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Early Experience with New Transcatheter Mitral Valve Replacement

Short title: Pilot Study of New Mitral Valve Replacement Valve

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ABSTRACT

Background. Transcatheter mitral valve replacement (TMVR) is a potential therapy for patients with symptomatic, severe mitral regurgitation (MR). The feasibility of this therapy remains to be defined.

Objective. We report our early experience with TMVR using a new valve system.

Methods. The valve is a self-expanding, nitinol valve with bovine pericardial leaflets that is placed using a transapical delivery system. Patients with symptomatic MR who were deemed high or extreme risk by the local heart teams were enrolled in a global pilot study at 14 sites (U.S., Australia, and Europe).

Results. 50 consecutively enrolled patients (mean age, 73±9 years; 58.0% men; 84% secondary MR) underwent TMVR with the valve. The mean STS score was 6.4±5.5%; 86% of patient were NYHA class III or IV, and the mean left ventricular ejection fraction was 43±12%. Device implant was successful in 48 patients with a median deployment time of 14 (IQR, 12, 17) minutes. The 30-day mortality was 14%, with no disabling strokes, or repeat interventions. Median follow-up was 173 (IQR, 54, 342) days. At latest follow-up, echocardiography confirmed mild or no residual MR in all implanted patients. Improvements in symptom class (79% in NYHA I or II at follow-up; $p<0.0001$ vs. baseline), and Minnesota heart failure questionnaire scores (56.2±26.8 vs. 31.7±22.1; $p=0.011$) were observed.

Conclusions. TMVR with the valve was feasible in a population at high-or extreme-risk for conventional mitral valve replacement. These results inform trial design of TMVR in lower-risk patients with severe mitral valve regurgitation.

Condensed Abstract:

Transcatheter mitral valve replacement (TMVR) is a potential therapy for mitral regurgitation (MR). We examined our early experience with TMVR using the new valve system in 50 patients (age, 73±9 years; 58.0% men). Implantation was successful in 48/49 patients (98%), with a 30-day mortality of 14%, no disabling strokes, or repeat interventions. In follow-up (median 173 days), echocardiography confirmed mild or no residual MR in all implanted patients, and there were significant improvements in symptoms (79% in NYHA I/II) and heart failure scores. TMVR with the valve was feasible in a population at high or extreme surgical risk.

Clinical Trial: NCT02322840

Keywords: Mitral valve regurgitation, prosthesis, transcatheter mitral valve replacement

ABBREVIATIONS AND ACRONYMS

CT = computed tomography
MLHFQ = Minnesota living with heart failure questionnaire
MR = mitral regurgitation
NYHA = New York Heart Association
STS-PROM = Society for Thoracic Surgery Predicted Risk of Mortality
TEE = transesophageal echocardiogram
TMVR = transcatheter mitral valve replacement
TTE = transthoracic echocardiogram

Introduction

Mitral regurgitation (MR) is the most common valvular lesion in the Western world (1). When left untreated, severe MR results in chronic volume overload and progressive dilatation of the left ventricle, leading to severe heart failure and impaired longevity (2-4). Mitral valve surgery remains the standard of care for patients with symptomatic severe mitral valve regurgitation. If mitral valve repair is not feasible then the valve is replaced with a mechanical or bioprosthetic heart valve.

Transcatheter aortic valve replacement is established as a standard of care in intermediate- or greater risk patients with aortic stenosis (5,6). In contrast, transcatheter mitral valve replacement (TMVR) is an emerging therapy that may offer patients with severe symptomatic MR a less invasive alternative to open surgical treatment.

We prospectively examined the safety and function of a novel, self-expanding valve (Intrepid TMVR System, Medtronic, Inc., Redwood City, CA) in patients with symptomatic MR that were deemed to be ineligible for conventional valve surgery.

Methods

Study population

Patients were recruited at 14 hospitals in Australia, Europe, and the United States (Online Table 1). Key inclusion criteria were age >18 years, symptomatic, severe MR, no or minimal mitral valve calcification, and left ventricular ejection fraction ≥20%. Key exclusion criteria were severe pulmonary hypertension (i.e., systolic pressure ≥70 mmHg), need for coronary revascularisation, hemodynamic instability, need for other surgical valvular therapy, severe renal insufficiency (serum creatinine >2.5 mg/dl), and prior mitral valve surgery or intervention. (Online Table 2 contains complete enrollment criteria). All patients were deemed to be high or

extreme risk by a local heart team for open mitral valve surgery. Institutional review board approval was obtained in all centers, and patients provided informed consent for study participation.

Patients underwent comprehensive imaging with transesophageal echocardiography (TEE) and cardiac contrast-enhanced, gated computed tomography (CT) to determine suitability of treatment with TMVR. Patient data were reviewed by an independent physician committee, leading to approval for study participation.

The TMVR system

The new TMVR system is composed of a self-expanding, nitinol valve and a transapical delivery system (**Figure 1**) (7). A circular outer fixation frame (43, 46, or 50 mm diameter) engages the dynamic mitral valve anatomy. A circular inner stent frame (27 mm) houses a tri-leaflet bovine valve. A flexible atrial brim is attached to the outer fixation frame to facilitate visualization under ultrasound during implantation. Fixation is achieved through the oversizing in combination with unique design features of the outer frame to wedge the valve in the sub-annular mitral space. The outer frame has a flexible atrial portion which allows it to conform to the native annulus, and a stiffer ventricular portion wider than the native mitral annulus. Additionally, there are small cleats on the outer frame which act as frictional members to engage the native mitral leaflets. The dual frame structure ensures that the inner frame remains circular throughout the cardiac cycle, independent of the shape and motion of the outer frame and mitral annulus. The conformable and symmetric design eliminates the need for rotational orientation and simplifies device implantation. The device profile is 17 to 18 mm, and thus helps minimize risk of LVOT obstruction. The TMVR valve's delivery system is currently designed for transapical delivery using a 35 Fr access sheath and a hydraulically actuated delivery catheter.

Using previously described methods, contrast-enhanced, cardiac computed tomography of the mitral valve annulus is performed for choice of the prosthesis size (8,9). A prosthesis size that allows10-30% oversizing in mitral annular perimeter, inter-commissural diameter, and septal-lateral diameter, while minimizing risk of left ventricular outflow tract obstruction was chosen. In general, a predicted neo-LVOT of <1.3 cm^2 was required for proceeding with device implantation.

Device implantation

The procedure is performed under general anesthesia with guidance by transesophageal echocardiography (TEE) and fluoroscopy (Figure 2). A small left thoracotomy is performed, and guided by data from the pre-procedural cardiac CT. Left ventricular apical purse string sutures are placed at the optimal access site. The device's access sheath is introduced over a guidewire, into the left ventricle. Following insertion of the delivery catheter into the access sheath, the delivery catheter is advanced into the left atrium using TEE guidance. The atrial brim is expanded using a hydraulic delivery mechanism, with confirmation on fluoroscopy. Under two-dimensional and three-dimensional TEE imaging, the brim is visualized to align the valve with the mitral annulus. A target zone is identified, followed by retracting the catheter to the desired location, and deploying the valve using a short run of rapid ventricular pacing. The delivery system is then withdrawn from the left ventricle and the apical access site is closed.

Transthoracic echocardiography was obtained prior to hospital discharge in all patients. Post-procedure anticoagulation was instituted for a minimum of 3 months with warfarin (INR target range, 2.5 to 3.5) and a single antiplatelet agent, consisting of either aspirin (75, 81, or 100 mg daily) or clopidogrel (75 mg daily).

Follow-up evaluation

Clinical follow-up, six-minute walk testing, and echocardiography was performed at one-month, 3-months, 6-months, and every 6-months thereafter. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was assessed at baseline and at 1-year.

