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

James S. Gammie, MD, Krzysztof Bartus, MD, PhD, Andrzej Gackowski, MD, PhD, Michael N. D'Ambra, MD;, Piotr Szymanski, MD, PhD, Agata Bilewska, MD, PhD, Mariusz Kusmierczyk, MD, PhD, Boguslaw Kapelak, MD, PhD, Jolanta Rzucidlo-Resil, MD, Mr. Neil Moat, MBBS, FRCS, Dr. Alison Duncan, MBBS, PhD, Ms. Rashmi Yadev, MBBS, PhD, FRCS (CTh), Mr. Steve Livesey, FRCS, Dr. Paul Diprose, FRCA, Gino Gerosa, MD, PhD, Augusto D'Onofrio, MD, Demetrio Pitterello, MD, Paolo Denti, MD, Giovanni La Canna, MD, Michele De Bonis, MD, FESC, FAHA, Ottavio Alfieri, MD, PhD, Judy Hung, MD, Piotr Kolsut, MD, PhD

PII: S0735-1097(17)41363-5

DOI: 10.1016/j.jacc.2017.10.062

Reference: JAC 24403

To appear in: *Journal of the American College of Cardiology*

Received Date: 12 October 2017

Revised Date: 24 October 2017

Accepted Date: 25 October 2017

Please cite this article as: Gammie JS, Bartus K, Gackowski A, D'Ambra MN, Szymanski P, Bilewska A, Kusmierczyk M, Kapelak B, Rzucidlo-Resil J, Moat N, Duncan A, Yadev R, Livesey S, Diprose P, Gerosa G, D'Onofrio A, Pitterello D, Denti P, La Canna G, De Bonis M, Alfieri O, Hung J, Kolsut P, Beating-Heart Mitral Valve Repair Using a Novel ePTFE Cordal Implantation Device: Prospective Trial, *Journal of the American College of Cardiology* (2017), doi: 10.1016/j.jacc.2017.10.062.

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

Short title: Beating-Heart Mitral Valve Repair Using a Novel ePTFE Cordal

James S. Gammie, MD[1]; Krzysztof Bartus, MD, PhD[2]; Andrzej Gackowski, MD, PhD[2]; Michael N. D'Ambra, MD;[3] Piotr Szymanski, MD, PhD[4]; Agata Bilewska, MD, PhD[4]; Mariusz Kusmierczyk, MD, PhD[4]; Boguslaw Kapelak, MD, PhD[2]; Jolanta Rzucidlo-Resil, MD[2]; Mr. Neil Moat, MBBS, FRCS[5]; Dr. Alison Duncan, MBBS, PhD[5]; Ms. Rashmi Yadev, MBBS, PhD, FRCS (CTh)[5]; Mr. Steve Livesey, FRCS[6]; Dr. Paul Diprose, FRCA[6]; Gino Gerosa, MD, PhD[7]; Augusto D'Onofrio, MD[7]; Demetrio Pitterello, MD[7]; Paolo Denti, MD[8]; Giovanni La Canna, MD[8]; Michele De Bonis, MD, FESC, FAHA[8]; Ottavio Alfieri, MD, PhD[8]; Judy Hung, MD[9]; Piotr Kolsut, MD, PhD[4]

[1] Division of Cardiac Surgery, University of Maryland School of Medicine, Baltimore, MD, USA
[2] Jagiellonian University John Paul II Hospital, Krakow Poland
[3] Brigham and Women's Hospital , Boston, MA, USA
[4] Institute of Cardiology, Warsaw Poland
[5] The Royal Brompton & Harefield NHS Foundation Trust, London UK
[6] University Hospital Southampton NHS Foundation Trust UK
[7] Padova University Hospital, Padova Italy
[8] Ospedale San Raffaele, Milan Italy
[9] Massachusetts General Hospital, Boston, MA, USA

Correspondence:
James S. Gammie, MD
Division of Cardiac Surgery
University of Maryland School of Medicine
110 S. Paca Street, 7th Floor
Baltimore, MD 21201
Telephone: 410 328 5842
Fax 410 328 2750
E-mail: Jsgammiemd@gmail.com

Funding Sources: Funding for this study was provided by Harpoon Medical, Inc.

Conflict of Interest Disclosures: Drs. Gammie, D'Ambra, Gackowski and Bartus have ownership of stock and/or options to purchase stock in Harpoon Medical, Inc. The remaining authors have nothing to disclose.

Acknowledgements: We are grateful for the support and input of Radoslaw Litwinowicz, MD and Anton Chrustowicz, MD.

Abstract

Background: We evaluated safety and performance of the Harpoon Mitral Valve Repair System (H-MVRS), 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 H-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 one month, MR was mild or less in 89 % (24/27) and was moderate in 11% (3/27). At 6 months, MR was mild or less in 85 % (22/26), moderate in 8% (2/26), and severe in 8% (2/26). Favorable cardiac remodeling at six months included decreases in end-diastolic (161 ± 36 to 122 ± 30 ml, $p < 0.001$) and left atrial volumes (106 ± 36 to 69 ± 24 ml, $p < 0.001$). The anterior-posterior mitral annular dimension decreased from 34.7 ± 5.8 to 28.2 ± 5.1 mm, $p < 0.001$ as did the mitral annular area (10.0 ± 2.7 vs 6.9 ± 2.0 cm^2, $p<0.0001$).

Conclusions: H-MVRS ePTFE cordal implantation can reduce the invasiveness and morbidity of conventional mitral valve surgery. The safety profile of the device is promising and prospective trials comparing the outcomes of H-MVRS to conventional mitral valve repair surgery are warranted.

Clinical Trial Registration

https://clinicaltrials.gov/ct2/show/NCT02768870?term=NCT02768870&rank=1

Key Words: Mitral valve; Regurgitation; Valvuloplasty; Surgery; echocardiography

Condensed Abstract: The Harpoon Mitral Valve Repair System (H-MVRS) is a transesophageal echocardiographic-guided device designed to implant artificial expanded polytetrafluoroethylene (ePTFE) cords on mitral leaflets in the beating heart. Thirty patients with severe mitral regurgitation (MR) were treated. Three patients required early conversion to open surgery. There were no deaths, strokes, or pacemaker implantations. At 6 months, MR was ≤ mild in 85 %, moderate in 8%, and severe in 8%. Favorable remodeling included decreases in end-diastolic and anterior-posterior mitral dimensions. H-MVRS can reduce the invasiveness and morbidity of conventional mitral valve surgery and may improve the quality and frequency of repair.

