Transapical Beating-Heart Mitral Valve Repair With an Expanded Polytetrafluoroethylene Cordal Implantation Device
Initial Clinical Experience

BACKGROUND: Degenerative mitral valve (MV) disease is a common cause of severe mitral regurgitation (MR) and accounts for the majority of MV operations. Conventional MV surgery requires cardiopulmonary bypass, aortic cross-clamping, cardioplegia, and a thoracotomy or sternotomy and, therefore, is associated with significant disability, risks, and unpredictable rates of MV repair. Transesophageal echocardiography–guided beating-heart MV repair with expanded polytetrafluoroethylene cordal insertion has the potential to significantly reduce surgical morbidity. We report the first-in-human clinical experience with a novel preformed expanded polytetrafluoroethylene knot implantation device (Harpoon TSD-5) designed to treat degenerative MR.

METHODS: Through a small left thoracotomy, the device was inserted into the heart and guided by transesophageal echocardiography to the ventricular surface of the prolapsed leaflet. Multiple expanded polytetrafluoroethylene cords were anchored in the leaflet and then adjusted to the correct length to restore MV leaflet coaptation and secured at the epicardium.

RESULTS: Eleven patients with posterior leaflet prolapse and severe MR, with mean±SD age of 65±13 years and mean ejection fraction of 69±7%, were treated with 100% procedural success. Immediate postprocedural mean MR grade was trace. At 1 month, the mean MR grade was mild with significant decreases in end-diastolic volume (139 to 107 mL; \( P = 0.03 \)) and left atrial volume (118 to 85 mL; \( P = 0.04 \)).

CONCLUSIONS: A novel device used for beating-heart image-guided MV repair demonstrates a significant reduction in MR with favorable left ventricular and left atrial reverse remodeling. This approach has the potential to decrease invasiveness and surgical morbidity. Further follow-up is necessary to assess long-term efficacy.

Clinical Perspective

What Is New?

- This report describes an initial clinical experience with a new device designed to implant expanded polytetrafluoroethylene artificial cords on the prolapsed mitral valve and to correct degenerative mitral regurgitation in the beating heart with the use of transesophageal echocardiographic image guidance.
- The main findings of this study were that in an initial 11-patient clinical experience, surgeons used the device to successfully implant multiple expanded polytetrafluoroethylene artificial cords and to effectively reduce mitral regurgitation in all patients.
- The results were stable at 30 days, and the procedure was safe, with no acute conversions to open heart surgery, blood transfusions, stroke, or death.

What Are the Clinical Implications?

- This study suggests that the Harpoon TSD-5 has the potential to facilitate less invasive beating-heart therapy for degenerative mitral regurgitation.
- This initial experience will require follow-up to ensure durability and effectiveness in larger numbers of patients.

Methods

Study Design and Oversight

We conducted this prospective, observational, early-feasibility trial to test the safety and performance of a novel ePTFE insertion device for mitral valve repair. The trial was conducted at 2 clinical centers (Jagiellonian University John Paul II Hospital, Krakow, and Institute of Cardiology, Warsaw, Poland) and was sponsored by Harpoon Medical Inc. The protocol was approved by the ethics committee at each participating institution and received central Polish Ministry of Health approval. All patients provided written informed consent before enrollment.

The authors had full access to the data and take full responsibility for the completeness and accuracy of the data and the analyses reported in this article.

Study Patients

Patients with severe degenerative MR resulting from isolated posterior leaflet prolapse were enrolled. Patients were selected if the predicted post-ePTFE artificial cord implantation coaptation surface was adequate to result in effective MR reduction in the judgment of the operating surgeon and the clinical trial team. This was a qualitative assessment based on 2- and 3-dimensional transesophageal echocardiography (TEE) that there was sufficient posterior leaflet tissue area in the prolapsed segment to occlude the regurgitant orifice when repositioned apically with the ePTFE cords.

Patients were excluded if they had functional MR, a Society of Thoracic Surgeons predicted risk of mortality (for repair) of >6%, severe pulmonary hypertension (systolic pulmonary artery pressure >60 mm Hg), or severe LV dysfunction (ejection fraction <40%). Full inclusion and exclusion criteria are available at https://clinicaltrials.gov/ct2/show/NCT02432196.

