EuroIntervention
2024;20:e239-e249
published online e-edition February 2024
DOI: 10.4244/EIJ-D-23-00361

ORIGINAL RESEARCH

Safety and efficacy of the DragonFly system for transcatheter valve repair of degenerative mitral regurgitation: one-year results of the DRAGONFLY-DMR trial

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00361

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ABSTRACT

BACKGROUND: Severe degenerative mitral regurgitation (DMR) can cause a poor prognosis if left untreated. For patients considered at prohibitive surgical risk, transcatheter edge-to-edge repair (TEER) has become an accepted alternative therapy. The DragonFly transcatheter valve repair system is an innovative evolution of the mitral TEER device family to treat DMR.

AIMS: Herein we report on the DRAGONFLY-DMR trial (ClinicalTrials.gov: NCT04734756), which was a prospective, single-arm, multicentre study on the safety and effectiveness of the DragonFly system.

METHODS: A total of 120 eligible patients with prohibitive surgical risk and DMR ≥3+ were screened by a central eligibility committee for enrolment. The study utilised an independent echocardiography core laboratory and clinical event committee. The primary endpoint was the clinical success rate, which measured freedom from all-cause mortality, mitral valve reintervention, and mitral regurgitation (MR) >2+ at 1-year follow-up.

RESULTS: At 1 year, the trial successfully achieved its prespecified primary efficacy endpoint, with a clinical success rate of 87.5% (95% confidence interval: 80.1-92.3%). The rates of major adverse events, all-cause mortality, mitral valve reintervention, and heart failure hospitalisation were 9.0%, 5.0%, 0.8%, and 3.4%, respectively. MR ≤2+ was 90.4% at 1 month and 92.0% at 1 year. Over time, left ventricular reverse remodelling was observed ($p<0.05$), along with significant improvements in the patients' functional and quality-of-life outcomes, shown by an increase in the New York Heart Association Class I/II from 32.4% at baseline to 93.6% at 12 months ($p<0.001$) and increased Kansas City Cardiomyopathy Questionnaire (KCCQ) score of 31.1±18.2 from baseline to 12 months ($p<0.001$).

CONCLUSIONS: The DRAGONFLY-DMR trial contributes to increasing evidence supporting the safety and efficacy of TEER therapy, specifically the DragonFly system, for treating patients with chronic symptomatic DMR 3+ to 4+ at prohibitive surgical risk.

KEYWORDS: mitral valve repair; transoesophageal echocardiogram; transthoracic echocardiogram

SUBMITTED ON 06/05/2023 - REVISION RECEIVED ON 08/10/2023 - ACCEPTED ON 20/10/2023

Mitral regurgitation (MR) is the most prevalent heart valve disease, particularly in populations aged >75 years[1]. MR increases left atrial and pulmonary venous pressure, leading to symptoms such as fatigue and dyspnoea[2]. Untreated severe MR is associated with pulmonary hypertension, atrial fibrillation, heart failure (HF), and mortality[3]. One of the more common aetiologies of MR is degenerative mitral regurgitation (DMR) which involves abnormities of the mitral valve, and in DMR, medical therapy does not improve survival[4]. Surgical mitral valve repair, with proven efficacy and a well-established safety profile, is a Class I recommendation in the current guidelines for symptomatic patients with DMR[5,6]. Nevertheless, owing to the perception of prohibitive surgical risk, aversion to surgery, or comorbid conditions[7,8], there remains an ongoing need for less invasive treatment options with the development of new technology and devices.

Transcatheter edge-to-edge repair (TEER) is an increasingly acknowledged treatment for patients with DMR who have a prohibitive surgical risk. The EVEREST II trial (Endovascular Valve Edge-to-Edge Repair Study) of the MitraClip (Abbott) demonstrated that TEER is a safe and effective therapy for these patients[9,10]. The MitraClip (now in its fourth generation) has been the mainstay of TEER therapy, used in over 150,000 patients worldwide. The PASCAL system (Edwards Lifesciences) was introduced more recently as another TEER therapy, and CLASP IID (Edwards PASCAL TrAnScatheter Valve RePair System Pivotal Clinical Trial) demonstrated its safety and effectiveness, which were comparable to those of the MitraClip[11]. With the accumulation of clinical evidence, recent guidelines from the American Heart Association/American College of Cardiology and European Society of Cardiology/European Association of Cardio-Thoracic Surgery have recommended that in symptomatic patients with severe DMR and high or prohibitive surgical risk, TEER can be appropriate[5,6].

The DragonFly transcatheter valve repair system (Valgen MedTech) is similar in concept to the MitraClip and PASCAL systems but has distinguishing and unique features. The system was initially studied in the first-in-human Dragonfly-M Early Feasibility Study, in which TEER using the DragonFly system was demonstrated to be feasible and safe for the treatment of patients with severe MR[12]. Herein, the DRAGONFLY-DMR trial aimed to further evaluate the safety and effectiveness of the DragonFly system for patients with symptomatic (moderate-severe and severe) DMR who are considered to be at high surgical risk and whose mitral anatomy is suitable for the TEER procedure.

Editorial, see page 225

Impact on daily practice

The DRAGONFLY-DMR trial provides important evidence for the safety and efficacy of the DragonFly transcatheter valve repair system in treating patients with symptomatic chronic DMR 3-4+ at high surgical risk. The unique design characteristics of DragonFly may expand new possibilities in the TEER armamentarium and lead to operator preferences in complex mitral anatomies. The suitability of DragonFly in treating DMR patients with a smaller baseline MVOA, especially those with prior annuloplasty or a higher baseline TMPG, may be of clinical interest and warrants further studies.

Methods

STUDY DESIGN AND POPULATION

This prospective, multicentre, single-arm study was conducted at 27 sites in China. Study inclusion criteria required that all patients be symptomatic with chronic moderate-to-severe (3+) or severe (4+) DMR and were assessed as having at least a high risk for surgical mitral repair by the cardiac team at the local clinical trial site. Patients were also required to meet the following criteria: age ≥18 years; New York Heart Association (NYHA) Functional Class II, III, or IV; left ventricular ejection fraction ≥20%; anatomically suitable for mitral valve repair with the DragonFly device; and at least a high surgical risk. High surgical risk was defined per the recommended reference criteria, as follows: surgical valve replacement Society of Thoracic Surgeons (STS) score of ≥8; surgical valve repair STS score of ≥6; or the presence of other surgical high-risk factors, such as the ≥2 moderate-to-severe indicators of frailty, surgery-specific impediments (including tracheostomy, heavily calcified [porcelain] ascending aorta, and chest malformation) according to the guidelines for management of valvular heart diseases, or the presence of ≥2 major organ dysfunction that cannot be improved in the postoperative period or other surgical high-risk factors, as judged by the cardiac team[5,13].

Patients were excluded if they had echocardiographic evidence of an intracardiac mass, thrombus, or vegetation; the presence of other severe non-mitral valve disease requiring intervention; history of previous mitral valve surgery or transcatheter mitral valve intervention; severe pulmonary arterial hypertension (pulmonary artery systolic pressure [PASP] >70 mmHg); history of acute myocardial infarction within 4 weeks; untreated severe coronary artery stenosis requiring revascularisation; any cardiovascular interventional procedure within 30 days; or any cardiac surgical procedure performed within 6 months. The complete inclusion and exclusion criteria are shown in **Supplementary Table 1**. Note that the determination of anatomical suitability was adjudicated by two independent experienced TEER operators on the eligibility committee.

The study protocol was designed following the guidelines of the Mitral Valve Academic Research Consortium; it was approved by the investigational review board/ethics

Abbreviations

CI	confidence interval	**MR**	mitral regurgitation	**TEER**	transcatheter edge-to-edge repair
DMR	degenerative mitral regurgitation	**NYHA**	New York Heart Association	**TMPG**	transmitral mean pressure gradient

committee at each participating site and conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent, and the study conformed to the Good Clinical Practice principles and ISO 14155:2020. Echocardiographic images were evaluated by an independent echocardiography core laboratory. A clinical event committee (CEC) adjudicated prespecified major adverse events (MAE). The sponsor participated in the site selection, trial management, and data analysis; however, all patients' study eligibility was determined by each site's Heart Team and confirmed by the independent eligibility committee.

After signing an informed consent form, participants were enrolled and treated using the DragonFly System (DragonFly transcatheter mitral valve repair system). Follow-up study visits were conducted immediately after the procedure, before discharge, and at 30 days, 6 months, and 12 months after the procedure.

This study is registered at ClinicalTrials.gov (NCT04734756; Safety and Effectiveness Study of Dragonfly System for Degenerative Mitral Regurgitation) and sponsored by Valgen Medtech. Trial organisation, leadership and participating sites are listed in **Supplementary Table 2** and **Supplementary Table 3**.

THE DRAGONFLY TRANSCATHETER MITRAL VALVE REPAIR SYSTEM AND PROCEDURAL DETAILS

The DragonFly system comprises four components: a stabiliser, a 24 Fr guiding sheath (big sheath), a steerable sheath (middle sheath), and a device delivery system (control handle), with the DragonFly implant preattached at the end. Four implant sizes are available for application in different anatomical conditions **(Central illustration A)**.

DragonFly has a compressible atrial-side central filler and a mechanically locked arm angle between 0° and 45°. As the arms are closed around the compressible filler, the filler distends on either side of the device, further blocking the regurgitant orifice. Control of the device's final arm angle allows for individual adjustment relative to the mitral valve orifice area. Additionally, the narrow design of the arms allows for placement amidst dense chordae, such as in the commissures. Additionally, the mechanical locking force of the device allows for sufficient clamping force to address cases with degrees of leaflet calcification at the device placement site. The implantation procedure has been previously described[13,14] and is outlined in **Supplementary Appendix 1**.

ENDPOINTS

The study's primary efficacy endpoint was clinical success at 12 months, which was defined as freedom from mortality, reintervention for mitral valve dysfunction, and moderate-to-severe or severe MR >2+. Secondary efficacy endpoints included acute procedural success (defined as the successful implantation of the device with MR ≤2+ at discharge), acute device implantation success (defined as the successful delivery and deployment of one or more devices, with echocardiography confirming secure leaflet insertion, and successful retrieval of the delivery catheter), reintervention due to mitral valve dysfunction, NYHA classification, and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores. Safety endpoints included MAE (defined as procedure-related mortality, stroke, myocardial infarction, renal failure, and cardiovascular reintervention related to the procedure or device), all-cause mortality, and cardiac mortality. Heart failure hospitalisation (HFH) was an extended observational endpoint.

ECHOCARDIOGRAPHIC ASSESSMENTS

Image acquisition was performed following the echocardiography core lab (ECL)-recommended protocol. All echocardiograms obtained at baseline, discharge, and follow-ups were assessed by the ECL according to pre-established protocols based on the American Society of Echocardiography guidelines. MR severity was graded on a scale of 0 to 4+[15,16]. Transthoracic echocardiography (TTE) or transoesophageal echocardiography (TOE) was utilised for baseline qualification, procedural planning, and intraprocedural imaging guidance, and TTE was used for follow-up assessments.

