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The REDUCE FMR Trial

A Randomized Sham-Controlled Study of Percutaneous Mitral Annuloplasty in Functional Mitral Regurgitation

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ABSTRACT

OBJECTIVES This study sought to evaluate the effects of the Carillon device on mitral regurgitation severity and left ventricular remodeling.

BACKGROUND Functional mitral regurgitation (FMR) complicates heart failure with reduced ejection fraction and is associated with a poor prognosis.

METHODS In this blinded, randomized, proof-of-concept, sham-controlled trial, 120 patients receiving optimal heart failure medical therapy were assigned to a coronary sinus-based mitral annular reduction approach for FMR or sham. The pre-specified primary endpoint was change in mitral regurgitant volume at 12 months, measured by quantitative echocardiography according to an intention-to-treat analysis.

RESULTS Patients (69.8 ± 9.5 years of age) were randomized to either the treatment (87) or the sham-controlled (33) arm. There were no significant differences in baseline characteristics between the groups. In the treatment group, 73 of 87 (84%) had the device implanted. The primary endpoint was met, with a statistically significant reduction in mitral regurgitant volume in the treatment group compared to the control group (decrease of 7.1 ml/beat [95% confidence interval [CI]: −11.7 to −2.5] vs. an increase of 3.3 ml/beat [95% CI: −6.0 to 12.6], respectively; p = 0.049). Additionally, there was a significant reduction in left ventricular volumes in patients receiving the device versus those in the control group (left ventricular end-diastolic volume decrease of 10.4 ml [95% CI: −18.5 to −2.4] vs. an increase of 6.5 ml [95% CI: −5.1 to 18.2]; p = 0.03 and left ventricular end-systolic volume decrease of 6.2 ml [95% CI: −12.8 to 0.4] vs. an increase of 6.1 ml [95% CI: −1.42 to 13.6]; p = 0.04).

CONCLUSIONS The Carillon device significantly reduced mitral regurgitant volume and left ventricular volumes in symptomatic patients with functional mitral regurgitation receiving optimal medical therapy. (Carillon Mitral Contour System for Reducing Functional Mitral Regurgitation [REDUCE FMR]; NCT02325830) (J Am Coll Cardiol HF 2019;■:■-■) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

FMR = functional mitral regurgitation

HFrEF = heart failure with reduced ejection fraction

KCCQ = Kansas City Cardiomyopathy Quality of Life Questionnaire

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVESV = left ventricular end-systolic volume

MAE = Major adverse events

NYHA = New York Heart Association

Chronic heart failure is common, occurring in 1% to 2% of adults in developed countries and ≥10% of those 70 years of age or older (1). Functional (or secondary) mitral regurgitation (FMR) is a frequent finding in patients with heart failure (2). Patients with FMR and heart failure with reduced ejection fraction (HFrEF) have worse morbidity and mortality than patients with HFrEF without FMR, even when the mitral regurgitation is mild (2-4). Therefore, strategies which reduce FMR may have a favorable impact on clinical outcomes. This hypothesis was supported by a recent trial which demonstrated an improvement in clinical outcomes in patients with moderate to severe FMR treated with a percutaneous leaflet clipping device (5).

The Carillon mitral contour system (Cardiac Dimensions, Kirkland, Washington), a mitral annuloplasty device delivered percutaneously to the coronary sinus (**Central Illustration**), is designed to reduce the mitral annular dimension by virtue of the close anatomic relationship between the coronary sinus and the posterior mitral annulus. Single-arm observational core laboratory-adjudicated studies have shown that this approach reduces mitral regurgitation and improves exercise capacity and symptoms and quality of life in patients with HFrEF and FMR (6-8). These studies have also provided evidence of left ventricular (LV) reverse remodeling.

The REDUCE-FMR (Carillon Mitral Contour System for Reducing Functional Mitral Regurgitation) study was the first sham-controlled randomized trial of any catheter-based therapy for patients with valvular heart disease. The aim was to evaluate the effects of the Carillon device on FMR severity and LV remodeling.

METHODS

STUDY DESIGN. The REDUCE-FMR trial was a double-blinded, multicenter, randomized, proof-of-concept, sham-controlled trial of the Carillon mitral contour system. The study design has been reported previously (9). The trial was approved by the institutional review board or local Competent Authority/Ethics Committee at each participating site, and patients provided written informed consent.

STUDY PATIENTS. Eligibility requirements at screening included an age of at least 18 years, symptoms of New York Heart Association (NYHA) functional class II, III, or IV, an LV ejection fraction (LVEF) of <50%, an LV end-diastolic diameter more than 55 mm, and an FMR grade of 2+, 3+, or 4+, despite the use of stable (≥3-month) guideline-directed medical therapy. In addition, patients had to have the ability to complete a 6-min walk distance of 150 to 450 m to confirm exercise limitation while proving capacity for serial 6-min walk testing.

Key exclusion criteria included percutaneous coronary intervention in the previous 30 days, prior mitral valve surgery, significant organic mitral valve pathology, severe mitral annular calcification, and existing or indication for cardiac resynchronization therapy.

STUDY PROCEDURES. After undergoing screening for clinical eligibility, patients provided informed written consent. They then underwent quantitative transthoracic echocardiography by appropriately trained local echocardiographers for the assessment of mitral regurgitation and LV structure and function. After review by the local investigator, with the support of the local heart valve multidisciplinary team according to local practice, a decision was made about the patient's suitability for mitral valve intervention and specifically for the REDUCE-FMR study.

