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ABSTRACT

Background: Transseptal transcatheter mitral valve replacement (TMVR) may offer a less invasive option than surgery for mitral regurgitation (MR) with greater efficacy and fewer anatomic limitations than transcatheter repair.

Objectives: To examine the initial experience with a novel transseptal TMVR system.

Methods: Patients were treated with the EVOQUE TMVR system from September 2018 to October 2019. Key inclusion criteria were ≥ moderate MR, New York Heart Association (NYHA) Class ≥ 2, and high/prohibitive surgical risk. Primary outcome was technical success defined by Mitral Valve Academic Research Consortium criteria.

Results: Fourteen patients were treated, all with ≥ moderate-severe MR. Median age was 84 years, and median STS score was 4.6%. MR was degenerative in 4 (28.6%), functional in 3 (21.4%) and mixed in 7 (50%). Technical success was achieved in thirteen patients (92.9%) and one patient was converted to surgery. At 30 days there was one non-cardiovascular mortality (7.1%), two strokes (14.3%), no myocardial infarctions, and no rehospitalizations. Two patients (14.3%) underwent PVL closure. One patient (7.1%) underwent alcohol septal ablation for left ventricular outflow tract obstruction. Including the 2 patients with PVL closure, MR was ≤ mild in all implanted patients at 30 days with no MR in ten (83.3%). Mean mitral gradient was 5.8mmHg (median). Functional class improved to NYHA Class ≤2 in nine patients (81.8%).

Conclusions: This first-in-human experience has demonstrated the feasibility of the transseptal EVOQUE TMVR system. Further clinical studies are required to establish safety and clinical outcomes.

KEY WORDS: mitral, TMVR, transcatheter

CONDENSED ABSTRACT

This is the first-in-human experience with the transseptal EVOQUE TMVR system. Fourteen patients with significant symptomatic MR were treated. Technical success was achieved in thirteen patients (92.9%). At 30 days there was one non-cardiovascular mortality (7.1%), two strokes (14.3%), no myocardial infarctions, and no rehospitalizations. Two patients (14.3%) underwent paravalvular leak closure and one (7.1%) underwent alcohol septal ablation for left ventricular outflow tract obstruction. Inclusive of the two patients who underwent PVL closure, MR at 30 days was ≤ mild in all implanted patients with no MR in 10 (83.3%). This first-in-human experience has demonstrated the feasibility of the transseptal EVOQUE TMVR system.

ABBREVIATIONS AND ACRONYMS

CT – Computed Tomography

EFS – Early Feasibility Study

HALT – HypoAttenuated Leaflet Thickening

INR – International Normalized Ratio

KCCQ-12 – Kansas City Cardiomyopathy Questionnaire

LVEF – Left Ventricular Ejection Fraction

LVOT – Left Ventricular Outflow Tract

MR – Mitral Regurgitation

MVARC – Mitral Valve Academic Research Consortium

NYHA – New York Heart Association

PVL – Paravalvular Leak

SAP – Special Access Program

TEE – Transesophageal Echocardiography

TMVR – Transcatheter Mitral Valve Replacement

6MWT – 6 Minute Walk Test

INTRODUCTION

Mitral regurgitation (MR) is a common condition that is associated with significant morbidity and mortality (1, 2). Surgery is considered the standard therapy for degenerative MR, with repair generally preferred over replacement (3). The role of surgery for functional MR is less clear. Transcatheter mitral leaflet plication is now an established alternative for the treatment of both degenerative and functional MR (4, 5), but not all anatomies are ideally suited to leaflet repair. Furthermore, residual MR is common post mitral leaflet plication and greater degrees of residual MR have been associated with greater morbidity and mortality (6). Combining transcatheter mitral repair technologies (e.g. annuloplasty and plication), as with complex surgery, has been proposed (7, 8). However, combination transcatheter therapies may be complex and resource intensive with uncertain benefits.