STATISTICAL ANALYSIS

All analyses were performed using the full analysis set. Continuous variables are summarised as the number of observations, mean±standard deviation (SD) or median (interquartile range: first quartile [Q1]-third quartile [Q3]), and 95% confidence interval (CI). The p-values for continuous variables were calculated using the Student's t-test. The paired analysis comprised data for the same patient during a specified follow-up. McNemar's test was used to assess binary repeated measures. Categorical variables are summarised as patient count, percentage, and 95% CI and were compared using the Wilcoxon signed-rank test. Kaplan-Meier estimates were used to analyse the time-to-event variables. Unless otherwise stated, patients with missing data were excluded from the denominator. Statistical analyses were performed using SAS software version 9.4 (SAS Institute).

Results

PATIENTS

A total of 120 patients from 27 sites in China were enrolled and treated between May 2021 and January 2022. The final follow-up was completed in December 2022. Of the 120 patients, one did not receive the device and, thus, was not included in the per-protocol analysis but was included in the full analysis set **(Figure 1)**. The mean age of the participants was 74.9±5.7 years, with 49.2% (59/120) being female. Overall, 39.2% (47/120) had coronary heart disease, 18.3% (22/120) had a prior history of cardiovascular intervention or surgery, and 70.8% (85/120) had chronic obstructive pulmonary disease. The mean STS score for replacement (version 4.20) was 6.9±2.8. In total, 65.9% (79/120) of patients were in NYHA Functional Class ≥III **(Table 1)**. All patients had MR grade ≥3+, with 73.3% (88/120) having MR grade >4+; 55.8% (67/120) of patients had prolapse involving the P2 area, whereas 13.3% (16/120) had prolapse in the A2 area **(Table 2)**. Moreover, the presence of ≥2 moderate-to-severe indicators of frailty was the most common reason for prohibitive risk **(Supplementary Table 4)**.

PROCEDURAL OUTCOMES

The success rate of the DragonFly device implantation was 99.2% (119/120); one patient's treatment was not successful because of inadequate MR reduction, leading to device removal. The median device implantation time was 90.0 (58.5-117.0) min, the median procedural time was 109.0 (75.5-143.5) min,

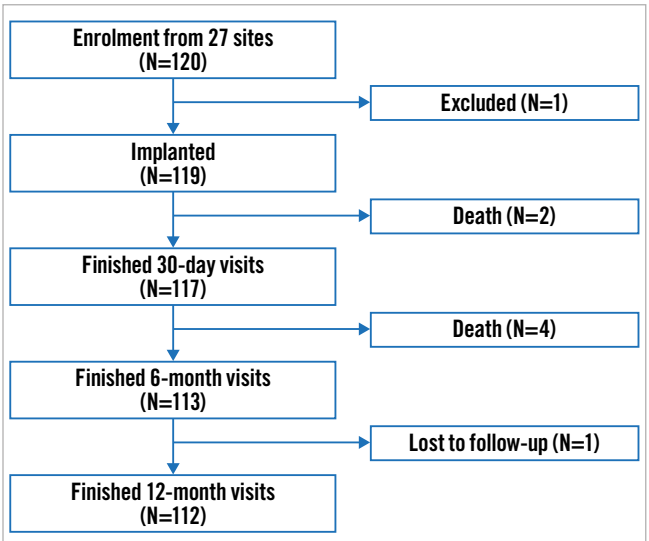


Figure 1. *Flowchart for safety and effectiveness study of the DragonFly System for degenerative mitral regurgitation. Illustration of patient enrolment and follow-up, with visit windows of 30±7 days, 6 months±30 days, and 12 months±30 days.*

and the median fluoroscopy time was 29.5 (19.5-41.9) min. One DragonFly device was successfully implanted in 52.5% (63/120) of patients and 2 devices in 42.5% (51/120). The additional procedural measures are shown in **Table 3**. A learning curve analysis revealed a trend of reduced procedural time with experience from 1 to >3 DragonFly procedures performed (median 82.0 min and 74.5 min) and from 2 to >3 procedures performed. A similar reduction trend was seen in device time (median 68.5 min and 60.5 min) with procedures involving implantation of only one device **(Supplementary Figure 1, Supplementary Figure 2)**.

PRIMARY EFFICACY ENDPOINT

Kaplan-Meier survival analysis was used to evaluate the full analysis set and demonstrated a clinical success rate of 87.5% at 12 months after the procedure (95% CI: 80.1-92.3) **(Central illustration B)**, surpassing the target value of 60% (p<0.001) prespecified in the statistical analysis plan **(Supplementary Appendix 2)**. All patients included in the baseline data had an MR grade ≥3+, as adjudicated by the independent echocardiographic core laboratory. At discharge, 30-day, 6-month, and 12-month follow-ups, the proportion of patients with MR grade ≤2+ was 100%, 90.4%, 93.0%, and 92.0% in the unpaired analysis, respectively. Compared with baseline, these improvements were statistically significant (p<0.001). The MR grade was ≤1+ with rates of 85.6%, 64.3%, 62.6%, and 69.7%, respectively, in the unpaired analysis **(Central illustration C)**. Patients with MR ≤1+ at 30 days post-procedure maintained a good reduction at 6- and 12-month follow-ups **(Supplementary Figure 3)**.

SAFETY ENDPOINTS

The Kaplan-Meier estimates for freedom from all-cause mortality, reintervention for mitral valve dysfunction, HFH, and a composite of the above events were 95.0%, 95.0%, 96.6%, and 92.5%, respectively **(Figure 2)**.

Table 1. Baseline characteristics.

Baseline characteristic	Degenerative MR (N=120)
Demographics	
Age, years	74.9±5.7 (120)
Female	59 (49.2)
BMI, kg/m^2	22.6±3.2 (120)
BSA, m^2	1.6±0.2 (120)
NYHA Class III/IV	79 (65.9)
KCCQ score	44.9±18.4 (120)
STS* score for mitral valve replacement	6.9±2.8 (120)
Medical history/comorbidity	
Coronary artery disease	47 (39.2)
MI	5 (4.2)
CABG	0 (0)
PCI	19 (15.8)
Other cardiovascular diseases	90 (75.0)
Other non-cardiovascular diseases	103 (85.8)
Cardiovascular intervention/surgery	22 (18.3)
Prior cardiac surgery	0 (0)
Transcatheter aortic valve intervention	1 (0.8)
Pacemaker implantation	2 (1.7)
ICD	0 (0)
Severe symptomatic carotid stenosis	0 (0)
Acute peptic ulcer or gastrointestinal bleeding	4 (3.3)
COPD	13 (10.8)
Diabetes	26 (21.7)
Hypertension	85 (70.8)
CVA	16 (13.3)
Active infection**	7 (5.8)
Allergy***	13 (10.8)
Modified Rankin score	0.9±1.1 (17)

Values are mean±SD (N) or N (%). For continuous variables, p-values were based on the Kruskal-Wallis test; for categorical variables, the p-values were based on Fisher's exact test. * Per protocol, a surgical valve replacement STS score of ≥8, surgical valve repair STS score of ≥6 or the presence of other surgical high-risk factors such as the presence of ≥2 moderate to severe indicators of frailty or the presence of possible surgical operative impairment or the presence of ≥2 major organ dysfunctions that will not improve in the postoperative period or other surgical high-risk factors judged by the cardiology team were recommended as inclusion criteria. As most of the published articles report the surgical valve replacement STS score, here we also show it to be comparable. ** Active infection means infection requiring current antibiotic therapy. According to the inclusion criteria, patients may be enrolled at least 14 days after discontinuation of antibiotics. In 6 of the 7 patients there was a history of recent pulmonary infection, and in the remaining patient there was a recent history of an upper respiratory tract infection.*** Nine of the 13 patients had a history of being allergic to penicillins, 2 to sulfonamides, one to tetracycline, and one to perindopril/indapamide. BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; ICD: implantable cardioverter-defibrillators; KCCQ: Kansas City Cardiomyopathy Questionnaire; MI: myocardial infarction; MR: mitral regurgitation; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SD: standard deviation; STS: Society of Thoracic Surgeons

All mortality and aetiologies were adjudicated by the CEC. The composite MAE rate at 1 year was 9.2% (11/120), with five (4.2%) cardiovascular mortalities, three (2.6%) strokes, three (2.6%) renal failures, and three (2.6%) cardiovascular

Table 2. Echocardiographic measures at baseline.

Echocardiographic measure	Degenerative MR (N=120)
Degenerative mitral regurgitation aetiology	120 (100)
LVEF, %	60.8±7.8 (120)
MR grade	
0	0 (0)
1+	0 (0)
2+	0 (0)
3+	32 (26.7)
4+	88 (73.3)
EROA, cm^2	0.5±0.2 (107)
RV, ml	76.9±24.8 (105)
TAPSE, mm	19.9±3.1 (81)
MVOA, cm^2	5.8±1.2 (120)
TMPG, mmHg	2.5±1.3 (119)
Length of anterior leaflet, cm	2.3±0.4 (120)
Length of posterior leaflet, cm	1.4±0.3 (120)
Leading MR mechanism	
Prolapse	91 (75.8)
Flail	26 (21.7)
Prolapse plus flail	3 (2.5)
Bileaflet prolapse	2 (1.7)
Prolapse width, mm	14.1±3.8 (120)
Prolapse/flail gap, mm	3.5±1.9 (120)
Prolapse location[a], N (%)	
Posterior leaflet	
P2	67 (55.8)
Non-P2	34 (28.3)
Anterior leaflet	
A2	16 (13.3)
Non-A2	5 (4.2)
Bileaflet	
A2P2	1 (0.8)
A3P3	1 (0.8)
PASP, mmHg	43.5±12.8 (98)
LAV, ml	114.1±45.9 (117)
LAVi, ml/m^2	70.2±29.1 (117)
LVESV, ml	48.2±20.1 (120)
LVEDV, ml	121.3±39.0 (120)
LVESD, cm	3.2±0.7 (120)
LVEDD, cm	5.1±0.6 (120)
TR	
No regurgitation	18 (15.0)
Mild	63 (52.5)
Moderate	37 (30.8)
Severe	2 (1.7)

Values are mean±SD (N) or N (%). For continuous variables, p-values were based on the Kruskal-Wallis test; for categorical variables, the p-values were based on Fisher's exact test. MR grade was evaluated on transoesophageal echocardiography by the echocardiography core lab. [a]There were two patients with prolapses involving both anterior and posterior leaflets: 1 patient's prolapse involved A3/P3/A2 (1.8%) and the other patient's involved A2/P2 (1.8%). EROA: effective regurgitation orifice area; LAV: left atrial volume; LAVi: left atrial volume index; 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; MVOA: mitral valve orifice area; PASP: pulmonary artery systolic pressure; RV: regurgitation volume; TAPSE: tricuspid annular plane systolic excursion; TMPG: transmitral mean pressure gradient; TR: tricuspid regurgitation

surgeries/procedures related to device or procedural complications, with two patients receiving pericardiocentesis and repair of arteriovenous fistula at the puncture site **(Supplementary Table 5)**. Six patients died, resulting in an all-cause mortality rate of 5.0%. Two patients died during the 30-day follow-up period, and four died between 30 days and 6 months. One patient had multisegment degenerative disease (Barlow's valve) and received 3 devices, but with inadequate MR reduction, prompting elective surgical mitral valve replacement, and then died 28 days post-procedure (26 days after the surgery). One patient died of new onset infection and septic shock at 30 days. Three patients died of unknown causes, and one died of severe pneumonia at 6 months. All of the preceding complications occurred during the COVID-19 pandemic.