Data analysis and endpoints

The analysis cohort includes the initial 50 consecutively enrolled patients who were approved for inclusion in the study (NCT02322840) between May 6, 2015 and July 21, 2017. All echocardiographic data were examined in a core echocardiography laboratory (Dr. Atif Qasim, University of California, San Francisco). Grading of valvular and paravalvular MR was performed using standard criteria and classified into none, mild, moderate, or severe (10). Left ventricular ejection fraction was assessed with biplane Simpson's method of discs using transthoracic echocardiography. Procedure time was defined as the duration from initial skin incision to final skin closure. Apical access time was defined as the duration from insertion of apical access needle to apical closure. Deployment time was defined as the duration from delivery catheter insertion into the left ventricle to completion of implantation of the valve.

The primary endpoint was assessment of the nature, severity, and frequency of complications associated with the delivery or implantation of the valve. An independent physician committee reviewed adverse clinical events for reporting including all-cause mortality, stroke, myocardial infarction (MI) bleeding, cardiovascular rehospitalization and reoperation. Standard definitions for clinical events reported, in accordance with MVARC criteria, were utilized (11).

Data are reported as medians with interquartile ranges (IQRs) or means ±standard deviation, unless otherwise noted. Adverse events are reported as the proportion of enrolled patients with an event. All-cause mortality at 1 year are reported as Kaplan-Meier estimates. The

change from baseline to last follow-up for NYHA, MLHFQ, 6-minute walk distance and echo parameters were calculated using the Wilcoxon signed rank test. All statistical analysis was performed using statistical software version SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

Role of the sponsor

The present investigation was made possible through financial and regulatory support of the sponsor (Medtronic Inc.). Data on patient demographics, medical history, echocardiographic findings, and clinical events were warehoused with the sponsor, who provided statistical analysis for this report.

Results

Baseline characteristics

Table 1 lists the baseline characteristics of the study population (mean age, 73 ± 9 years; 58% men). Debilitating heart failure was common, with 43 patients (86.0%) having NYHA class III or IV symptoms, and hospitalization for heart failure having occurred within the prior year in 29 patients (58.0%). Severe co-morbidities were frequent; overall, the STS-PROM was 6.4 ± 5.5% and the EuroSCORE II was 7.9 ± 6.2%.

MR, as assessed by the echocardiographic core laboratory, was severe in 47 patients (95.9%), with the predominant mechanism classified as either secondary (42 patients or 84%) or primary (8 patients, 16%) MR. Two patients were treated initially for severe MR, and were subsequently determined to have moderate severity during further formal review. Overall, the mean left ventricular ejection fraction at baseline was 43 ± 12% (range, 20% – 70%); only 15 of 49 patients (30.6%) had a left ventricular ejection fraction >50%. Five patients had well-functioning aortic valve prostheses, and 22 patients (44.9%) had concomitant moderate or severe tricuspid regurgitation.

Procedural results

One patient did not undergo TMVR implantation due to site bleeding during apical access. Successful implantation of the valve occurred in 48 of 49 remaining patients (98.0%), with a median procedure time of 100 minutes [IQR, 80, 124] (Online Table 3). The median time for device deployment was 14 minutes [IQR, 12, 17]. The only failure to implant successfully was related to sizing miscalculation and subsequent malpositioning of the valve. There were no incidences of device malfunction, device failure, nor conversions to open cardiac surgery. In five patients, an intra-aortic balloon pump was placed, with two patients having prophylactic placement and three others utilized for hemodynamic management. One patient also had extracorporeal membrane oxygenation (ECMO) performed prior to device implantation due to evidence of pulmonary hypertension that had worsened significantly during induction of anesthesia. Two additional patients were placed on ECMO while conducting apical repairs for bleeding complications.

Clinical outcomes

The median clinical follow-up duration for the entire cohort was 173 (IQR, 54, 342) days (**Figure 3 and 4**). There were seven deaths (14.0%) within 30 days (**Table 2**); three deaths were related to apical access site bleeding at or immediately after the initial procedure, one occurred in the patient with malposition, and three other patients died due to refractory heart failure early after the procedure (<30 days). Four additional patients died after 30 days (between days 54 and days 122) but there were no deaths after 4 months (**Figure 4**); three of these late deaths were due to sudden cardiac arrest and one due to intracranial haemorrhage in the setting of an unwitnessed fall. Among these four late deaths, the absence of structural valve degeneration was documented

either at autopsy or prior to death with echocardiography within the prior month. Other adverse events are listed in **Table 2**.

In five patients, re-operation was performed for bleeding observed in the immediate post-operative period. In one instance, minor bleeding was observed at the apical site and was controlled with a single stitch; in four other patients, chest wall bleeding was identified.

Among all alive patients with 30-day echocardiographic follow-up (n=42), significant reductions in MR severity and improvements in symptoms occurred (**Figures 5**). MR was either absent (i.e., grade 0) or mild (i.e., grade 1) in implanted patients at their last clinical evaluation (n=42; 100%), with no evidence of LVOT obstruction (change in peak LVOT gradient = 0.4 ± 4.5 mm Hg) or mitral stenosis (final mean gradient, 4.1 ± 1.3 mm Hg) (Online Table 4). Among patients with MR, all cases were mild; para-prosthetic mitral regurgitation in 3 patients (7.1%), while prosthetic mitral regurgitation occurred in 8 patients (19.0%). For patients with paired data, pulmonary artery systolic pressure, by transthoracic echocardiography, decreased from 46.7 ± 14.7 mm Hg to 37.2 ± 9.7 mm Hg at follow-up ($p < 0.0001$). There also was a decrease in left ventricular ejection fraction (43.6 ± 12.1% vs. 36.2 ± 10.2%; $p < 0.0001$), and an increase in left ventricular end-systolic dimension (4.8 ± 1.0 cm at baseline vs. 5.1 ± 0.9 cm at follow-up; $p = 0.0007$), without significant changes in left ventricular end-diastolic dimension (5.9 ± 0.7 cm at baseline vs. 5.9 ± 0.8 cm at follow-up; $p = 0.94$). In all implanted patients, there were no instances of hemolysis, device embolization or thrombosis.

Among the patients with NYHA class follow-up at 30 days (n=42), mild or no symptoms of heart failure (i.e., NYHA functional class I or II) were present in 79% ($p < 0.0001$ vs. baseline). During follow-up, a non-significant change in 6-minute walk distance was observed

(248.3 ± 103.6 m vs 267.6 ± 110.0; p = 0.31). Significant improvements in MLHFQ scores (56.2 ± 26.8 vs. 31.7 ± 22.1; p = 0.011) occurred.

Discussion

The principal findings of this pilot study were: 1) The valve was successfully implanted in all but 2 patients (96%), with reduction in MR to mild or none in all implanted patients; 2) The procedure was short and reproducible with a minimal learning curve, with no device malfunction or structural valve degeneration occurring acutely or during clinical follow-up (median 173 days); and; 3) improvements in symptom status and quality-of-life were observed in procedural survivors. These observations in a cohort of patients deemed to be ineligible for conventional open mitral valve surgery are provocative.

The valve design was shown to be advantageous. Implantation and fixation for anchoring was self-centering and symmetric, and the separation of the outer anchoring stent from the inner stent housing the functional valve components proved to be adaptable to a variety of anatomical situations. The lower profile of the valve also allowed implantation in previously contraindicated conditions, including prior prosthetic aortic valve replacement and patients, particularly women, with smaller ventricular size and who may be at risk for left ventricular outflow tract obstruction (9).

We targeted a high- or extreme-risk population of patients who were deemed to be ineligible for open mitral valve surgery, which may help to explain the high 30-day mortality. Apical bleeding was a concerning issue and was associated with mortality in 3 patients, emphasizing the need for diligent technical care as well as willingness to abort the procedure if the access site is felt to be unsafe. Three patients died due to exacerbation of heart failure suggesting the need for more intensive peri-operative heart failure management. This experience

highlights the recognition that patients undergoing TMVR may experience a complex recovery period and the need for careful patient selection. We were surprised by the high incidence of reoperation for chest wall bleeding, although this may have been partially due to overly aggressive institution of anti-coagulant therapies. Emphasis on chest wall hemostasis will be important, as this technology currently relies on a mini-thoracotomy for trans-apical access. Ongoing development of the new TMVR system for transfemoral, transseptal implantation, avoiding the need for anterior thoracotomy and resultant apical access complications, will likely further lower the morbidity of this technology in the future.