Abbreviations:

ePTFE	expanded polytetrafluoroethylene
MR	mitral regurgitation
H-MVRS	Harpoon mitral valve repair system
TEE	transesophageal echocardiography
TRACER	Mitral TransApical NeoCordal Echo-Guided Repair
ASE	American Society of Echocardiography
ESC	European Society of Cardiology
LA	left atrial
IQR	interquartile range
CI	confidence interval
MSSA	methicillin-sensitive staph aureus
SAM	systolic anterior motion
SAE	serious adverse event

MAC	mitral annular calcification
STS	Society of Thoracic Surgeons
ACC/AHA	American College of Cardiology/American Heart Association

Introduction

Mitral valve operations are most commonly performed for degenerative mitral regurgitation (MR) (1) and are indicated for patients with symptoms, left ventricular dysfunction, atrial arrhythmias, severe MR and/or pulmonary hypertension (2). Short- and long-term outcomes are superior after mitral valve repair compared to mitral valve replacement for patients with degenerative disease (3), and successful mitral valve repair alleviates symptoms, prevents and reverses unfavorable ventricular remodeling, and improves survival. While conventional mitral valve operations allow for complete direct visual anatomic assessment and repair using a variety of techniques on an arrested heart, they require cardiopulmonary bypass, aortic cross-clamping, sternotomy or thoracotomy, and cardioplegic cardiac arrest and are therefore associated with significant peri-operative disability as well as risks of morbidity and mortality.(4) Mitral valve repair rates are highly variable, with lower successful repair rates observed in low-volume centers.(5) The Harpoon Mitral Valve Repair System (H-MVRS) may provide an alternative treatment for patients with degenerative MR. In this procedure, access to the anterior wall of the left ventricle is secured through a small left thoracotomy and the Harpoon delivery system is utilized to anchor artificial ePTFE cords on the prolapsed segment of the mitral valve on the beating heart using transesophageal echocardiographic (TEE) guidance. The lengths of the ePTFE cords are then adjusted to optimize leaflet coaptation and minimize MR, and 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.

Methods

Study Design and Oversight

The TRACER (Mitral TransApical NeoCordal Echo-Guided Repair) trial is a prospective, nonrandomized multicenter clinical study designed to test the safety and performance of the Harpoon MVRS for mitral valve 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 CE Marking for the device. The trial was conducted at 6 clinical centers in Europe and was sponsored by the manufacturer of the H-MVRS (Harpoon Medical Inc., Baltimore, Maryland). The 30 patients enrolled in this study were distinct and subsequent to the eleven enrolled in the early feasibility study. The study protocol was approved by the relevant national authority in each country and the ethics committee at each institution. All patients provided written informed consent prior to enrollment. Serious adverse events were site reported and adjudicated by an independent data safety and monitoring committee consisting of independent physicians. Monitoring and collection of the data and initial data analyses were performed by the sponsor. The academic authors had full access to the data and are responsible for the completeness and accuracy of the data and analyses reported in this manuscript.

Participant Selection

Patients 18 years of age or older with severe degenerative MR resulting from isolated posterior leaflet prolapse were enrolled. All patients had Class I or IIa indications for operation (2). Patients underwent protocol-directed preoperative transesophageal echocardiography that included 2D and 3D analyses of mitral valve morphology to assess anatomic feasibility. A patient selection committee determined if the predicted post-repair coaptation surface would be adequate to result in effective MR reduction. In general, 3D imaging and analysis software (Tomtec imaging systems, TOMTEC USA Chicago, IL, 60661 USA) as well as 2D pan-through

TEE imaging (both 4-chamber and long-axis) was used to assess the mitral valve 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 A-P dimension of the regurgitant orifice). While a number of anatomical characteristics were evaluated, primary assessment of suitability was based on the ratio of posterior prolapse segment length (measured with linear polygonal assessment tools (Osirix, Pixmeo SARL, 266 Rue de Bernex, CH-1233 Bernex, Switzerland) to corresponding A-P distance between free edge of the anterior leaflet and the base of the prolapsed posterior leaflet segment. A minimum ratio of 1.5 to 1 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 prior cardiac operation, chronic renal insufficiency (stage 3b or worse), severe pulmonary hypertension (systolic pulmonary artery pressure > 70 mmHg, or a EuroSCORE II (for mitral valve repair) of greater than 8 % (7). Full inclusion and exclusion criteria are available at https://clinicaltrials.gov/ct2/show/NCT02768870?term=NCT02768870&rank=1 { HMCE-1002 CE Mark Study for the Harpoon Medical Device (TRACER)} and https://clinicaltrials.gov/ct2/show/NCT02432196 {HMFIM-1000 CE Mark Study for the Harpoon Medical Device in Poland.}

Primary performance and safety endpoints

The primary performance endpoint was successful implantation of one or more ePTFE artificial cords on the mitral valve with 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 serious adverse events during the procedure and through 30 days after operation. Peri-operative mortality was defined as the greater of 30-day mortality or in-hospital mortality.

The Harpoon Mitral Valve Repair System

The H-MVRS (Harpoon Medical, Inc., Baltimore, MD, USA) is comprised of two parts: a hemostatic introducer and a delivery system. The introducer has a 14F (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 preformed ePTFE knot wrapped on a purpose-designed 21-gauge needle and is designed to securely anchor artificial ePTFE cords on targeted locations on a prolapsed mitral valve 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 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-helical knot on the atrial surface of the leaflet.

The 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 4^{th}) and location for an incision on the left chest. A small thoracotomy is performed, the pericardium opened and a location on the epicardium approximately 3 cm basal to the true apex and one cm lateral to the left anterior descending coronary artery is identified for insertion of the hemostatic introducer. Rib-spreading is avoided if possible. Finger ballottment is performed on the proposed entrance site and TEE-assessment

performed to assure that the entrance site is just apical to the base of the antero-lateral 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 seconds. 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 2-D 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 two 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 tied. The ePTFE suture pairs are then threaded individually through a stiff ePTFE pledget and are tightened simultaneously and incrementally 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 (**Figure 1**). A video is available at https://www.harpoonmedical.com/the-procedure Aspirin (81 - 325 mg per day) is administered post-operatively. All implanting surgeons and imaging specialists were trained on a bench top simulator as well as 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

Preprocedural, intraprocedural and post-operative echocardiograms were performed by the sites. De-identified studies were securely transmitted in DICOM format to an independent

core laboratory (Massachusetts General Hospital, Boston, MA) for anonymized and standardized evaluation. The severity of MR was graded as none/trace, mild, moderate, or severe using integrative criteria as specified by the American Society of Echocardiography (ASE) and European Society of Cardiology (ESC) (8,9). LV dimensions, left atrial (LA) volumes (biplane area length) and LV volumes were measured (biplane method of discs) according to the ASE chamber quantification guidelines (10). To assess the effect of reducing mitral annular dimensions following the H-MVRS procedure, mitral annular dimensions were measured in the parasternal long axis dimension on 2D transthoracic echocardiogram as this imaging plane best measures septal-lateral (anterior-posterior) mitral annular dimension. Mitral annular area was calculated as π times (half of mitral annular dimension in parasternal long axis) times (half of mitral annular dimension in apical 2 chamber) using elliptical assumption for mitral annulus (11,12).

Baseline characteristics and clinical outcomes were described using counts and percentages for categorical variables and using means $\pm$ standard deviations, supported by ranges, for continuous measures. Exact 95% confidence intervals were constructed for the primary endpoints. The primary performance endpoint was tested against the pre-specified performance goal of 58% using the lower bound of the exact 95% confidence interval. There was no formal hypothesis tested for the primary safety endpoint. Echocardiographic continuous variables were compared at baseline, 30 day and 6 month stages using one-way analysis of variance test with repeated measures. Post-hoc pairwise comparisons were made with Bonferroni correction. MR grade was measured as a categorical variable and significant differences in MR grade in baseline, 30 day and 6 month stages were examined using Friedman test. Creatinine levels were compared using the non-parametric sign test. A p-value < 0.05 was considered

statistically significant. There is no imputation for missing data. Analyses were performed with IBM SPSS Statistical software, version 25.

