Transcatheter reshaping of the mitral annulus in patients with functional mitral regurgitation: one-year outcomes of the MAVERIC trial

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Abstract

Aims: The aim of this study was to assess the one-year safety and efficacy of the transcatheter ARTO system in the treatment of functional mitral regurgitation (FMR).

Methods and results: MAVERIC is a multicentre, prospective, non-randomised pre-commercial study. Eligible patients were on guideline-recommended therapy for NYHA Class II-IV systolic heart failure and had an FMR grade ≥2+. The ARTO system was implanted in forty-five (100%) patients. The primary safety composite endpoint (death, stroke, myocardial infarction, device-related surgery, cardiac tamponade, renal failure) at 30 days and one year was 4.4% (95% CI: 1.5-16.6) and 17.8% (95% CI: 9.3-32.4), respectively. Periprocedural complications occurred in seven patients (15.5% [95% CI: 6.5-29.5]), and five patients (11.1% [95% CI: 4.9-24.0]) died during one-year follow-up. Paired results for 36 patients demonstrated that 24 (66.7%) had grade 3+/4+ mitral regurgitation at baseline; however, only five (13.9%) and three (8.3%) patients remained at grade 3+/4+ 30 days and one year post procedure (p<0.0001). Echocardiographic parameters such as anteroposterior annulus diameter decreased from 41.4 mm (baseline) to 36.0 and 35.3 mm at 30 days and one year, respectively (p<0.0001). Twenty-five patients (69.4%) had baseline NYHA Class III/IV symptoms decreasing significantly to nine (25.0%) at 30 days and eight (22.2%) at one year post procedure (p<0.0001).

Conclusions: The ARTO transcatheter mitral valve repair system is both safe and effective in decreasing FMR up to one year post procedure.

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Abbreviations

AP diameter	anteroposterior diameter of mitral annulus
EROA	effective regurgitant orifice area
GCV	great cardiac vein
LA	left atrium
LV	left ventricle
PISA	proximal isovelocity surface area

Introduction

Functional mitral regurgitation (FMR) is often seen in heart failure (HF) patients with left ventricular (LV) dysfunction and mitral annular adverse remodelling resulting from either ischaemic or non-ischaemic dilated left heart disease[1]. There is a strong correlation between the severity of FMR and HF hospitalisations and an association with increased all-cause mortality[2-4]. Although pharmacological and/or cardiac synchronisation therapy is beneficial in some patients with FMR, others deteriorate, with surgical mitral valve annuloplasty remaining their only option[5,6]. Due to comorbidities, these patients are at increased operative risk and are not offered isolated surgical correction unless performed with other cardiac surgeries[7,8]. While alternatives such as the MitraClip® system (Abbott Vascular, Santa Clara, CA, USA) are available, it is unknown whether it is an appropriate treatment for the majority of HF patients[9]. Consequently, there remains an unmet need for alternative transcatheter technologies in the treatment of FMR. Initial results of the MitrAl ValvE RepaIr Clinical Trial (MAVERIC trial), using the ARTO™ (MVRx Inc., San Mateo, CA, USA) system, have been reported previously[10,11]. The device decreases FMR via a suture that connects interatrial-septal and great cardiac vein (GCV) anchors **(Supplementary Figure 1)**. The tension on this suture reduces the anteroposterior (AP) diameter of the mitral annulus, thereby improving mitral leaflet coaptation[11]. Previous reports have shown reductions in FMR grade, decreased LV volumes, and improved functional class. The positive outcomes achieved for the first 11 patients have allowed the study to be expanded to include a further 34 patients. We report the one-year data of this expanded cohort of 45 patients.

Methods

TRIAL DESIGN AND PATIENTS

MAVERIC is an ongoing, global, prospective, multicentre, non-blinded, non-randomised safety and efficacy study of patients treated for FMR. The primary safety outcome is the major adverse event (MAE) rate 30 days post procedure. MAEs are defined as death, stroke, MI, cardiac tamponade, device-related cardiac surgery and renal failure. Performance endpoints are technical success defined per the Mitral Valve Academic Research Consortium (MVARC)[12], mitral regurgitation grade and change from baseline to 30 days as evaluated by two-dimensional (2D) transthoracic echocardiogram (TTE). An independent core laboratory (Cardiovascular European Research Centre [CERC], Massy, France) analysed all echocardiographic data and graded FMR

as per the American Society of Echocardiography (ASE) guidelines[12]. All clinical events were adjudicated by an independent clinical events committee (CEC). Patients are followed at discharge, 30 days, six months, and yearly for three years.

The trial was designed in accordance with the Declaration of Helsinki and registered with ClinicalTrials.gov (Trial ID: NCT02302872). Details of patient eligibility and enrolment have been reported previously and are presented in **Supplementary Figure 2** [10,11]. Additional details are provided in **Supplementary Appendix 1** and **Supplementary Appendix 2**.

STATISTICAL ANALYSIS

This study included a sample size of 45 patients and was powered for two objectives: first, to provide an estimate of the rate of MAEs at 30 days; second, to have >90% power to demonstrate that the upper limit of a two-sided confidence interval for the proportion of patients with an MR grade of 2+ or higher at 30 days is not higher than 50% when assuming that the true proportion of patients with a 30-day MR grade of 2+ or lower is 75%.

Analysis of safety outcomes was performed on an intention-to-treat basis (including all patients who underwent the procedure) using the Kaplan-Meier method, censoring at the time of the outcome, death, or mitral valve replacement.

Analysis of efficacy outcomes excluded patients with an MR grade of 1+ at the echocardiography core laboratory **(Supplementary Figure 2)**, although findings were not sensitive to this choice (data not shown). Comparisons of echocardiographic and functional measurements during follow-up used paired t-tests for continuous and approximately normally distributed variables and used sign-rank tests for ordinal or heavily skewed variables. Analyses were restricted to the set of patients with complete information at all time points. Sensitivity analyses included all patients and used last observation carried forward to impute data in patients who died or did not have measurements.

Statistical tests were two-sided with p-values <0.05 considered statistically significant. Stata 15.1 (StataCorp LLC, College Station, TX, USA) and R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

Results

The ARTO system was implanted in 45 patients (60% males, 69.8±12.3 years). Baseline characteristics are shown in **Table 1** and **Supplementary Table 1**.

