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Initial Feasibility Study of a New Transcatheter Mitral Prosthesis

The First 100 Patients

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ABSTRACT

BACKGROUND Transcatheter mitral valve replacement (TMVR) is a rapidly evolving therapy. Follow-up of TMVR patients remains limited in duration and number treated.

OBJECTIVES The purpose of this study was to examine outcomes with expanded follow-up for the first 100 patients who underwent TMVR with the prosthesis.

METHODS The Global Feasibility Study enrolled symptomatic patients with either primary or secondary mitral regurgitation (MR) who were at high or prohibitive surgical risk. The present investigation examines the first 100 patients treated in this study. Clinical outcomes through last clinical follow-up were adjudicated independently.

RESULTS In the cohort (mean age 75.4 ± 8.1 years; 69% men), there was a high prevalence of severe heart failure symptoms (66%), left ventricular dysfunction (mean ejection fraction 46.4 ± 9.6%), and morbidities (Society of Thoracic Surgeons Predicted Risk of Mortality, 7.8 ± 5.7%). There were no intraprocedural deaths, 1 instance of major apical bleeding, and no acute conversion to surgery or need for cardiopulmonary bypass. Technical success was 96%. The 30-day rates of mortality and stroke were 6% and 2%, respectively. The 1-year survival free of all-cause mortality was 72.4% (95% confidence interval: 62.1% to 80.4%), with 84.6% of deaths due to cardiac causes. Among survivors at 1 year, 88.5% were New York Heart Association function class I/II, and improvements in 6-min walk distance ($p < 0.0001$) and quality-of-life measurements occurred ($p = 0.011$). In 73.4% of survivors, the Kansas City Cardiomyopathy Questionnaire score improved by ≥10 points.

CONCLUSIONS In this study of TMVR, which is the largest experience to date, the prosthesis was highly effective in relieving MR and improving symptoms, with an acceptable safety profile. Further study to optimize the impact on long-term survival is needed. (J Am Coll Cardiol 2019;73:1250–60)

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Mitral regurgitation (MR) is the most common valvular disease in the Western world, affecting 3 to 4 million persons in the United States alone (1). Survival impairment occurs with severe MR and whether the lesion is primary (i.e., due to leaflet pathology, such as myxomatous disease) or secondary (i.e., due to myocardial dysfunction, such as myocardial ischemia) (2–7). Surgery, consisting of either valve repair or chordal-sparing valve replacement, is the most effective means for relief of MR, and can be life-saving in selected patients (8,9). Transcatheter mitral valve repair also may be effective in selected patients (10,11). Nonetheless, a substantial number of patients with MR do not undergo surgery due to advanced age, procedural risk, or a perception of a low likelihood of clinical benefit (12,13).

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Transcatheter mitral valve replacement (TMVR) recently emerged as a potential therapy for patients with symptomatic MR, with early feasibility for TMVR demonstrated in several prior reports (14–19). TMVR may allow complete or near complete elimination of MR without cardiopulmonary bypass, and may potentially help address unmet clinical needs. Nonetheless, few data on TMVR with expanded follow-up are available. Such insight into the potential benefit and adverse outcomes for this therapy is needed, especially given the poor prognosis and potential high-risk for procedures in these patients. Moreover, the vast majority of patients who have been treated with TMVR thus far have left ventricular dysfunction, in which there remains considerable uncertainty regarding the effect of MR therapy (8,11,12).

Accordingly, we undertook this investigation to examine the early and long-term clinical outcomes of TMVR in patients with MR and who were at high or prohibitive surgical risk. The present investigation is an analysis of the first 100 patients treated with the Tendyne prosthesis (Abbott Structural, Santa Clara, California) in a global feasibility study (NCT02321514).

METHODS

STUDY DESIGN AND PARTICIPANTS. Details of the investigational design and methodology have been previously published (14). Patients were enrolled in a nonrandomized, prospective study between November 2014 and November 2017 at 24 hospitals (13 in the United States, 3 in Australia, and 8 in Europe) (**Figure 1**). Institutional review board approval was obtained at each site. Patients were eligible for enrollment if they were symptomatic (New York Heart Association [NYHA] functional class ≥II) with grade 3 or 4 MR, and were considered poor surgical candidates by the institution's heart team. Exclusion criteria included left ventricular end-diastolic diameter >70 mm, severe mitral annular or leaflet calcification, previous mitral or aortic valve surgery, intracardiac thrombus, severe pulmonary hypertension (pulmonary artery systolic pressure ≥70 mm Hg), severe tricuspid valve regurgitation, severe right ventricular dysfunction,

