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Characteristics and Outcomes of Patients Ineligible for Transcatheter Mitral Valve Replacement

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Introduction

Mitral transcatheter edge-to-edge repair (TEER) has proven to be a safe and effective treatment option in patients with primary mitral regurgitation (MR) at high or prohibitive surgical risk or those with secondary MR who remain symptomatic despite guideline-directed medical therapy (GDMT) and have favorable anatomy.[1] Transcatheter mitral valve replacement (TMVR) is emerging as an important therapy for patients with symptomatic severe primary or secondary MR who are deemed high surgical risk and have unfavorable anatomy for TEER.[2] Despite availability of multiple TMVR devices within the context of clinical trials, not all patients screened are suitable candidates for TMVR. As TEER is being reconsidered in these patients with challenging anatomies, outcomes of patients who screen failed for TMVR are not well understood. We sought to evaluate clinical, anatomic, and echocardiographic characteristics of patients who failed TMVR screening at our institution and compared clinical outcomes between patients undergoing MV surgery or TEER vs. those receiving GDMT alone.

Methods

Between November 2017 and October 2022, 65 patients were screened for TMVR trials at our institution of which 11 subsequently had TMVR. Patients who screen failed TMVR and had unfavorable but not prohibitive anatomy for TEER by transesophageal echocardiography underwent TEER, whereas those with prohibitive anatomy for TEER but not prohibitive surgical risk underwent MV surgery. Patients with very high or prohibitive surgical risk and prohibitive anatomy for TEER as determined by imaging and multidisciplinary heart team were assigned to receive GDMT alone. Baseline demographic, clinical, anatomic, and echocardiographic characteristics were compared between patients who subsequently underwent MV surgery/TEER vs. those who received GDMT alone. Each investigational TMVR device study has predefined anatomical suitability criteria for sizing and neo-left ventricular outflow tract obstruction (LVOTO) risk prediction determined by the study sponsor and evaluated by an imaging core laboratory by cardiac computed tomography. Typically, neo-LVOTO risk is high with neo-LVOT area of $<$1.7-1.9 cm^2. Primary outcome of interest was the composite of all-cause mortality and heart failure hospitalization at 1 year. Differences between groups were compared using chi-square analysis for categorical variables and Student's *t*-test for continuous variables. Using the Kaplan-Meier method, overall survival was compared between the 2 groups and a Cox regression analysis was used to determine hazard ratios and 95% CIs. The study was approved by the Houston Methodist Institutional Review Board.

Abbreviations: CT, computed tomography; GDMT, guideline-directed medical therapy; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; MV, mitral valve; TEER, transcatheter edge-to-edge repair; TMVR, transcatheter mitral valve replacement.

