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1-Year Results From a Multicenter Trial of a Polymer Surgical Mitral Valve

Insights Into New Technology

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ABSTRACT

BACKGROUND Polymer leaflet material may extend the durability of surgical mitral valve replacement (SMVR) to provide stable long-term hemodynamics. The India Mitral Surgical Trial sought to evaluate the safety and performance of a novel polymer leaflet material as part of a surgical mitral valve (MV) prosthesis.

OBJECTIVES In this study, the authors sought to report 1-year outcomes in patients undergoing SMVR for MV disease using the Tria Mitral Valve (Foldax).

METHODS Adult patients requiring MV replacement were enrolled in a prospective single-arm multicenter trial at 8 clinical sites in India from April to November 2023. An independent physician screening committee reviewed each patient for study eligibility before enrollment. Safety events were adjudicated per standard Valve Academic Research Consortium 3 criteria guidelines, and valve performance was assessed by means of echocardiographic and computed tomographic imaging at 30 days and 1 year. Patients were maintained on a vitamin K antagonist (target international normalized ratio: 2.5).

RESULTS Sixty-seven patients, of whom 64% were female (48% of childbearing age), with a mean age of 42 years (range: 19-67 years), mean body mass index of 22.7 kg/m^2, and body surface area of 1.6 cm^2 were treated with SMVR with 100% technical success. Most patients (54%) were NYHA functional class III or IV at baseline. The mean Society of Thoracic Surgeons score was 1.4%. The etiology of MV disease was stenosis in 27%, regurgitation in 30%, and mixed in 43% of patients, primarily secondary to rheumatic heart disease. The 1-year rates for all-cause mortality, thromboembolic events, stroke, structural valve deterioration, and valve reintervention were 9.1%, 7.5%, 4.9%, 0%, and 0%, respectively. No death was valve related. One-year effective orifice area and mean inflow gradient were 1.4 $\pm$ 0.4 cm^2 and 4.6 $\pm$ 1.7 mm Hg, respectively. There were 2 thrombotic events and 3 ischemic strokes, all in patients with subtherapeutic international normalized ratio.

CONCLUSIONS The polymer surgical MV demonstrated an acceptable safety profile and maintained stable hemodynamic performance through 1 year in patients undergoing MV replacement. Further study of this promising polymer leaflet technology is ongoing. (Clinical Investigation for the Foldax Tria Mitral Valve–India; NCT06191718) (JACC. 2025;86:515–526) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CTA = computed tomographic angiography

EOA = effective orifice area

EOAi = indexed effective orifice area

INR = international normalized ratio

MG = mean gradient

MV = mitral valve

MVR = mitral valve replacement

NSVD = nonstructural valve deterioration

PTFE = polytetrafluoroethylene

SVD = structural valve deterioration

TTE = transthoracic echocardiography

VKA = vitamin K antagonist

Mitral valve (MV) disease affects >24 million people globally.[1] In developing countries, untreated streptococcal infections and subsequent rheumatic heart disease often lead to significant MV disease, causing substantial morbidity, mortality, and financial burden, especially among younger patients.[2,3] While surgical mitral valve replacement (MVR) eliminates regurgitation, the optimal choice of a prosthetic valve is still widely debated, especially in patients under 65 years of age.[4] A number of important considerations factor into decision making, including leaflet durability and need for reintervention, hemodynamics, risks associated with anticoagulation, and quality of life. Mechanical valves offer potentially lifetime durability benefits but at the costs of requiring systemic anticoagulation precluding pregnancy and future transcatheter valve salvage option. In contrast, bioprosthetic valves—made with animal tissue leaflets—require minimal or no medications, allow for future transcatheter valve implantation, and are associated with higher quality of life than mechanical valves.[5,6] However, bioprosthetic valves suffer from limited durability, particularly in younger patients, which may necessitate multiple reoperations over a lifetime.[7]

SEE PAGES 527 AND 530

Synthetic polymer leaflet materials seek to address the root cause of bioprosthetic tissue failure—calcification or immunologic reactivity—by avoiding the use of xenogenic animal tissue. The Tria Mitral Valve (Foldax) uses a novel proprietary nonanimal-based polymeric material designed specifically for use in heart valves (Supplemental Figure 1). Based on siloxane polyurethane technology, this material is biostable and biocompatible with a similar chemical structure as used in pacing leads. The leaflets and valve frame have been developed with the use of computational design to withstand the boundary conditions specifically of the MV. In a sheep model, these valves exhibited no pannus formation and no calcification compared with bovine tissue preparations[8] (Supplemental Figure 2). The India Mitral Surgical Trial was conducted to evaluate the safety and performance of this novel polymer MV in human patients with MV disease. We here report, for the first time, 1-year outcomes in subjects undergoing polymer MVR.

METHODS

STUDY DESIGN AND PATIENTS. The Clinical Investigation for the Foldax Tria Mitral Valve-India (NCT06191718) is a prospective single-arm multicenter trial conducted to evaluate the safety and performance of the polymer MV in patients undergoing surgical MVR at 8 sites in India. Patients aged 18 to 80 years, who were candidates for surgical MVR owing to moderate to severe MV stenosis, regurgitation, or mixed pathology, were screened for enrollment by an independent clinical screening committee. Patients had to be able to tolerate vitamin K antagonist (VKA) anticoagulation. A complete list of inclusion and exclusion criteria is provided in Supplemental Table 1. Briefly, patients enrolled had to have moderate to severe MV stenosis, moderate to severe MV regurgitation, or moderate to severe mixed MV stenosis and regurgitation. Patients with a left ventricular ejection fraction of <30%, left ventricular end-diastolic dimension >7 cm, severe tricuspid regurgitation, or end-stage renal disease, those who recently had a heart attack or stroke, and those requiring chronic dialysis or concomitant procedures other than left atrial appendage closure were not eligible for inclusion in the study. A breakdown of screening failure reasons is shown in **Figure 1**.

