JACC: HEART FAILURE VOL. ■, NO. ■, 2021

PUBLISHED BY ELSEVIER

Percutaneous Mitral Valve Annuloplasty in Patients With Secondary Mitral Regurgitation and Severe Left Ventricular Enlargement

Stefan D. Anker, MD, PhD,[a,b] Randall C. Starling, MD, MPH,[c,d] Muhammad Shahzeb Khan, MD, MSc,[e] Tim Friede, PhD,[f,g] Gerasimos Filippatos, MD,[h] JoAnn Lindenfeld, MD,[i] Ralph Stephan von Bardeleben, MD,[j] Andrew J.S. Coats, MD,[k,l] Javed Butler, MD, MPH, MBA[e]

ABSTRACT

OBJECTIVES This study sought to determine the effect of percutaneous mitral valve annuloplasty with the Carillon device versus guideline-directed medical therapy (GDMT) alone in patients with secondary mitral regurgitation (MR) and severe left ventricular (LV) enlargement.

BACKGROUND The clinical impact of the Carillon device in patients with severe LV dilation is not well established.

METHODS This is a pooled analysis involving 3 prospective trials (TITAN [Transcatheter Implantation of Carillon Mitral Annuloplasty Device], TITAN II, and REDUCE FMR [CARILLON Mitral Contour System for Reducing Functional Mitral Regurgitation] trials) in which patients with functional MR and severe LV enlargement (LV end-diastolic diameter >65 mm) were treated with GDMT and the Carillon device versus GDMT alone. Key outcomes of this analysis were changes over 1 year of follow-up in mitral valve and LV echocardiographic parameters, functional outcome, quality of life, mortality, and heart failure hospitalization (HFH).

RESULTS A total of 95 patients (67 in the Carillon group, 28 in the GDMT group) with severe LV enlargement were included. In the Carillon group, all mitral valve and LV morphology parameters were significantly improved at 1 year. Regurgitant volume decreased by 12 ml ($p < 0.001$), MR grade decreased by 0.6 U ($p < 0.001$), LV end-diastolic volume decreased by 25 cm^3 ($p = 0.005$), and LV end-systolic volume decreased by 21 cm^3 ($p = 0.01$). Significant functional improvement differences were also noted between the Carillon group and the GDMT group including an improvement of Kansas City Cardiomyopathy Questionnaire score (15 ± 4 vs. 6 ± 6; $p = 0.03$). The incidence of HFH was 29.9% versus 50.0% and the cumulative rate of HFH was 0.43 versus 0.75 ($p < 0.001$).

CONCLUSIONS In patients with functional MR and severe LV enlargement, the Carillon device improved mitral valve function, LV morphology, and functional outcome compared with patients receiving GDMT only. Preoperative LV dimension should not be a limiting factor when evaluating patient eligibility or anticipated response to therapy with the Carillon device. (J Am Coll Cardiol HF 2021;■:■–■) © 2021 by the American College of Cardiology Foundation.

From the [a]Department of Cardiology, German Centre for Cardiovascular Research partner site Berlin, Charité Universitätsmedizin Berlin, Germany; [b]Berlin Institute of Health Center for Regenerative Therapies, German Centre for Cardiovascular Research, partner site Berlin, Charité Universitätsmedizin Berlin, Germany; [c]Kaufman Center for Heart Failure, Cleveland Clinic, Cleveland, Ohio, USA; [d]Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA; [e]Department of Medicine, University of Mississippi School of Medicine, Jackson, Mississippi, USA; [f]Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany; [g]Department of Medical Statistics, German Center of Cardiovascular Research, partner site Göttingen, Göttingen, Germany; [h]Department of Cardiology, University Hospital Attikon, National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [i]Heart Failure and Transplantation Section, Vanderbilt Heart and Vascular Institute, Nashville, Tennessee, USA; [j]Department of Cardiology I, Heart Valve Center, Universitätsmedizin Mainz, Germany; [k]Department of Cardiology, Monash University Australia and University of Warwick, Warwick, United Kingdom; and the [l]Department of Medical Sciences, Centre for Clinical and Basic Research, IRCCS San Raffaele Pisana, Rome, Italy. Barry Greenberg, MD, served as the Guest Editor for this paper.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2021.03.002

ABBREVIATIONS AND ACRONYMS

EROA = effective regurgitant orifice area

GDMT = guideline-directed medical therapy

HFH = heart failure hospitalization

KCCQ = Kansas City Cardiomyopathy Questionnaire

LV = left ventricle/ventricular

LVEDD = left ventricular end-diastolic diameter

MR = mitral regurgitation

NYHA = New York Heart Association

Secondary mitral regurgitation (MR), previously referred to as functional MR, is a consequence of remodeling from an underlying cardiomyopathy, impacting the atrium, ventricle, or both. One of the compensatory mechanisms resulting from decreased cardiac function efficiency is left ventricular (LV) remodeling resulting in LV enlargement and thus increased Frank-Starling forces and greater cardiac myocyte contraction (1,2). However, with untreated chronic MR, a transition to a decompensated hemodynamic state may occur with progressive and irreversible structural and functional LV changes.

Ideally, MR correction should occur prior to the onset of permanent LV dysfunction because mortality is elevated in patients with LV enlargement. Surgical repair remains of uncertain mortality benefit for secondary MR (3). Percutaneous treatment of secondary MR was clinically beneficial in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial but not in the MitraFR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trial (4,5). Despite the benefits of MitraClip in the COAPT trial, this otherwise effective therapy was not associated with reversal of ventricular enlargement (6).

One of the theories developed to explain the differences between the COAPT and MitraFR trials is of proportionate versus disproportionate MR (7,8). This theory suggests that the MR in patients enrolled in the COAPT trial was large compared with their degree of cardiomyopathy (LV size smaller), such that the MR was playing a more dominate role. Alternatively, in the MitraFR trial, the ventricles were larger (median LV end-diastolic diameter [LVEDD] 6.5 cm) with lesser degrees of MR (median effective regurgitant orifice area [EROA] 0.31 cm^2), suggesting more dominant cardiomyopathy with less significant MR. This has led to the perception that patients with larger ventricles are less suitable for treating secondary MR.

The Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, Washington) is a device designed to treat secondary MR. This is an indirect annuloplasty that uses a device placed into the coronary sinus to reduce its diameter and allow approximation of the mitral valve leaflets (Supplemental Figure 1). This treatment has been evaluated in several studies with no eligibility restrictions placed on the upper LV dimension, providing an opportunity to explore the clinical impact of mitral annuloplasty in patients with severe LV dilation (9–11). This analysis therefore specifically analyzes patients with larger ventricles who were evaluated in trials of the Carillon device. The objective of this study was to determine the effect of guideline-directed medical therapy (GDMT) and the Carillon device versus GDMT alone on structural, functional, quality-of-life, and clinical outcomes in patients with secondary MR and severe LV enlargement.

METHODS

The TITAN (Transcatheter Implantation of Carillon Mitral Annuloplasty Device) (10), TITAN II (9), and REDUCE FMR (CARILLON Mitral Contour System for Reducing Functional Mitral Regurgitation) (11) trials enrolled patients with secondary MR who were treated with GDMT and percutaneous mitral valve annuloplasty using the Carillon device (Carillon group) or GDMT alone (GDMT group). In the TITAN trial, a subset of patients did not receive the implant due to anatomic considerations and were followed through 1 year. In the TITAN II trial, only patients who received the Carillon device had additional follow-up. In the REDUCE FMR trial, patients were randomized to the Carillon group or GDMT group. Here, we present a pooled analysis from the 3 studies comparing the Carillon device with GDMT in patients with secondary MR and severe LV enlargement. In this analysis, patients who received Carillon devices are compared with patients who did not, either because of anatomic limitations or because they were randomized to sham-control in the REDUCE FMR study. In each of the studies, ethics committee approval was granted at each participating center, all patients provided written informed consent prior to participation, and all study procedures followed the principles of the Declaration of Helsinki.

Eligible patients presented with grade 2+ to 4+ secondary MR by echocardiographic core laboratory

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 19, 2020; revised manuscript received March 1, 2021, accepted March 3, 2021.

assessment (in the TITAN and TITAN II trials) or site assessment (in the REDUCE FMR trial), symptomatic heart failure (New York Heart Association [NYHA] functional class II to IV) despite at least 3 months of GDMT, reduced ejection fraction (<40% in the TITAN and TITAN II trials; <50% in the REDUCE FMR trial), and LV enlargement (>5.5 cm LVEDD). In the present analysis, only patients with severe LV enlargement based on the American Association of Thoracic Surgery guidelines (LVEDD >6.5 cm) were included (12). The TITAN and TITAN II studies were prospective, nonrandomized, and nonblinded trials. However, pre- and post-treatment echoes were read separately without reference to the companion study. In contrast, the REDUCE FMR was a randomized trial, in which clinical assessors and the core echocardiographic laboratory were blinded to the patient's allocation and follow-up time points. In particular, echocardiograms were not read consecutively, and all patients underwent standard echocardiograms at baseline and during follow-up, regardless of device implant status. Only transthoracic echocardiogram images were used for data analysis as at times the device was visible on transesophageal echocardiograms. Key exclusion criteria were recent cardiac-related hospitalization or cardiac surgery, previous mitral valve surgery, indwelling pacemaker or coronary stent that may anatomically interfere with device placement, and recent need for cardiac hemodynamic support. Complete listings of eligibility criteria for each trial have been published elsewhere (9–11).

The procedure for Carillon device implantation has been described in detail elsewhere (13). The aim of the procedure is to place a device into the coronary sinus to reduce its diameter and allow approximation of the mitral valve leaflets. This indirect annuloplasty approach is feasible due to the anatomic proximity of the coronary sinus to the posterior mitral annulus. Following hospital discharge, patients returned for clinical and echocardiographic follow-up at regular intervals through 1 year.

Key outcomes of this analysis included echocardiographic changes over 1 year of follow-up as well as functional outcome, quality of life, all-cause mortality, incidence of heart failure hospitalization (HFH), and the cumulative incidence of HFH. Quality-of-life measures included the NYHA functional class and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score, which is measured on a 0 to 100 scale, in which higher scores indicate better quality of life.

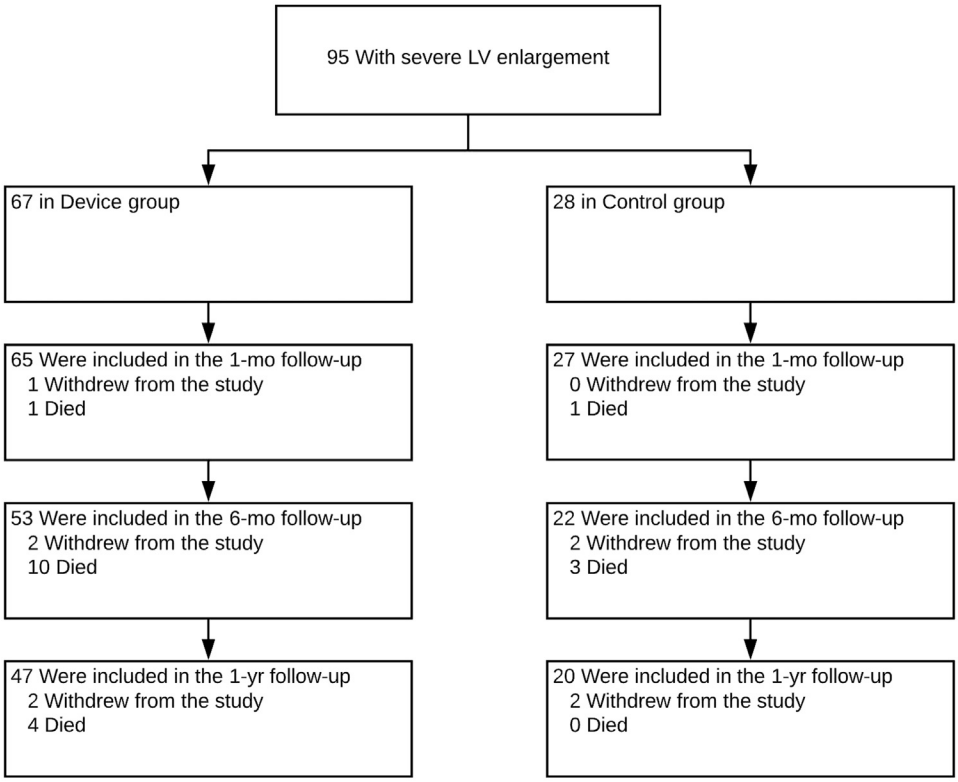
TABLE 1 Baseline Characteristics of Patients Treated With GDMT and Carillon Device or GDMT Alone for Functional Mitral Regurgitation and Severe LV Enlargement