Device Design and Implantation Procedure

The TSD-5 device (Harpoon Medical Inc) is a 3-mm-diameter shafted instrument designed to anchor ePTFE cords on the prolapsed mitral valve leaflet. A small (2–3 cm) anterolateral left thoracotomy is performed in the fourth or fifth intercostal space. The pericardium is opened; heparin is administered to maintain an activated clotting time of >350 seconds; and concentric pledgeted purse-string sutures are placed at the insertion site on the epicardium ≈ 3 to 4 cm basal to the apex of the heart (at the level of the base of the papillary muscles) and just lateral to the left anterior descending coronary artery. A purpose-designed 14F valved introducer is inserted over a guidewire into the ventricle and secured. A TSD-5 is inserted into the introducer and, with TEE guidance (simultaneous orthogonal [x plane] views at midcommissural and long-axis planes), is steered to the ventricular surface of the prolapsed leaflet. The target site on the prolapsed leaflet is stabilized with the device by applying pressure to the ventricular side of the leaflet with the end-effector of the device. Once proper positioning is confirmed in the orthogonal TEE planes, the device is actuated, which results in perforation of the leaflet by a specially designed 21-gauge needle wrapped with 50 coils of ePTFE in a preformed knot configuration (Figure 1). There is no need to grasp or catch the moving leaflet, and sutures are not needed to grip or catch the moving leaflet, and sutures are not...
Figure 1. Mitral valve repair using the expanded polytetrafluoroethylene (ePTFE) preformed knot implantation device (TSD-5).

A small anterolateral thoracotomy is performed in the fourth or fifth intercostal space. The valved introducer is inserted into the ventricle through a purse-string suture in a location that is 3 to 4 cm basal from the apex and lateral to the left anterior descending coronary artery. The TSD-5 is steered to the underside of the prolapsed leaflet at the targeted location, and once leaflet stabilization is achieved, the device is actuated, forming a double-helix knot on the atrial surface. Multiple ePTFE cords are anchored on the leaflet; the introducer is withdrawn; and the cords are titrated to maximize coaptation and to minimize mitral regurgitation. The cords are tied on a Teflon pledget on the epicardium at the insertion site.

limited to the free edge, allowing the operator to anchor ePTFE cords anywhere on the leaflet.

As the needle is automatically withdrawn, a double-helix coiled ePTFE knot is formed on the atrial surface of the leaflet, securing the associated pair of ePTFE artificial cords to the leaflet. The TSD-5 device is withdrawn through the valved introducer, and the ePTFE cords are exteriorized through the introducer. Additional TSD-5 devices are deployed to anchor the desired number of ePTFE cordal pairs to the leaflet (typically 3 or 4 pairs). Once insertions are complete, the valved introducer is withdrawn and the purse-string suture is tied. The ePTFE cords emanating from the ventricle are passed through separate holes in a single Teflon pledget and with a tourniquet are simultaneously titrated to an optimal length (defined as maximal coaptation on echocardiography and absent MR on color Doppler interrogation) with TEE guidance. Each pair is then tied on the single pledget, and the procedure is completed. Movie I in the online-only Data Supplement demonstrates the TSD-5 ePTFE artificial cord implantation procedure. Aspirin (325 mg) is administered after the operation and daily thereafter.

Study End Points

The prespecified primary performance outcome was procedural success, defined as successful implantation of ≥1 ePTFE artificial cords on the mitral valve, and demonstration of MR reduction from severe to moderate or less at the conclusion of the procedure and at 30 days. The primary safety end point was freedom from serious adverse events during the ePTFE implantation procedure, at discharge, and at 30 days after the procedure. We assessed the severity of MR using intraoperative TEE and predismissal, 30-day, and 6-month transthoracic echocardiography. Perioperative mortality was defined as the greater of 30-day mortality or in-hospital mortality. Adverse events were defined according to the Society of Thoracic Surgeons Adult Cardiac Surgery Database definitions. This study represents an interim analysis of an ongoing early-feasibility study. The common date for all analyses was January 1, 2016. The mean length of follow-up was 186 days (range, 64–319 days).

Echocardiographic Analyses

Echocardiographic analyses were performed independently by a core laboratory (Massachusetts General Hospital). LV dimensions, left atrial volumes (biplane area length), and LV volumes were measured (biplane method of disks) per American Society of Echocardiography chamber quantification guidelines. The degree of MR was graded as none, trace, mild, moderate, or severe (corresponding to numerical grading of 0 to 4+,
respectively), with the use of integrative criteria as specified by the American Society of Echocardiography. Septal-lateral mitral annular dimension was measured at end diastole in the apical 4-chamber view.

Statistical Analyses
Baseline characteristics and clinical outcomes were described using counts and percentages for categorical variables and mean±SD, sometimes supported by ranges, for continuous measures. Statistical testing of pre-post echocardiography measurements was done with matched-pair t tests. Statistical significance was based on a significance level of P=0.05. Analyses were performed with JMP 8.0 statistical software (SAS Institute Inc).