FUNCTIONAL EVALUATION

There were significant improvements in functional capacity and quality-of-life (QOL) outcomes (all $p<0.05$) compared to baseline in the paired analysis. At 12 months, the site-assessed NYHA Class showed significant improvement, with the percentage of patients categorised as Class I/II increasing from 32.4% at baseline to 93.6% at 12 months ($p<0.001$). Assessment using the KCCQ showed a mean improvement in self-assessed HF symptoms of 31.1±18.2 from baseline to 12 months ($p<0.001$) **(Figure 3)**. The unpaired analysis showed similar results **(Supplementary Figure 4)**.

ADDITIONAL OUTCOME MEASURES

There was a significant reduction in postoperative left atrial pressure compared to the screening phase from 16.1±7.0 mmHg to 11.3±6.0 mmHg ($p<0.001$) **(Supplementary Figure 5)**. Compared to baseline, the transmitral mean pressure gradient (TMPG) increased from a mean of 2.4±1.3 mmHg to 3.0±1.3 mmHg ($p<0.001$). However, it remained stable within a low range during follow-up (at 12 months: 3.2 mmHg; $p=0.06$) **(Supplementary Figure 6)**. A paired analysis showed a decrease in left ventricular end-diastolic volume (LVEDV) by 19.4±32.9 ml and a decrease in left ventricular end-systolic volume by 9.8±18.1 ml **(Supplementary Figure 7)**. Other echocardiographic data at follow-up are described in **Supplementary Table 6**.

Discussion

DMR is a prevalent disease globally[17,18]. If left untreated, severe DMR will lead to a poor prognosis[3]. However, undertreatment is common because of high operative risk, underreferral and aversion to surgery[7,8]. In the USA and Europe, mitral TEER has emerged as a safe and effective treatment option for patients with DMR who are at a prohibitive surgical risk[5]. MitraClip and PASCAL are two TEER devices that have received U.S. Food and Drug Administration and European conformity (CE mark) approvals[11]. The DragonFly transcatheter valve repair system adds to the TEER family of devices with specific innovations for treating DMR. The DRAGONFLY-DMR pivotal trial is a prospective, multicentre, single-arm, performance goal study conducted to evaluate the safety and efficacy of a new TEER device in patients with DMR who are not eligible for surgery. This study has several significant findings. Notably, the study achieved its prespecified primary efficacy endpoint, clinical success rate,

Table 3. Procedural measures.

Procedural measure	Degenerative MR (N=120)
Successful device implantation[a]	119 (99.2)
Device implantation time, min[b]	90.0 [58.5-117.0] (120)
Procedural time, min[c]	109.0 [75.5-143.5] (120)
Fluoroscopy time, min	29.5 [19.5-41.9] (120)
Number of devices implanted	
0[d]	1 (0.8)
1	63 (52.5)
2	51 (42.5)
3	4 (3.3)
4	1 (0.8)
Number of devices implanted	1.5±0.6 (120)
Size of device	181 (100)
SN0409	16 (8.8)
XN0412	25 (13.8)
SW0609	31 (17.1)
XW0612	109 (60.3)
Implantation location	181 (100)
A1P1	17 (9.4)
A2P2	129 (71.3)
A3P3	35 (19.3)

Values are presented as N (%), median [IQR] (N), or mean±SD (N). For continuous variables, p-values were based on the Kruskal-Wallis test; for categorical variables, p-values were based on Fisher's exact test. [a] Successful implantation: successful delivery and deployment of one or more devices, confirmed by echocardiography to demonstrate leaflet coaptation, and retrieval of the delivery catheter. [b] Device implantation duration: from when the guide sheath reaches the left atrium to when the device delivery system returns to the guide sheath. [c] Procedural duration: from transseptal start to guide sheath removal from the left atrium. [d] Device needed to be withdrawn in one patient because of anatomical reasons. IQR: interquartile range; MR: mitral regurgitation; SD: standard deviation

which measured freedom from all-cause mortality, mitral valve reintervention, and MR >2+ at the 1-year follow-up. The clinical success rate observed in the current study at 1 year (87.5%, 95% CI: 80.1-92.3) surpassed a more contemporary performance benchmark (60.0%) derived from a meta-analysis of mitral TEER studies on DMR conducted between 2011 and 2021 **(Supplementary Appendix 2)**[9,10,19-22]. Additionally, the study demonstrated a reassuring safety profile for the DragonFly system. The trial also observed a high degree of acute reduction in MR to 1+, which was sustained from 1 month to 1 year. Furthermore, the postprocedural mitral inflow gradients were low and remained stable, and the study showed a remarkable improvement in QOL during the follow-up period.

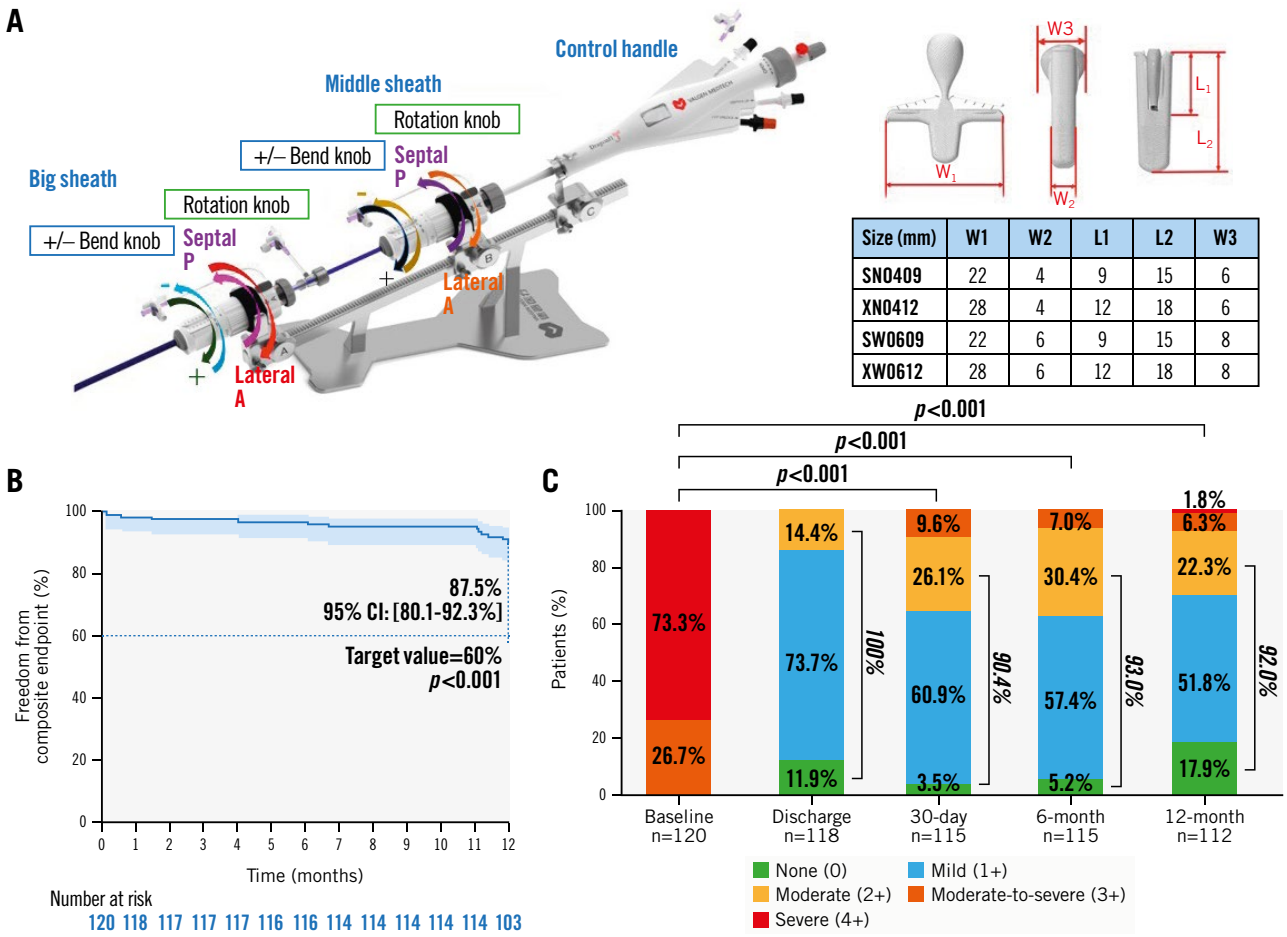
The TEER procedure is a relatively new technique in China compared to the USA and Europe, where this technique has a history of more than 15 years and has been utilised in more than 150,000 cases. Even though DragonFly TEER was performed by operators who were inexperienced with the TEER procedure, the incidence of MAE shown in this study was notably low from 30 days to 1 year post-procedure **(Supplementary Table 5)**, showing a favourable safety profile for the DragonFly over the early experience of MitraClip[22]. All-cause mortality, cardiovascular mortality, and HFH rates at 1 year were 5.0% (95% CI: 2.3-10.8), 4.2% (95% CI: 1.8-9.8) and 3.4% (95% CI: 1.3-8.8), respectively. Single-leaflet device attachment occurred in only 1 patient (0.8%) at the 1-month follow-up. These findings were comparable to those of the CLASP IID study[11] and the STS/American College of Cardiology Transcatheter Valve Therapy Registry conducted using two other major mitral TEER devices[23]. Despite the vertical design of the grippers' leaflet retention elements, which are similar to those of the MitraClip but different from the horizontal design of PASCAL, no leaflet injury was identified as occurring during the study. Furthermore, there were no incidents of chordal entrapment with the implant, which may be attributed to the narrow and slim design of the arms across all four DragonFly sizes, and the capability of both clip arms to revert to an obtuse angle (270°), which facilitates clip repositioning underneath the leaflets and manoeuvring among dense chordae close to the commissures.