Our results support the further exploration of image-guided beating heart TMVR as an alternative to open heart mitral valve surgery in appropriately selected patients. There was a decrement in left ventricular ejection fraction (44% to 36%) following implantation of the Intrepid prosthesis, similar to what has been reported in other TMVR series (12). In the CTSN trial of severe ischemic MR, whose study population shares some characteristics with ours, a decrement in left ventricular ejection fraction was minimally present, if at all, in the chordal-replacement arm (40.0% at baseline vs. 37.8% at 1-year follow-up) and the patients who had repair (42.4% at baseline vs. 41.5% at 1-year follow-up). Further evaluation of the significance of such change in ejection fraction among patients who receive TMVR, which is a chordal-sparing treatment, is needed (13). Of note, in the 3 sudden deaths that occurred in follow-up despite successful TMVR, none of the patients had been treated with an implantable cardioverter-defibrillator despite having clinical indications for the therapy. In comparison to the most recent registry data regarding transcatheter mitral valve *repair* in patients with functional MR that reported a relatively high rate of moderate or severe MR at one year (14), TMVR with the valve was found to be highly effective in eliminating significant mitral valve regurgitation.

Although the results of our initial feasibility trial demonstrate the promise of TMVR with the Intrepid valve system, further clinical investigations are required to define other patient populations with severe mitral regurgitation that may benefit from this procedure.

Limitations

The present investigation is an examination of the feasibility of a novel prosthesis for TMVR, which is a rapidly evolving field. While there were no instances of known device thrombosis, prospective screening with adjunctive multi-modality imaging (e.g., TEE or CT) was not performed and the incidence of subclinical abnormalities is not known. Measurement of MR severity was performed with transthoracic echocardiography in the resting state with no attempt to alter the hemodynamic milieu (e.g., raising or lowering blood pressure), though data on the effects of any subtle hemodynamic alterations on MR severity were not available. In addition, anticoagulation with warfarin was recommended for >3 months, but the rate of continuation or discontinuation was unknown. The target population for the study was high or extreme risk patients. Extenuating circumstances (e.g., frailty) were used to justify therapeutic intervention with TMVR, yet formal testing or objective measurement of such variables was not consistently performed or available. Such information would be of benefit for optimizing patient selection for TMVR therapy.

Conclusions

TMVR with the new TMVR system resulted in the correction of mitral regurgitation in symptomatic patients deemed to be at high- or extreme-risk for open heart surgery. Stable valve function was observed longitudinally, and a majority of patients experienced significant improvement in their clinical symptoms and functional class. Further investigations will determine the role of this therapeutic option in a broader population of patients with mitral valve

disease compared with both surgical mitral valve replacement and transcatheter mitral valve repair techniques.

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Figure Legends

Central Illustration: Early Clinical Experience of TMVR with the New Valve Prosthesis. Follow-up time for the 50 patients is illustrated with patients listed on the y-axis in descending order of treatment. X-axis indicates duration of follow-up. All deaths occurred prior to 365 days (dotted line). Blue = surviving patients; Gray = deceased patients.

Figure 1. The valve design. The device is a transapical, self-expanding, symmetrical nitinol valve. (A) An atrial brim (arrowhead) is used for device placement under echocardiographic imaging, while an outer stent frame (arrow) facilitates fixation to the mitral valve annulus. (B) The inner frame houses a 27mm bovine pericardial valve (arrowhead). (C) The outer frame has different degrees of radial stiffness along its axial length to create a 'cork-like' effect conformation that, along with small cleats, facilitates anchoring.

Figure 2. Implantation of the valve. A, Baseline transesophageal echocardiography (TEE) demonstrates severe mitral regurgitation (arrow; blood pressure = 128/75 mm Hg). B, Following a left thoracotomy, the point of apical access is confirmed manually (arrowheads) with TEE guidance. C, A 35 Fr sheath is placed transapically and centered in the mitral valve orifice. D, Following deployment of the atrial brim, a 6 mm landing zone is identified on orthogonal views of the mitral valve annulus. E, Three-dimensional TEE (i.e., "surgeon's" view) demonstrates complete deployment. F, Two-dimensional color flow imaging shows no residual mitral regurgitation (blood pressure = 120/60 mm Hg). Ao, aorta; AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve.

Figure 3. Clinical follow-up for the treated patients. Follow-up time for the 50 patients is illustrated with patients listed on the y-axis in descending order of treatment. X-axis indicates

duration of follow-up in days for each treated patient. All deaths occurred prior to 365 days (dotted line). Blue = surviving patients; Grey = deceased patients

Figure 4. Survival during follow-up. One-year survival reported as % [95% Confidence Interval].

Figure 5. Mitral regurgitation, symptoms and quality of life at baseline and following implantation of the valve.

(A) Severity of mitral regurgitation at baseline, 30 days, and last follow-up (B), Symptom status (New York Heart Association [NYHA] functional class) at baseline, 30 days, and last follow-up. (C) Paired data demonstrating change in Minnesota Living with Heart Failure total score. *Three patients (7.1%) had mild paravalvular MR and eight patients (19.0%) had mild transvalvular MR graded.

Table 1: Patient characteristics.

	Patients (n=50)
Age (years)	72.6 ± 9.4
Men	29 (58.0%)
Treatment location	
United States	23 (46.0%)
Outside United States	27 (54.0%)
NYHA functional class	
II	7 (14.0%)
III	35 (70.0%)
IV	8 (16.0%)
Heart failure hospitalization within past year (≥1)	29 (58.0%)
Chronic obstructive pulmonary disease	25 (50.0%)
Diabetes mellitus	21 (42.0%)
Chronic renal insufficiency	29 (58.0%)
GFR 30 – 60 ml/min/m^2*	25 (50.0%)
Atrial fibrillation	29 (58.0%)
Prior stroke	8 (16.0%)
Coronary artery disease	34 (68.0%)
Peripheral artery disease	11 (22.0%)
Prior myocardial infarction	22 (44.0%)
Prior percutaneous coronary intervention	21 (42.0%)
Number of sternotomies ≥1	22 (44.0%)
Prior coronary artery bypass surgery	19 (38.0%)
Prior aortic valve replacement	5 (10.0%)

History of ICD or PPM	21 (42.0%)
Body mass index (kg/m^2)	28.7 ± 5.9
Etiology of MR	
Primary	8 (16.0%)
Secondary	36 (72.0%)
Both primary and secondary	6 (12.0%)
Severity of mitral regurgitation	
Moderate	2 (4.1%)
Severe	47 (95.9%)
Mild or worse mitral annular calcification	17 (34.0%)
Moderate or severe tricuspid regurgitation	22 (44.9%)
Moderate	16 (32.7%)
Severe	6 (12.2%)
Left ventricular ejection fraction (%)	43.4 ± 11.8
Extenuating circumstances	
Frailty	16 (32.0%)
Pulmonary hypertension (PASP, 55 to 70 mm Hg)**	20 (40.0%)
Poor mobility	7 (14.0%)
Albumin < 3.3 g/dL#	9 (23.1%)
Anemia†	22 (44.0%)
Liver dysfunction††	4 (9.5%)
Malignancy	15 (30.0%)
Immunosuppression	2.0 (4.0%)
STS predicted risk of mortality for mitral replacement (%)	6.4 ± 5.5
EuroSCORE II (%)	7.9 ± 6.2

Data are n (%) or mean ± SD. GFR = glomerular filtration rate. ICD = implantable cardioverter defibrillator. NYHA = New York Heart Association. PASP = pulmonary artery systolic pressure. PPM = permanent pacemaker. STS = Society of Thoracic Surgeons. *Patients with GFR <30 ml/min/m^2 were excluded. **Patients with PASP >70 mmHg were excluded. #Albumin was not measured in 11 patients. †Anemia was defined as haemoglobin <13.0 g/dL in men or <12.0 g/dL in women. ††Defined as alanine transferase ≥40 U/l and was measured in 42 patients.

