JACC: ASIA VOL. 2, NO. 3, 2022

CUTTING EDGE TECHNOLOGY

First-in-Human Study of the Novel Transcatheter Mitral Valve Repair System for Mitral Regurgitation

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ABSTRACT

Transcatheter mitral valve intervention treatment is a promising alternative therapy for patients with severe mitral regurgitation (MR). This is a multicenter, prospective, first-in-human study of transcatheter edge-to-edge repair (TEER) using a novel device for severe MR. Safety and efficacy were assessed immediately after the procedure and at 30-day follow-up. Twenty-three patients (age 70.0 ± 5.2 years) who were at high/prohibitive surgical risk underwent successful procedures without major periprocedural complications. All patients achieved residual MR ≤2+ at discharge, with 73.9% with 1+ residual MR. The left ventricular end-systolic diameter improved from 4.1 cm at baseline to 3.4 cm at 30-day follow-up. New York Heart Association functional class I/II after TEER was achieved in 87% of patients. This study demonstrated that TEER with the device was feasible and safe for the treatment of patients with severe MR. (Dragonfly-M Transcatheter Mitral Valve Repair System Early Feasibility Study; NCT04528576) (JACC: Asia 2022;2:390–394) © 2022 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/).

Mitral regurgitation (MR) is the most prevalent valvular heart disease in the population older than 75 years.[1] Untreated severe MR is associated with increased risk of cardiovascular mortality and heart failure hospitalization.[2] Surgery, the gold standard for the treatment of severe degenerative mitral regurgitation (DMR), is challenging for patients at high or prohibitive risk because of advanced age and multiple comorbid conditions.[3] Within the past decade, transcatheter edge-to-edge repair (TEER) has emerged as a viable option for patients with DMR deemed high surgical risk or for those with functional mitral regurgitation (FMR) despite guideline-directed medical therapy (GDMT).[4] Current guidelines recommend TEER for prohibitive risk patients with DMR and FMR for those failing GDMT.[5,6]

The principle of TEER is to bring the surfaces of the anterior and posterior mitral leaflets into coaptation together, and therefore convert the regurgitant single-orifice into a smaller double-orifice mitral valve. MitraClip (Abbott Vascular), the first TEER device, has been widely used in treatment of patients with MR with high surgical risk. More recently, a number of TEER devices are in development. The device in our study, the first domestic transfemoral

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Paul Sorajja, MD, served as Guest Associate Editor for this paper. William F. Fearon, MD, served as Guest Editor-in-Chief for this paper.

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.

Manuscript received October 6, 2021; revised manuscript received March 15, 2022, accepted March 17, 2022.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2022.03.010

TEER device in China, has unique design features and is capable of treating both straight-forward and anatomically complex MR (**Figure 1B**).

Our previous work reported the first-in-human application in a high surgical risk patient with DMR.[7] Herein, this multicenter prospective study was designed to elaborate on the short-term safety and efficacy of the device.

METHODS

This was a multicenter, prospective single-arm study conducted in 3 medical centers in China. All patients enrolled underwent transthoracic and transesophageal echocardiography reviewed by an independent echocardiographic core laboratory (Asia Cardiovascular Imaging Corelab, Hong Kong, China). Patients with MR ≥3+ considered as candidates for TEER by a multidisciplinary heart team, were then reviewed by an independent eligibility committee for high or prohibitive surgical risk status of patients with DMR and having achieved maximally tolerated GDMT in patients with FMR. We used maximally tolerated dose of GDMT (angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, β receptor blocker, and aldosterone antagonist, and/or sacubitril/valsartan) for patients with FMR at stable doses for at least 30 days before trial registration according to the updated guidelines. Patients were excluded if they had left ventricular ejection fraction <20%, mitral valve area <3.5 cm^2, previous mitral valve surgery or transcatheter mitral valve procedures, significant calcium in the device landing zone, leaflet length <7 mm, stroke within 90 days before intervention, or percutaneous cardiovascular intervention within 30 days before intervention. The TEER system (DragonFly) was implanted as previously reported.[7] The study was approved by the medical ethics committee of each participating hospital and carried out according to the principles of the Declaration of Helsinki. All patients provided written informed consent for research.

The definitions of study endpoints followed Mitral Valve Academic Research Consortium criteria. The primary performance endpoint was defined as successful deployment with MR reduction to ≤2+ at discharge. The primary safety outcome was reported as freedom from major adverse events (MAEs), including procedure-related death, myocardial infarction, stroke, renal failure, and nonselective cardiovascular surgery, by an independent clinical events committee. New York Heart Association (NYHA) functional classification was assessed by site cardiologists.