RESULTS
Baseline Characteristics
From February 2015 through October 2015, 30 patients were screened and 11 consecutive patients were enrolled in the trial. All implanting surgeons were trained on a bench-top simulator and in an animal laboratory. The mean age of the patients was 65±13 years (range, 42–89 years), and 91% were men. The baseline characteristics of the patients who underwent beating-heart mitral valve repair are shown in Table 1. Most patients were low risk for conventional surgical mitral valve repair, and all but 1 patient had class 1 indications for mitral valve repair.

Procedural Results
There was a 100% procedural success rate. An average of 3.6±0.7 (range, 3–5) pairs of ePTFE artificial cords were implanted, with reduction of MR during the procedure from severe to none/trace in 8 patients and to mild in 3 patients. Total procedure time averaged 108±30 minutes (range, 72–167 minutes), and the total time that the introducer was in the ventricle averaged 38±14 minutes (range, 20–58 minutes). No patient required intraoperative inotropic or vasopressor support. There was no perioperative mortality and no intraoperative conversion to conventional cardiac surgery. There were no perioperative strokes, new-onset renal failure, postoperative AF, or myocardial infarction. No blood transfusions were required during the procedure or hospitalization. At 1 month, all 4 patients with preoperative paroxysmal AF were in sinus rhythm, and 1 patient with preoperative persistent AF remained in AF. The patient was discharged from the hospital in good condition.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±13</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>10 (91)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25±4</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (36)</td>
</tr>
<tr>
<td>II</td>
<td>6 (55)</td>
</tr>
<tr>
<td>III</td>
<td>1 (9)</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
</tr>
<tr>
<td>STS PROM, %</td>
<td>1.3±1.3</td>
</tr>
<tr>
<td>AF, n (%)</td>
<td>5 (45)*</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>0</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL·min⁻¹·m⁻²</td>
<td>70±19</td>
</tr>
<tr>
<td>Cardiac structure/function</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, mean, %</td>
<td>69±7</td>
</tr>
<tr>
<td>LA diameter, cm</td>
<td>4.6±0.7</td>
</tr>
<tr>
<td>LV end-diastolic diameter, cm</td>
<td>5.4±0.3</td>
</tr>
<tr>
<td>LV end-systolic diameter, cm</td>
<td>3.2±0.4</td>
</tr>
<tr>
<td>sPAP, mm Hg</td>
<td>47±15</td>
</tr>
</tbody>
</table>

Values are mean±SD when appropriate. AF indicates atrial fibrillation; BMI, body mass index; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure; and STS PROM, Society of Thoracic Surgeons predicted risk of mortality.

*Four paroxysmal and 1 persistent.

Reoperation
One patient required conventional cardiac surgical operation on postoperative day 72 for recurrent symptomatic severe MR. Moderate MR was recognized on the predismissal echocardiogram. Recurrent severe MR was identified 60 days postoperatively and was associated with recurrence of dyspnea. At reoperation, all 3 ePTFE knots were intact and located on the atrial surface of the P2 segment of the posterior leaflet with evidence of early endothelialization (Figure 2). There was no evidence of leaflet damage. One of the 3 pairs of ePTFE artificial cords was found to have become untied from the epicardial apical pledget, and this end of the suture pair was free within the ventricle but remained anchored at the knot to the leaflet.

In addition, 1 native edge cord to A2 was ruptured. A quadrangular resection incorporating the P2 segment of the posterior leaflet and all 3 ePTFE knots was performed with insertion of a size 34 complete semirigid annuloplasty ring. An ePTFE cord was placed to A2. The patient was discharged home in good condition with no MR.
MR Reduction
The severity of MR at the conclusion of the procedure, before dismissal, and at 30 days is reported in Table 2. Clinical and echocardiographic follow-up was 100% complete. There was no evidence of mitral stenosis at 1 month after the procedure, with peak and mean transmural gradients of 3.2 and 1.5 mmHg, respectively. Four patients had 6-month follow-up echocardiography. All are in New York Heart Association class I. In all cases, the ePTFE artificial cords and knots are in stable positions. Three patients have none/trace MR, and 1 patient has moderate MR.

Echocardiographic Results
Preoperative and 30-day echocardiographic measurements are reported in Table 3.

There was evidence of early ventricular remodeling, with a decrease in the end-diastolic dimension of 11% (54±3 to 48±5 mm), end-diastolic volumes of 18% (142±41 to 116±36 mL), and the septal-lateral dimension from 40.0 to 37.9 mm. There were no important differences in ejection fraction and no wall motion abnormalities after the procedure. There was favorable early remodeling of the left atrium with a decrease in anterior-posterior left atrial dimension and volumes. Figure 3 demonstrates representative preprocedural and postprocedural TEE images, and Figure 4 is a representative 6-month transthoracic follow-up study.

