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ORIGINAL RESEARCH ARTICLE

Long-term prognosis of patients treated by coronary sinus-based percutaneous annuloplasty: single centre experience

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Abstract

Aims This study aims to report long-term mortality, echocardiographic, and clinical outcomes of patients receiving treatment for functional mitral regurgitation (FMR) with the Carillon device.

Methods and results This was a single centre analysis of prospectively collected data from patients treated with the Carillon Mitral Contour System for symptomatic congestive heart failure despite guideline-directed medical therapy, who were included from a single centre from the TITAN II study. All patients presented with New York Heart Association (NYHA) class 2 or greater symptoms, grade 2+ to 4+ FMR, left ventricular enlargement, and reduced ejection fraction. Surviving patients were evaluated for long-term follow-up post-procedure, averaging 6.9 years. Fifteen (15) patients (mean age 72 years, 60% male, 100% NYHA class III or IV, 50% MR grade 3+ or 4+) were treated with the Carillon device. The Kaplan–Meier mortality rate was 40% at 6 years of follow-up. Long-term survival through 6 years was associated with echocardiographic improvement in mitral regurgitation (change in effective regurgitant orifice area in survivors versus non-survivors from baseline to 1 year follow-up, -9.0 ± 5.6 vs. -1.7 ± 1.5, $P = 0.02$) and clinical status at 12 months (difference in NYHA at 1 year follow-up between survivors versus non-survivors, $P = 0.05$) which was sustained throughout follow-up. All patients at 6 year follow-up had $\leq$2+ MR, with 6 of 7 having 0–1+ MR. Left ventricular end-diastolic volume was reduced from 154.0 ± 65.7 mL at baseline to 104.5 ± 59.2 mL at 6 year follow-up, $P = 0.03$ in survivors with both measurements.

Conclusions Among patients with congestive heart failure treated with the Carillon device, long-term survival is associated with favourable 1 year and sustained improvements in mitral regurgitation, left ventricular volume, ejection fraction, and clinical status.

Keywords Functional mitral regurgitation; Heart failure; Carillon; Indirect annuloplasty; Survival

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Introduction

Secondary, or functional, mitral regurgitation (FMR) imparts a worse prognosis in heart failure patients, even when the FMR is mild.[1] Recent studies have suggested that percutaneous treatment of FMR may have clinically beneficial effects, including a favourable impact on mortality.[2] The Carillon Mitral Contour System was developed by Cardiac Dimensions Inc. (Kirkland, WA, USA) to treat FMR, using the proximity between the coronary venous system and the mitral annulus. This device has been assessed prospectively in four trials, establishing safety of the procedure, as well as efficacy in the reduction of the severity of FMR.[3–6] Importantly, this was also associated with reverse remodelling of the left ventricle (LV) in each of the trials, a phenomenon associated with favourable mortality benefits.[7–9] The clinical follow-up of subjects included in these studies varied from 6 months (AMADEUS trial) to 2 years (TITAN trial). Long-term survival

has recently been reported; however, long-term echocardiography was not available.[10] In the TITAN II trial, among 30 successfully implanted patients in the trial, 15 were treated in one centre in France, where long-term follow-up was performed, even though that was not a formal part of TITAN II. The purpose of this study was to analyse the long-term outcome of these patients with clinical and echocardiography follow-up.

Methods

The results of the TITAN II trial have been published previously.[3] This study was performed to evaluate the safety and integrity of a modified Carillon Mitral Contour System.[5] The trial was approved by the local Competent Authority/Ethics Committee at each participating site, and subjects were provided written informed consent. It was a prospective, single arm, multicentre, safety study undertaken at five centres in Germany, Poland, and France. Patients were included if they had symptomatic heart failure of at least NYHA class II, who were stabilized on guideline-directed heart failure medications for at least 1 month. In order to qualify, patients had to have 2+ or greater FMR, a 6 min walk test (6MWT) of 150–450 m, left ventricular (LV) dilatation [left ventricular end-diastolic diameter (LVEDD) $>$ 55 mm], and LV ejection fraction $<$40%. Successfully implanted patients were followed at 1, 6, and 12 months for clinical and echocardiographic parameters. Across all trial sites in the TITAN II study, 30 patients successfully received permanent Carillon implants out of 36 included in the study. The 1 year mortality rate was 23% (7 of 30 patients).

A single centre in France (Clermont Ferrand) enrolled 18 patients in the TITAN II trial between September 2011 and January 2013. Although not mandated by the TITAN II trial, patients at this centre were continued to be followed longitudinally, and this follow-up is the basis for this analysis. Successful implantation of the Carillon device was obtained in 15 of the 18 patients. The 1 year mortality was 7% (1 of 15 patients).