At a subsequent study visit, patients underwent a 6-min walk test, submitted blood tests for renal function and natriuretic peptides, and completed a Kansas City Cardiomyopathy Quality of Life Questionnaire (KCCQ). (10)

Following this, patients were taken to the cardiac catheterization laboratory, where they were put under either general anesthesia (n = 47) or conscious sedation, using headphones and blindfolds (n = 73) as required to maintain blinding. Patients underwent coronary angiography through radial or femoral access. A 10-F sheath was inserted into the right internal jugular vein, and a Carillon delivery catheter was used to engage the coronary sinus. Quantitative

of and holds stock in Cardiac Dimensions. Dr. Sievert has received grants from Cardiac Dimensions; and has received grants, fees, and nonfinancial support from 4tech Cardio, Abbott, Ablative Solutions, Ancora Heart, Bavaria Medizin Technologie GmbH, Bioventrix, Boston Scientific, Carag, Celonova, Comed BV, Contego, CVRx, Dinova, Edwards, Endologix, Hemoteq, Hangzhou Nuomao Medtech, Lifetech, Maquet Getinge Group, Medtronic, Mitralign, Mokita, Occlutech, pfm Medical, Recor, Renal Guard, Rox Medical, Terumo, Vascular Dynamics, Vectorious Medtech, Venus, and Vivasure Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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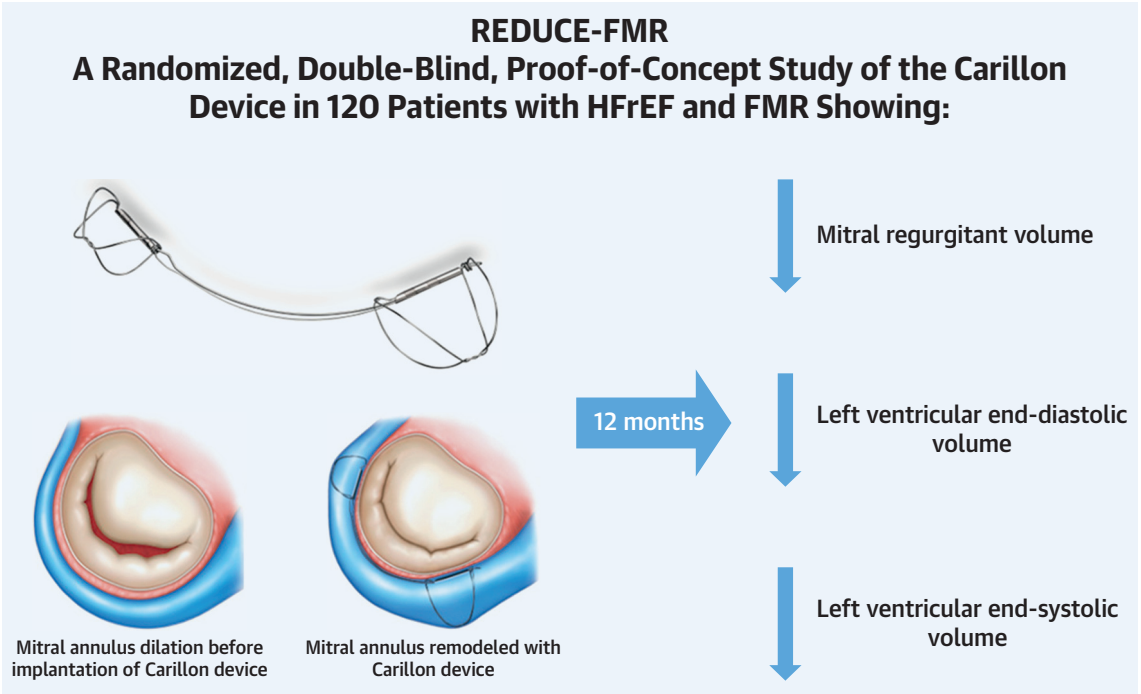
CENTRAL ILLUSTRATION The REDUCE-FMR Trial



