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Improved Functional Status and Quality of Life in Prohibitive Surgical Risk Patients With Degenerative Mitral Regurgitation After Transcatheter Mitral Valve Repair

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ABSTRACT

BACKGROUND Surgical mitral valve repair (SMVR) remains the gold standard for severe degenerative mitral regurgitation (DMR). However, the results with transcatheter mitral valve repair (TMVR) in prohibitive-risk DMR patients have not been previously reported.

OBJECTIVES This study aimed to evaluate treatment of mitral regurgitation (MR) in patients with severe DMR at prohibitive surgical risk undergoing TMVR.

METHODS A prohibitive-risk DMR cohort was identified by a multidisciplinary heart team that retrospectively evaluated high-risk DMR patients enrolled in the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II studies.

RESULTS A total of 141 high-risk DMR patients were consecutively enrolled; 127 of these patients were retrospectively identified as meeting the definition of *prohibitive risk* and had 1-year follow-up (median: 1.47 years) available. Patients were elderly (mean age: 82.4 years), severely symptomatic (87% New York Heart Association class III/IV), and at prohibitive surgical risk (STS score: 13.2 ± 7.3%). TMVR (MitraClip) was successfully performed in 95.3%; hospital stay was 2.9 ± 3.1 days. Major adverse events at 30 days included death in 6.3%, myocardial infarction in 0.8%, and stroke in 2.4%. Through 1 year, there were a total of 30 deaths (23.6%), with no survival difference between patients discharged with MR ≤1+ or MR 2+. At 1 year, the majority of surviving patients (82.9%) remained MR ≤2+ at 1 year, and 86.9% were in New York Heart Association functional class I or II. Left ventricular end-diastolic volume decreased (from 125.1 ± 40.1 ml to 108.5 ± 37.9 ml; $p < 0.0001$ [n = 69 survivors with paired data]). SF-36 quality-of-life scores improved and hospitalizations for heart failure were reduced in patients whose MR was reduced.

CONCLUSIONS TMVR in prohibitive surgical risk patients is associated with safety and good clinical outcomes, including decreases in rehospitalization, functional improvements, and favorable ventricular remodeling, at 1 year. (Real World Expanded Multi-center Study of the MitraClip System [REALISM]; NCT01931956)
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The most common cause of mitral regurgitation (MR) in the United States is primary or degenerative mitral valve (MV) disease, which results from congenital or degenerative changes of the valve. Degenerative MR (DMR) initiates a cascade of events, which when left untreated, eventually develop into heart failure (HF) and death. Surgical mitral valve repair (SMVR) remains the gold standard for treatment of severe MR, with the strongest indications (Class I and IIa) for patients with

SEE PAGE 193

DMR (1). However, DMR patients who have a prohibitive risk of surgical mortality have a poor prognosis, as no medical therapy has been found to improve outcomes. The transcatheter mitral valve repair (TMVR) device (MitraClip, Abbott Vascular, Santa Clara, California) has shown promise in reducing MR severity and improving clinical and functional outcomes and quality of life (QoL) in patients with severe MR (2). The objective of this study was to evaluate the relationship between reduction of MR with TMVR and improvement in functional status in patients with severe DMR at prohibitive surgical risk.

METHODS

PROPOSED DEFINITION OF *PROHIBITIVE SURGICAL RISK*. *Prohibitive risk* includes patients with a Society of Thoracic Surgery (STS) predicted risk of mortality for MV replacement of ≥8% (STS calculator version 2.73), or if the patient has factors for prohibitive surgical risk not included in the STS risk calculator.

For purposes of this study, *prohibitive risk for surgical repair of DMR* is defined as the presence of one or more of the following documented surgical risk factors: 1) STS predicted risk of 30-day mortality of ≥8% for MV replacement; 2) porcelain aorta or extensively calcified ascending aorta; 3) frailty (assessed by 2 or more indices); 4) hostile chest; 5) severe liver disease/cirrhosis (Model of End-stage Liver Disease (MELD) score >12); 6) severe pulmonary hypertension (systolic pulmonary artery pressure more than two-thirds systemic pressure); 7) unusual extenuating circumstance, such as right ventricular dysfunction with severe tricuspid regurgitation, chemotherapy for malignancy, major bleeding diathesis, immobility, Acquired Immune Deficiency Syndrome, severe dementia, high risk of aspiration, and internal mammary artery grafts at high risk of injury in a graft-dependent patient.

DETERMINATION OF PROHIBITIVE SURGICAL RISK AND MV ANATOMIC SUITABILITY. From 2003 to 2012, 544 patients with severe (≥3+) DMR were prospectively enrolled in EVEREST I (Endovascular Valve Edge-to-Edge Repair Study), EVEREST II RCT, EVEREST II High Risk Registry, and REALISM (Real World Expanded Multi-center Study of the MitraClip System) continued-access registry (which included both a non-high-risk arm and a high-risk arm). Transthoracic echocardiography and transesophageal echocardiography screening was used to establish protocol-based eligibility for the TMVR procedure (2). Those patients enrolled in the EVEREST II RCT and in the early part of the REALISM studies were of low to moderate surgical risk. However, patients enrolled in the EVEREST II High Risk study (enrollment: February 14, 2007, through January 30, 2008) and the later REALISM continued-access registry (enrollment began January 22, 2009, and is ongoing) were at high surgical risk; pooling of data from these 2 studies was pre-specified in the latter protocol. Selection criteria for both studies were identical. Of the 544 patients with severe DMR, 141 constituted a consecutively enrolled high surgical risk group. The case files for each of these 141 patients from these studies were retrospectively reviewed for prohibitive-risk status by a team of physicians, including 2 experienced mitral valve surgeons and 1 experienced mitral valve cardiologist. For inclusion in the current cohort, all 3 physicians had to concur that a patient met the pre-specified definition of *prohibitive risk*. After enrollment, MR severity was graded by the independent Echocardiographic

ABBREVIATIONS AND ACRONYMS

DMR = degenerative mitral regurgitation
HF = heart failure
LV = left ventricular
MCS = Mental Component Summary
MR = mitral regurgitation
MV = mitral valve
NYHA = New York Heart Association
PCS = Physical Component Summary
QoL = quality of life
STS = Society of Thoracic Surgery
SMVR = surgical mitral valve repair
TMVR = transcatheter mitral valve repair

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Core Laboratory (University of California, San Francisco, California, or MedStar Health Research Institute, Washington, DC) at baseline and all follow-up visits, following the American Society of Echocardiography criteria (3).