Baseline characteristics, and procedural and clinical outcomes were collected prospectively. Transthoracic echocardiography measurement was performed at baseline, discharge, and 30 days after intervention. Baseline echocardiographic data included location of MR, vena contracta width, effective mitral regurgitation orifice area, and regurgitation volume by the proximal isovelocity surface area method. Postprocedurally, MR severity was assessed using an integrative approach based on qualitative and quantitative parameters by the proximal isovelocity surface area method, the vena contracta width, and the change of pulmonary venous blood flow. The mean transmitral pressure gradient was calculated using continuous-wave Doppler. MR severity was graded (0 to 4+) according to the latest American Society of Echocardiography guidelines. The procedural time was defined as the time from the introduction of the guiding sheath into the left atrium to the removal.

The continuous variables were reported as mean ± SD or median (IQR) according to the distribution. Categorical variables were summarized as frequencies and percentages. Data were analyzed using SPSS (version 25.0).

ABBREVIATIONS AND ACRONYMS

DMR = degenerative mitral regurgitation

FMR = functional mitral regurgitation

GDMT = guideline-directed medical therapy

MAE = major adverse event

MR = mitral regurgitation

NYHA = New York Heart Association

TEER = transcatheter edge-to-edge repair

RESULTS

BASELINE CHARACTERISTICS. A total of 23 patients were enrolled and treated with the TEER system in this study between September 2020 and April 2021. Male patients consisted of 56.5% of the cohort and the average age was 70.0 ± 5.2 years. Five patients (21.7%) had MR grade 3+ and 18 (78.3%) patients had MR grade 4+ with a median effective mitral regurgitation orifice area of 0.5 cm^2 (IQR: 0.4 to 0.6 cm^2). Twelve patients underwent TEER for DMR, 10 for FMR, and 1 for mixed MR. The Society for Thoracic Surgery score for mitral valve replacement was 4.7% ± 2.3%. All patients met the latest guidelines recommendation for mitral valve interventional treatment.[5,6] All patients with FMR had ≥3+ MR despite optimized GDMT; 56.5% of patients were classified as NYHA functional class III/IV at baseline.

Comorbidities, such as atherosclerotic coronary artery disease, previous myocardial infarction, atrial fibrillation, and diabetes, were common in this cohort. Four subjects with FMR had implantable cardioverter-defibrillator/cardiac resynchronization therapy based on the guideline recommendations. The mean left ventricular ejection fraction was 63.8% in DMR and 43.5% in FMR, respectively; 77.3% of

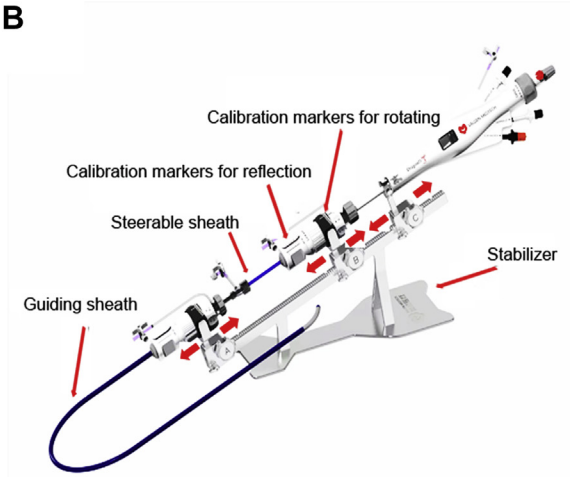
FIGURE 1 Characteristics of the TEER Device

A

Choice making for different clip sizes of DragonFly

MV lesion anatomy		SN0409	SW0609	XN0412	XW0612
Leaflet length	<9mm	+	+		
	≥9mm			+	+
Jet width	>6mm		+		+
MVOA	Small	+			
	Large		+	+	+
Segment	Zone 1 or 3	+	+		
	Zone 2			+	+

B



(A) Four sizes of clip (SN0409: width 4 mm, length 9 mm; XN0412: width 4 mm, length 12 mm; SW0609: width 6 mm, length 9 mm; XW0612: width 6 mm, length 12 mm) and choice making. **(B)** The entire delivery system of the device; the handle of the guiding sheath and steering sheath with calibration markers. The stabilizer is used on the sterile field to support and position the entire delivery system during the procedure. MVOA = Mitral Valve Orifice Area; TEER = transcatheter edge-to-edge repair.

patients presented left ventricular dilation. Eight patients (34.8%) had moderate-to-severe concomitant tricuspid regurgitation.