DISCUSSION
In this study, we describe the initial evaluation of the Harpoon ePTFE artificial cord implantation device in a first-in-human series of 11 consecutive patients with severe degenerative MR. The device was used to implant artificial ePTFE cords in the posterior leaflet of the beating heart with TEE image guidance. Procedural success occurred in all patients, with the insertion of between 3 and 5 pairs of ePTFE artificial cords resulting in a reduction in MR from severe to moderate or less in all patients at 30 days. MR reduction was stable in 3 of 4 patients followed up to 6 months.

Expanded ePTFE sutures were first described for use in surgical mitral valve repair by Zussa et al and introduced clinically by David. In a large series of 606 consecutive patients with degenerative MR repaired with ePTFE artificial cords with a mean clinical follow-up of 10.1 years, the freedom from recurrent severe MR at 18 years was 91% and the freedom from reoperation on the mitral valve was 90%. One randomized trial compared results of conventional resection techniques with ePTFE cordal replacement techniques and found equivalent early results, with evidence of greater coaptation surface in the ePTFE group. Recent studies have suggested that LV performance is superior in patients with degenerative MR repaired with ePTFE artificial cordal techniques compared with resection methods. In North America, there is increasing use of ePTFE in mitral valve repair: Between 2011 and 2014, among 20,523 patients undergoing mitral valve repair for degenerative disease, ePTFE cordal replacement was used in 31% (6370).

We reasoned that a shafted instrument with a narrow diameter that could reliably anchor ePTFE artificial cords to a prolapsed mitral valve leaflet with the use of transapical access and TEE guidance would enable reliable and durable mitral valve repair through a small nonsternotomy incision on the beating heart. We found that the Harpoon TSD-5 device performed as designed and enabled the operator to anchor ePTFE artificial cords in precise targeted locations on the prolapsed segment of the mitral valve. The procedure was efficient, with an average procedural time of 108±30 minutes and an introducer dwell time of 38±14 minutes, and was characterized by complete hemodynamic stability. Transapical mitral valve repair with a device designed to grasp the free edge of the prolapsed mitral valve leaflet and secure an ePTFE cord (NeoChord, Inc, Minneapolis, MN) has previously been reported, with intermediate-term results from patients treated after an initial learning curve suggesting a strong safety profile and an effective reduction in MR. Compared with the NeoChord device, the Harpoon device is characterized by a smaller-diameter shaft (3 versus 8 mm), a valved introducer to minimize intraprocedural bleeding, the ability to insert the ePTFE cords anywhere on the leaflet rather than within 4 mm of the free edge, and a fundamentally different anchoring mechanism.

One challenge of conventional mitral valve repair surgery with ePTFE artificial cords is correct determination of the optimal length of the ePTFE cords on the
open and arrested heart. Beating-heart image-guided transapical mitral valve repair with the Harpoon TSD-5 device enabled the surgeon to precisely titrate the length of the ePTFE artificial cords in real time on the beating, working heart. In all cases, the operator was able to tighten or loosen the ePTFE cords to maximize leaflet coaptation and to minimize MR. The only intracardiac implant in this procedure is the ePTFE suture and knot, analogous to conventional ePTFE-based surgical repair, which has a long clinical record of safety and effectiveness. Preclinical testing with fresh human autopsy hearts has demonstrated that the Harpoon preformed knot has anchoring forces equivalent to conventionally sutured ePTFE.

One patient in this initial clinical experience required reoperation for recurrent MR. The cause of recurrence was multifactorial and included unfastening and detachment of 1 pair of ePTFE cords from the pledget on the epicardium; an unrecognized and untreated anterior leaflet, which prolapsed 1 to 2 mm above the plane of the mitral annulus; and progression of disease with rupture of a native anterior leaflet edge cord. Improved surgical training, better methods of securing the ePTFE cords to the epicardial pledget, deployment of ePTFE cords on the anterior leaflet, and increased experience with patient selection based on analysis of reconstructed 3-dimensional TEE data sets should all contribute to minimizing the likelihood of this type of failure in future patients.