Results

Characteristics of the patients

From December 2015 through November 2016, 89 patients were screened for the trial. Thirty consecutive patients were enrolled in the trial at six clinical sites in three countries. The most frequent reasons for trial exclusion included anterior leaflet prolapse, inadequate predicted coaptation surface, functional MR, leaflet injury or defect, and refusal to consent. All patients completed the 6-month echocardiographic and clinical follow-up by July 2017. The mean age of the patients was 61 ± 13 years (range, 40-85), and 77% (23/30) were men. Class I indications for mitral valve operation were present in 17 patients (57 percent) and Class IIa indications in 13 (43 percent). The 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 % (28/30). An average of 3.9 ± 1 (range 1 to 5, IQR 3-5) pairs of ePTFE artificial cords were implanted in patients successfully treated with the Harpoon device. Total procedure time averaged 125 minutes (± 43 min, range 84 - 199 min) and the introducer was in the ventricle for an average of 43 minutes (± 22 min, range 16-103mins). During the procedure MR was reduced from severe to none/trace in 24 (86%) patients and to mild in 4 (14%) patients. 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 27/30 (90 %; 95% CI: [73%, 98%]) of patients enrolled, meeting the pre-specified performance goal of 58% ($P<0.001$). At 30 day follow-up, 85% (23/27) of patients were in NYHA Class I and 89% (24/27) had mild or less MR. At 6

months follow-up 93 % (25/27) were in NYHA Class I, MR was mild or less in 85 % (22/26), moderate in 8% (2/26), and severe in 8% (2/26).

Two patients required intraoperative conversion to conventional cardiac surgery and underwent successful mitral valve repair operations. The first patient enrolled in the study had 4 ePTFE artificial cords inserted using the H-MVRS. Suboptimal echocardiographic equipment was responsible for poor quality images of the Harpoon 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 mitral valve surgery. Direct intra-operative inspection of the mitral valve demonstrated that three knots were placed at the base of the leaflet, rather than the free edge, and one was intraventricular. The knots were removed and the valve was repaired by resuspending the intact leaflet with three ePTFE sutures and inserting a size 30 annuloplasty ring: post-bypass TEE demonstrated no MR. The patient was discharged in good condition with none/trace MR nine 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 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/trace MR. One patient required conventional cardiac surgical operation on post-operative day 27 for recurrent symptomatic severe mitral regurgitation caused by methicillin-sensitive staph aureus (MSSA) infective endocarditis. This patient had an elevated WBC on the morning of the H-MVRS procedure and dental caries that were not reported. Although the Harpoon procedure and post-operative course

were uneventful and the patient was discharged to rehab 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 via conventional sternotomy was performed on post-operative day 27. There was a 5x6 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 of the mitral valve (SAM) with MR and LVOT obstruction. In both cases additional shortening of the cords completely resolved the SAM and the patients were left with none/trace MR at the conclusion of the procedure. Follow-up echocardiography has demonstrated no evidence of recurrent SAM or MR at 6 months post-procedure.

Safety Endpoints

There was no periperative or late mortality. There were no peri-operative strokes, renal failure, or myocardial infaction. No patient required temporary epicardial pacing or permanent pacemaker insertion. No patient required intra-operative inotropic support. The average intra-procedural blood loss was 276ml ± 196 (range 50-700) ml. A single blood transfusion was required in one 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 (range 3-9) days. No patient required reintubation or readmission to the intensive care unit.

The median maximal creatinine level measured after operation was similar to the preoperative value (0.93 vs. 0.92 (range 0.65 – 1.48, IQR 0.86 - 1.15 vs. range 0.60 – 1.44, IQR 0.83 - 1.05) mg/Dl, p = .0614). Among the 27 patients with implanted Harpoon artificial ePTFE cords clinical follow-up is 100 % complete (range 7 - 16 months), and there has been no late stroke, thromboembolism, infective endocarditis, or death. There were 6 patients with SAEs within 30 days (6/30 (20%); 95% CI [8%,39%]). Serious adverse events included the three patients that required conversion to conventional mitral valve surgery, chest pain requiring readmission for 24 hours on post-operative day 5, 2 pleural effusions requiring drainage (post-operative day 8 and 9), chronic cholecystitis treated with an elective cholecystectomy on post-operative day 86, and one patient with new atrial flutter on post-operative day 38 treated with amiodarone. Two patients (2/21; 10 %) developed new post-operative atrial fibrillation that resolved by the 30-day visit. All patients (n = 9) that were in atrial fibrillation prior to operation were in normal sinus rhythm at the 30-day and 6-month visits.

Mitral Regurgitation Reduction and Reverse Remodeling

Core-lab adjudicated MR severity at the conclusion of the procedure, prior to dismissal, and at 30 days and 6 months is displayed **in Figure 2**. Among the 26 patients with echocardiographic follow-up and H-MVRS cords in place at 6 months, 85 % (22/26) had none/trace or mild mitral regurgitation. Two patients with moderate MR (8 %; 2/26) 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 on the 6 month assessment; this patient had dense mitral annular calcification that extended into the ventricle beneath the entire posterior leaflet. The severe MAC led to 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. She 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/trace MR.

*Echocardiographic Variables (**Table 2**)*

There was evidence of favorable early ventricular reverse remodeling, with significant decreases in end-diastolic volumes by 25 % (161±36 to 121±30 ml) and end-systolic volumes by 14% (52 ±20 to 45 ± 14) at 6 months. There was a significant decrease in septal to lateral mitral annular dimension (34.7 ± 5.8 vs 31.2 ± 4.0 mm; baseline vs 30 days; $p<0.0001$) and mitral annular area (10.0 ± 2.7 vs 8.4 ± 2.0 cm^2; baseline vs 30 days $p<0.0001$) at 30 days post procedure (**Table 2**). At six 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 to 61 ± 6 percent at 30 days and improved to 66 ± 7 at 6 months, consistent with previously reported experience with conventional mitral valve surgery (13). The mean transmitral gradient was 1.3 ± 1.1 mmHg at 30 days and 1.5 ± 0.7 mmHg 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 (left atrial volume decreased from106 ± 36 to 69 ± 24 ml at

6 months, p <0.001). **Figure 3** is a representative preoperative and 6-month transthoracic follow-up study.

Discussion

The H-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. Harpoon mitral valve repair was associated with restoration of normal functional status and favorable echocardiographic reverse remodeling.

It is well accepted that mitral valve repair is preferable to mitral valve replacement for patients with degenerative MR.(3) The rate and quality of repair in contemporary conventional cardiac surgical practice is unsatisfactory .(5) ACC/AHA 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, related to surgeon experience, and for patients with degenerative leaflet prolapse average only 80% in North America. (1) (5) Although durability of conventional surgical mitral valve 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 on the rate of recurrent mitral regurgitation. In one large series of 2575 patients with isolated posterior leaflet prolapse, predischarge echocardiography demonstrated moderate MR in 6 % and moderate to severe or severe MR in an additional 5% (15). In the prospective randomized Everest II trial that compared Mitraclip to conventional mitral valve surgery, patients randomized to surgery had a 14% mitral valve replacement rate, a 6.25% mortality rate, and recurrent moderate or greater MR in 16% of the remaining patients at 12 months (16).