PROCEDURAL OUTCOMES. The primary performance endpoint was achieved in all patients without any major procedure-related complications (Table 1). There were no cases of post-procedural mitral stenosis, with mean transmitral gradients of all patients below 5 mm Hg. The number of implanted devices per patient was 1.5 on average (1 device in 60.9% of patients, 2 devices in 34.8%, and 3 devices in 4.4%). Procedurally, in 22% of cases, operators used the independent leaflet capture feature of the device, particularly for those with large flail gaps (6-10 mm), short posterior leaflets, or highly fluctuating prolapse movements. The procedural time was 104.0 minutes (range 93.0-201.0 minutes), and postoperative hospital stay was 4.0 days(range 3.0-5.0 days). All patients were followed up in person at 30 days and no MAEs occurred; 86.9% of patients were in NYHA functional class I/II at 30 days.

ECHOCARDIOGRAPHIC RESULTS. All patients achieved residual MR ≤2+ at discharge, among whom 73.9% were graded as ≤1+. Reduction of MR by more than 2 grades was achieved in 90.9%. Residual MR ≤2+ was maintained in all patients at 30 days. The left ventricular end-systolic diameter decreased from 3.7 cm at baseline to 3.1 cm at 30-day follow-up in DMR, 5.2 cm to 3.9 cm in FMR, and 3.9 cm to 2.9 cm in mixed MR.

DISCUSSION

This is the first preliminary report on the procedural results and 30-day outcomes of the novel device. The device used in this cohort was safe and effective, with all patients achieving the primary safety and performance endpoints. Symptomatic improvement (86.9% were NYHA functional class I/II) and effective left ventricular remodeling were noted in all patients at 30-day follow-up.

The widely used TEER device MitraClip has regulatory approval by the US Food and Drug Administration and European Conformite Europeenne, and the PASCAL TEER system (Edwards Lifesciences) is approved by the Conformite Europeenne. Several well-designed multicenter clinical trials have demonstrated the safety and efficacy of these 2 devices.[4,8-10] Of patients treated with the next-generation MitraClip G4 system, 96.6% achieved MR ≤2+ at 30 days.[10] In CLASP IID (Edwards PASCAL CLASP IID/IIF Pivotal Clinical Trial) with the PASCAL device, the rates of MR grade ≤1+ and ≤2+ were 73% and 98%, with 8% composite MAE rate at 30 days.[8] At the 30-day follow-up of our study, the proportion of MR grade ≤1+ and ≤2+ were 56.5% and 100% without any major post-procedural complications, which is comparable with contemporary research of MitraClip