Table 2: Adverse Events.

	0-30 Days (n=50)	>30 Days (n=41)
Death	7 (14.0%)	4 (9.8%)
Cardiovascular	7 (14.0%)	4 (9.8%)
Non-cardiovascular	0 (0.0%)	0 (0.0%)
Stroke	2 (4.0%)	1 (2.4%)
Disabling stroke	0 (0.0%)	0 (0.0%)
Non-disabling stroke	2 (4.0%)	1 (2.4%)
Myocardial infarction	0 (0.0%)	0 (0.0%)
Acute renal impairment, stage 3	5 (10.0%)	0 (0.0%)
Major vascular complications	0 (0.0%)	0 (0.0%)
Major cardiac structural complication	2 (4.0%)	0 (0.0%)
Major bleeding	9 (18.0%)	0 (0.0%)
Reoperation for any reason	5 (10.0%)	1 (2.4%)
Reoperation for bleeding	5 (10.0%)	0 (0.0%)
Reoperation for other*	0 (0.0%)	1 (2.4%)
New-onset atrial fibrillation	7 (14.0%)	2 (4.9%)
Hemolysis	0 (0.0%)	0 (0.0%)
Endocarditis†	1 (2.0%)	1 (2.4%)
Device embolization	0 (0.0%)	0 (0.0%)
Device thrombosis	0 (0.0%)	0 (0.0%)
Cardiovascular re-hospitalization	8 (16.0%)	13 (31.7%)

Re-hospitalization for heart failure	4 (8.0%)	8 (19.5%)

Data are n (%). *Reoperation for wound infection at incision site. †The endocarditis event was related to placement of a pacemaker lead.