PROCEDURAL CHARACTERISTICS AND OUTCOMES

Median length of the ARTO procedure was 88 minutes (interquartile range [IQR]: 65-110 minutes) and median discharge rate was 2 days (IQR: 1-5 days) **(Table 2)**. Seven patients (15.5%) had procedural complications – 2 minor bleeds, 2 major bleeds and 3 minor vascular access-site complications. One of the major bleeds was due to central line insertion and the other was due to a delayed pseudoaneurysm at the access site resulting in a drop in Hb level of more than 3 g/dL necessitating a transfusion and

Table 1. Baseline characteristics (n=45).

Characteristics		n/N (%), mean±SD or median (IQR)
Age, years		69.8±12.3
Male		27/45 (60.0)
Female		18/45 (40.0)
Current smoker		8/44 (18.2)
Echocardiographic characteristics		
MR grade*	1+	3/45 (6.7)
	2+	13/45 (28.9)
	3+	14/45 (31.1)
	4+	15/45 (33.3)
LVEDD, mm		63 (9)
LVESD, mm		54 (9)
LVEDVi, ml/m²		107 (26)
LVESVi, ml/m²		65 (24)
LVEF, %		40 (9)
Functional characteristics		
NYHA Class	II	12/45 (26.7)
	III	30/45 (66.7)
	IV	3/45 (6.7)
6-minute walk distance in metres, median (IQR)		280 (200-408)
EQ5D-5L quality of life scale#, median (IQR)		0.75 (0.70-0.84)
EQ5D visual analogue health status score (0-100)		52.5 (50.0-70.0)
EuroSCORE, %		5.0±7.6
Society of Thoracic Surgeons (STS) score, %		3.8±3.4
Cardiovascular history		
Myocardial infarction		17/45 (37.8)
CABG		6/45 (13.3)
PTCA (bare metal stent or drug-eluting)		15/45 (33.3)
Pacemaker/AICD		12/45 (26.7)
Atrial fibrillation		20/45 (44.4)
Peripheral vascular disease		2/44 (4.5)
No. of hospitalisations for heart failure in last 2 years		0.7±0.8
0		21/44 (47.7%)
1		19/44 (43.2%)
2 or more		4/44 (9.1%)
Baseline medications		
ACE inhibitor or ARB		38/45 (84.4%)
Beta-blocker		40/45 (88.9%)
Diuretic		44/45 (97.7%)

* 3 patients enrolled with locally assessed MR grade of 2+ but were determined to have MR grade of 1+ by the echo core laboratory. # Using UK weighting[14].

rendering it a major bleed per MVARC guidelines[13]. Thus, none of the complications was device-related, and technical success per MVARC[12] definition was 100%.

Table 2. Procedural characteristics and outcomes (n=45).

Procedural characteristics	n/N (%), mean±SD or median (IQR)
Technical success (by MVARC)*	45/45 (100)
Intubation time, minutes	178 (151-253)
Total ARTO procedure time, minutes	88 (65-110)
Total procedure time, minutes	98 (76-120)
Total contrast volume, ml	60 (37-120)
Total X-ray dose, mGy	2,478 (926-5,633)
Total fluoroscopy time, minutes	39 (36-46)
Length of stay, days	2 (1-5)
Procedural outcomes	**n (%)**
Vascular access complications	3 (6.7%)
Major bleeding#	2 (4.4%)
Minor bleeding#	2 (4.4%)
Compression or compromise of left circumflex or coronary artery	0 (0.0%)
New-onset atrial fibrillation	0 (0.0%)

* Mitral Valve Academic Research Consortium. # As per Valve Academic Research Consortium-2 criteria.

SAFETY OUTCOMES

Thirty-day, six-month and one-year safety outcomes are shown in **Table 3** and **Figure 1**. By day 30, two MAEs (4.4%) were reported. One was a pericardial effusion requiring surgical drainage resulting in complete recovery. In another patient the CT scan was performed two days prior to the ARTO procedure and together resulted in acute kidney injury (AKI) followed by full recovery. This patient died 305 days post procedure from HF deterioration.

Seven MAEs from 30 days to six months included three deaths (all adjudicated as cardiovascular unrelated to the device or procedure), one each for stroke, MI, device-related reoperation and renal failure. The causes of the above deaths as per autopsy were either complications arising from ischaemic heart disease or sequelae of HF.

Table 3. Major adverse events in all enrolled patients.

	30 days n (%)	6 months n (%)	1 year n (%)
Primary safety composite endpoint*	2 (4.4%)	7 (15.6%)	8 (17.8%)
Death	0 (0.0%)	3 (6.7%)	5 (11.3%)
Cardiovascular	0 (0.0%)	3 (6.7%)	5 (11.3%)
Non-cardiovascular	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stroke	0 (0.0%)	1 (2.3%)	1 (2.3%)
Myocardial infarction	0 (0.0%)	1 (2.3%)	1 (2.3%)
Mitral surgery/intervention	0 (0.0%)	1 (2.3%)	1 (2.3%)
Cardiac effusion/tamponade	1 (2.2%)	1 (2.2%)	1 (2.2%)
Renal failure	1 (2.2%)	3 (6.8%)	3 (6.8%)