The present experience with the Harpoon 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 four patients with suboptimal MR reduction (moderate or severe) at six month follow-up, the presence of MR was related to use of an inadequate imaging platform, selection issues (advanced MAC), 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 ultrasound guidance of the Harpoon 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 echo signature of the Harpoon device. Artifact attenuation is handled differently by various vendors and we learned in the early conversion cases that one vendor's approach does not provide clear images of the location of the H-MVRS device.

Although very early in the clinical experience with this technology, the primary endpoint was met in ninety percent 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 mitral valve surgical repair at a large institution with extensive experience in mitral valve repair (17).

The H-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 coapatation to a degree that is not possible with conventional surgical repair on an arrested heart.

Other advantages of H-MVRS include a small incision and avoidance of cardiopulmonary bypass, aortic cross-clamping, atrial incisions and cardioplegic cardiac arrest.

Similar to the experience with conventional surgical mitral valve operations, the patient population treated with H-MVRS had a low STS predicted risk of mortality (0.69 percent) (18). H-MVRS may expand the number of treatable patients on both ends of the risk spectrum, including the large population of extreme risk patients that are currently deemed inoperable (19-22).

as well as asymptomatic patients with severe MR and no evidence of left ventricular dysfunction who might 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 half have evidence of impaired ventricular ejection performance (1).

In this series, H-MVRS was an efficient and safe procedure. Operative times were approximately half those reported for conventional surgical mitral valve repair.(23) Intraoperative blood loss was minimal and is underscored by the fact that only one patient (3%) required a perioperative blood transfusion. This is in comparison to conventional isolated mitral valve operations, where transfusion is required in more than 30 % of patients.(19) Patients were hemodynamically stable during the H-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 Harpoon 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 mitral valve repair and replacement operations, where rates are 3.1 and 10.5 percent, respectively. (1) No patient suffered a stroke either during the procedure or through 6 month follow-up.

Systolic anterior motion (SAM) of the mitral valve remains a relatively common complication after conventional surgical mitral valve repair (6-8%) and often requires an additional period of cardiac arrest and sometimes necessitates mitral valve replacement (25) In the two patients in this trial that 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 H-MVRS may represent a new and welcome paradigm for managing this challenging complication of mitral valve repair surgery.

Favorable ventricular remodeling was seen at both 30 days and 6 months and was similar to that seen after conventional mitral valve repair for degenerative disease, with substantial and significant decreases in left-ventricular 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 six 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 two components of this effect include systolic reduction of AP diameter as a result of restoration of coaptation, as well as an anterior force vector imparted on the posterior annulus through the ePTFE cords that enter the ventricle in an anterior location (**Figure 4**).

The mean gradient of 1.5 ± 0.6 mmHg observed 6 months after Harpoon repair in this series is lower than that seen after conventional mitral valve repair or Mitraclip and is identical to gradients measured in healthy normal controls (28).

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

One key advantage of the Harpoon approach is that sole intracardiac implant is an ePTFE suture in the leaflet that preserves the option for future conventional mitral valve repair. In the two cases that required intraprocedure conversion, both underwent successful nonresectional mitral valve repair. There was no evidence that implantation of ePTFE suture/knots resulted in damage to the leaflet. In the patient that required reoperation at eight 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 mitral valve repair, particularly beyond a few months after the procedure (15).

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

In conclusion, this prospective, multicenter, observational study of the H-MVRS demonstrated good procedural success with an outstanding safety profile. The H- MVRS enabled targeted and titratable less-invasive ePTFE cordal replacement and physiologic mitral valve repair that was durable and was associated with favorable cardiac remodeling. MR reduction was stable at 6 months. The H-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. While it remains early in the clinical experience with this device and further investigation with longer term follow-up and direct comparison to conventional mitral valve surgery is necessary, the initial results are promising.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with severe degenerative MR and posterior leaflet prolapse, a transesophageal echocardiographic device that implants ePTFE cords on mitral leaflets in the beating heart is safe an effective in reducing MR.

TRANSLATIONAL OUTLOOK: Ongoing procedural and device improvements may improve results and should be evaluated in future trials that compare the outcomes of beating-heart image-guided mitral valve repair with conventional mitral valve surgery.

References

1. Gammie J, et al. . Isolated Mitral Valve Surgery in North America. Analysis of the STS Adult Cardiac Surgery Database Ann Thorac Surg 2017;in press

2. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017.

3. Gammie JS, Sheng S, Griffith BP, et al. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg 2009;87:1431-7; discussion 7-9.

4. Suri RM, Taggarse A, Burkhart HM, et al. Robotic Mitral Valve Repair for Simple and Complex Degenerative Disease. Midterm Clinical and Echocardiographic Quality Outcomes 2015;132:1961-8.

5. Chikwe J, Toyoda N, Anyanwu AC, et al. Relation of Mitral Valve Surgery Volume to Repair Rate, Durability, and Survival. Journal of the American College of Cardiology 2017;69:2397-406.

6. Gammie JS, Wilson P, Bartus K, et al. Transapical Beating-Heart Mitral Valve Repair With an Expanded Polytetrafluoroethylene Cordal Implantation Device: Initial Clinical Experience. Circulation 2016;134:189-97.

7. Nashef SAM, Roques F, Sharples LD, et al. EuroSCORE II†. European Journal of Cardio-Thoracic Surgery 2012;41:734-45.

8. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography

Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303-71.

9. H B, V F, JJ B, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease: The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal [Eur Heart J] 2017;2017 Aug 26:1-53.

10. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.

11. Kaplan SR, Bashein G, Sheehan FH, et al. Three-dimensional echocardiographic assessment of annular shape changes in the normal and regurgitant mitral valve. American Heart Journal 2000;139:378-87.

12. Ormiston JA, Shah PM, Tei C, Wong M. Size and motion of the mitral valve annulus in man. I. A two-dimensional echocardiographic method and findings in normal subjects. Circulation 1981;64:113-20.

13. Suri RM, Schaff HV, Dearani JA, et al. Recovery of left ventricular function after surgical correction of mitral regurgitation caused by leaflet prolapse. The Journal of Thoracic and Cardiovascular Surgery;137:1071-6.

14. Castillo JG, Anyanwu AC, Fuster V, Adams DH. A near 100% repair rate for mitral valve prolapse is achievable in a reference center: Implications for future guidelines. The Journal of Thoracic and Cardiovascular Surgery;144:308-12.

15. Johnston DR, Gillinov AM, Blackstone EH, et al. Surgical Repair of Posterior Mitral Valve Prolapse: Implications for Guidelines and Percutaneous Repair. The Annals of Thoracic Surgery 2010;89:1385-94.

16. Feldman T, Foster E, Glower DD, et al. Percutaneous Repair or Surgery for Mitral Regurgitation. New England Journal of Medicine 2011;364:1395-406.

17. Pandis D, Grapsa J, Athanasiou T, Punjabi P, Nihoyannopoulos P. Left ventricular remodeling and mitral valve surgery: Prospective study with real-time 3-dimensional echocardiography and speckle tracking. The Journal of Thoracic and Cardiovascular Surgery;142:641-9.

18. Chatterjee S, Rankin JS, Gammie JS, et al. Isolated Mitral Valve Surgery Risk in 77,836 Patients From The Society of Thoracic Surgeons Database. The Annals of Thoracic Surgery;96:1587-95.

19. Wallenborn J, Störk S, Herrmann S, et al. Prevalence of severe mitral regurgitation eligible for edge-to-edge mitral valve repair (MitraClip). Clinical Research in Cardiology 2016;105:699-709.

