Percutaneous mitral annuloplasty with the Carillon device: Outcomes in proportionate and disproportionate functional mitral regurgitation

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Background It has been suggested that the disparity of outcomes between the studies of transcutaneous edge-to-edge repair (TEER) for functional mitral regurgitation (FMR) in heart failure with reduced ejection fraction (HFrEF) could be due to systematic differences in the populations studied. One proposal is that there are 2 broad groups: those with proportional FMR who respond less favorably, and those in whom the FMR is greater than expected (disproportionate) FMR where edge-to-edge TEER seems to be more effective. Whether this grouping is relevant for other percutaneous interventions for FMR is unknown.

Objectives We sought to compare clinical and echocardiographic outcomes of patients with HFrEF and proportionate and disproportionate FMR treated with indirect annuloplasty using the Carillon device.

Methods This is a pooled analysis from 3 trials of patients with FMR. Key patient eligibility in these trials specified persistent grade 2+ to 4+ FMR with >5.5 cm left ventricular (LV) end-diastolic diameter (LVEDD) and reduced ejection fraction. Patients with an effective regurgitant orifice area/LV end-diastolic volume (EROA/LVEDV) ratio under 0.15 were assigned to the proportionate FMR group (n = 74;65%) and those with a ratio above 0.15 were classed as having disproportionate FMR (n = 39;35%).

Results At 12 months following treatment, both groups showed improvements in all MR variables including regurgitation volume, EROA and vena contracta. Moreover, in patients with proportionate MR there were clinically relevant and statistically significant improvements in LV volumes and diameters. There was no independent relationship between the degree of proportionality as a continuous variable and the remodeling response to Carillon therapy (change in LVEDV r = 0.17; change in LVESV r = 0.14).

Conclusion Percutaneous mitral annuloplasty with the Carillon device reduces MR in patients with both proportionate and disproportionate FMR, and also results in LV reverse remodeling in those with proportionate FMR. The effect on remodeling remains to be verified in a large-scale trial. (Am Heart J 2023;265:137–142.)

Background

Secondary mitral regurgitation (MR) is common in patients with chronic heart failure (HF) due to reduced ejection fraction (HFrEF) and portends a worse prognosis.[1,2] The 2 most common approaches to percutaneous mitral valve repair are transcatheter edge-to-edge repair (TEER), which targets the mitral valve leaflets, and a catheter-based approach to reduce the dimensions of the mitral annulus. TEER has been evaluated in 2 large, controlled studies. Whilst the "Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR)" did not show a benefit on mortality or hospitalization, the "Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (The COAPT Trial)" trial demonstrated early and persistent benefits on total mortality and hospitalization.[3,4]

It has been hypothesized that the divergent clinical outcomes were partly attributable to differences in the inclusion criteria of the trials. MITRA-FR selected a cohort with more left ventricular (LV) dilation in relation to the degree of MR whereas patients in COAPT had a

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greater degree of MR and lesser LV dilatation. Thus, reports have suggested that edge-to-edge repair procedures in FMR show differential outcomes related to the type of mitral regurgitation. This observation, led to the, as yet unproven, concept of "proportionate" and "disproportionate" MR. In the latter case, it is proposed that the degree of MR is greater than might be expected by the degree of LV remodeling, whereas in the former the magnitude of MR is expected by the degree of LV dilatation.[5,6] Although whether these are indeed 2 categories of disease, or simply one disease continuum, international guidelines have reflected this hypothesis with a higher recommendation for edge-to-edge mitral valve repair in patients with disproportionate MR than in those with proportional MR.[7]

The Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, WA, United States) utilizes indirect annuloplasty to improve approximation of the mitral valve leaflets by altering LV and left atrial geometry such that the limitations of TEER with respect to the degree of LV dilatation may not apply. The current study aimed to compare LV remodeling and clinical outcomes of patients with HF due to reduced ejection fraction displaying features consistent with either proportionate or disproportionate MR treated with indirect annuloplasty using the Carillon device.