* Death, stroke, myocardial infarction, cardiac effusion/tamponade, device-related cardiac surgery, renal failure.
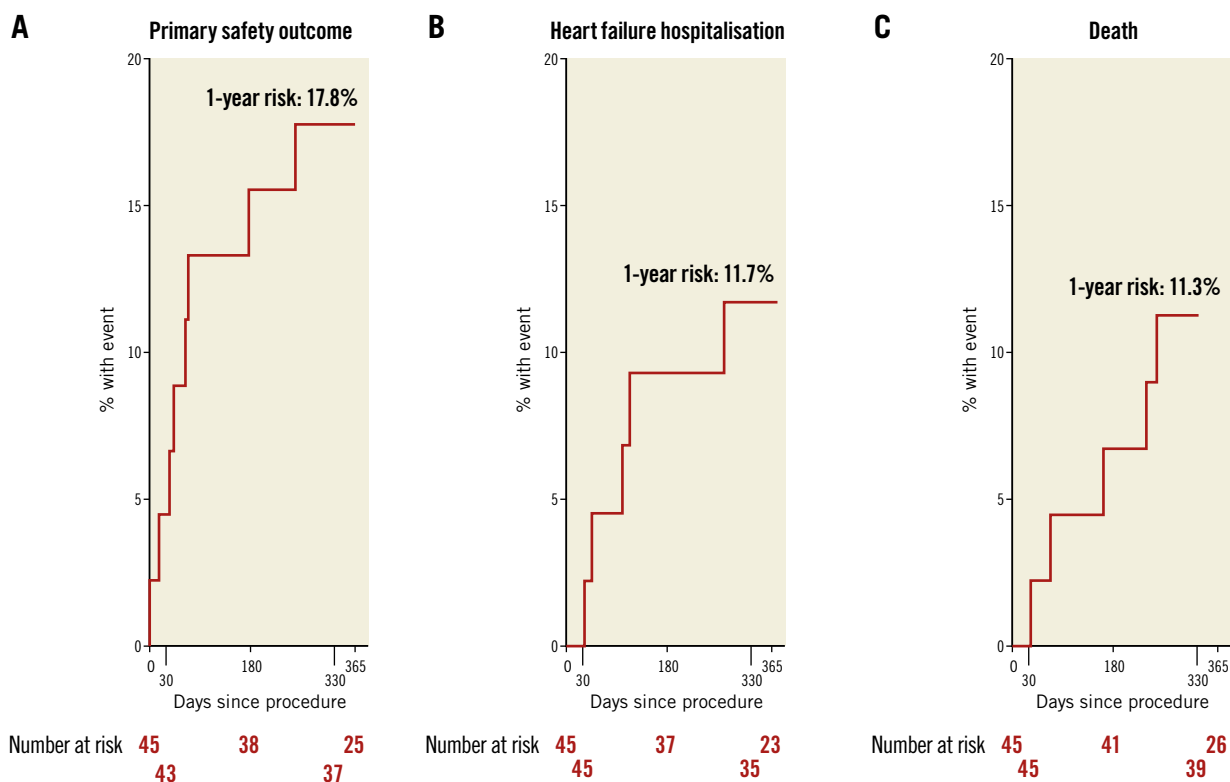
Figure 1. *Kaplan-Meier time-to-event curves for the primary safety outcome (A), heart failure hospitalisation (B) and all-cause death (C). The primary safety outcome was defined as death, stroke, myocardial infarction, cardiac effusion/tamponade, device-related cardiac surgery, renal failure.*

Within one year, MAEs occurred in eight patients (17.8% [95% CI: 9.3-32.4]) including five deaths (11.1% [95% CI: 4.9-24.0]).

EFFICACY OUTCOMES
REDUCTION IN MR AS ASSESSED BY ECHOCARDIOGRAPHIC PARAMETERS

MR reduced significantly at 30 days compared to baseline (p<0.0001) **(Table 4, Figure 2)**, with no evidence of any change in MR grade between 30 days and one year (p=0.30). In paired analyses of 36 patients, MR grade 3+/4+ was present in 24 (66.7%) at baseline, 5 (13.9%) at one month and 3 (8.3%) at one year (p<0.0001). Significant improvements were noted in other echocardiographic indices at one month compared to baseline **(Table 4, Figure 2)**, including a 13% decrease in AP diameter (41.4 vs 36.0 mm, p<0.0001), 47% decrease in regurgitant volume (44.8 vs 23.2 ml, p=0.0001), 48% decrease in effective regurgitant orifice area (EROA; 26.9 vs 13.9 mm^2, p=0.0001) and 33% improvement in vena contracta (6.0 vs 4.0 mm, p<0.0001), all of which were sustained at one year post procedure.

Improvements in cardiac function one year post procedure were demonstrated by a 13% decrease in LV end-systolic volume (LVESVi; 65.7 vs 57.1 ml/m^2, p=0.0102), 14% decrease in LV end-diastolic volume (LVEDVi; 107.9 vs 92.9 ml/m^2, p=0.0013) and 21% reduction in left atrial volumes (62.1 vs 48.9 ml/m^2, p=0.0004), all indexed to body surface area.

FUNCTIONAL IMPROVEMENTS POST PROCEDURE

NYHA class improved whereby 8 patients (22.2%) were classified as NYHA Class III/IV at one year, compared to 9 (25.0%) at 30 days and 25 patients (69.4%) at baseline (p-value for improvements in NYHA <0.0001 for both classes). Additionally, there were no significant changes in medication use **(Supplementary Table 2)**, and there were only five HF-related hospitalisations (11.7% [95% CI: 5.1-25.9]). Significant improvements at 30 days compared to baseline were reported in the EQ-5D self-assessed health status (visual analogue scale from 0-100, median 75% at 30 days vs median 52.5% at baseline, p-value=0.0002)[14]. Paired analyses for six-minute walk tests (6MWT) in 43 patients showed ~16.67% improvement in distance covered at 30-day follow-up compared to baseline (p=0.0286); no further improvements were observed from 30 days to one year (p=0.20) **(Supplementary Figure 3)**. Findings were similar in sensitivity analyses **(Supplementary Table 3)**.

Discussion

The MAVERIC study, designed to assess the safety and efficacy of the ARTO transcatheter mitral valve repair system, showed that the device was a safe therapeutic option for patients[15]. One-year follow-up data showed that patients implanted with the ARTO system had significant echocardiographic and functional improvements.

Imaging parameters such as EROA ≥20 mm^2, left ventricular end-diastolic diameter (LVEDD) >65 mm, regurgitant volume

Table 4. Selected functional parameters over time. To enable paired comparisons, we restricted analysis to patients with data at all three visits.