Between April and June 2019, all implanted patients or their relatives, personal cardiologists, and/or general practitioners were contacted to ascertain who died during that time. Surviving patients were offered an additional clinical visit with echocardiographic assessment. Study procedures were conducted in accordance with the Declaration of Helsinki.

All baseline and 1 year echos were read by a core echo lab (Brigham and Women's Medical Center, Boston, MA, USA). The long-term echos were read by site echocardiographers and independently reviewed by another cardiologist to assess for possible discrepancies.

Patients who survived long-term were compared with the patients who died. Between-group comparisons were performed using the Student's *t*-test. Binomial proportions were compared between groups using Fisher's exact test. Wilcoxon's rank sum test was used to compare ordinal outcomes such as change in NYHA at 1 year between groups. Additional outcomes are presented as mean change from baseline for continuous variables and number and frequency for categorical variables. A two-sided *P*-value of $<$0.05 was considered significant in all analyses. Statistical analysis was performed with JMP v14.3 software (SAS Institute, Cary, NC, USA).

Results

The baseline characteristics of implanted patients are shown in *Table 1*. The mean age of patients was 72 ± 7 years. Most were in NYHA class III (87%) with 13% in NYHA class IV at baseline. The aetiology of the cardiomyopathy was ischaemic in 47% (7 of 15 patients). Half of patients were judged to have MR grade 3+ or greater by the core lab evaluation. Whereas baseline regurgitant volume (32.8 mL) and EROA (0.22 cm^2) were analysed to be moderate, baseline vena contracta measurements (0.66 cm) were close to the criteria for being considered to be severe.[11]

The follow-up period from the implantation procedure extended to 90 months (7.5 years). All surviving patients had at least 72 months (6 years) post-implant follow-up. The 6 year Kaplan–Meier estimate for mortality is 40.0% (*Figure 1*). *Table 2* compares the heart failure hospitalization rates in the year prior to the Carillon implantation, and the 1 and 6 years after implant. Overall, and specifically in those with long-term survival, there was a decrease in the rate of heart failure hospitalizations after Carillon implantation. This change was not seen in the patients who did not have long-term survival, but their incidence of heart failure hospitalization prior to the Carillon procedure was lower than those that survived long-term.

Table 3 depicts the baseline clinical and echocardiographic parameters of patients who survived at least 6 years after Carillon implantation (Group 1, n = 9) in comparison with patients who died (Group 2, n = 6). Group 1 patients tended to have more favourable baseline clinical characteristics, with NYHA class average 3.0 vs. 3.3 in Group 2 (P = 0.09), and 6MWT of 353 m vs. 227 m in Group 2 (P = 0.02). Global LVEF was more depressed at baseline in the latter group as well (23% for those in Group 2 vs. 33% for those that survived $>$6 year, $P < 0.05$). There were no statistically significant differences in baseline MR grade, regurgitant volume, or LV volumes.

All but one patient survived through 12 months. Because most baseline differences between groups were not clinically

Table 1 Baseline clinical and echocardiographic parameters

	Total (n = 15)
Male sex, *n* (%)	9 (60.0)
Age (years)	71.9 ± 6.7
Aetiology, *n* (%)	
Ischaemic heart disease	7 (46.7)
Non-ischaemic cardiomyopathy	8 (53.3)
Diabetes mellitus, *n* (%)	4 (26.7)
History of atrial fibrillation, *n* (%)	8 (53.3)
BMI (kg/m^2)	25.8 ± 4.4
NYHA, *n* (%)	
III	13 (86.7)
IV	2 (13.3)
Baseline heart rate (b.p.m.)	75 ± 13
Systolic BP (mmHg)	126 ± 17
Diastolic BP (mmHg)	76 ± 9
6 min walk test (m)	298.6 ± 92.4
Beta-blocker, *n* (%)	12 (80.0)
Diuretic, *n* (%)	
Any	13 (86.7)
MRA	4 (26.7)
ACEi/ARB, *n* (%)	9 (60.0)
Hydralazine/nitrates, *n* (%)	3 (20.0)
LVEF (%)	30 ± 9
LVEDD (cm)	6.0 ± 0.8
LVESD (cm)	5.1 ± 0.9
LVEDV (mL)	157.5 ± 51.1
LVESV (mL)	112.1 ± 42.1
Vena contracta (cm)	0.66 ± 0.15
EROA (mm^2)	22 ± 9.9
Mitral regurgitant volume (mL/bt)	32.8 ± 17.1
Mitral regurgitant grade, *n* (%)	
2+	6 (50.0)
3+	4 (33.3)
4+	2 (16.7)

