JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 64, NO. 2, 2014

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jacc.2013.12.062

Percutaneous Mitral Valve Repair for Mitral Regurgitation in High-Risk Patients

Results of the EVEREST II Study

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ABSTRACT

BACKGROUND The EVEREST II (Endovascular Valve Edge-to-Edge REpair STudy) High-Risk registry and REALISM Continued Access Study High-Risk Arm are prospective registries of patients who received the MitraClip device (Abbott Vascular, Santa Clara, California) for mitral regurgitation (MR) in the United States.

OBJECTIVES The purpose of this study was to report 12-month outcomes in high-risk patients treated with the percutaneous mitral valve edge-to-edge repair.

METHODS Patients with grades 3 to 4+ MR and a surgical mortality risk of ≥12%, based on the Society of Thoracic Surgeons risk calculator or the estimate of a surgeon coinvestigator following pre-specified protocol criteria, were enrolled.

RESULTS In the studies, 327 of 351 patients completed 12 months of follow-up. Patients were elderly (76 ± 11 years of age), with 70% having functional MR and 60% having prior cardiac surgery. The mitral valve device reduced MR to ≤2+ in 86% of patients at discharge ($n = 325$; $p < 0.0001$). Major adverse events at 30 days included death in 4.8%, myocardial infarction in 1.1%, and stroke in 2.6%. At 12 months, MR was ≤2+ in 84% of patients ($n = 225$; $p < 0.0001$). From baseline to 12 months, left ventricular (LV) end-diastolic volume improved from 161 ± 56 ml to 143 ± 53 ml ($n = 203$; $p < 0.0001$) and LV end-systolic volume improved from 87 ± 47 ml to 79 ± 44 ml ($n = 202$; $p < 0.0001$). New York Heart Association functional class improved from 82% in class III/IV at baseline to 83% in class I/II at 12 months ($n = 234$; $p < 0.0001$). The 36-item Short Form Health Survey physical and mental quality-of-life scores improved from baseline to 12 months ($n = 191$; $p < 0.0001$). Annual hospitalization rate for heart failure fell from 0.79% pre-procedure to 0.41% post-procedure ($n = 338$; $p < 0.0001$). Kaplan-Meier survival estimate at 12 months was 77.2%.

CONCLUSIONS The percutaneous mitral valve device significantly reduced MR, improved clinical symptoms, and decreased LV dimensions at 12 months in this high-surgical-risk cohort. (Endovascular Valve Edge-to-Edge REpair STudy [EVERESTIIRCT]; NCT00209274) (J Am Coll Cardiol 2014;64:172–81) © 2014 by the American College of Cardiology Foundation.

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In the United States today, approximately 40,000 patients per year undergo mitral valve (MV) surgery, mostly for treating significant grade 3 to 4+ mitral regurgitation (MR). Based on American College of Cardiology/American Heart Association practice guidelines (1,2) and the literature (3,4), surgical MV repair or replacement is considered the treatment of choice for patients with significant MR who are either symptomatic or have experienced mechanical consequences of MR. Yet, some studies estimate that only one-half of the patients with an indication for surgery for MR actually undergo surgery (5). Although this may be partly due to patient choice or problems in the healthcare delivery system, many patients are not offered surgery based on their high surgical risk status (6). Evidence of this unmet medical need is clearly demonstrated by the fact that only 5.6% of patients who underwent isolated MV surgery in the Society of Thoracic Surgeons (STS) database from 2008 to 2012 had an STS-predicted mortality rate of >12% (response to a query of the STS database conducted in December 2012 of all isolated MV surgeries between 2008 and 2012).

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Globally, the percutaneous mitral valve edge-to-edge repair device (MitraClip, Abbott Vascular, Santa Clara, California) has been used in more than 10,000 patients to mechanically reduce MR without the incisions and cardiopulmonary bypass needed for MV surgery. Although initial MV trials included patients with low to medium surgical risk, current usage and evidence suggest that a primary role for the MV device may be to treat symptomatic MR in patients who are either unsuitable or at high risk for MV surgery (7).

The EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) clinical trial was designed to assess the safety and efficacy of MV in treating patients with significant MR (8). The EVEREST II trial included 2 prospective registries of high-surgical-risk patients who received the MV device: the EVEREST II High-Risk Registry (EVEREST II HRR), which enrolled 78 high-risk patients between 2007 and 2008, and the ongoing EVEREST II REALISM HR Continued Access Study High-Risk arm, which has enrolled more than 300 patients from 2009 to the present. Both EVEREST II HRR and REALISM HR have included symptomatic patients with grades 3 to 4+ MR for whom surgical risk for perioperative mortality was ≥12%, as estimated using the STS calculator (9) or by a surgeon coinvestigator based on pre-specified criteria (described in the Methods section). The inclusion/exclusion criteria of these 2 registries were essentially the same, allowing data from both of these studies to be pooled and analyzed together. The current investigation is a prospective, multicenter evaluation of the safety and effectiveness of the MV device in patients from both of the EVEREST II high-risk studies who had completed 12 months of follow-up.