Characteristics		N	n (%), mean (SD) or median (IQR)			p-value		
			Baseline	1 month	1 year	Baseline vs 1 month	Baseline vs 1 year	1 year vs 1 month
MR grade	0	36	0 (0.0%)	4 (11.1%)	3 (8.3%)	<0.0001	<0.0001	0.2975
	1	36	0 (0.0%)	15 (41.7%)	20 (55.6%)			
	2	36	12 (33.3%)	12 (33.3%)	10 (27.8%)			
	3	36	12 (33.3%)	5 (13.9%)	3 (8.3%)			
	4	36	12 (33.3%)	0 (0.0%)	0 (0.0%)			
AP annulus diameter, mm		35	41.4 (4.3)	36.0 (4.7)	35.3 (5.2)	<0.0001	<0.0001	0.4121
Regurgitant volume*		26	44.8 (15.3)	23.2 (12.0)	25.6 (10.8)	<0.0001	<0.0001	0.2984
Effective orifice area, mm^2		16	26.9 (10.4)	13.9 (6.0)	17.6 (7.1)	0.0001	0.0034	0.0506
Vena contracta#, mm		28	6.0 (5.0-8.0)	4.0 (1.8-5.0)	3.5 (3.0-5.0)	<0.0001	0.0001	0.6376
LVESVi, ml/m^2		35	65.7 (25.1)	62.5 (22.1)	57.1 (22.0)	0.1369	0.0102	0.0137
LVESV, ml		35	125.8 (51.4)	119.3 (44.5)	110.4 (47.7)	0.1122	0.0206	0.0482
LVEDVi, ml/m^2		35	107.9 (27.1)	101.1 (23.2)	92.9 (27.5)	0.0086	0.0013	0.0203
LVEDV, ml		35	206.3 (61.0)	192.1 (50.4)	179.0 (63.0)	0.0043	0.0024	0.0564
LAVi, ml/m^2		32	62.1 (21.9)	50.9 (17.7)	48.9 (20.3)	0.0001	0.0004	0.4122
Left atrium volume, ml		32	118.3 (47.3)	96.4 (36.6)	93.2 (42.9)	0.0001	0.0003	0.4591
LVEDD, mm		35	63.9 (8.0)	62.4 (8.1)	62.0 (8.9)	0.0563	0.0718	0.6125
LVESD, mm		33	55.2 (8.5)	53.5 (9.1)	52.0 (9.3)	0.1327	0.0052	0.1184
LVEF, %		35	39.8 (9.1)	40.0 (10.2)	40.5 (9.7)	0.7997	0.5946	0.6947
Tenting area, cm^2		33	2.4 (0.9)	1.8 (0.6)	1.4 (0.7)	0.0010	<0.0001	0.0033
Tenting height, mm		33	9.2 (3.0)	7.9 (2.1)	6.7 (1.8)	0.0267	<0.0001	0.0066
Tricuspid regurgitation	0	35	1 (2.9%)	3 (8.6%)	7 (20.0%)	0.0954	0.0008	0.0110
	1	35	13 (37.1%)	19 (54.3%)	20 (57.1%)			
	2	35	19 (54.3%)	9 (25.7%)	6 (17.1%)			
	3	35	1 (2.9%)	3 (8.6%)	2 (5.7%)			
	4	35	1 (2.9%)	1 (2.9%)	0 (0.0%)			
NYHA Class	I	36	0 (0.0%)	5 (13.9%)	8 (22.2%)	<0.0001	<0.0001	0.1533
	II	36	11 (30.6%)	22 (61.1%)	20 (55.6%)			
	III	36	22 (61.1%)	9 (25.0%)	8 (22.2%)			
	IV	36	3 (8.3%)	0 (0.0%)	0 (0.0%)			
EQ-5D visual analogue health status score (0-100)		26	52.5 (50.0-70.0)	75.0 (60.0-75.0)	67.5 (60.0-75.0)	0.0002	0.0116	0.6228
EQ5D-5L quality of life scale		21	0.75 (0.71-0.86)	0.86 (0.75-0.89)	0.80 (0.70-0.88)	0.0699	0.3094	0.5716
6-minute walk test distance (metres)		33	325.0 (240-411)	390.0 (225-432)	363 (220-450)	0.0286	0.2014	0.3256

*Regurgitant volume was measured by the PISA method. Where no PISA measurement was available, we imputed estimated regurgitant volume by PISA using the measurement with the volume. # Where vena contracta was less than the lower limit of detection of 3 mm, we imputed 1.5 mm.

>30 ml and others have been associated with worse outcomes in FMR patients[2,16]. Patients with data available at all time points showed 35% and 37% improvements in EROA and regurgitant volumes, respectively, at one year. A reduction in FMR has a positive correlation with reverse remodelling and improved survival[17,18]. Importantly, MAVERIC imaging assessments revealed significant improvements in cardiac volumes (decrease ≥13% in LVESVi/LVEDVi and decrease ≥20% in atrial volumes), suggestive of early reverse LV remodelling. LVESV reductions >10% have been shown to result in significant decreases in mortality and hospitalisations in advanced HF patients[19]. Functional improvements were also evident with NYHA class that improved significantly at 30 days and remained significant at one year. Furthermore, at one month there were significant improvements in 6MWT and EQ-5D visual analogue health status scores. This is particularly meaningful when considering that the positive 6MWT outcome reported
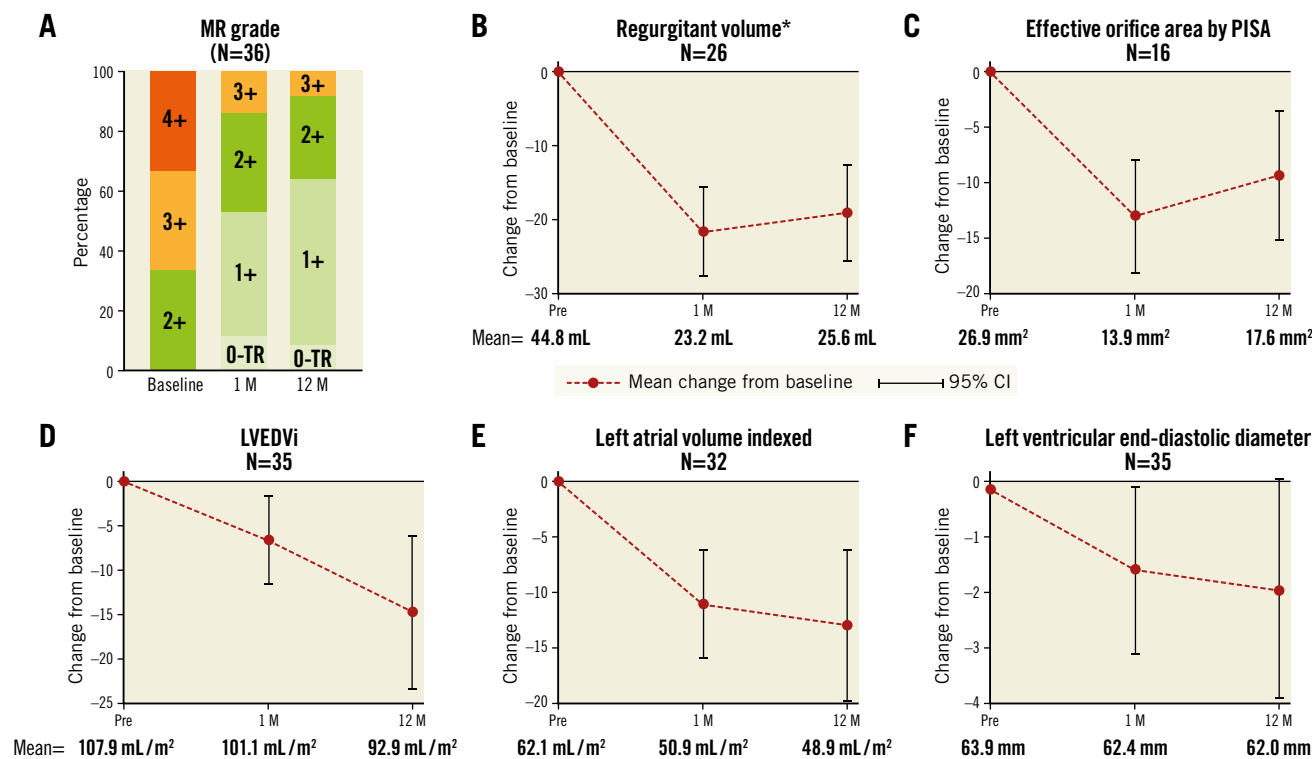
Figure 2. *Selected change in echocardiographic parameters between baseline visit and 30-day or one-year visits. MR grade (A) at baseline, one month (1 M) and 12 months (12 M). Echocardiographic parameters: regurgitant volume (B), effective orifice area by PISA (C), LV end-diastolic volume (LVEDVi) (D), left atrial volume indexed (E) and LV end-diastolic diameter (F). P-values are from paired comparisons between time points. *Regurgitant volume was measured by the PISA method. Where no PISA measurement was available, regurgitant volume was estimated by using the measurement with the volume method.*