COMPOSITION OF PROHIBITIVE-RISK DMR COHORT. The retrospective review identified 127 of the 141 high-risk DMR patients who met the definition of *prohibitive risk* (treated between 2003 and 2012 at 34 investigational sites) with 1-year follow-up (median follow-up: 1.47 years). The resulting prohibitive-risk DMR cohort includes 25 patients from the EVEREST II High Risk Registry, 98 patients from the high-risk arm of the REALISM continued-access registry, and 4 patients treated under "compassionate use" who met the definition of *prohibitive risk* and all MV anatomic criteria for eligibility. Patients were enrolled under historical STS versions 2.52 and 2.61 in the High Risk Registry and version 2.61 in the high-risk arm of REALISM. For consistency in reporting on the retrospectively identified prohibitive-risk DMR cohort, all STS scores were recalculated using the most current version of the STS calculator (version 2.73), and all results are reported using this version.

TMVR PROCEDURE. The TMVR procedure was performed under general anesthesia, via echocardiographic and fluoroscopic guidance as described in a prior publication (2).

STUDY PROCEDURES. The ECL measured MR severity and LV size at baseline, discharge, and 12 months. New York Heart Association (NYHA) functional class was assessed at baseline, 30 days, and 12 months. The SF-36 QoL questionnaire (4) was administered at baseline, 30 days, and 12 months. Patients in the high-risk arm of the REALISM continued-access registry also completed the SF-36 QoL questionnaires at 6 months. HF hospitalizations 12 months prior to and following the TMVR procedure were recorded; length of follow-up post-TMVR was adjusted for in the analysis. An independent clinical events committee adjudicated major adverse events through 1 year.

STATISTICAL ANALYSIS. Continuous data are summarized as mean ± SD, and paired comparisons are performed using the paired *t* test. The Kaplan-Meier method was used for survival analysis. Pairwise comparisons of survival by discharge MR were performed using log-rank tests. SF-36 surveys were scored using standard methods. SF-36 summary scores are reported using the norm-based scoring (population mean: 50; population standard deviation: 10; higher = better), while SF-36 subscales are reported according to their original 0-100 scales (higher = better). Pairwise comparisons using the chi-square test were performed on 2-sample proportions to assess the relationship between discharge MR severity and NYHA functional class at 1 year. The rate of HF hospitalization is estimated and evaluated using a Poisson regression model, with length of follow-up post-discharge as an offset. In all analyses, a p value <0.05 is considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. Table 1 shows baseline demographics and comorbidities for the prohibitive-risk DMR cohort.

The patients had poor functional status: 86.6% were NYHA class III/IV at baseline. As expected, SF-36 QoL scores were well below population norms. Measures of physical function in particular were markedly reduced: the mean Physical Component Summary (PCS) score was 32.0 points at baseline—nearly a full SD below the age-adjusted (age ≥75 years) U.S. norm of 39.9 (5). Likewise, the mean Mental Component Summary (MCS) score of 46.1 was below the age-adjusted population norm of 50.2 for the MCS score.

The reasons for prohibitive risk are summarized in Table 2. A majority of patients (78 of 127 [61.4%]) presented with more than 1 prohibitive risk factor.

PROCEDURAL RESULTS. The mean *procedure time,* defined as the start time of the trans-septal catheterization to the time the steerable guide catheter was removed, was 157 ± 81 min, or approximately 2.5 h. The mean fluoroscopy duration was 46 ± 26 min. There were no intraprocedural deaths.

The TMVR device was implanted successfully in 95.3% of patients (121 of 127). Fifty-six patients (44.1%) received 1 TMVR, and 65 patients (51.2%) received 2 TMVR devices. Six patients (4.7%) did not have a TMVR device implanted. Four of the 6 patients did not receive the device due to technical reasons, including an inability to adequately reduce MR (n = 1), inadequate MV area (n = 1), an inability to place the delivery catheter in the right atrium due to tortuous anatomy (severe scoliosis) (n = 1), and the observation of right atrial thrombus noted on intraprocedural TEE (n = 1). The remaining 2 patients did not receive a device due to complications that occurred during the procedure: trans-septal complication resulting in cardiac tamponade (n = 1) and hemodynamic instability (n = 1). Of the 6 patients who did not receive a device, 1 patient underwent MV surgery 26 days after the TMVR attempt and

TABLE 1 Baseline Demographics and Comorbidities in Prohibitive-Risk DMR Cohort (N = 127)*