20. Mirabel M, Iung B, Baron G, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? Eur Heart J 2007;28:1358-65.

21. Trochu J-N, Dillon R, Gustafsson F, Mitchell SA, Mitrovic V, Alfieri O. Mitral regurgitation — Unmet need for improved management strategies. IJC Heart & Vasculature 2014;5:26-41.

22. Andell P, Li X, Martinsson A, et al. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. Heart 2017.

23. Data Analyses of the Society of Thoracic Surgeons National Adult Cardiac Surgery Database December 31, 2016

24. Siontis GCM, Jüni P, Pilgrim T, et al. Predictors of Permanent Pacemaker Implantation in Patients With Severe Aortic Stenosis Undergoing TAVR. Journal of the American College of Cardiology 2014;64:129-40.

25. Varghese R, Anyanwu AC, Itagaki S, Milla F, Castillo J, Adams DH. Management of systolic anterior motion after mitral valve repair: An algorithm. The Journal of Thoracic and Cardiovascular Surgery;143:S2-S7.

26. Shafii AE, Gillinov AM, Mihaljevic T, Stewart W, Batizy LH, Blackstone EH. Changes in Left Ventricular Morphology and Function After Mitral Valve Surgery. Am J Cardiol 2012;110:403-8.e3.

27. Normal Values of TTE Echopedia.org 2016. at https://www.echopedia.org/wiki/Normal_Values_of_TTE%23Left_Ventricular_Diastolic_Function.)

28. Prajapati D, Sharma D, Baidya S, Shakya U, Shrestha N. Normal Echocardiographic Parameters of Healthy Adult Individuals working in National Heart Centre Nepalese Heart Journal 2012;9:3-6.

29. Colli A, Manzan E, Zucchetta F, et al. Transapical off-pump mitral valve repair with Neochord implantation: Early clinical results. International Journal of Cardiology 2016;204:23-8.

Figure Legends

Figure 1. The Harpoon mitral valve repair procedure. 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 3-4 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 forming an ePTFE knot on the atrial surface. Multiple ePTFE cords are anchored on the leaflet, the introducer withdrawn, and the cordal lengths adjusted to maximize coaptation and minimize MR. The cords are tied on a Teflon pledget on the epicardium at the insertion site.

Figure 2: MR grades. Excludes 3 patients converted to conventional open cardiac surgery. Three echocardiographic studies (2 discharge and 1 six month) were incomplete due to poor acoustic window postprocedure and could not be adjudicated by the core lab.

Figure 3. Transthoracic echocardiography – apical four-chamber view and parasternal long axis view at baseline (panels A, B, C, D) and 12 months post Harpoon mitral valve repair (panels E, F, G, H). Red arrows – severe prolapse of the posterior mitral leaflet (PML). Color Doppler shows an anteriorly-directed wrap-around jet of severe mitral regurgitation (white arrows). Yellow arrows show knots of the ePTFE artificial cords implanted close to the edge of the PML and proper position of the posterior leaflet. No mitral regurgitation is visible in a one year follow-up study (panels F and H).

Figure 4: Forces applied to the posterior leaflet and annulus. Insertion of Harpoon artificial ePTFE cords from the anterior aspect of the ventricle impart both apical as well as anterior forces on the posterior leaflet and annulus. Harpoon repair results in a significant reduction in the anterior-posterior mitral annular dimension.

Table 1: Baseline Characteristics of the Patients

Characteristic	No. (%), or Mean ± SD
Age (years)	61 ± 13
Male gender	23 (77%)
BMI (Kg/m2)	26.2 ± 3.7
NYHA Class – no. (%)	
I	15 (50 %)
II	10 (33 %)
III	5 (17 %)
IV	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	79.1 ± 15.5 mL/min/m2
Cardiac structure – function	
LV ejection fraction, mean, %	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%)

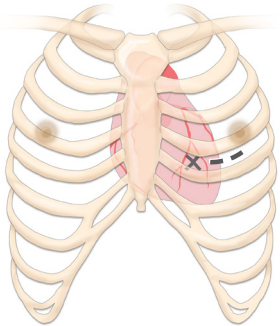
* BMI, Body mass index; NYHA, New York Heart Association; STS PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; LV, Left Ventricular; LA, left atrial; sPAP, Systolic pulmonary artery pressure; **7 paroxysmal, 2 continuous.

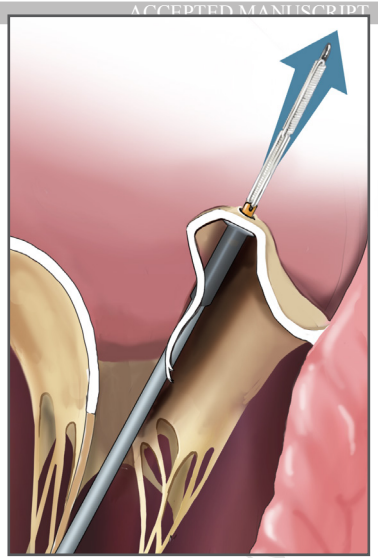
Table 2: Echocardiographic results

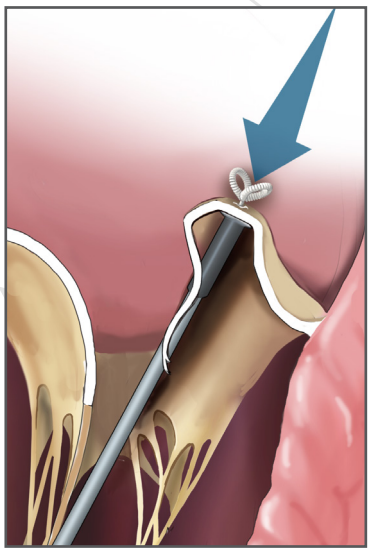
	Screening	30 Day	6 Month	pValue
LVEDD (mm)	53 ± 6	49 ± 5[#]	48 ± 6[#]	< 0.001
LVESD (mm)	33 ± 6	33 ± 5	32 ± 5	0.31
LA volume (ml)	106 ± 36	72 ± 26[#]	69 ± 24[#]	< 0.001
LV EDV (ml)	161 ± 36	123 ± 28[#]	122 ± 30[#]	< 0.001
LV ESV (ml)	52 ±20	49 ± 13	45 ± 14*	< 0.001
LVEF (%)	69 ± 7	61 ± 6[#]	66 ± 7*	< 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
MV gradient (mean) mmHg	N/A	1.3 ± 0.5	1.5 ± 0.6	0.30