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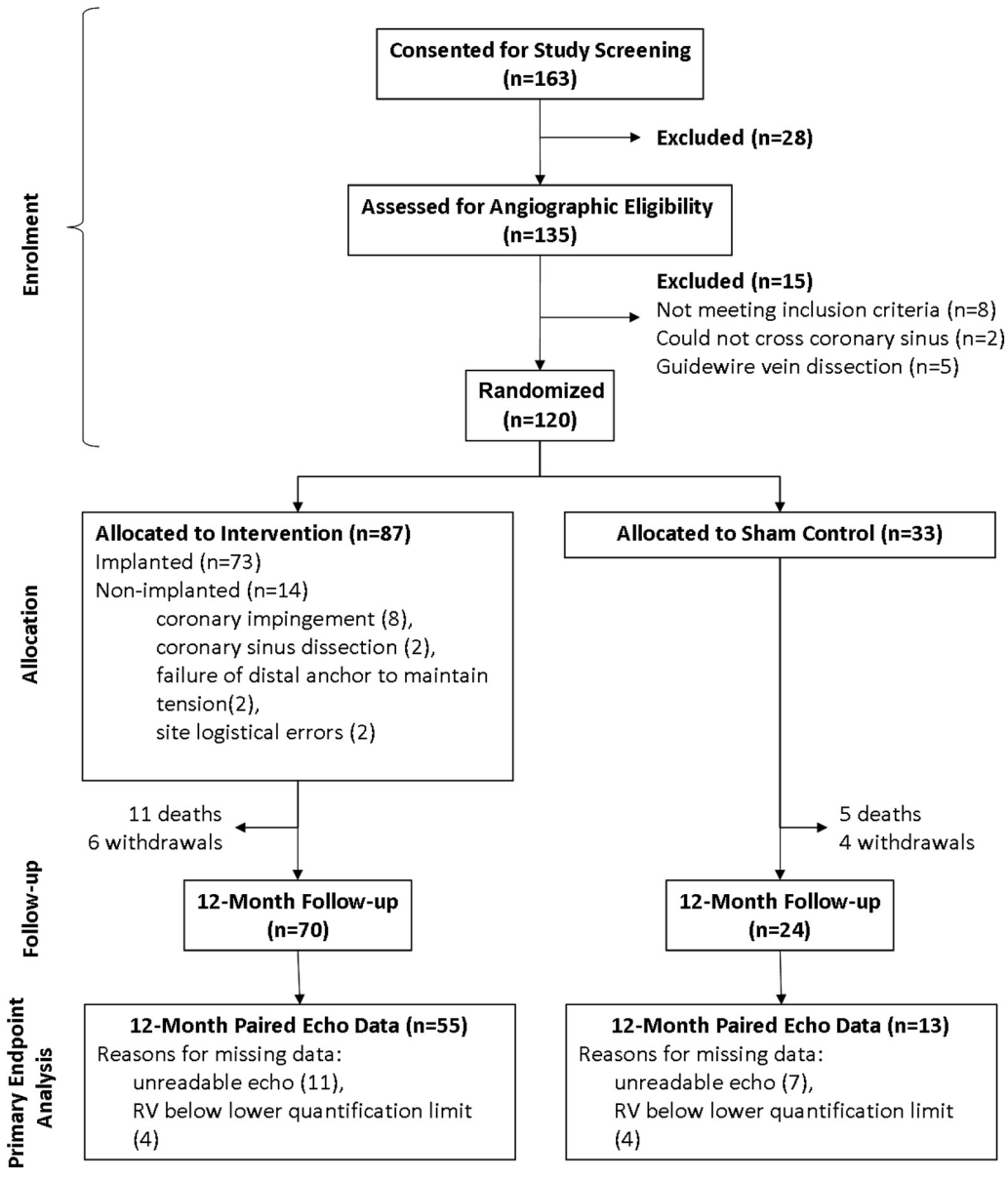
The REDUCE-FMR (Carillon Mitral Contour System for Reducing Functional Mitral Regurgitation) trial was a randomized, placebo-controlled, double-blind, proof-of-concept study that demonstrated significant reductions in mitral regurgitation as well as reverse remodeling at 1 year in a comparison between the Carillon mitral contour system and a sham procedure.

venous angiography was performed. If the venous dimensions were suitable in diameter and length for a Carillon device, randomization was performed. In patients randomized to sham control, the procedure was terminated and the sheaths withdrawn. In patients randomized to device implantation, an appropriately sized device was inserted into the delivery catheter and deployed (**Central Illustration**). The distal anchor was unsheathed and locked in a suitable segment of the great cardiac vein. Tension was applied, and the proximal anchor was deployed in the desired location if left coronary angiography had confirmed no impingement of or obstruction to flow in the circumflex coronary artery or its branches. Subsequently, patients underwent echocardiographic and clinical follow-up at 1, 6, and 12 months after the procedure. All echocardiograms were interpreted according to established guidelines (11,12). Specifically, in the assessment of mitral regurgitation, a multiparametric and quantitative approach was used to divide FMR into 4 grades (12) (see the Online Appendix for trial definitions of FMR).

RANDOMIZATION AND MASKING. Randomization was performed through a Web portal, in a device-to-control ratio of 3:1. A 3:1 ratio was chosen to improve recruitment and to provide more data for patients carrying implanted devices with a view to post hoc mechanistic work (9). Randomization was stratified according to investigation center in a randomized permuted blocks design. The study statistician generated the randomization schedule (independent of the sponsor). Clinical assessors and the core echocardiographic laboratory (Cleveland Clinic) were blinded to the patient's allocation and follow-up time points. Specifically, echocardiograms were not read sequentially, and all patients underwent standard echocardiograms at baseline and during follow-up, including those not implanted with a device. Although occasionally the device was visible

FIGURE 1 CONSORT Flow Diagram



Patient disposition during the trial. CONSORT = Consolidated Standards of Reporting Trials.

on transesophageal echocardiograms, only transthoracic echocardiogram images were used for data analysis. Care was taken to avoid documentation in the medical records as to whether the patients received a device. Patients were questioned after the procedure at discharge and at each visit as to whether they thought they received a device or not, to assess for effectiveness of blinding.

STUDY OUTCOMES. The pre-specified primary endpoint was a comparison of changes in mitral regurgitant volumes at 1 year compared with baseline, between the treatment group and the sham control group, as assessed by the independent, blinded echocardiographic core laboratory using quantitative echocardiography. Secondary safety endpoints were major adverse events (MAEs), defined as death, myocardial infarction, device embolization, vessel erosion, cardiac perforation, need for cardiac surgery or percutaneous coronary intervention associated with device failure, and heart failure hospitalizations.

Secondary efficacy endpoints were changes in LV end-diastolic and end-systolic volumes, changes in 6-min walk distances, NYHA functional class, and quality of life at 12 months compared to baseline. A 5-point change in KCCQ score was considered clinically significant (13).

STATISTICAL ANALYSIS. The minimum required sample size was calculated as 76 randomized patients. This assumed a reduction in mitral regurgitant volume of 12.4 ml/beat and 2.4 ml/beat in treatment and control groups, respectively, with an assumed SD of ±13 ml/beat. It was predicted that a loss to follow-up of 30% would give 80% power to identify this difference with a 0.05 alpha value. Analyses were performed and are presented according to intent-to-treat with subjects analyzed according to the randomized assignment regardless of actual treatment received, unless otherwise specified.