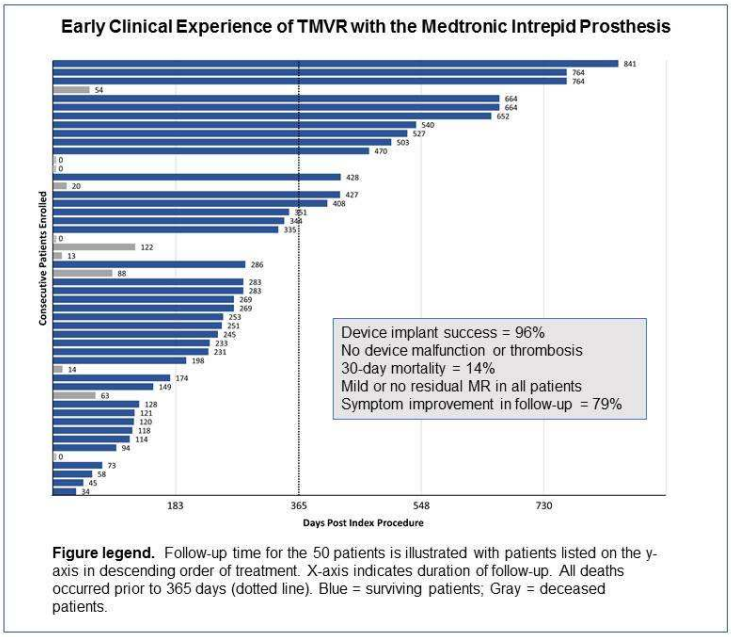
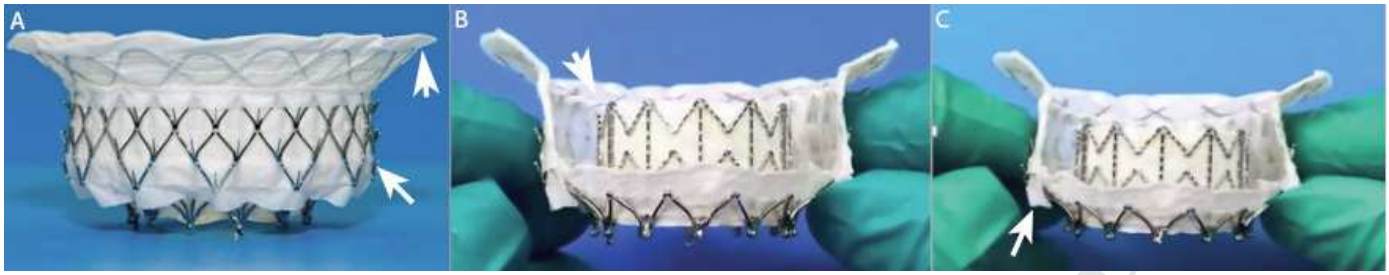
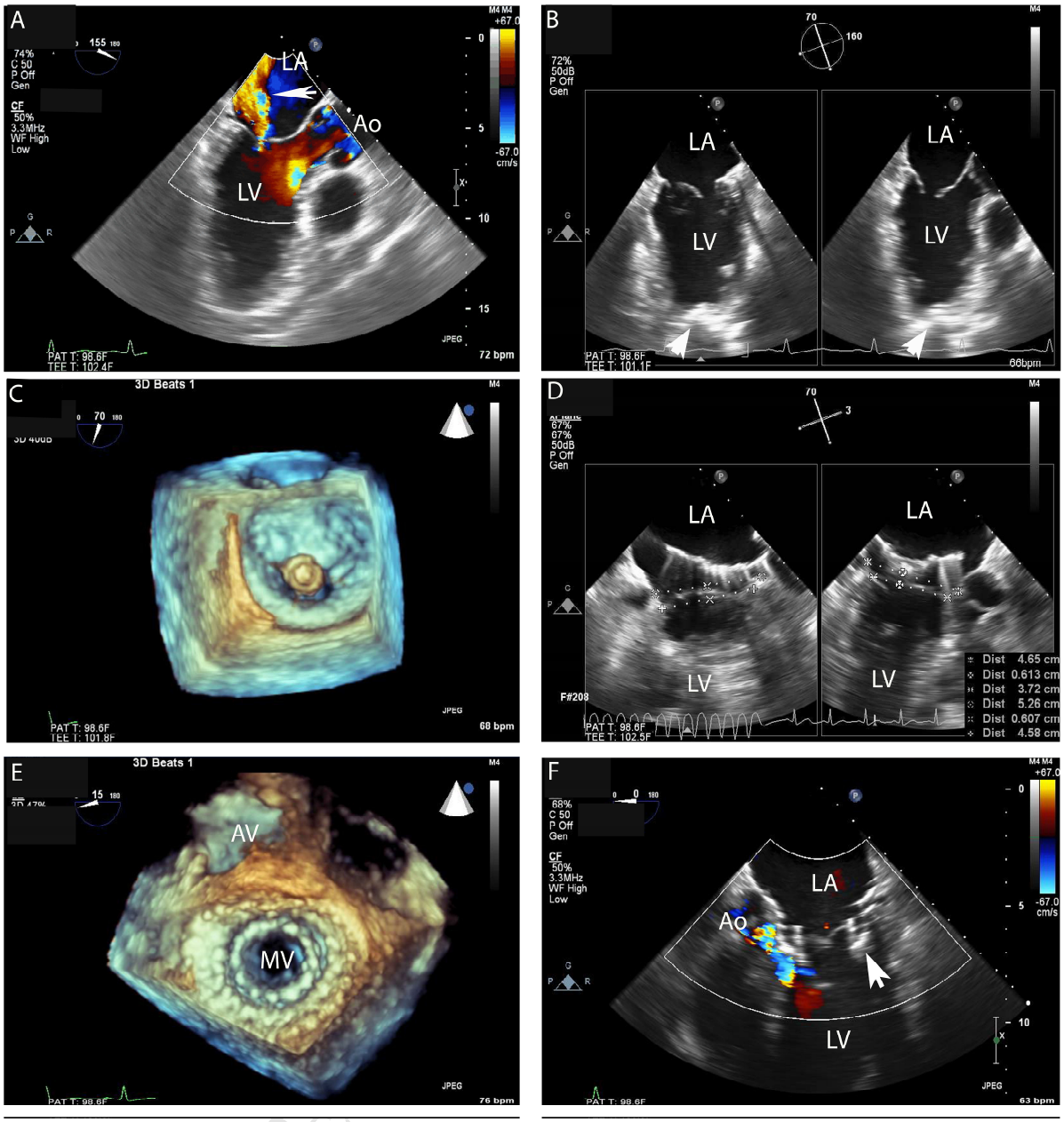
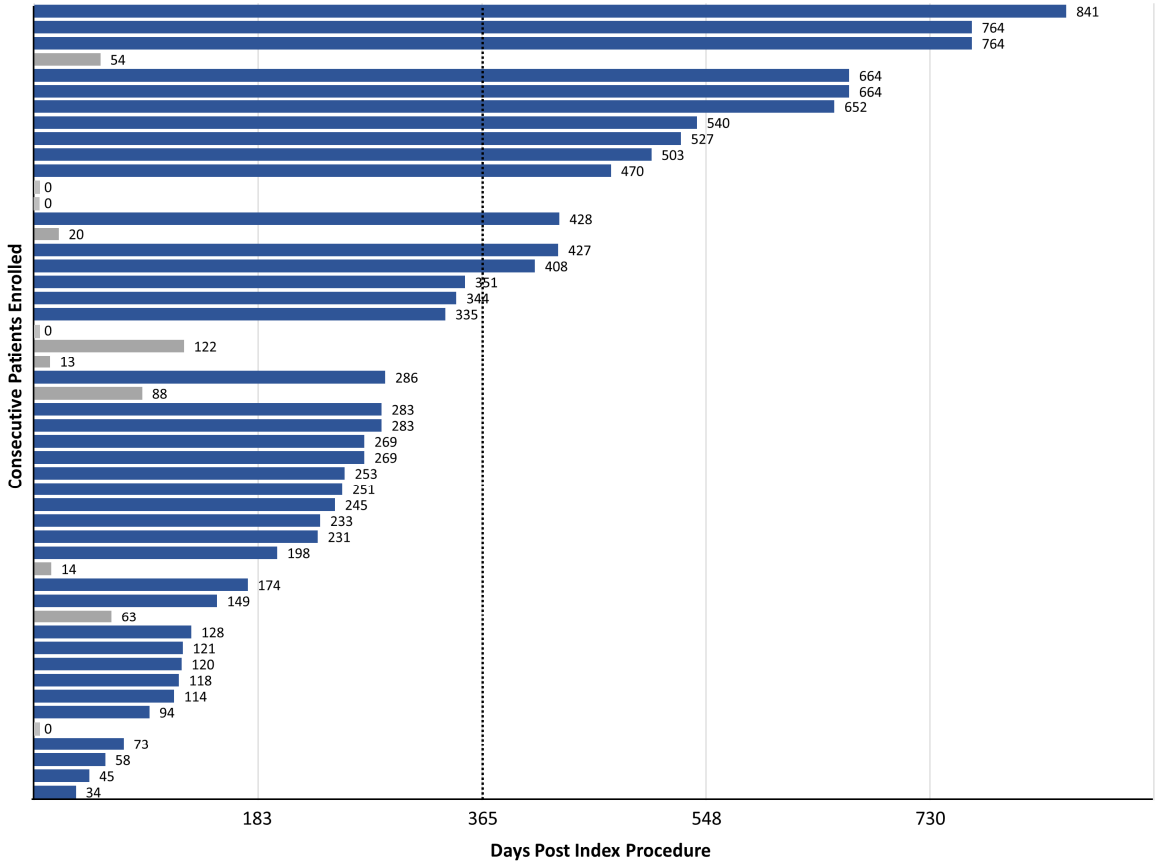
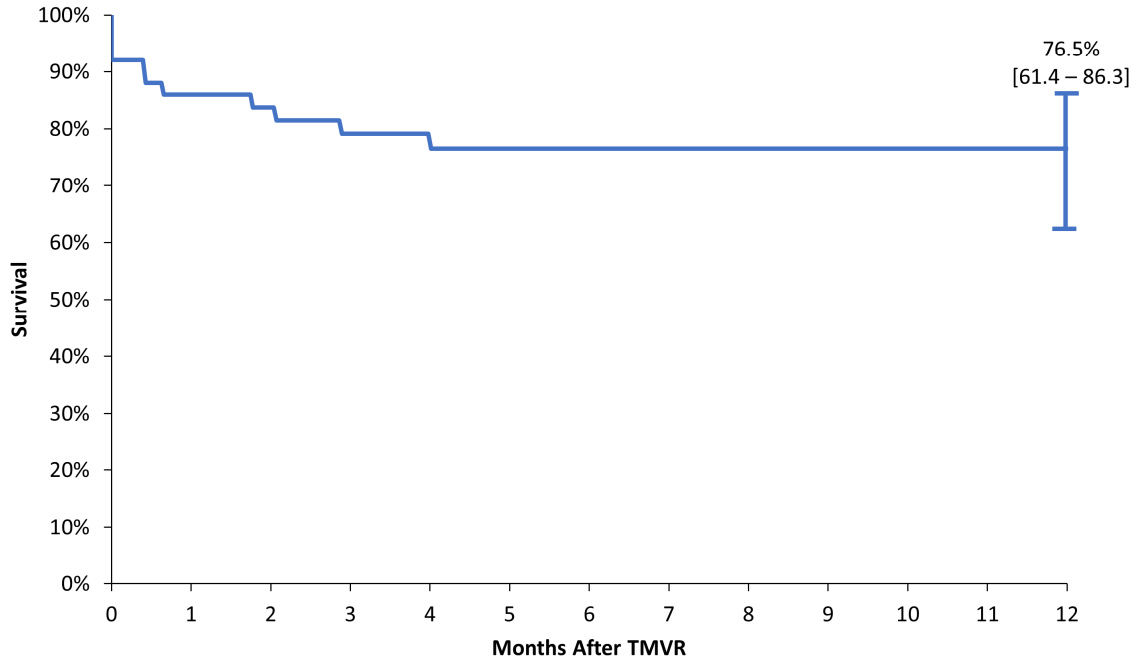


Figure legend. Follow-up time for the 50 patients is illustrated with patients listed on the y-axis in descending order of treatment. X-axis indicates duration of follow-up. All deaths occurred prior to 365 days (dotted line). Blue = surviving patients; Gray = deceased patients.