Age (yrs)	82.4 ± 8.7
>75 yrs	83.5% (106/127)
Sex	
Female	44.9% (57/127)
Male	55.1% (70/127)
Comorbidities	
Congestive heart failure	98.4% (125/127)
Hypertension	88.2% (112/127)
Coronary artery disease	72.8% (91/125)
Atrial fibrillation history	70.5% (86/122)
Angina	39.3% (46/117)
COPD	31.5% (40/127)
Diabetes	29.9% (38/127)
Moderate to severe renal disease	28.3% (36/127)
Prior myocardial infarction	24.4% (31/127)
Cardiomyopathy	23.6% (30/127)
Cerebrovascular disease history	18.9% (24/127)
Peripheral vascular disease	15.0% (19/127)
Prior stroke	10.2% (13/127)
Treatment history	
Previous cardiovascular surgery	48.0% (61/127)
Previous CABG surgery	40.9% (52/127)
Previous PCI	33.3% (42/126)
Cardiac rhythm device implant	
Pacemaker	21.1% (26/123)
ICD	7.3% (9/123)
NYHA functional class	
I	2.4% (3/127)
II	11.0% (14/127)
III	63.8% (81/127)
IV	22.8% (29/127)
STS replacement mortality risk (%)†	13.2 ± 7.3 (127)
Risk ≥8%	79.5% (101/127)
LV function	
LV ejection fraction (%)	60.6 ± 9.5 (112)
LV internal diameter, systole (cm)	3.4 ± 0.8 (113)
LV end-diastolic volume (ml)	127.0 ± 40.5 (112)
Quality of life	
SF-36 PCS score	32.0 ± 8.7 (121)
SF-36 MCS score	46.1 ± 12.5 (121)

Values are mean ± SD (N) or % (n/N). *Sample sizes or denominators <N reflect missing data. †Scores were recalculated by the sponsor using the STS Calculator version 2.73 (http://riskcalc.sts.org/STSWebRiskCalc273).

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; DMR = degenerative mitral regurgitation. ICD = implantable cardioverter-defibrillator; LV = left ventricular; MCS = Mental Component Summary; NYHA = New York Heart Association; PCI = percutaneous intervention; PCS = Physical Component Summary; SF-36 = 36-item Short Form Health Survey; STS = Society of Thoracic Surgery.

subsequently died on day 110. Three additional patients died without further intervention for MR, at days 9, 25, and 128. The remaining 2 patients withdrew from the study without further intervention for DMR.

SAFETY OUTCOMES. Table 3 presents safety outcomes in the prohibitive-risk DMR cohort. Rates of nonfatal events were consistent with the published safety profile for TMVR observed in the EVEREST II High Risk Registry (2) and the ACCESS-EU Study (ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe) (6).

Eight patients died within 30 days of the TMVR procedure. This observed 30-day mortality rate of 6.3% was considerably less than the study population's mean STS-predicted surgical mortality of

TABLE 2 Prohibitive Surgical Risk Factors in This Prohibitive-Risk DMR Cohort (N = 127)*

STS mortality risk score ≥8%	101 (79.5%)
Risk factors in patients with STS mortality risk score <8% not captured in the STS calculator	
Porcelain aorta	8 (6.3%)
Hostile chest	5 (3.9%)
Severe liver disease or cirrhosis	4 (3.1%)
Severe pulmonary hypertension	3 (2.4%)
Frailty	2 (1.6%)
Unusual extenuating circumstance	
High risk of aspiration	4 (3.1%)
IMA at high risk of injury	4 (3.1%)
Major bleeding diathesis	2 (1.6%)
Severe dementia	2 (1.6%)
AIDS	1 (0.8%)
Chemotherapy for malignancy	1 (0.8%)
Immobility	1 (0.8%)

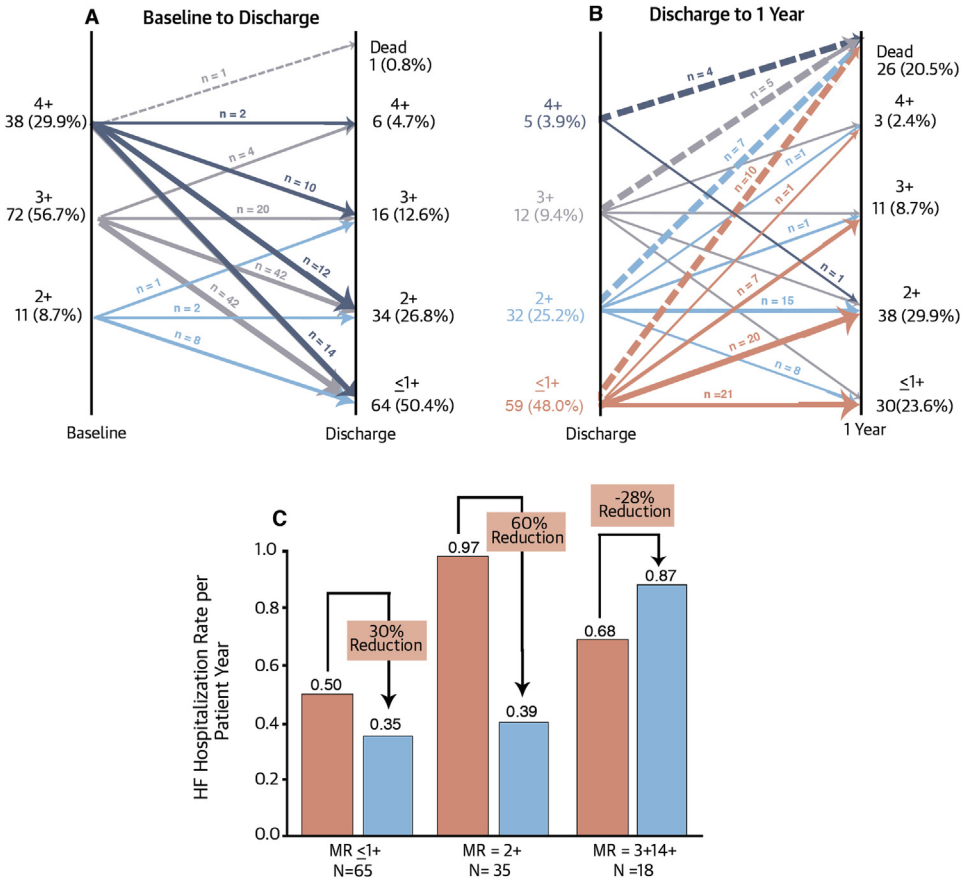
Values are n (%). *Nonhierarchical listing; patients may present at baseline with more than 1 prohibitive risk factor.