The primary efficacy endpoint of change in mitral regurgitant volume was calculated as the mean change between groups among subjects with evaluable data. Between-group comparisons were performed using Student's *t*-test. Binomial proportions were compared between treatment groups using Fisher exact test, whereas within-arm differences in binomial proportions between baseline and 12 months were tested using McNemar's test. Wilcoxon's rank sum test was used to compare ordinal outcomes such as changes in NYHA functional class between groups, whereas the Wilcoxon signed rank test was used to test for a statistically significant change within each treatment arm. Additional outcomes are presented as mean change from baseline for continuous variables and number and frequency for categorical variables. The study was not powered to assess differences in clinical outcomes. Post hoc analyses were conducted of patients with severe FMR (≥grade 3+) at baseline. A 2-sided p value of <0.05 was considered significant in all analyses. Statistical analysis was performed with SAS version 9.4 software (SAS Institute, Cary, North Carolina).

TABLE 1 Characteristics of Randomized Patients at Baseline According to ITT Analysis

	Total (N = 120)	Control (n = 33)	Treatment (n = 87)
Men	87 (72.5)	24 (72.7)	63 (72.4)
Mean age, yrs	69.8 ± 9.5	69.1 ± 8.9	70.1 ± 9.7
Cause			
Ischemic heart disease	80 (66.7)	21 (63.6)	59 (67.8)
Nonischemic cardiomyopathy	40 (33.3)	12 (36.4)	28 (32.2)
Diabetes mellitus	36 (30.0)	12 (36.4)	24 (27.6)
BMI, kg/m^2	27.1 ± 5.6	28.1 ± 6.2	26.7 ± 5.3
NYHA functional class			
II	55 (45.8)	16 (48.5)	39 (44.8)
III	63 (52.5)	17 (51.5)	46 (52.9)
IV	2 (1.7)	0 (0.0)	2 (2.3)
Beta blockers	109 (90.8)	32 (97.0)	77 (88.5)
ACE inhibitor/ARB/ARNi	108 (90.0)	29 (87.9)	79 (90.8)
Diuretic agent	118 (98.3)	33 (100)	85 (97.7)
MRA diuretic agent	73 (60.8)	19 (57.6)	54 (62.1)
NT-pro-BNP	2,430 (1,092-4,440)	2,410 (1,151-4,820)	2,505 (1,095-4,386)
Device (ICD or PPM)	55 (45.8)	12 (36.4)	43 (49.4)
Atrial fibrillation	71 (59.2)	20 (60.6)	51 (58.6)
Baseline heart rate, beats/min	70 ± 12	70 ± 11	70 ± 13
Systolic BP, mm Hg	119 ± 17	119 ± 19	118 ± 16
Diastolic BP, mm Hg	70 ± 11	67 ± 13	71 ± 11
6-min walk test	302.6 ± 90.6	292.6 ± 91.5	306.4 ± 90.5
LVEF, %	34 ± 9	37 ± 9	34 ± 9
LVEDD, cm	6.4 ± 0.9	6.4 ± 0.9	6.4 ± 0.9
LVESD, cm	5.5 ± 1.0	5.3 ± 1.1	5.5 ± 1.0
LVEDV, ml	187.4 ± 67.9	188.6 ± 75.7	187.0 ± 65.6
LVESV, ml	126.1 ± 56.8	122.0 ± 59.8	127.4 ± 56.1
Mitral regurgitant volume, ml/beat	39.9 ± 23.8	38.1 ± 24.0	40.4 ± 23.9
Mitral regurgitant grade			
1+	35 (29.7)	10 (32.3)	25 (28.7)
2+	42 (35.6)	8 (25.8)	34 (39.1)
3+	34 (28.8)	11 (35.5)	23 (26.4)
4+	7 (5.9)	2 (6.5)	5 (5.7)
Mean creatinine, mmol/l	114.1 ± 31.9	118.8 ± 34.1	112.3 ± 31.1

Values are n (%), mean ± SD, or median (interquartile range). There were no significant differences between the groups on appropriate post hoc testing. Conversion factors: creatinine mmol/l × 0.011 = mg/dl;

ACE = angiotensin-converting enzyme inhibitor; ARB = aldosterone receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; BP = blood pressure; ICD = implantable cardioverter-defibrillator; ITT = intention to treat; 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; MRA = mineralocorticoid receptor antagonists; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PPM = permanent pacemaker.

RESULTS

Between March 2015 and July 2017, 163 patients consented to undergo detailed baseline screening, of whom 135 patients were enrolled at 24 centers in Europe and Australia. Of these patients, 15 patients were excluded before randomization because they did not meet inclusion criteria (n = 8), there was failure to adequately engage the coronary sinus (n = 2), or there was guidewire vein dissection (n = 5). Therefore, 120 patients were randomized, 87 to treatment and 33 to sham control (Figure 1). In 14 of those allocated to treatment (16%) no device was implanted due most commonly to coronary impingement (n = 8), which resolved in all instances following device removal. Other reasons included coronary venous dissection (n = 2), failure of the distal anchor to maintain tension (n = 2), and clinical site logistical issues (n = 2: no correct size device available and misunderstanding of the outcome of randomization at site level).