Participating investigators identified potential study subjects who were screened for adherence to the inclusion and exclusion criteria. The screening committee comprised 6 physicians from India, Europe, and the United States. The committee reviewed and approved all potential subjects based on preoperative clinical data and imaging, specifically transthoracic echocardiography (TTE), coronary angiography, and cardiac computed tomographic angiography (CTA). In addition, TTE and CTA core laboratories (echo core lab: ClinNext, Vastrapur, Ahmedabad, Gujarat, India; CTA core lab: Intermountain Medical Center, Murray, Utah, USA), clinical events committee, and data safety monitoring board provided trial oversight. Written informed consent was obtained from each study

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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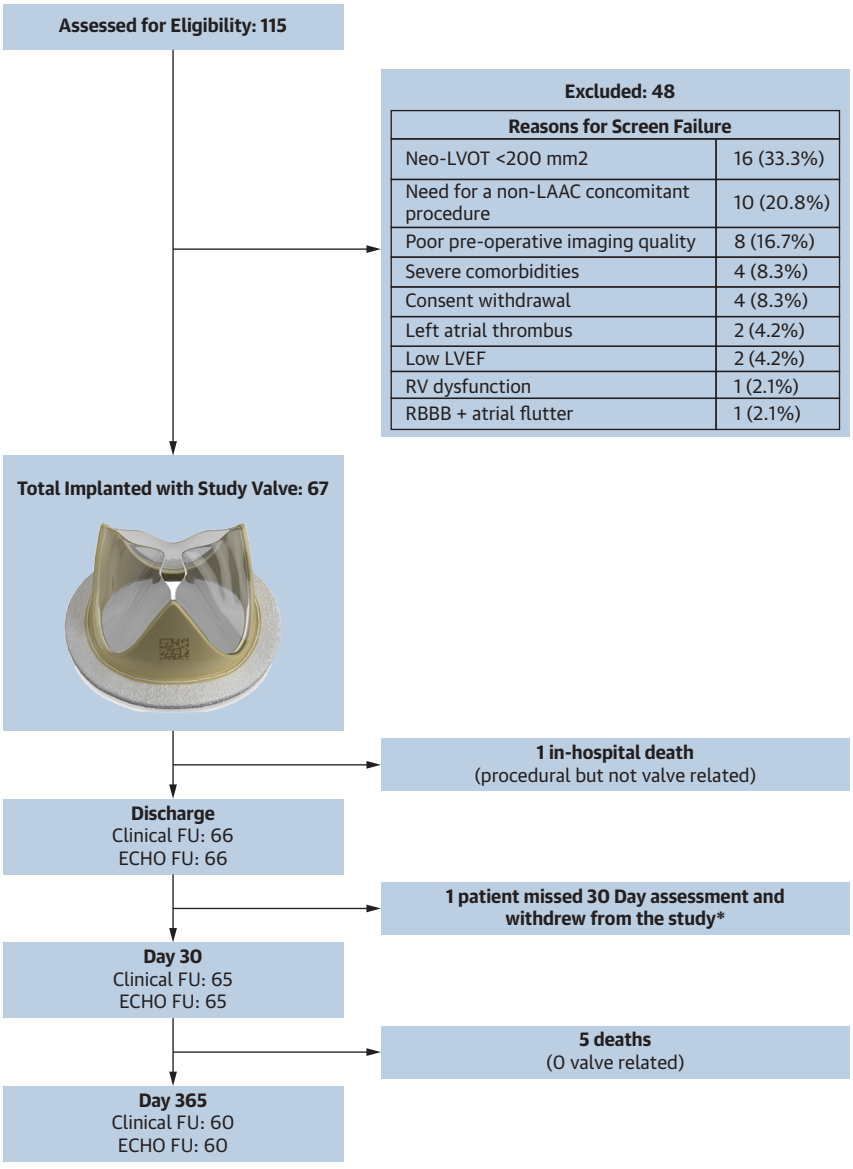
FIGURE 1 Study Flow Diagram



A total of 115 patients aged 18 to 80 years who were candidates for surgical mitral valve replacement due to moderate-to-severe mitral valve stenosis, regurgitation, or mixed pathology were screened for enrollment by an independent clinical screening committee based on clinical characteristics, preoperative transthoracic echocardiography, and computed tomographic angiography. Forty-eight patients were excluded owing to a small predicted neo-LVOT or for not meeting the inclusion and exclusion criteria. A final cohort of 67 patients received the study valve, which uses a novel proprietary non-animal-based polymeric material designed specifically for use in heart valves. This valve features a single thin polymer leaflet draping adherently to 3 geometrically equidistant poly-ether-ether-ketone struts and attached polytetrafluoroethylene sewing cuff. Based on siloxane polyurethane technology, this material is biostable and biocompatible. There was 1 in-hospital death, 1 patient lost to follow-up at 30 days, and 5 deaths throughout the study period. Thus, 60 patients completed the 1-year echocardiographic and clinical follow-up. *Patient responded over the telephone, indicating inability to complete follow-up owing to travel issue. He eventually withdrew from the study. ECHO = transthoracic echocardiography; FU = follow-up; LAAC = left atrial appendage closure; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; RBBB = right bundle branch block; RV = right ventricular.

patient, and institutional review board approval was granted at each site.

STUDY OUTCOMES. The study protocol included patient visits and data collection at baseline, 30 days, 180 days, and 365 days. Primary safety endpoints, including early and late occurrence of thromboembolism, valve thrombosis, major hemorrhage, major perivalvular leak, endocarditis, structural valve deterioration (SVD), nonstructural valve dysfunction (NSVD), valve-related hemolysis, all-cause death, valve-related reoperation or explantation, and valve-related deaths were reviewed and adjudicated by the independent clinical events committee and data safety monitoring board. Clinical events were adjudicated according to Valve Academic Research Consortium 3 criteria[9] as agreed to by the India regulatory approval board. SVD was defined as any intrinsic permanent change to the prosthetic valve, including wear and tear, leaflet disruption, fibrosis or calcification, and strut fracture or deformation. NSVD was defined as any abnormality not intrinsic to the prosthetic valve resulting in valve dysfunction (ie, intra- or paraprosthetic regurgitation, pannus, inappropriate positioning or sizing, prosthesis-patient mismatch, and embolization). Valve thrombosis was reported as a separate endpoint and was not considered to be NSVD.[9] Primary valve performance was assessed by change in NYHA functional class, as well as baseline and postprocedural echocardiographic measures including mean gradient (MG), peak gradient, effective orifice area (EOA), indexed effective orifice area (EOAi), and total valvular regurgitation. Secondary endpoints included changes in quality of life as determined by Kansas City Cardiomyopathy Questionnaire results and functional outcome as evaluated by 6-minute walk test distance. Additional measurements, including left ventricular end-systolic diameter and volume, left ventricular end-diastolic diameter and volume, left ventricular ejection fraction, and left ventricular mass were obtained at each follow-up, together with paravalvular and total regurgitation. Primary and secondary endpoints are listed in Supplemental Table 2.

POLYMER SURGICAL MV. The Tria Mitral Valve is a fully synthetic prosthetic heart valve with a flexible polymer stent and annular base. The lightweight frame is made of implantable-grade poly-ether-ether-ketone (Solvay Zeniva), which is impregnated with 6% barium sulfate for radiopacity. Three flexible polymer leaflets are bonded to the frame by means of a casting process. The polymeric leaflet material surrounds the apertures in the frame, leaving a central opening in each aperture. A porous polytetraflourothylene (PTFE) sewing ring is mounted on the heart valve by suturing the ring through the apertures with the use of polyester suture. The valve is provided in 5 sizes: 23, 25, 27, 29, and 31 mm. The leaflets are one-third the thickness of pericardial tissue and are not limited by constraints and variability of animal tissue. The valve is provided sterile in a dry state and requires no preparation before implantation.

SURGICAL TECHNIQUE. All surgeons underwent procedural and investigator training with an initial 2 cases considered to be roll-in. Although the operating surgeon had liberty to decide on implanted valve size intraoperatively, the screening committee outlined parameters for valve sizing based on criteria with respect to predicted EOAi >0.85 cm^2/m^2 according to TTE and predicted neo-left ventricular outflow tract (neo-LVOT) >200 mm^2 according to CTA. No concomitant procedures, except ligation of the left atrial appendage, were permitted. Surgeons implanted all valves via sternotomy with the patient on cardiopulmonary bypass with cardiac arrest. Valves were secured to the mitral annulus with hand-tied 2-0 pledgeted sutures. Intraoperative evaluation with transesophageal echocardiography confirmed valve position and functional integrity.

ANTICOAGULATION. VKA was initiated on postoperative day 1, unless contraindicated, with an INR target of 2.5 (2.0-3.0). Patients remained on VKA for 12 months after the procedure with daily monitoring during index admission and careful outpatient monitoring to maintain INR target compliance. Aspirin (75-100 mg) was started when the patient was clinically stable and maintained throughout the study period.

PRE- AND POSTPROCEDURAL IMAGING. Pre- and postprocedural TTE was performed according to American Society of Echocardiography criteria.[10,11] Gated CTA images at baseline were analyzed for assessment of the predicted neo-LVOT area using predicted valve implantation of specific sizes as a covered cylinder (Supplemental Figure 3); this was performed to simulate future transcatheter MV-in-valve implantation into the study valve.

Valve size selection was based on prosthetic size criteria with respect to predicted EOAi >0.85 cm^2/m^2 and predicted outflow tract >200 mm^2 from both baseline CTA and TTE, and this selection was outlined in the screening evaluation. Sizing of the polymer MV was done in diastole and neo-LVOT analysis in systole 30%, according to previous

TABLE 1 Baseline Patient Characteristics (N = 67)