	Device Group (n = 67)	Control Group (n = 28)	p Value
Demographics			
Age, yrs	65 ± 12	63 ± 13	0.64
Male	91 (61/67)	82 (23/28)	0.29
Body mass index, kg/m^2	27 ± 6	27 ± 6	0.66
Medical history			
Ischemic etiology	73 (48/66)	50 (14/28)	0.06
Prior myocardial infarction	58 (39/67)	50 (14/28)	0.50
Atrial fibrillation	46 (31/67)	43 (12/28)	0.82
Diabetes mellitus	27 (18/67)	29 (8/28)	>0.99
Heart failure medications			
ACE inhibitor/ARB/ARN inhibitor	88 (59/67)	96 (27/28)	0.24
Beta-blockers	91 (61/67)	93 (26/28)	>0.99
Diuretic agent	94 (63/67)	93 (26/28)	>0.99
Diuretic MRA agent	78 (52/67)	82 (23/28)	0.78
Functional status			
NYHA functional class	2.7 ± 0.5	2.7 ± 0.5	0.76
II	30 (20/66)	32 (9/28)	
III	68 (45/66)	68 (19/28)	
IV	2 (1/66)	0 (0/28)	
6-min walk distance, m	329 ± 83	295 ± 88	0.07
KCCQ score	54 ± 21	43 ± 20	0.02
Biomarker			
NT-proBNP, pg/ml	2,877 (1,323–4,340)	2,196 (979–5,284)	0.64
LA parameters			
LA volume, cm^3	115 ± 36	144 ± 122	0.22
LV parameters			
LV ejection fraction, %	28 ± 8	29 ± 9	0.61
LV end-diastolic diameter, cm	7.3 ± 0.5	7.2 ± 0.4	0.75
LV end-systolic diameter, cm	6.3 ± 0.7	6.0 ± 0.9	0.10
LV end-diastolic volume, cm^3	235 ± 54	250 ± 88	0.46
Indexed by BSA, cm^3/m^2	124 ± 30	133 ± 55	0.33
LV end-systolic volume, cm^3	171 ± 50	182 ± 85	0.56
Mitral valve parameters			
Regurgitant volume, ml	41 ± 19	45 ± 24	0.38
Vena contracta, cm	0.56 ± 0.19	0.55 ± 0.18	0.77
EROA, cm^2	0.29 ± 0.12	0.31 ± 0.16	0.37
MR grade*	2.6 ± 1.0	2.7 ± 0.9	0.87
1	15 (10/67)	14 (4/28)	
2	28 (19/67)	21 (6/28)	
3	34 (23/67)	46 (13/28)	
4	22 (15/67)	18 (5/28)	
Mitral valve area, cm^2	13.8 ± 2.6	13.1 ± 3.8	0.33
Mitral valve diameter, AP, cm	4.1 ± 0.4	4.0 ± 0.6	0.43
Mitral valve diameter, ML, cm	4.2 ± 0.4	4.1 ± 0.5	0.24

Values are mean ± SD, % (n/N), or median (interquartile range). *Patient eligibility in each trial specified MR grade 2+, 3+, or 4+. In the REDUCE FMR (CARILLON Mitral Contour System for Reducing Functional Mitral Regurgitation) trial, patient eligibility was determined by site investigators and all patients met MR grade eligibility criteria. Post hoc core laboratory evaluations reported here classified some enrolled patients as MR grade 1+.

ACE = angiotensin-converting enzyme; AP = anteroposterior; ARB = angiotensin receptor blocker; ARN = angiotensin receptor neprilysin; BSA = body surface area; EROA = effective regurgitant orifice area; GDMT = guideline-directed medical therapy; KCCQ = Kansas City Cardiomyopathy Questionnaire; LA = left atrial; LV = left ventricular; ML = mediolateral; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

FIGURE 1 CONSORT Flow Diagram



Patient disposition during the trial. CONSORT = Consolidated Standards of Reporting Trials; LV = left ventricular.

Quantitative echocardiographic assessment was performed by an independent core laboratory. Mitral valve regurgitation grading followed the guidelines set forth by the American Society of Echocardiography (14).

Baseline patient characteristics were reported as the mean ± SD for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables, and count and percentage for categorical outcomes. Group comparisons were performed using t tests or the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. An analysis of covariance model was used to compare mean changes in continuous variables from baseline to follow-up between groups. All-cause mortality, incidence of HFH, and the composite outcome of all-cause mortality or HFH were analyzed using Kaplan-Meier methods, and the SE was estimated with the Greenwood method. The cumulative number of HFHs in each group was assessed using the Nelson-Aalen cumulative hazard function. Associations between regurgitant volume and LV morphology were analyzed using the Pearson correlation coefficient. A 2-sided p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of Stata version 16 (StataCorp, College Station, Texas).