in the COAPT trial was achieved mainly by deterioration in the control arm[9]. A technical success rate of 100% indicates a safe procedure and a device success rate of 71.4% is noteworthy for a first-generation device, suggesting that the therapy is comparable to other established percutaneous mitral repair therapies[20,21].

The ARTO system has several beneficial features: (1) a short procedure performed entirely at the atrial level decreasing ventricular arrhythmias and preserving haemodynamic stability; (2) preprocedural computed tomography (CT) coupled with a coronary angiogram that helps to determine the anatomy of the coronary sinus and circumflex coronary artery, avoiding coronary artery compression; (3) flexibility to adjust/remove the device prior to lock-and-release of the system as required, and (4) individually tailored decrease in AP diameter with immediate MR reduction.

There is a relatively small learning curve for the procedure that led to minor procedural and device modifications. For example, pericardial effusion was reduced by the replacement of the angled wire with a J-tipped wire[11]. Dislocation of the GCV T-Bar into the left atrium (LA) detected early in the trial in two asymptomatic patients was either corrected surgically or left untouched, at the investigator's discretion. An atraumatic tip separation noted at follow-up imaging required no intervention since the patient was asymptomatic and MR reduction of 4+ to 1+ was maintained.

The current landscape of transcatheter repair devices for FMR consists of leaflet approaches such as the MitraClip, and indirect/direct annuloplasty approaches. The clinical experience with the MitraClip procedure and FMR has been well reported and has been shown to demonstrate acute MR reduction, improved functional class and low rehospitalisation, but with ~20% FMR >2+ recurrence at 12 months in patients with challenging anatomies[22]. The latest data from the STS/TVT registry of FMR patients reported 31.2% one-year mortality, 32.6% HF rehospitalisation and death or HF hospitalisation of 49%[23]. The MITRA-FR trial using the MitraClip device for severe secondary MR failed to show any significant difference between patients who underwent percutaneous mitral valve repair in addition to receiving medical therapy and those who received medical therapy alone[24]. This was attributed mainly to significant underlying cardiomyopathy, incomplete correction of MR and the severity of the disease in the trial population. Conversely, the COAPT trial demonstrated a lower rate of hospitalisation, lower mortality, better prognosis and better functional capacity in subjects who received the device in addition to guideline-directed medical therapy compared to those receiving only guideline-directed medical therapy[9]. This further emphasises the need for novel technologies, especially for those patients who are ineligible for a MitraClip device. The recent one-year outcomes of a cohort of sixty patients using the Cardioband system (Edwards Lifesciences, Irvine, CA, USA)

indicated an 87% one-year survival with 66% having freedom from HF and 78% freedom from a secondary intervention[24]. The outcomes from the randomised REDUCE FMR trial using the Carillon Mitral Contour System® (Cardiac Dimensions Inc., Kirkland, WA, USA) show one-year mortality of 14%, and HF hospitalisations of 11% with 9% having device removal for coronary artery compromise[25]. Although transcatheter mitral valve replacement is being refined in early clinical trials, further investigations are necessary to establish the role of transcatheter repair versus replacement, since the FMR cohort is at increased risk of morbidity and mortality by virtue of underlying LV dysfunction and comorbidities.

Limitations

A small sample size with no control group is always a limitation in studies such as MAVERIC investigating new technologies. The inclusion criteria required subjects to be ineligible for surgery, implying that patients were at higher risk of mortality, morbidity and worse outcomes. That said, no mortality in this study was associated with the ARTO system or procedure. Although MR grade improved significantly and was assessed by the core lab for all patients, individual parameters were not available for all patients – a well-recognised challenge in evaluating FMR patients[25]. The first eleven patients in the study were not evaluated by EQ-5D at baseline (protocol amended), hampering our ability to show significant improvements in this parameter.

Conclusions

This study shows that the ARTO system has some outstanding features and results, as demonstrated by short procedure times, 100% technical success as per MVARC criteria, small contrast volumes, 86% survival rates at one year, improved MR grades and a 12% hospitalisation rate. NYHA class improved significantly at 30 days and one year. In summary, these data demonstrate that the ARTO system is safe and effective in reducing MR significantly and improving functional status in patients with symptomatic FMR up to one year.

Impact on daily practice

Mitral valve surgery is a proven therapeutic option for FMR; however, operative risks remain high in patients with comorbidities. The ARTO transcatheter mitral valve repair system is a less invasive method for FMR treatment that appears to be safe and effective, especially in patients ineligible for other CE-marked devices.

Conflict of interest statement

A. Erglis has received research grants from MVRx, Inc. S. Redwood is a proctor for MVRx, Inc. D. Hildick-Smith is a consultant to MVRx, Inc. All other authors have reported no relationships relevant to the contents of this paper.

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Supplementary data

Supplementary Appendix 1. Inclusion/exclusion criteria.

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Supplementary Figure 1. The transcatheter ARTO device.

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Supplementary data

**Supplementary Appendix 1. Inclusion/exclusion criteria**

A local Heart Team consisting of a cardiologist, cardiac surgeon, and heart failure specialist evaluated all patients; only patients who were deemed unfit for surgery due to underlying comorbidities were included in the trial. Briefly, key inclusion criteria are as follows: FMR grade ≥2+ as determined by the core lab with New York Heart Association (NYHA) Class II-IV systolic heart failure of any aetiology; left ventricular ejection fraction (LVEF) >20%; left ventricular end-diastolic diameter (LVEDD) between >50 mm and ≤70 mm; and transseptal puncture was feasible. Key exclusion criteria in addition to standard exclusion criteria for catheterisation procedures included: structural abnormality of the mitral valve (e.g., flail, prolapse, or leaflet calcification); significant mitral annular calcification; prior mitral valve surgery or valvuloplasty or currently implanted prosthetic valve or ventricular assist device; history of rheumatic heart disease; atrial septal defect or PFO associated with clinical symptoms; atrial septal aneurysm; active infection, endocarditis, or intracardiac thrombus and severe tricuspid regurgitation.

