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Transcatheter Mitral Valve Replacement for Patients With Symptomatic Mitral Regurgitation

A Global Feasibility Trial

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on behalf of the Tendyne Global Feasibility Trial Investigators

ABSTRACT

BACKGROUND Symptomatic mitral regurgitation (MR) is associated with high morbidity and mortality that can be ameliorated by surgical valve repair or replacement. Despite this, many patients with MR do not undergo surgery. Transcatheter mitral valve replacement (TMVR) may be an option for selected patients with severe MR.

OBJECTIVES This study aimed to examine the effectiveness and safety of TMVR in a cohort of patients with native valve MR who were at high risk for cardiac surgery.

METHODS Patients underwent transcatheter, transapical delivery of a self-expanding mitral valve prosthesis and were examined in a prospective registry for short-term and 30-day outcomes.

RESULTS Thirty patients (age 75.6 ± 9.2 years; 25 men) with grade 3 or 4 MR underwent TMVR. The MR etiology was secondary (n = 23), primary (n = 3), or mixed pathology (n = 4). The Society of Thoracic Surgeons Predicted Risk of Mortality was 7.3 ± 5.7%. Successful device implantation was achieved in 28 patients (93.3%). There were no acute deaths, strokes, or myocardial infarctions. One patient died 13 days after TMVR from hospital-acquired pneumonia. Prosthetic leaflet thrombosis was detected in 1 patient at follow-up and resolved after increased oral anticoagulation with warfarin. At 30 days, transthoracic echocardiography showed mild (1+) central MR in 1 patient, and no residual MR in the remaining 26 patients with valves in situ. The left ventricular end-diastolic volume index decreased (90.1 ± 28.2 ml/m^2 at baseline vs. 72.1 ± 19.3 ml/m^2 at follow-up; p = 0.0012), as did the left ventricular end-systolic volume index (48.4 ± 19.7 ml/m^2 vs. 43.1 ± 16.2 ml/m^2; p = 0.18). Seventy-five percent of the patients reported mild or no symptoms at follow-up (New York Heart Association functional class I or II). Successful device implantation free of cardiovascular mortality, stroke, and device malfunction at 30 days was 86.6%.

CONCLUSIONS TMVR is an effective and safe therapy for selected patients with symptomatic native MR. Further evaluation of TMVR using prostheses specifically designed for the mitral valve is warranted. This intervention may help address an unmet need in patients at high risk for surgery. (Early Feasibility Study of the Tendyne Mitral Valve System [Global Feasibility Study]; NCT02321514) (J Am Coll Cardiol 2017;69:381–91) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CT = computed tomography

LV = left ventricular/ventricle

LVEDVI = left ventricular end-diastolic volume index

LVESVI = left ventricular end-systolic volume index

LVOT = left ventricular outflow tract

MR = mitral valve regurgitation

NYHA = New York Heart Association

STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality

TEE = transesophageal echocardiography

TMVR = transcatheter mitral valve replacement

TTE = transthoracic echocardiography

Mitral valve regurgitation (MR) is common, with an estimated prevalence of 2 to 4 million people in the United States alone (1,2). The prevalence is age-dependent, affecting >6% of those age >65 years, and is expected to increase with current demographic trends. The prognosis of untreated MR is poor, with progressive left ventricular (LV) dilation, myocardial dysfunction, and cardiac failure, leading to substantial morbidity and mortality, and a considerable economic burden (3–6). Despite current practice guidelines, which advocate surgery for patients with symptoms or LV systolic dysfunction, the majority of patients with severe MR do not undergo surgery (7–11). The reasons include high surgical risk from advanced age or multiple comorbidities, and a lack of clear data supporting valve surgery for secondary MR with LV dysfunction (7,8,11).

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Over the past decade, transcatheter valve replacement has emerged as a therapy for selected patients with valvular heart disease (12–15), particularly those with severe aortic valve stenosis. Although transcatheter aortic valve replacement has become the standard of care for high surgical risk patients with aortic stenosis, the regurgitant mitral valve poses unique challenges for successful transcatheter therapy. The valve is noncircular, relatively large, dynamic in shape, usually noncalcified, and subject to cyclical, high LV systolic pressures. In addition, the subvalvular apparatus is complex, is variable in anatomy, and lies in close proximity to the LV outflow tract (LVOT). Clinical experience with transcatheter mitral valve replacement (TMVR) has been limited to date and provides little insight into its potential as a viable therapy for MR (16–19).

This prospective study examined the feasibility of TMVR using a self-expanding prosthesis in symptomatic patients with native MR who were at high risk for cardiac surgery.

METHODS

PATIENT POPULATION. This Global Feasibility Study (NCT02321514) enrolled patients at 8 study sites in Australia, the United States, and Norway between November 2014 and March 2016 (the Online Appendix contains participating sites and investigators). The study was conducted in compliance with the Declaration of Helsinki for human investigation under an Investigational Device Exemption, with individual institutional review board approval at each site. Inclusion criteria for the study were: age ≥18 years, MR grade 3 or 4 (primary or secondary), symptoms of dyspnea (New York Heart Association [NYHA] functional class ≥II), and ability to provide informed consent. Exclusion criteria were: LV end-diastolic diameter >70 mm, severe mitral annular or leaflet calcification, left atrial or LV thrombus, prior mitral or aortic valve surgery, prior transcatheter mitral intervention, pulmonary artery systolic pressure ≥70 mm Hg, severe tricuspid regurgitation, and severe right ventricular dysfunction with evidence of right heart failure. The data coordinating center excluded patients if the LVEF at the time of their qualifying transthoracic echo was <30%. However, 3 patients who were accepted as meeting all the inclusion criteria were subsequently found to have an EF <30% at the time of the intervention. These 3 patients were not disqualified. Patients who had cardiac