STUDY PATIENTS. Patient characteristics are listed in Table 1. The cohorts were well matched with regard to key inclusion and clinical severity. Patients were

TABLE 2 Primary and Secondary Outcomes According to ITT Analysis

Endpoint	Randomized Treatment	Mean Change (95% CI) or Median (Interquartile Range) After 12 Months	Difference in Mean Change or Estimate (95% CI)	p Value
Primary outcome				
Mitral regurgitant volume, ml/beat	Control (n = 13)	3.32 (−5.98, 12.62)	10.39 (0.06, 20.71)	0.049
	Treatment (n = 55)	−7.07 (−11.68, −2.46)		
Secondary outcomes: LV parameters				
LVEDV, ml	Control (n = 16)	6.54 (−5.14, 18.22)	16.96 (1.81, 32.12)	0.03
	Treatment (n = 47)	−10.42 (−18.48, −2.37)		
LVESV, ml	Control (n = 16)	6.10 (−1.42, 13.63)	12.29 (0.32, 24.28)	0.04
	Treatment (n = 47)	−6.19 (−12.78, 0.39)		
LVEF, %	Control (n = 16)	−0.40 (−3.15, 2.36)	−0.59 (−4.11, 2.93)	0.74
	Treatment (n = 47)	0.19 (−1.67, 2.06)		
Secondary outcomes: patient-oriented				
6-min walk distance, m*	Control (n = 20)	17.5 (−20.0, 46.5)	−14.5 (−46.0, 20.0)	0.37
	Treatment (n = 65)	32.0 (−10.0, 70.0)		
KCCQ score	Control (n = 24)	7.63 (0.22, 15.05)	−1.86 (−11.36, 7.65)	0.70
	Treatment (n = 70)	9.49 (3.26, 15.71)		

*Median measurement with interquartile range (Hodges-Lehmann location shift) and 95% CI due to non-normality of data

CI = confidence interval; KCCQ = Kansas City Cardiomyopathy Quality of Life Questionnaire; other abbreviations as in Table 1.

taking optimally tolerated doses of guideline-directed therapy, including beta-blockers, renin-angiotensin-aldosterone system blockers, and loop diuretics. Although echocardiographic evaluation was performed at the site prior to enrolment, 35 patients (29.7%) were later judged by the echocardiography core laboratory to have had <2+ FMR at baseline.

EFFECTIVENESS OF BLINDING. In 285 of 298 patient visits (96.5%), patients indicated that they felt uncertain about their treatment assignment. Overall, 97.5% of control patients, 96.9% of nonimplanted, treatment group patients, and 94.6% of implanted patients indicated that they remained blinded throughout the study. The echocardiographic core laboratory indicated that they remained blinded. Although the artifact of the Carillon device can occasionally be seen on echocardiography, this can be mimicked by mitral annular calcification, or other artifacts in patients without Carillon devices. All scans were anonymized with regard to patient identifiers and date and were analyzed in random order after completion of follow-up, which contributed to the effectiveness of the blinding.

PROCEDURAL AND SAFETY OUTCOMES. There were no instances of device embolization or fractures, cardiac perforations, or intraprocedural ischemic events. Device implant time averaged 64.2 ± 34.8 min and total procedure times averaged 102.7 ± 54.9 min. Procedure time in the control group averaged 62.7 ± 29.4 min. There were 2 deaths within 30 days, both in implanted patients, due to progressive cardiorenal deterioration. One of these events, in which the patient experienced a general deterioration due to heart failure after the procedure was judged by the Clinical Endpoints Committee as "possibly" related to the procedure itself. Both of these patients had previously occluded circumflex arteries, and neither had apparent coronary artery compression.

There were 3 myocardial infarctions in the device group within 30 days (defined by electrocardiogram changes or coronary flow limitation and troponin rise to 5× the upper limit of normal). Only 1 of these infarctions was associated with coronary artery compression of an AV groove branch of the circumflex coronary artery. This patient developed small Q waves in leads I and aVL but completed 12-months of follow-up with no further events or hospitalizations. There were no new Q-waves or changes in EF in either of the other 2 patients. There were no late myocardial infarctions or other device-related deaths in implanted patients. A control patient also experienced a late myocardial infarction during the follow-up period, which was adjudicated as not related to their (sham) procedure. A table of all serious adverse events over 12 months is included in the appendix (Online Table 1).

PRIMARY ENDPOINT: MITRAL REGURGITATION. At 12 months, there was a 10.4 ml/beat [95% confidence interval [CI]: 0.1 to 20.7] difference in mean mitral regurgitant volume between the 2 groups (−7.1 ml/beat [95% CI: −11.7 to −2.5] vs. 3.3 ml/beat [95% CI: −5.98 to 12.62]; p = 0.049) (Table 2). This represented a median 22.4% decrease in mitral regurgitant volume in the treatment group and a

median 1.5% increase in mitral regurgitant volume in the control arm (Figures 2A and 2B). Sensitivity analysis using imputation for unmeasurable values (as determined by the independent core laboratory) and last observation carry forward for missing data at 12 months confirmed the primary analysis (p = 0.03).

Paired echocardiography data of sufficient quality to allow for quantitative assessment of mitral regurgitation severity, as evaluated independently by the echocardiographic core laboratory, were available in 68 patients (57%) (control patients: n = 13 [39%]; patients who received implants: 45 [62%]; patients who did not receive implants: 10 [71%]). Reasons for missed 1-year echocardiography studies included death (n = 16 deaths), insufficient echocardiographic quality to quantitate regurgitant volume (n = 18), and regurgitant volume below the lower quantification limit (n = 8). Echocardiographs were deemed "unreadable" if there was insufficient ability to obtain a quality proximal isovelocity surface area measurement to allow for regurgitant volume assessment. There were no significant differences in baseline variables between those patients with and those without paired echocardiography data. Baseline characteristics of patients who contributed to the primary endpoint analysis were similar to the overall baseline subject characteristics in regard to regurgitant volume, ischemic cause, NYHA functional class, left ventricular volume and diameter, and mitral regurgitation grade.