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a

Baseline Clinical Characteristics		Overall (N=54)	GDMT (N=33)	MV Intervention (N=21)	P-value
Age, years		76.71 ± 7.51	76.52 ± 7.71	77.01 ± 7.35	0.81
Female		36 (66.7)	24 (72.7)	12 (57.1)	0.25
Coronary Artery Disease		28 (51.9)	19 (57.6)	9 (42.9)	0.40
Hypertension		46 (85.2)	30 (90.9)	16 (76.2)	0.23
Diabetes Mellitus II		22 (40.7)	13 (39.4)	9 (42.9)	0.80
Stroke		4 (7.4)	4 (12.1)	0 (0)	0.14
Peripheral Vascular Disease		6 (11.1)	3 (9.1)	3 (14.3)	0.66
Chronic Obstructive Pulmonary Disease		13 (24.1)	8 (24.2)	5 (23.8)	0.97
Atrial Fibrillation		38 (70.4)	24 (72.7)	14 (66.7)	0.63
Chronic Kidney Disease		21 (38.9)	14 (42.4)	7 (33.3)	0.50
Pre GFR (mL/min)		68.6 ± 24.8	64.1 ± 20.1	75.7 ± 29.9	0.09
Pulmonary Hypertension		46 (85.2)	30 (90.9)	16 (76.2)	0.23
Prior Pacemaker		13 (24.1)	12 (36.4)	1 (4.8)	**0.008**
Prior cardiac surgery		20 (37)	14 (42.4)	6 (28.6)	0.30
NYHA III and IV		46 (85.2)	30 (90.9)	16 (76.2)	0.23
STS MV replacement (%)		6.8 ± 3.4	7.0 ± 2.9	6.3 ± 4.1	0.48
Reason for Screen failure	LVOTO	24 (44.4)	16 (48.5)	8 (38.1)	0.58
	Small annulus	7 (13)	5 (15.2)	2 (9.5)	
	Large Annulus	6 (11.1)	2 (6.1)	4 (19.0)	
	Risk of embolization/Para-valvular Leak	6 (11.1)	4 (12.1)	2 (9.5)	
	Clinical Considerations (Low EF, dialysis, short life expectancy, severe COPD, frailty)	11 (20.4)	6 (18.2)	5 (23.8)	
Baseline Echocardiographic Characteristics					
MR Etiology	Primary	39 (75)	22 (71)	17 (81)	0.46
	Secondary	9 (17.3)	7 (22.6)	2 (9.5)	
	Mixed	4 (7.7)	2 (6.5)	2 (9.5)	
≥moderate TR		35 (66.1)	23 (72)	12 (57.2)	0.20
≥moderate Mitral Annular Calcification		30 (56.6)	19 (59.4)	11 (52.4)	0.30
LVEF (%)		56.3 ± 12.3	55.1 ± 13.0	58.1 ± 11.1	0.38
Mitral Valve Area (cm^2)		4.0 ± 1.0	3.9 ± 1.0	4.2 ± 1.1	0.63
Mitral Mean Gradient (mmHg)		5.3 ± 4.0	5.2 ± 3.3	5.5 ± 4.9	0.82
Aorto-mitral angle		111 ± 29	107 ± 31	119 ± 24	0.29
LVEDV (ml)		183 ± 58	181 ± 50	186 ± 69	0.80
LVESV (ml)		78 ± 49	85 ± 46	70 ± 54	0.28
LVOT area (cm^2)		3.0 ± 0.5	2.9 ± 0.5	3.1 ± 0.5	0.34
Complex Anatomy (Mitral Valve perforation, aneurysm, severe valvular and leaflet calcification)		15 (27.7)	13 (39.4)	2 (9.6)	**0.01**
Outcomes (1-year)					
In-hospital Mortality		-	-	3 (14.28)	-
Death		14 (25.9)	10 (30.3)	4 (19.0)	0.35
HFH		29 (53.7)	25 (75.8)	4 (19.0)	**<0.001**
Death or HFH		33 (61.1)	26 (78.8)	7 (33.3)	**<0.001**
Renal Replacement Therapy		11 (20.4)	8 (24.2)	3 (14.3)	0.49

b

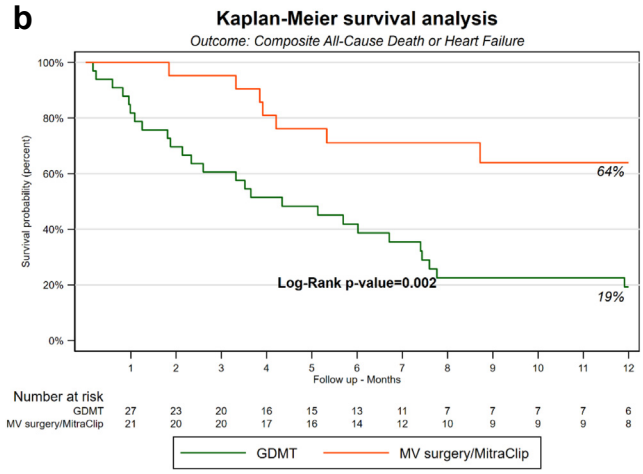

Figure 1. (a) Table of baseline clinical, echocardiographic, and outcomes. (b) Kaplan-Meier survival analysis.
Abbreviations: COPD, chronic obstructive pulmonary disease; EF, ejection fraction; GDMT, guideline-directed medical therapy; HFH, heart failure hospitalization; LVEDV, left ventricle end diastolic volume; LVESV, left ventricle end systolic volume; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; MV, mitral valve; NYHA IV, New York Heart Association functional class IV; STS, Society of Thoracic Surgeons; TR, tricuspid regurgitation.