Methods

Patients

This is a pooled analysis of patients with secondary MR treated with a percutaneous mitral annuloplasty procedure utilizing the coronary sinus-based Carillon device in the TITAN,[8] TITAN II,[9] and REDUCE FMR[10] trials. Ethics committees at each site approved the protocols of each trial, provided written informed consent, and study procedures complied with the Declaration of Helsinki. Inclusion and exclusion criteria have been published previously.[8-10] Key patient eligibility included ongoing symptomatic HF and grade 2+ to 4+ secondary MR despite guideline-directed HF medication, with >5.5 cm LV end-diastolic diameter (LVEDD), and reduced LV ejection fraction (<40% in TITAN and TITAN II, <50% in REDUCE-FMR). Key exclusion criteria included revascularization or percutaneous coronary intervention within the previous 30 days, severe mitral valve degenerative pathology, severe mitral annular calcification, previous mitral valve surgery, current or indicated cardiac resynchronization device due to the shared coronary sinus space used by mitral annuloplasty. In TITAN and TITAN II, the echocardiography core laboratory pre-screened patients and excluded patients with 1+ MR. REDUCE FMR, as a pragmatic trial allowed local investigators to decide upon eligibility, and blinded core echocardiography laboratory analysis was undertaken at study termination.

Indirect mitral annuloplasty procedure

The Carillon Mitral Contour System procedure has been described previously.[11] Briefly, the Carillon device is a fixed-length double anchor device. The distal anchor is deployed distally in the coronary sinus. Traction is applied to plicate the posterior mitral annulus. A proximal anchor is then deployed near the coronary sinus ostium to maintain the plication.

Echocardiography

Independent core laboratories read echocardiograms for quantitative parameters blinded to allocation (for REDUCE-FMR) and visit date (TITAN, TITAN II and REDUCE-FMR). MR grading was based upon American Society of Echocardiography recommendations.[12] Forward stroke volume was assessed as a measure of LV function that takes into account the degree of MR.[13,14]

Statistical analysis

The pooled dataset included baseline patient characteristics and echocardiographic data along with vital status results 1 year after the implantation. Continuous variables are reported as mean and standard deviation for normally distributed data, or median and interquartile range for nonparametric data. Categorical variables are presented as counts and percentages. Changes in echocardiographic variables over 1 year relative to baseline were analysed with a paired samples *t*-test. As previously described, patients with an effective regurgitant orifice area (EROA)/LV end-diastolic volume (LVEDV) ratio under 0.15 were assigned to the proportionate MR group and those with a ratio above 0.15 were classed as having disproportionate MR.[15] Comparison of LV and mitral valve change values in proportionate MR and disproportionate MR groups were analysed with analysis of covariance adjusted for baseline values. Mortality was analysed with Kaplan-Meier methods with a log-rank test for group comparisons. Logistic regression was performed to identify predictors of LV remodelling at 1 year, defined as a decrease of at least 10% in LVESV from baseline. All tests were two-sided but should be considered in the context of this retrospective, post hoc setting. Statistical analyses were performed by an independent biostatistician using Stata v16 (StataCorp, College Station, TX, United States).

Results

Across the 3 studies, a total of 139 patients were treated with the Carillon device. Baseline characteristics of these patients have been previously reported.[16] For the current analysis, baseline echocardiographic measures for the purposes of classification of MR were available for 113 (81%) patients.

The characteristics of those included in the present analysis are shown in Table I. Mean age was 67 ± 11 years