IMA = internal mammary artery; STS = Society of Thoracic Surgery.

TABLE 3 Safety Outcomes in Prohibitive-Risk DMR Cohort (N = 127)

Description of Event	30 Days	12 Months
Major bleeding complications	12.6% (16/127)	15.7% (20/127)
Death*	6.3% (8/127)	23.6% (30/127)
Major vascular complications	5.5% (7/127)	7.1% (9/127)
Ventilation >48 h*	3.1% (4/127)	4.7% (6/127)
Stroke*	2.4% (3/127)	2.4% (3/127)
Renal failure*	1.6% (2/127)	3.9% (5/127)
Atrial septal defect	1.6% (2/127)	2.4% (3/127)
Noncerebral thromboembolism	1.6% (2/127)	1.6% (2/127)
GI complication requiring surgery*	0.8% (1/127)	2.4% (3/127)
Myocardial infarction*	0.8% (1/127)	0.8% (1/127)
Nonelective cardiovascular surgery for adverse events*	0.8% (1/127)	0.8% (1/127)
Mitral valve stenosis	0	2.4% (3/127)
Heart block/other arrhythmia requiring permanent pacemaker	0	1.6% (2/127)
New onset of permanent AF*	0	0

Values are % (n/N). Major bleeding complications, defined as procedure-related bleeding requiring transfusions of at least 2 units or surgery, occurred at a rate of 12.6% at 30 days. The majority of bleeding events required transfusions rather than surgery. *Clinical Event Committee adjudicated.



CENTRAL ILLUSTRATION **Impact of TMVR on MR and Reduction of HF Rehospitalization Rate**

(A) From baseline to discharge and **(B)** from discharge to 1 year (n and % based on 127 [100%]). **(C)** Mitral regurgitation (MR) grade at discharge and with deaths treated as heart failure (HF) hospitalizations.

13.2% with SMVR. Through 12 months, there were a total of 30 deaths (23.6%).

The median age of patients who died prior to 30 days was 86 years; 3 were female and 5 were male. Four (4) of the 8 patients received 2 devices, 2 patients received 1 device, and 2 patients did not receive any TMVR. The mean predicted surgical mortality risk of the 8 patients (using STS version 2.73 replacement score) was 17.6%. Six deaths were clinical event committee-adjudicated as cardiac related, and 1 of these was further adjudicated as device related due to a prolonged procedure. Reasons for the 8 deaths included septic shock (n = 1), existing comorbidities (n = 2), gastrointestinal bleed (n = 1), renal failure and cardiac tamponade (n = 1), myocardial infarction (n = 1), vascular bleeding (n = 1), and stroke (n = 1).

There have been no reports of a TMVR device embolization or single leaflet device attachment in the prohibitive-risk DMR cohort through the observed follow-up (median: 1.47 years).

POST-PROCEDURAL STATUS AND LENGTH OF HOSPITAL STAY. The mean post-procedure length of stay in the intensive care unit was 1.4 ± 1.8 days. The average length of hospital stay was 2.9 ± 3.1 days. Despite the elderly, highly comorbid nature of this population, 88% of the prohibitive-risk DMR patients were discharged home following the TMVR procedure.

MR SEVERITY. Central Illustration, panel A, shows MR severity at baseline and discharge in patients with paired measurements available (patients in the REALISM continued-access registry were permitted

to enroll based on site-determined MR severity, which underwent subsequent ECL assessment. Improvements to MR ≤2+ were observed in 62 of the 72 (86.1%) patients with baseline MR of 3+ and in 26 of the 38 (68.4%) patients with baseline 4+ MR. Improvements to MR ≤1+ were observed in 42 of the 72 (58.3%) patients with baseline MR of 3+ and in 14 of the 38 (36.8%) patients with baseline MR of 4+.

Central Illustration, panel B, shows MR severity at discharge and 1 year in patients with paired measurements. Of 91 patients discharged with MR ≤2+, 64 patients (70.3%) sustained MR ≤2+ at 1 year, 10 (11.0%) experienced worsening MR to 3+ or 4+, and 17 (18.7%) died. Of 59 patients discharged with MR ≤1+, 21 patients (35.6%) sustained MR ≤1+ at 1 year, 20 (33.9%) experienced MR increase to 2+, 8 (13.6%) experienced worsening MR to 3+ or 4+, and 10 (16.9%) died.

CONVERSION TO OPEN MITRAL SURGERY IN SURVIVING PATIENTS. Despite their high surgical risk, 3 patients (2.4%) underwent open MV surgery through 12 months following the TMVR procedure. One patient who received 2 TMVR but did not achieve adequate MR reduction; this patient underwent successful MV replacement 2 days post TMVR procedure and was alive at 1 year, with core-lab-rated MR 1+. The second patient who received 2 devices but experienced continued HF after discharge; this patient underwent successful MV replacement 56 days post TMVR and was alive at 1 year, with core-lab-rated MR 1+. The third patient underwent the TMVR but did not receive a device due to leaflet pathology; this patient underwent successful MV repair 26 days post TMVR but died of congestive HF 84 days after surgery.

SF-36 QOL MEASURES. **Figure 1** shows the SF-36 QoL PCS and MCS mean scores at baseline and through follow-up. Mean scores, in particular for PCS, were markedly depressed at baseline, but approximated population norms for adults who are ≥75 years of age at 1, 6, and 12 months post TMVR.

Group changes from baseline, based on available paired comparisons at each time point for the SF-36 summary scores as well as the 8 SF-36 subscales, are shown in **Table 4**. The PCS scores at each follow-up time point improved by ~6 points from baseline, and the MCS scores improved by ~3 points at 30 days and 5 to 6 points thereafter ($p < 0.01$ for all comparisons). These changes exceeded the 2- to 3-point threshold generally considered to indicate a minimum clinically important difference (5). Highly significant improvements were seen for all SF-36 subscales at every time point, except bodily pain (which is not a typical manifestation of MR) and the role-emotional scale at 30 days.