Transcatheter mitral valve replacement (TMVR) offers an additional option in the treatment of patients with MR, particularly if they are at high or prohibitive risk for surgical intervention and are not well suited for transcatheter repair. Initial experience with TMVR has primarily involved a transapical approach (9). Recent experience with transseptal TMVR has been favourable (10). We report the first-in-human experience with the novel EVOQUE mitral valve replacement system (Edwards Lifesciences Inc., Irvine, CA, USA).

Study device:

The EVOQUE valve consists of a self-expanding nitinol frame, bovine pericardial leaflets, and fabric skirt to minimize paravalvular leak. The valve has a unique anchoring mechanism to utilize the annulus, leaflets and chords for secure placement in the anatomy. (Central Illustration). The valve is currently available in 44mm and 48mm sizes and is designed to be implanted using a transseptal approach.

The EVOQUE delivery system is 28Fr and is compatible with both valve sizes.

The system actively facilitates 3 planes of motion. Two planes of flexion facilitate crossing the inter-atrial septum and coaxial alignment within the mitral valve. An independent depth control allows for precise positioning at the level of the mitral annulus while maintaining coaxial alignment. The system is secured in a stabilizer stand to allow increased control during the procedure.

General anesthesia is utilized to facilitate real time procedural guidance by transesophageal echocardiography (TEE). Percutaneous femoral venous puncture is followed by a standard mid posterior transseptal puncture. A 12 Fr deflectable sheath (Oscor Inc., FL) is advanced into the left atrium to facilitate passage of a pigtail catheter and subsequently a 0.035” pre-curved guidewire (Safari Extra small, Boston Scientific Inc., MN) through the mitral valve and into the left ventricular apex. The atrial septum is dilated with a 14mm diameter balloon (Armada, Abbott Inc, CA) (Fig 1A). A wire free of entanglement in the subvalvular apparatus is confirmed by unconstrained passage of a balloon across the mitral valve to the left ventricular apex (Reliant, Medtronic Inc, CA) (Fig 1B).

The valve delivery system is then advanced over the guidewire using fluoroscopic guidance (Fig 1C). Transseptal access to the mitral valve and subsequent coaxial alignment are achieved by active anterior-posterior and septal-lateral flexion guided by real time 3D TEE. The procedure is heavily guided by iterative TEE guidance and in particular by real time 3D TEE to ensure appropriate alignment and positioning are achieved (Fig 2 A-C). Once the system has been advanced across the mitral valve annulus, the ventricular outflow portion of the valve is partially expanded by precisely controlled withdrawal of an outer restraining capsule (Fig 1 D-F). An independent depth control allows for controlled and precise movement of the ventricular anchors into position without loss of coaxial alignment. Further expansion of the outflow portion results in the ventricular anchors capturing the mitral leaflets and subvalvular apparatus. Capturing is monitored by TEE guidance to ensure that the anchors are optimally positioned and engaged in the mitral valve apparatus. The atrial inflow portion of the valve with its sealing skirt is subsequently expanded to facilitate sealing before release of the valve. Once deployed the delivery system is removed. The interatrial septum is interrogated by TEE to determine if closure of the septal puncture site is required. The femoral puncture site is closed with a previously placed percutaneous or subcutaneous suture.

METHODS

All patients treated with the EVOQUE system from September 2018 to October 2019 were included in this analysis. Patients were treated either in the Canadian special access program (SAP) or the US early feasibility study (EFS, NCT02718001) Eligibility criteria were ≥18 years old, with ≥ moderate MR and symptoms of heart failure [New York Heart Association (NYHA) Class ≥2]. All patients were reviewed by a multidisciplinary heart team and considered: 1) suitable for mitral valve intervention; 2) at high or prohibitive surgical risk as deemed by the local heart team; 3) not ideally suited to other available transcatheter mitral valve interventions (i.e. leaflet repair); 4) anatomically suitable for the EVOQUE device as determined by echocardiography and computed tomography (CT) analysis and 5) stable on heart failure medications for at least 30 days prior to procedure. Major exclusion criteria were left ventricular ejection fraction (LVEF) <30%, severe chronic kidney disease (creatinine >2.2mg/dL), other significant valvular heart disease, high risk of left-ventricular outflow (LVOT) obstruction as assessed by predicted neo-LVOT on CT (excluded if ≤1.5cm2), history of deep venous thrombosis or pulmonary embolism in the past 12 months and history of bleeding diathesis or coagulopathy.

Clinical follow-up and transthoracic echocardiography were performed in-hospital and at 30 days. One institution performed routine CT assessment at 30 days per institutional protocol. The primary outcome was technical success as defined by Mitral Valve Academic

Research Consortium (MVARC) criteria at completion of the index procedure upon exit from the catheterization laboratory, specifically: absence of procedural mortality; and successful access, delivery and retrieval of the device delivery system; and successful deployment and correct positioning of the first intended device; and freedom from emergency surgery or reintervention related to the device or access procedure. Secondary clinical and echocardiographic outcomes were defined as per MVARC criteria. Echocardiography analysis was performed by a core laboratory (Cardiovascular Core Lab at Morristown Medical Center, Morristown, NJ) in the EFS only, and by institutional cardiac imaging specialists in the SAP. Adverse events were adjudicated by an independent Data Monitoring Committee in the EFS and by the institution for the SAP. Procedure time was defined as femoral vein access to closure, and device time was defined as delivery system insertion to removal.

Research was conducted in compliance with the Declaration of Helsinki for human investigation. Patients provided written informed consent. Research approval was granted by the institutional ethics review board.

Statistics

Continuous data are presented as median (Q1, Q3); categorical variables are presented as count and percentage.

RESULTS

Fourteen patients were treated, 8 in SAP and 6 in EFS. Nine patients (64.3%) were male. Median age was 84 years. Median STS score was 4.6%. Nine patients (64.3%) had NYHA class ≥3 symptoms at baseline. Baseline clinical and echocardiographic characteristics are provided in Table 1.

MR was severe in 13 patients (92.9%) and moderate-severe in one patient (7.1%). MR etiology was classified as degenerative in 4 (28.6%), functional in 3 (21.4%) and mixed in 7 (50%). Median LVEF was 54%, 9 patients (64.3%) had LVEF ≥50% and the remaining 5 (35.7%) had LVEF of 30-49%.

Technical success was achieved in 13 patients (92.9%). One patient experienced severe paravalvular leak (PVL) post-implant resulting in conversion to surgical mitral valve replacement. Procedural characteristics can be seen in Table 2. Three patients had mild PVL post-implant, of which one was addressed with non-emergent PVL closure during the procedure at the discretion of the implanting physician to optimize result, successfully reducing PVL from mild to none. Immediate post-implant MR reduction to ≤ mild was achieved in 13 of 14 patients (92.9%). Within the implanted group, the mean mitral gradient immediately post-implant was 3mmHg (median). Eleven (78.6%) patients had atrial septal defect closure at the discretion of the implanting physician.

Thirty-day outcomes are presented in Table 3. One patient missed the 30-day visit and follow up was performed at 90 days, this patient is included in the 30-day analysis for completeness. The patient who underwent surgical mitral valve replacement had no subsequent adverse events and was NYHA Class I. There was one 30-day non-cardiovascular mortality (7.1%) due to pneumonia. There was one device-related ischemic stroke (7.1%) on post-operative day 1 with resolution at 30 days. There was one procedure-related disabling hemorrhagic stroke (7.1%) on post-operative day 2, also considered a life-threatening bleed, in a patient on anticoagulation for pre-existing atrial fibrillation. The patient was on therapeutic unfractionated heparin and aspirin at the time of the hemorrhagic stroke. There were 2 (14.3%) major bleeding complications. There was one requirement for permanent pacemaker insertion (7.1%) for development of complete heart block; this patient had a baseline bifascicular block. There was no myocardial infarction, rehospitalizations or renal failure requiring renal replacement therapy.

Two patients (14.3%) underwent PVL closure, one during the procedure as previously mentioned, and the other due to progression from mild to moderate PVL on post-procedure day 1, thereafter reduced to mild post-PVL closure and stable at 30 days. The third patient with mild PVL post-implant remained stable at 30 days without closure. Two patients had a peak post-procedural LVOT gradient >20mmHg, which was resolved with medical therapy in one patient, while one patient (7.1%) underwent successful alcohol-septal ablation on day 4 post-procedure.

Asymptomatic hypoattenuated leaflet thickening (HALT) was incidentally observed in 2 of 4 patients in the single institution performing routine 30-day CT assessment. One patient had inadvertently stopped anticoagulation, the other was on warfarin with a target international normalized ratio (INR) of 2-3 and was therapeutic. Both patients were in NYHA Class II and mean gradients were 7mmHg (6mmHg on discharge) and 5mmHg (5mmHg on discharge), respectively. The first patient was restarted on warfarin with complete resolution of leaflet thickening on CT at 6 months, sustained at one year, and mean gradient of 4mmHg at one year. The second patient was addressed by increasing target INR to 2.5-3.5 and the addition of 81mg aspirin, resulting in near-complete resolution at 6 months and stable mean gradient of 5mmHg.

MR was ≤ mild in implanted patients at 30-day follow up (n=12) including those with PVL closure, and 10 patients (83.3%) had no MR (Central Illustration).

Baseline and 30-day NYHA Class data were available in 11 implanted patients. Functional class improved to ≤ NYHA Class 2 in 9 patients (81.8%) (Central Illustration). Baseline and 30-day Kansas City cardiomyopathy questionnaire (KCCQ-12) data were available in 8 patients; median KCCQ-12 score increased from 36.2 points at baseline to 58.4 at 30 days.

DISCUSSION

This early experience has demonstrated the feasibility of the transseptal EVOQUE TMVR system in a high surgical-risk population including functional and degenerative MR. Good echocardiographic results were noted within successfully implanted cases. There was an improvement in patients' symptoms and functional capacity. These results are comparable to early experiences with other TMVR systems however given the small numbers within this study, direct comparison cannot be drawn (10-12). Furthermore, there is limited data from a transseptal approach which, although less invasive than a transapical approach, provides different technical challenges.

There have been some early learnings, in particular related to prediction of LVOT obstruction and PVL resulting in screening and procedural improvements. To reduce the risk of LVOT obstruction, further CT analysis is performed to predict risk with both optimal and sub-optimal positioning of the valve thereby offering a more complete assessment. Furthermore, manoeuvres have been developed to allow tilting of the valve to raise the anterior aspect of the valve away from the LVOT. Two patients had PVL ≥moderate requiring intervention (conversion to surgery or PVL closure) attributed to implant size mismatch or suboptimal final valve positioning, resulting in sizing and procedural refinements.

TMVR offers several potential advantages over transcatheter leaflet repair. Firstly, TMVR is applicable to a wider range of anatomies; for instance, mixed regurgitation and stenosis, calcified/rheumatic mitral valve disease, broad/multiple jets, large flails and leaflet perforations. In this and other studies of TMVR devices, the degree of MR reduction was greater than observed with edge-to-edge repair (10-13). Residual MR of ≥3+ at 12 months was present in 17% in the MitraFR trial and residual MR of ≥ 2+ at 12 months was present in 31% in the COAPT trial (4, 14). In the EVEREST II trial comparing transcatheter edge-to-edge repair versus surgical repair in degenerative MR, there was a high rate of surgical intervention at 5 years with higher rates in the transcatheter group as compared to surgical repair (27.9% vs. 8.9%; p = 0.003) (15). The long-term presence of residual MR after both surgical and transcatheter repair has been shown to be associated with poor late outcomes (16, 17). Therefore, TMVR may be preferable in patients in whom an optimal result would not be expected with leaflet repair.

There was evidence of HALT on routine 30-day CT scans in 2 out of 4 patients scanned at one institution. Since 30-day CT was not specified in the EFS protocol and not routinely performed in other institutions, the rate of leaflet thickening cannot be ascertained. In observed cases, leaflet thickening was not associated with a significant increase in transvalvular gradient and the clinical relevance of this is not known. One patient who had inadvertently ceased anticoagulation was restarted on warfarin with complete resolution of leaflet thickening on CT at 6 months, sustained at one year with mean gradient of 4mmHg. The other patient was addressed by increasing the target INR to 2.5-3.5 and the addition of 81mg aspirin, resulting in near-complete resolution with very minimal thickening evident at the tips of the leaflets at 6 months and stable mean gradient of 5mmHg. In recent analysis of the PARTNER 3 data, HALT was found in 13% of transcatheter heart valves and 5% of surgical valves at 30 days (p=0.03) but this had spontaneously resolved in 54% at one year (18). In the same analysis, HALT appeared in 21% of patients at 1 year who had no evidence of HALT at 30 days. There was no significant difference in HALT at one year between transcatheter and surgical valves (28% vs. 20%; p=0.19). The clinical significance of these findings is unclear and further investigation in regard to HALT’s impact on valve durability is required.

Optimal anticoagulation strategy following TMVR, or indeed post transcatheter valve replacement in any position, has not been established. In this analysis, post-implantation anticoagulation was administered in all patients, 10 (76.9%) with oral vitamin K antagonist and 3 (23.1%) with a direct oral anticoagulant. Seven (53.8%) of the 13 patients were treated with concomitant single antiplatelet therapy with planned continuation for 6 months. Of note, 13 of 14 patients (92.9%) had atrial fibrillation and therefore had pre-existing indications for anticoagulation prior to TMVR.

The EVOQUE device has a unique anchoring system which utilizes the annulus, leaflets and chords while respecting the native valve anatomy. The delivery system offers extensive maneuverability and stability resulting in a controlled deployment without hemodynamic compromise. These properties would make the system potentially applicable for treatment of tricuspid valve disease as recently reported (19).

LIMITATIONS

These early results comprise of SAP and EFS experience and may not be comparable to those within a controlled clinical trial. Numbers were small and long-term outcomes, including durability, are not available. A central core laboratory performed echocardiographic assessment in the EFS but not in the SAP. Similarly, a Data Monitoring Committee was used for assessment of adverse events in the EFS but not the SAP. The EFS continues to enroll and will provide further assessment of safety and clinical outcomes.

CONCLUSIONS

This first-in-human experience has demonstrated the feasibility of the transseptal EVOQUE TMVR system. TMVR is a welcome addition to the range of options available in the contemporary management of mitral valve disease. This transseptal approach to TMVR potentially offers advantages over a transapical approach. Continued clinical studies will continue to clarify its role within the armoury of mitral interventions.

PERSPECTIVES

WHAT IS KNOWN?

MR is a common condition carrying significant morbidity and mortality. Transcatheter technologies for mitral valve repair are expanding however not all anatomies are suitable and residual MR is common. Transcatheter mitral valve replacement represents an alternative to repair, and a transseptal approach has potential advantages compared to transapical TMVR.

WHAT IS NEW?

The EVOQUE valve is a novel self-expanding nitinol valve with bovine pericardial leaflets delivered via a less invasive transseptal approach. Fourteen patients were included in this first-in-human experience. Implant success was high (92.9%) with low complication rates at 30 days. MR was reduced to ≤ mild at 30 days in all implanted patients with no MR in over 80% and an improvement in functional class.

WHAT IS NEXT?

An ongoing early feasibility study will further investigate the safety and efficacy of the EVOQUE system. There is also promise for use in tricuspid valve disease.

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Baseline Characteristics (n=14)

FIGU

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LEGENDS

Figure 1. Transseptal EVOQUE mitral valve implantation.

(A) Transseptal puncture performed and preformed left ventricular guidewire placed in the apex. Septum dilated with 14mm diameter balloon. (B) Wire path confirmed with large balloon. (C) EVOQUE transcatheter mitral valve replacement system advanced into mitral annulus. (D) Ventricular portion deployed and anchors revealed. (E) Atrial expansion and valve release. (F) Final fluoroscopic image.

Figure 2. Transesophageal echocardiography.

(A) Severe mitral regurgitation at baseline as seen by color Doppler in mid-esophageal view. (B) Post-transseptal mitral valve replacement with the EVOQUE TMVR system. (C) 3D volume rendered image of the EVOQUE valve. In this case the septal access site has been closed.

Central Illustration – Transseptal EVOQUE mitral valve replacement system and 30-day outcomes (paired).

(A) EVOQUE transcatheter heart valve; self-expanding nitinol frame with bovine pericardial leaflets, intra-annular sealing skirt and ventricular anchors. (B) EVOQUE mitral delivery system; 28 Fr system with multiple planes of flexion and independent depth control. (C) Mitral regurgitation at baseline and 30-days post implant – paired analysis. (D) NYHA class at baseline and 30-days post implantation – paired analysis.

**Study cohort 14 patients: One patient converted to surgery, one patient mortality prior to 30-day follow-up. Two patients underwent PVL closure.*

Procedural Characteristics (n=14)	
Technical success – no (%)	13 (92.9%)
Death – no (%)	0 (0%)
Device embolization – no (%)	0 (0%)
Myocardial infarction – no (%)	0 (0%)

Diabetes – n (%)	2 (14.2%)
Coronary artery disease – n (%)	9 (64.3%)
Prior myocardial infarction – n (%)	3 (21.4%)
Prior PCI – n (%)	4 (28.6%)
COPD – n (%)	2 (14.2%)
Prior stroke/TIA – n (%)	0 (0%)
Chronic kidney disease (eGFR ≤ 60ml/min/1.73m^2) – n (%)	9 (64.3%)
Prior cardiac surgery – n (%)	6 (42.9%)
Atrial fibrillation/flutter – n (%)	13 (92.9%)
NYHA Class – n (%) - I - II - III - IV	 0 (0%) 5 (35.7%) 9 (64.3%) 0 (0%)
KCCQ-12 score (n=8)	36.2 (24.9, 48.8)
LVEF – %	54 (43.5, 60)
LVEDD – mm	56 (51.3, 59)
Severe MR – n (%)	13 (92.9%)
MR classification – n (%) - Functional - Degenerative - Mixed	 3 (21.4%) 4 (28.6%) 7 (50%)

Table 1. Baseline characteristics. *STS; Society of Thoracic Surgery, PCI; Percutaneous Coronary Intervention, COPD; Chronic Obstructive Pulmonary Disease, TIA; Transient Ischemic Attack, eGFR; Estimated Glomerular Filtration Rate, NYHA; New York Heart Association, KCCQ-12; Kansas City Cordiomoyopathy Questionnaire-12, LVEF; Left Ventricular Ejection Fraction, LVEDD; Left Ventricular End Diastolic dimension, MR; Mitral Regurgitation*

30-Day Outcomes (n=14)	
Death – no (%)	1 (7.1%)
Conversion to surgery – no (%)	1 (7.1%)
Myocardial infarction – no (%)	0 (0%)
Stroke – no (%)	
- Disabling	1 (7.1%)
- Non-disabling	1 (7.1%)
Rehospitalization – no (%)	0 (0%)
Permanent pacemaker – no (%)	1 (7.1%)
PVL closure – no (%)	2 (14.3%)
Acute kidney injury (MVARC) – no (%)	
- Stage I	0 (0%)
- Stage II	0 (0%)
- Stage III†	3 (21.4%)
Bleeding (MVARC) – no (%)	
- I - Minor	
- II -Major	1 (7.1%)
- III - Extensive	2 (14.3%)

Table 2. Procedural characteristics. *PVL; Paravalvular Leak, ASD; Atrial Septal Defect, MR; Mitral Regurgitation*

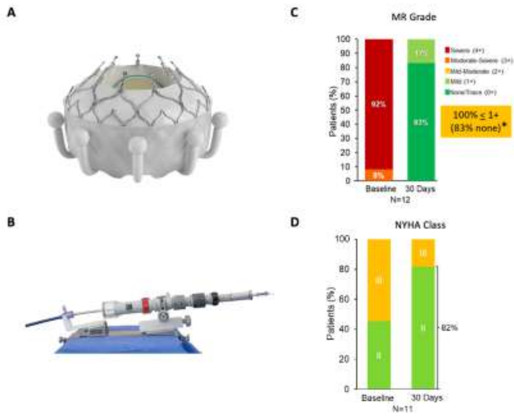
† *PVL Non-emergent, elective closure performed for mild PVL for optimization of result,* * Femoral vein access to femoral vein closure, ** *Delivery system insertion to removal*

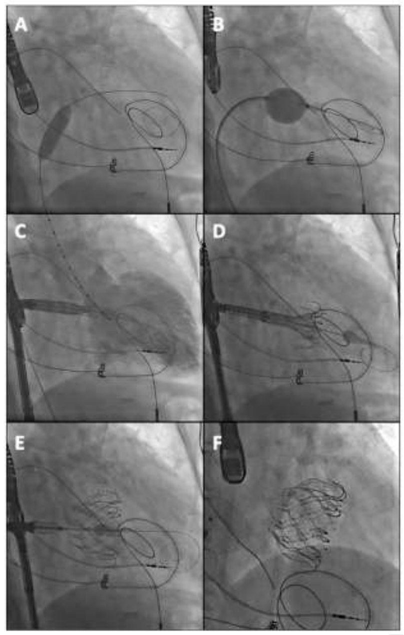
- IV - Life-threatening - V - Fatal	0 (0%) 1 (7.1%)* 0 (0%)
Hypoattenuated leaflet thickening – no - Subclinical - Clinical	 2 0
NYHA Class (n=11) – no (%) - I - II - III - IV	 0 (0%) 9 (81.8%) 2 (18.2%) 0 (0%)
KCCQ-12 score (n=8)	58.4 (34.6, 72)
LVEF (n=12) – %	43.5 (38, 51.5)
LVEDD (n=11) – mm	59 (56, 61.5)
MR grade ≤ mild (n=12) – no (%)	12 (100%)
Mean mitral gradient (n=12) - mmHg	5.8 (5, 6.8)
PVL ≤ mild (n=12) – no (%)	12 (100%)
LVOT peak gradient (n=12) - mmHg	8.2 (4.3, 12.3)
LVOT obstruction requiring intervention	1 (7.1%)**

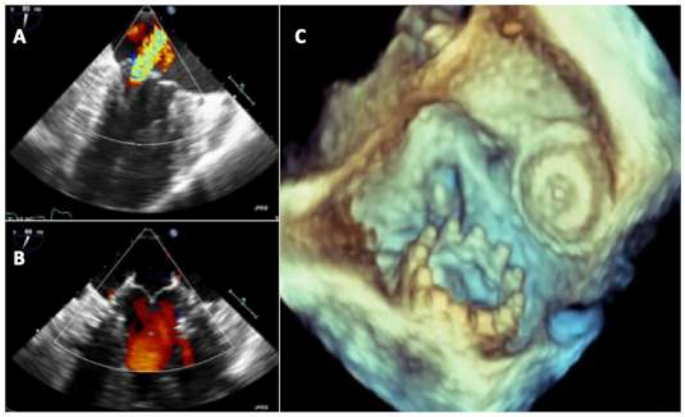
Table 3. 30-Day outcomes.

PVL; Paravalvular Leak; MVARC; Mitral Valve Academic Research Consortium, NYHA; New York Heart Association, KCCQ; Kansas City Cardiomyopathy Questionnaire, LVEF; Left Ventricular Ejection Fraction, LVEDD; Left Ventricular End Diastolic dimension, MR; Mitral Regurgitation, PVL; Paravalvular Leak, LVOT; Left Ventricular Outflow Tract

*† No requirement for dialysis, * Represents hemorrhagic stroke, **Septal ablation day 4 with normalization of LVOT gradient*


A
B
C
MR Grade
Patients (%)
92%
8%
83%
17%
Baseline
30 Days
N=12
100% ≤ 1+
(83% none)*
D
NYHA Class
Patients (%)
III
II
82%
Baseline
30 Days
N=11


A
B
C
D
E
F


A
B
C