Demographics	
Age, y	42.2 ± 12.3
	42.0 (19.0-67.0)
Age range, y	
≤25	6 (9.0)
26-35	17 (25.4)
36-45	18 (26.9)
46-55	13 (19.0)
56-65	11 (16.4)
>65	2 (3.0)
Height, cm	157.1 ± 10.1
Weight, kg	56.1 ± 13.0
BMI, kg/m^2	22.7 ± 4.7
BSA, m^2	1.6 ± 0.2
Sex	
Male	24 (35.8)
Female	43 (64.2)
Women of childbearing age	32 (47.8)
STS Risk Score, %	1.4 ± 0.8
Medical history and comorbidities	
Rheumatic heart disease	49 (73.1)
Arterial hypertension	4 (6.0)
Smoking	5 (7.5)
Previous stroke	0 (0)
Diabetes mellitus	1 (1.5)
Peripheral vascular disease	0 (0)
History of atrial fibrillation	42%
On anticoagulation	13 (19.4)
Coronary artery disease	1 (1.5)
Previous myocardial infarction	1 (1.5)
Previous CABG	0 (0)
Previous PCI	1 (1.5)
Permanent pacemaker	1 (1.5)
Previous valve surgery or procedure	5 (7.4)
Functional assessments and laboratory values	
NYHA functional class III or IV	36 (53.7)
Creatinine, mg/dL	1.0 ± 0.6
BNP, pg/mL	382.0 (5.0-6,311.0)
6-minute walk distance, m	298.1 ± 127.5
KCCQ overall score	57.5 ± 19.4
Echocardiographic Parameters	
LVEF, %	63.0 ± 11.1
LVEDD, mm	48.9 ± 8.5
LVEDV, mL	116.8 ± 47.2
LVESD, mm	31.5 ± 7.9
LVESV, mL	44.1 ± 26.2
MR	
Moderate	11 (16.7)
Moderate to severe	8 (12.1)
Severe	12 (18.2)
MS	
Severe	18 (27.2)
Mixed MR/MS	50 (75.6)
Mitral mean gradient, mm Hg	9.7 ± 5.6
EOA, cm^2	0.9 ± 0.5
EOAi, cm^2/m^2	0.6 ± 0.4
Cardiac output, L/min	4.6 ± 1.4

Values are mean ± SD, median (range), or n (%).

BMI = body mass index; BNP = B-type natriuretic peptide; BSA = body surface area; CABG = coronary artery bypass grafting; EOA = effective orifice area; EOAi = EOA indexed to body surface area; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; MS = mitral stenosis; PCI = percutaneous coronary intervention; PM = pacemaker; ICD = implantable cardioverter-defibrillator; STS = Society of Thoracic Surgeons.

Continued on the next column

literature.[12] A predicted neo-LVOT <200 mm^2, from CTA core lab report, was an exclusion criterion.

Repeated CTA was performed at 6 months and 1 year, and TTE was repeated at 30 days, 90 days, 6 months, and 1 year. Follow-up imaging was evaluated by the core laboratories.

STATISTICAL ANALYSIS. Analysis of the safety and effectiveness data was conducted as a comparative estimate to clinical data reported in the literature for surgical MVR and as reported by Objective Performance Criteria standards.[13] Thirty-day outcomes are presented as incidence rates. Twelve-month data for primary and secondary endpoints are presented as Kaplan-Meier estimates. NYHA functional class is reported as percentage of patients in each class, comparing baseline and 12 months. Echocardiographic reports for hemodynamic performance were analyzed by the independent echocardiography core laboratory with data summarized as continuous variables. Changes in hemodynamic endpoints from baseline through each follow-up period were calculated, and all hemodynamic data were stratified by valve size. A paired Student's *t*-test with Bonferroni correction was used to compare hemodynamic values at different timepoints. Adverse event and effectiveness data reported in the literature were compared with the adverse event and effectiveness data for the valve. A *P* value of <0.05 was considered to be significant.

ROLE OF THE FUNDING SOURCE. The sponsor (Foldax) was involved in study design, data analysis, and site selection.

RESULTS

PATIENT ENROLLMENT AND BASELINE CHARACTERISTICS. From April to November 2023, 67 patients were enrolled at 8 centers across India, with all patients successfully receiving the study valve. Screening failures occurred in 48 patients; reasons for exclusion included neo-LVOT <200 mm^2,

TABLE 2 Safety Events and Late Outcomes

	Early (≤30 d)	Cumulative at 1 y[a]	Probability Event-Free at 1 y, %[a]
All-cause mortality	1 (1.5)	6 (9.1)	90.9%
Valve or cardiovascular related mortality	0 (0)	0 (0)	100%
Valve reintervention/reoperation	0 (0)	0 (0)	100%
Study valve explant	0 (0)	0 (0)	100%
Structural valve deterioration	0 (0)	0 (0)	100%
Nonstructural valve dysfunction	1 (1.5)	1 (1.6)	98.4%
Thromboembolism	1 (1.5)	5 (7.5)	92.5%
Ischemic stroke	1 (1.5)	3 (4.9)	95.1%
Hemorrhagic stroke	0 (0)	0 (0)	100%
Transient ischemic attack	0 (0)	0 (0)	100%
Valve thrombosis	0 (0)	2 (4.3)	95.7%
Endocarditis	0 (0)	0 (0)	100%
All bleeding			
Major bleeding	1 (1.5)	1 (1.5)	98.5%
Hemolysis	0 (0)	0 (0)	100%
Kidney failure	0 (0)	0 (0)	100%
Newly diagnosed atrial fibrillation or other arrhythmias	0 (0)	1 (1.6)	98.4%
New pacemaker	0 (0)	0 (0)	100%
New or worsening heart failure	1 (1.5)	1 (1.6)	98.4%

Values are n (%) unless otherwise indicated. [a]These percentages are Kaplan-Meier estimates at the specific timepoint and thus do not equal the number of patients with events divided by the total number of patients.

need for a concomitant procedure, and poor imaging (Figure 1). No patients were excluded intraoperatively for any reason. The median follow-up period for the study was 12 months, covering a total of 67 patient-years. At the conclusion of 1 year, 60 patients remained in the study (Figure 1).