Table I. Baseline patient characteristics

	All patients (n = 113)	Proportionate (n = 74)	Disproportionate (n = 39)	*P*-value
Demographics				
Age (years)	67 ± 11	65 ± 12	72 ± 7	<.001
Male sex	87 (77)	60 (81)	27 (69)	.17
Body mass index (kg/m^2)	26 ± 5	27 ± 5	25 ± 4	.16
Medical history				
Ischemic etiology	78 (70)	51 (69)	27 (71)	>.99
Prior myocardial infarction	60 (53)	39 (53)	21 (54)	>.99
Atrial fibrillation	57 (50)	33 (45)	24 (62)	.11
Diabetes mellitus	24 (21)	16 (22)	8 (21)	>.99
Clinical status				
NYHA classification				.71
II	28 (25)	19 (26)	9 (23)	
III	78 (70)	51 (70)	27 (69)	
IV	6 (5)	3 (4)	3 (8)	
6-minute walk distance (meters)	312 ± 87	331 ± 81	274 ± 87	<.001
KCCQ (units)	52 ± 22	54 ± 20	46 ± 26	.13
Left atrial variables				
LA volume, cc	104 ± 43	101 ± 40	109 ± 49	.34
Left ventricular variables				
LV ejection fraction (%)	31 ± 8	29 ± 8	34 ± 8	.005
LV end-diastolic diameter (cm)	6.6 ± 0.8	6.8 ± 0.8	6.3 ± 0.9	.01
LV end-systolic diameter (cm)	5.6 ± 1.0	5.8 ± 1.0	5.3 ± 0.9	.005
LV end-diastolic volume (cc)	194 ± 62	206 ± 64	173 ± 53	.007
LV end-systolic volume (cc)	136 ± 54	148 ± 58	114 ± 38	<.001
Forward stroke volume (cc)	48 ± 17	49 ± 16	48 ± 18	.72
Mitral valve variables				
Mitral valve area (mm^2)	12.7 ± 2.9	12.5 ± 2.7	13.1 ± 3.2	.32
Regurgitant volume (ml)	38 ± 19	30 ± 12	51 ± 21	<.001
Vena contracta (cm)	0.57 ± 0.19	0.55 ± 0.19	0.61 ± 0.20	.14
EROA (cm^2)	0.25 ± 0.12	0.20 ± 0.08	0.35 ± 0.12	<.001
EROA (mm^2) to LVEDV (cc) ratio	0.14 ± 0.07	0.10 ± 0.03	0.21 ± 0.06	<.001
MR grade				<.001
1	16 (14)	16 (22)	0 (0/)	
2	32 (29)	25 (34)	7 (18)	
3	45 (40)	26 (35)	19 (50)	
4	19 (17)	7 (10)	12 (32)	
Biomarker				
NT-proBNP (pg/ml)	3373 ± 3038	2987 ± 2657	4003 ± 3560	.26

Values are mean ± SD for continuous variables and number (%) for categorical data.
P-values derived from independent samples *t*-test for continuous variables and Fisher's exact test for categorical variables.
EROA, effective regurgitant orifice area; KCCQ, Kansas City Cardiomyopathy Questionnaire; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; TA, tenting area.

and 77% were male. Mean baseline LVEF was 31 ± 8% and mean LVEDV was 194 ± 62 ml. A total of 74 (65%) patients were classified with proportionate MR and 39 (35%) with disproportionate MR. Patients in the proportionate MR group were younger (65 ± 12 vs 72±7 years; $P<.001$), had greater LV dilatation ($P\leq.01$ for all LV diameter and volume measures), had lower ejection fraction (29 ± 8 vs 34 ± 8%; $P = .005$), and less severe MR ($P < .001$) than the disproportionate group, although forward stroke volume was comparable between the groups (Table I).

Table II shows the changes in echocardiographic variables at 1 year after treatment with the Carillon device. Patients with proportionate MR experienced clinically and statistically relevant improvements in all LV and MR parameters including forward stroke volume. In the disproportionate MR group MR parameters improved whilst the LV parameters were largely unchanged (Table II).

Whilst greater baseline LV dimensions and greater impairment of LVEF were independently associated with a significant reduction in LVESV at 12 months (Table III), this was not the case for MR proportionality. Once LV dimensions were taken into account, there was no correlation between the ratio of EROA/LVEDV as a continuous variable and the response to Carillon therapy in terms of change in LV volumes (LVEDV r = 0.17; LVESV r = 0.14) . There was also no statistical difference in mortality over 1 year between those with proportionate and disproportionate MR (15.3% vs 25.6%, log-rank $P = .16$).