Results

Screen failure rate was 83%. Of the 54 screen failures (mean age 76.7±7.5 years; 67% female, 75% primary MR), 21 (39%) underwent MV intervention (13 MV surgery; 8 mitral TEER) while 33 (61%) were managed with GDMT alone. Baseline clinical characteristics and screen failure causes are summarized in Figure 1a. Tricuspid regurgitation grade ≥ moderate was present in 60% of patients while 56% had ≥ moderate mitral annular calcification (MAC). Primary reasons for screen failure for TMVR were risk of LVOTO (44.4%), clinical considerations (20.4%),

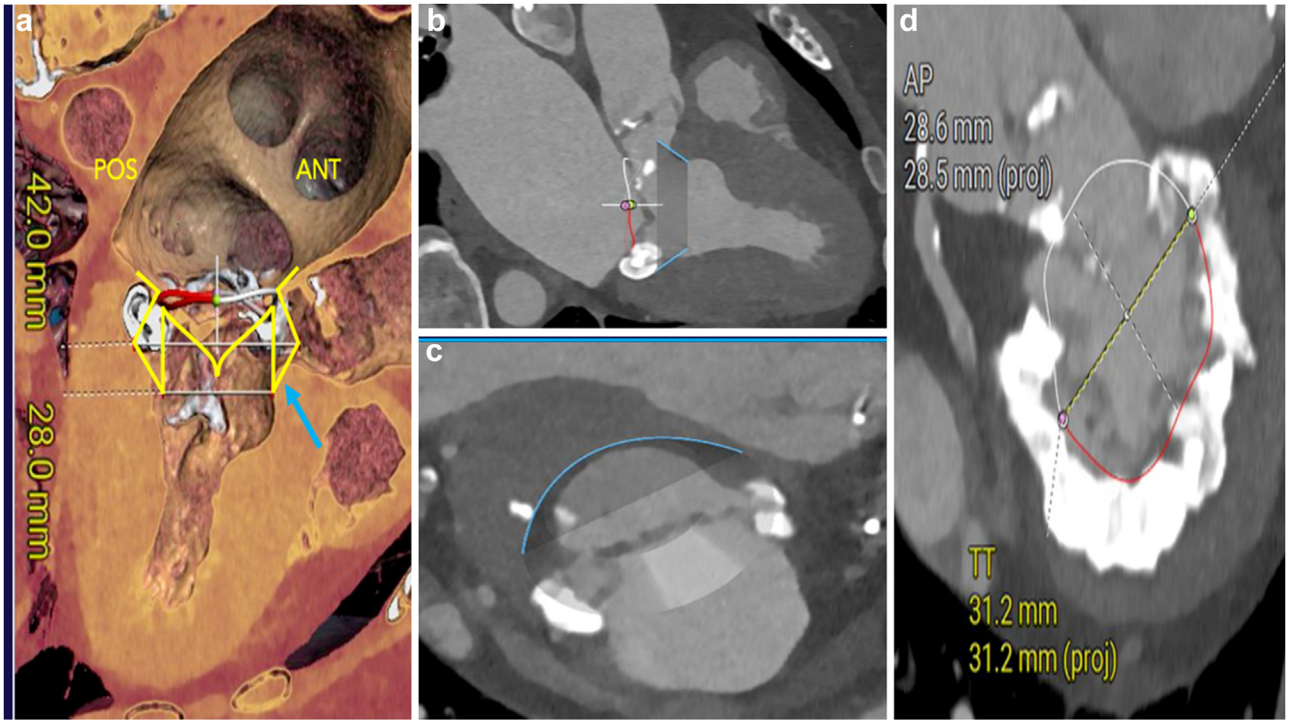

Figure 2. (a-c) CT reconstruction with virtual valve showing neo-LVOT of 0 cm^2. (d) Cardiac gated CT showing severe MAC.
Abbreviations: CT, computed tomography; LVOT, left ventricular outflow tract; MAC, mitral annular calcification.