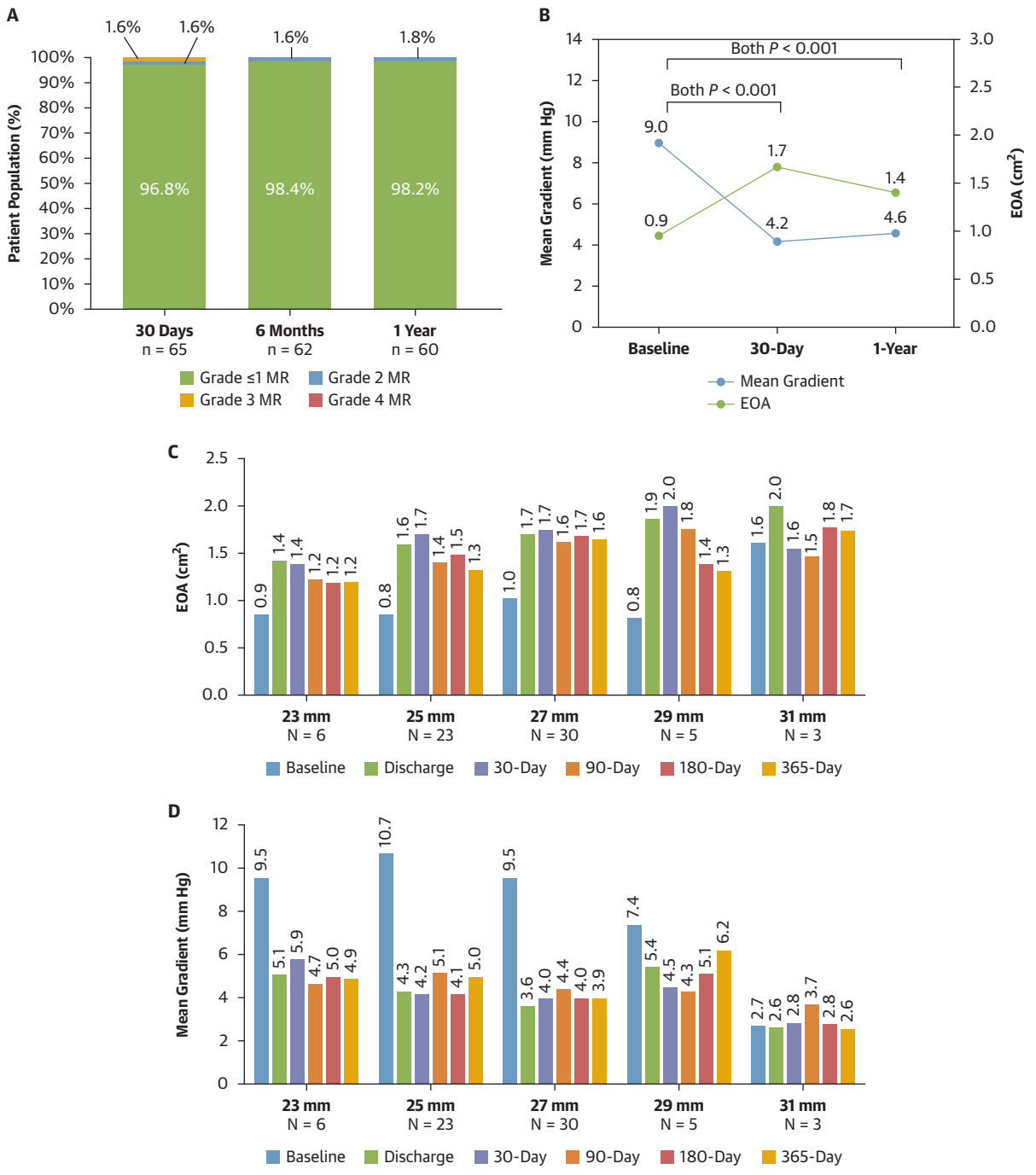
Patient demographics are presented in Table 1. Study patients were generally young and low risk (mean Society of Thoracic Surgeons score: 1.4% ± 0.8%), with a mean age of 42.2 ± 12.3 years (range: 19.0-67.0 years). Most enrolled subjects were female (64%), and among them, 48% were of childbearing age. The majority of the patients (73%) had rheumatic heart disease. Atrial fibrillation was common (42%); however, despite a high rate of rheumatic atrial fibrillation, only 13 patients (19.4%) were on anticoagulant therapy at baseline. The most common diagnosis among participants was mixed MV stenosis/regurgitation (50/67; 75.6%). Most of the patients had preserved preoperative left ventricular ejection fraction.

PROCEDURE CHARACTERISTICS AND PERIOPERATIVE SAFETY. Intraoperative and in-hospital course and adverse events are summarized in Supplemental Table 3. All patients received open complete sternotomy, and there were no intraoperative deaths. The most common implanted valve size was 27 mm (30/67; 47%), and the entire cohort underwent concomitant suture-mediated left atrial appendage closure. In-hospital adverse events included no cases of acute kidney injury, no mediastinitis, and one re-exploration for bleeding. One patient experienced an intraoperative free wall rupture unrelated to the study valve and died the next day; this event occurred immediately after weaning from cardiopulmonary bypass, when a left ventricular rupture of the free wall was encountered. Bypass was immediately restarted, and the free wall was repaired with a patch. The chest was closed but the patient ultimately expired within 24 hours. The valve itself was intact and had good function during intraoperative echocardiography.