RESULTS

Among the 3 studies, 95 patients with severe LV enlargement were included in the pooled dataset—67 in the Carillon group and 28 in the GDMT group. Baseline patient characteristics were well matched between the treatment groups. Comparing the Carillon device versus GDMT, mean patient age was 65 years versus 63 years, 91% versus 82% were male, mean NYHA functional class was 2.7 in each group, mean LVEDD was 7.3 cm versus 7.2 cm, and mean MR grade was 2.6 versus 2.7. The mean KCCQ score statistically differed between the 2 groups (**Table 1**). Characteristics of individual trials included in our analysis are outlined in Supplemental Table 1. Group

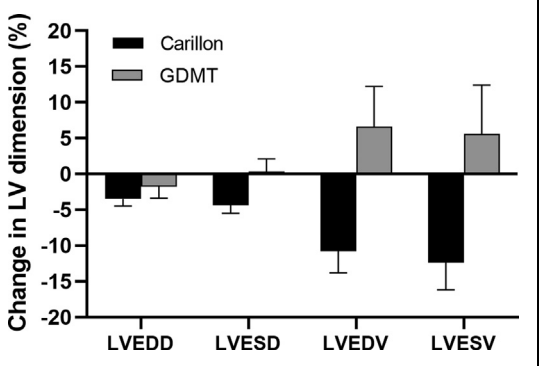
comparisons by baseline MR grade are provided in Supplemental Tables 2 and 3.

Most periprocedural complications were mild in severity and occurred in 7.5% of Carillon patients and 7.1% in the GDMT group, which included access site complication for patient monitoring (not device related), transient arrythmia, lactic acidosis, and dyspnea. Most complications were unrelated to the device; however, acute coronary syndrome developed in 1 patient, resulting from device impingement of a branch artery of the circumflex. The impingement was judged to be clinically insignificant at the time of device implant; however, shortly after device deployment the patient developed small Q waves in 2 leads. The patient was treated conservatively and completed 1-year follow-up. In another patient, device recapture was complicated, and a decision was made to not change device size as was intended. Although no adverse event was directly attributable, the failure to recapture the device was recorded as an event. The patient completed 1-year follow-up.

Over the 1-year follow-up period, 19 patients died and 5 patients withdrew from the study, with an additional 4 patients receiving additional interventions and exiting, leaving 67 patients available for clinical follow-up at 1 year (**Figure 1**). Changes in medical therapy were infrequent during follow-up. A total of 11 patients, 8 (17%) in the Carillon group and 3 (15%) in the GDMT arm, had a medication added or discontinued. Of note, 3 patients in the Carillon group had discontinuation of diuretic. Comparing Carillon device and GDMT versus GDMT alone, the cumulative incidence of all-cause mortality or HFH was 45.7% (SE 6.2%) versus 57.8% (SE 9.5%) (log-rank $p = 0.40$), all-cause mortality was 23.3% (SE 5.3%) versus 14.7% (SE 6.8%) (log-rank $p = 0.41$), and the incidence of HFH was 29.9% (SE 5.6%) versus 50.0% (SE 9.4%) (log-rank $p = 0.07$). Overall, there were 35 HFHs in the Carillon group and 24 HFHs in the GDMT group, resulting in a cumulative HFH rate of 0.43 versus 0.75 ($p < 0.001$) (**Central Illustration**).

In the Carillon group, all mitral valve functional parameters and LV morphology parameters were significantly improved at 1 year (**Table 2**). Specifically, regurgitant volume decreased by 12 ml ($p < 0.001$), MR grade decreased by 0.6 U ($p < 0.001$), LVEDD decreased by 0.3 cm ($p = 0.005$), LV end-systolic diameter decreased by 0.3 cm ($p < 0.001$), LV end-diastolic volume decreased by 25 cm^3 ($p = 0.005$), and LV end-systolic volume decreased by 21 cm^3 ($p = 0.01$) (**Figure 2**). Significant changes in mitral morphology were apparent by the first imaging follow-up visit at 1 month (anteroposterior diameter change was -0.29 ± 0.51 cm in implanted patient's versus -0.01 ± 0.41 cm in GDMT alone; $p = 0.02$). Subsequently, significant reductions in LV volumes were first identified at the 6-month follow-up visit, with further reductions noted at 1 year (**Figure 3**). Significant functional improvement was also noted, including a mean NYHA functional class improvement of 0.5 U ($p < 0.001$) and a 62-m increase in 6-min walk test distance ($p = 0.007$). In contrast, there were no statistically significant beneficial changes in any echocardiographic or functional status variable in the GDMT group. Group comparisons revealed statistically significant differences between treatment groups for change in NYHA functional class, KCCQ, left atrial volume, LV end-systolic diameter, LV end-diastolic volume, LV end-systolic volume, regurgitant volume, EROA, MR grade, and mitral valve morphology, all favoring the Carillon group. In the Carillon group, reduction in regurgitant volume was associated with reductions in LVEDV ($r = 0.48$; $p = 0.004$) and LVESV ($r = 0.52$; $p = 0.002$) over 1 year (**Figure 4**). Group comparisons of 1-year outcomes by baseline MR grade are provided in Supplemental Tables 4 and 5.