RELATIONSHIP OF ONGOING RESIDUAL MR TO SURVIVAL. The relationship of residual MR to survival is shown in **Figure 2**. Notably, patients who were discharged with MR severity of 2+ had survival 12-month survival as those with MR ≤1+ at discharge. In contrast, patients with either MR ≤1+ or 2+ at discharge exhibited better 12-month survival than those discharged with MR 3+/4. Of the 22 patients discharged with MR 3+ or 4+, survival at 1 year was 52.4% (95% CI: 28.6% to 71.6%). Similarly, survival at 12 months was 83.3% (95% CI: 70.9% to 90.8%) for patients discharged with MR ≤1+ and 80.0%

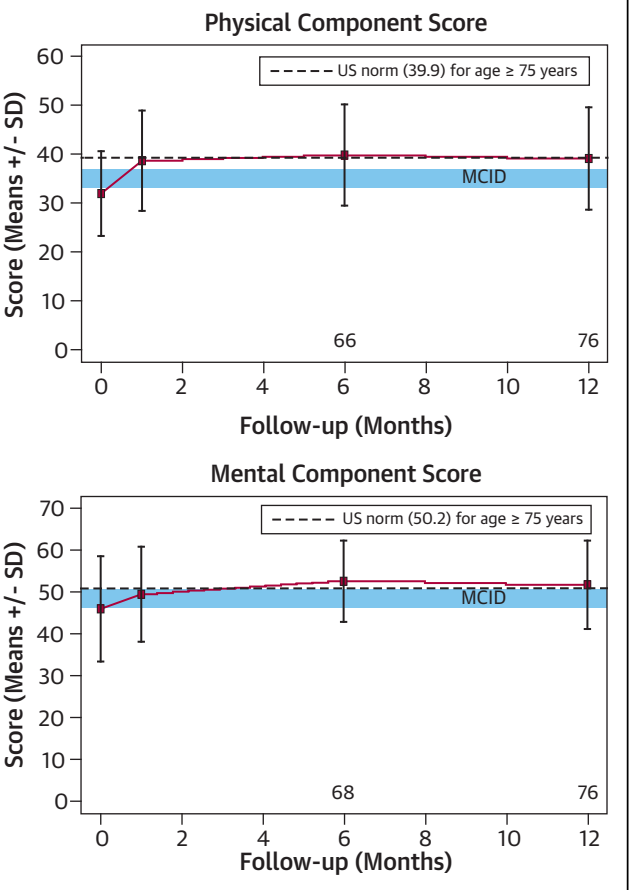


FIGURE 1 SF-36 QoL Measures Through 1 Year

There were significant improvements in the SF-36 quality of life questionnaire results on both physical and mental components above the minimal clinically important difference. MCID = minimal clinically important difference; SF-36 QoL = quality of life as measured using the 36-item Short Form Health Survey.

TABLE 4 SF-36 QoL Scores at Baseline and Changes From Baseline (n = 122 Evaluable Patients)

	QoL Score		Δ vs. Baseline*		
Item/Time Point	Mean ± SD (n)	95% CI	Mean	95% CI	p Value
Physical summary					
Baseline	32.0 ± 8.7 (121)	(30.4 to 33.6)	-	-	-
30 days	38.7 ± 10.3 (101)	(36.6 to 40.7)	6.2	(4.3 to 8.2)	<0.0001
6 months	39.9 ± 10.4 (66)	(37.4 to 42.5)	5.9	(3.4 to 8.3)	<0.0001
12 months	39.2 ± 10.5 (76)	(36.8 to 41.6)	6.0	(4.0 to 8.0)	<0.0001
Physical function					
Baseline	30.9 ± 23.9 (122)	(26.6 to 35.2)	-	-	-
30 days	47.2 ± 27.1 (103)	(41.9 to 52.5)	15.7	(10.1 to 21.3)	<0.0001
6 months	52.4 ± 25.5 (67)	(46.2 to 58.7)	15.1	(8.9 to 21.3)	<0.0001
12 months	51.8 ± 25.2 (76)	(46.0 to 57.5)	16.6	(11.0 to 22.3)	<0.0001
Role physical					
Baseline	28.0 ± 24.7 (122)	(23.6 to 32.4)	-	-	-
30 days	47.0 ± 28.3 (101)	(41.4 to 52.6)	18.5	(12.2 to 24.7)	<0.0001
6 months	55.5 ± 30.5 (68)	(48.1 to 62.9)	25.2	(16.6 to 33.9)	<0.0001
12 months	55.2 ± 29.4 (76)	(48.5 to 62.0)	24.4	(16.7 to 32.1)	<0.0001
Bodily pain					
Baseline	61.8 ± 30.6 (122)	(56.3 to 67.3)	-	-	-
30 days	68.1 ± 30.5 (102)	(62.1 to 74.1)	5.9	(0.7 to 11.2)	0.0279
6 months	67.1 ± 28.1 (66)	(60.2 to 74.0)	3.8	(-3.5 to 11.2)	0.2994
12 months	64.6 ± 29.8 (76)	(57.8 to 71.4)	2.5	(-3.5 to 8.5)	0.4108
General health					
Baseline	50.3 ± 19.1 (122)	(46.9 to 53.8)	-	-	-
30 days	62.5 ± 20.3 (103)	(58.5 to 66.5)	11.2	(7.5 to 15.0)	<0.0001
6 months	65.4 ± 21.2 (69)	(60.3 to 70.5)	12.5	(7.8 to 17.2)	<0.0001
12 months	61.3 ± 21.0 (76)	(56.5 to 66.1)	9.3	(4.7 to 14.0)	0.0001
Mental summary					
Baseline	46.1 ± 12.5 (121)	(43.9 to 48.4)	-	-	-
30 days	49.5 ± 11.3 (101)	(47.3 to 51.8)	3.4	(1.0 to 5.9)	0.0064
6 months	52.7 ± 9.7 (68)	(50.3 to 55.0)	6.1	(2.9 to 9.3)	0.0004
12 months	51.8 ± 10.5 (76)	(49.4 to 54.2)	5.6	(2.3 to 8.9)	0.0011
Vitality					
Baseline	37.5 ± 21.9 (121)	(33.6 to 41.4)	-	-	-
30 days	52.3 ± 23.3 (102)	(47.7 to 56.8)	14.0	(8.8 to 19.2)	<0.0001
6 months	54.3 ± 20.5 (69)	(49.4 to 59.2)	13.8	(7.1 to 20.5)	0.0001
12 months	54.9 ± 20.1 (76)	(50.3 to 59.5)	16.4	(10.5 to 22.4)	0.0001
Social function					
Baseline	53.2 ± 31.1 (122)	(47.6 to 58.8)	-	-	-
30 days	68.8 ± 27.8 (102)	(63.3 to 74.2)	16.7	(10.1 to 23.3)	<0.0001
6 months	76.8 ± 24.2 (69)	(71.0 to 82.6)	21.7	(14.0 to 29.4)	<0.0001
12 months	75.0 ± 27.8 (76)	(68.7 to 81.3)	19.9	(11.9 to 27.9)	<0.0001
Role emotional					
Baseline	63.3 ± 35.1 (122)	(57.0 to 69.6)	-	-	-
30 days	69.3 ± 31.5 (100)	(63.1 to 75.6)	4.1	(-2.7 to 11.0)	0.2342
6 months	78.4 ± 25.6 (68)	(72.2 to 84.6)	14.1	(5.1 to 23.0)	0.0025
12 months	74.3 ± 29.3 (76)	(67.6 to 81.0)	10.4	(1.4 to 19.4)	0.0246
Mental health index					
Baseline	70.9 ± 19.7 (121)	(67.3 to 74.4)	-	-	-
30 days	76.5 ± 18.4 (102)	(72.9 to 80.1)	5.6	(2.0 to 9.3)	0.0028
6 months	79.0 ± 16.1 (69)	(75.2 to 82.9)	7.1	(2.7 to 11.5)	0.0021
12 months	79.4 ± 16.8 (76)	(75.6 to 83.2)	8.0	(3.4 to 12.6)	0.0008