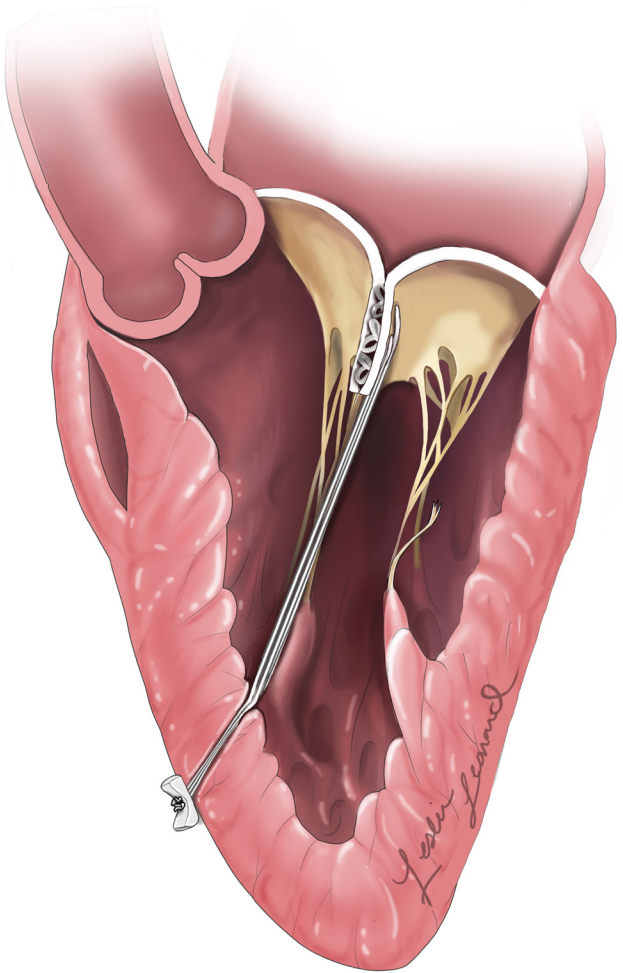
[#] P value <0.001 vs baseline; [*] p value <0.05 compared to baseline

LVEDD=left ventricular end-diastolic dimension, LVESD=left ventricular end-systolic dimension, LA=left atrial, LV EDV=left ventricular end-diastolic volume, LV ESV=left ventricular end-systolic volume, MV=mitral valve









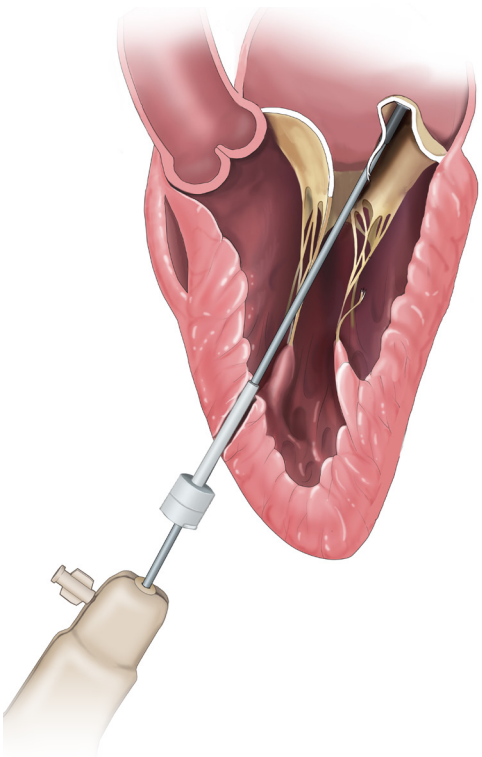


FIGURE 2A

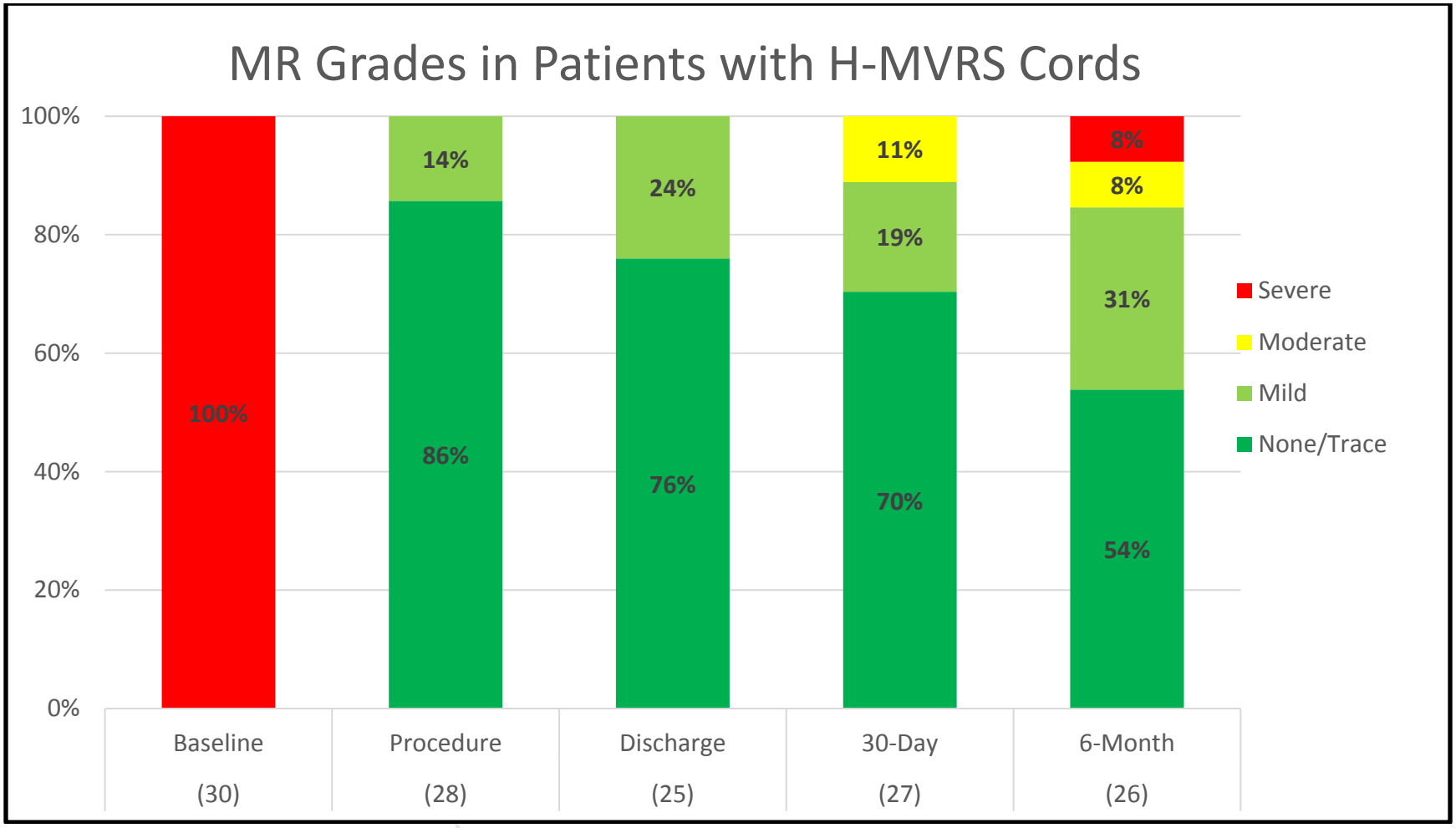
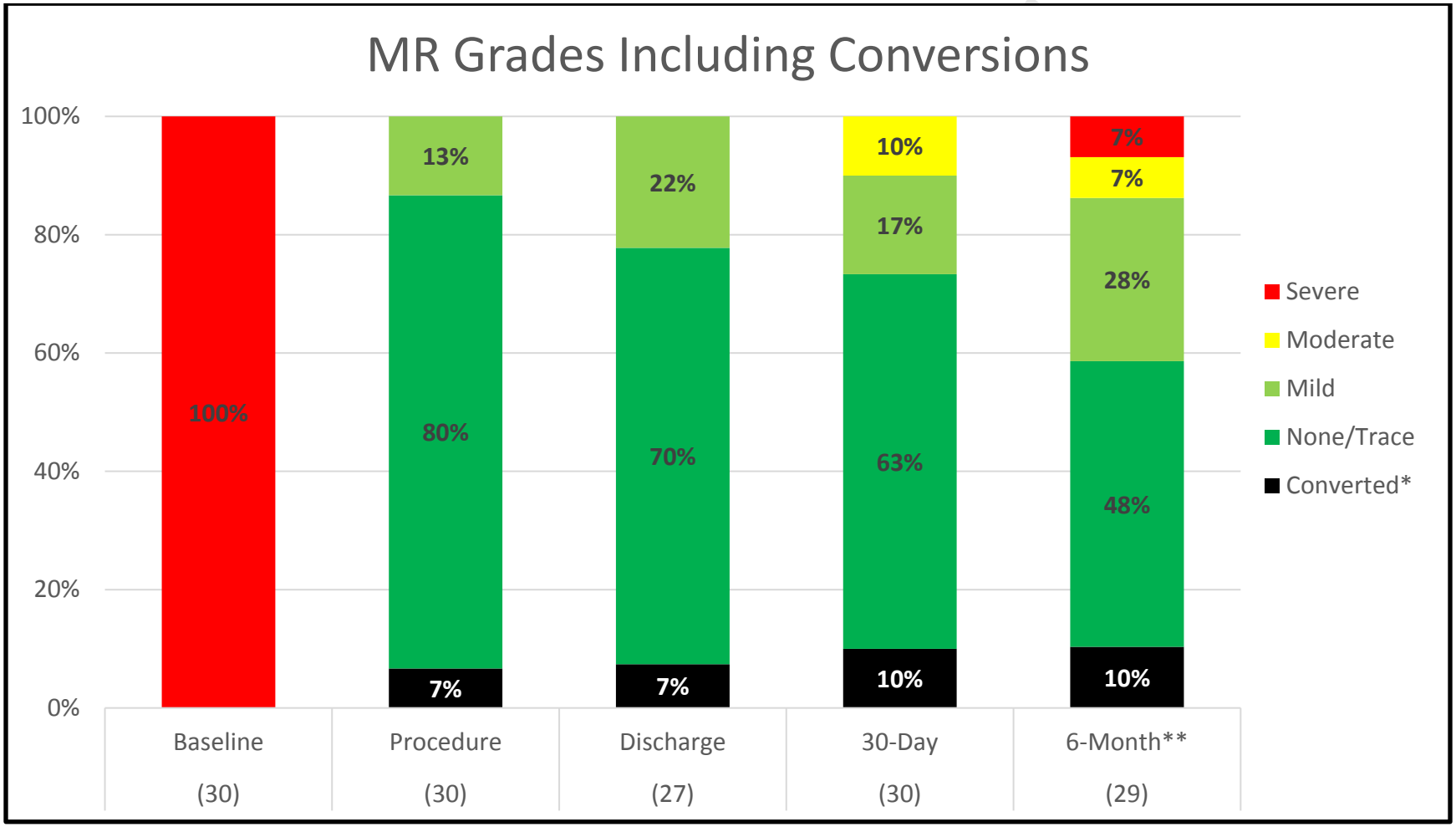