It is unlikely that ePTFE knots placed on the mitral leaflet with the Harpoon ePTFE cordal implantation device will compromise subsequent surgical mitral valve repair. We found that to be the case in this patient, in whom at reoperation the ePTFE knots did not appreciably change the structure of the mitral valve leaflet at 2 months after implantation and a resectional repair was successful. Although in this case the surgeon chose to perform a resectional repair, a nonresectional repair would have been equally feasible. This is in contrast to experience with the MitraClip device, in which a fibrous reaction to the clip commonly precludes subsequent successful surgical repair in most patients.13

MR reduction was excellent in all cases, with 30-day MR grading of mild or less in all but 2 patients, 1 patient who required reoperation and another with evidence of modest reprolapse of the posterior leaflet. In the patient who developed moderate MR by the 6-month follow-up (the second patient ever treated with the device), we identified progressive prolapse of a lateral segment of P2 that was not targeted for ePTFE resuspension during

### Table 2. MR Grade

<table>
<thead>
<tr>
<th>Patient</th>
<th>Preoperatively</th>
<th>Procedural</th>
<th>Before Dismissal</th>
<th>At 30 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe</td>
<td>None/trace</td>
<td>None/trace</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Severe</td>
<td>None/trace</td>
<td>None/trace</td>
<td>None/trace</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>None/trace</td>
<td>None/trace</td>
<td>None/trace</td>
</tr>
<tr>
<td>4*</td>
<td>Severe</td>
<td>Mild</td>
<td>Moderate*</td>
<td>Moderate*</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
<td>None/trace</td>
<td>None/trace</td>
<td>None/trace</td>
</tr>
<tr>
<td>6</td>
<td>Severe</td>
<td>Mild</td>
<td>None/trace</td>
<td>Moderate</td>
</tr>
<tr>
<td>7</td>
<td>Severe</td>
<td>None/trace</td>
<td>None/trace</td>
<td>Mild</td>
</tr>
<tr>
<td>8</td>
<td>Severe</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>9</td>
<td>Severe</td>
<td>None/trace</td>
<td>None/trace</td>
<td>Mild</td>
</tr>
<tr>
<td>10</td>
<td>Severe</td>
<td>None/trace</td>
<td>None/trace</td>
<td>Mild</td>
</tr>
<tr>
<td>11</td>
<td>Severe</td>
<td>None/trace</td>
<td>None/trace</td>
<td>None/trace</td>
</tr>
</tbody>
</table>

MR indicates mitral regurgitation.

*Patient 4 required reoperation at postoperative day 72.
the initial procedure. Now that we have gained experience, in retrospect, we would have specifically targeted this segment for ePTFE cord implantation. In the remaining 3 patients with 6 month follow-up, the posterior leaflet position was stable with a generous surface of coaptation. As expected after successful surgical mitral valve repair, the MR reduction was associated with favorable LV, mitral annular, and left atrial remodeling, with decreases in LV dimensions and volumes, septal-lateral mitral annulus dimension, and left atrial volumes.

This initial clinical experience supports the conclusion that surgical-grade MR reduction is possible with the device and that the repair is durable at the 1-month follow-up. We do not believe that annular dilation per se mandates annular downsizing with an annuloplasty ring but rather that the key predictor of successful mitral valve repair is the ratio of total leaflet tissue to mitral orifice area, which if adequate allows sufficient coaptation. The ePTFE artificial cords placed in this experience are not implanted on the tip of the papillary muscles as in conventional mitral valve surgery but rather are inserted through the myocardium on the anterior surface of the LV in proximity to the left anterior descending coronary artery. The resulting force vectors on the leaflet therefore include both apical and anterior forces, the latter of which serves to decrease and sta-
bilibize the septal-lateral (anterior-posterior) dimension of the mitral annulus. Reduction of MR with the Harpoon TSD-5 resulted in modest but significant early reductions in septal-lateral dimensions as a component of postprocedural LV remodeling.

Mitral valve repair is clearly superior to replacement for degenerative disease, with an operative risk of approximately half compared with replacement, improved LV function, and superior freedom from reoperation, structural valvular deterioration, thromboembolism, anticoagulation-related complications, and infective endocarditis. Current American College of Cardiology/American Heart Association guidelines indicate mitral valve repair in preference to replacement for degenerative disease (Class I recommendation) and prohibit (Class III: harm) mitral replacement for severe primary MR limited to less than one half of the posterior leaflet. Despite clear evidence of the short- and long-term benefits of mitral valve repair for degenerative MR, at present, mitral valve repair rates are between 60% and 85% in North America, and there is substantial variability based on center and surgeon experience, reflecting the complexity of mitral valve repair for degenerative disease. As a result of real-time echocardiographic titration of ePTFE cordal lengths on the loaded working heart, image-guided beating-heart mitral valve repair for degenerative disease with the Harpoon TSD-5 has the potential to increase mitral valve repair rates.