Supplementary Appendix 2. Methods - procedure and device description

The ARTO system and procedure have been described in detail previously. Briefly, the procedure is performed in the cardiac catheterisation laboratory under general anaesthesia with fluoroscopic and transoesophageal echocardiographic (TEE) guidance. Two interventionists were involved in the procedure: one placed the magnetic catheter in the coronary sinus through the right internal jugular vein, and the other worked from the right femoral vein for both transseptal puncture and placement of the second magnetic catheter in the left atrium. Using these magnetically linked catheters and routine catheter exchanges, the GCV anchor (T-Bar) is placed and connected by an adjustable length suture to an atrial septal anchor **(Supplementary Figure 1)**. The suture can then be tensioned to reshape and decrease the anteroposterior (AP) diameter of the mitral annulus, resulting in decreased FMR.

Echocardiographic evaluations were performed on site for all patients; however, three of the 45 patients were judged by the echocardiographic core laboratory to have <2+ MR at baseline and thus were excluded from subsequent efficacy analyses.

(A)
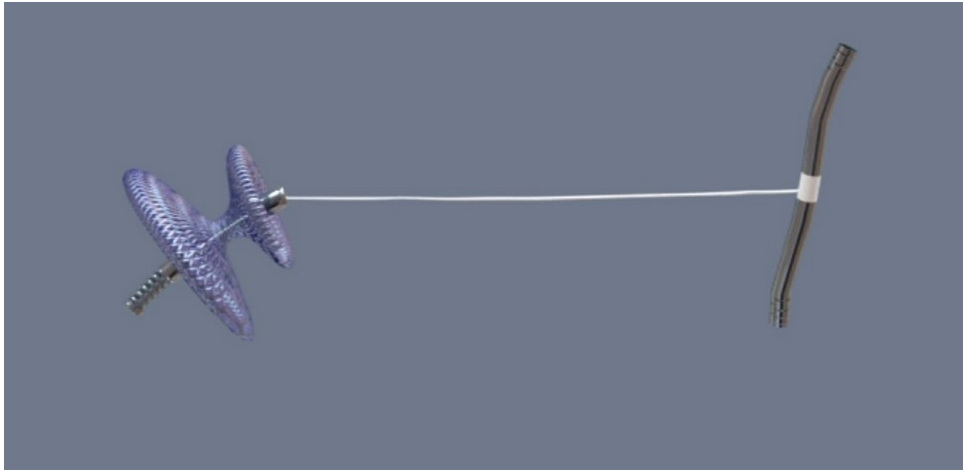
(B)
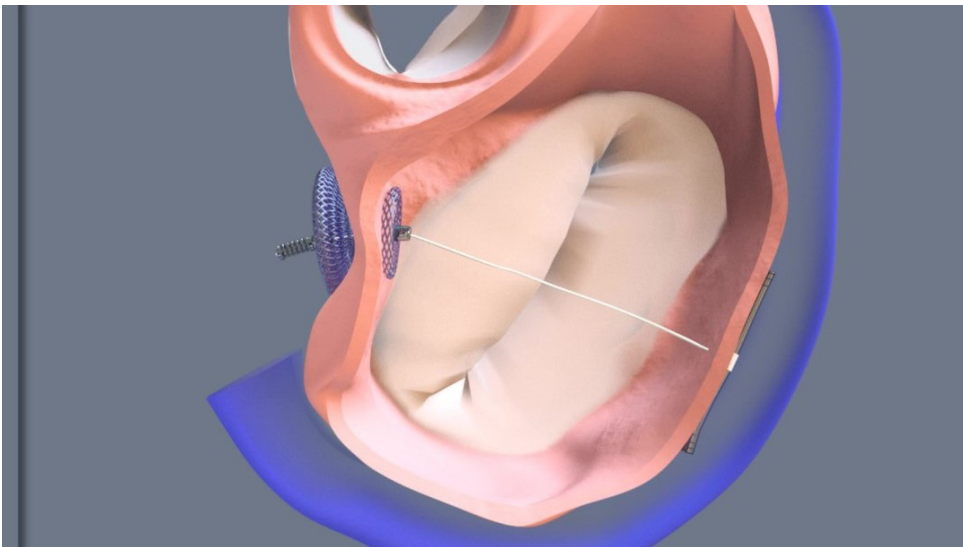
Supplementary Figure 1. The transcatheter ARTO device.

Device ex vivo (A), and device in situ (B) demonstrating decrease in the anteroposterior diameter of the mitral annulus.

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┌──────────────────────────────┐
│ 45 Patients                  │
│ Met the study inclusion criteria │
│ and underwent ARTO           │
│ procedure                    │
└──────────────────────────────┘
                                  ┌──────────────────────────────┐
                                  │ 3 Patients had MR grade of   │
                                  │ 1+ when measured at the      │
                                  │ core laboratory              │
                                  └──────────────────────────────┘

                                  ┌──────────────────────────────┐
                                  │ 5 died                       │
                                  │ 1 mitral valve replacement   │
                                  │ and therefore withdrawn      │
                                  │ from study                   │
                                  └──────────────────────────────┘