In the current trial, 90.0% of patients achieved MR reduction to grade 2+ or less at 1 month; notably, 65.5% of patients achieved MR reduction to 1+. Importantly, residual MR ≤1+ has been associated with better clinical outcomes compared with residual MR ≤2+[24,25], and 91.2% of those with a reduction of MR to ≤1+ at 1 month maintained the effect 1 year later **(Supplementary Figure 3)**. These findings were consistent with the findings from CLASP IID and underscore the importance of resolving MR as much as possible through mitral TEER. With a decrease of 19.4±32.9 ml in LVEDV compared to baseline at 12 months, DragonFly showed its effect on left ventricular reverse remodelling, which was comparable or even favourable to the historical data from MitraClip/PASCAL devices in the current study[22]. In addition, even with the complexity of prolapse anatomies at baseline **(Table 1)**, the mean number of devices implanted in this trial to achieve the aforementioned MR reduction was low and comparable to the results of more recent studies with the MitraClip and PASCAL devices[11,22]. Moreover, the procedure and device times were surprisingly shorter than the time taken by physicians in the USA and Europe to implant MitraClip at a similarly early stage of mitral TEER[22]. Taking into account that the trial was conducted in China, where the TEER procedure is relatively new to the physicians, as well as restrictions due to the coronavirus disease pandemic, proctoring for these cases with TEER experts overseas could only be done through remote online teaching. Most sites had no prior mitral TEER experience. A reduced procedural time was observed with greater operator experience **(Supplementary Figure 2)**, demonstrating the intuitiveness and procedural efficiency of the DragonFly system. The Transcatheter Valve Therapy Registry reported a comparable pattern of learning curves, revealing that there is a correlation between experience and a reduction in procedural time when using TEER devices in real-world scenarios[26]. Further improvement in procedural time can be anticipated if operators gain greater experience with the DragonFly system.

Furthermore, the acute increase in TMPG levels after the DragonFly TEER was insignificant. At 1 year, the entire cohort of patients maintained a satisfactorily low

EuroIntervention Central Illustration

The DragonFly transcatheter mitral valve repair system with 1-year outcomes.



Size (mm)	W1	W2	L1	L2	W3
SN0409	22	4	9	15	6
XN0412	28	4	12	18	6
SW0609	22	6	9	15	8
XW0612	28	6	12	18	8

Jian'an Wang *et al.* • *EuroIntervention* 2024;20:e239-e249 • DOI: 10.4244/EIJ-D-23-00361

A) DragonFly transcatheter mitral valve repair system design and device implantation parameters. The four clips are suitable for diverse anatomical conditions. B) Kaplan-Meier estimates for the primary composite endpoints. The error bars represent 95% CI. The primary composite endpoints included freedom from death, mitral valve-related reintervention due to mitral valve dysfunction, and moderate-to-severe or severe mitral regurgitation (MR) >2+ at 12 months. MR >2+ was determined based on the 12-month transthoracic echocardiography with echocardiography core laboratory confirmation. C) MR severity assessed by the echocardiography core laboratory using transthoracic echocardiography. The graph shows unpaired analyses, and p-values were calculated using the Wilcoxon signed-rank test. CI: confidence interval; L1: length of the arms; L2: length of the clip; N: narrow; S: short; W: wide; W1: width of arm opening at 180°; W2: width of the clip; W3: width of central compressible filler; X: extra

TMPG, with a mean inflow gradient of 3.2±1.4 mmHg **(Supplementary Figure 6)**. The acute decrease in left atrial pressure was significant and likely contributed to significant symptomatic improvement **(Supplementary Figure 5)**. Along with the durable reduction in MR and left ventricular reverse remodelling over time, the impact of mitral TEER with DragonFly on patients with DMR in this study translated to the alleviation of HF symptoms, improvement in patients' NYHA Functional Class and QOL, and a significant increase in KCCQ score compared to baseline (Δ=31.1±18.2).

The differentiating features of the DragonFly device compared to other TEER devices are the central compressible filler, the mechanically locked arms of the device, and the indexed articulation of the delivery system. Unlike the MitraClip device but similarly to the PASCAL device, the central compressible filler acts to block the regurgitant orifice without pulling the mitral leaflets so tightly together, as they are instead brought towards the filler. However, unlike the PASCAL device's central non-compressible spacer, the DragonFly's filler is compliant, allowing it to be compressed by the device arms, which in turn distends medially and

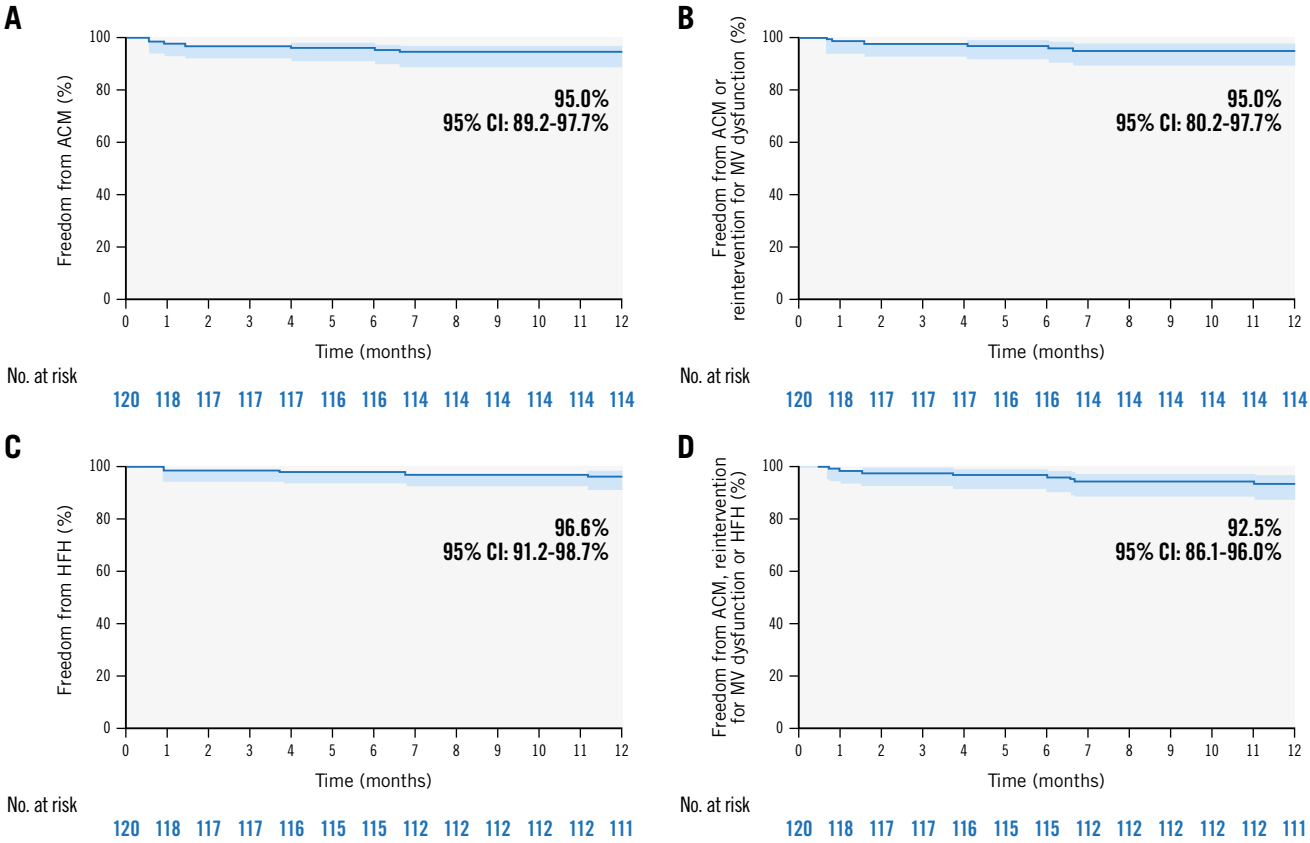


Figure 2. *Kaplan-Meier analyses for estimating the freedom from all-cause mortality, reintervention for MV dysfunction and HFH at 1 year. Kaplan-Meier estimates for freedom from (A) all-cause mortality, (B) all-cause mortality or reintervention for MV dysfunction, (C) HFH, and (D) a composite of events rates at 1 year. Error bars represent 95% CI. ACM: all-cause mortality; CI: confidence interval; HFH: heart failure hospitalisation; MV: mitral valve*

laterally, further blocking the regurgitant orifice. Similar to the PASCAL Ace (Edwards Lifesciences) device, this allows operators to pull redundant leaflet tissue closer together when necessary. This is a unique feature of the DragonFly implant that may have contributed to the significant and sustained MR reduction while maintaining the inflow gradient at a low level over time. Also, this potentially allows operators to use the DragonFly device to address a wider regurgitation orifice using fewer devices, leaving a larger mitral valve orifice area post-procedure and a lower residual inflow gradient. In addition, operators have the option to decrease the tension on both leaflets after device implantation by mechanically locking the arms of DragonFly at a range of angles, and implantation is secured by firmly sandwiching the leaflets between the arms and the central filler to maximise leaflet coaptation. The robust mechanical locking force of the device delivers clamping force to the leaflets, even in complicated cases of fibrotic leaflets or those with scattered leaflet calcification in the grasping area. Other features, such as the same articulating mechanical delivery system shared by both the mitral and tricuspid sides and gauge windows of the DragonFly system, are designed to provide a shortened learning curve for operators, promoting confidence in making stable, precise, and replicable movements at each step during the procedure. The availability of different sized TEER devices expands the treatment options for patients with DMR and accommodates various anatomical and mitral aspects. The unique design characteristics of the DragonFly device may add new possibilities to the TEER armamentarium and lead to operator preference for complex mitral anatomies. For instance, the suitability of DragonFly in treating DMR in patients with a smaller baseline MVOA, especially those with prior annuloplasty or a higher baseline mitral inflow gradient, is sure to arouse clinical interest and warrants further studies.