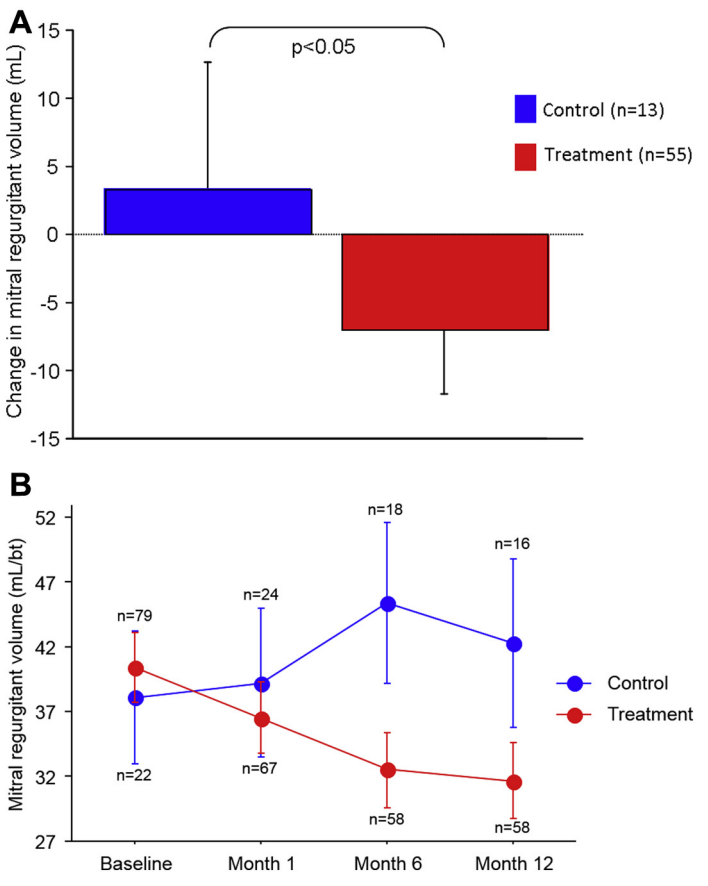
The post hoc analysis of changes in mean mitral regurgitant volume, including only patients with severe FMR (mitral regurgitation grade ≥3+) at baseline as determined by the core laboratory assessment, was limited by patient numbers (n = 15 in the treatment arm and n = 8 in the control arm), but revealed a similar pattern of change (−12.8 ml/beat [95% CI: −24.7 to −0.8] vs. 0.6 ml/beat [95% CI: −13.0 to 14.2]; p = 0.14)) (Online Table 2). A further post hoc as-treated analysis revealing similar outcomes is shown in Online Tables 3 and 4.

The proportion of patients judged to have an improvement in grade of FMR at 1 year was higher in patients allocated to treatment than in those allocated to control (50.0% vs. 20.0%, respectively; p = 0.02) (Figure 3). In patients with more severe FMR (mitral regurgitation grade ≥3+) at baseline (n = 44), the treatment effect was greater, with more implanted patients judged to have had at least 1 grade improvement in FMR at 1 year compared with control patients (63% [10 of 16] vs. 10% [1 of 10], respectively; p = 0.01).

SECONDARY ENDPOINTS. There was evidence of reverse remodeling with a significant decrease in LV end-diastolic volume (LVEDV) at 1 year in patients allocated to treatment versus an increase in those allocated to control (−10.4 ml [95% CI: −18.5 to −2.4] vs. 6.5 ml [95% CI: −5.1 to 18.2], respectively; p = 0.03). A similar effect was seen in end-systolic volume (LVESV) at 1 year (−6.2 ml [95% CI: −12.8 to 0.4] vs. 6.1 ml [95% CI: −1.4 to 13.6, respectively; p = 0.04) (Table 2, Figures 4A and 4B). These changes in volumes between the 2 groups were greater in patients with more severe mitral regurgitation grades at baseline (≥3+) (LVEDV: −26.9 ml [95% CI: −38.8 to −20.2] vs. 10.2 ml [95% CI: −16.2 to 34.3], respectively; p < 0.001) (LVESV: −17.5 ml [95% CI: −28.9 to −6.1] vs. 7.0 ml [95% CI: −4.2 to 18.3], respectively; p < 0.005). There were no overall differences in changes in LVEF between the groups.

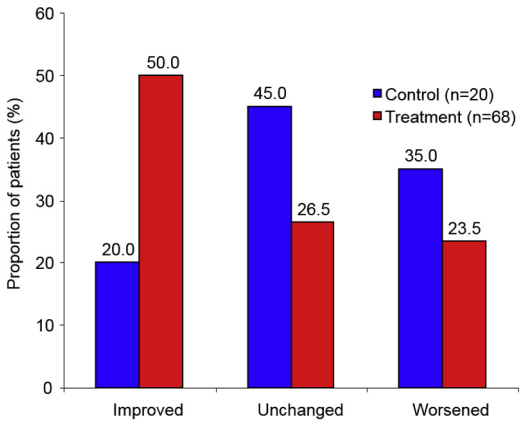
Table 2 shows the changes in 6-min walk test distances and KCCQ scores. Patients in the treatment group had a significant improvement in 6-min walk

FIGURE 2 Primary Endpoint: Mitral Regurgitant Volume



(A) Mean change in regurgitant volume at 12 months from paired data (−7.1 ml/beat vs. 3.3 ml/beat; p = 0.049). **(B)** Mean mitral regurgitation data at each time point (unpaired data).

FIGURE 3 Change in Mitral Regurgitation Grade at 12 Months

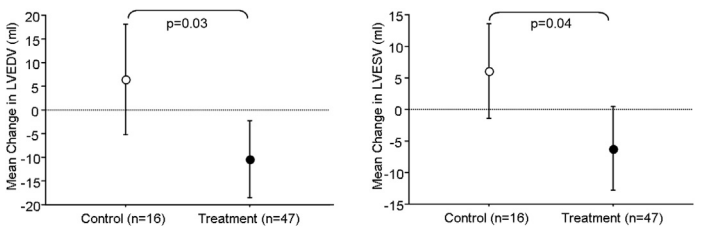


At 12 months, a greater proportion of patients in the treatment group experienced improvement in mitral regurgitation grade than in the control group ($p = 0.02$).

distances at 12 months compared with their baseline distances ($p = 0.002$), whereas patients allocated to the control group did not ($p = 0.29$). Figure 5 shows symptoms assessed by the NYHA functional classification from baseline to follow-up in the 2 groups. Patients in the treatment group had a significant improvement in NYHA functional class at 12 months compared with their baseline measurements ($p = 0.002$), whereas patients allocated to the control group did not ($p = 0.75$). The REDUCE-FMR trial was not powered for these clinical variables, and the between-group analyses did not show significance.