┌──────────────────────────┐   ┌──────────────────────────────┐
│ 45 Patients              │   │ 36 Patients with all data available │
│ Included in analysis of  │   │ are included in analysis of  │
│ safety and procedural    │   │ echocardiographic parameters │
│ outcomes                 │   │                              │
└──────────────────────────┘   └──────────────────────────────┘
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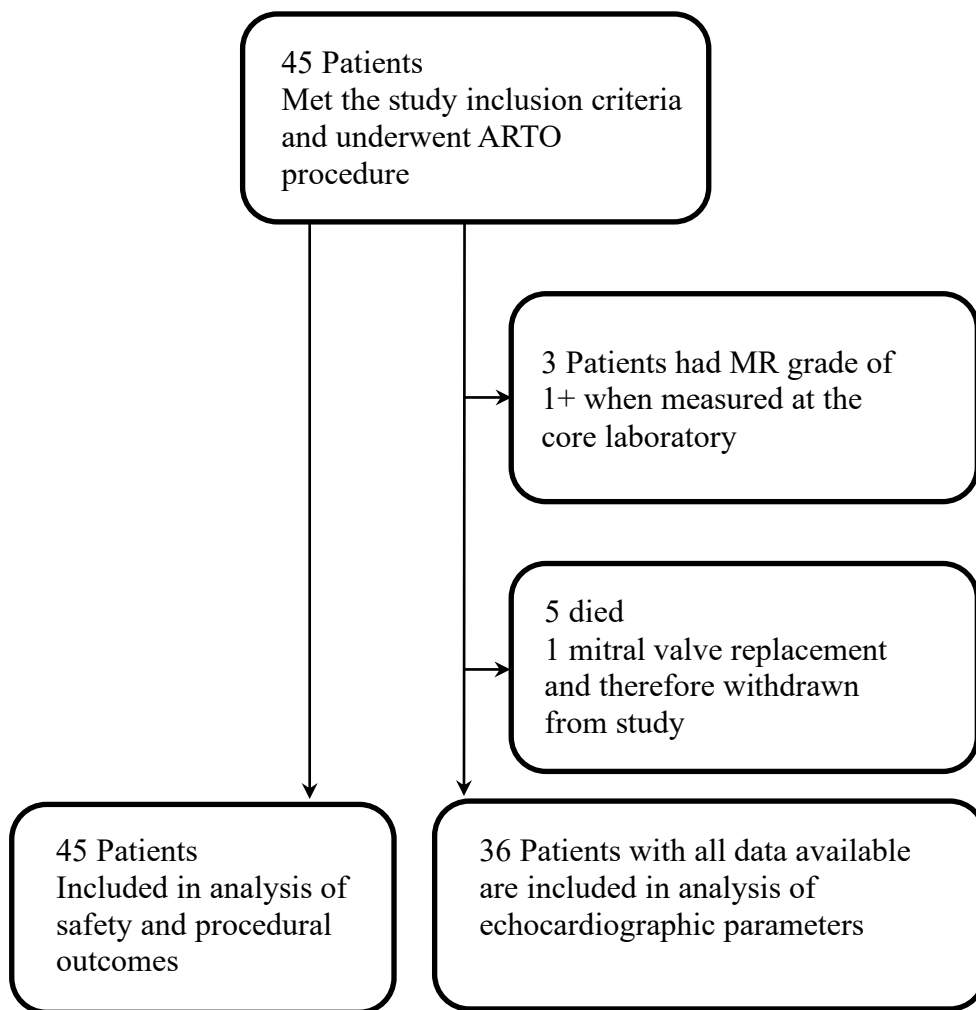
Supplementary Figure 2. Flow chart of the number of patients contributing to specific statistical analyses.
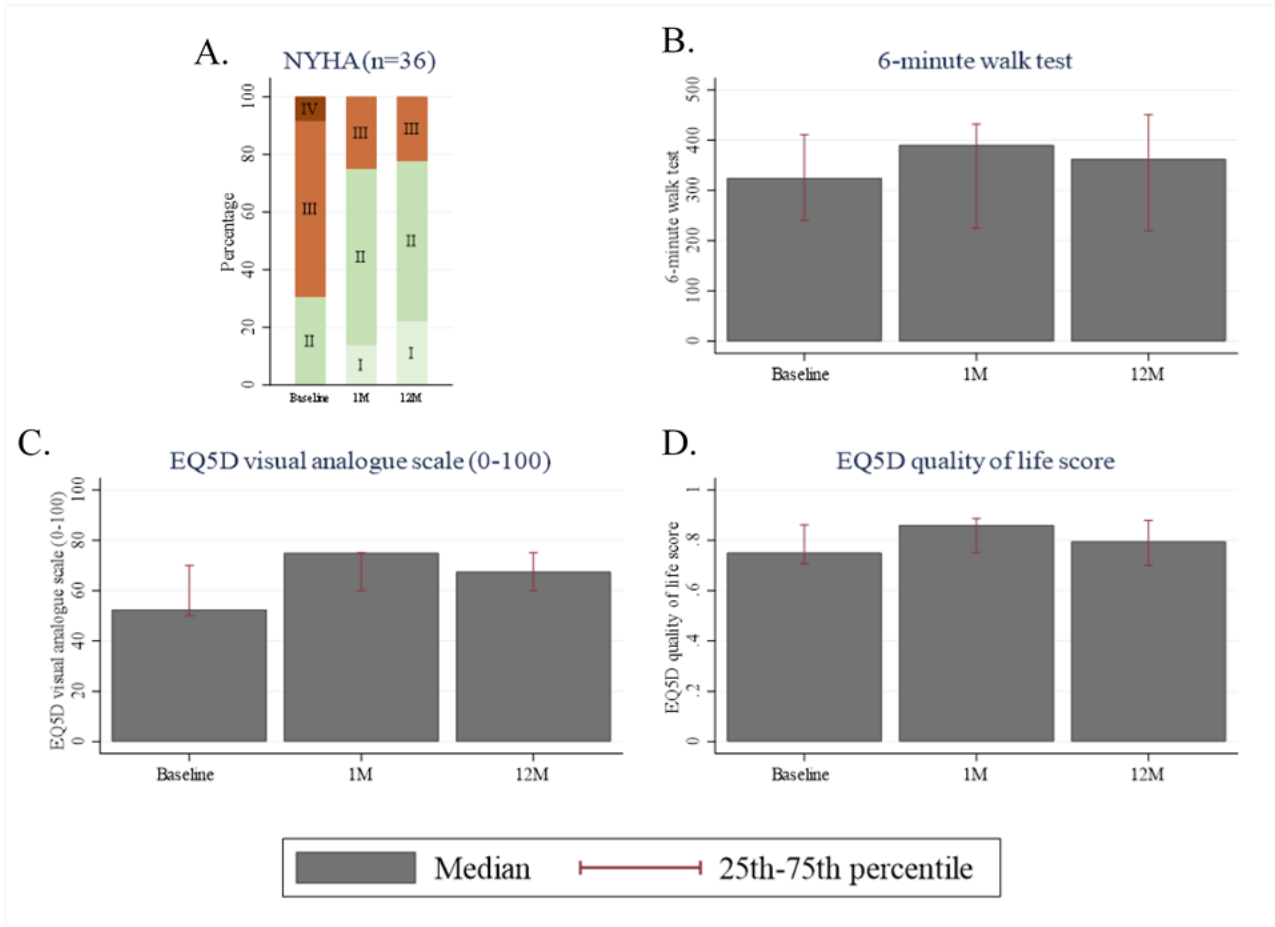
Supplementary Figure 3. Changes in functional parameters and self-assessment.
Functional parameters and self-assessment include (A) the New York Heart Association (NYHA) functional classification at baseline, 1 month (1 M) and 12 months (12 M), (B) 6-minute walk test, (C) EQ-5D visual analogue scale, and (D) EQ-5D quality-of-life score.