Limitations

This study has some limitations. Firstly, the study design was a single-arm performance goal trial, as positive control devices such as the MitraClip and experience with the TEER technique were inaccessible in China during the trial design and execution. This may introduce bias and limit our ability to draw conclusions. However, to mitigate potential bias, the study employed several designs, such as clear inclusion/exclusion criteria, a centralised screening committee for patient enrolment, objective outcome measures as primary endpoints, a standardised protocol across participating sites, an independent image core laboratory, and an independent clinical event committee to ensure objectivity and data accuracy. Secondly, the follow-up period for the primary effectiveness endpoint

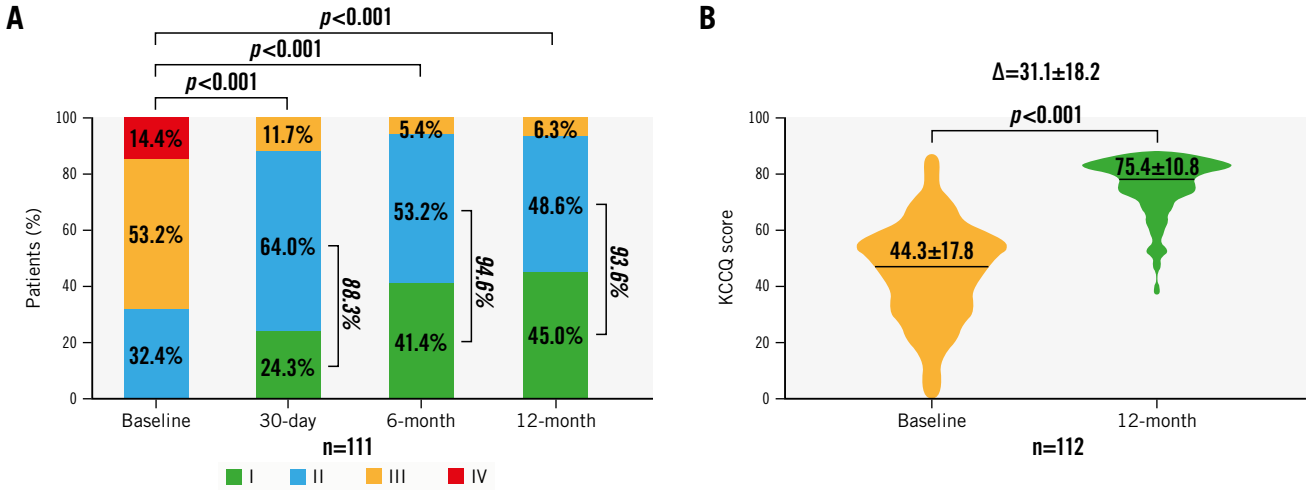


Figure 3. *Paired analysis for NYHA Functional Class and KCCQ outcomes at baseline and follow-up. The graph shows the paired analysis of (A) New York Heart Association (NYHA) Functional Classification and (B) Kansas City Cardiomyopathy Questionnaire (KCCQ) scores. The p-values for group comparisons were calculated using the Student's t-test for continuous variables and the Wilcoxon signed-rank test for categorical variables.*

was relatively short, which may have hindered the assessment of the long-term benefits and safety of the treatment. Finally, the study was conducted during the coronavirus disease pandemic, which may have affected patient follow-up and data collection. Nevertheless, the study findings are encouraging and promising. Future research with larger sample sizes and longer follow-up periods is necessary to validate the results and assess the long-term benefits and safety of this treatment.

Conclusions

In summary, the DragonFly transcatheter valve repair system has been investigated in this current DRAGONFLY-DMR study, which represents the first pivotal trial to evaluate the safety and efficacy of this system in patients with significant symptomatic DMR (3+ and 4+, as adjudicated by the independent echocardiographic core laboratory) who were at high risk for mitral valve surgery. The trial's prespecified primary efficacy endpoint was successfully achieved, and the results demonstrated that treatment with the DragonFly system had a low occurrence of adverse events and delivered sustained MR reduction with low mitral inflow gradient and left ventricular reverse remodelling over time. The therapy successfully demonstrated its safety and efficacy in treating degenerative mitral regurgitation and in improving patients' quality of life, indicating its potential as a beneficial therapy for such patients.

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Acknowledgements

The authors thank all patients and sites that participated in the trial and Mengmeng Gong, MS, Yi Duan, MS, Xiaoyue Tang, MS, and Guoliang Wu, MS, for their assistance with manuscript preparation.

Conflict of interest statement

K. Ma receives a salary from Valgen as Chief Medical Officer. S. Lim receives personal consulting fees from LagunaTech, Philips, Valgen, and Venus; and his institution receives research grants on his behalf from Abbott, Boston Scientific, Corvia, Edwards Lifesciences, Medtronic, V-Wave, and W.L. Gore & Associates. All other authors report their institutions receiving institutional research grants from Valgen for the conduct of the study.

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Supplementary data

Supplementary Appendix 1. DragonFly system and implantation procedure.
Supplementary Appendix 2. Power and sample size calculation and statistical methodology.
Supplementary Table 1A. Inclusion and exclusion criteria.
Supplementary Table 1B. Detailed anatomical criteria for screening.
Supplementary Table 1C. The most frequent reasons for DragonFly screen failure.
Supplementary Table 2. Trial organisation and leadership.
Supplementary Table 3. Participating sites.
Supplementary Table 4. Reasons for prohibitive surgical risk.
Supplementary Table 5. Adverse events up to 12 months.
Supplementary Table 6. Echocardiographic measures up to 12 months.
Supplementary Figure 1. Representative pre- and post-implant echocardiography and fluoroscopy images.
Supplementary Figure 2. Learning curve analysis.
Supplementary Figure 3. MR reduction to ≤1 at 30 days, 6 months, and 12 months.
Supplementary Figure 4. Unpaired analysis for NYHA Functional Class and KCCQ outcomes at baseline and follow-up.
Supplementary Figure 5. Mean left atrial pressure pre-/post-operation.
Supplementary Figure 6. Transmitral mean pressure gradient by echocardiographic core laboratory.
Supplementary Figure 7. Left ventricular end-diastolic/systolic volume.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00361

Supplementary data

Supplementary Appendix 1. DragonFly system and implantation procedure.

The DragonFly System consists of four components: a 24F Guiding Sheath (Big Sheath), a steerable sheath (Middle Sheath), and a stabiliser and device delivery system (Control Handle), with four clip sizes for application in diverse anatomical conditions.

The procedure was conducted under general anaesthesia with endotracheal intubation, and transoesophageal echocardiography (TEE) and fluoroscopic guidance were performed in a hybrid operating room/catheterisation laboratory. Under TEE guidance, following transseptal puncture, the big sheath was inserted into the left atrium, allowing the middle and control handle to pass through to the left atrium and mitral valve.

The middle sheath was adjusted to ensure that the DragonFly device trajectory was perpendicular and coaxial to the mitral annulus. Subsequently, the device arms were opened to an oblique angle and then advanced below the mitral valve. The arm angle of the device was changed to an angle suitable for grasping the leaflets, the bilateral grippers are released simultaneously, and the mitral leaflets were captured after confirmation of leaflet insertion. Before releasing the device, the transmitral mean pressure gradient was assessed as well as the leaflet insertion by echocardiography. The compressible atrial-side central filler of the DragonFly System extends medially and laterally to the device with closure of the device arms, to further reduce mitral regurgitation on either side of the device, with the anticipation of using fewer devices

and, in turn, with a shorter procedural duration, even in more complex cases. The grasping arms can lock at any angle, from 0° to 45°, to allow operators to secure the grasped leaflets and control the degree of residual mitral inflow orifice areas. The independent leaflet capture feature also allows the anterior and posterior leaflets to be grasped independently, permitting the treatment of complex mitral pathoanatomy. The mechanical locking feature assures sufficient clamping force to treat scattered leaflet calcification in the grasping area while minimising single leaflet device attachment. The stabiliser unit has geared rails with bracket knobs to provide incremental and repeatable forward and backward control of the DragonFly delivery system. The indexed transmission of forces in the delivery system via its mechanical system provides for a repeatable articulation of the delivery system, with the intent of providing both safety and a shortened learning curve for operators of the DragonFly system.

Supplementary Appendix 2. Power and sample size calculation and statistical methodology.

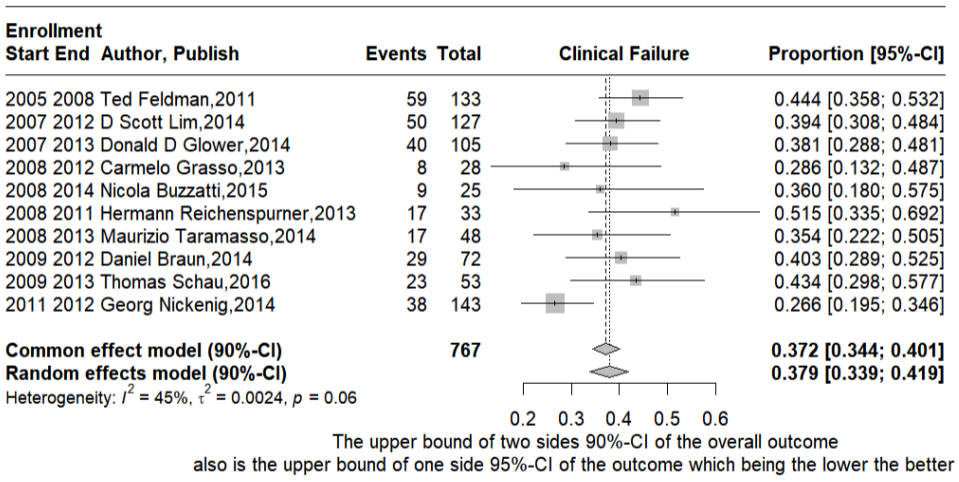
Power and sample size calculation: Assuming a composite event rate (using the definition of events in the primary endpoint of this study) of 40.0% at 12 months with a one-sided type I error of 0.025 and an expected result of 27.0%, a sample size of 106 patients was calculated to provide 80.3% power for the primary efficacy endpoint. Power and sample size calculations were performed using SAS®9.4(SAS Institute Inc., Cary, NC, USA). A total of 120 participants were planned for enrolment, with an estimated attrition rate.

Population Analysis: The Full Analysis Set (FAS) was determined on the intention-to-treat principle and included all datasets from patients participating in the trial (recorded in the central registry) who took the investigational product. The per-protocol set refers to the subgroup of treated patients who completed the trial and were excluded from serious protocol violations (such as violation of eligibility criteria).

Analysis of the primary efficacy endpoint was performed on both the FAS and per-protocol set. All baseline demographics analysis, secondary efficacy analysis, and safety evaluations were performed on the FAS (no safety set was defined independently).

Meta-analysis: Additional literature spanning from 2011 to 2021 for the TEER for DMR was retrieved. The inclusion criteria for the study involved selecting articles

that reported composite events of freedom from all-cause mortality, mitral valve reintervention, and MR> 2+ at 12 months, or articles that reported individual outcomes of composite events simultaneously. Furthermore, the included patients had to consist of individuals with DMR who were also at high risk for surgical procedures. Ultimately, 10 studies were chosen to perform a meta-analysis for the composite event rate with the definition of the events in the primary endpoint of this study. The upper limit of the one-sided 95% CI of the overall effect size was 41.9% in the random effect model, and was 40.1% in a common effect model. The performance benchmark was then set as 60.0% (1-40%), conservatively.



Supplementary Table 1A. Inclusion and exclusion criteria.