FIGURE 2 Effect of Carillon Device on LV Remodeling

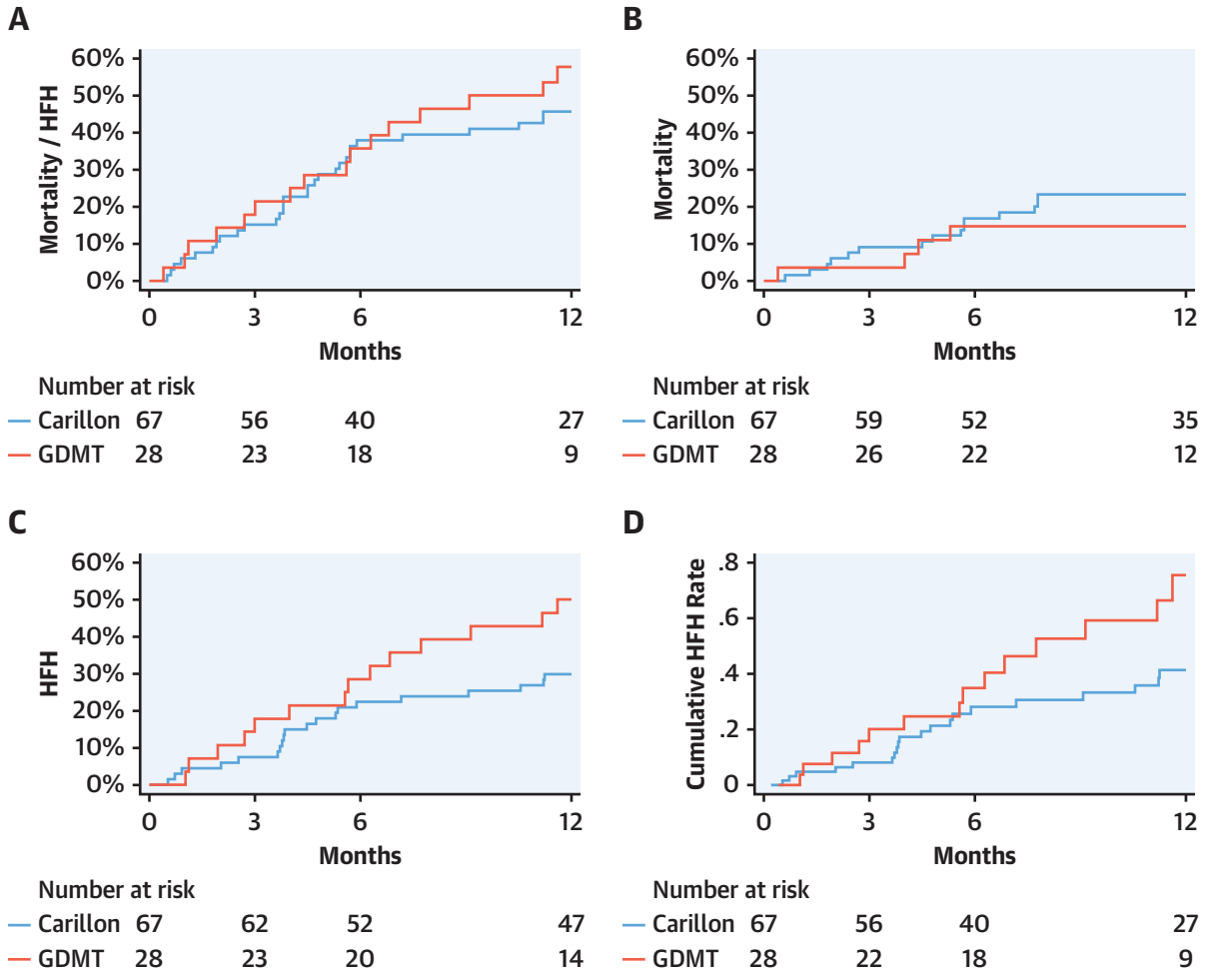


Left ventricular (LV) remodeling over 1 year in patients with functional mitral regurgitation and severe left ventricular enlargement after percutaneous mitral valve annuloplasty with guideline-directed medical therapy (GDMT) and the Carillon device or GDMT alone. Plotted values are mean change and SE based on analysis of covariance adjusted for the baseline value. LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.

DISCUSSION

In patients with heart failure and cardiomyopathy, an increasing LV size is associated with poor prognosis (15,16). When medical therapy is associated with

CENTRAL ILLUSTRATION **Clinical Outcomes With the Carillon Device**



Anker, S.D. et al. J Am Coll Cardiol HF. 2021;■(■):■-■.

Incidence over 1 year in the composite of all-cause mortality or hospital failure hospitalization (HFH) was 45.7% (SE 6.2%) for patients treated with guideline-directed medical therapy (GDMT) and the Carillon device versus 57.8% (SE 9.5%) with GDMT alone (log-rank $p = 0.40$) **(A)**, all-cause mortality was 23.3% (SE 5.3%) versus 14.7% (SE 6.8%) (log-rank $p = 0.41$) **(B)**, HFH was 29.9% (SE 5.6%) versus 50.0% (SE 9.4%) (log-rank $p = 0.07$) **(C)**, and the cumulative annual rate of HFH was 0.43 versus 0.75 ($p < 0.001$) **(D)**.

reduction in LV dimensions, there is invariably a significant clinical benefit (16). However, mechanical treatment of secondary MR has not been as successful in cardiomyopathy patients with enlarged LVs (4,17). Surgical ring annuloplasty for secondary MR seems to be favorable when ventricles are not overly large, but lose effectiveness at larger ventricular dimensions (17). One of the theories as to why the MitraClip (Abbott Vascular, Santa Clara, California) was clinically beneficial in the COAPT trial but ineffective in the MitraFR trial is that COAPT trial patients had smaller ventricles with more MR (disproportionate MR: median LVEDD 6.1 cm and EROA 0.37 mm^2), whereas larger ventricles with lesser severities of MR were seen in the MitraFR trial (proportionate MR: median LVEDD 6.5 cm and EROA 0.31 mm^2) (7,8). MitraFR trial patients implanted with the MitraClip did not show any relative improvement in mortality, HFH, symptom relief (NYHA functional class), or exercise tolerance compared with patients who received only GDMT. This suggests that percutaneous treatment of secondary MR may not be effective, at least not with the MitraClip device, when the ventricle is too large. With this background, the current analysis

TABLE 2 1-Year Change in Functional and Echocardiographic Parameters After GDMT and Carillon Device or GDMT Alone