Table II. Change in echocardiographic variables 12 months after treatment

Characteristic	Proportionate (n = 74)		Disproportionate (n = 39)	
	Value	*P*-value ** (pre-post)	Value	*P*-value ** (pre-post)
Left atrial variables				
LA volume (cc)	-6 (-12, -1)	.03	2 (-6, 9)	0.68
Left ventricular variables				
LV ejection fraction (%)	2 (0, 4)	.06	1 (-2, 4)	0.47
LV end-diastolic diameter (cm)	-0.2 (-0.4, -0.1)	.002	0.0 (-0.2, 0.2)	0.91
LV end-systolic diameter (cm)	-0.3 (-0.5, -0.2)	.001	0.0 (-0.1, 0.2)	0.65
LV end-diastolic volume (cc)	-20 (-33, -7)	.003	-7 (-16, 2)	0.12
LV end-systolic volume (cc)	-18 (-30, -6)	.005	-6 (-15, 2)	0.13
Forward stroke volume (cc)	5 (0, 10)	.05	2 (-5, 9)	0.55
Mitral valve variables				
Mitral valve area (mm^2)	-1 (-2, -1)	<.001	-1 (-2, 0)	0.005
Regurgitant volume (ml)	-9 (-13, -6)	<.001	-13 (-21, -5)	0.004
Vena contracta (cm)	-0.19 (-0.27, -0.10)	<.001	-0.14 (-0.22, -0.06)	0.001
EROA (cm^2)	-0.06 (-0.08, -0.03)	<.001	-0.10 (-0.16, -0.04)	0.003
MR grade	-0.6 (-0.9, -0.4)	<.001	-0.7 (-1.2, -0.2)	0.006

Values are mean change after 12 months (95% CI) relative to baseline.

** p-values derived from paired samples *t*-test.EROA, effective regurgitant orifice area; LA, left atrial; LV, left ventricular; MR, mitral regurgitation.

Table III. Association of key baseline characteristics with clinically relevant LV reverse remodeling at 12 months defined as >10% change in LVESV from baseline

Variable	Unit of measure	Odds ratio	95% CI
LV ejection fraction	Per 5-unit decrease	1.87	1.27, 2.76
LVESV	Per 50-unit increase	2.21	1.35, 3.79
LVEDV	Per 50-unit increase	1.73	1.11, 2.69
Ischemic etiology	No vs. yes	3.27	1.15, 9.35
Age	Per 5-year decrease	1.25	1.01, 1.57
Proportionate MR	Yes vs. no	1.78	0.56, 5.69
Regurgitant volume	Per 5-unit increase	1.07	0.94, 1.22
Atrial fibrillation	Yes vs. no	1.34	0.50, 3.60

LV, left ventricular; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; MR, mitral regurgitation.

Discussion

In this analysis of patients with HF and MR treated with the Carillon device, there were several important findings. First, patients with both proportionate and disproportionate MR had important reductions in all measures of mitral valve regurgitation and forward stroke volume. Thus, there was a significant improvement in LV volumes and regurgitation in a subanalysis from Carillon trials whether the FMR was proportionate or disproportionate. Second, those with proportionate MR underwent significant LV reverse remodeling over the 1 year following treatment. Third, the classification into proportional or disproportional or the ratio of EROA/LVEDV as a continuous variable was not independently related to the degree of LV reverse remodeling defined as a change in LV volumes (LVEDV and LVESV).

Despite a lack of heterogeneity of effects on clinical outcomes in patients by baseline LV volume in COAPT,[17,18] the proposal that the diverging clinical results of MITRA-FR and COAPT studies are the result of the different inclusion criteria of these patients within the trials persists. This, and the finding that neither study demonstrated LV reverse remodeling following TEER, has led to suggestions that patients with HF and disproportionate MR should have treatments targeted at the mitral valve whilst those with proportional MR should receive treatments aimed at reversing LV remodeling. Whilst appealing, this hypothesis remains unproven, and the different categories may simply be patients at a different stage of their disease. Although the guidelines place patients with FMR fulfilling the COAPT criteria in a higher class of indication, further data are required, including more data in patients taking contemporary optimal medical therapy, before the indications for percutaneous therapy in patients with FMR can be refined and especially before patients with proportional FMR could be deselected for TEER.