As expected, transapical beating-heart mitral valve repair had an excellent safety profile, with no perioperative mortality and little morbidity. We believe that compared with conventional mitral valve surgery, beating-heart mitral valve repair will be associated with a shorter hospital length of stay, substantially less resource use, and faster return to preoperative functional status.

The Harpoon TSD-5 device is suitable for both low-risk degenerative MR patients (those currently referred for surgical therapy) and high- and extreme-risk patients who currently are not candidates for conventional surgery. We anticipate continued procedural refinement and, as these learnings are implemented, continued improvement in clinical results.

This trial did not have a control arm of patients undergoing conventional mitral valve repair surgery; thus, we cannot make definitive statements comparing this approach with conventional mitral valve operation. This report represents an interim analysis of an ongoing study. This initial series was limited to patients with posterior mitral leaflet prolapse only. However, as additional experience is achieved, we plan on broadening this approach to bileaflet prolapse and complex mitral degenerative pathology.

**CONCLUSIONS**

In this first-in-human experience, the Harpoon TSD-5 enabled less invasive beating-heart image-guided transapical mitral valve repair with 100% procedural success and safe and reliable reduction in MR. This initial experience will require follow-up to ensure durability and effectiveness in larger numbers of patients.

**ACKNOWLEDGMENTS**

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

**DISCLOSURES**

Drs Gammie, D’Ambra, and Bartus and Mr. Wilson have stock in and/or options to purchase stock in Harpoon Medical, Inc. Dr Ghoreishi is a coinventor of the technology, which has been licensed from the University of Maryland by Harpoon Medical Inc. The other authors report no conflicts.
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FOOTNOTES
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Welcome to Circulation on the Run, your weekly podcast summary and backstage pass to the journal and its editors. I'm Dr. Carolyn Lam, Associate Editor from the National Heart Center and Duke National University of Singapore. Joining me in just a moment are Dr. James Gammie and Dr. Timothy Gardner to discuss our feature paper this week describing the first-in-human clinical experience with a novel transapical beating heart mitral valve repair.

First, here are the highlights of this week's journal. The first paper is from co-primary authors doctors Yoon, [Tsue 00:00:49], and [Cha 00:00:50] as well as corresponding authors Dr. [Che 00:00:55] and Dr. Kim from the Seoul National University College of Medicine. These authors examine mechanisms underlying diabetes-induced microvasculopathy, testing the hypothesis that Notch signaling in endothelial cells may play an important role in this condition.

The authors tested this hypothesis by inducing diabetes in eight-week-old adult mice using intravenous streptozotocin. They then modulated endothelial Notch signaling using chemical inhibitors in both wild type and transgenic mice. Results showed that the Notch ligand called Jagged-1 was markedly increased in endothelial cells of diabetic mice. Using endothelial specific Jagged-1 knocked down mice, they found that blocking Jagged-1 prevented diabetic microvasculopathy. Furthermore, using the inducible endothelium-specific Jagged-1 knocked down mice, blocking Jagged-1 even at four weeks after the establishment of diabetic microvasculopathy could reverse the condition.

In summary, these findings show that diabetes induces Jagged-1 over expression and suppresses Notch signalling in endothelial cells leading to diabetic microvasculopathy in adult mice. The clinical implications are that dysregulated intercellular Notch signalling may therefore represent a novel molecular target in the treatment of diabetic retinopathy.

The next study by Dr. Smith and colleagues at the Leiden University Medical Center in the Netherlands evaluated the association between LDL cholesterol variability and four cognitive domains at 30 months in the 4428 participants of the prosper study.

Results showed that a higher LDL cholesterol variability was associated with lower cognitive test performance for intermediate and delayed memory-related tasks, selective attention, and processing speed. Higher LDL cholesterol variability was also associated with lower cerebral blood flow and greater white matter hyperintensity load in an MRI substudy of 535 patients.

In addition to being independent of the mean LDL cholesterol levels and of clinically overt cardiovascular diseases, these associations were present both in the placebo and pravastatin treatment [inaudible 00:03:43] of the prosper trial suggesting that the findings did not mearly reflect pleiotropic effects of statins or of nonadherence.

The study importantly provides the first observational evidence that lipid variability, not just absolute or mean values, but the variability, maybe of importance to neurocognitive
function and thus contributes while understanding potential pathways of neurocognitive decline.

The next study is by first author, Dr. [Huh 00:04:19], and corresponding author, Dr. Ralph, from the Menzies School of Health Research Charles Darwin University in Australia. These authors aimed to investigate the long term outcomes from acute rheumatic fever and rheumatic heart disease.