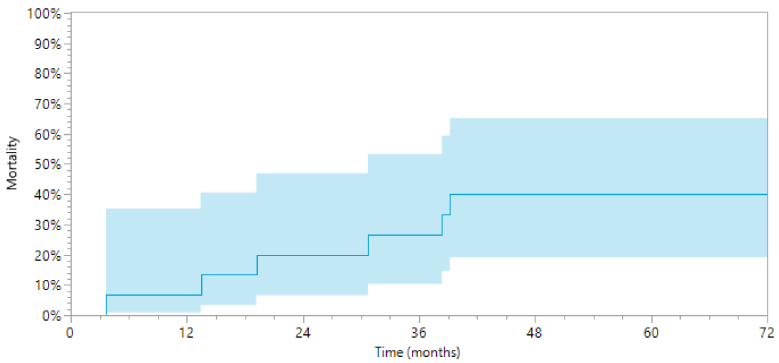
ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; EROA, effective regurgitant orifice area; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SD, standard deviation.
Values are ±SD.

meaningful, relative change from baseline was examined. At 12 month follow-up (*Table 4*), there was a significant difference in MR grade between the two groups (P = 0.04) which was associated with a significant reduction of EROA in Group 1 (21.7 mm^2 baseline vs. 9.7 mm^2 12 months, P = 0.02). Although between-group differences in reduction of LVEDV and improvement in LVEF did not reach statistical significance, a signal in both parameters was observed in Group 1, with a decrease in LVEDV of 14.2 mL and an increase in EF from 33.0% to 37.5%. Symptomology, as assessed by NYHA classification at 12 months, was also improved in long-term surviving patients as compared with non-survivors (P = 0.05).

In addition to the six patients who died within 6 years of the follow-up period, another patient died at 7.2 years prior to the long-term follow-up visit. Death was cardiac in 5 of the 7 cases with one death of unknown cause and another due to renal adenocarcinoma. Among the eight surviving patients, seven agreed to have a clinical and echocardiographic assessment. NYHA class and clinical status information were obtained by phone contact on the other surviving patient at 7.3 years post-procedure. Surviving patients improved their NYHA class during follow-up compared with baseline at 6 and 12 months, which remained unchanged at last follow-up in 7 of 8 patients. Measures of mitral regurgitation decreased significantly (EROA change from baseline 21.7 mm^2 vs. 8.0 mm^2 at 12 months vs. 6.6 mm^2 at long term, P = 0.02 from baseline). Although the reduction in LV volume was not statistically significant at 1 year, the LV volume continued to remodel such that the LVEDV reduced from 154.0 ± 65.7 mL at baseline to 104.5 ± 59.2 mL at 6 year follow-up, P = 0.03. It is notable that 6 of 7 patients with long-term echos had 0–1+ MR 6 years after Carillon implantation, with one patient having 2+ MR (*Figure 2*).

A comparison of medical management of the overall cohort and specifically these eight patients at baseline and at

Figure 1 Kaplan–Meier curves for overall mortality through 6 years. Number of patients at risk and estimate of mortality by year.



No at risk	15	14	12	11	9	9	9
P(mortality)	100.0 ± 0.0%	6.7±6.4%	20.0±10.3%	26.7±11.4%	40.0±12.7%	40.0±12.7%	40.0±12.7%

Table 2 Heart failure hospitalizations before and after implant procedure

	Pre-procedure	Post-procedure		
	12 months prior to implant	12 months after implant	*P*-value*	All follow-up after implant
All patients				
Total number of hospitalizations	27	10		36
Rate per patient year [95% CI]	1.8 [1.18, 2.61]	0.70 [0.33, 1.28]	0.03	0.55 [0.38, 0.75]
Group 1 survivors >6 years				
Total number of hospitalizations	19	4		23
Rate per patient year [95% CI]	2.11 [1.27, 3.29]	0.44 [0.12, 1.13]	0.02	0.43 [0.27, 0.63]
Group 2 survivors <6 years				
Total number of hospitalizations	8	6		13
Rate per patient year [95% CI]	1.33 [0.57, 2.62]	1.13 [0.41, 2.46]	ns	1.08 [0.57, 1.84]

CI, confidence interval.
*Difference between 12 months prior to implant and 12 months after implant.