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

MR = mitral regurgitation

NYHA = New York Heart Association

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

TEE = transesophageal echocardiography

TMVR = transcatheter mitral valve replacement

Boston Scientific, and Abbott Vascular. Dr. Paone has served as a consultant for Edwards Lifesciences. Dr. Bethea has served as a consultant, proctor, and is on the speaker's bureau for Abbott Vascular and Medtronic. Drs. Bae and Dahle have served on the Speakers Bureau for Abbott Vascular. Dr. Mumtaz has served as a consultant for and received grant support from Abbott Vascular, Medtronic, Millipede, Terumo, Atricure, Edwards Lifesciences, Japanese Organization for Medical Device Development, Keystone, and Boston Scientific. Dr. Grayburn has received grant support from Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, and Neochord; has served as a consultant for Abbott Vascular, Edwards Lifesciences, Medtronic, and Neochord; and has received core laboratory support from Edwards Lifesciences and Neochord. Dr. Kapadia has stock options in Navigate. Dr. Babaliaros has served as a consultant and researcher for Edwards Lifesciences and Abbott Vascular. Dr. Guerrero has served as a proctor for and received research support from Edwards Lifesciences; and has served as a consultant and is on the Speakers Bureau for Boston Scientific. Dr. Thourani has served as a consultant for Abbott Vascular. Dr. Bedogni has served as a consultant for Abbott Vascular, Medtronic, Boston Scientific, and Terumo. Dr. Rizik has served on the Advisory Board for Abbott Vascular, Cordis/Cardinal, Biotronik, and Boston Scientific; has received grant or research support from Abbott Vascular and Boston Scientific; and has received licensing fees from Boston Scientific. Dr. Denti has served as a consultant for and received speaker honoraria from Abbott Vascular. Dr. Dumonteil has served as a consultant and proctor for Abbott Vascular, Boston Scientific, Edwards Lifesciences, and Medtronic. Dr. Sinhal has served as a proctor and consultant for Edwards Lifesciences, Medtronic, and Boston Scientific. Dr. Popma has received institutional grants from Abbott, Medtronic, Edwards, and Boston Scientific; and has served on the Medical Advisory Board of Boston Scientific. Dr. Blanke has served as a consultant for Abbott Vascular, Circle Cardiovascular Imaging, Edwards Lifesciences, Tendyne, and Neovasc. Dr. Leipsic has served as a consultant for and has stock options in Circle Cardiovascular Imaging and HeartFlow; and has core laboratory agreements with Abbott Vascular, Medtronic, and Edwards Lifesciences. Dr. Muller has served as a consultant for Abbott and Cephea; has received research support from Medtronic, Tendyne, and Cephea; has served as a proctor for Medtronic; and has served on the Advisory Board of Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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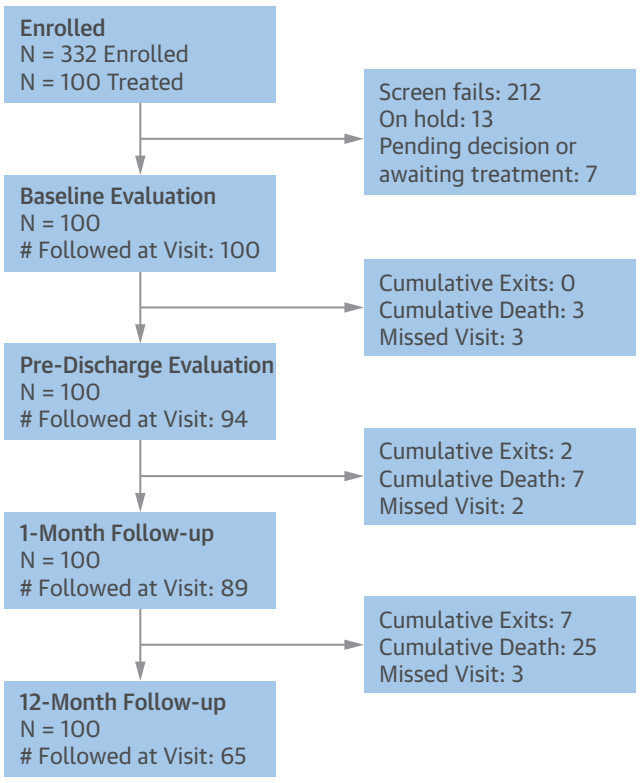
FIGURE 1 Patient Flow From Enrollment Through End of Follow-Up



Flow chart showing number of patients who participated in the study, those who were treated, and study deaths or exits through 12-month follow-up.

and left ventricular ejection fraction (LVEF) <30%. Anatomic suitability for TMVR was performed using transthoracic echocardiography, transesophageal echocardiography (TEE), and contrast-enhanced, gated cardiac computed tomography (CT) as previously described (14,20). All cardiac imaging studies were independently evaluated in a core laboratory (Beth Israel Deaconess Medical Center, Boston, Massachusetts, for echocardiography; St Paul's Hospital, Vancouver, British Columbia, for cardiac CT). Data on 30-day outcomes for the first 30 patients in this study have been previously published (14). The present investigation includes results from that study, and data from the subsequent 70 patients treated through November 20, 2017.

TRANSCATHETER MITRAL VALVE REPLACEMENT. The procedure was performed under general anesthesia using an ~5-cm, left anterolateral thoracotomy. A 34- or 36-F delivery sheath was inserted over a 0.035-inch guidewire through or near the left ventricular apex, with a site and trajectory determined from pre-procedural CT and intraoperative TEE imaging. The valve prosthesis, which consists of 2 self-expanding nitinol frames and a trileaflet porcine pericardial valve, was delivered through the sheath and partially deployed in the left atrium. The outer frame is contoured to fit the mitral annulus and aligned with the straight edge oriented anteriorly against the aorto-mitral continuity using TEE guidance. The delivery sheath was then retracted, deploying the remainder of the prosthesis in the mitral annulus, without the need for rapid right ventricular pacing or cardiopulmonary bypass. The prosthesis was secured in a stable position using a braided, high-molecular-weight polyethylene tether, which was attached to an epicardial pad. The length and tension of the tether were adjusted to optimize seating of the prosthesis for MR reduction and to minimize the risk of device displacement. Initially, post-operative medical therapy consisted solely of antiplatelet therapy (aspirin 81 to 325 mg daily). During the study, a protocol change was made to specify anticoagulation post-operatively using warfarin with a target international normalized ratio of 2.5 to 3.5 for >3 months. Patients with atrial fibrillation were treated with warfarin indefinitely.