MR Grades in Patients with H-MVRS Cords
100%
80%
60%
40%
20%
0%
100%
14%
86%
24%
76%
11%
19%
70%
8%
8%
31%
54%
Severe
Moderate
Mild
None/Trace
Baseline
(30)
Procedure
(28)
Discharge
(25)
30-Day
(27)
6-Month
(26)

FIGURE 2B



* Two patients converted to successful on-pump mitral valve repair operations during the procedure and one patient required a conventional mitral valve replacement operation on POD 27. All three patients exited the study in NYHA Class I with none/trace MR 30 days after the on-pump operation in accordance with the protocol design.

** One H-MVRS patient had incomplete echo follow-up at 6-months. The three patients who were converted to conventional mitral valve operations were not evaluated at 6-months per protocol but their status was carried forward.

FIGURE 2A

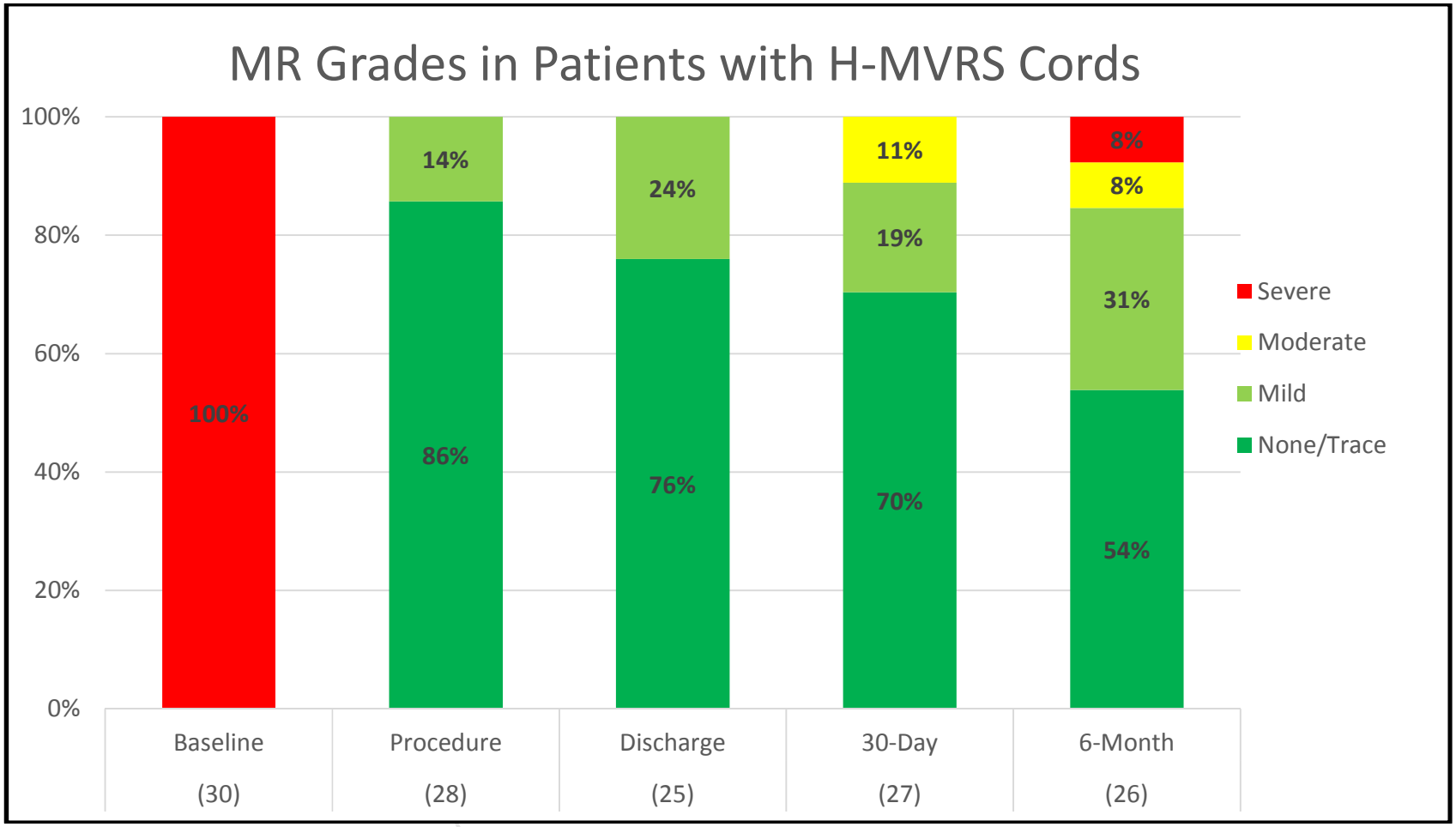