Patients who did not receive a device (including controls and nonimplanted patients) were much more likely to drop out of the study to receive another device-based therapy or transplantation (12.8% [6 of 47] vs. 1.4% [1 of 73], respectively; $p = 0.01$). The incidence of MAEs was similar between groups through the follow-up period (Table 3). There was a nonsignificant difference in heart failure hospitalization rate between the groups (0.57 [95% CI: 0.41 to 0.72] for treatment vs. 0.73 [95% CI: 0.44 to 1.03], respectively, for control per patient year; $p = 0.34$). Patients allocated to the treatment group spent approximately 1 month more alive and out of the hospital than patients in the control group (319 vs. 291 days, respectively; $p = 0.33$) and were one-half as likely to have had multiple (>1) heart failure hospitalizations during follow-up (11% vs. 21%, respectively; $p = 0.23$).

FIGURE 4 Change in Left Ventricular End Diastolic and Left Ventricular Systolic Volumes at 12 Months



There was evidence of reverse remodeling with a decrease LVEDV at 1 year in patients allocated to treatment versus an increase in those allocated to control (−10.4 ml [95% CI: −18.5 to −2.4] vs. 6.5 ml [95% CI: −5.1 to 18.2]; $p = 0.03$). A similar effect was seen in LVESV at 1 year (−6.2 ml [95% CI: −12.8 to 0.4] vs. 6.1 ml [95% CI: −1.4 to 13.6; $p = 0.04$]). LVEDV = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume.

DISCUSSION

REDUCE-FMR is the first blinded, sham-controlled study of a percutaneous device for valve therapy, and the results should be put in the context that many blinded sham-controlled trials in interventional cardiology have shown neutral results (14-18). Patients randomly allocated to treatment with the Carillon device experienced a significant reduction in mitral regurgitant volume at 12 months compared with those allocated to the control arm. Importantly, the implanted patients also had favorable LV remodeling, which was greater in those with more severe mitral regurgitation. Moreover, those allocated to treatment had significant improvements compared with their baseline measurements in all clinical outcomes at 12 months.

As a proof-of-concept study, the REDUCE-FMR trial was not powered to show between-group differences in the pre-specified exploratory patient-orientated clinical endpoints of NYHA functional class, 6-min walk test distance, and quality of life. Furthermore, blinding of patients reduces the placebo effect associated with treatment and reduces the nocebo effect in the control group (19), although also potentially having an impact on the Hawthorne effect on the control group (20). Accordingly, in the REDUCE-FMR trial, patients allocated to the control group also experienced trends toward an improved quality of life and an increase in 6-min walk test distance, despite a deterioration in their hemodynamic data. Thus, although there were attenuations of the clinical improvements compared to prior nonblinded studies (6-8), despite blinding, the treatment group in REDUCE-FMR experienced benefits in multiple clinical variables compared with baseline.

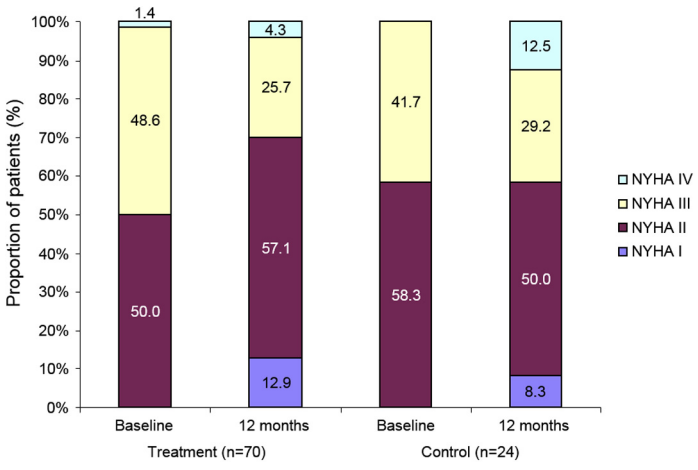
Another percutaneous mitral intervention for FMR, the MitraClip (Abbott Laboratories, Rockville, Maryland), has recently been assessed in 2 unblinded randomized trials, with discordant results (5,21). Lack of treatment blinding, patient selection strategies, and imbalances in medical management between the intervention and standard of care arms of these trials may have contributed to the dramatically different results seen in the 2 MitraClip trials.

Additional novel features of REDUCE-FMR were the use of quantitative echo parameters as the primary endpoint for the study and the inclusion of patients with mitral regurgitation grade 2+. This is in contrast to the MitraClip studies COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) (5) and MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) (21), which only enrolled patients with 3+ and 4+ mitral regurgitation. Enrollment in the current trial was determined by investigator assessment of baseline images at the time of the procedure, but formal echo analyses were later done by a core echocardiography laboratory. There were several discrepancies between the site and core laboratory assessment of FMR severity at baseline, with approximately 30% of enrolled patients having mitral regurgitation grades <2+ on core laboratory assessment. Examination of transmitted images suggests that the poor correlation between the color jet area and more robust quantitative measurements may be partially responsible (12). Although this phenomenon was matched across the 2 arms, the enrollment of a patient population with a lesser degree of mitral regurgitation would, if anything, make it more difficult to demonstrate any improvement in the primary endpoint in those allocated to treatment. However, treating mitral regurgitation early might be associated with better longer-term results than waiting until LV remodeling has progressed, by which time the degree of the mitral regurgitation loses its effect on prognosis (22).