They achieved this aim by using linked data between the rheumatic heart disease register, hospital data, and death register for residents of the northern territory of Australia, and examined 1248 patients with rheumatic heart disease as well as 572 patients with acute rheumatic fever in the period 1997 to 2013.

The main findings were that in the first year after an acute rheumatic fever episode, the incidents of progression to rheumatic heart disease was 10 times higher than acute rheumatic fever recurrence; 10% of rheumatic heart disease patients had severe disease at diagnosis. The presence of comorbidities was associated with higher incidence of rheumatic heart disease complications and mortality. In particular, comorbid renal failure and hazardous alcohol use accounted for 28% of the access indigenous mortality.

These findings have global relevance for settings with high acute rheumatic fever, rheumatic heart disease rates and really emphasized the need for integrated chronic disease management strategies for these patients.

The final paper is by first author Dr Bettencourt, corresponding author Dr. Blankstein, and colleagues from Brigman and Women's Hospital in Boston, Massachusetts. These authors sought to answer the question what is the most appropriate score for evaluating the pretest probability of obstructive coronary artery disease?

To answer the question, the authors compared the Diamond-Forrester score with the two CAD consortium scores recently recommended by the European Society of Cardiology, and they did this in 2274 consecutive patients without prior CAD referred for coronary CT angiography. CT angiography findings were used to determine the presence or absence of obstructive CAD defined as 50% or more stenosis.

Here's a refresher of the different probability scores. The Diamond-Forrester score is calculated based on chest pain type such as non-anginal, atypical or typical angina, gender, and age. The first CAD consortium model score called CAD consortium basic is also based on these factors, but was developed using more advanced statistical modeling strategies which were not available when the Diamond-Forrester model was derived. Additionally, the population had a lower prevalence of disease than the original Diamond-Forrester derivation cohort.

The second CAD consortium score called CAD consortium clinical included the same characteristics as CAD basic, but also included the following clinical risk factors; diabetes, smoking status, hypertension, and dyslipidemia. Moreover, the presence of typical chest pain was weighted less in diabetics compared to nondiabetics in the CAD
clinical score. Results showed that among symptomatic individuals referred for coronary CT angiography, the CAD consortium clinical pretest probability score demonstrated improved calibration and discrimination for the prediction of obstructive CAD compared to the Diamond-Forrester classification.

Driving home the clinical implications of this, the authors applied these observed differences in pretest probability of obstructive CAD to guidelines-based patient management algorithms and projected that the use of the newest score could decrease the proportion of individuals in whom testing would be recommended and increase the yield of diagnosing obstructive CAD.

Those were the highlights of these weeks issue. Now, for our feature paper. Our feature paper today is about the first-in-human clinical experience with the transapical beating heart mitral valve repair using a expanded polytetrafluoroethylene chordal insertion device. We're really lucky today to have the first and corresponding author, Dr. James Gammie from the University of Maryland Medical Center as well as Dr. Timothy Gardner, associate editor from Christiana Care Health System to discuss this exciting paper. Welcome, both of you.

Tim: Thank you.

James: Thank you.

Speaker 1: James, may I start with you? What an exciting title, a first-in-human experience, and this is really sounding very reminiscent of our experience with TAVR and aortic stenosis valves. Could I ask you, with so many exciting things, what is it about the results that excited you most?

James: This is an exciting project in that we believe it affords a new treatment option for patients with degenerative mitral regurgitation. We believe that this is a less invasive way of achieving surgical grade reduction of mitral regurgitation. This is a project which has involved a great number of people on our team both within the university and then within Harpoon Medical, as well as our colleagues in Europe to bring this device from an idea which was asked more than a decade ago into a clinical experience.

It really rose out of our recognition in particularly my own practice that virtually, every patient with degenerative mitral regurgitation could be fixed with ePTFE or Gore-Tex neo-chords, and the question became how can we place neo chords on a prolapsed mitral leaflets without doing open heart surgery?

We begin working on that in the laboratory a number of years ago and went through a variety of prototypes, and ultimately, came up with this idea where we could use a 3 millimeter shafted instrument with a specially designed wrap of Gore-Tex on a 21-gauge needle such that we could land on the underside of the mitral leaflet, deploy device, and create a specially designed knot on the atrial surface of the leaflet, and that would anchor the ePTFE on the leaflet. We could repeat that a few times transapically and then adjust the length of those chords in real time using transesophageal echo.
guidance.

We got this to work in the laboratory and we had hoped that we would have some modest success in humans, but we've been quite pleasantly surprised that it has just worked and we've outlines this initial clinical experience in the manuscript.