Only patients in the high-risk arm of the REALISM (Real World Expanded Multi-center Study of the MitraClip System) continued-access registry completed SF-36 QoL (36-item Short Form Health Survey) questionnaires at 6 months. *Reported for patients with paired measurements at baseline and follow-up.

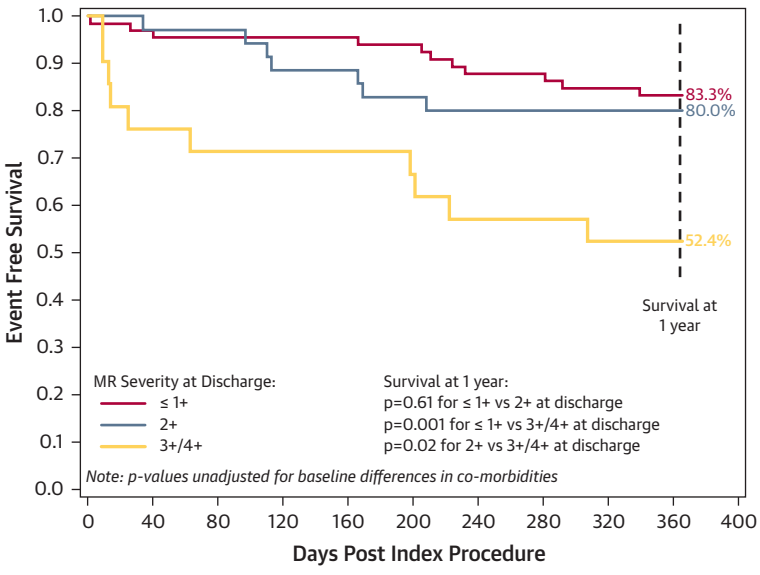
(95% CI: 62.2% to 90.1%) for patients discharged with MR 2+.

HF HOSPITALIZATIONS. HF hospitalizations 12 months prior to and 12 months following the MitraClip procedures were recorded and analyzed. Length of follow-up post TMVR was adjusted for in the analysis. As shown in Figure 3A, a significant decrease in the rate of hospitalization for HF was observed following discharge after TMVR, from 0.67 (95% CI: 0.54 to 0.83) to 0.18 (95% CI: 0.11 to 0.28) per patient-year, a 73% reduction. When death was treated as a HF hospitalization in a sensitivity analysis, the HF hospitalization rate was still significantly reduced, from 0.67 (95% CI: 0.54 to 0.83) to 0.44 (95% CI: 0.33 to 0.60) per patient-year, as shown in Figure 3B. In contrast, as shown in the Central Illustration (panel C), patients with ongoing or untreated severe MR at discharge had no reduction in the rate of HF hospitalization or death following TMVR.

NYHA FUNCTIONAL CLASS. Figure 4A shows NYHA functional class at baseline and 30 days for patients with paired data available. Improvements to NYHA functional class I or II were observed in 60 of 79 patients (75.9%) with baseline class III and in 17 of 26 patients (65.3%) with baseline class IV. Figure 4B shows NYHA functional class at baseline and 1 year for patients with paired data available. Of 98 patients with baseline NYHA functional class III/IV, 30 (30.6%) patients experienced an improvement of at least 2 classes.