Criteria #	Inclusion criteria
1.	Age ≥18 years
2.	Patients with clinical symptoms and moderate-to-severe (3+) or severe (4+) chronic degenerative mitral valve regurgitation diagnosed by transthoracic echocardiography
3.	NYHA Class II/III/IV
4.	LVEF≥ 20%
5.	Patients' mitral valve anatomical structure are suitable for mitral valve repair and suitable for the use of this study device
6.	In the judgement of the cardiology team of local clinical trial institution, patients have high surgical risk, with recommended reference criteria: surgical valve replacement STS score of ≥ 8, surgical valve repair STS score of ≥ 6 or the presence of other surgical high-risk factors such as the presence of ≥ 2 moderate to severe indicators of frailty or the presence of possible surgical operative impairment or the presence of ≥ 2 major organ dysfunctions that will not improve in the postoperative period or other surgical high-risk factors judged by the cardiology team*
7.	Trans-septal catheterisation and femoral vein access are determined to be feasible
8.	Subject must be informed of the nature of the study, fully understand its provisions, and has provided written ICF

***** Organ dysfunction was defined according to the major organ system compromise described in *2020 ACC-AHA Guideline for the Management of Patients With Valvular Heart Disease*, whereas examples of major organ system compromise include cardiac dysfunction (severe LV systolic or diastolic dysfunction or RV dysfunction, fixed pulmonary hypertension); kidney dysfunction (chronic kidney disease, stage 3 or worse); pulmonary dysfunction (FEV1 <50% or DLCO2 <50% of predicted); central nervous system dysfunction (dementia, Alzheimer's disease, Parkinson's disease, cerebrovascular accident with persistent physical limitation); gastrointestinal dysfunction (Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin <3.0); cancer (active malignancy); and liver dysfunction (any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy).

Criteria #	Exclusion criteria
1.	Echocardiographic evidence of intracardiac mass, thrombus or vegetation
2.	Presence of other severe heart valve disease requiring intervention
3.	Prior medical history of mitral valve surgery or transcatheter mitral valve intervention
4.	Severe pulmonary arterial hypertension (echocardiography or right heart catheterisation shows pulmonary artery systolic pressure>70mmHg)
5.	History of acute myocardial infarction within 4 weeks; or untreated severe coronary artery stenosis requiring revascularisation

Criteria #	Exclusion criteria
6.	Any cardiovascular intervention procedure within 30 days; or cardiac surgical procedure performed within 6 months; or in the judgement of the Investigator, the femoral vein cannot accommodate a 24F catheter; or has ipsilateral deep vein thrombosis; or trans-septal catheterisation is not feasible
7.	Patients who are contraindicated for TEE or general anaesthesia
8.	End-stage heart failure (ACC/AHA stage D); or post-heart transplantation; or awaiting heart transplantation
9.	Active endocarditis or active rheumatic heart disease; or mitral valve leaflet pathological changes due to endocarditis and rheumatic heart valve disease
10.	History of stroke (ischaemic) within 30 days; or severe symptomatic carotid artery stenosis (echocardiography shows stenosis > 70%); or carotid artery revascularisation within 30 days; or cerebrovascular accident (haemorrhagic) occurred within 6 months
11.	History of acute peptic ulcer or gastrointestinal bleeding within 3 months
12.	Haemorrhagic disease or coagulation disorder; or there is contraindication of antithrombotic drug treatments
13.	Modified Rankin Score ≥ 4
14.	Diseases that make the evaluation of treatment difficult (cancer, severe metabolic disease, mental illness, etc.)
15.	Pregnant or lactating women
16.	Haemodynamic instability defined as systolic pressure < 90 mmHg without afterload reduction medicine or cardiogenic shock or need for an intra-aortic balloon pump or other haemodynamic support devices
17.	Active infections requiring current antibiotic therapy (if temporary illness, patients may enrol at least 14 days after discontinuation of antibiotics)
18.	Currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints. (Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials)
19.	In the judgement of the Investigator, patients who have poor compliance and are unable to complete the study as required; or other circumstances that make the subject unsuitable for participation in the study
20.	Mitral valve orifice area < 3.5 cm^2
21.	In the opinion of the eligibility committee and echo core laboratory, leaflet anatomy which may preclude DragonFly device implantation, proper device positioning on the leaflets or sufficient reduction in MR

ACC/AHA= American College of Cardiology/American Heart Association; ICF = Informed consent form; LVEF = Left ventricular ejection fraction; MR = Mitral regurgitation; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; TEE = Transoesophageal echocardiography.

Supplementary Table 2B. Detailed anatomical criteria for screening.

The specific anatomical inclusion criteria included：
Mitral valve orifice area $\geqslant$ 4.0cm^2
Posterior leaflet length $\geqslant$ 8mm
The specific anatomical exclusion criteria included：
Prolapse/Flail gap > 10mm.
Barlow's disease or three or more multi-segmental prolapse
Presence of multiple jets
The significant regurgitant jets from the commissural area
Rheumatic mitral valve lesions
Presence of severe calcification of the annulus or subvalvular organs
Severe calcification in the clamping area
Presence of significant cleft or perforation in the grasping area
Severely restricted posterior leaflet

Supplementary Table 3C. The most frequent reasons for DragonFly screen failure.

mitral stenosis would likely result	MVA < 4cm²	5
	Severe mitral annular calcification with mitral stenosis or calcium extension into the leaflets, or restricted leaflet motion	15
inadequate reduction of mitral regurgitation would be expected to occur	Extreme mitral valve complexity, e.g., significant regurgitant jets from the commissural area, presence of multiple jets, Barlow's disease or three or more multi-segmental prolapse, severe calcification in the clamping area	137
	Short or restricted Posterior Mitral Leaflet (<8 mm in the intended grasping location)	6
Specified exclusion	Mixed MR	30
	Other severe regurgitation or stenosis	11
The procedure should not be performed due to technical, imaging, or anatomic reasons	Inability to do a TEE (patient anatomy/oesophageal pathology, pneumonectomy, etc.) Or Inability to obtain grasping views	35
There is futility in performing the procedure secondary to cardiac or non-cardiac co-morbidities	Patients with less than 3+/4 + mitral regurgitation by quantitative echocardiographic assessment	12
	Other clinical situations	47

Supplementary Table 4. Trial organisation and leadership.

Trial Leadership		
Jian'an Wang, MD, PhD	Second Affiliated Hospital, Zhejiang University School of Medical, Hangzhou, Zhejiang, China	Study PI
Chen Mao, MD, PhD	West China Hospital, Sichuan University, Chengdu, Sichuan, China	Study PI
Steering Committee		
Jian'an Wang, MD, PhD	Second Affiliated Hospital, Zhejiang University School of Medical, Hangzhou, Zhejiang, China	Study PI
D. Scott Lim, MD	University of Virginia Health System Hospital, Charlottesville, Virginia, USA	Interventional Cardiologist
Yat-Yin Lam, MD	Hong Kong Asia Heart Centre at Canossa Hospital, Hong Kong, China	Echocardiologist
Kangmu Ma, MD, PhD	Valgen Medtech, Hangzhou, China	Chief Medical Officer
Central Screening Committee		
D. Scott Lim, MD	University of Virginia Health System Hospital, Charlottesville, Virginia, USA	Interventional Cardiologist
Yat-Yin Lam, MD	Hong Kong Asia Heart Centre at Canossa Hospital, Hong Kong, China	Echocardiologist
Echocardiographic Core Laboratory		
Fangfang, MD	Fuwai Hospital of Chinese Academy of Medical Sciences, Beijing, China	Echocardiologist
Yinjia Zhang, MD	Huadong hospital affiliated to Fudan University, Shanghai, China	Echocardiologist
Clinical Events Committee		
Yongquan Xie, MD	Fuwai Hospital of Chinese Academy of Medical Sciences, Beijing, China	Interventional Cardiologist
Wei Sun, MD	Jiangsu Provincial People's Hospital, Nanjing, Jiangsu, China	Interventional Cardiologist
Ran Guo, MD	The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China	Interventional Cardiologist
Medical Affairs		
Kangmu Ma, MD, PhD	Valgen Medtech, Hangzhou, China	Chief Medical Officer
Ping Fan, BA; Yi Duan, MS; Mengmeng Gong, MS; Xiaoyue Tang, MS; Kai Hu, MS; Guoliang Wu, MS		
Clinical Science		
Kangmu Ma, MD, PhD	Valgen Medtech, Hangzhou, China	Chief Medical Officer
Data Management & Biostatistics		

Wei Li, PhD	Department of Medical Statistics, National Center for Cardiovascular Disease, Beijing, China	Biometrics
Safety		
Guoliang Wu, MS	Valgen Medtech, Hangzhou, China	Medical Affairs
Scientific Communications		
Kangmu Ma, MD, PhD	Valgen Medtech, Hangzhou, China	Chief Medical Officer

Supplementary Table 5. Participating sites.

Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang	
Principal Investigator	Jian'an Wang, MD, PhD
West China Hospital, Sichuan University, Sichuan	
Principal Investigator	Mao Chen, MD, PhD
Union Hospital, Fujian Medical University, Fujian	
Principal Investigator	Lianglong Chen, MD, PhD
Ningbo First Hospital, Zhejiang	
Principal Investigator	Xiaomin Chen, MD, PhD
The First Affiliated Hospital of Zhengzhou University, Henan	
Principal Investigator	Jianzeng Dong, MD, PhD
The Second Xiangya Hospital, Central South University, Hunan	
Principal Investigator	Zhenfei Fang, MD, PhD
Fujian Provincial Hospital, Fujian	
Principal Investigator	Yansong Guo, MD, PhD
Shanghai Chest Hospital, Shanghai	
Principal Investigator	Ben He, MD, PhD
The Second Affiliated Hospital, Army Medical University, Chongqing	
Principal Investigator	Jun Jin, MD
Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong	
Principal Investigator	Jianfang Luo, MD
Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, Guangdong	
Principal Investigator	Jingfeng Wang, MD, PhD
Xiamen University Cardiovascular Hospital, Fujian	
Principal Investigator	Yan Wang, MD, PhD
General Hospital of the Northern Theater of the Chinese People's Liberation Army, Liaoning	
Principal Investigator	Yaling Han, MD, PhD; Kai Xu[23], MD
The First Affiliated Hospital, Xinjiang Medical University, Xinjiang	

Principal Investigator	Yining Yang, MD, PhD
Zhongshan Hospital, Fudan University, Shanghai	
Principal Investigator	Junbo Ge[25], MD, PhD; Daxin Zhou, MD, PhD
Fuwai Yunnan Hospital, Yunnan	
Principal Investigator	Gejun Zhang, MD, PhD
Peking University Third Hospital, Beijing	
Principal Investigator	Yida Tang, MD, PhD
Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Jiangxi	
Principal Investigator	Lang Hong, MD
Renmin Hospital of Wuhan University, Hubei	
Principal Investigator	Hong Jiang, MD, PhD
The Second Affiliated Hospital of Nanchang University, Jiangxi	
Principal Investigator	Yanqing Wu, MD, PhD
Shanghai East Hospital, Tongji University, Shanghai	
Principal Investigator	Qi Zhang, MD, PhD
Qingdao Municipal Hospital, Shandong	
Principal Investigator	Yibing Shao, MD, PhD
The First Affiliated Hospital, Sun Yat-Sen University, Guangdong	
Principal Investigator	Yi Li, MD
Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Sichuan	
Principal Investigator	Biao Cheng, MD
Nanfang Hospital, Southern Medical University, Guangdong	
Principal Investigator	Jiancheng Xiu, MD, PhD
Beijing Anzhen Hospital, Capital Medical University, Beijing	
Principal Investigator	Guangyuan Song, MD, PhD
Henan Chest Hospital, Henan	
Principal Investigator	Yiqiang Yuan, MD