CLINICAL OUTCOMES. Safety events and clinical outcomes during the study period are presented in Table 2. Thirty-day and 1-year all-cause mortality rates were 1.5% and 9.1%, respectively. No death was valve related. Besides the patient experiencing left ventricular rupture, the recorded causes of death were septic shock (n = 2) and aspiration asphyxia (n = 1). Two patients died at home, and the cause of death could not be identified, but both had a normally functioning MV prosthesis at the last echocardiographic examination. During follow-up, there were 3 ischemic strokes (1-year cumulative Kaplan-Meier rate: 4.9%), 2 valve thromboses (4.3%), and 1 major bleeding event (1.5%) related to the procedure. All strokes occurred during periods of subtherapeutic INR. In one case, thrombolysis was performed in the context of an acute cortical infarct. In the other 2 patients, brain magnetic resonance imaging showed subacute lesions that were treated conservatively with VKA dosage optimization. In 1 patient, concomitant spontaneous echo contrast was found in the left atrium (with normal valve function), and he was therefore kept on heparin infusion for 1 day. The neurologic symptoms resolved with treatment to baseline with no deficits in all patients. Both cases of valve thrombosis were discovered during follow-up visits (90-day for one patient, 1-year for the other) in asymptomatic subjects with subtherapeutic INR. Both were promptly hospitalized and underwent thrombolysis, with complete resolution and normalization of valve gradients. One patient was readmitted at 30 days for worsening heart failure (with normal valve function according to TTE). No structural valve dysfunctions, valve explantations, endocarditis, hemolysis, or reoperations were observed up to 1 year after the procedure.

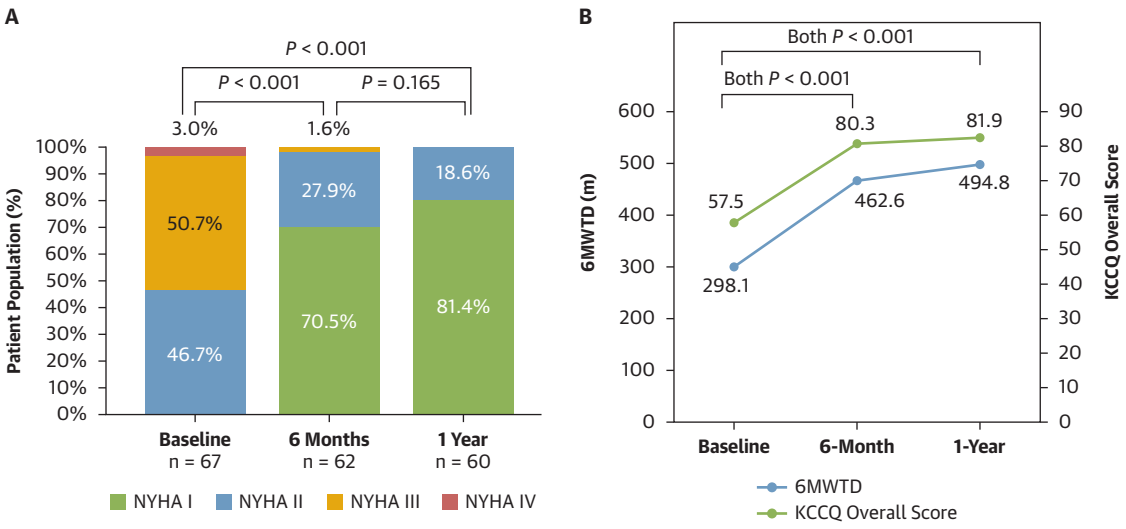
ANTICOAGULATION COMPLIANCE. Compliance with VKA is documented in Supplemental Table 4. Only

FIGURE 2 Residual MR and Echocardiography-Derived Hemodynamics



(A) After mitral valve replacement, most of the subjects were free from significant MR: 96.8% of the patients who completed 30-day follow-up, 98.4% of those who completed 6-month follow-up, and 98.2% of those who completed 1-year follow-up had MR ≤1, with only 1 case of more than moderate paravalvular leak at 1 year. MR is graded as follows: 1 = mild; 2 = moderate; 3 = moderate to severe; 4 = severe. (B) In patients with paired echocardiograms, a significant increase in the effective orifice area (EOA) with corresponding significant decrease in mean mitral gradient was registered across the study period. As expected, larger valve sizes were associated with (C) higher EOA and (D) lower mitral gradient across the entire study period.

FIGURE 3 Functional Status (NYHA Functional Class, 6MWTD, and KCCQ Overall Score) at Baseline and Follow-Up



At baseline, all enrolled subjects were symptomatic for dyspnea (NYHA functional class ≥II). Mitral valve replacement with the Foldax Tria valve was associated with a significant improvement in functional class at both 6 months (NYHA functional class ≤II: 98.4%) and 1 year (NYHA functional class ≤II: 100%), together with a considerable increase in 6-minute walk test distance (from 298.1 ± 127.5 at baseline to 494.8 ± 151.6 at 1 year; $P < 0.001$) and KCCQ overall score (from 57.5 ± 19.4 at baseline to 81.9 ± 14.7 at 1 year; $P < 0.001$). KCCQ = Kansas City Cardiomyopathy Questionnaire.