	Device		Control		
	Change Value	p Value (Pre-Post)	Change Value	p Value (Pre-Post)	p Value (Between Groups)*
Functional status					
NYHA functional class	−0.5 ± 0.1	<0.001	0.0 ± 0.2	>0.99	0.007
Improvement	54 (25/46)		32 (6/19)		
No change	35 (16/46)		42 (8/19)		
Worsening	11 (5/46)		26 (5/19)		
6-min walk distance, m	62 ± 22	0.007	3 ± 20	0.87	0.16
KCCQ score	15 ± 4	<0.001	6 ± 6	0.36	0.03
Biomarker					
NT-proBNP, %	−16 (−49 to 30)	0.17	48 (−42 to 113)	0.16	0.09
LA parameters					
LA volume, cm^3	−7 ± 4	0.08	15 ± 9	0.13	0.04
LV parameters					
LV ejection fraction, %	1 ± 1	0.34	0 ± 2	0.84	0.81
LV end-diastolic diameter, cm	−0.3 ± 0.1	0.005	−0.1 ± 0.1	0.21	0.36
LV end-systolic diameter, cm	−0.3 ± 0.1	<0.001	0.1 ± 0.1	0.52	0.03
LV end-diastolic volume, cm^3	−25 ± 8	0.005	11 ± 11	0.36	0.009
LV end-systolic volume, cm^3	−21 ± 8	0.01	7 ± 9	0.47	0.03
Mitral valve parameters					
Regurgitant volume, ml	−12 ± 3	<0.001	1 ± 5	0.81	0.003
Vena contracta, cm	−0.16 ± 0.05	0.002	−0.03 ± 0.04	0.49	0.17
EROA, cm^2	−0.07 ± 0.02	<0.001	0.00 ± 0.04	0.99	0.02
MR grade	−0.6 ± 0.2	<0.001	−0.1 ± 0.2	0.58	0.049
Improvement	48 (21/44)		29 (5/17)		
No change	36 (16/44)		47 (8/17)		
Worsening	16 (7/44)		24 (4/17)		
Mitral valve area, cm^2	−0.7 ± 0.4	0.12	1.8 ± 0.7	0.03	0.008
Mitral valve diameter, AP, cm	−0.4 ± 0.1	<0.001	0.1 ± 0.1	0.31	0.001
Mitral valve diameter, ML, cm	−0.1 ± 0.1	0.29	0.3 ± 0.1	0.03	0.02

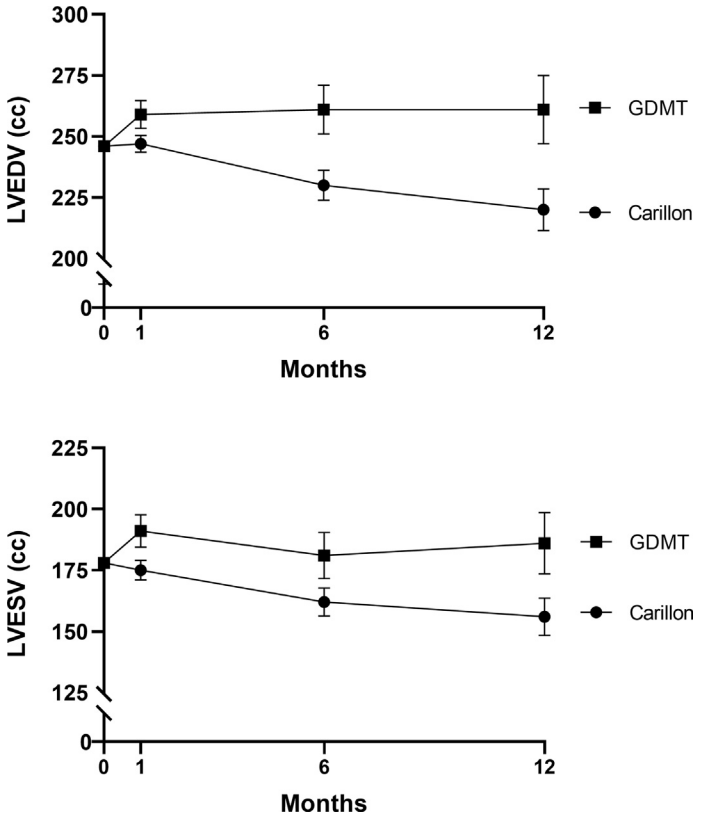
Values are mean ± SD, % (n/N), or median (interquartile range). *Calculated using analysis of covariance model adjusted for baseline value.
Abbreviations as in Table 1.

focused on patients with large ventricles treated as part of prospective trials assessing the role of the Carillon Mitral Contour System in the treatment of secondary MR in patients with heart failure and reduced LV function (median LVEDD 7.1 cm and EROA 0.29 cm^2).

In this study, we report for the first time that statistically significant and clinically relevant improvements in mitral valve, LV, and functional parameters were realized in patients with secondary MR and severe LV enlargement who were treated with the Carillon device. This was in stark contrast to patients receiving GDMT in which negligible changes relative to baseline were observed during the first year of clinical follow-up. In addition to improvements in MR, patients receiving the Carillon device had favorable remodeling evidenced by a decrease in LV size (~20-ml reductions). It is notable that favorable ventricular remodeling has been associated with substantial clinical benefits, including mortality reduction, with other medical or device therapies (16). Indeed, Kramer et al. (16) demonstrated there was a significant benefit associated with each 10-ml reduction in LV end-systolic volume or LV end-diastolic volume in patients with LV dysfunction. In this analysis, patients in the Carillon group were markedly less likely to experience HFH. These results are novel because no known mechanical mitral valve treatment study has demonstrated these clinical benefits in a patient population with severe LV dysfunction.