CLINICAL EVALUATION. Clinical follow-up was performed at 1, 3, 6, and 12 months, and annually thereafter. NYHA functional class, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, and 6-min walk distance were assessed at each time point. Echocardiographic data were analyzed in the core laboratory, and clinical events were adjudicated by an independent clinical events committee. Device and procedure success were defined using standard criteria (21-23). The primary performance endpoint for the investigation was reduction of MR to ≤2+ at 1 month post-procedure. The primary safety endpoint was evaluated at 30 days and was a composite of device success and freedom from cardiovascular death, reintervention for valve-related dysfunction, disabling stroke, myocardial infarction, life-threatening bleeding, major vascular complications, renal failure requiring dialysis, or other device- or procedure-related serious adverse events. Life-threatening bleeding was defined as Bleeding Academic Research Consortium (BARC) types 2, 3, or 5 (23). Device success was defined as permanent implantation of the prosthesis, freedom from mortality and disabling stroke, no subsequent surgical or interventional procedures related to either access or the device, and maintenance of the intended performance of the device. The intended performance of the device included freedom from device-

TABLE 1 Baseline Patient Characteristics (N = 100)

Age, yrs	75.4 ± 8.1
Men	69 (69)
NYHA functional class	
II	34 (34)
III	62 (62)
IV	4 (4)
Diabetes mellitus	38 (38)
Coronary artery disease	74 (74)
Prior myocardial infarction	57 (57)
Peripheral artery disease	13 (13)
Prior CABG	47 (47)
Prior valve intervention/surgery	0 (0)
Hospitalization for heart failure within 6 months	39 (39)
GFR <60 ml/min	60 (60)
Hypertension	80 (80)
COPD	39 (39)
Current or prior smoker	61 (61)
Prior stroke or TIA	16 (16)
BMI, kg/m^2	27.5 ± 5.9
LV ejection fraction, %	46.4 ± 9.6
Grade III or IV MR severity	99 (99)
Etiology of MR	
Primary	11 (11)
Secondary	89 (89)
STS-PROM, %	7.8 ± 5.7
Medications	
ACE inhibitor or ARB	59 (59)
Beta-receptor antagonist	81 (81)
Vasodilator	19 (19)
Diuretic	81 (81)
Digoxin	9 (9)
Anticoagulant	47 (47)
Aspirin or antiplatelet	97 (97)

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; LV = left ventricular; MR = mitral regurgitation; NYHA = New York Heart Association; PAD = peripheral artery disease; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TIA = transient ischemic attack.

TABLE 2 Procedure and In-Hospital Outcomes

Device time, min	53.5 ± 15.9
Procedure time, min	136.1 ± 36.3
Fluoroscopy duration, min	15.3 ± 28.2
Contrast volume, ml	29.1 ± 34.0
Implant rate	97 (97)
Cardiopulmonary bypass or ECMO	0 (0)
Intra-aortic balloon pump insertion	4 (4)
Procedural device-specific adverse events	
Bioprosthetic valve dysfunction	0 (0)
Embolization	0 (0)
Malposition	1 (1)
Device retrieval	3 (3)
Technical success	96 (96)
Discharge MR grade	
None/trace	87 (99)
1+	0 (0)
2+	0 (0)
3+	1 (1.1)
4+	0 (0)
Reintervention related to MV	1 (1)
BARC 2, 3, or 5 bleeding	18 (18)
Apical access site complications	
Major	1 (1)
Minor	2 (2)
Major vascular complications	1 (1)
Disabling stroke	2 (2)
TIA	0 (0)
New-onset atrial fibrillation	2 (2)
Acute kidney injury	8 (8)
Myocardial infarction	2 (2)
Length of stay, days	11.1 ± 8.7

Values are mean ± SD or n (%).

BARC = Bleeding Academic Research Consortium; ECMO = extracorporeal membrane oxygenation; MV = mitral valve; other abbreviations as in Table 1.

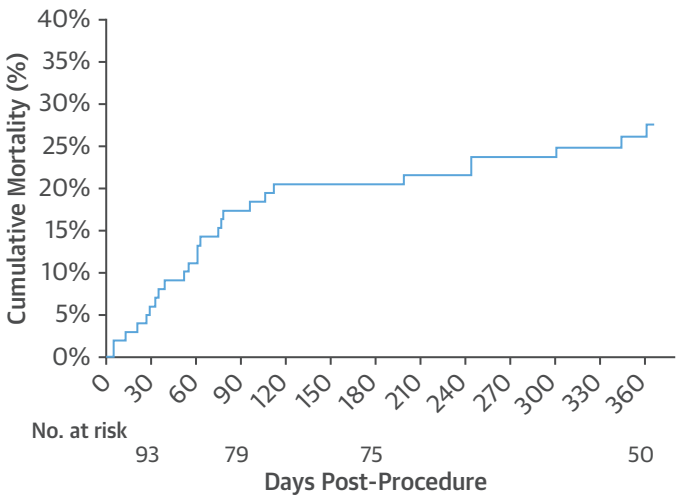
specific adverse events, such as valve migration, embolization, fracture, hemolysis, thrombosis, or endocarditis, as well as central or paravalvular mitral regurgitation (MR) ≥1+, mitral stenosis (i.e., mitral valve gradient ≥6 mm Hg and effective orifice area ≤1.5 cm^2), left ventricular outflow tract (LVOT) obstruction (i.e., ≥20 mm Hg increase in LVOT gradient vs. baseline), damage to surrounding cardiac structures, or need for permanent pacemaker implantation. Secondary endpoints were all-cause mortality at 30 days, change from baseline in distance walked on the 6-min walk test at 6 and 12 months, change from baseline in quality of life, as measured by KCCQ at 6 and 12 months, and change in proportion of NYHA functional classification at 12 months. Device time was defined as the time elapsed from the start of the apical puncture to final tensioning of the positioning tether.

STATISTICAL ANALYSIS. Continuous data are reported as mean ± SD or median (interquartile range [IQR]) unless otherwise stated. Categorical variables are reported as number and percentage of observed data. The Kaplan-Meier method was used to generate survival estimates for freedom from all-cause mortality. Comparisons between baseline and follow-up parameters were made using a paired Student's *t*-test for continuous variables or McNemar's test for categorical variables. A p value <0.05 was considered statistically significant. Statistical analyses were performed using statistical software SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. Table 1 describes the baseline characteristics of the study cohort (mean age 75.4 ± 8.1 years; 69% men). The majority of patients

FIGURE 2 Cumulative Incidence of Mortality



Cumulative incidence of mortality due to any cause is displayed for the study period.

had class III or IV heart failure (66%). The mean LV ejection fraction was 46.4 ± 9.6%, with secondary MR present in 89%. One patient initially was enrolled with grade 3 MR, but was later adjudicated to have grade 2 MR at baseline by the core laboratory after TMVR; all other patients had grade 3 or 4 MR. Overall, morbidities were common, with a mean Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) of 7.8 ± 5.7%.

TABLE 3 Clinical Events in Follow-Up (N= 100)

	30 Days	1 Year
Any mortality	6 (6)	26 (26)
Cardiovascular mortality	4 (4)	22 (22)
Disabling stroke	2 (2)	3 (3)
TIA	0 (0)	3 (3)
Myocardial infarction	2 (2)	4 (4)
Heart failure hospitalization	12 (12)	31 (31)
Reintervention for MV*	1(1)	4 (4)
BARC 2, 3, or 5 bleeding	20 (20)	32 (32)
Device-specific adverse events	4 (4)	12 (12)
Bioprosthetic valve dysfunction	0 (0)	0 (0)
Hemolysis	1 (1)	3 (3)
Embolization	0 (0)	0 (0)
Thrombosis	1 (1)	6 (6)
Erosion, migration, malposition	2 (2)	4 (4)
Fracture	0 (0)	0 (0)
Endocarditis	1 (1)	2 (2)
New onset atrial fibrillation	4 (4)	4 (4)
New permanent pacemaker	4 (4)	7 (7)

Values are n (%). *1 percutaneous repair of paravalvular leakage, 3 procedures to increase tension on tether (all <40 days post-TMVR).

Abbreviations as in Tables 1 and 2.

PROCEDURE DATA. The prosthesis was implanted in 97 of the 100 patients (Table 2). MR was eliminated acutely in all patients with implants, except for 1 in whom the prosthesis was misaligned and anterior paravalvular leak occurred, leading to a technical success rate of 96% for the entire cohort. For the patient with the malpositioned device, no central MR was present but trace paravalvular leak was observed at the pre-discharge evaluation. Three months post-TMVR, moderate PVL was observed and reintervention was performed with percutaneous repair and placement of Amplatzer Vascular Plug II devices in a subsequent procedure, reducing the severity to 1+. For the 3 patients without Tendyne implantation, 1 was placed and then retrieved due to LVOT obstruction, 1 could not be implanted due to poor apical access and misalignment, and 1 experienced hemodynamic instability during guidewire displacement and the procedure was aborted. Each of these failed procedures occurred within the first 41 cases, and thus was early in the experience. In the subsequent 59 cases, all enrolled patients had the prosthesis successfully implanted. Of note, there were no instances of need for extracorporeal membrane oxygenation or cardiopulmonary bypass; 4 patients had intra-aortic balloon pump placement. There were 18 in-hospital bleeding events (BARC types 2, 3, or 5). In the entire cohort, 1 major episode of apical bleeding occurred. This event was in a patient who had unsuccessful implantation, and a large mass of clotted blood was removed via video-assisted thoracoscopic surgery without further complication. Two other patients had minor apical access complications. Notably, there were no instances of device embolization, and no intraprocedural deaths occurred in the entire cohort.

CLINICAL EVENTS IN FOLLOW-UP. Mean follow-up for the cohort was 13.7 months. Overall, there were 26 deaths during follow-up, with 6 events occurring in the first 30 days (Figure 2, Table 3). Survival free of all-cause mortality at 1 year for the cohort was 72.4% (95% confidence interval: 62.1% to 80.4%). Cardiac death accounted for the majority of the deaths (22 of 26, or 85%), with death due to heart failure in 7 patients, sudden cardiac death observed in 5 patients, myocardial infarction in 1 patient, and stroke in 1 patient. One of the sudden cardiac deaths occurred in a patient who was later found to have amyloidosis on autopsy. A total of 20 other patients were rehospitalized for heart failure. There was no echocardiographic evidence of recurrent MR >1+ among the patients who died or who had heart failure in follow-up.

Following hospital discharge, there were 8 patients who experienced bleeding events. Reintervention for the mitral valve occurred in 4 patients, including the aforementioned percutaneous repair for paravalvular regurgitation. A total of 3 other patients had evidence of valve instability that was addressed by intervention to increase tension on the tether. One of the patients who underwent surgery to increase the tension died of post-operative complications. Evidence of thrombus was detected in 6 patients (6%), with involvement of leaflets in 4 patients, the tether in 1 patient, and the cuff in 1 patient. Each of these instances occurred in the early part of the study (within the first 35 cases), when anticoagulation with warfarin was not specified by the study protocol. Following a protocol change and post-procedural initiation of warfarin with an international normalized ratio goal of 2.5 to 3.5 for >3 months after implantation, there were no other instances of thrombosis. One patient died from endocarditis at day 29 post-operatively. Another patient presented on day 52 post-operatively with a vegetation on the prosthesis that could not be determined to be due to either endocarditis or thrombus, and died from heart failure during the hospitalization. Another patient had blood cultures positive for *S. lugdunensis* with no prosthetic dysfunction, and was treated successfully with intravenous antibiotics with no further evidence of septicemia in follow-up.

ECHOCARDIOGRAPHIC DATA. Overall, the MR reduction that occurred acutely with the prosthesis persisted in follow-up. MR was absent in 95.3% (61 of 64 patients) at 6 months, and absent in 98.4% (61 of 62 patients) at 1 year of follow-up. In paired analyses, improvements in LVEDV ($p = 0.019$) and less pulmonary hypertension ($p = 0.03$) were evident, while there was also was a decrement in LVEF (45.4 ± 9.1% vs. 39.2 ± 10.3%; $p = 0.0001$) (Table 4). LVOT gradient was slightly increased (1.4 ± 0.6 mm Hg vs. 1.7 ± 1.0 mm Hg; $p = 0.07$), but there were no occurrences of LVOT obstruction. No patients had significant mitral stenosis (mean gradient at 1 year, 3.0 ± 1.1 mm Hg).

SYMPTOMS, FUNCTIONAL CAPACITY, AND QUALITY OF LIFE. Among the survivors, significant improvement in symptoms and quality of life were evident (Central Illustration). At one year, 88.5% of survivors were NYHA functional class I or II, compared with 34.0% at baseline ($p < 0.0001$). For the 66 patients who were NYHA functional class III or IV at baseline, 39 patients were alive and assessed for symptom class at 1 year; among these 39 patients, improvement by 1 functional class (i.e., to NYHA functional class I or II) occurred in 34 patients (87%), 5 remained as functional class III or IV (13%). Among the 34 patients who were NYHA functional class II at baseline, 22 patients were alive and assessed for symptom class at 1 year; among these 22 patients, improvement by 1 functional class (i.e., to NYHA functional class I) occurred in 6 patients, 14 remained as functional class II, and 2 were functional class III.

TABLE 4 Paired Analysis of Changes in Echocardiographic Parameters

	n	Baseline	1 Year	Change	p Value
LV ejection fraction, %	49	45.4 ± 9.1	39.2 ± 10.3	−6.2 ± 10.1	0.0001
LVEDV, ml	41	174.0 ± 60.4	159.0 ± 41.4	−15.0 ± 39.3	0.019
LVESV, ml	41	97.6 ± 40.2	98.4 ± 35.5	0.9 ± 29.1	0.852
Forward stroke volume, ml	39	54.0 ± 16.3	56.4 ± 16.7	2.3 ± 17.6	0.411
Cardiac output, l/min	37	3.9 ± 1.1	4.0 ± 1.1	0.1 ± 1.3	0.563
RVSP, mm Hg	20	43.5 ±11.3	35.5 ± 12.4	−8.0 ± 15.6	0.034
LVOT gradient, mm Hg	43	1.4 ± 0.6	1.7 ± 1.0	0.3 ± 1.0	0.073
Mean mitral gradient, mm Hg	38	2.9 ± 1.3	3.0 ± 1.1	0.1 ± 1.6	0.627

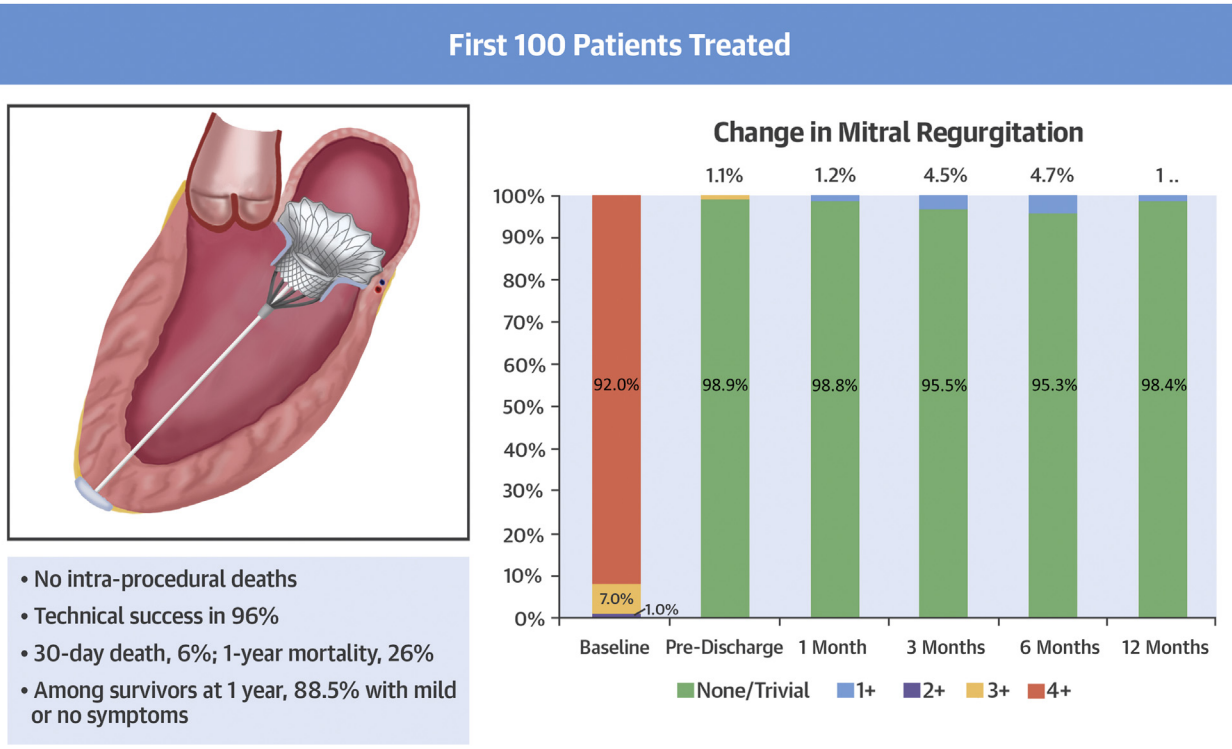
Values are n or mean ± SD.
LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end systolic volume; LVOT = left ventricular outflow tract; RVSP =right ventricular systolic pressure.

Among all survivors, significant improvement in 6-min walk distance also occurred (245.8 ± 130.1 m at baseline vs. 299.8 ± 134.7 m at 12 months; $p = 0.011$), with the majority of this change occurring in the first 3 months post-procedure (Figure 3). Of note, 27 of the 55 survivors (49.1%) had >50 m improvement in 6-min walk distance at 1-year follow-up. In analyses of quality of life, KCCQ score increased significantly with improvements occurring at 1 month of follow-up. At 1 year, the KCCQ increased by ≥5 points in 52 of 64 survivors (81.3%), and by ≥10 points in 47 of 64 survivors (73.4%).

DISCUSSION

The present investigation is a global feasibility study that represents the largest experience with TMVR reported to date, with expanded follow-up of 100 consecutively-treated patients for an evaluation of survival and symptom improvement (Central Illustration). In this investigation of high-risk patients with symptomatic MR, the key findings were: 1) TMVR with the prosthesis demonstrated favorable early safety and effectiveness, with no intraprocedural deaths, no conversions to cardiac surgery or need for cardiopulmonary bypass, a low rate of major apical bleeding (1%), and elimination of MR in 98% of patients treated; 2) mortality for

CENTRAL ILLUSTRATION **Clinical Outcomes With Transcatheter Mitral Valve Replacement With the Prosthesis**



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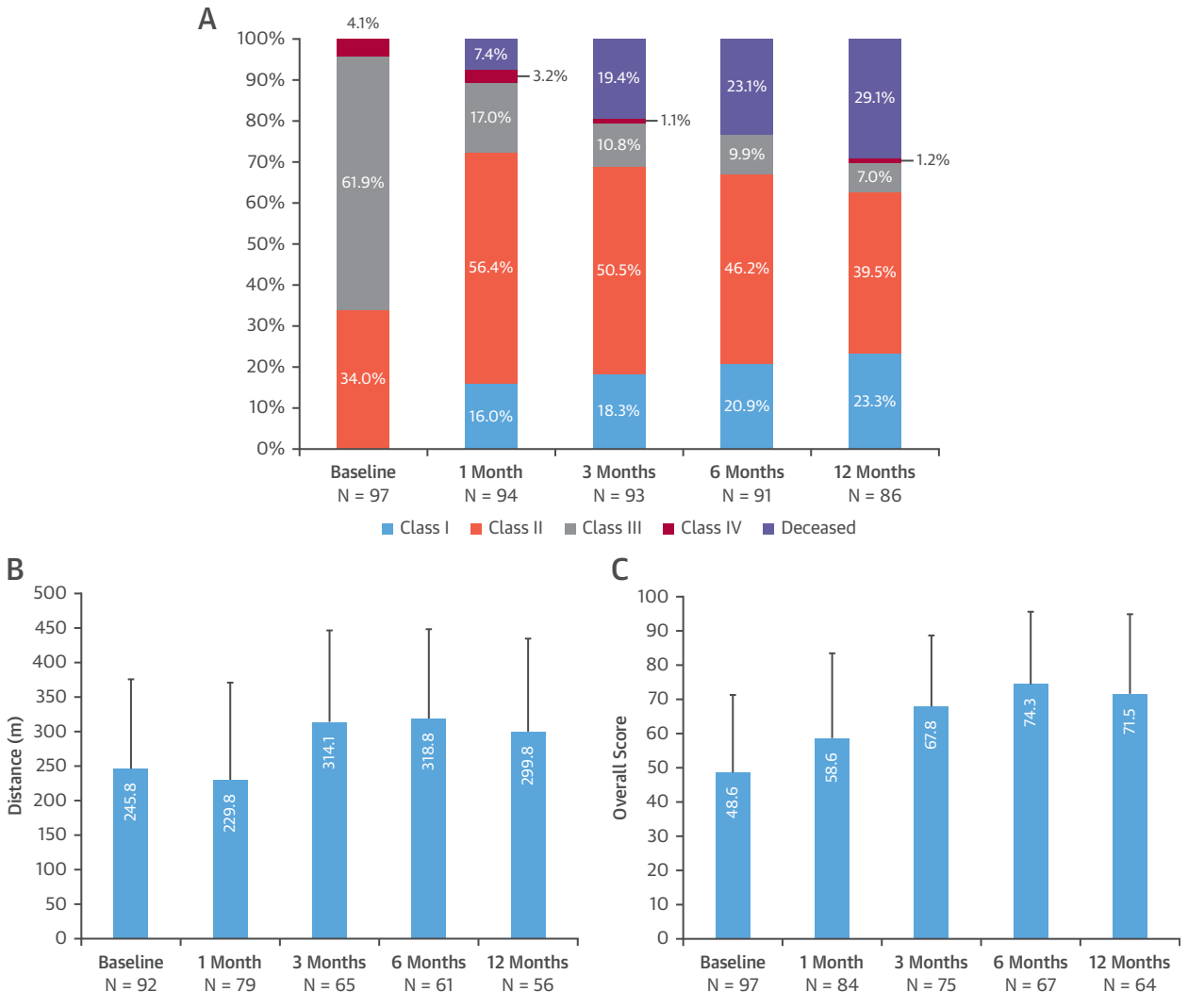
(Left) The Tendyne prosthesis. **(Right)** Changes in mitral regurgitation at baseline and after treatment with the prosthesis. Severity of mitral regurgitation was determined in a core echocardiography laboratory at baseline and through 12-month follow-up for survivors.

the cohort at 1 year was 26%, with most deaths (22 of 26 or 85%) due to cardiac causes; and 3) symptom improvement among survivors occurred, with 88.5% of patients in NYHA functional class I or II at 1 year, and there were significant increases in both 6-min walk distance and KCCQ quality-of-life scores during follow-up.

The present investigation demonstrates the potential for TMVR as a procedure that can effectively treat high-risk MR without cardiopulmonary bypass, with a reasonable safety profile, and improve symptoms and quality of life in patients with heart failure. During the study, there were no intra-procedural deaths, there was a low rate of major apical bleeding (1%), there was a 30-day mortality of 6%, and overall technical success was high (96%). These findings expand the experience with the prosthesis, and are in contrast to outcomes observed with earlier reports of TMVR, where considerably higher rates of apical bleeding and mortality has been described (e.g., 30-day rates of 16% and 14%, respectively) (14,15,19).

Certainly, differences in patient populations may account for such variation in the clinical outcomes observed with TMVR. Nonetheless, it is important to note that the patient population in the present study was elderly (mean age 75 years), with 92% having grade 4 MR, and there were frequent morbidities that led to a high average predicted surgical mortality risk (i.e., 7.8 ± 5.7%). The prosthesis is anatomically-shaped, and anchoring is achieved primarily through the tether and epicardial pad rather than annular fixation. Thus, significant device oversizing generally is not required, which theoretically helps to minimize distension of the mitral annulus. The epicardial pad helps to promote hemostasis and reduce risk of bleeding due to transapical or transventricular access. Rapid ventricular pacing is not required during deployment, thereby facilitating hemodynamic stability, which may be of particular importance in

FIGURE 3 **Functional Status Change During the Study**



For survivors, changes in New York Heart Association (NYHA) functional class **(A)**, 6-min walk distance **(B)**, and Kansas City Cardiomyopathy Questionnaire scores **(C)** at baseline and following transcatheter mitral valve replacement are depicted. For **B and C**, values are mean with **bars** indicating SD.

TMVR patients, in whom reduction in left ventricular function is common (mean ejection fraction 46%). These potential advantages for the Tendyne TMVR system are designed to facilitate implantation and may help contribute to favorable procedural outcomes, although further comparative analyses in similar patient populations would be required for definitive conclusions on relative efficacy and safety.

Although acute safety and effectiveness for the prosthesis was demonstrated in our investigation, we did observe mortality in 26% of patients at 1-year follow-up. The most common cause was worsening heart failure (7 of 26 causes), with noncardiac causes accounting for 4 deaths or 15% of cases. Mortality in these patients occurred despite amelioration of MR. Persistent risk of mortality, despite early procedure success, has been an observation with multiple transcatheter valve therapies, due to the high-risk nature of these patients and their frequent, severe comorbidities that negatively affect their long-term survival. As examples, 1-year mortality for the PARTNER IA (Placement of AoRtic TraNscatheteR Valves) study (STS-PROM, 11.7%) was 24%, and was 31% in the U.S. commercial registry of transcatheter repair of MR of secondary MR with MitraClip (STS-PROM, 6.1%) (24,25).

For patients with left ventricular dysfunction, the potential effect of MR correction has had uncertainty. The recent, randomized MITRA-FR (Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) study found no effect of transcatheter repair with MitraClip in patients with secondary MR on medical therapy, whereas the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) study showed remarkably improved symptoms, less heart failure hospitalization, and better survival (11,12). In the CTSN (Cardiothoracic Surgical Network) study, durable elimination of MR with mitral surgery was associated with improvement in left ventricular remodeling (26,27). In our investigation, we enrolled patients based primarily on the presence of significant, symptomatic MR, high surgical risk, and anatomical appropriateness for the Tendyne prosthesis. Left ventricular systolic dysfunction with chamber dilatation was common (mean ejection fraction, 46.4 ± 9.6%). We believe considerable study is needed to determine which patients with secondary MR will benefit from MR correction, especially those with ventricular dilatation, not only from technical success but also long-term clinical outcomes, with an emphasis on the facets of symptom improvement, left ventricular remodeling, and survival. There also was a high rate of screen failures, which were multifactorial and related to study exclusion criteria, potential LVOT obstruction, and annular dimensions outside of the treatable range. Further study to improve therapy for such excluded patients is needed.

In our study, we observed a slight decrement in LVEF in follow-up, but also some improvement in LVEDV and forward stroke volume. There was considerable variability in the extent and direction of ventricular remodeling. The decline in LVEF, as also described in prior TMVR reports, may be associated with persistent symptoms. In 3 patients (3%), early favorable left ventricular remodeling occurred that led to valve instability. Subsequent procedures were performed in these patients to increase tether tension, although there was no evidence of late device migration. The heterogeneous nature of the pathology in this study did not permit an analysis of the predictors of ventricular response, although further study is being undertaken to gain insight into this ability. We also did not have sufficient data on changes in medical therapy in follow-up, an essential component of management for these patients. Nonetheless, the improvements in symptoms and quality-of-life in the survivors is noteworthy, with a positive change of ≥5 points in KCCQ score observed in 81.3% of survivors, and 73.4% having an increase of ≥10 points. These meaningful changes in quality of life coincided with durable correction of MR, with 98.4% of patients (i.e., 61 of 62 patients) having no regurgitation at 1 year. We believe these observations highlight the potential for TMVR, and the ongoing pivotal trials will hopefully provide more insight as well as comparative data that were not available in the present investigation.

Although the participating hospitals were highly experienced mitral centers, we found beneficial practice changes for patients undergoing TMVR in our feasibility study. For some TMVR prostheses, the approach is described as transapical, but the actual access site is commonly remote from the true left ventricular apex. The trajectory for TMVR placement ideally is perpendicular to the mitral valve plane, in orthogonal directions (i.e., anterior-posterior and medial-lateral), to optimize sealing of the annulus and stability of the prosthesis, and to minimize risk of LVOT obstruction. In 1 early procedure (case no. 15), perpendicular trajectory could not be achieved due to incorrect access, and refined, meticulous case planning led to success in subsequent procedures. A recent study by Blanke et al. (28) has described the average location for the orthogonal access point for TMVR to be ~1.7 cm from the true apex, typically in the anterolateral segment of the left ventricle. In another early procedure (case no. 2), LVOT obstruction occurred with prosthesis placement due to systolic motion of the anterior mitral leaflet, leading to device retrieval. Use of an ample predicted neo-LVOT area as measured by pre-procedural CT (i.e., >2.5 cm^2) was helpful but will vary by device type, size, neo-LVOT measurement method, and patient anatomy; prediction of LVOT obstruction post-TMVR remains an active area of investigation (29). Finally, although antiplatelet therapy has been mandatory, anticoagulation for patients without traditional indications (e.g., atrial fibrillation) was not a requirement at study initiation. In several patients, there was evidence of thrombus formation on the prosthesis without neurological sequelae. Our study protocol was modified with the recommendation of initiation of warfarin post-operatively for an international normalized ratio of 2.5 to 3.5, with a minimal treatment duration of 3 months. This management is similar to current practice guidelines for mitral bioprostheses placed with traditional surgery, and there were no further episodes of valve thrombus in subsequent patients (8).

CONCLUSIONS

TMVR with the new prosthesis was effective in the treatment of high-risk patients with MR with an

acceptable safety profile, and with durable correction of the regurgitation in follow-up to 1 year. There is a long-term risk of mortality related to left ventricular dysfunction and accompanying morbidities, and further study into patient selection for long-term clinical success is required. Among survivors, TMVR with prosthesis can lead to significant improvements in symptoms and quality of life.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In an initial study of 100 patients, TMVR with the new prosthesis eliminated MR in nearly all cases. The 1-year mortality was 26%. Among survivors, functional status and quality of life improved.

TRANSLATIONAL OUTLOOK: Larger studies are needed to confirm the intermediate and longer-term outcomes of TMVR using this method and to compare the results with other options for carefully defined patients with symptomatic MR who are at high surgical risk.

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