Supplementary Table 6. **Reasons for prohibitive surgical risk.**

Characteristic	N = 120
STS predicted risk of mortality score ≥ 8% for mitral valve replacement	55 (45.8)
Have ≥ 2 moderate to severe indicators of frailty*	103 (85.8)
Unable to bathe independently	69 (57.5)
Inability to independently perform bed and chair transfers	60 (50.0)
Inability to use the toilet independently	28 (23.3)
Unable to walk independently	25 (20.8)
Inability to eat independently	13 (10.8)
Can't dress independently	8 (6.7)
Loss of independent bladder and bowel control	1 (0.8)
Other severe indicators of frailty	17 (14.2)
Presence of ≥ 2 major organ injuries that do not improve after surgery*#	2 (1.7)
Damage to cardiac function (including left and right heart)	1 (0.8)
Grade 3 or more severe chronic kidney disease	1 (0.8)
Lung dysfunction	1 (0.8)
Gastrointestinal dysfunction	1 (0.8)
Other surgery-related disorders	1 (0.8)

Categorical variables: n (%). Patients may present more than one prohibitive risk factor.
STS = Society of Thoracic Surgeons
*Ref: Stone, Gregg W et al. "Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 1: Clinical Trial Design Principles: A Consensus Document from the Mitral Valve Academic Research Consortium." Journal of the American College of Cardiology vol. 66,3 (2015): 278-307.
#Examples of major organ system compromise: Cardiac: severe LV systolic or diastolic dysfunction or RV dysfunction, or fixed pulmonary hypertension; CKD stage 3 or worse; pulmonary dysfunction with FEV1 ,50% or DLCO2 ,50% of predicted; CNS dysfunction: dementia, Alzheimer's disease, Parkinson's disease, or CVA with persistent physical limitation; GI dysfunction: Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin ,3.0; cancer: active malignancy; and liver: any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy.

Supplementary Table 7. **Adverse events up to 12 months.**

	Procedural	**30 days**	**6 months**	**12 months**
CEC-adjudicated MAEs	0 (0.0)	6 (5.0)	10 (8.3)	11 (9.2)
Mortality	0 (0.0)	2 (1.7)	6 (5.0)	6 (5.0)
Cardiovascular mortality	0 (0.0)	2 (1.7)	5 (4.2)	5 (4.2)
Valve-related mortality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-cardiovascular mortality	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)
Stroke	0 (0.0)	2 (1.7)	2 (1.7)	3 (2.6)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal failure	0 (0.0)	2 (1.7)	3 (2.5)	3 (2.5)
Cardiovascular reintervention due to device or procedure related adverse events	0 (0.0)	3* (2.5)	3* (2.5)	3*(2.6)
CEC-adjudicated minor AEs	6 (5.0)	8 (6.6)	8 (6.6)	8 (6.6)
Severe bleeding#	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
Vascular complication	5 (4.2)	7 (6.7)	7 (6.7)	7 (6.7)

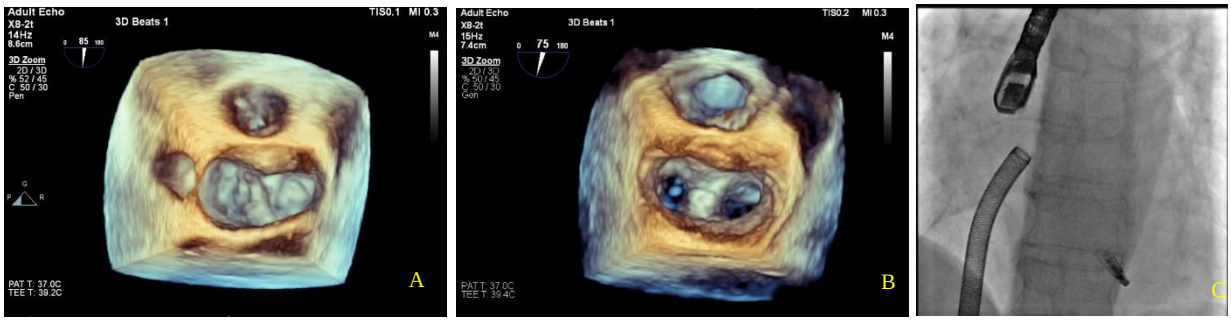
Categorical variables: n (%).
AE = Adverse event; CEC = Clinical events committee; MAE = Major adverse event.
* 3 patients were involved in cardiovascular surgeries related to device or procedural complications. One was the patient who transferred to surgical valve replacement 2 days post TEER, and died later. The Other 2 patients went with pericardiocentesis due to pericardial effusion.
# Major, extensive, life-threatening, or fatal bleeding defined by the Mitral Valve Academic Research Consortium criteria. The patient experienced sudden haematemesis 2 hours postoperatively. Emergency endoscopy was performed, which indicated the presence of oesophageal haematoma with bleeding.

Supplementary Table 6. Echocardiographic measures up to 12 months.

Echocardiographic measures	Baseline (N=120)	30 days (N=115)	6 months (N=115)	12 months (N=112)	P value*
LVEF (%), Mean ± SD (N)	60.8 ± 7.8	58.6 ± 9.3	60.6 ± 7.3	62.1 ± 6.4	0.048
LVEDV (ml), Mean ± SD (N)	121.3 ± 39.0	109.2 ± 21.0	104.7 ± 23.4	102.4 ± 17.7	<0.001
LVEDD (cm), Mean ± SD (N)	5.1 ± 0.6	4.9 ± 0.5	4.8 ± 0.4	4.7 ± 0.4	<0.001
LVESV (ml), Mean ± SD (N)	48.2 ± 20.1	45.4 ± 16.2	41.7 ± 12.7	39.0 ± 10.5	<0.001
LVESD (cm), Mean ± SD (N)	3.2 ± 0.7	3.2 ± 0.5	3.1 ± 0.4	3.1 ± 0.4	0.004
LAV (ml), Mean ± SD (N)	114.1 ± 45.9 (117)	92.9 ± 40.4 (115)	85.7 ± 42.1 (115)	83.4 ± 38.7 (112)	<0.001
PASP (mmHg), Mean ± SD (N)	43.5 ± 12.8 (98)	40.2 ± 13.1 (68)	38.6 ± 10.9 (89)	39.1 ± 10.7 (91)	0.001
TAPSE (mm), Mean ± SD (N)	19.9 ± 3.1 (81)	19.5 ± 2.8 (75)	19.8 ± 2.8 (78)	20.8 ± 3.4 (82)	0.002
TR, N (%)	(n=120)	(n=97)	(n=104)	(n=112)	0.028
No regurgitation	18 (15.0)	19 (15.8)	13 (10.8)	17 (14.2)	
Mild	63 (52.5)	67 (55.8)	74 (61.7)	71 (59.2)	
Moderate	37 (30.8)	9 (7.5)	15 (12.5)	22 (18.3)	
Severe	2 (1.7)	2 (1.7)	2 (1.7)	2 (1.7)	

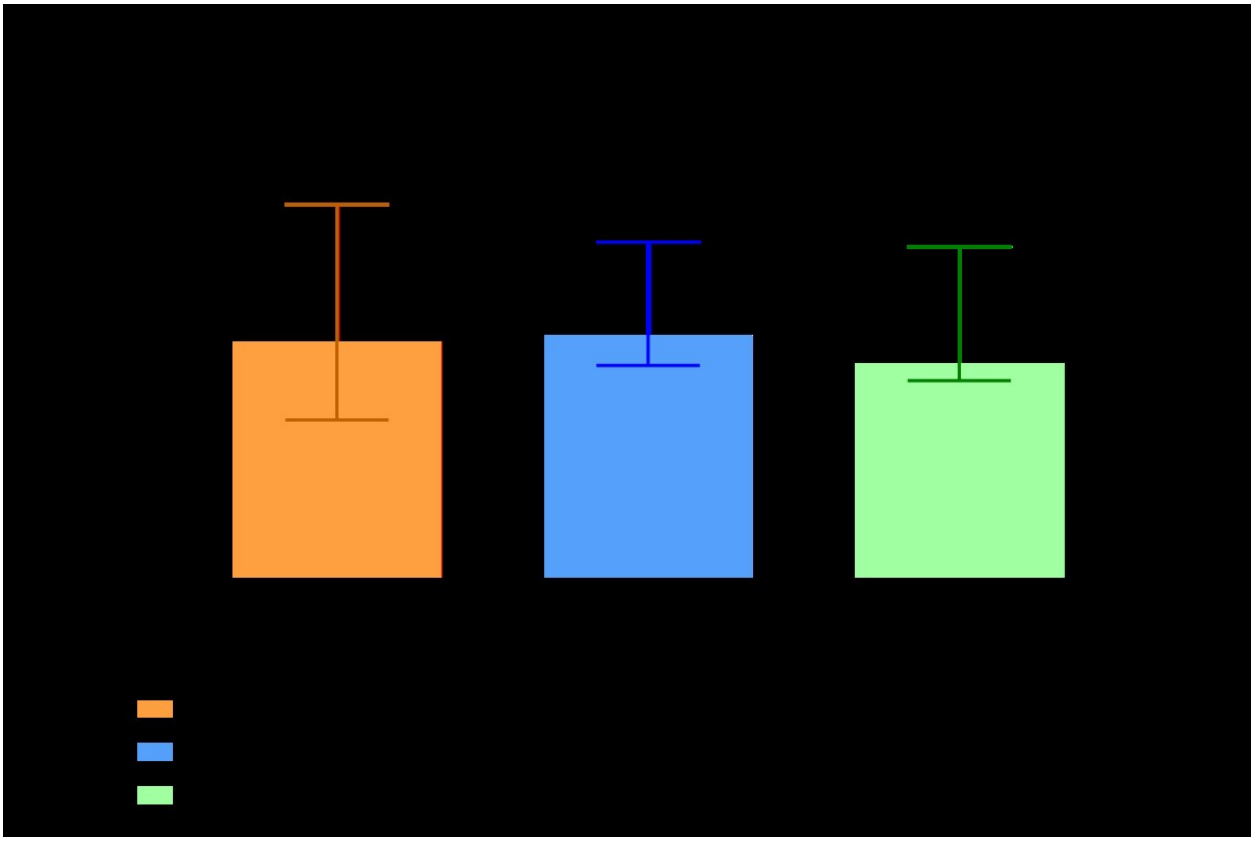
Values are mean ± SD (N) or N (%). LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVEDD: left ventricular end-diastolic diameter; LVESV: left ventricular end-systolic volume; LVESD: left ventricular end-systolic diameter; LAV: left atrial volume; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation

*p value calculated using t-tests represents the difference between baseline and 12 months.



Supplementary Figure 1. Representative pre- and post-implant echocardiography and fluoroscopy images.