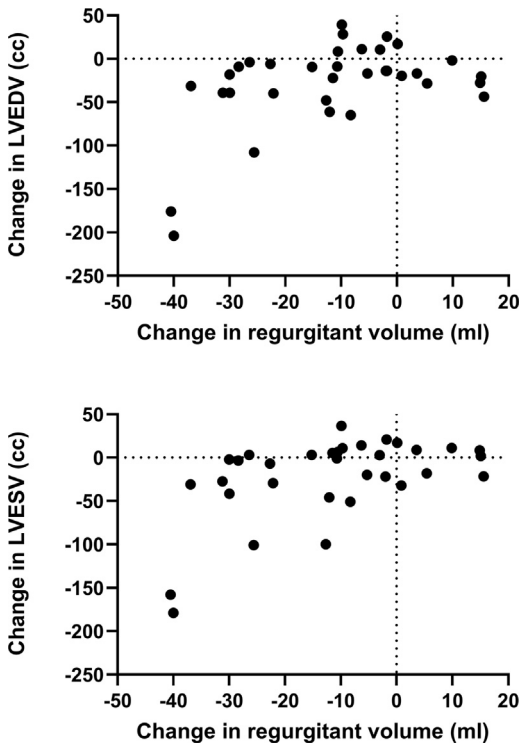
In multiple studies of surgical treatment for secondary MR, LV size was an important predictor as to when surgery was ineffective (18,19). Braun et al. (17) noted that reverse remodeling was rarely seen after surgical mitral valve repair when the LVEDD was >65 mm. It is notable, therefore, that in the current analysis in which all patients treated with the Carillon

FIGURE 3 Effect of Carillon Device on LV Volumes



Changes in LVEDV and LVESV at each follow-up visit over 1 year in patients with functional mitral regurgitation and severe left ventricular enlargement after percutaneous mitral valve annuloplasty with GDMT and the Carillon device or GDMT alone. Plotted values are mean change and SE based on analysis of covariance adjusted for the baseline value. Abbreviations as in Figure 2.

FIGURE 4 Correlation of Regurgitant Volume and LV Morphology



Association of change in regurgitant volume with change in LV morphology over 1 year following treatment with GDMT and the Carillon device. Pearson correlation coefficients were $r = 0.48$ ($p = 0.004$) for LVEDV and $r = 0.52$ ($p = 0.002$) for LVESV over 1 year. Abbreviations as in Figure 2.

device had LVEDD >65 mm (mean 73 mm), reverse remodeling was observed at 6 and 12 months. Our results demonstrate that the extent of LV disease is not necessarily the limiting factor in the process of reverse remodeling. In the current study, even patients with the largest preoperative LVEDD, several >80 mm, experienced significant reverse remodeling after implant with the Carillon device. The clinical implication of these new observations is that preoperative LV dimension may not be a limiting factor when evaluating patient eligibility or predicted response to therapy with the Carillon device.

It is not possible from these data to know why this percutaneous mitral annuloplasty treatment might be effective in large ventricles when other mechanical treatments appear to be ineffective. The failure of mechanical therapies to work in large ventricles is often presupposed to be due to the ventricles having exceeded the benefits of Frank-Starling myocellular elongation (20). It is also possible that different treatments may impact cardiovascular efficiency in different ways. Increased mitral valve tenting has been known to be another poor prognostic feature with regard to surgical effectiveness for mitral annular rings and is typically associated with larger ventricles (21–23). Tenting may play a role in myocardial and papillary muscle efficiency and may actually be exacerbated by the tension applied by a surgical annular ring. Because the Carillon device applies a different vector of force, with the tension arising from the ostium of the coronary sinus above the mitral annulus, this may have a different impact on the tenting of the mitral leaflets than a surgical ring. In addition, the Carillon device is quite flexible. This flexibility may be of benefit with regard to mitral annular function, which diminishes with secondary MR. Any improvement in mitral annular

function may improve the efficiency of cardiac function beyond simply reducing resting MR. Whether vector forces or mitral annular function is impacted differently with a Carillon device than a MitraClip is currently unknown, but these and other mechanical explanations may contribute to differential benefits in various anatomic circumstances such as enlarged LVs.

STUDY LIMITATIONS. These studies were mechanistic in design, so there are insufficient numbers of patients to be powered for clinical endpoints such as mortality. These data should therefore be considered to be preliminary but support additional research using clinical primary endpoints. Although a substantial cohort of the present analysis comes from the blinded, randomized, sham-controlled REDUCE FMR study, patients in the nonblinded TITAN and TITAN II studies were also included. Therefore, personnel in the TITAN and TITAN II studies were aware of allocation status when conducting clinical assessment, and this may possibly have led to observer bias. In addition, patients who did not receive a Carillon device were limited not only to those in the medical treatment randomized arm of the REDUCE FMR study, but also to those in whom placing a device was unsuccessful and without complications. Although there were no significant follow-up differences between the nonimplanted patients in the 3 studies and the blinded sham-controlled patients in the REDUCE FMR study (Supplemental Tables 6 and 7), a more optimal study would be limited to patients in the control arm of a randomized trial. This data support development of clinically powered, larger randomized trials, and specifically the inclusion of patients with larger ventricles.

Another limitation of this study was that patients were followed through only 1 year. Because other trials of percutaneous mitral valve therapies have reported disparate outcomes with extended follow-up periods (5), prospective trials with 5 years of patient follow-up would help to fully elucidate the long-term clinical course in this patient population. Finally, these data encompass some of the early experience with the Carillon device and therefore may not reflect the current skill of device users.

CONCLUSIONS

In patients with secondary MR and severe LV enlargement, GDMT and the Carillon device improved mitral valve function, LV morphology, and functional outcome compared with patients receiving GDMT only. Preoperative LV dimension should not be a limiting factor when evaluating patient eligibility or anticipated response to therapy with the Carillon device. These data support development of clinically powered, larger randomized trials, and specifically the inclusion of patients with larger ventricles.