LV reverse remodeling is a consistent finding in studies utilizing the Carillon device.[19] The present data extend this observation showing that percutaneous indirect annuloplasty is associated with reductions in MR and LV dimensions even in the subgroup of patients satisfying echocardiographic characteristics of MITRA-FR[20] raising the tantalizing concept that mitral annuloplasty could be regarded as a treatment targeting the remodeled annulus where deciding whether MR is proportionate or disproportionate to the LV dilatation is less critical.[21] However, the benefit in LV remodeling of patients with FMR with the Carillon device remains to be demonstrated in prospective randomized trials.

Although the presence of LV reverse remodeling is reliably associated with benefits on prognosis,[22] the rela-

tionship between the degree LV reverse remodeling and the benefit on prognosis can be highly variable depending upon other features and the degree of LV dilatation at baseline. The remodeling data following Carillon implantation is therefore similar to the patterns seen with CRT, where greater LV dilatation is associated with greater LV reverse remodeling.[23] Here too, one sees a smaller magnitude of LV reverse remodeling in patients with less dilatation, probably simply reflecting the ceiling effect of improvements possible in people without significant LV dilatation at baseline. The importance of context is also exemplified following CRT implantation, where, despite lesser LV reverse remodeling, those with an ischemic aetiology has a similar improvement in prognosis.

Not only does the clinical efficacy of the changes seen with the present analysis require further elucidation in a larger population of patients with both proportionate and disproportionate MR, but further information is required on the benefits of TEER in a broad patient population. The EMPOWER study, is enrolling patients with a wide range of MR severity and LV dilatation and will provide the information to answer the former question,[24] whilst RESHAPE-2 will hopefully answer outstanding questions about the indication for and efficacy of TEER in subgroups.[25] Both are needed to refine and personalize device prescription for patients with HF and MR.

Limitations

There are several limitations of this study. First, the classification of MR into proportional and disproportionate remains an unproven hypothesis that requires further data from large randomized studies. Second, our sample size was small and the analysis was post hoc and retrospective such that these data, including the *P*-values to describe statistical significance, should be regarded as hypothesis-stimulating. Third, the lack of LV reverse remodeling might simply be a type 2 error due to low numbers and smaller ventricular dimensions. This is underpinned by the lack of an independent relationship between the classification or degree of proportionality and the degree of LV reverse remodeling suggesting that remodeling was not driven by the presence of proportionate MR. Fourthly, this analysis is unable to evaluate the long-term clinical implications or morbidity and mortality outcomes of patients with proportionate and disproportionate MR following Carillon device treatment due to small the modest sample size and incomplete follow-up data beyond 12 months. Finally, whilst each trial required patients to be on optimally tolerated doses of guideline directed medical therapy we have no information available on doses or titration during follow-up, although investigators were allowed to titrate all medications as required throughout the follow-up period of each of the trials.

Conclusion

The Carillon percutaneous mitral annuloplasty device reduces mitral regurgitation in people with both disproportionate and proportionate MR and leads to beneficial LV reverse remodeling even in patients with proportionate MR.

Clinical perspectives

It has been proposed that edge-to-edge repair for functional mitral regurgitation is more challenging and seems less effective in people with greater LV dilatation–known as proportionate mitral regurgitation. Due to the consistent efficacy on stimulating LV reverse remodeling, the Carillon device, a percutaneous annular therapies might not have this limitation. Whether the proposed concept of proportionate and disproportionate MR remains static or is adjusted as we learn more, those patients with LV dilatation are often the most challenging to manage. Studies of devices in this field must continue to recruit a wide range of patients to help develop the hypothesis and refine which device should be offered to which patient at which time.

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