Speaker 1: First of all, I'd just like to pick up on the point that this is degenerative mitral regurgitation, so this is limited to the primary mitral regurgitation, not secondary?

James: That's correct and we know that right now, at least in North America, that two-thirds of mitral valve operations are done for degenerative disease. That's correct.

Speaker 1: I think a lot of the audience out there is going to be wondering how this new technique compares to the MitraClip. Could you tell us a little bit more about that?

James: I do MitraClip as well, so I think I'm well positioned to comment on the differences. The Harpoon device right now is still in operation. It does require a small one or two-inch incision. We anticipate it's going to be a thoracoscopic approach in the very near future and then, beyond that, we would hope to extend it to a transcatheter approach. That's one difference.

The MitraClip now is certainly across the world. It's used predominantly for functional mitral regurgitation. In our own experience, it seems to work best for functional mitral regurgitation and as you know, there are anatomic limitations for MitraClip in degenerative disease. The MiraClip replicates the LCRA surgical approach and I think what we've learned from all the less invasive approaches to treat mitral valve disease is that we have to respect what we've learned from our surgical experience, and we know that the LCRA approach works best when it's combined with an annuloplasty ring, and certainly, the MitraClip, again, is mostly this perfunctional MR.

Another point I'd bring up is that the experience with MitraClip has been that when you place a MitraClip, you get a fairly strong fibrous reaction and in most of the series, it's not been possible to then go back and surgical repair the valve, but you have to do a replacement because you've compromised the leaflets. Our own approach were simply putting Gore-Tex sutures in the leaflets and we believe that one advantage is that we're not burning any bridges, and that you can go back and do an open repair of you had to.

In our experience, you asked about our results, we had great results in 10 out of 11 of our patients. One patient did require a reoperation. Actually, one of the chords had come untied on the surface in that patient. We were able to go ahead and do a repair and we saw as we had anticipated it based on our animal experience, there was not much compromised to the leaflets.

One of the advantages of our approach is that we can titrate the length to the Gore-Tex chords to optimize the amount of coaptation and maximize the quality of the repair, and that's something that we can't do an open cardiac surgery, and one of the challenges of mitral valve repair is that you have to figure out how long to make those chords while
the heart is arrested and placid, and that's one of the challenges in why mitral valve repair is certainly some degree of an art to doing that.

What we've found is that the imager is incredibly important, and so we've teamed up with our echocardiography colleagues, and they really provide essential input into the procedure, and it's done not looking directly at the valve, but looking up at the screens. I think as surgeons, with this procedure, we're moving more into almost becoming interventionalists.

Speaker 1: Thank you, James. That was so exciting. Tim, I have to bring you into this now. Now that James has said they're becoming like the interventionalist. Back to my original comment of TAVR and aortic stenosis, are we witnessing history in the making now? You invited an editorial by Dr. Michael Mack and his title was very provocative, Transcatheter Treatment of Mitral Valve Disease. Is it deja vu all over again? What are your thoughts?

Tim: I think this is an exciting report and I think that this is the wave of the future. I agree completely with Michael Mack that we are beginning to see interventions for mitral valve disease that are effective, less invasive, in some instances catheter based, but this is just the beginning. In fact, mitral valve disease is somewhat more complex even than aortic stenosis, but this type of experience and the ingenuity and the technical prowess, and the ability to do this minimally, invasively, and so on really portend a whole new era.

I agree with Jim. This is sort of the common ground between the interventional structural cardiologist and the surgeon, and we're becoming even more entwined, more collaborative, and more mutually supportive. We are in a new era and I think over those next decade or so, we're going to see this and similar, and even different procedures tried and proven to be useful for the variety of mitral valve disorders that we encounter. Perhaps the era of the full sternotomy for fairly straightforward, single, focused operations will become something of a thing of the past.

Speaker 1: That's beautifully put. James, with that comment, what are the next steps?

James: As we said in the manuscript, this isn't barely experience and we're continuing to learn as we move [inaudible 00:17:07] to the clinical arena. We are currently in the midst of a CE Mark trial in Europe. We rolled it out to eight separate centers. As we approve clinical experience, we will learn more about precisely which patients work best with this approach and we will accrue longer term data. We now have a number of patient out to a year with stable results and so, as the numbers go up, we'll do that, and then we anticipate a randomized trial in the United States in the early to mid portion of 2017 where we'll compare this approach to conventional open cardiac surgery.

Speaker 1: That's fantastic. Thank you so much to both of you, gentlemen, for joining me on our podcast today.

Tim: Thank you.
James: Thank you.

Speaker 1: You've been listening to Circulation on the Run. Thank you for joining us this week and don't forget to tune in next week.

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