board member and consultant to Medtronic, Boston Scientific, and Edwards Lifesciences; has received research grant support from Tendyne Holdings, Abbott Vascular, and Medtronic; and is a proctor for Medtronic and Abbott Vascular. Dr. Farivar is a medical advisory board member and consultant to Edwards Lifesciences, Abbott Vascular, and Medtronic. Dr. Walters is an advisory board member for Edwards Lifesciences and Boston Scientific; a proctor for Abbott Vascular and Edwards Lifesciences; a consultant for Abbott Vascular; and has received research funding from Abbott Vascular. Dr. Grayburn is a consultant to Abbott Vascular, Edwards Lifesciences, Tendyne Holdings, Valtech Cardio, and NeoChord; has received research grants from Abbott Vascular, Boston Scientific, Medtronic, Edwards Lifesciences, Valtech Cardio, Tendyne Holdings, and NeoChord; and has provided echocardiography core lab support for NeoChord and Valtech. Dr. Stoler is an advisory board member and proctor for Medtronic and Boston Scientific. Dr. Guerrero is a proctor for and has received research grant support from Edwards Lifesciences; and is a consultant to Tendyne Holdings, and Edwards Lifesciences. Dr. Gillinov is a consultant to Abbott, Edwards Lifesciences, Medtronic, AtriCure, and CryoLife. Dr. Popma has received institutional grant support from Medtronic, Boston Scientific, Abbott Vascular, and Direct Flow Medical; is on the medical advisory board of Boston Scientific; and has equity in Direct Flow Medical. Dr. Blanke has received institutional grant support from Neovasc; and is a consultant for Tendyne Holdings, Edwards Lifesciences, and Circle Cardiovascular Imaging. Dr. Leipsic has received institutional grant support from Neovasc; is a consultant for Edwards Lifesciences and Circle Cardiovascular Imaging; and through the University of British Columbia, provides core laboratory support for Tendyne Holdings, Edwards Lifesciences, Neovasc, and Medtronic. Dr. Sorajja is a consultant to Abbott Vascular, Medtronic, Boston Scientific, and Lake Regions Medical; and has received institutional grant support from Abbott Vascular.

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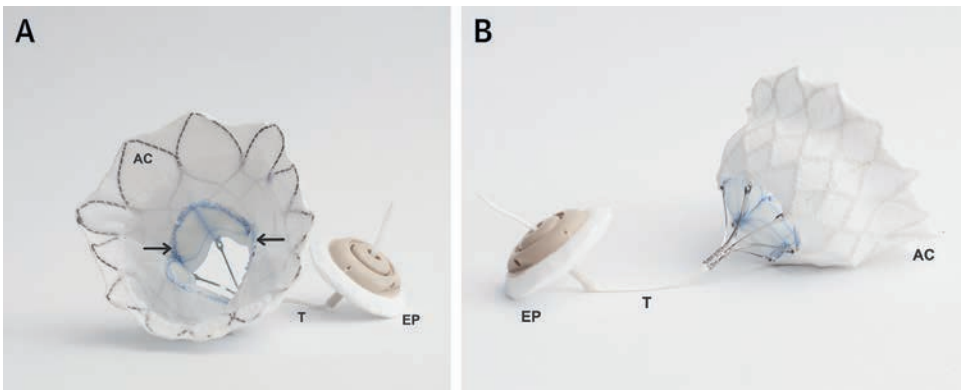
FIGURE 1 The Valve Prosthesis



En face **(A)** and longitudinal **(B)** views of the Tendyne transcatheter mitral valve (Tendyne Holdings, LLC, a subsidiary of Abbott Vascular, Roseville, Minnesota). The self-expanding prosthesis has an outer frame with a cuff (AC) that rests against the anterior left atrial wall and aorta. The inner frame **(black arrows)** houses the valve leaflets. The prosthesis is anchored to an epicardial pad (EP) by a tether (T).

resynchronization therapy were ineligible for inclusion until ≥3 months after their index event. Patients with an acute myocardial infarction were ineligible for 30 days. The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) and EuroSCORE II scores were calculated for each patient using online tools. All patients were evaluated by local multidisciplinary heart teams consisting of cardiologists, cardiothoracic surgeons, anesthesiologists, and imaging specialists, and were considered to be high risk for mitral valve surgery.

ECHOCARDIOGRAPHY. Comprehensive screening transthoracic (TTE) and transesophageal echocardiography (TEE) was performed using 2- and 3-dimensional imaging, paying particular attention to the mitral apparatus and mechanism of MR, LVOT dimensions and orientation, and the presence of systolic anterior motion of the anterior mitral leaflet. All images were evaluated at a core echocardiographic laboratory (Beth Israel Deaconness Medical Center, Boston, Massachusetts).

CARDIAC COMPUTED TOMOGRAPHY. Contrast-enhanced cardiac computed tomography (CT) images were also examined in a core laboratory (St. Paul's Hospital, Vancouver, British Columbia, Canada) for screening and procedure planning. CT examinations were performed using retrospectively electrocardiogram-synchronized, multiphase protocols. Mitral annular segmentation was performed, yielding a D-shaped mitral orifice contour with the following parameters: annular area, perimeter, septal-to-lateral and intercommissural diameters, and degree of mitral annular calcification (20). These data were used to select prosthesis size, identify the LV myocardial entry site, and evaluate the potential for LVOT obstruction.