small annulus (13%), large annulus (11.1%), and risk of embolization/paravalvular leak (11.1%). There were no differences in baseline clinical characteristics between the 2 groups ($p > 0.05$), except for fewer prior pacemaker and complex anatomy as defined using transesophageal echocardiography in the MV intervention group (9.6% vs. 39.4%, $p = 0.01$). The median follow-up was 8 (interquartile range: 5-20) months, with a higher cumulative 1-year event-free survival in the MV intervention group (81% vs. 19%, hazard ratio = 0.37 [0.16-0.89], $p = 0.02$) (Figure 1b). At the last follow-up, MV intervention patients continued to have acceptable residual MR (77.8% ≤mild MR) and mean gradient (4 mmHg).

To illustrate - A 78-year-old female patient with Society of Thoracic Surgeons predicted risk of mortality for MV replacement of 8.7% screen failed TMVR due to risk of LVOTO (neo-LVOT = 0 cm^2). She was at a prohibitive surgical risk and anatomy was deemed prohibitive for TEER due to severe MAC extending to MV leaflets (Figure 2).

Discussion

The present study examined the characteristics and outcomes of patients who screen failed for TMVR. The key findings are as follows: 1) screen failure rate was 83%, 2) the cohort represented a very morbid, high surgical risk population with a mean age>75 years and ≥moderate MAC in >50% of patients, 3) risk of LVOTO was the primary reason for screen failure, and 4) MV intervention group was associated with lower risk of all-cause mortality and heart failure hospitalization.

Screen failure rate for TMVR in our cohort was comparable to that reported by Niikura et al (83% vs. 89%).[3] Screen failure rate is high due to anatomic complexities of TMVR and limited valve sizes available in current trials. In our population, anatomical considerations constituted around 80% of the total screen failure causes with LVOTO risk being the most common. Innovation in valve technology to reduce LVOTO risk, increase in valve sizes, reduced delivery sheath profiles, and growth of strategies to mitigate LVOTO risk such as alcohol septal ablation and various transcatheter electrosurgical techniques will allow more patients to be eligible for TMVR in the near future.

It is important to note that 67% of the screen failed patients were females. Although men and women have different anatomical and clinical risk profiles, data are lacking regarding sex-based differences in patients undergoing TMVR. Compared to men, women tend to have more disproportionate MR, atrial fibrillation, MAC, and smaller ventricles, increasing the risk of screen failure based on anatomic complexity.[4]

Patients with significant MAC and severe TR were excluded from early TMVR trials. In the light of growing evidence on the feasibility of TMVR in MAC, this is the first study to report outcomes in this population, where 56% had ≥ moderate MAC and 19% had severe TR.[5] In the MV surgery/TEER group, less complex anatomy and a high prevalence of primary MR (81%) were present, which may explain the favorable outcomes seen in this group.[1]

Limitations of this study include small sample size, short follow-up, and single-center retrospective nature of the study.

Conclusion

In our cohort, patients ineligible for TMVR undergoing subsequent MV surgery or TEER had more favorable outcomes compared to those medically managed alone despite no differences in baseline characteristics. In a carefully selected population at acceptable surgical risk and nonprohibitive anatomy, MV surgery or TEER, respectively, may be viable options.

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Ethics Statement

This study received the proper ethical overview from the Houston Methodist Institutional Review Board.

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Disclosure Statement

Dr Reardon is a consultant for Medtronic, Boston Scientific, Abbott, W L Gore & Associates. Dr Atkins is a consultant for W L Gore & Associates. Dr Kleiman is a local principal investigator in trials sponsored by Boston Scientific, Medtronic, Abbott, and Edwards Lifesciences. Dr Goel is a consultant for Medtronic, W L Gore & Associates, and on the Speakers Bureau for Abbott Structural Heart. The other authors had no conflicts to declare.

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