ACKNOWLEDGMENTS The authors thank Larry Miller, PhD, PStat, for data analysis and providing critical review and editorial assistance, and Matthew Stark, PhD (Cardiac Dimensions, Kirkland, Washington) for critical review and data compilation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The trial was sponsored by Cardiac Dimensions (Kirkland, Washington). Dr. Anker has received grants and personal fees from Vifor and Abbott Vascular; and personal fees from AstraZeneca, Bayer, Brahms, Boehringer Ingelheim, Cardiac Dimensions, Novartis, Occlutech, Servier, and Vifor. Dr. Starling has served on the advisory board for the PARAGLIDE Trial (Novartis) and Cardiac Dimensions; and has conducted sponsored research Corvia. Dr. Filippatos has received lecture fees and/or Committee Member contributions in trials sponsored by Medtronic, Vifor, Servier, Novartis, Bayer, Amgen, and Boehringer Ingelheim. Dr. Butler has received consulting fees from Boehringer Ingelheim, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave, Vifor, and Cardiac Dimensions. Dr. von Bardeleben has received consultancy and lecture honoraria from Abbott Vascular, Cardiac Dimensions, Edwards Lifesciences, GE Health Systems, and Philips Healthcare. Dr. Lindenfeld has received grant support from AstraZeneca; and consulting income from Abbott Vascular, Edwards Lifesciences, Boston Scientific, RESMED, Relypsa, Boehringer Ingelheim, and V-Wave. Dr. Coats has received honoraria and/or lecture fees from AstraZeneca, Bayer, Menarini, Novartis, Nutricia, Servier, Vifor, Actimed, Cardiac Dimensions, CVRx, Enopace, Faraday, Gore, Impulse Dynamics, Respicardia, Stealth Peptides, V-Wave, Corvia, Arena, and ESN Cleer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Stefan D. Anker, Department of Cardiology (CVK), Charité Universitätsmedizin Berlin, Augustenburger Platz 1, D-13353 Berlin, Germany. E-mail: s.anker@cachexia.de.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: It has been suggested that patients with larger ventricles are less attractive as candidates for devices treating secondary MR. In patients with secondary MR and severe LV enlargement, the Carillon Mitral Contour System improved mitral valve function, LV morphology, and functional outcome compared with patients receiving GDMT only. Preoperative LV dimension should not be a limiting factor when evaluating patient eligibility or anticipated response to therapy with the Carillon device.

TRANSLATIONAL OUTLOOK: These results support development of clinically powered, larger randomized trials, and specifically the inclusion of patients with larger LVs.

REFERENCES

1. Silbiger JJ. Novel pathogenetic mechanisms and structural adaptations in ischemic mitral regurgitation. J Am Soc Echocardiogr 2013;26:1107–17.

2. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol 2015;65:1231–48.

3. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol 2005;45:381–7.

4. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018.

5. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307–18.

6. Asch FM, Grayburn PA, Siegel RJ, et al. Transcatheter mitral valve replacement in patients with heart failure and secondary mitral regurgitation: from COAPT trial. J Am Coll Cardiol 2019;74:2969–79.

7. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. J Am Coll Cardiol Img 2019;12:353–62.

8. Packer M, Grayburn PA. Neurohormonal and transcatheter repair strategies for proportionate and disproportionate functional mitral regurgitation in heart failure. J Am Coll Cardiol HF 2019;7:518–21.

9. Lipiecki J, Siminiak T, Sievert H, et al. Coronary sinus-based percutaneous annuloplasty as treatment for functional mitral regurgitation: The TITAN II Trial. Open Heart 2016;3:e000411.

10. Siminiak T, Wu JC, Haude M, et al. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. Eur J Heart Fail 2012;14:931–8.

11. Witte KK, Lipiecki J, Siminiak T, et al. The REDUCE FMR trial: a randomized sham-controlled study of percutaneous mitral annuloplasty in functional mitral regurgitation. J Am Coll Cardiol HF 2019;7:945–55.

12. AATS Ischemic Mitral Regurgitation Consensus Guidelines Writing Committee, Kron IL, LaPar DJ, Acker MA, et al. 2016 update to The American Association for Thoracic Surgery (AATS) consensus guidelines: ischemic mitral valve regurgitation. J Thorac Cardiovasc Surg 2017;153:e97–114.

13. Schofer J, Siminiak T, Haude M, et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. Circulation 2009;120:326–33.

14. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: a report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303–71.

15. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. J Am Coll Cardiol Img 2011;4:98–108.

16. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. J Am Coll Cardiol 2010;56:392–406.

17. Braun J, van de Veire NR, Klautz RJ, et al. Restrictive mitral annuloplasty cures ischemic mitral regurgitation and heart failure. Ann Thorac Surg 2008;85:430–6; discussion 436–7.

18. Braun J, Bax JJ, Versteegh MI, et al. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. Eur J Cardiothorac Surg 2005;27:847–53.

19. Horii T, Suma H, Isomura T, Nomura F, Hoshino J. Left ventricle volume affects the result of mitral valve surgery for idiopathic dilated cardiomyopathy to treat congestive heart failure. Ann Thorac Surg 2006;82:1349–54; discussion 1354–5.

20. Gaasch WH, Meyer TE. Left ventricular response to mitral regurgitation: implications for management. Circulation 2008;118:2298–303.

21. Hubscher A, Schwerg M, Hoffmann S, et al. Automated quantification of mitral valve tenting volume in functional mitral regurgitation by three-dimensional echocardiography. Echocardiography 2020;37:1043–8.

22. Magne J, Pibarot P, Dagenais F, Hachicha Z, Dumesnil JG, Senechal M. Preoperative posterior leaflet angle accurately predicts outcome after restrictive mitral valve annuloplasty for ischemic mitral regurgitation. Circulation 2007;115:782–91.

23. Mihos CG, Santana O. Mitral valve repair for ischemic mitral regurgitation: lessons from the Cardiothoracic Surgical Trials Network randomized study. J Thorac Dis 2016;8:E94–9.

KEY WORDS Carillon, congestive heart failure, functional mitral regurgitation, indirect annuloplasty, left ventricular enlargement

APPENDIX For supplemental tables and a figure, please see the online version of this paper.