Supplementary Table 1. Additional baseline patient characteristics.

Comorbidities	N (%) or median (interquartile range)
Diabetes	9/45 (20.0)
Chronic kidney disease (defined by eGFR <60 mL/min/1.73 m^2)	23 (51.0)
Hypertension	21/45 (46.7)
Hypercholesterolaemia	19/43 (44.2)
Chronic obstructive pulmonary disease (COPD)	9/45 (20.0)
Cerebrovascular disease	3/45 (6.7)
Pulmonary hypertension	
Moderate (PA systolic 31-55 mmHg)	14/44 (31.8)
Severe (PA systolic >55 mmHg)	7/44 (15.9)
Medication history	
Anticoagulant	14/45 (31.1)
Antiplatelet	24/45 (53.3)
Biophosphonate therapy	0/45 (0.0)
Calcium channel blocker	4/45 (8.9)
Statin	32/45 (71.1)
Antiarrhythmic	11/45 (24.4)
Insulin	6/45 (13.3)
NSAID	0/45 (0.0)
Oral steroid	1/45 (2.2)
Thyroid	5/45 (11.1)

Supplementary Table 2. Medication history.

	30 days n (%)	6 months n (%)	1 year n (%)
ACE inhibitor or ARB	35 (77.8%)	33 (78.6%)	30 (76.9%)
Beta-blocker	39 (86.7%)	38 (90.5%)	35 (89.7%)
Diuretic (including Spirix/Spir)	40 (91.1%)	40 (95.2%)	37 (94.9%)

Supplementary Table 3. Selected functional parameters over time using imputation with last observation carried forward.

Characteristics		N with data at baseline^	n (%), mean (SD) or median (IQR)			p-value		
			Pre-procedure	1 month	1 year	Pre-procedure vs 1 month	Pre-procedure vs 1 year	1 year vs 1 month
MR grade	0	42	0 (0.0%)	4 (9.5%)	3 (7.1%)	<0.0001	<0.0001	0.3156
	1	42	0 (0.0%)	17 (40.5%)	22 (52.4%)			
	2	42	13 (31.0%)	15 (35.7%)	13 (31.0%)			
	3	42	14 (33.3%)	5 (11.9%)	3 (7.1%)			
	4	42	15 (35.7%)	1 (2.4%)	1 (2.4%)			
Tricuspid regurgitation	0	42	1 (2.4%)	3 (7.1%)	7 (16.7%)	0.0714	0.0013	0.0345
	1	42	16 (38.1%)	22 (52.4%)	23 (54.8%)			
	2	42	21 (50.0%)	12 (28.6%)	8 (19.0%)			
	3	42	1 (2.4%)	3 (7.1%)	2 (4.8%)			
	4	42	3 (7.1%)	2 (4.8%)	2 (4.8%)			
LVEDD, mm		41	64.0 (8.3)	62.5 (8.2)	62.2 (8.9)	0.0334	0.0425	0.5857
LVESVi, ml/m^2		42	66.2 (23.9)	64.1 (21.9)	60.3 (23.0)	0.2824	0.0513	0.0512
LVESV, ml		42	128.5 (50.2)	123.8 (46.4)	117.8 (50.8)	0.2131	0.0740	0.1311
LVEDVi, ml/m^2		42	108.7 (26.3)	102.9 (22.9)	97.2 (28.4)	0.0143	0.0047	0.0619
LVEDV, ml		42	210.6 (60.9)	197.5 (52.0)	188.8 (65.6)	0.0051	0.0058	0.1456
LVESD, mm		40	54.4 (8.5)	53.3 (8.9)	51.9 (9.1)	0.2365	0.0108	0.0768
LVEF, %		42	39.7 (8.6)	39.4 (10.0)	39.8 (9.6)	0.6936	0.9797	0.7027
Vena contracta, mm$^+$		41	6.0 (5.0 to 8.0)	4.0 (2.0 to 5.0)	3.5 (2.0 to 5.0)	<0.0001	<0.0001	0.7082
Regurgitant volume by PISA, ml		32	42.7 (15.6)	23.3 (12.9)	25.9 (11.2)	<0.0001	<0.0001	0.2356
Regurgitant volume, ml*		40	42.9 (15.3)	23.2 (12.8)	25.6 (11.6)	<0.0001	<0.0001	0.2598*
Left atrium volume, ml		41	120.5 (45.5)	100.5 (38.5)	98.8 (43.3)	<0.0001	0.0001	0.6272
Left atrium volume indexed, mL/m^2		41	62.4 (21.2)	52.4 (18.4)	51.3 (20.6)	<0.0001	0.0003	0.5704
AP annulus diameter		42	41.1 (5.1)	36.3 (4.8)	35.8 (5.5)	<0.0001	<0.0001	0.4824
Tenting area, cm^2		41	2.4 (0.9)	1.9 (0.7)	1.6 (0.8)	0.0023	<0.0001	0.0115
Tenting height, mm		41	9.2 (2.7)	8.3 (2.2)	7.4 (2.2)	0.0505	0.0003	0.0160
6-minute walk test distance, metres		42	297.0 (160.0 to 408.0)	335.0 (165.0 to 420.0)	300.0 (182.0 to 440.0)	0.0573	0.3141	0.6078
NYHA Class	I	42	0 (0.0%)	6 (14.3%)	9 (21.4%)	<0.0001	<0.0001	0.1882
	II	42	11 (26.2%)	24 (57.1%)	22 (52.4%)			
	III	42	28 (66.7%)	12 (28.6%)	11 (26.2%)			
	IV	42	3 (7.1%)	0 (0.0%)	0 (0.0%)			
EQ5D-5L quality-of-life scale		31	0.75 (0.66 to 0.82)	0.81 (0.67 to 0.88)	0.78 (0.58 to 0.87)	0.0906	0.382	0.5131
Health status, %		31	50.0 (50.0 to 70.0)	70.0 (50.0 to 75.0)	65.0 (40.0 to 75.0)	0.0017	0.1493	0.2187

^ Those with data at baseline had data at all times when last observation carried forward is used.

+ Where vena contracta was less than the lower limit of detection of 3 mm, we imputed 1.5 mm.

* Regurgitant volume was measured by the PISA method. Where no PISA measurement was available, we imputed estimated regurgitant volume by PISA using the measurement with the volume method.