ABBREVIATIONS AND ACRONYMS

DMR = degenerative mitral regurgitation

ECL = echocardiographic core laboratory

FMR = functional mitral regurgitation

HF = heart failure

LVEF = left ventricular ejection

MR = mitral regurgitation

MV = mitral valve

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

METHODS

PATIENT SELECTION. For inclusion in these studies, patients had to be symptomatic with grades 3 to 4+ MR and have valve morphology meeting the criteria necessary for MV device placement (10). Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) screening tests were used to establish protocol-based eligibility for the procedure (11–14). MR severity and jet origin were assessed by TTE. The primary regurgitant jet had to originate from leaflet malcoaptation at the A2/P2 region (10). TEE was used to assess MV leaflet anatomy and corroborate MR jet origin. Patients were excluded if they had evidence of an acute myocardial infarction within 2 weeks; a left ventricular ejection fraction (LVEF) of ≤20% and/or an LV end-systolic dimension of >60 mm; an MV area <4.0 cm^2; an MV leaflet anatomy that might preclude successful device implantation; a history of MV leaflet surgery; echocardiographic evidence of an intracardiac mass, thrombus, or vegetation; or active endocarditis.

For both EVEREST II HRR and REALISM HR, the definition of high risk was a surgical mortality risk of ≥12%, based on either the STS risk calculator or an estimate by the surgeon coinvestigator following pre-specified protocol criteria. Potentially qualifying criteria ascertained by a surgeon coinvestigator included porcelain aorta, mobile ascending aortic atheroma, post-mediastinal radiation, functional mitral regurgitation (FMR) with LVEF <40%, age of 75 years or older with LVEF <40%, previous median

Lifesciences; and receives royalties from Edwards Lifesciences. Dr. Feldman is a consultant for and has received honoraria and institutional research support from Abbott, Boston Scientific, Edwards Lifesciences, and WL Gore. All other authors have reported they have no relationships relevant to the contents of this paper to disclose.

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Manuscript received September 7, 2013; revised manuscript received November 18, 2013, accepted December 17, 2013.

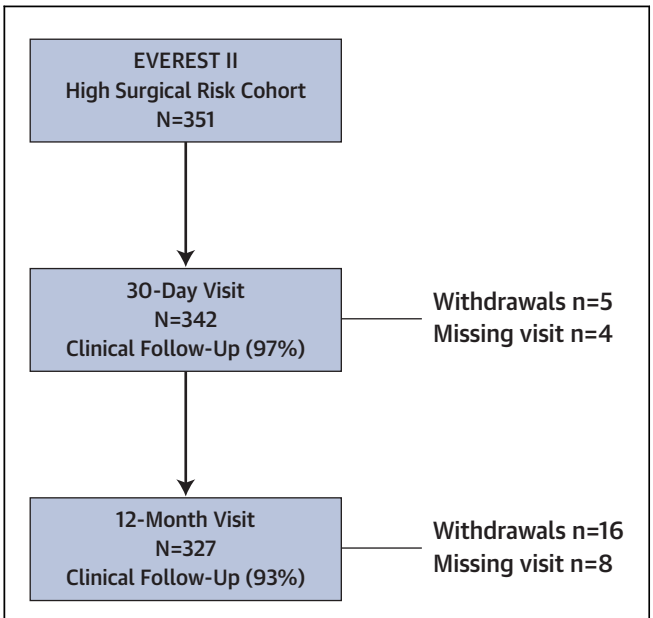


FIGURE 1 Clinical Follow-Up and Patient Compliance

The EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) high-surgical-risk cohort was composed of 78 patients from the EVEREST II HRR and 273 patients from the high-risk arm of the REALISM Continued Access Study. Complete patient accountability from baseline through 12 months is shown. Compliance rates include patients who expired before the follow-up visit. A total of 16 patients withdrew, and 80 deaths occurred over the 12-month period.

sternotomy with patent bypass graft(s), 2 previous chest surgeries, hepatic cirrhosis, or 3 of the following STS high-risk criteria: creatinine level >2.5 mg/dl, previous chest surgery, age older than 75 years, or LVEF <35%. If the patient met all inclusion and no exclusion criteria, the percutaneous MV repair procedure as well as the options for continued medical management and MV surgery were explained to the patient. Patients provided signed informed consent and were enrolled in the studies. The study protocols were approved by the U.S. Food and Drug Administration, and the Institutional Review Board at the participating institutions reviewed the informed consent document (EVEREST II is registered at www.clinicaltrials.gov; NCT00209274).

All pre-procedure, post-procedure, and follow-up TTEs were reviewed and analyzed by a central independent echocardiographic core laboratory (ECL) (University of California, San Francisco, California; or MedStar Health Research Institute, Washington, DC) using American Society of Echocardiography criteria (15,16).

STATISTICAL ANALYSIS. Continuous data are summarized as mean ± SD and evaluated using the paired *t*-test. Categorical data are summarized as proportions and evaluated using the Fisher exact test. Paired binary data are evaluated using the McNemar test, whereas paired ordinal data were evaluated using the Bowker test. The Kaplan-Meier method was used for survival analysis. The 97.5% upper confidence boundary for the 30-day mortality rate was compared to the mean surgical risk as determined by the STS calculator. The rate of hospitalization for heart failure (HF) was estimated and evaluated using a Poisson regression model. In all analyses, a p value <0.05 was considered statistically significant.

RESULTS

Analyses included data from 351 patients enrolled in either EVEREST II HRR (n = 78) or REALISM HR (n = 273). Data were presented to the U.S. Food and Drug Administration's Circulatory System Devices Panel on March 20, 2013. Of the 351 patients, 342 patients (97.4%) had 30-day clinical follow-up available, and 327 patients (93.2%) had 1-year clinical follow-up available (Fig. 1).

All 351 patients met protocol entry criteria for high surgical risk: 151 patients (43.0%) had an STS score of at least 12%, and 200 patients (57.0%) had an STS score <12% but had at least 1 of the protocol-defined risk factors, which characterized the patient as high risk. Among the 200 patients with an STS score <12%, 83 (41.5%) had at least 2 of the 9 pre-defined risk factors. In addition to having at least 1 of the protocol-defined risk factors, patients also had risk factors such as cancer, acquired immunodeficiency syndrome, end-stage renal disease, or connective tissue disease. All 351 patients were confirmed to be at high risk of surgical mortality by a cardiothoracic surgeon.

Overall, the mean STS-predicted mortality risk was 11.3 ± 7.7% for all 351 patients. Baseline demographics are listed in Table 1. Patients were elderly, with an average age of 76 ± 11 years, and presented with primarily FMR (70.1%). The majority of patients had a history of congestive HF (98.0%) and coronary artery disease (82.2%), as well as other significant comorbidities including a history of atrial fibrillation (68.5%), angina (50.8%), hypertension (89.5%), and cardiac surgery (59.8%). Eighty-five percent of patients were symptomatic, with New York Heart Association (NYHA) functional class III or IV.

MITRACLIP PROCEDURE

Of the 351 patients, 15 patients (4.3%) had no MitraClip device implanted, 201 patients (57.3%) had 1 MV device implanted, and 135 (38.5%) had 2 MV devices implanted. In 12 of the 15 patients, the MV device was

TABLE 1 Patient Demographics

	EVEREST Integrated High-Risk Cohort (N = 351)
Age, yrs	75.7 ± 10.5 (351)
Patients over 75 yrs of age	58.1 (204/351)
Male	61.0 (214/351)
Body mass index, kg/m^2	26.9 ± 11.6 (351)
Congestive heart failure	98.0 (344/351)
Coronary artery disease	82.2 (287/349)
Myocardial infarction	50.7 (177/349)
Angina	50.8 (168/331)
Atrial fibrillation	68.5 (217/317)
Cerebrovascular disease	20.5 (72/351)
Stroke	12.8 (45/351)
Peripheral vascular disease	19.0 (66/348)
Cardiomyopathy	57.5 (202/351)
Chronic obstructive pulmonary disease	28.9 (101/350)
Hypertension	89.5 (314/351)
Diabetes	39.4 (138/350)
Moderate to severe renal disease	30.5 (107/351)
Functional MR causes	70.1 (246/351)
Previous cardiovascular surgery	59.8 (210/351)
Previous percutaneous coronary intervention	49.9 (175/331)
Cardiac rhythm device implant	
Pacemaker	20.3 (69/340)
Implantable cardioverter-defibrillator	30.0 (102/340)
NYHA functional class	
I	2.6 (9/351)
II	12.5 (44/351)
III	61.5 (216/351)
IV	23.4 (82/351)
LV ejection fraction	47.5 ± 14.2 (318)
LV internal diameter (systole, cm)	4.4 ± 1.1 (323)

Values are mean ± SD (n) or % (n/N).
LV = left ventricular; MR = mitral regurgitation; NYHA = New York Heart Association.

not implanted due to an inability of the operator to grasp the MV leaflets during implantation. The remaining 3 patients did not have a device implanted because of cardiac tamponade that occurred during transseptal puncture; vascular complication; and right atrial thrombus identified during the TEE, which resulted in the procedure being aborted. No intraprocedural death occurred, and there was no immediate conversion to surgery. Mean procedure time was 157 ± 72 min, and mean fluoroscopy time was 43 ± 24 min.

HOSPITAL STAY AND DISCHARGE. Post-procedure, patients stayed in intensive care for an average of 37 ± 61 h, and the mean hospital stay was 3.2 ± 4.9 days. Most commonly, patients were discharged home (322 of 351 [91.7%]), 5.7% (20 of 351) were transferred to other care facilities, and the remaining 2.6% (9 of 351) either died in hospital or their data were missing. At discharge, 84.6% (275 of 325) of patients achieved at least 1 grade reduction in MR, as determined by the ECL, and 85.8% (279 of 325) of patients had an MR reduction to ≤2+.

MAJOR ADVERSE EVENTS AT 30 DAYS AND AT 12 MONTHS. Death within 30 days of MitraClip procedure occurred in 4.8% (17 of 351) of patients. Of the 17 deaths, 5 occurred in patients that experienced a stroke, 2 occurred in patients who experienced a post-procedure myocardial infarction, 2 were related to vascular complications associated with arterial access in the contralateral groin, 1 was related to a gastrointestinal complication, 1 was related to renal failure, 1 was related to intraprocedural cardiac tamponade, and the 5 remaining deaths were related to underlying patient comorbidities. None of the deaths was related to a device malfunction. The 97.5% upper confidence boundary for 30-day mortality was 7.6%, which was lower than the predicted STS mortality. Additional 30-day major adverse event rates were low (Table 2). The most common adverse event was transfusion of at least 2 U of blood occurring in 13.4% of patients, the majority of which was given for bleeding related to access during the procedure. Additional transfusions were given prophylactically or due to anemia.

Of the 9 strokes that occurred within 30 days, 7 were ischemic and 2 were hemorrhagic. Strokes occurred in patients with a median age of 78 years

TABLE 2 Major Adverse Events at 30 Days and at 12 Months

	EVEREST High-Risk Cohort (N = 351)	
	30 Days	12 Months
Death	4.8 (17/351)	22.8 (80/351)
Myocardial infarction	1.1 (4/351)	2.3 (8/351)
Reoperation for failed surgical repair or replacement	0.0 (0/351)	0.0 (0/351)
Nonelective cardiovascular surgery for adverse events	0.3 (1/351)	0.3 (1/351)
Stroke	2.6 (9/351)	3.4 (12/351)
Renal failure	1.7 (6/351)	5.4 (19/351)
Deep wound infection	0.0 (0/351)	0.0 (0/351)
Ventilation >48 h	2.8 (10/351)	5.4 (19/351)
Gastrointestinal complication requiring surgery	0.3 (1/351)	1.4 (5/351)
New onset of permanent atrial fibrillation	0.3 (1/351)	0.3 (1/351)
Septicemia	0.9 (3/351)	4.3 (15/351)
Blood transfusion ≥2 U	13.4 (47/351)	22.5 (79/351)
Total*	18.8 (66/351)	37.6 (132/351)
Total* (excluding blood transfusions ≥2 U)	9.1 (32/351)	27.9 (98/351)

Values are % (n/N). *Total number of patients may not equal the sum of patients in each row because 1 patient may experience multiple events.

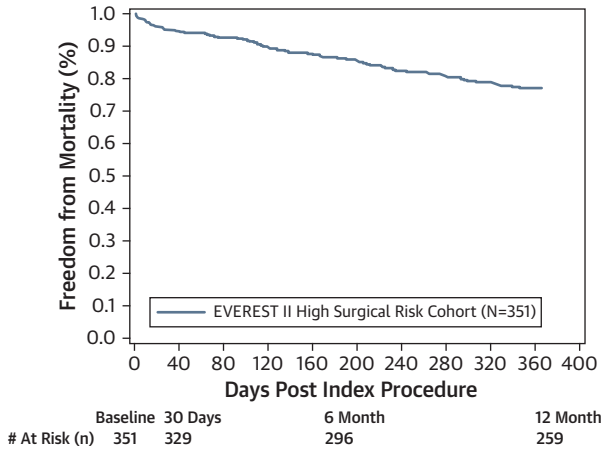


FIGURE 2 Kaplan-Meier Freedom From All-Cause Mortality Compared With Age-Matched Control Subjects

A total of 80 deaths (22.8%) were reported within 12 months of the procedure. The Kaplan-Meier estimate of freedom from mortality at 12 months was 77.2% (95% confidence interval: 72.4% to 81.4%).

and a mean predicted mortality score of 19.9%. Four of the strokes occurred in patients with a history of cerebral vascular accidents and/or chronic atrial fibrillation. Seven strokes were fatal, and 2 resolved. None was determined to be due to the device or air embolization.

Major vascular complications were notably infrequent, occurring in 12 patients (3.4%), consisting of 4 hematomas, 5 access site repairs, and 3 arteriovenous fistulas.

At 12 months, Kaplan-Meier freedom from death was 77.2% (95% confidence interval [CI]: 72.4% to 81.4%) (Fig. 2) and freedom from MV surgery was 97.8%. Between 30 days and 12 months, 63 patients died, of which 64% were assessed as cardiac related and the remaining 36% were assessed as noncardiac related, reflecting the overall comorbid nature of these patients.

Few additional complications occurred between 30 days and 12 months. The 1-year stroke rate was 3.4%, which was expected considering that 69% of the population had a history of atrial fibrillation. Other event rates remained low, with the most common event being transfusion of at least 2 U of blood (Table 2). Transfusions administered beyond 30 days were most often for bleeding unrelated to the MitraClip procedure or for anemia, with only 1 transfusion administered after 30 days for access site bleeding.

DEVICE COMPLICATIONS. Complications specifically related to the device occurred at a low rate (Table 3). No case of device embolization occurred. Single-leaflet device attachment occurs when the device is attached to only 1 of the 2 MV leaflets. Through 12 months, single-leaflet device attachment occurred in 8 patients, with most occurring early (<30 days). Of these 8 patients, 1 had no further intervention, 3 had successful MV surgery, and 4 underwent a successful second procedure. Six of the 7 secondary interventions had successful MR reduction to grade ≤2+. No device embolization occurred. Mitral stenosis (defined as MV area <1.5 cm^2) occurred in 1 patient between 30 days and 12 months, requiring no further intervention.

EFFECTIVENESS AT 12 MONTHS. Effectiveness of the procedure, defined as MR reduction to grade ≤2+, is presented in Figure 3. As measured by the ECL, in patients with paired data at baseline and follow-up, MR grade improved over baseline to ≤2+ in 279 of 325 (85.8%) of patients at discharge and 188 of 225 (83.6%) of patients at 12 months. MR grade improvements observed in patients with paired data across all 3 time points (i.e., at baseline, discharge, and 12 months) are similar: 200 of 223 patients (89.7%) had MR ≤2+ at discharge, and 186 of 223 patients (83.4%) had MR ≤2+ at 12 months. At 12 months, MR grade was <2+ in 81 of 223 patients (36.3%). NYHA functional class improved in most patients (Table 4, Central Illustration). Physical and mental quality-of-life scores improved significantly from baseline to 12 months (Table 4, Fig. 4). LV end-systolic and end-diastolic volumes were significantly reduced from baseline to 12 months (Table 4). The rate of HF hospitalizations decreased significantly from 0.79 in the 12 months before the procedure to 0.41 in the 12 months after the procedure. The proportion of patients hospitalized for HF was reduced from 42.5% (149 of 351) to 19.8% (67 of 338) (Table 5).

TABLE 3 MitraClip Device Complications

	EVEREST High-Risk Cohort (N = 351)	
	Early Phase (Through 30 Days)	Late Phase (>30 Days)
Single leaflet device attachment rate	1.7 (6/351)	0.6 (2/351)
Mitral valve surgery	0.3 (1/351)	0.6 (2/351)
Second MitraClip procedure	1.1 (4/351)	0.0 (0/351)
MitraClip embolization	0.0 (0/351)	0.0 (0/351)
Mitral valve stenosis	0.0 (0/351)	0.9 (3/351)

Values are % (n/N).

OUTCOMES BY DEGENERATIVE MR AND FMR CAUSES. Both FMR and degenerative mitral regurgitation (DMR) causes were represented in EVEREST II HRR and REALISM HR, with FMR present in the majority of patients (70.1%) (Table 1). Safety and effectiveness outcomes also were examined by MR cause (Table 6). DMR patients were older, on average, than FMR patients (by 9 years), but the 2 groups were otherwise comparable. Safety outcomes were similar between the 2 groups, and both of the groups experienced improvements in effectiveness measures.

DISCUSSION

Results of the randomized, controlled EVEREST II trial, comparing percutaneous device repair with MV surgery in surgical candidates, were reported by Feldman et al. (11), with durability reported recently through 4 years (17). Most patients in EVEREST II had DMR. Initial results from clinical experience with the MV device in high-surgical-risk patients were reported by Whitlow et al. (18). The present study was limited to symptomatic patients with moderate to severe or severe MR at high risk for MV surgery. The high-risk nature of the patients in this series is supported by the low rate of MV surgery (2.2%) at 12 months, despite 16.4% of patients who had MR >2+ at 12 months. There has been some criticism of using the STS MV replacement score rather than MV repair score to select patients in this series. However, according to the STS database, among patients who had an STS-predicted mortality of >12% and who underwent isolated MV surgery between 2008 and 2012, 85% underwent MV replacement (response to a query of the STS database conducted in December 2012 of all isolated MV surgeries between 2008 and 2012).

The current study results show that patients who are at very high risk and are either ineligible or marginal candidates for surgery can be successfully treated with the MV device, with morbidity and mortality less than that predicted for surgery using a well-validated surgical risk calculator. Additionally, patients remained in the hospital for an average of only 3 days post-procedure, and 91% of patients were discharged home. These high-risk patients experienced benefit from the procedure at 12 months as shown by significant reduction in MR, improvement in HF symptoms, reduction of HF hospitalization, and reduction of LV dimensions, despite extensive comorbidities that included extensive cardiac and noncardiac diseases. Concerns have been raised that high-risk patients might not benefit from an intervention such as the MV device either because of excessive periprocedural morbidity and mortality or because of significant residual comorbidity that might threaten length and quality of life. These data suggest that this population of high-risk patients can achieve significant improvement in quality of life with relatively little morbidity. Continuing advances in patient selection, patient management, and the procedure itself may further reduce this morbidity.

The patient demographics and results reported in the current study are similar to the recently published 1-year results of the Access-EU post-market registry (7), although the EVEREST II high-surgical-risk patients described here were slightly sicker than those in ACCESS-EU and more often had FMR (7). Overall, however, the safety and effectiveness results in the 2 studies are comparable, and both of the studies have significant clinical implications about the role of the MV device in real-world practice.

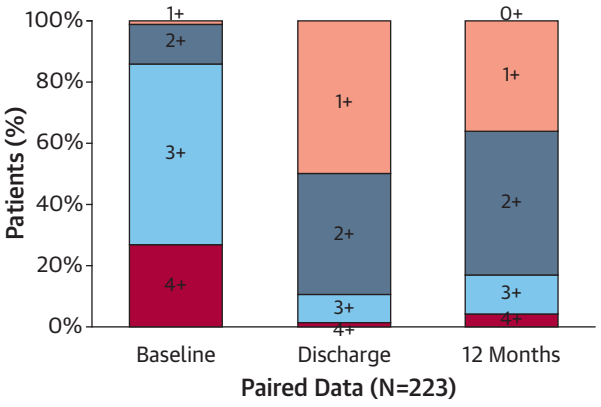


FIGURE 3 Mitral Regurgitation Grade

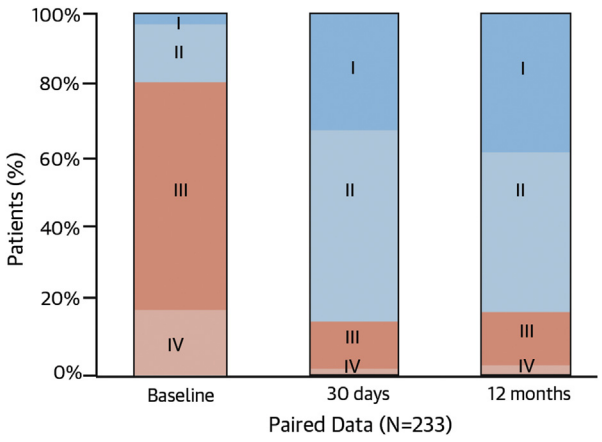
Change in mitral regurgitation severity is shown at baseline, discharge, and 12 months, using paired analysis.

TABLE 4 Clinical Results

	Baseline	12 Months	p Value*
MR grade ≤2+	14.2 (32/225)	83.6 (188/225)	<0.0001
NYHA functional class III to IV	82.1 (192/234)	17.1 (40/234)	<0.0001
SF-36 quality of life			
Physical component score	34.0 ± 9.1 (191)	38.8 ± 11.3 (191)	<0.0001
Mental component score	44.9 ± 13.5 (191)	49.8 ± 12.2 (191)	<0.0001
LV end-diastolic volume, ml	160.5 ± 55.9 (203)	142.6 ± 53.1 (203)	<0.0001
LV end-systolic volume, ml	87.0 ± 46.8 (202)	78.9 ± 43.9 (202)	<0.0001
Ejection fraction, %	48.4 ± 14.0 (202)	47.5 ± 13.4 (202)	0.16

Values are % (n/N) or mean ± SD (n). *All p values are based on data for surviving patients with baseline and 12-month data.

SF-36 = 36-item Short Form Health Survey; other abbreviations as in Table 1.



CENTRAL ILLUSTRATION **Symptoms of Heart Failure (NYHA Functional Class) at Baseline, 30 Days, and 12 Months After Percutaneous MitraClip Placement in High-Risk Patients**

In high-risk patients with severe mitral regurgitation, percutaneous MitraClip therapy significantly improved New York Heart Association (NYHA) functional class at 30 days and at 12 months relative to baseline ($p < 0.001$).

STUDY LIMITATIONS. These data were collected in a narrowly defined group of patients based on specific surgical risk factors and specific anatomic suitability for the MV device. Whether the results can be generalized to even higher-risk patients with life expectancies of <12 months is uncertain. At some point, the net value of a procedure like MitraClip might be less significant in moribund patients with other life-threatening conditions that cannot be treated. Further refinement in all patient selection criteria such as FMR versus DMR, severe pulmonary hypertension, right ventricular dysfunction, tricuspid regurgitation, severe obstructive/restrictive lung disease, dialysis, patient frailty, and a range of ejection fraction that is suitable for the MV device need to be examined in larger studies with greater numbers in each of these subsets and/or appropriate controls.

This study provides only 12 months of data, leaving concerns that MV repair without ring stabilization of the mitral annulus could diminish the long-term benefits of percutaneous repair. In these high-risk patients, the results of MV device placement appear to be very stable from 30 days to 12 months. Other studies have reported stable results up to 4 years (17). Long-term results beyond 10 years will be of less concern in these high-risk patients with limited life expectancy.

There was no parallel surgical or medical control group in this study. While critics consider this a limitation, there are some challenges that justify the absence of a prospective control group in the patient population described. In the current report, percutaneous device is evaluated in both high-risk DMR and FMR patients. Surgical repair or replacement is the treatment of choice for patients with DMR who are suitable MV surgical candidates, with little role for medical therapy. The safety of percutaneous repair

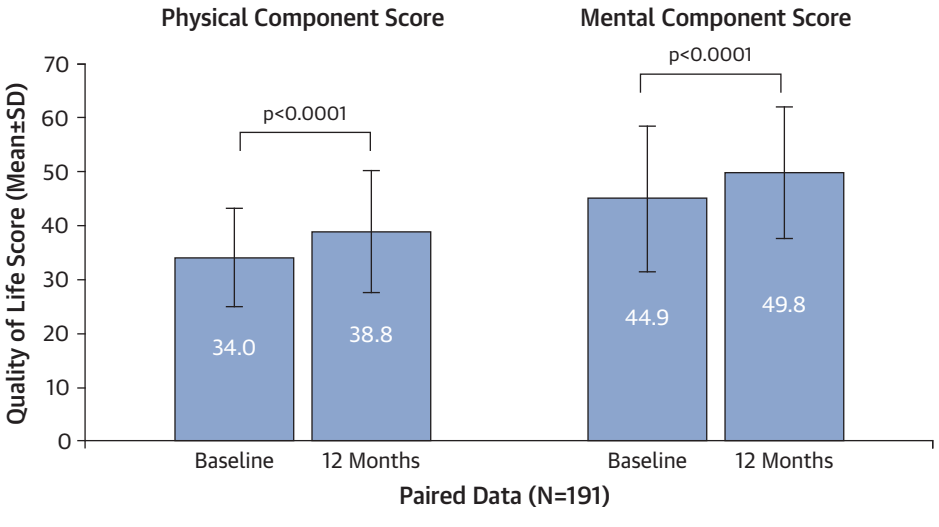


FIGURE 4 **Change in SF-36 Quality of Life Scores From Baseline to 12 Months**

Change in the 36-item Short Form Health Survey (SF-36) physical and mental component scores from baseline to 12 months, using paired analysis.

in comparison to that of surgery has already been shown in EVEREST II; it would therefore be unethical to randomize this subset of high-risk patients to medical treatment. In patients with FMR, however, where the role of surgery remains unclear, a comparison of the MV device to medical therapy seems justified. The positive results reported in the current nonrandomized study, which includes a majority of FMR patients, are therefore the basis of the ongoing COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for Extremely High-Surgical-Risk Patients) trial, which will ultimately compare outcomes of medical therapy to those of

TABLE 5 Hospitalizations for Heart Failure

Parameter	12 Months Pre-Enrollment	Post-Discharge Through 12 Months	p Value
% of patients (n/N)	42.5 (149/351)	19.8 (67/338)*	<0.0001
No. of events	277	118	
Rate (2-sided 95% CI)	0.79 (0.70–0.89)	0.41 (0.34–0.49)	<0.0001

*9 patients died, and 4 patients withdrew before discharge and thus do not provide data for post-discharge hospitalizations.
CI = confidence interval.

TABLE 6 Safety and Effectiveness Outcomes by MR Cause (Degenerative or Functional)

	Degenerative MR (n = 105)	Functional MR (n = 246)
Age, yrs	81.8 ± 8.9 (105)	73.2 ± 10 (246)
Patients over 75 yrs of age	81.0 (85/105)	48.4 (119/246)
Female	40.0 (42/105)	38.6 (95/246)
Previous coronary artery disease	74.8 (77/105)	85.4 (210/246)
Prior myocardial infarction	29.5 (31/105)	59.8 (146/244)
History of atrial fibrillation	71.6 (73/102)	67.0 (144/215)
Prior stroke	9.5 (10/105)	14.2 (35/246)
Diabetes	29.5 (31/105)	43.7 (107/245)
Moderate to severe renal disease	26.7 (28/105)	32.1 (79/246)
Chronic obstructive pulmonary disease (with or without O_2 at home)	28.5 (30/105)	29.0 (71/245)
Hypertension	89.5 (94/105)	89.4 (220/246)
Previous cardiovascular surgery	50.5 (53/105)	63.8 (157/246)
Previous percutaneous coronary intervention	35.2 (37/105)	56.1 (138/246)
NYHA functional class III to IV heart failure	81.9 (86/105)	86.2 (212/246)
LV ejection fraction, %	61.0 ± 10.1 (95)	41.7 ± 11.5 (223)
LV end systolic diameter, cm	3.4 ± 0.8 (92)	4.7 ± 1.0 (231)
Safety outcome		
30-day mortality	6.7 (7/105)	4.1 (10/246)
30-day major adverse event	18.1 (19/105)	19.1 (47/246)
30-day major adverse event (excluding transfusions)	8.6 (9/105)	9.3 (23/246)
30-day major bleeding complication	11.4 (12/105)	8.9 (22/246)
12-month mortality	23.8 (25/105)	22.4 (55/246)
12-month major adverse event	36.2 (38/105)	38.2 (94/246)
12-month major adverse event (excluding transfusions)	26.7 (28/105)	28.5 (70/246)
Effectiveness measure		
Implant success: MR grade	95 (100/105)	96 (236/246)
≤1+ at discharge	48.5 (48/99)	45.1 (102/226)
≤2+ at discharge	80.8 (80/99)	88.1 (199/226)
≤1+ at 12 months	30.9 (21/68)	39.4 (62/157)
≤2+ at 12 months	85.3 (58/68)	82.8 (130/157)
Improvement in LVEDV at 12 months, ml	18.6 ± 22.3 (58)	17.6 ± 35.0 (145)
Improvement in LVESV at 12 months, ml	4.3 ± 14.7 (58)	9.6 ± 25.7 (144)
Improvement in SF-36 physical component score at 12 months, points	6.3 (62)	4.2 (129)
Improvement in SF-36 mental component score at 12 months, points	4.3 (62)	5.3 (129)
NYHA functional class III or IV from baseline → 12 months, %	78.9 → 12.7 (71)	83.4 → 19.0 (63)
Rate of hospitalizations for heart failure (12 months pre-procedure → 12 months post-discharge)	0.71 → 0.21 (105)	0.83 → 0.49 (246)

Values are mean ± SD (n) or % (n/N) unless otherwise indicated.
LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; other abbreviations as in Tables 1 and 4.

percutaneous MV device therapy in selected patients with FMR.

Furthermore, patients in the current study had an unblinded control of medical therapy prior to device implantation, with demonstrated clinical and physiological improvements over time after device therapy relative to baseline medical therapy. Although a placebo effect on quality-of-life measures cannot be excluded, 36% of device patients had a 2-grade improvement in NYHA functional class. In the MIRACLE (Multi-center InSync Randomized Clinical Evaluation) trial, only 6% of patients in the placebo arm and 16% of patients in the treatment arm had a 2-grade improvement (19). Moreover, the placebo effect is unlikely to explain reductions in MR and LV volumes. However, improvement in clinical parameters was evaluated only in surviving patients with paired data at baseline and 12 months, which may introduce potential bias.

Whether MV device imparts a survival benefit in this patient group is less clear from these data and merits further study. Several studies have suggested that the device does, on average, improve HF symptoms and quality of life in selected patients (11,18). A survival advantage and even symptomatic benefit for any therapy may be more difficult to establish in MR than in aortic stenosis (20) because of the more protracted natural history of MR, along with confounding morbidity from conditions like atrial fibrillation, tricuspid valve disease, and biventricular dysfunction.

CONCLUSIONS

These data are unique in that they represent the largest prospective dataset evaluating the outcomes of percutaneous repair in symptomatic patients with grade 3 to 4+ MR who are at high risk of mortality with MV surgery. The MV device is feasible and relatively safe and is effective in reducing symptoms and improving clinical status in this high-risk group of patients who are unlikely to receive surgery and essentially have no other option to reduce MR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with severe MR at high surgical risk, the percutaneous MitraClip device reduced MR, improved symptoms, and decreased LV dimensions 12 months after deployment.

COMPETENCY IN PATIENT CARE: Patients with severe MR, high surgical risk, and suitable mitral anatomy should be considered for MitraClip placement to reduce the severity of MR and LV volume, improve symptoms and quality of life, and prevent hospitalization for HF.

TRANSLATIONAL OUTLOOK 1: More information from ongoing randomized trials is needed to clarify the role of the MitraClip procedure in comparison to clearly-defined medical therapy in patients with severe MR who are not candidates for surgical valve repair or replacement.

TRANSLATIONAL OUTLOOK 2: Refinement of patient selection criteria, such as distinguishing those with functional versus degenerative MR, reduced LVEF, severe pulmonary hypertension, right ventricular dysfunction, tricuspid regurgitation, pulmonary disease, renal impairment, and overall frailty, are needed to define those who stand to gain the most benefit from the MitraClip procedure.

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KEY WORDS high surgical risk, mitral valve insufficiency, percutaneous