TABLE 1 Baseline Characteristics, Procedural and Clinical Outcomes

	All (N = 23)	Degenerated MR (n = 12)	Functional MR (n = 10)	Mixed MR (n = 1)
Baseline characteristics				
Age, y	76.0 ± 5.2	78.1 ± 5.1	74.0 ± 4.5	81.0
Male	13 (56.5)	8 (66.7)	5 (50.0)	0 (0.0)
Coronary artery atherosclerosis disease	13 (56.5)	5 (41.7)	7 (70.0)	1 (100.0)
Previous MI	4 (17.4)	1 (8.3)	3 (30.0)	0 (0.0)
Atrial fibrillation	10 (43.5)	4 (33.3)	5 (50.0)	1 (100.0)
ICD/CRT	4 (17.4)	0 (0)	4 (40)	0 (0.0)
Baseline echocardiographic variables				
LVESD, cm	4.1 (3.4-5.2)	3.7 (3.1-4.3)	5.2 (4.0-6.3)	3.9
LVEF, %	59.0 (45.0-65.7)	63.8 (56.5-67.5)	43.5 (30.1-60.0)	77.0
Mitral regurgitation severity				
3+	5 (21.7)	3 (25.0)	2 (20.0)	0 (0.0)
4+	18 (78.3)	9 (75.0)	8 (80.0)	1 (100.0)
EROA, cm2	0.5 (0.4-0.6)	0.6 (0.4-0.7)	0.5 (0.4-0.6)	0.2
Regurgitant volume, mL	76.0 (64.0-105.0)	91.8 (68.3-111.0)	75.0 (63.0-83.8)	31.0
Vena contracta width, cm	0.6 ± 0.2	0.7 ± 0.1	0.6 ± 0.2	0.4
Flail width, cm	–	1.5 ± 0.5	–	0.9
Flail gaps, mm	–	4.7 ± 1.8	–	4.2
Location of MR jet				
Central	13 (56.5)	12 (100.0)	1 (10.0)	0 (0.0)
Noncentral	10 (43.5)	0 (0.0)	9 (90.0)	1 (100.0)
Procedural outcome				
Device success	100 (100)	100 (100)	100 (100)	100 (100)
Leaflet tear	0 (0)	0 (0)	0 (0)	0 (0)
Device embolization	0 (0)	0 (0)	0 (0)	0 (0)
Conversion to surgery	0 (0)	0 (0)	0 (0)	0 (0)
Major bleeding	0 (0)	0 (0)	0 (0)	0 (0)
Mean gradients, mm Hg				
1 clip	3.5 ± 1.7	2.3 ± 1.3	4.2 ± 1.6	2.5
2 clips	3.9 ± 1.1	4.1 ± 0.9	2.0	–
3 clips	3.0	–	3.0	–
Mitral regurgitation severity				
0	6 (26.1)	4 (33.3)	1 (10.0)	1 (100.0)
1+	11 (47.8)	4 (33.3)	7 (70.0)	0 (0.0)
2+	6 (26.1)	4 (33.3)	2 (20.0)	0 (0.0)
30-day outcomes				
All-cause mortality	0 (0)	0 (0)	0 (0)	0 (0)
Reintervention	0 (0)	0 (0)	0 (0)	0 (0)
MI	0 (0)	0 (0)	0 (0)	0 (0)
Dialysis	0 (0)	0 (0)	0 (0)	0 (0)
30-day echocardiographic variables				
LVESD, cm	3.4 (2.9-4.8)	3.1 (2.8-3.7)	4.9 (4.0-5.9)	2.9
LVEF, %	50.5 (39.5-58.7)	58.0 (50.9-61.8)	38.7 (26.9-48.5)	64.4
Mean gradient, mm Hg	3.7 ± 1.3	3.6 ± 1.1	3.9 ± 1.4	2.0
Mitral regurgitation severity				
0	5 (21.7)	4 (33.3)	0 (0.0)	1 (100.0)
1+	8 (34.8)	3 (25.0)	5 (50.0)	0 (0.0)
2+	10 (43.5)	5 (41.7)	5 (50.0)	0 (0.0)

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

CRT = cardiac resynchronization therapy; EROA = effective mitral regurgitation orifice area; ICD = implantable cardioverter-defibrillator; LVESD = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MR = mitral regurgitation.

and PASCAL systems.[8,10] The final 5-year results of the EVEREST II (Pivotal Study of a Percutaneous Mitral Valve System [EVERESTIIRCT]) trial supported the long-term safety of the MitraClip and the durability of MR reduction.[4] The final 2-year results of the CLASP trial showed high survival and a significantly reduced annualized heart failure hospitalization rate.[9] Longer-term studies are needed to explore

effectiveness and durability of the device in our study, but its early experiences seem to be similar to these other TEER devices.

The device in our study has the following characteristics. 1) The device features a central, compressible filler, which makes it unique, as with closure of the grasping arms causes this filler to spread out to fill the residual regurgitant orifice. This can be accomplished with the grasping arms locking in any angles ranging from 0° to 45°, which delivers a secure leaflet holding while decreasing the strain concentration on the clipping areas when dealing with small mitral valve orifice area or relatively short leaflet situations to avoid increasing transvalvular gradient after TEER procedure. 2) The device comes in 4 sizes (**Figure 1A**). 3) The delivery system (**Figure 1B**) includes a guide catheter and a steerable sleeve with readable reflection graduations on each handle. 4) The metal stabilizer with gear design on the rail and bracket knobs (**Figure 1B**) provides accurate and reliable forward and backward control of the clip delivery system. The device arms are closed simultaneously and mechanically locked (not self-locking) via the central compressible filler and the mechanical locking mechanism. Of the cases in this study, in 22% the operators used the independent capture feature of the device, especially for those with large flail gaps or very fluctuating prolapse movements during the TEER procedure.

CONCLUSIONS

This first-in-human study has demonstrated encouraging results in terms of the safety and efficacy of the novel TEER device for the treatment of severe MR in different etiologies. A larger pivotal trial with longer-term follow-up is enrolling.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work obtained funding support from the Zhejiang Province Science and Technology Department Key R & D Program (2021C03097), China, and Zhejiang Province Science and Technology Department Key R & D Program (2018C03084), China. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS a novel system, degenerated mitral regurgitation, functional mitral regurgitation, transcatheter edge-to-edge repair