61.5% of patients reached the target INR of 2.0 to 2.5 within the first 30 days, and that number increased to 79% at 180 days and to 95% at 1 year.

IMAGING FINDINGS. Echocardiographic baseline, 30-day, and 1-year characteristics of the treated population are presented in Supplemental Table 5. The polymer MV showed excellent performance in both the short-term and the mid-term. Mitral regurgitation was mild or less in 96.8% and 98.2% of the patients at 30-day and 1-year follow-ups, respectively (**Figure 2**). More than mild paravalvular leak (PVL) was present in 2 patients (1 with moderate PVL, 1 with moderate to severe PVL); there was no transvalvular regurgitation. The mean MG decreased from 9.0 ± 4.9 mm Hg at baseline to 4.2 ± 1.5 mm Hg at 30 days and remained stable up to one year. Consistently, mean EOA increased from 0.9 ± 0.5 cm^2 to 1.7 ± 0.6 cm^2 at 30 days and did not change significantly up to 1 year (**Figure 2**, Supplemental Figure 5).

The predicted neo-LVOTs per valve size are presented in Supplemental Table 6, with all sizes well over the inclusion threshold of 200 mm^2. The average left atrial diameter in diastole was 49.4 ± 9.9 mm (range: 35-96 mm). CTA assessment at 1 year showed no calcifications of the valve, and there was no evidence of valve thrombus.

FUNCTIONAL OUTCOMES. Functional outcomes of the study population at different timepoints are presented in Supplemental Table 7 and **Figure 3**. Valve replacement effectively improved symptoms in almost all of the patients. Indeed, at baseline the whole cohort was in NYHA functional class ≥II, and 1 year after the procedure 81.4% of the patients were in NYHA functional class I and 18.6% in NYHA functional class II. Similarly, 6-minute walk test distance from 298.1 ± 127.5 m to 494.8 ± 151.6 m, and Kansas City Cardiomyopathy Questionnaire Overall Summary Score increased and from 57.5 ± 19.4 to 81.9 ± 14.7 (both $P < 0.001$).

DISCUSSION

In this study, we report, for the first time, the clinical outcomes, safety, and valve performance of a novel polymer leaflet within a surgical MV prosthesis in 67 patients. The main findings are as follows: 1) 1-year mortality of 9.1% and overall safety were similar to commercial bioprosthetic surgical valves; 2) favorable valve performance was demonstrated by EOA and MG at 1 year; 3) there were no cases of SVD within 1 year; 4) all patients experienced significant improvement in functional status and quality of life; and 5) no evidence of calcification or thrombus was

seen by CTA at 1 year. These results support the continued investigation of polymer technology as a biological tissue or mechanical valve substitute, particularly in vulnerable populations such as younger women of childbearing age or those with rheumatic valvular disease.

Polymer valves have historical precedent, with the composition of materials ranging from PTFE, polyurethanes, and newer polymer compounds.[14,15] The polymer used in the present study (LifePolymer) is a siloxane polyurethane urea, a member of the polymer family that has formed the basis for other biomedical applications (pacing lead insulation, coronary stent coverings). The addition of siloxane soft segments enhance biostability, and resistance to oxidative and hydrolytic degradation. The urethane-urea hard block segments provide characteristics amenable to heart valve tissue: high tensile and tear strength, high resistance to creep, and appropriate dynamic moduli.[8] Previously, this polymer has displayed freedom from calcification in a 6-month ovine model (Supplemental Figure 1).[8] The clinical validity of this polymer was reported in a preliminary report of 14 patients implanted with a surgical aortic valve replacement.[16]

The primary clinical outcomes demonstrate a number of important findings. First, although some fluctuations were registered across the follow-up timeframes, valve hemodynamics, including EOA and MG, remained stable from 30 days to 1 year. At 1 year, MG and EOA were 4.6 mm Hg and 1.4 cm^2, respectively, which compare favorably to the outcomes of the latest-generation pericardial valve (MG 3.6 mm Hg, EOA 1.3 cm^2)[17] (Supplemental Table 8 presents a comparison with contemporary MVs, and Supplemental Table 6 presents the predicted EOA chart). Total regurgitation and paravalvular regurgitation were not significant. Second, despite an average young patient age of 42 years, no fibrosis or early calcium deposits could be seen on 1-year postoperative CTA. Moreover, valve and polymer leaflet biocompatibility by imaging was established at 1 year: Echocardiographic analysis did not show reduced leaflet motion, hypoattenuated leaflet thickening, sewing ring abnormality, or restriction of leaflets. Dark matter was quantified qualitatively on CTA according to standard protocols and was not found at 1 year, with the caveat that patients were maintained on VKA and low-dose aspirin. Two patients did experience valve thrombosis, in the setting of anticoagulation noncompliance at 90-day and 1-year follow-up. This was successfully treated with intravenous thrombolytics, with thrombus resolution and normalization of valve gradients. Moreover, biocompatibility of the sewing ring and molded valve frame was acceptable, with no overt thrombus on the remaining valve components noted.