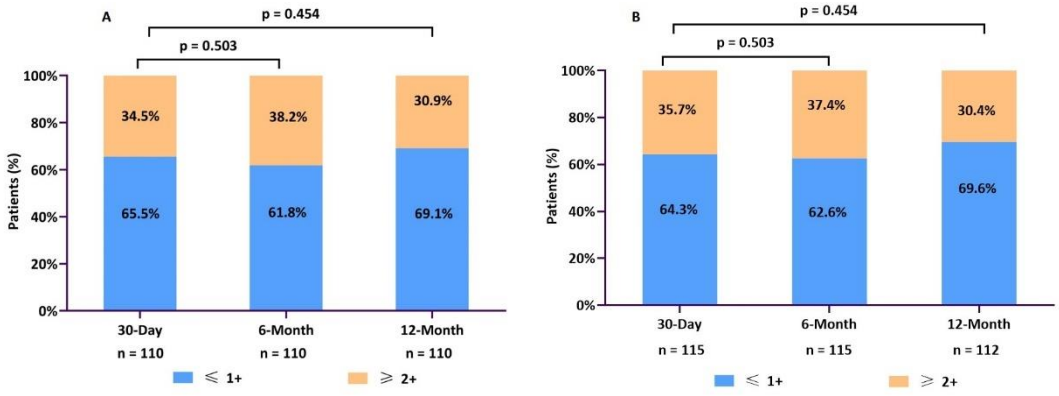
Graphs show (A) 3D echo image pre implant, (B) 3D echo image post implant, and (C) Fluoroscopy image post implant



Supplementary Figure 2. Learning curve analysis.

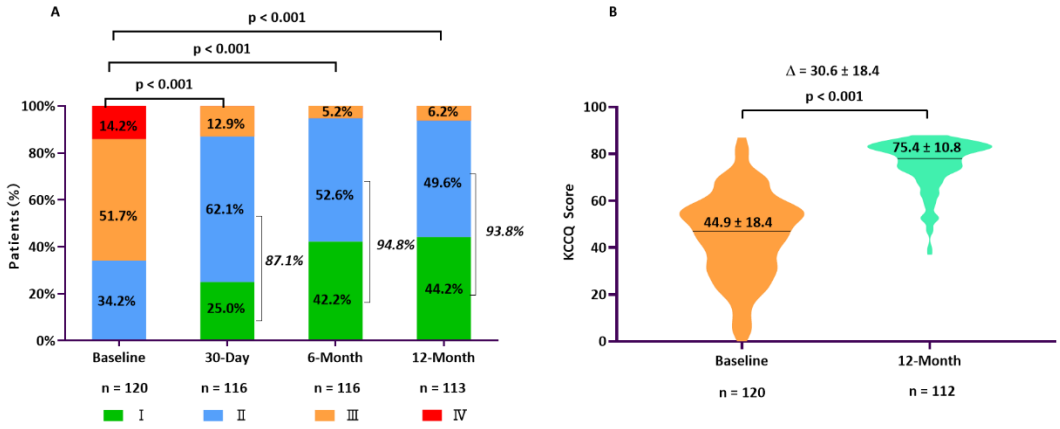
Graphs show (A) procedure time (median (IQR)) and (B) device times (median (IQR)) 1st, 2nd, and 3rd, and >3 study procedures with implantation of only one clip. The p values were calculated using Mann-Whitney tests.

IQR = interquartile range.



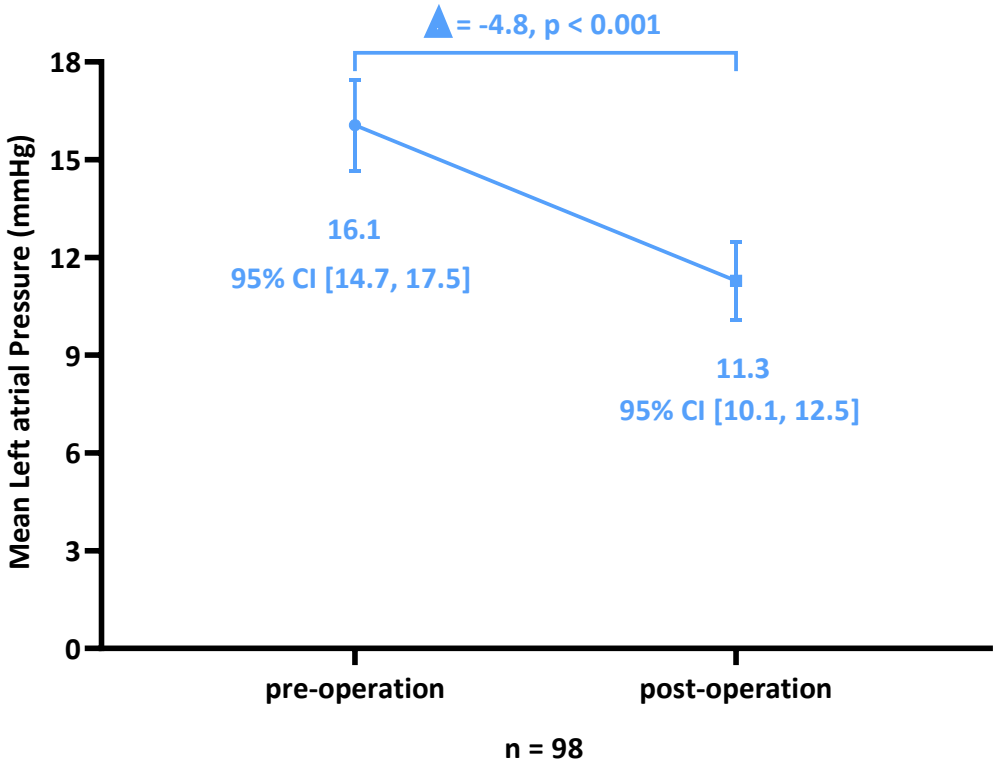
Supplementary Figure 3. MR reduction to ≤1 at 30 days, 6 months, and 12 months.

The p values for (A) paired and (B) unpaired analyses between time points were calculated using McNemar's test.



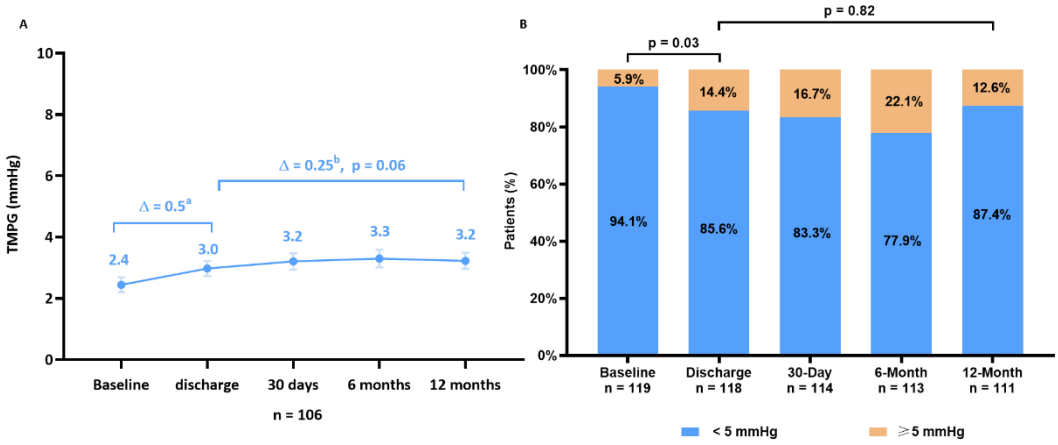
Supplementary Figure 4. Unpaired analysis for NYHA Functional Class and KCCQ outcomes at baseline and follow-up.

The graph shows unpaired analysis for (A) New York Heart Association (NYHA) functional class and (B) Kansas City Cardiomyopathy Questionnaire (KCCQ) scores. p values for group comparisons were calculated using Student's t-test for continuous variables and the Wilcoxon signed-rank test for categorical variables.



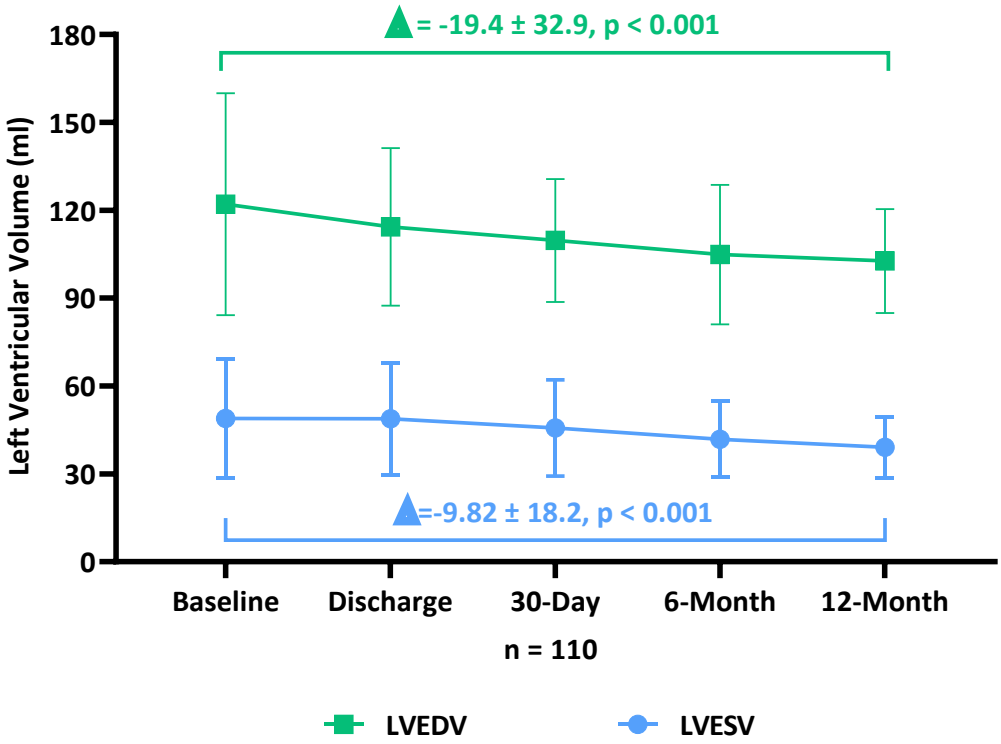
Supplementary Figure 5. Mean left atrial pressure pre-/post-operation.

Graph shows paired analysis. The error bars represent 95% CI. The p values were calculated using t-tests.



Supplementary Figure 6. Transmitral mean pressure gradient by echocardiographic core laboratory.

Graph shows the change of TMPG in paired analysis (A) and the proportion of patients with gradient ≥ 5 mmHg (B). The error bars represent 95% CI. Δ represents paired change (mean ± 95% CI) :[a]0.5 (0.2, 0.8), [b]0.25 (-0.01, 0.51), n = 106. The p values for group comparisons were calculated using Student's t-test for continuous variables and McNemar's test for paired nominal data. TMPG = transmitral mean pressure gradient.



Supplementary Figure 7. Left ventricular end-diastolic/systolic volume.

Graph shows paired analysis. Error bars represent mean ± SD. The p values were calculated using a t-test. LVEDV =left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume.