JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 71, NO. 1, 2018

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2017.10.062

Beating-Heart Mitral Valve Repair Using a Novel ePTFE Cordal Implantation Device

A Prospective Trial

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ABSTRACT

BACKGROUND Conventional mitral valve (MV) operations allow direct anatomic assessment and repair on an arrested heart, but require cardiopulmonary bypass, aortic cross-clamping, sternotomy or thoracotomy, and cardioplegic cardiac arrest, and are associated with significant perioperative disability, and risks of morbidity and mortality.

OBJECTIVES This study evaluated safety and performance of a transesophageal echocardiographic-guided device designed to implant artificial expanded polytetrafluoroethylene (ePTFE) cords on mitral leaflets in the beating heart.

METHODS In a prospective multicenter study, 30 consecutive patients with severe degenerative mitral regurgitation (MR) were treated with a mitral valve repair system (MVRS) via small left thoracotomy. The primary (30-day) endpoint was successful implantation of cords with MR reduction to moderate or less.

RESULTS The primary endpoint was met in 27 of 30 patients (90%). Three patients required conversion to open mitral surgery. There were no deaths, strokes, or permanent pacemaker implantations. At 1 month, MR was mild or less in 89% (24 of 27) and was moderate in 11% (3 of 27). At 6 months, MR was mild or less in 85 % (22 of 26), moderate in 8% (2 of 26), and severe in 8% (2 of 26). Favorable cardiac remodeling at 6 months included decreases in end-diastolic (161 ± 36 ml to 122 ± 30 ml; $p < 0.001$) and left atrial volumes (106 ± 36 ml to 69 ± 24 ml; $p < 0.001$). The anterior-posterior mitral annular dimension decreased from 34.7 ± 5.8 mm to 28.2 ± 5.1 mm; $p < 0.001$ as did the mitral annular area (10.0 ± 2.7 cm^2 vs. 6.9 ± 2.0 cm^2; $p < 0.0001$).

CONCLUSIONS MVRS ePTFE cordal implantation can reduce the invasiveness and morbidity of conventional MV surgery. The device's safety profile is promising and prospective trials comparing the outcomes of the MVRS to conventional MV repair surgery are warranted. (CE Mark Study for the Harpoon Medical Device [TRACER]; NCT02768870)
(J Am Coll Cardiol 2018;71:25–36)

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Manuscript received October 12, 2017; revised manuscript received October 24, 2017, accepted October 25, 2017.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

ePTFE = expanded polytetrafluoroethylene

H-MVRS = Harpoon mitral valve repair system

IQR = interquartile range

LA = left atrial

LV = left ventricular

MAC = mitral annular calcification

MR = mitral regurgitation

MSSA = methicillin-sensitive *Staphylococcus aureus*

MV = mitral valve

MVRS = mitral valve repair system

SAE = serious adverse event

SAM = systolic anterior motion

TEE = transesophageal echocardiography

Mitral valve (MV) operations are performed most commonly for degenerative mitral regurgitation (MR) (1) and are indicated for patients with symptoms of left ventricular dysfunction, atrial arrhythmias, severe MR, and/or pulmonary hypertension (2). Short- and long-term outcomes after mitral valve repair are superior to outcomes after MV replacements for patients with degenerative disease (3), and successful MV repair alleviates symptoms, prevents and reverses unfavorable ventricular remodeling, and improves survival. Although conventional MV operations allow for complete direct visual anatomic assessment and repair, using a variety of techniques in an arrested heart, they require cardiopulmonary bypass, aortic cross-clamping, sternotomy or thoracotomy, and cardioplegic cardiac arrest and are therefore associated with significant perioperative disability as well as risks of morbidity and mortality (4). MV repair rates are highly variable, with lower successful repair rates observed in low-volume centers (5). The Harpoon MV repair system (H-MVRS) (Harpoon Medical Inc., Baltimore, Maryland) may provide an alternative treatment for patients with degenerative MR. In this procedure, access to the anterior wall of the LV is secured through a small left thoracotomy, and the delivery system is used to anchor artificial expanded polytetrafluoroethylene (ePTFE) cords on the prolapsed segment of the MV on the beating heart by using transesophageal echocardiographic (TEE) guidance. The lengths of the ePTFE cords are then adjusted to optimize leaflet coaptation and minimize MR, and are then secured on the anterior wall of the heart on an ePTFE pledget. The feasibility of this concept has been demonstrated in a pilot study that included the first 11 patients treated with the device (6). We conducted a prospective multicenter observational study to evaluate the safety and performance of this device.

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METHODS

STUDY DESIGN AND OVERSIGHT. The TRACER (Mitral TransApical NeoCordal Echo-Guided Repair; NCT02768870) trial is a prospective, nonrandomized, multicenter clinical study designed to test the safety and performance of the Harpoon MVRS (Harpoon Medical Inc., Baltimore, Maryland) for MV repair. This planned interim analysis includes protocol-specified clinical and echocardiographic follow-up conducted during the 30-day and 6-month visits from 30 consecutive patients enrolled in the study to support Conformité Européene (CE) Marking for the device. The trial was conducted at 6 clinical centers in Europe and was sponsored by the manufacturer of the MVRS. The 30 patients enrolled in this study were distinct and subsequent to the 11 enrolled in the early feasibility study. The study protocol was approved by the relevant national authorities in each country and the ethics committee at each institution. All patients provided written informed consent prior to enrollment. Serious adverse events (SAEs) were reported by site and adjudicated by an independent data safety and monitoring committee consisting of independent physicians. Monitoring and collection of data and initial data analyses were performed by the sponsor.

PARTICIPANT SELECTION. Patients 18 years of age or older with severe degenerative MR resulting from isolated posterior leaflet prolapse were enrolled. Class I indications for MV operation were present in 17 patients (57%) and Class IIa indications in 13 (43%) (2). Patients underwent protocol-directed pre-operative TEE that included 2-dimensional (2D) and 3D analyses of MV morphology to assess anatomic feasibility. A patient selection committee determined whether the predicted post-repair coaptation surface would be adequate to result in effective MR reduction. Generally, 3D imaging and analysis software (Tomtec imaging systems, Tomtec, Chicago, Illinois) and 2D pan-through TEE imaging (both 4-chamber and long-axis) were used to assess the MV anatomy, with a particular focus on the maximal distance between the free edge of the anterior leaflet and the base of the posterior leaflet (the anteroposterior dimension of the regurgitant orifice). Although a number of anatomical characteristics were evaluated, primary assessment of suitability was based on the ratio of the posterior prolapse segment length (measured with linear polygonal assessment tools (Osirix, Pixmeo SARL, Bernex, Switzerland) to the corresponding anteroposterior distance between the free edge of the anterior leaflet and the base of the prolapsed posterior leaflet segment. A minimum 1.5:1 ratio or higher indicated suitability. This ratio was measured multiple times in succession during a "pan-through" of the valve in both 4-chamber and long-axis views, and the smallest measured ratio was used. Key exclusion criteria included the presence of anterior or bileaflet prolapse, functional MR, severe calcification of the

leaflets, moderate or severe aortic stenosis or insufficiency, requirement for concomitant cardiac surgery, severe tricuspid regurgitation, a history of previous cardiac operation, chronic renal insufficiency (stage 3b or worse), severe pulmonary hypertension (systolic pulmonary artery pressure >70 mm Hg), or a EuroSCORE II (for MV repair) of >8% (7). Full inclusion and exclusion criteria are available at the Clinical Trials Web site (NCT02768870).

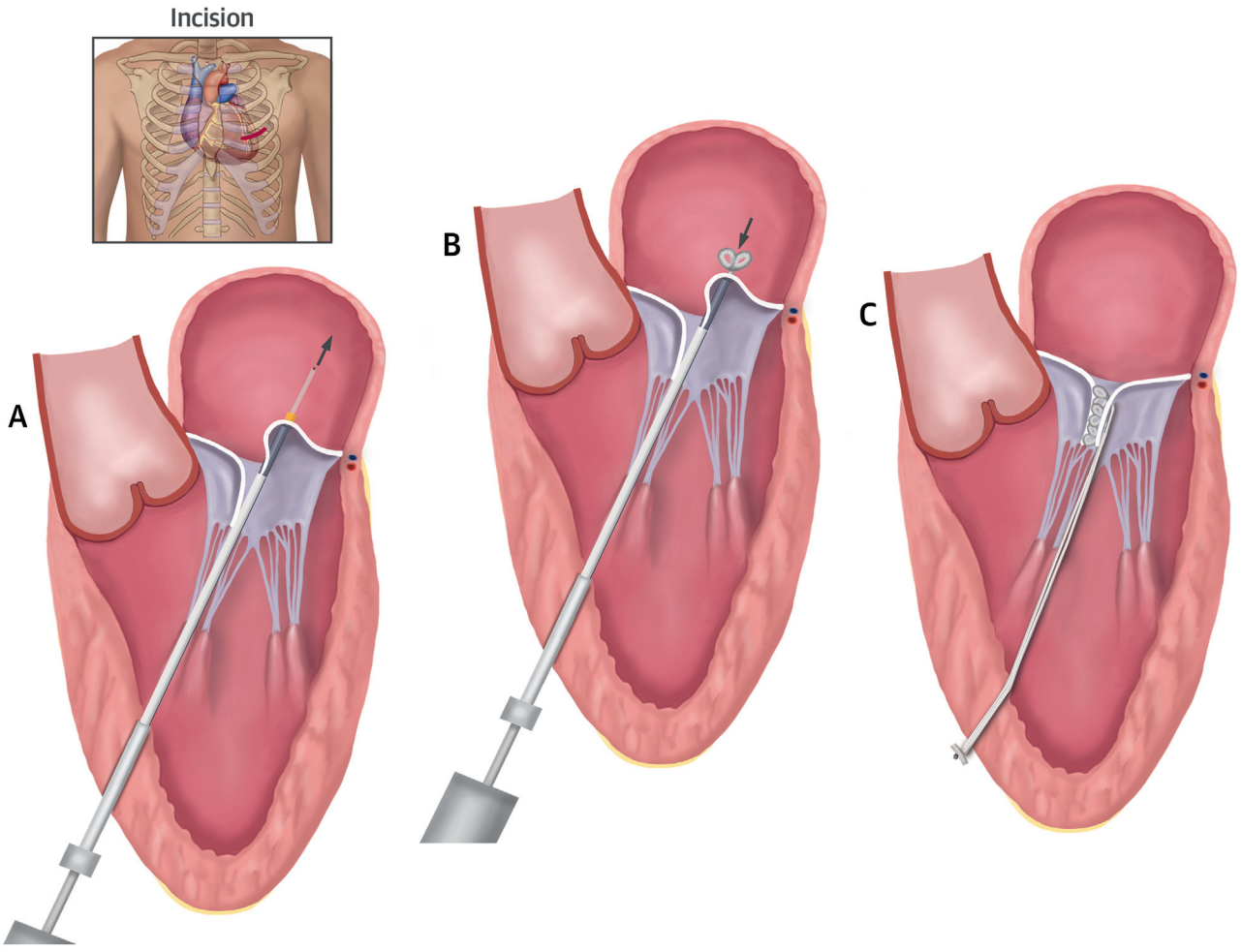
PRIMARY PERFORMANCE AND SAFETY ENDPOINTS. The primary performance endpoint was successful implantation of 1 or more ePTFE artificial cords on the MV, with subsequent reduction of MR from severe to moderate or less at the conclusion of and 30 days after the procedure. The primary safety endpoint was freedom from SAEs during the procedure and through 30 days after operation. Perioperative mortality was defined as the greater of 30-day mortality or in-hospital mortality.

MITRAL VALVE REPAIR SYSTEM. The MVRS consists of 2 parts: a hemostatic introducer and a delivery system. The introducer has a 14-F (4.7-mm) external diameter with internal valves that maintain hemostasis during insertion and withdrawal of multiple delivery systems during the procedure. The delivery system contains a pre-formed ePTFE knot wrapped on a purposely designed 21-gauge needle and is designed to securely anchor artificial ePTFE cords on targeted locations on a prolapsed MV leaflet. When the end-effector on the tip of the 3-mm diameter delivery system shaft is positioned by the operator on the targeted segment of the mitral leaflet by using echocardiographic guidance, the device is deployed, causing the needle and ePTFE wrap to penetrate the leaflet tissue. The needle is rapidly withdrawn and the coil of ePTFE is tightened to form a double-helix knot on the atrial surface of the leaflet.

PROCEDURE. The procedure is performed under general endotracheal anesthesia and has been previously described (6). Transthoracic echocardiography is used to identify the optimal intercostal space (usually the fourth intercostal space) and location for an incision on the left chest. A small thoracotomy is performed, the pericardium is opened, and a location on the epicardium approximately 3 cm basal to the true apex and 1 cm lateral to the left anterior descending coronary artery is identified for insertion of the hemostatic introducer. Rib spreading is avoided if possible. Finger ballottement is performed on the proposed entrance site, and TEE assessment is performed to ensure that the entrance site is just apical to the base of the anterolateral papillary muscle. Two concentric pledgeted purse-string sutures (3-0 monofilament) are placed in the myocardium. Intravenous heparin is administered to achieve an activated clotting time above 350 s. The delivery system is then inserted through the introducer and guided to the target on the prolapsed segment of the mitral leaflet using TEE guidance. Close coordination between the imaging specialist and the surgeon is essential. Simultaneous orthogonal 2D images (bicommissural and long-axis views) are required for device guidance. Once the delivery system is steered to the targeted location on the leaflet, the end effector on the tip of the delivery system is used to stabilize the leaflet throughout the cardiac cycle, and the knot is deployed. After each knot deployment, the delivery system is withdrawn from the heart, leaving 2 ePTFE strands exteriorized through the introducer lumen. One delivery system is used for each knot deployment. This sequence is repeated for the desired number of knots (usually 4 to 6), then the introducer is withdrawn, and the purse-string sutures are tied. The ePTFE suture pairs are then threaded individually through a stiff ePTFE pledget and are tightened simultaneously and incrementally by using TEE guidance to optimize coaptation and minimize MR. Once the optimal length of the artificial cords is achieved, each pair is tied over the pledget (**Central Illustration**). Aspirin (81 to 325 mg/day) is administered post-operatively. All implanting surgeons and imaging specialists were trained using a benchtop simulator and performing the procedure in an animal laboratory, and both an echocardiographic and a surgical proctor from the first site were available for cases at subsequent sites.

ECHOCARDIOGRAPHIC ANALYSES. Pre-procedural, intraprocedural, and post-operative echocardiograms were performed by the study sites. Deidentified studies were securely transmitted in Digital Imaging and Communications in Medicine (NEMA, Rosslyn, Virginia) format to an independent core laboratory (Massachusetts General Hospital, Boston, Massachusetts) for anonymized and standardized evaluation. The severity of MR was graded as none or trace, mild, moderate, or severe by using integrative criteria specified by the American Society of Echocardiography and European Society of Cardiology (8,9). Left ventricle (LV) dimensions and left atrial (LA) (biplane area length) and LV volumes were measured (biplane method of discs) according to American Society of Echocardiography chamber quantification guidelines (10). To assess the effect of reducing mitral annular dimensions following the MVRS procedure, we measured mitral annular dimensions in the parasternal long-axis dimension on 2D TTE because this

CENTRAL ILLUSTRATION **Beating-Heart Mitral Valve Repair Procedure**



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A small thoracotomy is performed in the 4th or 5th intercostal space. The valved introducer is inserted through a purse string suture in an anterior location that is 3 to 4 cm from the apex and just lateral to the left anterior descending coronary artery. The delivery device is directed to the underside of the prolapsed leaflet, and once leaflet stabilization is achieved, the device is actuated **(A)**, forming an ePTFE knot on the atrial surface **(B)**. Multiple ePTFE cords are anchored on the leaflet, the introducer is withdrawn, and the cordal lengths are adjusted to maximize coaptation and minimize MR **(C)**. The cords are tied on a ePTFE pledget on the epicardium at the insertion site. ePTFE = expanded polytetrafluoroethylene; MR = mitral regurgitation.

imaging plane best measures septal-lateral (anteroposterior) mitral annular dimension. Mitral annular area was calculated as: [$\pi \times$ (one-half of mitral annular dimension in parasternal long axis) $\times$ (one-half of mitral annular dimension in apical 2-chamber)], using elliptical assumption for the mitral annulus (11,12).

Baseline characteristics and clinical outcomes were described using counts and percentages for categorical variables and mean $\pm$ SD, supported by ranges, for continuous measurements. Exact 95% confidence intervals (CIs) were constructed for the primary endpoints. The primary performance endpoint was tested relative to the pre-specified performance goal of 58% by using the lower bound of the exact 95% CI. There was no formal hypothesis tested for the primary safety endpoint. Echocardiographic continuous variables were compared at baseline, 30-day, and 6-month stages by using 1-way analysis of variance test with repeated measures. Post hoc pairwise comparisons were made using Bonferroni correction. MR grade was measured as a categorical variable, and significant differences in MR grades at baseline, 30 days, and 6 months were examined by using the Friedman test. Creatinine levels were compared using

TABLE 1 Baseline Characteristics of the Patients

Age, yrs	61 ± 13
Males	23 (77)
BMI, kg/m^2	26.2 ± 3.7
NYHA Class, %	
I	15 (50)
II	10 (33)
III	5 (17)
IV	0 (0)
STS PROM, %	0.69 ± 0.72
EuroSCORE II, %	1.2 ± 1.3
Atrial fibrillation	9 (30)*
Hypertension	22 (73)
Diabetes mellitus	3 (10)
Glomerular filtration rate, ml/min/m^2	79.1 ± 15.5
Cardiac structure and function	
Mean LV ejection fraction, %	69 ± 7
LA diameter, cm	46 ± 7
LV end-diastolic diameter, cm	53 ± 6
LV end-systolic diameter, cm	32 ± 6
sPAP, mm Hg	42 ± 13
Isolated P2 prolapse	28 (93)
Isolated P3 prolapse	1 (3)
P2/P3 prolapse	1 (3)

Values are mean ± SD or n (%). *7 paroxysmal, 2 continuous.

BMI = body mass index; LA = left atrial; LV = left ventricular; NYHA = New York Heart Association; sPAP = systolic pulmonary artery pressure; STS PROM = Society of Thoracic Surgeons predicted risk of mortality.

the nonparametric sign test. A p value of <0.05 was considered statistically significant. There was no imputation for missing data. Analyses were performed using SPSS version 25 software (IBM, Armonk, New York).

RESULTS

PATIENT CHARACTERISTICS. From December 2015 through November 2016, 89 patients were screened for the trial. Thirty consecutive patients were enrolled in the trial at 6 clinical sites in 3 countries. The most frequent reasons for exclusion from the trial included anterior leaflet prolapse, inadequately predicted coaptation surface, functional MR, leaflet injury or defect, and refusal to consent. All patients completed 6-month echocardiographic and clinical follow-up by July 2017. Patients were 61 ± 13 years of age (range: 40 to 85 years of age), and 77% (23 of 30) were men. Class I indications for MV operation were present in 17 patients (57%) and Class IIa indications in 13 (43%). Characteristics of the patients in the study cohort are shown in Table 1.

PRIMARY PERFORMANCE ENDPOINT. The technical success rate at exit from operating room was 93% (28 of 30 patients). An average of 3.9 ± 1 (range: 1 to 5; interquartile range [IQR]: 3 to 5) pairs of ePTFE artificial cords were implanted in patients successfully treated by using the device. Total procedure time averaged 125 ± 43 min (range: 84 to 199 min), and the introducer was in the ventricle for an average of 43 ± 22 min (range: 16 to 103 min). During the procedure, MR was reduced from severe to none or trace in 24 patients (86%) and to mild in 4 patients (14%). The average 30-day follow-up visit occurred at 41 ± 17 days, and the average 6-month visit was performed at 184 ± 21 days post-procedure. The primary performance endpoint was met in 27 of 30 patients (90%; 95% CI: 73% to 98%) enrolled, meeting the pre-specified performance goal of 58% ($p < 0.001$). At 30-day follow-up, 85% (23 of 27) of patients were in NYHA Class I and 89% (24 of 27) had mild or less MR. At the 6-month follow-up 93% of patients (25 of 27) were in NYHA Class I, MR was mild or less in 85% (22 of 26), moderate in 8% (2 of 26), and severe in 8% (2 of 26).

Two patients required intraoperative conversion to conventional cardiac surgery and underwent successful MV repair operations. The first patient enrolled in the study had 4 ePTFE artificial cords inserted using the MVRS. Suboptimal echocardiographic equipment was responsible for poor quality images of the device and prevented accurate placement of ePTFE knots on the leaflet. Tensioning of the cords did not result in acceptable resolution of MR, and the decision was made to electively convert to conventional MV surgery. Direct intraoperative inspection of the mitral valve demonstrated that 3 knots were placed at the base of the leaflet rather than at the free edge, and 1 knot was placed intraventricularly. The knots were removed, and the valve was repaired by resuspending the intact leaflet with 3 ePTFE sutures and inserting a size 30 annuloplasty ring; post-bypass TEE demonstrated no MR. The patient was discharged in good condition with none or trace MR 9 days after the operation. In the other converted case, TEE imaging using the same equipment was equally poor and led to a prolonged procedure. Two ePTFE cords were successfully implanted, but during insertion of the device for a planned third knot placement, bleeding occurred around the introducer. The patient was converted to conventional sternotomy, the defect was repaired, and a conventional nonresectional repair that included 3 pairs of ePTFE cords and a complete ring was performed. This patient left the hospital in good condition on post-operative day 8 with none or trace MR. One patient required conventional cardiac surgical surgery on post-operative day 27 for recurrent symptomatic severe mitral regurgitation caused by methicillin-sensitive *Staphylococcus aureus* (MSSA)

infective endocarditis. This patient had an elevated white blood cell count on the morning of the MVRS procedure and dental caries that had not been reported. Although the procedure and post-operative course were uneventful and the patient was discharged to rehabilitation with mild MR on post-operative day 9, the patient was readmitted on post-operative day 22 with complaints of malaise. Transthoracic echocardiography showed recurrence of severe MR due to perforation of the posterior leaflet with associated vegetations, and multiple blood cultures were positive for MSSA. Reoperation using conventional sternotomy was performed on post-operative day 27. There was a 5- × 6-mm defect in the posterior leaflet surrounded by inflammatory tissue consistent with infective endocarditis. The valve was replaced with a size 27 bileaflet mechanical valve. The patient was treated with intravenous antibiotics and discharged from the hospital in good condition on post-operative day 28.

In 2 patients, initial tensioning of the ePTFE cords resulted in significant systolic anterior motion (SAM) of the MV with MR and LV outflow tract obstruction. In both cases, additional shortening of the cords completely resolved the SAM, and the patients were left with none or trace MR at the conclusion of the procedure. Follow-up echocardiography demonstrated no evidence of recurrent SAM or MR at 6 months' post-procedure.

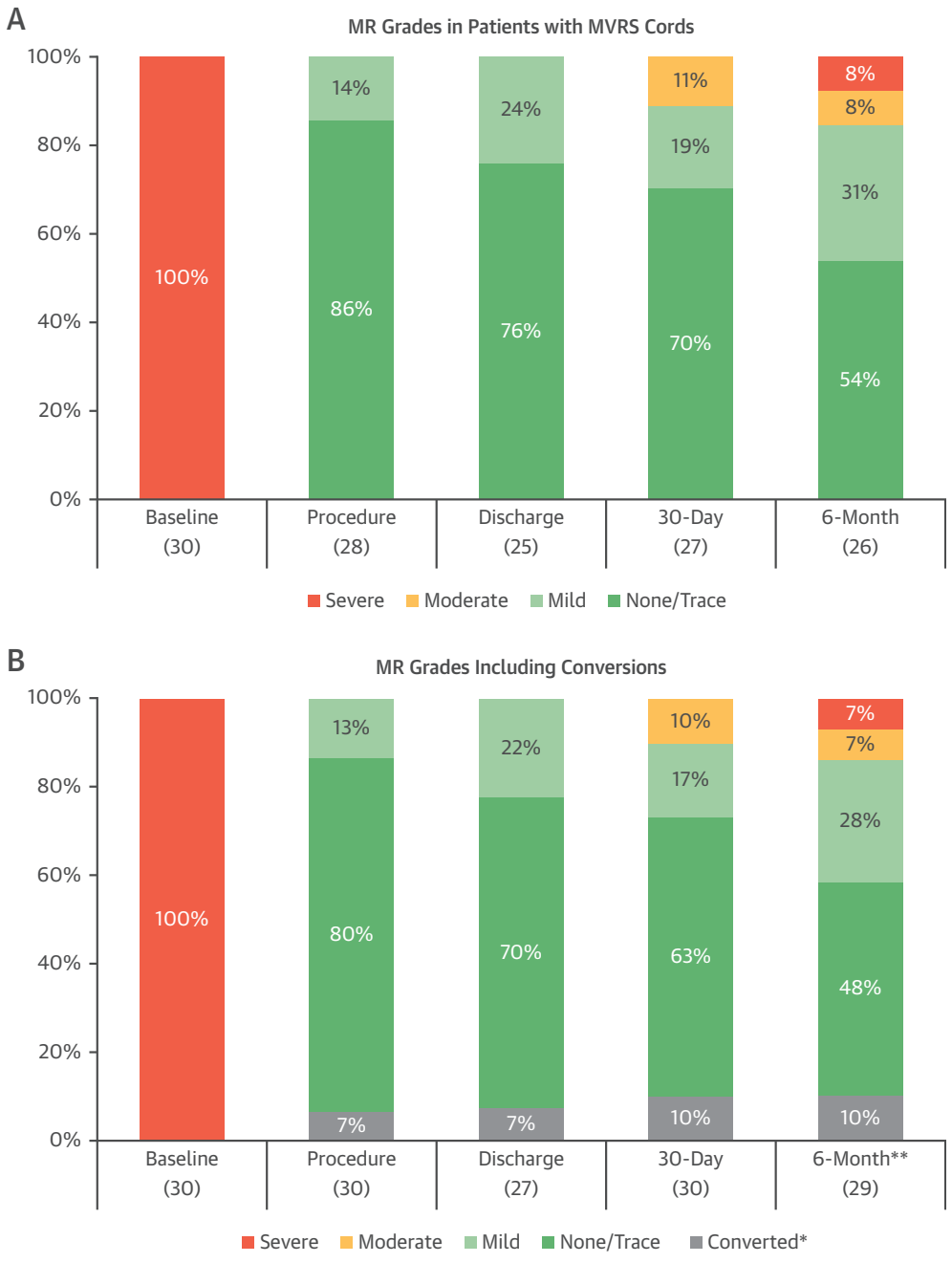
SAFETY ENDPOINTS. There was no perioperative or late mortality. There were no occurrences of perioperative strokes, renal failure, or myocardial infarction. No patient required temporary epicardial pacing or permanent pacemaker insertion. No patient required intraoperative inotropic support. The average intraprocedural blood loss was 276 ± 196 ml (range: 50 to 700 ml). A single blood transfusion was required in 1 patient (3%) who underwent intraoperative conversion to conventional cardiac surgery with cardiopulmonary bypass. The mean post-operative hospital length of stay was 6.7 ± 1.6 days (range: 3 to 9 days). No patient required reintubation or readmission to the intensive care unit.

The median maximal creatinine concentration measured after operation was similar to the pre-operative value (0.93 vs. 0.92 mg/dl, respectively; range: 0.65 to 1.48 mg/dl; IQR: 0.86 to 1.15 mg/dl vs. range: 0.60 to 1.44 mg/dl, respectively; IQR: 0.83 to 1.05 mg/dl; $p = 0.0614$). Among the 27 patients with implanted artificial ePTFE cords, clinical follow-up was 100% complete (range: 7 to 16 months), and there were no late occurrences of stroke, thromboembolism, infective endocarditis, or death. There were 6 patients with SAEs within 30 days (6 of 30 [20%]; 95% CI: 8% to 39%). SAEs included the 3 patients who required conversion to conventional MV surgery, a case of chest pain requiring readmission for 24 h on post-operative day 5, 2 instances of pleural effusion requiring drainage (post-operative days 8 and 9), a case of chronic cholecystitis treated with an elective cholecystectomy on post-operative day 86, and 1 patient with new atrial flutter on post-operative day 38, treated with amiodarone. Two patients (2 of 21; 10%) developed new post-operative atrial fibrillation that resolved by the 30-day visit. All patients ($n = 9$) who were in atrial fibrillation before operation were in normal sinus rhythm at the 30-day and 6-month visits.

MITRAL REGURGITATION REDUCTION AND REVERSE REMODELING. Core laboratory-adjudicated MR severity at the conclusion of the procedure, before dismissal and at 30 days and 6 months, is displayed in Figure 1. Among the 26 patients with echocardiographic follow-up and MVRS cords in place at 6 months, 85% (22 of 26) had none or trace or mild MR. The 2 patients with moderate MR (8%; 2 of 26) at 6 months were treated early in the series (Patients #2 and #3) with inadequate imaging equipment resulting in suboptimal artificial cordal placement on the leaflets. A third patient developed progressive MR that was moderate at 30 days and severe at the 6-month assessment; this patient had dense mitral annular calcification that extended into the ventricle beneath the entire posterior leaflet. The severe mitral annular calcification produced echocardiographic shadowing and impaired visualization of the device. The calcium bar limited the degree to which the prolapsed posterior leaflet could be repositioned into the ventricle. A fourth patient experienced a perforation of the midportion of the prolapsed segment early in the procedure, such that only a single knot was placed near the free edge of the prolapsed segment. That patient developed moderate MR at 30 days, which progressed to severe MR at 6 months. An elective reoperation 8 months after the initial procedure confirmed the leaflet perforation and demonstrated endothelialization and incorporation of the knot into the leaflet. The valve was repaired with suture closure of the defect, insertion of 3 pairs of ePTFE artificial cords, and an annuloplasty ring. The patient was discharged in good condition with none or trace MR.

ECHOCARDIOGRAPHIC VARIABLES. There was evidence of favorable early ventricular reverse remodeling, with significant decreases in end-diastolic

FIGURE 1 MR Grade Data



(A) MR grades in patients with MRVS cords. **(B)** MR grades including conversions. *Two patients converted to successful on-pump MV repair operations during the procedure and 1 patient required a conventional MV replacement operation on POD 27. All 3 patients exited the study in Class I with none/trace MR 30 days after the on-pump operation in accordance with the protocol design. **Three echocardiographic studies (2 discharge and 1 6-month) were incomplete due to poor acoustic window post-procedure and could not be adjudicated by the core lab. The 3 patients who were converted to conventional MV operations were not evaluated at 6 months per protocol but their status was carried forward. MR = mitral regurgitation; MVRS = mitral valve repair system.

TABLE 2 Echocardiographic Results

	Screening	30 Day	6 Month	p Value
LVEDD, mm	53 ± 6	49 ± 5*	48 ± 6*	<0.001
LVESD, mm	33 ± 6	33 ± 5	32 ± 5	0.31
LA volume, ml	106 ± 36	72 ± 26*	69 ± 24*	<0.001
LV EDV, ml	161 ± 36	123 ± 28*	122 ± 30*	<0.001
LV ESV, ml	52 ± 20	49 ± 13	45 ± 14	<0.001
LVEF, %	69 ± 7	61 ± 6*	66 ± 7	<0.001
MV annular diameter, mm	34.7 ± 5.8	31.2 ± 4.0	28.2 ± 5.1*	<0.001
Mitral annular area, cm^2	10.0 ± 2.7	8.4 ± 2.0†	6.9 ± 2.0*	<0.001
Mean MV gradient, mm Hg	NA	1.3 ± 0.5	1.5 ± 0.6	0.30

Values are mean ± SD. *p < 0.001 vs. baseline. †p < 0.05 compared to baseline.
LA = left atrial; LV EDV = left ventricular end-diastolic volume; LV ESV = left ventricular end-systolic volume; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; MV=mitral valve.

volumes by 25% (161 ± 36 ml to 121 ± 30 ml, respectively) and end-systolic volumes by 14% (52 ± 20 ml to 45 ± 14 ml, respectively) at 6 months (Table 2). There was a significant decrease in septal-to-lateral mitral annular dimension (34.7 ± 5.8 mm vs. 31.2 ± 4.0 mm, from baseline to 30 days; $p < 0.0001$) and mitral annular area (10.0 ± 2.7 cm^2 vs. 8.4 ± 2.0 cm^2 from baseline to 30 days; $p < 0.0001$) at 30 days post-procedure (Table 2). At 6 months, the reverse remodeling was unchanged, and there were continued decreases in both mitral annular diameters and areas. The LV ejection fraction declined significantly from 69 ± 7% at baseline to 61 ± 6% at 30 days and improved to 66 ± 7% at 6 months, consistent with previously reported experience with conventional MV surgery (13). The mean transmitral gradients were 1.3 ± 1.1 mm Hg at 30 days and 1.5 ± 0.7 mm Hg at 6 months. No patient developed right ventricular dysfunction either in the perioperative period or during follow-up. There was favorable early reverse remodeling of the left atrium with significant decreases in LA volumes (LA volume decreased from 106 ± 36 ml to 69 ± 24 ml at 6 months; $p < 0.001$). Figure 2 shows results of a representative preoperative and 6-month transthoracic follow-up study.

DISCUSSION

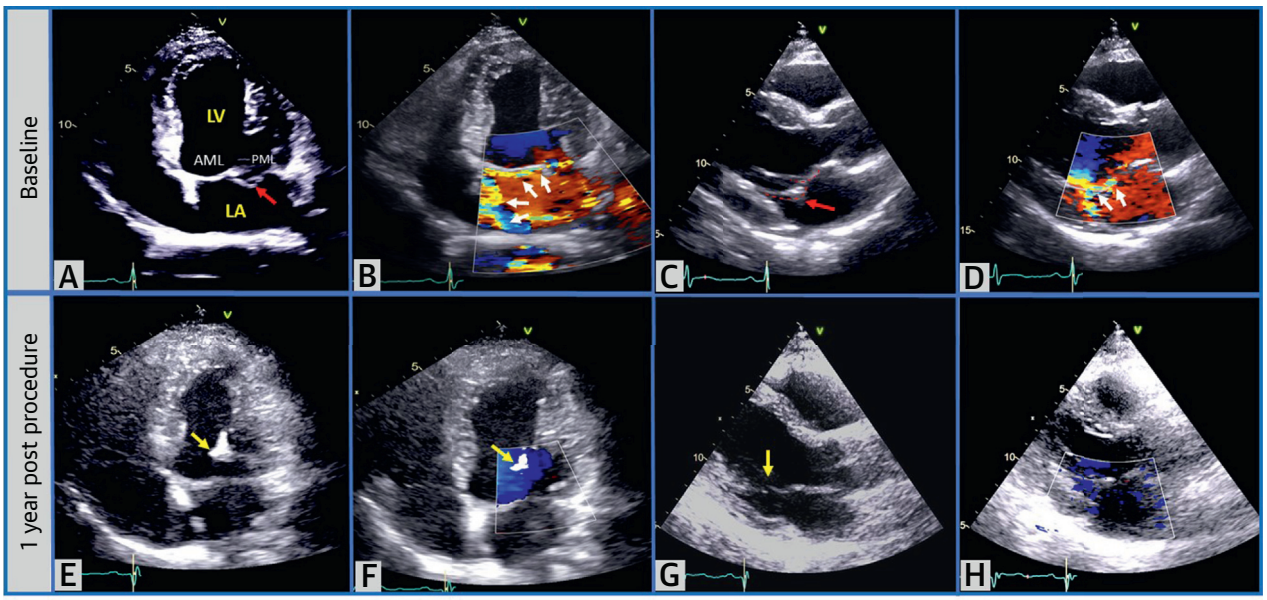
The MVRS enabled successful, less-invasive treatment of degenerative MR with few complications and immediate and stable reduction of MR with follow-up through 6 months. MV repair with the MVRS was associated with restoration of normal functional status and favorable echocardiographic reverse remodeling.

It is well accepted that MV repair is preferable to MV replacement for patients with degenerative MR (3). The rate and quality of repair in contemporary conventional cardiac surgical practice is unsatisfactory (5). American College of Cardiology/American Heart Association guidelines specify that replacement for isolated posterior leaflet prolapse is a Class III (harm) recommendation (2). However, repair rates for degenerative MR are highly variable, they are related to surgeon experience, and average only 80% for patients with degenerative leaflet prolapse in North America (1,5). Although durability of conventional surgical MV repair is reported to be outstanding in single-center retrospective series (14), there are few core laboratory-adjudicated series available to provide mid- and long-term data for the rate of recurrent MR. In 1 large series of 2,575 patients with isolated posterior leaflet prolapse, pre-discharge echocardiography demonstrated moderate MR in 6% and moderate to severe or severe MR in an additional 5% (15). In the prospective randomized EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II that compared Mitraclip (Abbott Vascular, Abbott Park, Illinois) implantation with conventional MV surgery, patients randomized to surgery had a 14% MV replacement rate, a 6.25% mortality rate, and a 16% moderate or greater recurrence of MR in the remaining patients at 12 months (16).

The present experience with the MVRS was characterized by a 100% repair rate in the 28 patients with procedural success and acceptable freedom from recurrent MR at 6 months. In all 4 patients with suboptimal MR reduction (moderate or severe) at 6-month follow-up, the presence of MR was related to use of an inadequate imaging platform, selection issues (advanced mitral annular calcification), or operator error (leaflet perforation), all of which are likely to be mitigated as accumulated clinical experience is applied in future cases. Precise real-time ultrasonography guidance of the procedure requires that the device tip and shaft orientation be clearly depicted by the imaging system. Side-lobe and reverberation artifact management by the echocardiographic system is extremely important in this regard as those artifacts make up the echocardiographic signature of the device. Artifact attenuation is handled differently by various vendors, and we learned in the early conversion cases that 1 vendor's approach does not provide clear images of the location of the MVRS device.

Although very early in the clinical experience with this technology, the primary endpoint was met in 90% of patients and the rate of moderate MR at 30 days (11%) was comparable to rates of moderate MR at discharge for patients undergoing posterior leaflet MV surgical repair at a large institution with extensive experience in MV repair (17).

FIGURE 2 **Transthoracic Echocardiography**



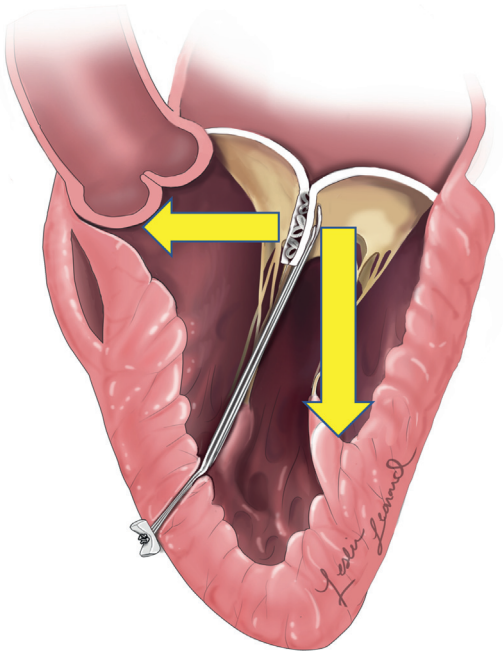
(A to D) Apical 4-chamber view and parasternal long-axis view at baseline and **(E to H)** at 12 months post-Harpoon mitral valve repair. **(A and C) Red arrows** indicate severe prolapse of the posterior mitral leaflet. Color Doppler shows an anteriorly-directed wrap-around jet of severe mitral regurgitation **(white arrows)**. **(E to G) Yellow arrows** show knots of the ePTFE artificial cords implanted close to the edge of the posterior mitral leaflet and proper position of the posterior leaflet. **(F and H)** No mitral regurgitation is visible at the 1-year follow-up study. AML = anterior mitral leaflet; LA = left atrium; LV = left ventricle; PML = posterior mitral leaflet.

The MVRS has the potential to simplify MV repair operations and increase the rate and quality of repair. Titration of the length of the ePTFE artificial cords using real-time echocardiographic imaging enables optimization of ePTFE cordal lengths on a fully loaded beating heart to maximize coaptation to a degree that is not possible with conventional surgical repair on an arrested heart.

Other advantages of MVRS include a small incision and avoidance of cardiopulmonary bypass, aortic cross-clamping, atrial incisions, and cardioplegic cardiac arrest. Similar to the experience in patients treated by using conventional surgical MV operations, the study patients treated with the MVRS had a low predicted risk of mortality (0.69%) according to Society of Thoracic Surgeons criteria (18). MVRS may expand the number of treatable patients on both ends of the risk spectrum, including the large population of patients at extreme risk who are currently deemed inoperable (19-22) and asymptomatic patients with severe MR and no evidence of LV dysfunction who may opt for earlier intervention with the availability of a less-invasive beating-heart therapy. This is of particular importance, given that one-third of patients currently referred for surgery have atrial fibrillation and more than one-half have evidence of impaired ventricular ejection performance (1).

In this series, MVRS was an efficient and safe procedure. Operative times were approximately one-half those reported for conventional surgical MV repair (23). Intraoperative blood loss was minimal and is underscored by the fact that only 1 patient (3%) required a perioperative blood transfusion, compared with conventional isolated MV operations, in which transfusion is required in more than 30% of patients (19). Patients were hemodynamically stable during the MVRS procedure and in no case were intraoperative inotropes or mechanical circulatory support required. New permanent pacemaker implantation was not required in any patient, as would be expected given that the MVRS procedure only impacts tissue that is distant from the conduction system. This is in contrast to transcatheter aortic valve replacement, where permanent pacemaker implantation rates average 17% (6% for balloon-expandable and 28% for self-expandable devices) (24) and conventional MV

FIGURE 3 Forces Applied to the Posterior Leaflet and Annulus



Insertion of artificial ePTFE cords from the anterior aspect of the ventricle impart both apical as well as anterior forces **(yellow arrows)** on the posterior leaflet and annulus. Repair results in a significant reduction in anterior-posterior mitral annular dimension.

repair and replacement operations, where rates are 3.1% and 10.5%, respectively (1). No patient suffered a stroke either during the procedure or at 6-month follow-up.

SAM of the MV remains a relatively common complication after conventional surgical MV repair (6% to 8%) and often requires an additional period of cardiac arrest and sometimes necessitates MV replacement (25). In the 2 patients in this trial who had evidence of SAM on initial tensioning of the ePTFE cords, treatment simply involved additional shortening of the artificial ePTFE cords, with complete and immediate resolution and no evidence of late recurrence. Thus, MVRS may represent a new and welcome paradigm for managing this challenging complication of MV repair surgery.

Favorable ventricular remodeling was seen at both 30 days and 6 months and was similar to that seen after conventional MV repair for degenerative disease, with substantial and significant decreases in LV end-diastolic and end-systolic volumes to normal (13,17,26,27).

There was a significant and important reduction in mitral annular area to normal ranges at 6 months compared to baseline (12). We observed an average reduction of 31% in the mitral annular area and a 19% reduction in septal-lateral dimension (mean absolute decrease of 6.5 mm) at 6 months after the procedure. This suggests that insertion and tensioning of ePTFE artificial cords using the Harpoon system is associated with a substantial annuloplasty effect. The 2 components of this effect include systolic reduction of anteroposterior diameter as a result of restoration of coaptation, as well as an anterior force vector imparted to the posterior annulus through the ePTFE cords that enter the ventricle in an anterior location (**Figure 3**).

The mean pressure gradient of 1.5 ± 0.6 mm Hg observed 6 months after MVRS repair in this series is lower than that seen after conventional MV repair or Mitraclip procedure and is identical to gradients measured in healthy controls (28).

Experience with transapical beating-heart MV repair has also been reported using a larger diameter device that grasps the free edge of MV leaflet and deploys an ePTFE cord in a girth hitch configuration (Neochord, Inc., Minneapolis, Minnesota). In a single-center series, this device demonstrated procedural safety and effective reduction of MR at 3-month follow-up (29).

One key advantage of the MVRS approach is that the sole intracardiac implantation consists of an ePTFE suture in the leaflet that preserves the option for future conventional MV repair. In the 2 cases that required intraprocedural conversion, both patients underwent successful nonresectional MV repair. There was no evidence that implantation of ePTFE suture and knots resulted in damage to the leaflet. In the patient who required reoperation at 8 months, the ePTFE knot was well incorporated within the mitral leaflet and did not compromise an effective nonresectional repair. This is in contradistinction to the Mitraclip procedure, where the implanted device leads to leaflet tissue fibrosis and usually precludes subsequent MV repair, particularly beyond a few months after the procedure (15).

STUDY LIMITATIONS. This trial did not include a control arm of patients undergoing conventional surgical MV repair operations. The study protocol limited MVRS repairs to patients with isolated posterior leaflet prolapse. Future clinical trials will include patients with anterior and bileaflet prolapse.

CONCLUSIONS

This prospective, multicenter, observational study of the MVRS demonstrated good procedural success with an outstanding safety profile. The MVRS enabled targeted and titratable less invasive ePTFE cordal replacement and physiologic MV repair that was durable and associated with favorable cardiac remodeling. MR reduction was stable at 6 months. The MVRS has the potential to simplify and increase the quality and rates of MV repair and decrease the morbidity associated with conventional open cardiac surgical MV operations. Although it remains early in the clinical experience with this device and further investigation with longer-term follow-up and direct comparison with conventional mitral valve surgery is necessary, the initial results are promising.

ACKNOWLEDGMENTS The authors are grateful for the support of and input from Radoslaw Litwinowicz, MD, and Anton Chrustowicz, MD.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In patients with degenerative posterior leaflet prolapse and severe MR, a TEE-guided device that implants ePTFE cords on mitral leaflets in the beating heart can be safe and effective in reducing MR.

TRANSLATIONAL OUTLOOK:

Further device and procedural improvements should be evaluated in clinical trials that compare the outcomes of beating-heart image-guided mitral valve repair with conventional mitral valve surgery.

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KEY WORDS echocardiography, mitral valve, regurgitation, valvuloplasty, surgery