Moreover, there were fewer paired echocardiogram scans that were suitable for quantitative assessment than expected; for example, only 39% of control patients had paired interpretable cardiac ultrasonography scans at 1 year, considerably lower than patients assigned to treatment (62%). This was in part due to a higher dropout rate among control patients to undergo alternative therapies. Acquisition of echocardiograms of sufficient quality has also been a limitation in other studies in this field. Adequate imaging for quantitative assessment of FMR was available in 57% of COAPT and 43% of patients with MITRA-FR (5,21).

Finally, most procedures were performed in institutions without prior experience with the Carillon mitral contour system. Physician proctors were present for initial cases, but all early system results are included in the data presented. Importantly, the device was suitable for most patients, with only a small portion (8 of 87) of patients who had

FIGURE 5 NYHA Functional Classification Change at 12 Months



NYHA functional class at baseline and 12 months comparing the treatment and control groups. At 12 months, the distribution of NYHA functional class altered favorably in the treatment group ($p = 0.002$ for change) and stayed constant in the control group ($p = 0.75$). NYHA = New York Heart Association.

TABLE 3 Key Safety Outcomes During 12-Month Follow-up According to ITT Analysis

	Total (N = 120)	Control (n = 33)	Treatment (n = 87)
Cumulative major adverse events	16.7 (10.5-24.6)	18.2 (7.0-35.5)	16.1 (9.1-25.5)
Deaths	13.3 (7.8-20.7)	15.2 (5.1-31.9)	12.6 (6.5-21.5)
Myocardial infarction	3.3 (0.9-8.3)	3.0 (0.1-15.8)	3.4 (0.7-9.7)
Cardiac perforation	0.0 (0.0-3.0)	0.0 (0.0-10.6)	0.0 (0.0-4.2)
Device embolism	0.0 (0.0-3.0)	0.0 (0.0-10.6)	0.0 (0.0-4.2)
Surgery or PCI related to device	0.0 (0.0-3.0)	0.0 (0.0-10.6)	0.0 (0.0-4.2)
Post-procedure interventions			
Post-procedural CRT implantation	4.2 (1.4-9.5)	6.1* (0.7-20.2)	3.4 (0.7-9.7)
Exit for percutaneous mitral valve repair, surgery, LVAD, CRT or heart transplantation	5.8 (2.4-11.7)	12.1† (3.4-28.2)	3.4‡ (0.7-9.7)
Heart failure hospitalization	30.0 (22.0-39.0)	36.4 (20.4-54.9)	27.6 (18.5-38.2)

Values are % (95% confidence interval). There were no significant between-group differences. *1 patient withdrew from CRT implantation. All other subjects who underwent CRT implantation remained in the study. †One additional subject completed the final follow-up visit after placement on heart transplant list. ‡2 of the 3 treatment patients who exited the study for alternative therapies did not receive an implant.

CRT = cardiac resynchronization therapy; LVAD = left ventricular assist device; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

the device was not anatomically suitable for implantation.

In spite of these challenges, use of the Carillon mitral contour system was associated with a statistically significant reduction in mitral regurgitant volume and in LV volumes at 1 year compared to a blinded, sham-controlled population, on an intention-to-treat analysis. Because beneficial LV remodeling is consistently associated with mortality benefit (23), these data suggest that the Carillon device may be associated with important clinical benefits; this will need to be assessed in future trials.

STUDY LIMITATIONS. As previously outlined, not all patients had echocardiogram scans of sufficient quality for mitral regurgitation quantification, and LV volumes assessment and fewer patients with moderate-severe FMR at baseline were enrolled than planned or anticipated. Despite these limitations, the study achieved its primary endpoint. REDUCE-FMR was not powered to evaluate clinical endpoints. Finally, duration of follow-up was limited to 1 year. Therefore, long-term effectiveness and safety of the device is unknown, although for patients with HFrEF and mitral regurgitation, 1 year is a significant proportion of their remaining life expectancy. The currently enrolling, blinded, sham-controlled CARILLON trial has been powered to assess the impact of the Carillon indirect mitral annuloplasty device on mortality and hospitalization in patients with FMR with 5 years of follow-up.

CONCLUSIONS

In this first blinded and sham-controlled randomized controlled trial of a percutaneous heart valve therapy, REDUCE-FMR has demonstrated that a low-risk transvenous approach to mitral annuloplasty can successfully and safely reduce FMR. This reduction is associated with reverse LV remodeling. The simplicity of this approach is supported by the study being largely done by centers previously unfamiliar with the technology. Other advantages include the right-sided approach, avoidance of trans-septal puncture, and the fact that Carillon device placement does not preclude any future mitral valve treatment if needed later. Studies are now underway to assess the effect of this approach on clinical outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: FMR is a common finding in patients with HFrEF and is associated with a poor prognosis. Transcatheter mitral valve repair is a rapidly emerging field. An indirect annuloplasty device, accessed through the jugular vein can reduce regurgitant volume.

TRANSLATIONAL OUTLOOK: Randomized, double-blind, controlled studies can be completed safely in interventional cardiology and should be the ambition for future studies in this field. More data are needed to determine if reducing FMR in patients with HFrEF improves quality of life and hospitalization and survival rates.

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KEY WORDS functional mitral regurgitation, heart failure, percutaneous mitral annuloplasty, transcatheter mitral valve repair

APPENDIX For an expanded Methods and supplemental tables, please see the online version of this paper.