Finally, mortality in this series, slightly higher than in current Western experience (6.2%),[17] was lower than in previous reports of patients who underwent MVR in India (9.1% at 1 year vs 13% in the Dafodil trial).[17,18] The specifics of the deaths in the present study reflect the study population of both urban and rural Indian patients; events leading to death included sepsis (gynecologic source, unknown source; n = 2), aspiration (n = 1), and unknown (n = 2). Three cerebrovascular events occurred and deserve mention. In all 3 cases, the patients were noncompliant with anticoagulation and a subtherapeutic INR was measured at the time of the event, but echocardiography did not suggest an embolic valve-related source. In 1 patient, concomitant spontaneous echo contrast was found in the left atrium (with normal valve function); it completely disappeared with 1 day of heparin infusion. No other major safety events were notable.

Polymer leaflet technology may alter the lifetime management strategy of many valve disease types, by virtue of several theoretical features: 1) very long durability free from structural valve degeneration; 2) the ability to reduce or cease anticoagulation temporarily or even permanently; and 3) being able to provide a transcatheter salvage solution.[19-23] The ability to salvage a failed surgical valve with valve-in-valve was essential for inclusion into the present study, in the event that a catastrophic valve failure occurred. In developing countries, mechanical valves have higher rates of re-operation owing to low medication compliance. A polymer valve that is able to safely bridge patients for days, weeks, months, or years without anticoagulation and that also has a nonsurgical salvage option could save numerous lives. The MV is uniquely positioned to take advantage of polymer valve features with respect to lifetime management. A durable MV prosthesis with the potential for reduced anticoagulation is a critical unmet need, particularly in developing countries which face disproportionate rates of rheumatic heart disease. Bioprosthetic valves specifically suffer from early SVD in up to 11% at 3 years in developing countries,[24] making mechanical valves the preferred valve of choice. In addition, the burden of repeated operations or procedures is borne by patients desiring a bioprosthetic valve, such as childbearing women, who face extraordinary risk in the setting of pregnancy and very high risk with MV reoperation.[25,26] Maternal and fetal mortality rates can range to as high as 11% and 33%, respectively, in this

setting.[27] In the present study, the average age of female patients was 40.8 years, with 48% of them in childbearing range. In fact, many of these patients cited the desire for children as their primary motivation for entering the trial. Providing an alternative to the unenviable choice of early reoperation with a bioprosthetic valve or high pregnancy risk with a mechanical valve is a global health imperative that may strengthen maternal-fetal outcomes in developing countries. Of note, all patients in this study were kept on VKA at 1 year, therefore limiting our ability to draw conclusions regarding the potential to lower anticoagulation requirements of polymeric valves. Despite anticoagulation, some patients still experienced embolic events, but this must be interpreted in the context of a study cohort mainly composed of rheumatic patients with preexisting atrial fibrillation and suboptimal anticoagulation adherence.[26] Further studies are ongoing to better characterize a suitable reduced anticoagulation protocol for this valve. Indeed, the preclinical findings in sheep models, together with the absence of thrombus detected through dark matter quantification in this study, provide an encouraging foundation for the hypothesis that this valve may ultimately not require long-term anticoagulation. Finally, the immunologic implications of rheumatic heart disease and younger patients is notable. Group A streptococcal infections, the causative organism in rheumatic heart disease, stimulate immune cells and cross-reactive antibodies to valve tissue that can continue to damage valves long after acute infection.[28-31] A biologically and immunologically inert polymer valve that can function in this scenario is an important scientific advance, given that there is no effective method to neutralize various xenoantigens such as GAS or alpha-Gal.[28-31]

STUDY LIMITATIONS. This study has many limitations that must be mentioned. This first-in-human experience was performed in India as a single-arm nonblinded nonrandomized study with no control group. No patients were taken off VKA at 1 year. Moreover, as presented in Supplemental Table 4, there was a high rate of medication noncompliance, resulting in significant INR variability and fluctuations. Although this poses challenges similarly to mechanical valve technologies and for later commercial clinical use, it must be interpreted within the context of the geographic and socioeconomic constraints of the health system in rural India, where patients often live far from hospitals and have limited access to regular follow-up and INR monitoring. Moreover, the rates of thromboembolic complications compare favorably to mechanical valves in developing counties, in which rates can be as high as 10%[32] (vs 7.5% for the current valve). Anticoagulation compliance may limit the generalizability of our findings to other health care settings. Further studies conducted in different countries, where more consistent anticoagulation adherence can be expected, will be essential to evaluate the feasibility of INR reduction as a future strategy. Finally, because only 1-year data are currently available, it would be premature to draw conclusions regarding superior durability compared with commercially available pericardial valves. Longer-term follow-up is required to establish the mid-term efficacy, further evaluate the integrity of the polymer, and understand the thrombotic risk of this valve. A study in the United States is currently planned to confirm safety and clinical outcomes in a U.S. population, which will address many of the limitations outlined above. In addition, studies to assess the safety and feasibility of INR reduction, with the ultimate goal of evaluating whether anticoagulation can be minimized or potentially avoided altogether, are being planned with regulatory agencies.

CONCLUSIONS

Through 1-year follow-up, the core laboratory-adjudicated India Surgical Mitral Trial demonstrated an acceptable safety profile, a low thrombotic event rate, and clinically stable hemodynamic performance of a novel surgical polymer MV. In this young, mainly rheumatic, population, the Tria Mitral Valve provided significant benefit in clinical, echocardiographic, and functional outcomes. The potential for a polymer MV to improve quality of life compared with a mechanical or bioprosthetic valve in childbearing women and rheumatic patients makes this technology a critical advancement in developing countries. Further investigation to establish longer-term durability and implement anticoagulation protocols are necessary and are underway.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.