Reduction of MR to ≤2+ at discharge was associated with a higher probability of being alive with NYHA functional class I/II at 1 year (71.7% of patients discharged with MR ≤1+, 69.7% of patients discharged with MR = 2+, and 36.8% of patients discharged with MR 3+ or 4+) compared with continued or untreated severe MR at discharge. There was no statistically significant difference in the probability of NYHA class I/II at 1 year between the discharge MR ≤1+ and MR = 2+ groups. Additionally, the probabilities of NYHA class I/II at 1 year in the MR ≤1+ and MR = 2+ groups were significantly different than in the MR 3+/4+ group ($p = 0.013$ and 0.044, respectively).

LV FUNCTION. Compared with baseline, LV end-diastolic volume decreased significantly, from 125.1 ± 40.1 ml to 108.5 ± 37.9 ml at 12 months ($p < 0.0001$) in survivors with paired data (n = 69). LV end-systolic volume decreased from 49.1 ± 24.5 ml to 46.1 ± 21.4 ml at 12 months ($p = 0.07$) in survivors with paired data (n = 69).



Time Post Index Procedure	Baseline	30 Days	12 Month
MR=0+/1+			
# At Risk	66	64	48
% Event Free	100%	97.0%	83.3%
95% CI	-	[88.4%, 99.2%]	[70.9%, 90.8%]
MR=2+			
# At Risk	35	35	27
% Event Free	100%	100%	80.0%
95% CI	-	-	[62.2%, 90.1%]
MR=3+/4+			
# At Risk	22	16	10
% Event Free	100%	76.2%	52.4%
95% CI	-	[51.9%, 89.3%]	[28.6%, 71.6%]

FIGURE 2 Kaplan-Meier Survival Curves by Discharge MR Severity (≤1+, 2+, 3+/4+)

p values unadjusted for baseline differences in comorbidities. Stratification of patients by residual MR severity is demonstrated as it pertains to event-free survival. MR = mitral regurgitation.

DISCUSSION

This is the first report on the use of the TMVR device specifically in patients with DMR considered at prohibitive risk for MV surgery. In this population, as in others, TMVR had a high initial success rate (95%) with a low rate of serious complications, 30-day mortality, and subsequent MV surgery. A large majority of these patients achieved reduction in their MR to 2+ or less, and this was associated with improvements in NYHA functional class and QoL, reductions in HF hospitalization, and LV reverse remodeling. In addition, patients with 2+ residual MR at discharge were found to have similar survival rates to those with ≤1+ MR, with both having better survival than patients with 3+/4+ MR at discharge.

Since TMVR with the MitraClip was first described by St. Goar et al. (7), there has been significant interest in the potential of this less invasive therapy. Patients who initially received this novel therapy in the United States were randomized against gold-standard MV surgery in the EVEREST II trial and thus comprised a relatively low-risk and predominantly degenerative etiology population who were shown to have more complete MR reduction with surgery than the percutaneous method. However, given the results of the EVEREST II trial in patients too high risk for surgery (High Risk Registry and REALISM high risk), it has become clear that the initial clinical

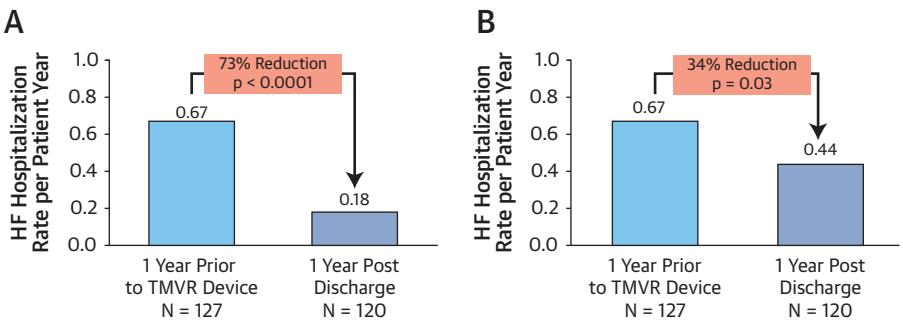


FIGURE 3 Reduction in HF Hospitalizations

(A) 1 year prior to TMVR and 1 year post-discharge, and **(B)** with deaths treated as heart failure (HF) hospitalizations.

role for this percutaneous valve repair technology lies with patients at prohibitive risk for open SMVR of their degenerative (primary) MR.

Over time, the description of patients at significant operative risk for open MV repair has changed, but the concept remains the same. The term *prohibitive risk* was defined as those patients with a predicted risk of mortality for open MV replacement of ≥8% based on the STS risk calculator, or by considering other serious comorbidities shown to be associated with high risk that are not taken into account in the STS risk calculator. Notably, only 5% of all isolated MV surgeries in the STS database had a score ≥8%, and 85% of those underwent MV replacement (data