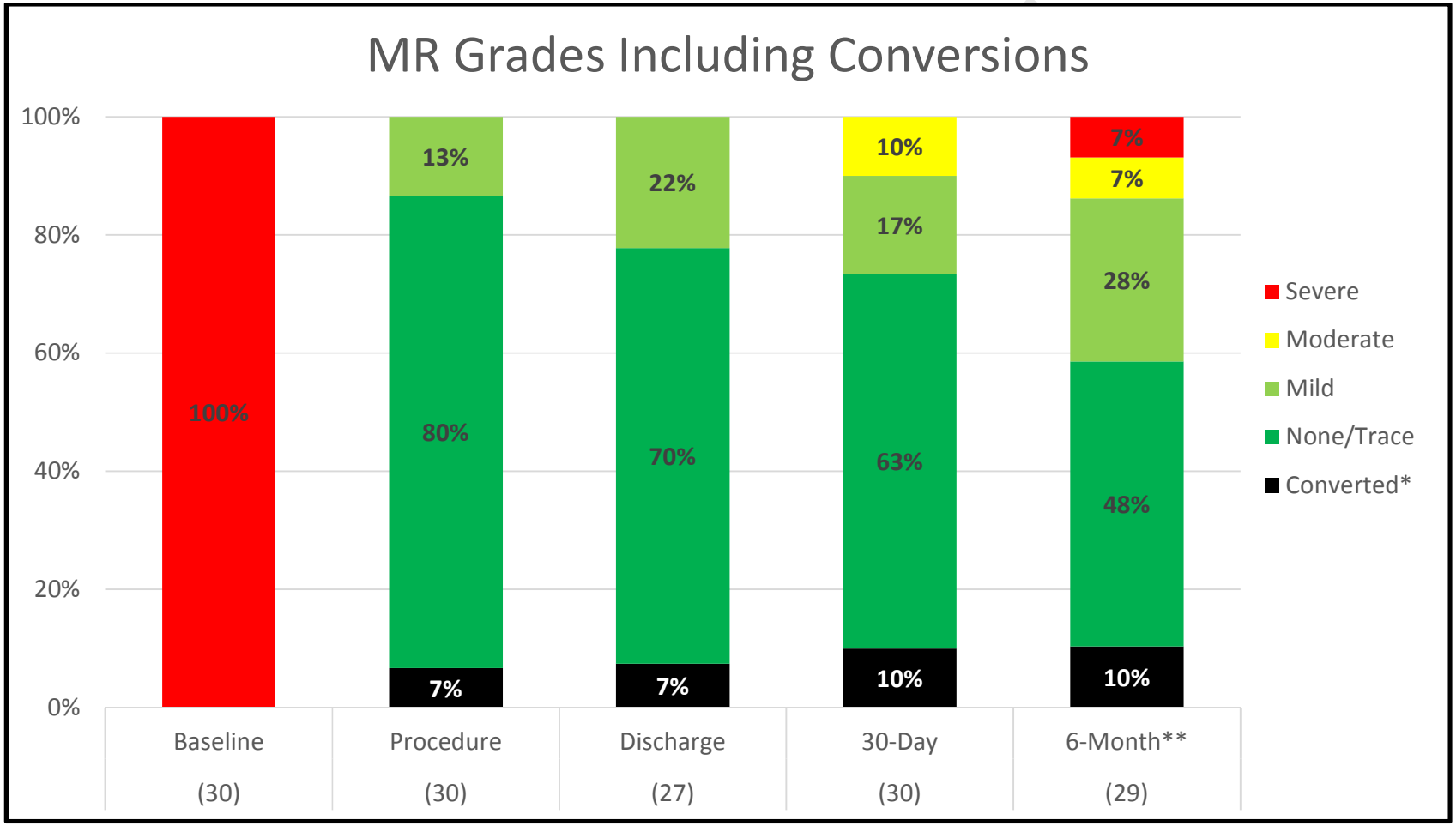


FIGURE 2B



* Two patients converted to successful on-pump mitral valve repair operations during the procedure and one patient required a conventional mitral valve replacement operation on POD 27. All three patients exited the study in NYHA Class I with none/trace MR 30 days after the on-pump operation in accordance with the protocol design.

** One H-MVRS patient had incomplete echo follow-up at 6-months. The three patients who were converted to conventional mitral valve operations were not evaluated at 6-months per protocol but their status was carried forward.

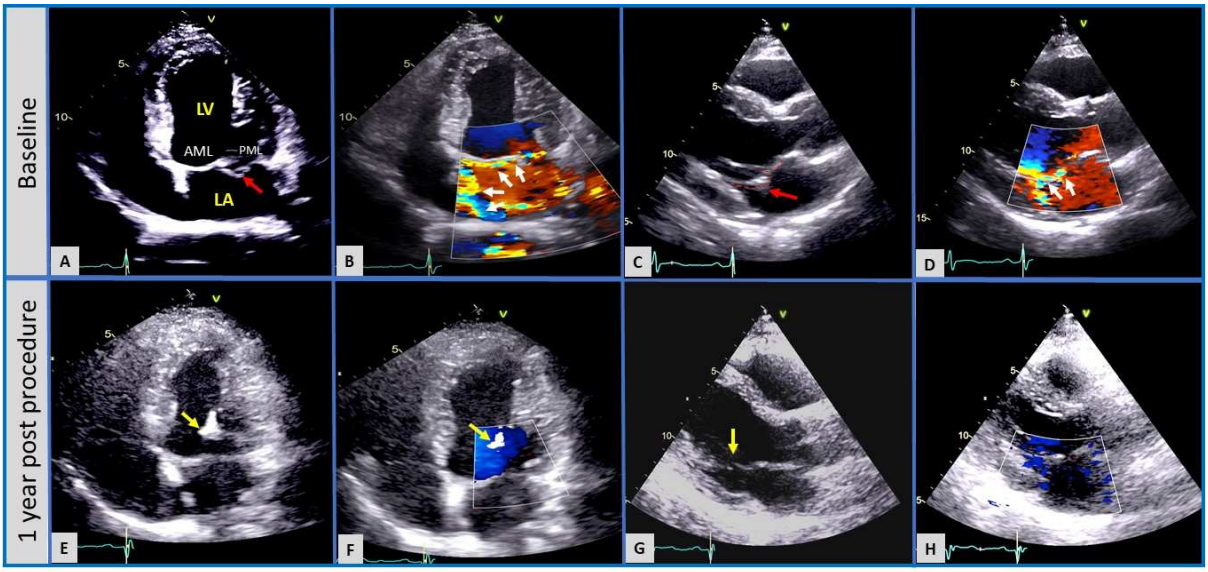


Figure 4: Insertion of Harpoon artificial ePTFE cords from an anterior aspect of the ventricle impart both apical as well as anterior forces on the posterior leaflet and annulus.