during the global experience with this first-in-class new technology, and both the acute procedure success rates and SLDA rates have improved significantly in recently reported registry experiences (15,18). Not surprisingly, there has been a significant learning curve, with contemporary acute procedure success rates exceeding 95% in most reports, and SLDA rates of 1% in more recent series (15,18,19).

Treatment effect heterogeneity was observed on the basis of age, etiology of MR, and LVEF such that patients with age ≥70 years, functional MR, or LVEF <60% had similar outcomes with percutaneous repair versus surgery. The complex interplay between the mitral apparatus, concurrent coronary artery disease, and/or cardiomyopathy in functional MR, more prevalent in elderly subjects, results in a clinical challenge for which treatment options are limited (20,21). An efficacious percutaneous treatment option, such as the one studied here, for these high-risk patients is appealing; however, it remains unclear

TABLE 4 Subgroup Analyses for Freedom From Death, MV Surgery or Reoperation, and 3+ or 4+ MR at 5 Years

Subgroup	Percutaneous Repair	Surgery	Difference (95% CI)	p value	Interaction p value
Sex					0.89
Male	42.9 (42/98)	63.9 (23/36)	-21.0% (-39.5% to -2.5%)	0.03	
Female	46.4 (26/56)	65.0 (13/20)	-18.6% (-43.2% to 6.1%)	0.15	
Age					0.005
Age ≥70 yrs	45.1 (32/71)	42.3 (11/26)	2.8% (-19.5% to 25.0%)	0.81	
Age <70 yrs	43.4 (36/83)	83.3 (25/30)	-40.0% (-57.0% to -22.9%)	<0.001	
Type of MR					0.02
Functional MR	40.5 (17/42)	28.6 (4/14)	11.9% (-16.0% to 39.8%)	0.43	
Degenerative MR	45.5 (51/112)	76.2 (32/42)	-30.7% (-46.5% to -14.8%)	<0.001	
LVEF					0.04
LVEF <60%	44.1 (26/59)	41.2 (7/17)	2.9% (-23.7% to 29.5%)	0.83	
LVEF ≥60%	44.1 (41/93)	74.4 (29/39)	-30.3% (-47.3% to -13.3%)	0.001	



Values are % (n/N) unless otherwise indicated.
Abbreviations as in Table 1.

whether either surgery or percutaneous repair are superior to optimal medical therapy alone. The efficacy of this device compared with optimal medical therapy for functional MR is the focus of the ongoing COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial.

TABLE 5 Baseline Predictors of 5-Year Mortality

	Univariable		Multivariable*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Moderate-to-severe renal disease	12.7 (5.2–30.6)	<0.001		
COPD	4.5 (2.5–8.2)	<0.001	2.9 (1.5–5.6)	0.001
Functional MR	4.2 (2.4–7.4)	<0.001	2.7 (1.4–5.0)	0.003
LVEF, %	0.95 (0.93–0.97)	<0.001		
Myocardial infarction	3.8 (2.1–6.8)	<0.001		
Age, yrs	1.1 (1.0–1.1)	<0.001	1.1 (1.0–1.1)	<0.001
NYHA functional class III/IV	4.5 (2.2–9.0)	<0.001		
Coronary artery disease	3.9 (2.0–7.6)	<0.001		
Peripheral artery disease	3.9 (1.9–7.9)	<0.001	2.1 (0.99–4.5)	0.05
Prior cardiac surgery	2.7 (1.5–4.8)	<0.001		
Atrial fibrillation	2.5 (1.4–4.6)	0.003		
Diabetes mellitus	3.2 (1.5–6.8)	0.003	2.3 (1.0–5.1)	0.05
Cerebrovascular disease	2.8 (1.3–6.3)	0.01		
Hypertension	3.0 (1.2–7.6)	0.02		
Hypercholesterolemia	1.9 (1.0–3.8)	0.06		
Stroke	2.8 (0.69–11.8)	0.15		
Male	0.8 (0.46–1.5)	0.54		
BMI (<25.6 vs. ≥25.6 kg/m^2)	1.2 (0.67–2.1)	0.55		
White	0.8 (0.33–1.8)	0.57		
Baseline 4+ MR	0.84 (0.42–1.7)	0.63		
Percutaneous repair vs. surgery	0.94 (0.51–1.7)	0.85		

*Stepwise model with p value of entry of 0.20 and p value to stay of 0.10.
BMI = body mass index; HR = hazard ratio; other abbreviations as in Tables 1 and 3.

Long-term survival in the EVEREST II trial was similar between treatment arms, yet functional MR and advanced age remained important predictors of decreased survival, regardless of percutaneous or surgical treatment. Thus, although MV repair may improve symptoms, the mortality risk associated with functional MR may be related to underlying comorbid conditions leading to LV dilation and not to the MR per se, as has been shown previously (22).

Prior surgical series have reported reoperation rates of 3% per year in patients with degenerative MR, similar to the rate seen in the surgical arm of this study (23). Although most historical surgical reports tend to be single-center, retrospective, self-reported, and without the use of core laboratory echocardiographic review, the prospective nature of this trial helped clearly define the reoperation rate.

STUDY LIMITATIONS. The randomized comparison of percutaneous repair versus surgery, the use of an echocardiographic core laboratory, the prospective 5-year follow-up, and the independent adjudication of clinical events are major strengths of the EVEREST II trial; however, several limitations must be considered. The EVEREST II trial was an open-label study and more patients within the surgical arm withdrew from the study before undergoing MV surgery. Therefore, to better estimate the impact of each

intervention, we opted to analyze the all-treated comparison even though doing so diminished some benefits of randomization. LVEF was well-preserved in the EVEREST II cohort, even among patients with functional MR, making inferences regarding MitraClip outcomes in patients with functional MR and severely depressed LV function difficult. Also, data on septal-lateral annular dimensions after surgery and results of subgroup analyses regarding MR etiology, specifically in demonstrating areas of potential equipoise between surgery and percutaneous repair, should be considered exploratory given the relatively small sample size within these subgroups of patients. It should be noted that the population we studied included both degenerative and functional MR, and is distinct from the populations that are being treated in global practice, those who are the subject of the COAPT trial, and those for whom MitraClip has been approved in the United States.

CONCLUSIONS

The final 5-year results of the EVEREST II trial supported the superiority of surgery in reducing MR but clearly supported the long-term safety of the MitraClip and the durability of MR reduction after percutaneous repair. Beyond 1 year, worsening MR and surgery for MV dysfunction occurred rarely after either surgery or percutaneous repair. Similarly, improvements in heart failure symptoms and in LV dimensions remained stable through 5-year follow-up, mitigating concerns that residual MR after device placement and the absence of an annuloplasty ring with the device would result in progressive worsening of MR and LV dilation. Finally, despite reduction of MR with either percutaneous repair or surgery, functional MR portended increased risk of long-term mortality. Whether reduction of MR in such patients prolongs survival remains to be determined within the ongoing COAPT trial.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Although mitral valve repair surgery is superior to percutaneous mitral valve intervention using the MitraClip device in reducing the severity of MR, the device reduces symptoms, produces durable reduction of MR, and promotes favorable reverse remodeling of the left ventricle 5 years after intervention.

TRANSLATIONAL OUTLOOK: Despite reduction in MR severity either by surgery or deployment of the device, patients with functional MR face an increased long-term risk of mortality, and further studies are needed to determine whether either of these interventions improves survival compared with optimal medical therapy alone.

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KEY WORDS mitral insufficiency, regurgitant lesion, valve therapy

APPENDIX For a supplemental table, please see the online version of this article.