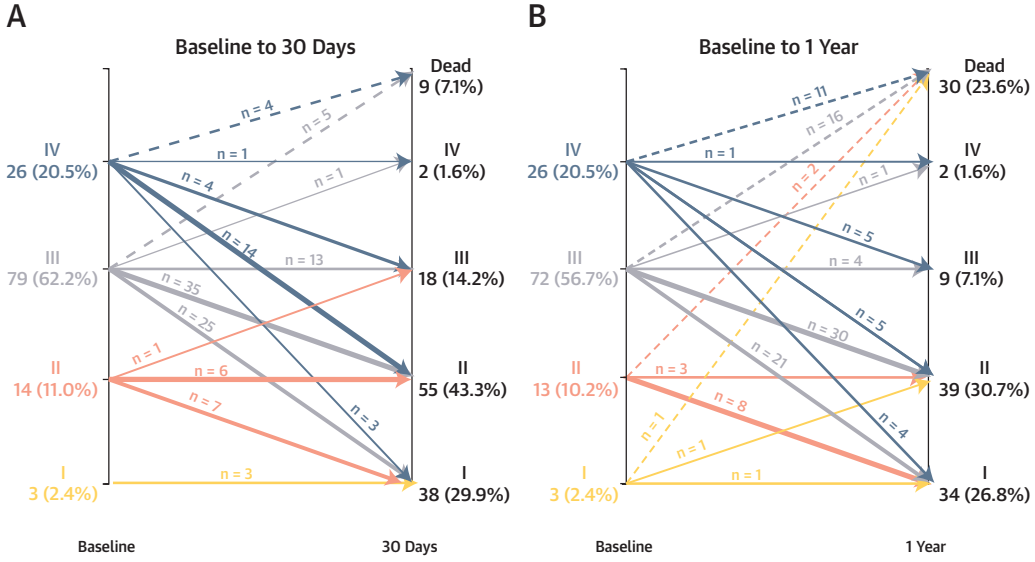


FIGURE 4 Change in NYHA Functional Class

(A) From baseline to 30 days and **(B)** from baseline to 1 year (n and % based on 127 [100%]).

on file from a query of the STS database conducted in December 2012 of all isolated MV surgeries between 2008 and 2012, Abbott Vascular). Prohibitive risk does not imply "inoperable," but rather that the risk of open surgery significantly outweighs the usual expected benefit. A similar definition of *risk* was used in the EVEREST High Risk study (2).

The increased operative risk is related not to the patients' MV disease but rather to the person "wrapped around" the regurgitant valve. Despite their risk, the procedural outcomes were favorable, with no intraprocedural deaths, few device related complications, safety results not worse than for surgery in the lower-risk randomized trial, a procedure time of approximately 2.5 h on average, and a procedure success rate of more than 95%. In terms of resource utilization, it is impressive that, in this elderly population with multiple comorbidities, the hospital length of stay following TMVR was approximately 3 days, with nearly 90% of patients discharged to their homes. These resource patterns suggest that TMVR may be less expensive than MV surgery would be for similar patients (8).

One of the points of concern that has been raised previously in comparison to open SMVR is that TMVR achieves a lesser degree of MR reduction. In this prohibitive-risk cohort of patients, nearly 80% of patients with MR 3+ or 4+ at baseline achieved a MR reduction to ≤2+ at time of discharge. Were these patients at lower operative risk, it is likely that highly experienced MV surgeons could have achieved a lower residual MR in a greater proportion of patients. Despite this lesser degree of MR reduction, the results with TMVR in this population are stable over time, with more than 85% of survivors maintaining their MR reduction of ≤2+ at 1-year follow-up. The reduction in MR has been durable to 4 years' follow-up in the EVEREST II RCT (9). Given that these prohibitive-risk patients have no other medical or surgical option, the expectation of clinical benefit from the procedure has been met in the majority.

This procedural benefit clearly has translated to clinical benefits as evidenced by improvement in functional status and QoL. These changes were statistically robust and clinically meaningful. The mean changes in SF-36 summary scales following TMVR in this population were not only well above established thresholds, but in fact returned the group means to previously reported age-adjusted norms. The finding of improved LV function is consistent with the expected reduced pre-load as a result of the reduction in MR severity achieved with the TMVR device and provides a physiologic basis for the observed functional improvements.

Importantly, this study did not find a marked difference in patient outcomes between the groups with 1+ residual MR versus those with 2+ residual MR. In both cases, there were significant improvements compared with those with 3+ or 4+ residual MR. It is likely that for such a high-risk comorbid cohort, being able to achieve MR reduction to below surgical referral standards without the biologic cost of a more invasive approach is a success on the individual level.

STUDY LIMITATIONS. These data encompass the early experience with TMVR and are thus limited by relative inexperience of the individual TMVR operators in the United States. These data also were limited by the lack of randomization, because medical therapy, does not have a treatment role for DMR and surgical options were prohibitive, so a control arm was not possible. Because the cohort was retrospectively identified, all analyses were post-hoc. Another limitation is that follow-up echocardiographic and functional data were obtained and reported for surviving patients only. No imputation for deceased patients' data was performed, although deaths and missing data were reported.

CONCLUSIONS

The TMVR device is safe in patients with severe degenerative (primary) MR for whom a heart team has determined that MV surgery is associated with a prohibitive risk/benefit ratio. Transcatheter reduction of DMR in these patients provides significant benefits, including improvements in symptoms and functional status, a decrease in hospitalizations, and favorable LV remodeling at 1 year.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: For patients with severe, DMR, valve repair surgery in an experienced center effectively addresses the intrinsic valvular abnormality more effectively than medical therapy alone.

COMPETENCY IN PATIENT CARE: Transcatheter deployment of the MitraClip® device may be considered for patients with severe DMR who would face a prohibitive risk of morbidity or mortality related to valve surgery.

TRANSLATIONAL OUTLOOK 1: More information about clinical outcomes of the MitraClip procedure in patients with functional MR secondary to cardiomyopathy rather than intrinsic valvular pathology is needed from ongoing randomized trials.

REFERENCES

1. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008;52:e1–142.

2. Whitlow PL, Feldman T, Pedersen WR, et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. J Am Coll Cardiol 2012;59:130–9.

3. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.

4. Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.

5. Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's manual for the SF-36v2 Health Survey. Lincoln, RI: QualityMetric; 2007.

6. Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. J Am Coll Cardiol 2013;62:1052–61.

7. St Goar FG, Fann JI, Komptebedde J. Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. Circulation 2003;108:1990–3.

8. Reynolds MR, Galper B, Apruzzese P, et al. Cost-effectiveness of the MitraClip compared with mitral valve surgery: 12-month results from the EVEREST II randomized controlled trial. J Am Coll Cardiol 2012;60:B229.

9. Buzzatti N, Maisano F, Latib A, et al. Computed tomography-based evaluation of aortic annulus, prosthesis size and impact on early residual aortic regurgitation after transcatheter aortic valve implantation. Eur J Cardiothorac Surg 2013;43:43–50, discussion 50–1.

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