THE TRANSCATHETER MITRAL VALVE SYSTEM. The Tendyne Mitral Valve System (Tendyne Holdings, LLC, a subsidiary of Abbott Vascular, Roseville, Minnesota) is constructed from self-expanding nitinol with a double-frame design (Figure 1). The inner frame of the prosthesis is circular and supports a trileaflet porcine pericardial valve with an effective orifice area >3.2 cm^2. The size of the outer (sealing) frame ranges from 30 to 43 mm in the septal-lateral dimension and 34 to 50 mm in the intercommissural dimension. Implanted valves are selected to be larger than the native mitral orifice (extent of oversizing subject to ongoing evaluation). The valve is D-shaped to conform to the anatomic shape of the mitral orifice. It has a porcine pericardial covering and a polyethylene terephthalate cuff to aid valve sealing in the mitral annulus. Anteriorly, the cuff of the outer frame extends above the plane of the annulus, abutting the anterior atrial wall and aortomitral continuity.

TRANSCATHETER MITRAL VALVE REPLACEMENT. The procedure is performed under general anesthesia through a left lateral mini-thoracotomy. The site for LV apical access and optimal coaxial alignment is derived from the pre-procedural cardiac CT and intraprocedural TEE as described earlier in the text. After pledgeted purse-string sutures are placed, a 34-F delivery sheath is inserted over a 0.035-inch guidewire, ensuring there is no entanglement with the mitral subvalvular apparatus. The prosthesis is introduced through the sheath, partially unsheathed

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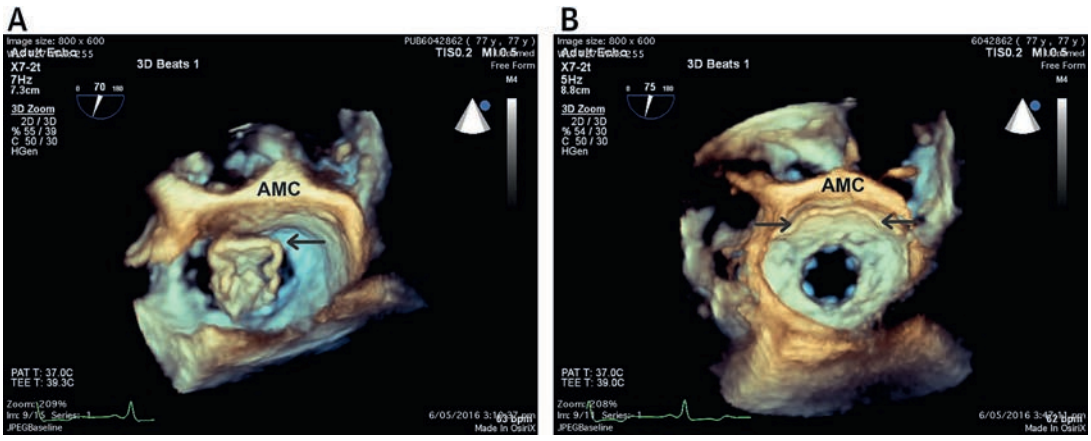
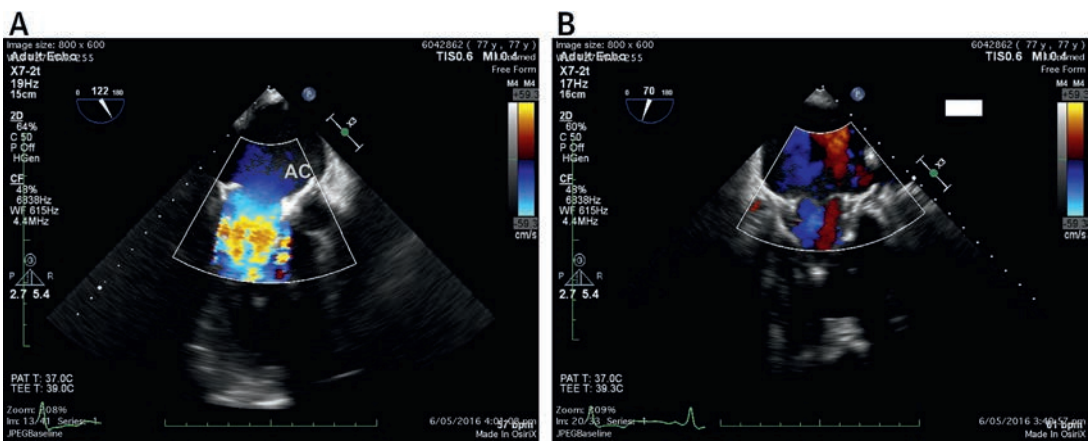
FIGURE 2 Transcatheter Mitral Valve Implantation



Three-dimensional transesophageal echocardiography image (surgeon's view) demonstrating partial deployment **(A)** and final position **(B)** of the valve prosthesis. The straight edge of the anterior cuff **(arrows)** is aligned with the aortomitral curtain (AMC) as the device is unsheathed **(A)**.

in the left atrium, aligned with the aortomitral continuity using TEE, and retracted until the cuff of the device rests on the floor of the left atrium (Figure 2). The remainder of the prosthesis is deployed within the annulus and secured with a braided, high-molecular-weight polyethylene tether that is attached to an epicardial pad (Figure 1). The tension of the tether is adjusted after deployment to optimize the seating of the prosthesis and to minimize movement of the device within the annulus (Figure 3). If the function of the prosthesis is not acceptable, or LVOT obstruction occurs, it can be recaptured and repositioned or fully retrieved. The procedure is performed without cardiopulmonary bypass and without rapid ventricular pacing. Left ventriculography may be performed to assess MR severity, but is not required for prosthesis placement. Post-procedurally, all patients were treated with aspirin (81 to 100 mg daily) or clopidogrel (75 mg daily), and were anticoagulated with heparin followed by warfarin for ≥3 months, with a target international normalized ratio of 2.5 to 3.5.

FIGURE 3 Post-Deployment Images



Transesophageal echocardiogram (Doppler color flow) showing laminar flow in diastole **(A)** and no mitral regurgitation in systole **(B)**. The anterior cuff (AC) lies to the right against the atrial wall.

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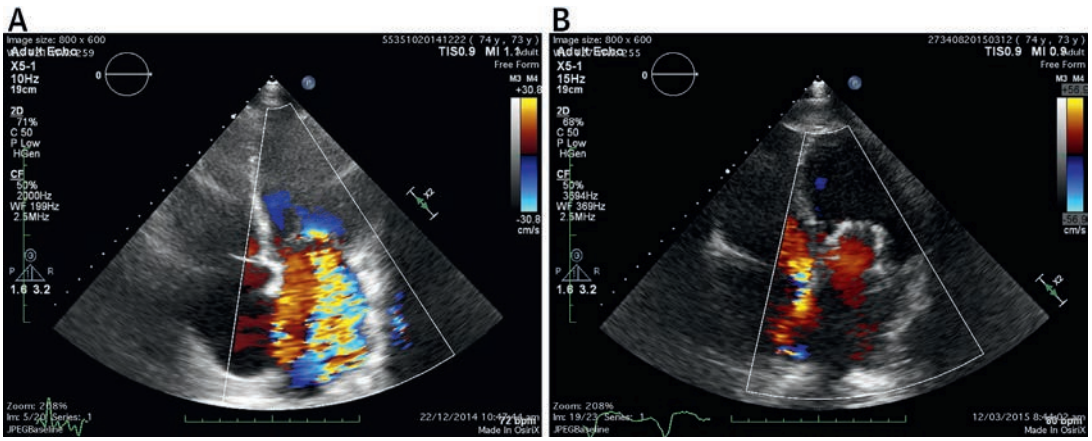
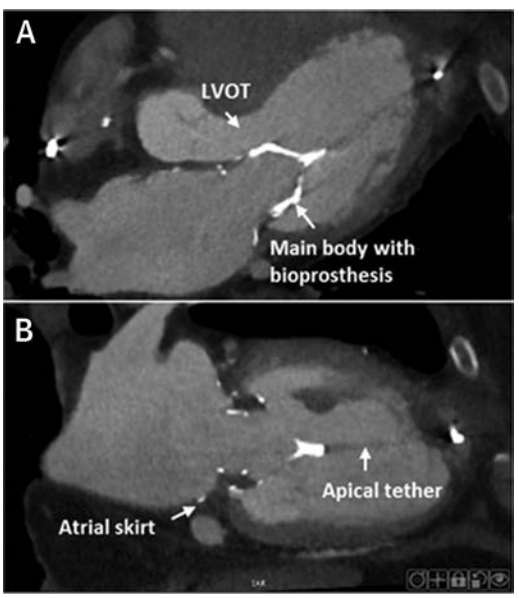
FIGURE 4 Baseline and 30-Day Follow-Up TTE



Severe secondary mitral regurgitation (MR) at baseline **(A)**, with no MR at 30-day follow-up **(B)**. TTE = transthoracic echocardiography.

DATA ANALYSIS AND STUDY ENDPOINTS. Clinical follow-up was performed at 30 days for all patients. Imaging studies were performed using the same parameters as at baseline (Figures 4 and 5), and were analyzed at the independent core laboratories. Clinical events were adjudicated by an independent clinical events committee. The primary performance endpoint for the study was successful device implantation and freedom from cardiovascular mortality, stroke, and device dysfunction (MR grade >1, mitral gradient >6 mm Hg, LVOT gradient >20 mm Hg, and paravalvular leak) at 30-day follow-up. Pre-specified secondary performance endpoints at 30-day follow-up were MR severity, change in left ventricular end-diastolic volume index (LVEDVI), change in left ventricular end-systolic volume index (LVESVI) and changes in NYHA functional class, 6-min walk distance, and Kansas City Cardiomyopathy Questionnaire score. The primary safety endpoint was 30-day freedom from major adverse events including cardiovascular mortality, disabling stroke, myocardial infarction, reintervention for valve-related dysfunction, life-threatening bleeding (BARC [Bleeding Academic Research Consortium] type 2, 3, or 5), and renal failure requiring dialysis. Stroke and myocardial infarction were defined according to the Mitral Valve Academic Research Consortium criteria (21,22). Periprocedural bleeding was defined according to the BARC criteria (23). Other pre-specified variables were rehospitalization for heart failure and reintervention for valve dysfunction at any time during follow-up.

FIGURE 5 ECG-Gated, Contrast CT Showing Position of the Prosthesis in the LVOT and Intercommissural Views



(A) LVOT and **(B)** intercommissural views. The device is anchored by the tether to the epicardial pad **(arrow)**. CT = computed tomography; ECG = electrocardiogram; LVOT = left ventricular outflow tract.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD. Categorical variables are presented as number and percentage of observed data. Comparisons between baseline and 30-day parameters were made using the Wilcoxon signed rank test. A 2-tailed probability of <0.05 was considered

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TABLE 1 Baseline Patient Characteristics and Comorbidities

Age, yrs	75.6 ± 9.2
Sex	
Male	83.3 (25/30)
Female	16.7 (5/30)
Comorbidities	
Diabetes mellitus	36.7 (11/30)
Chronic kidney disease, eGFR <60 ml/min	56.7 (17/30)
Chronic obstructive pulmonary disease	33.3 (10/30)
Atrial fibrillation	56.7 (17/30)
Prior stroke	6.7 (2/30)
Prior myocardial infarction	53.3 (16/30)
Body mass index, kg/m^2	27.2 ± 5.8
Prior treatment	
Prior percutaneous revascularization	26.7 (8/30)
Prior coronary artery bypass surgery	46.7 (14/30)
Prior ICD/BiV PPM	50.0 (15/30)
STS predicted risk of mortality, %	7.3 ± 5.7 (30)
EuroSCORE II, %	6.5 ± 5.0 (27)
Medications	
ACE inhibitors, ARBs, or vasodilators	53.3 (16/30)
Aspirin or antiplatelet agent	80.0 (24/30)
Oral anticoagulant	46.7 (14/30)
Beta-receptor antagonist	76.7 (23/30)
Calcium-channel blocker	0.0 (0/30)
Digoxin	13.3 (4/30)
Diuretics	80.0 (24/30)
Statin	46.7 (14/30)
Inotropes	0.0 (0/30)
NYHA functional class	
I	0.0 (0/30)
II	46.7 (14/30)
III	53.3 (16/30)
IV	0.0 (0/30)

Values are mean ± SD, % (n/N), or mean ± SD (N).
ACE = angiotensin-converting inhibitor; ARB = angiotensin receptor blocker; BiV PPM = biventricular permanent pacemaker; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons.

TABLE 2 Baseline Echocardiography Parameters

Mitral valve pathology	
Primary	10.0 (3/30)
Secondary	76.7 (23/30)
Mixed	13.3 (4/30)
Severity of mitral regurgitation	
None/trivial	0.0 (0/29)
1+	0.0 (0/29)
2+	0.0 (0/29)
3+	6.9 (2/29)
4+	93.1 (27/29)
Mitral mean gradient, mm Hg	2.8 ± 1.5 (24)
LV dimensions	
LV end-diastolic diameter, cm	6.1 ± 0.5 (28)
LV end-systolic diameter, cm	4.9 ± 0.6 (28)
LV end-diastolic volume index, ml/m^2	90.1 ± 28.2 (24)
LV end-systolic volume index, ml/m^2	48.4 ± 19.7 (24)
LVEF	47.1 ± 9.2 (29)
<30%	10.3 (3/29)
30%-50%	48.3 (14/29)
>50%	41.4 (12/29)

Values are % (n/N) or mean ± SD (N).
LV = left ventricular; LVEF = left ventricular ejection fraction.

statistically significant. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. The study cohort consisted of 30 patients (age 75.6 ± 9.2 years, range 55.1 to 91.4 years). There were 25 men (83.3%). The procedural volume per study site ranged from 1 to 10 cases, with 3 sites treating ≥2 patients. All patients were symptomatic with multiple comorbidities (Table 1). The mean STS-PROM was 7.3 ± 5.7% (range 2.0% to 30.0%). MR severity was grade 4 in 93.1% and grade 3 in 6.9%. A majority of the patients (76.7%) had secondary MR due to ischemic chordal tethering (52.2%) or failure of leaflet coaptation (47.8%). LV dimensions were moderately enlarged (LV end-diastolic dimension 6.1 ± 0.5 cm; LVEDVI 90.1 ± 28.2 ml/m^2; LVESVI 48.4 ± 19.7 ml/m^2). LV systolic function was moderately impaired (LVEF 30% to 50%) in 48.3% and severely impaired (LVEF <30%) in 10.3% (Table 2). CT analysis showed a baseline mitral annular area of 11.8 ± 1.9 cm^2 (range 8.1 to 15.3 cm^2), a perimeter of 126.1 ± 9.9 mm (range 107.0 to 144.0 mm), septal-lateral diameter of 33.1 ± 3.4 mm (range 26.0 to 41.7 mm), and an intercommissural diameter of 41.7 ± 3.3 mm (range 36.2 to 47.2 mm).

PROCEDURAL OUTCOMES. A mitral prosthesis was successfully implanted in 28 of the 30 patients (93.3%). In these 28 patients, the residual MR (valvular or paravalvular) was grade 0 in all but 1 patient and there was no LVOT obstruction (peak gradient all <5 mm Hg). There was no device embolization or cardiac perforation. No patient required mechanical circulatory support, but 1 patient required intraoperative direct current cardioversion for ventricular tachycardia before instrumentation of the LV. Intraprocedural inotropic support was used in 26 procedures (86.7%), and was discontinued early in the post-operative period in all but 1 patient (3.7%), who required treatment for >7 days. For the entire 30-patient cohort, the mean device time, defined as time from apical entry of the delivery sheath to application of the apical tether pad, was 33.2 ± 13.3 min (range 9.0 to 78.0 min). The total procedure time, defined as time from first skin

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incision to final wound closure, was 135.8 ± 30.4 min (range 73.0 to 197.0 min).

In 3 patients, prostheses were retrieved through the delivery sheath without complications and without increasing the original MR severity. In 1 patient, an initial deployment attempt resulted in subluxation of part of the cuff below the mitral annulus, necessitating retrieval. This was followed by successful placement of a larger prosthesis. In a second patient, the prosthesis was implanted with no residual MR, but systolic anterior motion of the anterior mitral leaflet occurred with LVOT obstruction (peak gradient 80 mm Hg) that persisted despite repositioning of the device. In another patient, the prosthesis could not be seated appropriately as the ventricular access point was not coaxial to the plane of the mitral annulus. In the latter 2 patients, the prostheses were retrieved without incident and were not replaced.

In 1 additional patient, the prosthesis was inadvertently deployed with the anterior margin of the device oriented posteriorly. The incorrect valve orientation was not recognized until after full release of the valve, and closure of the apical access. This was associated with a mild posterior paravalvular leak, with no evidence of regurgitant flow through the prosthetic valve itself.

IN-HOSPITAL OUTCOMES. In the entire cohort (n = 30), there was 1 death, which occurred 13 days post-operatively due to hospital-acquired pneumonia and respiratory failure (Table 3). Repeat echocardiography showed no evidence of prosthesis dysfunction. There were no strokes, no myocardial infarctions, and no additional device-related complications during hospitalization. Three patients (10%) required blood transfusion for access-site bleeding, and 1 required transfusion for paravalvular leak-related hemolysis. Three patients with existing chronic renal impairment had a transient decline in renal function. Two patients with normal baseline renal function had acute kidney injury caused by hemodynamic instability or high contrast use. One of the latter 2 patients required temporary dialysis. No patient developed complete atrioventricular block or required permanent pacing, but new left bundle branch block occurred in 2 patients. One patient developed new-onset atrial fibrillation. Nineteen patients (65.5%) were discharged home. The remainder were transferred to an extended care facility for further rehabilitation. The time to hospital discharge was 9.7 ± 5.9 days (range 5 to 35 days).

30-DAY OUTCOMES. No additional deaths occurred during the 30-day follow-up period (Table 3). Repeat TTE was performed in 26 of the 27 living patients with a prosthesis in situ and showed MR grade 0 in all but 1 patient (96.2%), who had mild (1+) centrally directed regurgitation (Central Illustration, panel A). No patient had paravalvular regurgitation documented. The patient with an incorrectly oriented device had evidence of ongoing hemolysis biochemically, and was assumed to have a residual paravalvular leak that was not evident by TTE. There was no device migration, embolization, or conversion to mitral surgery. Four patients were rehospitalized for heart failure. One patient, whose anticoagulation was subtherapeutic (international normalized ratio = 1.5), had a mean mitral gradient of 10 mm Hg at 30-day follow-up echocardiography, and evidence of leaflet thrombosis on CT imaging. Following intensification of the oral anticoagulation, complete resolution of the thrombus occurred on CT with normal function of the prosthesis documented by TTE (mean gradient <5 mm Hg). Overall, successful device implantation free of cardiovascular death, stroke, and device dysfunction at 30 days was 86.7%. Freedom from

TABLE 3 30-Day Clinical Outcomes

Death	
Cardiovascular	0.0 (0/30)
Noncardiovascular	3.3 (1/30)
Stroke	
Disabling	0.0 (0/30)
Nondisabling	0.0 (0/30)
Myocardial infarction	0.0 (0/30)
Bleeding (BARC classification)	
Type 2	6.7 (2/30)
Type 3	0.0 (0/30)
Type 4	3.3 (1/30)
Type 5	0.0 (0/30)
Acute renal insufficiency	
Not requiring dialysis	13.3 (4/30)
Requiring dialysis	3.3 (1/30)
Sepsis	
Cardiac	0.0 (0/30)
Noncardiac	10.0 (3/30)
Arrhythmia	
New-onset atrial fibrillation	3.3 (1/30)
New LBBB	10.0 (3/30)
Ventricular arrhythmia	0.0 (0/30)
Prosthesis dysfunction	
Thrombosis	3.3 (1/30)
Embolism or migration	0.0 (0/30)
Hemolysis	3.3 (1/30)
Mitral valve surgery	0.0 (0/30)
Rehospitalization for heart failure	13.8 (4/29)

Values are % (n/N).

BARC = Bleeding Academic Research Consortium; LBBB = left bundle branch block.

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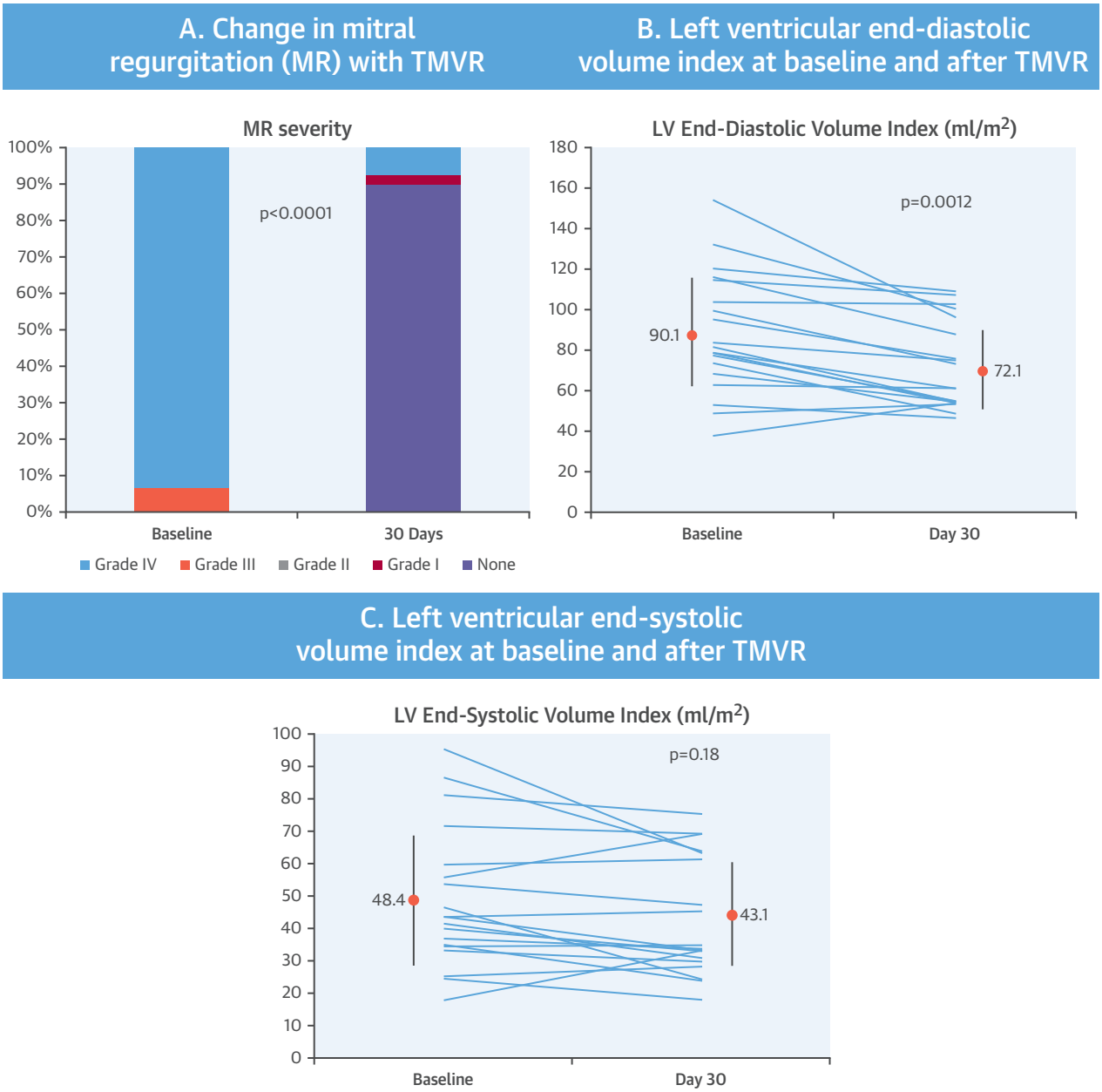
CENTRAL ILLUSTRATION **Change in Mitral Regurgitation and LV Volumes After TMVR**



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(A) Change in mitral regurgitation (MR) with transcatheter mitral valve replacement (TMVR). Of the 30 patients treated, 26 had successful transcatheter mitral valve implantation with no MR at 30-day follow-up. One patient had mild central MR. One patient with a successful implant and no MR died on day 13. Two patients with unsuccessful device implantation had residual grade 4 MR. **(B)** Left ventricular (LV) end-diastolic volume index at baseline and after transcatheter mitral valve implantation (day 30). Individual patient data are shown. **(C)** LV end-systolic volume index at baseline and after transcatheter mitral valve implantation (day 30). Individual patient data are shown. **Vertical lines** represent standard deviations of the means.

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TABLE 4 Echocardiographic and Functional Outcomes at Day 30 in Survivors With Valve In Situ

Mitral regurgitation severity	
None	96.2 (25/26)
1+	3.8 (1/26)
2+	0.0 (0/26)
3+	0.0 (0/26)
4+	0.0 (0/26)
Mitral valve gradient, mm Hg	3.4 ± 1.7 (25)
LVOT gradient, mm Hg	1.9 ± 0.7 (24)
LV dimensions	
End-diastolic diameter, cm	6.1 ± 0.7 (26)
End-systolic diameter, cm	4.9 ± 0.8 (26)
End-diastolic volume index, ml/m^2	72.1 ± 19.3 (24)
End-systolic volume index, ml/m^2	43.1 ± 16.2 (24)
LVEF	41.3 ± 9.5 (25)
<30%	16.0 (3/25)
30%-50%	68.0 (17/25)
>50%	16.0 (4/25)
NYHA functional class	
I	25.0 (7/28)
II	50.0 (14/28)
III	17.9 (5/28)
IV	7.1 (2/28)
6MWT, m	294.4 ± 136.9 (22)
KCCQ	64.6 ± 26.3 (27)

Values are % (n/N) or mean ± SD (N).

6MWT = 6-min walk test; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVOT = left ventricular outflow tract; other abbreviations as in Tables 1 and 2.

major adverse events, the primary safety endpoint, was 83.3%.

Echocardiography showed a reduction in LVEF (47.1 ± 9.2% at baseline vs. 41.3 ± 9.5% at 30 days; p = 0.043). LVEDVI decreased significantly (90.1 ± 28.2 ml/m^2 at baseline vs. 72.1 ± 19.3 ml/m^2 at 30 days; p = 0.0012). The LVESVI was 48.4 ± 19.7 ml/m^2 at baseline vs. 43.1 ± 16.2 ml/m^2 at 30 days (p = 0.18) (**Central Illustration, panels B and C**). The mean mitral gradient in patients with a device in situ was 3.4 ± 1.7 mm Hg. The LVOT gradient was 1.9 ± 0.7 mm Hg. NYHA functional class improved with mild or no symptoms (class I to II) reported in 75.0% (**Table 4**). There was no change in 6-min walk distance (299.7 ± 210.6 m at baseline vs. 294.4 ± 136.9 m at 30-day follow-up), but the Kansas City Cardiomyopathy Questionnaire quality-of-life score improved from 50.2 ± 23.5 to 64.6 ± 26.3 (p = 0.0018).

DISCUSSION

This study evaluated a new device for the treatment of native valve MR in patients at high risk for surgery. The key findings of the study are: 1) TMVR using a prosthesis specifically designed for the mitral valve is feasible, with successful implantation and abolition of MR in 93% of the cohort; 2) TMVR can be performed safely, with a low risk of procedural death and major adverse events; and 3) the ability to reposition or retrieve a fully deployed prosthesis facilitated the safe and successful performance of TMVR.

The pathophysiology of MR consists of alterations in ventricular loading causing LV dilation, dysfunction, and heart failure. Surgical treatment of MR, whether primary or secondary, can lead to improvements in symptoms, LV remodeling, and survival in selected patients (9), but many patients have a very high perioperative risk. In this study, successful treatment of MR was achieved in 28 of 30 patients using transapical delivery of a dedicated mitral prosthesis without the need for cardiopulmonary bypass. Although the population consisted of patients at high risk for surgery, the adverse event rate was low, and the majority of the patients were discharged directly home.

Successful TMVR was facilitated by several features of the mitral valve system. First, the double-frame design allows adaptability to the asymmetric shape of the mitral valve annulus, which is dynamic throughout the cardiac cycle, while preserving antegrade laminar blood flow through a large circular orifice (effective area >3.2 cm^2). Second, the anchoring tether maintains stability, minimizing the risk of prosthesis migration or embolization, neither of which occurred in our study. Device instability, and associated adverse patient outcomes, has been described for other TMVR approaches that typically rely on leaflet attachment or radial force for annular fixation (12). Third, secure closure of the apex is facilitated by the application of the epicardial pad, minimizing periprocedural bleeding. A fourth important feature is the ease with which the prosthesis can be repositioned or retrieved, even after full deployment in the mitral annulus. This obviates the need for conversion to emergency open surgery to treat device malposition or dysfunction, which carries significant risk, particularly in elderly patients with multiple comorbidities.

The predominant pathology treated in our study was MR secondary to ischemic LV remodeling. Although early studies (24,25) suggested better outcomes in this population for valve repair than replacement, this may not always be the case. A recent trial suggested a potential benefit for surgical valve replacement over valve repair, with a reduction in recurrent MR (3.8% vs. 58.8% at 2 years; p < 0.01), and lower heart-failure-related adverse events and cardiovascular readmissions (26). Residual or recurrent MR is also common after transcatheter mitral

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repair (27–32). Although this may be considered acceptable for inoperable patients, moderate or severe MR does have adverse clinical consequences, with an increased risk of heart failure, atrial fibrillation, repeat interventions, and reduced survival (26,33,34). Importantly, complete abolition of MR was well tolerated in our patients, many of whom had poor LV systolic function.

STUDY LIMITATIONS. First, the study was nonrandomized, with a relatively small patient cohort. It represents very early experience in which more than one-half of the study sites treated only 1 or 2 patients. As a feasibility study, patients were selected to maximize the likelihood of procedure success. Our results need to be confirmed in larger, comparative trials with longer-term follow-up. It is encouraging to note that even in this small cohort, LV remodeling was evident at 30 days, an observation that has been associated with improved longer-term clinical outcomes in other studies (35,36). The role of the tether in supporting this remodeling process is uncertain, and is the subject of ongoing study. Second, optimization of medical therapy for heart failure was strongly recommended, but not a requirement for study entry. Although MR severity is known to be dynamic and sensitive to medical therapy, the reduction in MR in our study was undoubtedly due to valve implantation because the effect was immediate and sustained through the follow-up period. Third, the risk of leaflet thrombosis, a phenomenon that has been described for both transcatheter and surgical valve therapies (37–39), and the optimal requirements for anticoagulation, need further study. Finally, the short-term nature of this study does not allow for conclusions regarding durability of the prosthesis, the effect of TMVR on late outcomes, or a comparison with other mitral valve therapies.

CONCLUSIONS

TMVR is feasible, and can be performed with high procedural success and a low adverse clinical event rate. If these findings are confirmed with further study, TMVR may become an established therapy for selected patients with native mitral valve regurgitation.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In an initial global feasibility trial of patients with severe MR at high surgical risk, TMVR abolished MR in 90% of cases with a low rate of major adverse events.

TRANSLATIONAL OUTLOOK: Larger studies with longer-term follow-up are necessary to confirm the generalizability of these observations and better characterize the utility of TMVR as an alternative to surgery for patients with severe, symptomatic MR.

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KEY WORDS heart failure, mitral prosthesis, mitral regurgitation, mitral valve implantation, transcatheter

APPENDIX For a list of the study investigators and sites, please see the online version of this article.

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