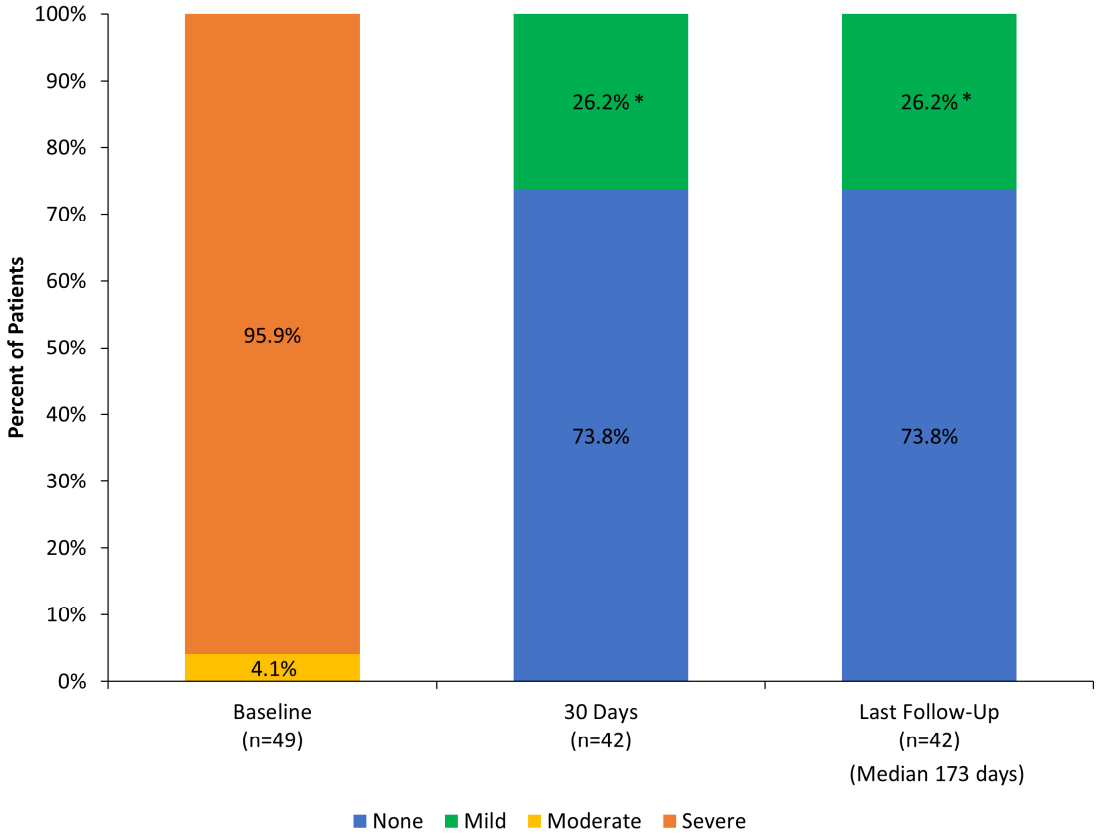


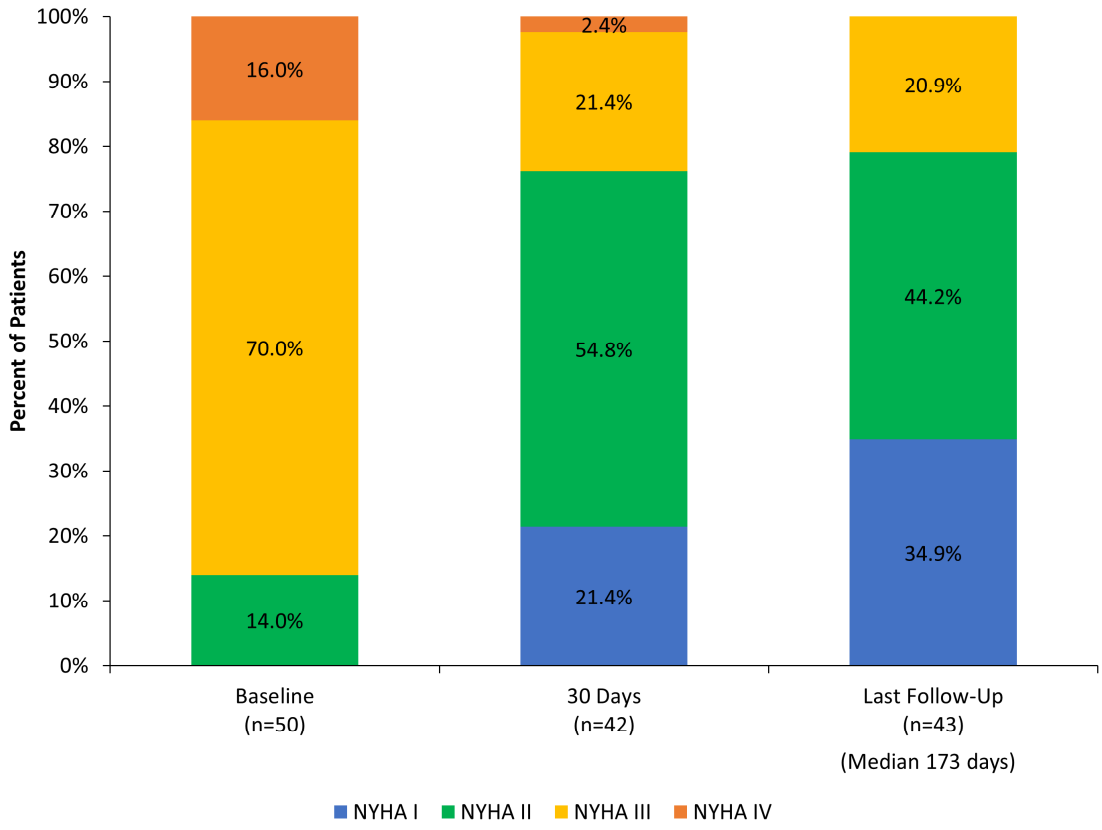


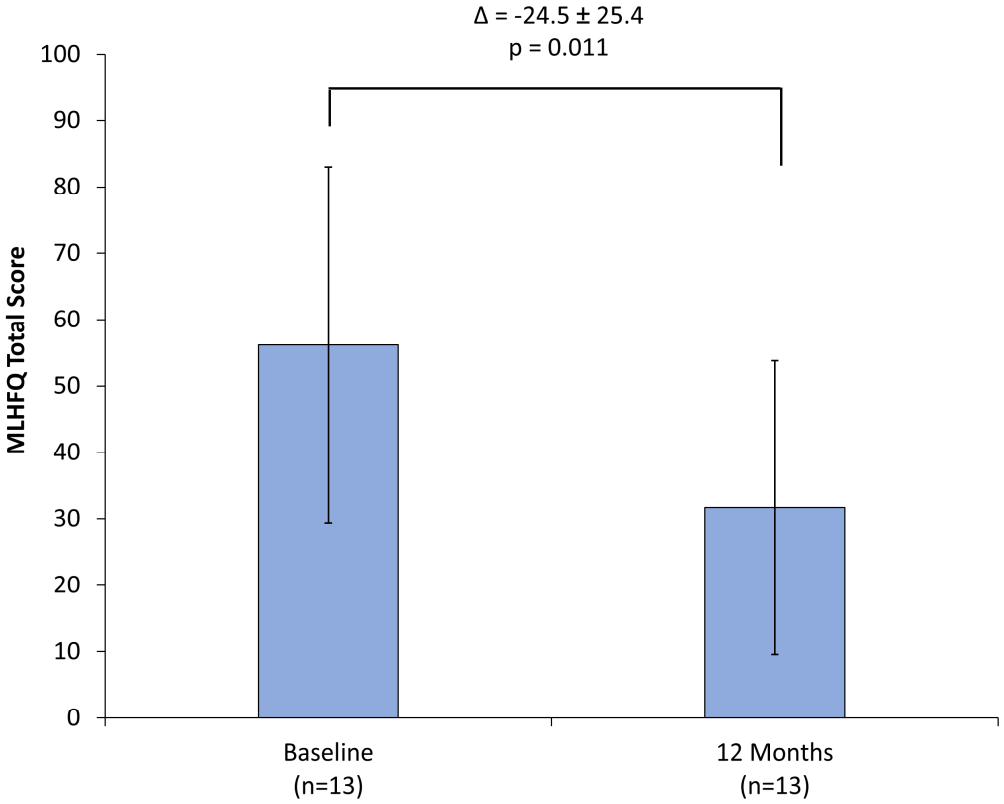


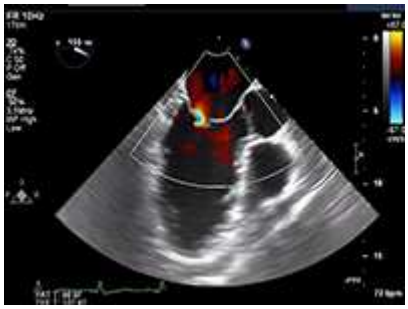
Number at risk:

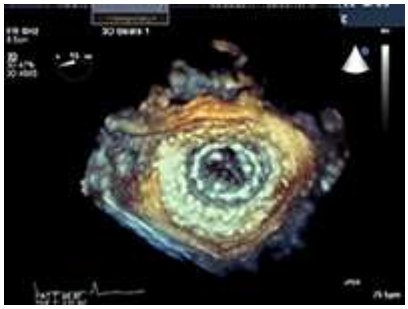
50	41	21	10

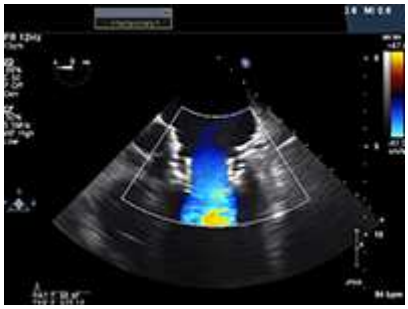












Online Appendix

Intrepid Global Pilot Study Investigators

Neal S. Kleiman, MD and Michael Reardon, MD from Houston-Methodist-DeBakey Heart and Vascular Center/The Methodist Hospital, Houston, TX; Tanvir Bajwa, MD and Daniel O'Hair, MD from St. Luke's Medical Center Aurora Health Center Milwaukee, WI; Vivek Rajagopal, MD and Christopher Meduri, MD from Piedmont Heart Institute, Atlanta, GA; Mathew Williams, MD and Hasan Jilaihawi, MD from New York University/Langone Medical Center, New York, NY; Paul Sorajja, MD and R. Saied Farivar, MD from Abbott Northwestern Minneapolis, MN; Antony Walton, MD and Stephen Duffy, MBBS, PhD, from The Alfred, Melbourne, Australia; Robert Gooley, MD and Aubrey Almeida, MD from Monash Heart, Melbourne, Australia; Martin Ng, MD and Michael Wilson, MD from Royal Prince Alfred Hospital, Sydney, Australia; Konstantinos Spargias, MD and Stratis Pattakos, MD from Hygeia Hospital, Athens, Greece; Mika Laine, MD and Helena Haenninen, MD from Helsinki University Hospital, Helsinki, Finland; Thomas Modine, MD and Augustine Coisne, MD from Centre Hospitalier Regional Univeritaire de Lille, Lille, France; David Hildick-Smith, MD and Uday Trivedi, MD from Brighton and Sussex University Hospitals, Brighton, United Kingdom; Daniel Blackman, MD and Betsy Evans, MD from Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; Ronak, MD and Simon Redwood, MD from St. Thomas' Hospital, United Kingdom.

Online Table 1: Participating Investigators, sites and personnel

Participating Investigational Sites & Personnel	
United States	
Houston-Methodist-DeBakey Heart and Vascular Center/ The Methodist Hospital Houston, TX	Principal Investigators: Neal S. Kleiman, Michael Reardon Co-investigators: Steve Little, Colin Baker, Ross Reul, Mahesh Ramchandi Research Coordinators: Pamela Hazen, LaShawna Green, Jeannie Arrendondo, Patricia Brinegar, Lisa Green, Amber Jacobs, Saba Khan, Mary Mata, Wesley Oglesby, Carol Underwood, Kurt White, Meagan Griffin, Tammara Moore
The Mount Sinai Medical Center New York, NY	Principal Investigators: David H. Adams, Barry Love Co-investigators: George Dangas, Anelechi Anyanwu, Ahmed El-eshmawi, Julie Swain, Barry Love, Alexander Mittnacht, Menachem Weiner, Himani Bhatt, Gilbert Tang, Farooq Chaudry Research Coordinators: Michael Fusilero, Jerome Tonog, Vanessa Coulibaly
St. Luke's Medical Center Aurora Health Center Milwaukee, WI	Principal Investigators: Tanvir Bajwa, Daniel O'Hair Co-investigators: Reuka Jain, Bijoy Khandheria Research Coordinators: Wendy Dunaj, Michelle Bennett, Deb Waller, Kathleen Behrens
University of Michigan Health System Ann Arbor, MI	Principal Investigators: Stanley Chetcuti, Steven F. Bolling Co-investigators: Matthew Romano, Daniel Menees, Troy LaBounty, Ann Bhat Research Coordinators: Jessica Oakley, Sarah Rubin
Baylor Heart and Vascular Hospital Dallas, TX	Principal Investigators: Paul Grayburn, Robert Hebeler Co-investigators: Michael Mack, Robert Stoler, Research Coordinators: Emily Labile, Kim Waters, Leslie Willcott, Angela Mendez
Piedmont Heart Institute Atlanta, GA	Principal Investigators: Vivek Rajagopal, James Kauten Co-investigators: Christopher Meduri, Mani Vannan,

Participating Investigational Sites & Personnel	
	Federico Milla Research Coordinators: Shelley Holt, Elisa Amoroso, Kashaine Gray,
New York University/Langone Medical Center New York, NY	Principal Investigators: Mathew Williams, Hasan Jilaihawi Co-investigators: Aubrey Galloway, Cezar Staniloae, Muhamed Saric Research Coordinator: Jessie Van Daele, Zachary Taylor, Eleonora Vapheas, Raissa Nunes, Namrata Nepal, Tonya Robin, Pascale Houanche
Abbott Northwestern Minneapolis, MN	Principal Investigators: Paul Sorajja, Robert Farivar Co-investigators: Richard Bae, Mario Goessl, Judah Askew Research Coordinator: Kate Jappe, Pam Morley, Aisha Ahmed, Kari Thomas, Brittany Fitzpatrick, Sara Olson, Karen Meyer
Columbia University Medical Center New York, NY	Principal Investigators: Martin Leon, Isaac George Co-investigators: Susheel Kodali, Rebecca Hahn, Torsten Vahl, Tamim Nazif, Michael Borger, Omar Khalique Research Coordinator: Alex Kantor, Deniz Akkoc, Kate Dalton, Juan Mendez
Barnes Jewish St. Louis, MO	Principal Investigators: Alan Zajarias, Hersh Maniar Co-investigators: Majesh Makan, Spencer Melby Research Coordinator: Michelle Myers, Kelly Koogler
Northwestern Chicago, IL	Principal Investigators: Patrick McCarthy, Charles Davidson Co-investigators: James Thomas, Mark Ricciardi, Chris Malaisrie, Jyothy Puthumana Research Coordinator: Caitlyn Brady
Australia	
The Alfred, Melbourne, Australia	Principal Investigators: Antony Walton Co-investigators: Stephen Duffy, Silvana Marasco,

Participating Investigational Sites & Personnel	
	Helen Thomson, Dion Stub Research Coordinator: Rox Johnston, Samantha Holland, Brianna Davidson
Monash Heart, Melbourne, Australia	Principal Investigators: Robert Gooley Co-investigators: Aubrey Almeida, Siobhan Lockwood, Liam McCormick, Phillip Mottram Research Coordinator: Mary-Anne Austin, Wendy Wallace-Mitchell
Royal Prince Alfred Hospital, Sydney, Australia	Principal Investigators: Martin Ng Co-investigators: Michael Wilson, Bruce Cartwright, Lisa Simmons Research Coordinator: Jun Wu
Europe	
Hygeia Hospital, Athens, Greece	Principal Investigators: Konstantinos Spargias Co-investigators: Nick Boumpoulis, Stratis Pattakos, Spyros Skardoutsos, Michael Chrissoheris, Konstantinos Papadopoulos Research Coordinator: Evgenia Dafnomili
Helsinki University Hospital, Helsinki, Finland	Principal Investigators: Mika Laine Co-investigators: Antero Sahlman, Tommi Vahasilta, Suvi Tuohinen, Helena Haenninen, Janne Rapola, Seppo Hiippala Research Coordinator: Christina Salmen
Centre Hospitalier Regional Univeritaire de Lille, Lille, France	Principal Investigators: Thomas Modine Co-investigators: Arnaud Sudre, Augustine Coisne, Emmanuel Robin Research Coordinator: Justine Lerooy
Clinique Pasteur, Toulouse, France	Principal Investigators: Didier Tchetche Co-investigators: Pascal Chambran, Laurent Sidobre Research Coordinator: Frederic Petit

Participating Investigational Sites & Personnel	
Brighton and Sussex University Hospitals, Brighton, United Kingdom	Principal Investigators: David Hildick-Smith Co-investigators: Uday Trivedi, Arionilson Gomes Research Coordinator: Jessica Parker
Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom	Principal Investigators: Daniel Blackman Co-investigators: Betsy Evans, Christopher Malkin, Dominik Schlosshan, Christopher Munsch Research Coordinator: Kathryn Somers, Helen Reed, Natalie Burtonwood
St. Thomas' Hospital, United Kingdom	Principal Investigators: Vinayak Bapat Co-investigators: Bernard Prendergast, Simon Redwood, Jane Hancock, Ronak Rajani Research Coordinator: Karen Wilson, Megan Smith, Sophie Jones

Online Table 2: Inclusion and exclusion criteria

The Intrepid™ TMVR Pilot Study Inclusion and Exclusion Criteria	
Inclusion Criteria	**Exclusion Criteria**
1. Severe mitral regurgitation (MR Grade 3-4+) 2. Symptomatic mitral regurgitation (NYHA Class II-IV) 3. Deemed to be at high risk for conventional mitral valve surgery by the local heart team (including, at minimum, a cardiac surgeon, interventional cardiologist, and an echocardiologist) 4. Age ≥ 18 yrs 5. Native mitral valve geometry and size compatible with the Intrepid™ TMVR 6. No or minimal mitral valve calcification 7. Willing to sign Informed Consent for participation in the study and return for all required post-procedure follow-up visits	1. Left ventricular ejection fraction (LVEF) < 20% 2. Evidence of intracardiac mass, thrombus, or vegetation 3. Pulmonary hypertension (> 70 mmHg systolic) 4. Hypertrophic Obstructive Cardiomyopathy (HOCM) 5. Prior mitral valve surgery or endovascular procedure, any currently implanted mechanical prosthetic valve, or need for other valve surgery/procedure 6. Any endovascular therapeutic interventional or surgical procedure performed within 30 days prior to enrollment 7. Prior stroke within 30 days 8. Need for coronary revascularization 9. Need for emergent surgery 10. History of, or active, endocarditis 11. GI bleeding within 6 months 12. History of bleeding diathesis or coagulopathy or patient will refuse blood transfusion 13. Hemodynamic instability 14. Platelet count of <75,000 cells/mm3 15. Renal insufficiency (Creatinine > 2.5 mg/dL) 16. Active infections requiring current antibiotic therapy (if temporary illness, patients may enroll 2 weeks after discontinuation of antibiotics) 17. Contraindication to transesophageal echocardiography (TEE)

The Intrepid™ TMVR Pilot Study Inclusion and Exclusion Criteria	
Inclusion Criteria	**Exclusion Criteria**
	18. Known hypersensitivity or contraindication to study or procedure medications/contrast which cannot be adequately managed medically. 19. Pregnant, nursing or planning to be pregnant. (Female participants of childbearing potential must have a negative pregnancy test prior to enrollment).

Online Table 3: Procedural Data.

	Patients (n=50)
Surgical procedure duration (min)	100.0 (80.0, 124.0)
Apical access duration (min)	26.0 (23.0, 35.0)
Deployment time (min)	14.0 (12.0, 17.0)
Pacing time (sec)	29.0 (23.0, 36.0)
Fluoroscopy time (min)	7.5 (5.1, 9.8)
Procedure aborted	1 (2.0%)
TMVR successfully implanted	48/49 (98.0%)
Device malfunction	0/48 (0.0%)
Device failure	0/48 (0.0%)
Conversion to open MV replacement	0 (0.0%)
Intra-aortic balloon pump utilized	5 (10.0%)
ECMO support utilized	3 (6.0%)

Data are n (%) or median (IQR). ECMO = extracorporeal membrane support. MV = mitral valve. TMVR = transcatheter mitral valve replacement.

Online Table 4: Echocardiography Data

Implanted (N=49)	Baseline	30-Day	Last Follow-up
MR Grade ≤ Mild (1+)	0/49 (0%)	42/42 (100%)	42/42 (100%)
Left ventricular ejection fraction (%)	43.3 ± 11.8 (n=49)	36.9 ± 11.7 (n=36)	37.1 ± 11.4 (n=40)
Mean mitral gradient (mm Hg)	3.2 ± 1.7 (n=40)	4.3 ± 1.3 (n=39)	4.1 ± 1.3 (n=42)
Mean LVOT gradient (mm Hg)	5.4 ± 5.3 (n=44)	6.7 ± 7.4 (n=40)	5.6 ± 5.2 (n=42)
Peak LVOT gradient (mm Hg)	9.5 ± 8.7 (n=44)	11.7 ± 11.7 (n=40)	10.0 ± 8.9 (n=42)
Left ventricular end-diastolic dimension (cm)	6.0 ± 0.8 (n=49)	5.8 ± 0.8 (n=41)	5.9 ± 0.8 (n=41)
Left ventricular end-systolic dimension (cm)	4.8 ± 1.0 (n=49)	4.9 ± 1.0 (n=41)	5.1 ± 1.0 (n=41)
Pulmonary arterial systolic pressure (mm Hg)	46.9 ± 14.4 (n=41)	38.8 ± 11.8 (n=32)	37.3 ± 10.2 (n=40)

Data are n/N (%) or mean ± SD.

Online Table 5: Causes of death

Causes of death during the study		
Patient death	**Days after TMVR**	**Description**
1	0	Hemothorax related to post-operative apical bleeding
2	0	Device malpositioning
3	0	Left ventricular laceration during apical access
4	0	Post-operative apical bleeding
5	13	Re-hospitalization for heart failure after successful implant
6	14	Heart failure during post-operative recovery
7	20	Heart failure during post-operative recovery
8	54	Intracranial hemorrhage after unwitnessed fall in rehabilitation center
9	63	Sudden cardiac death at home
10	88	Sudden cardiac death at home
11	122	Sudden cardiac death at home

Online Table 6: Reasons for exclusion. There were a total of 166 patients screened for possible study participation. The most common reason for exclusion was lack of anatomical suitability, which was evident in 84 patients (i.e., native mitral valve too large in 20%, mitral valve too small in 8%, and concern for LVOT obstruction in 22%). Of the 82 patients with suitable anatomy, 50 were enrolled and 32 were excluded. Reasons for exclusion of these latter 32 patients are described in the table below.

Variable	**Number of patients with exclusion**
Poor left ventricular function	6
Low surgical risk	5
Mechanical AVR	5
Mitral regurgitation not severe	4
Other mitral treatment received	4
Futility	3
Patient declined	1
Patient no longer symptomatic	1
Baseline systolic anterior motion	1
Severe pulmonary hypertension	1
Severe mitral annular calcification	1

Online Video Legends

Figure 2A. Baseline transesophageal echocardiography. Prior to device implantation, there was severe secondary mitral regurgitation.

Figure 2E. Echocardiographic imaging following Intrepid deployment. Three-dimensional TEE (i.e., "surgeon's" view) demonstrates complete deployment with a normally functioning prosthesis.

Figure 2F. Color-flow imaging after Intrepid deployment. Following placement of the Intrepid prosthesis, two-dimensional color flow imaging shows no residual mitral regurgitation.