Table 3 Baseline parameters comparing patients who survived from those who did not survive through 6 years post-procedure

	Group 1 survivors >6 years (n = 9)	Group 2 survivors <6 years (n = 6)	*P*-value
Baseline age (years)	71.1 ± 8.4	73.2 ± 3.1	0.75
Male % (n)	55.6 (5)	66.7 (4)	0.58
Ischaemic % (n)	55.6 (5)	33.3(2)	1.00
History of Afib.	55.6 (5)	33.3(2)	1.00
NYHA %(n)			0.09
III	100 (9)	66.7 (4)	
IV	0 (0)	33.3 (2)	
6 min walk distance (m)	352.5 ± 69.2	226.7 ± 68.2	0.01
LVEF (%)	33.0 ± 7.3	22.8 ± 7.3	0.05
LVEDV (mL)	159.3 ± 57.0	154.0 ± 44.3	0.88
Vena contracta (cm)	0.67 ± 0.18	0.66 ± 0.11	0.93
EROA (mm^2)	22 ± 13	21 ± 3	0.95
Regurgitant volume (mL)	35.8 ± 21.3	27.5 ± 3.0	0.46
MR grade % (n)			0.64
2+	62.5 (5)	25.0 (1)	
3+	12.5 (1)	75.0 (3)	
4+	25.0 (2)	0 (0)	

ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; EROA, effective regurgitant orifice area; 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 antagonist; MR, mitral regurgitation; NYHA, New York Heart Association; SD, standard deviation.
Values are ±SD.

long-term follow-up revealed a decrease in the use of beta-blockers over time, from 87.5% to 50% (80% in overall population), although this difference was attenuated if amiodarone use was included—87.5% to 75%. Overall, 64.2% of the entire population was on an ACE inhibitor or angiotensin receptor blocker at baseline. One patient who was not on an ACE inhibitor or angiotensin receptor blocker at baseline was placed on angiotensin receptor-neprilysin inhibition. All but one patient (75%) was on an ACE inhibitor or angiotensin receptor blocker at baseline and remained on one at follow-up (87.5%), with two of those patients switched to angiotensin receptor-neprilysin inhibition. All but one long-term surviving patient required a diuretic at baseline (87.5%), similar to the overall population (86.7%), with only 67.5% requiring a diuretic at follow-up. The use of aldosterone antagonist was low at baseline in the overall population (26.7%) as well as in the long-term cohort (25%) and at follow-up (12.5%).

Discussion

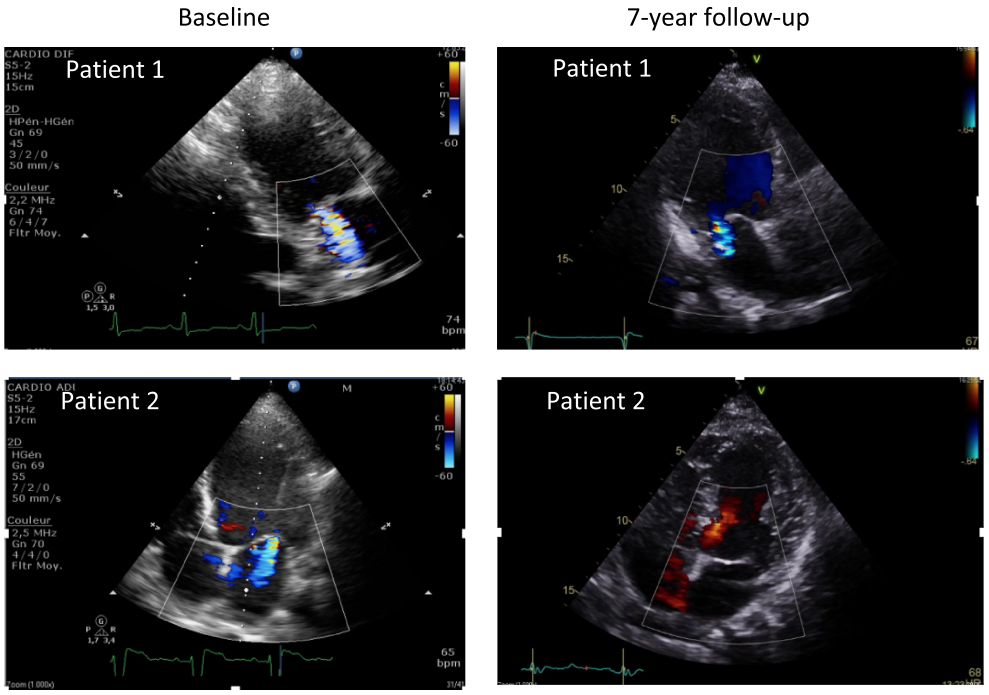
Functional mitral regurgitation (FMR) is common in patients with advanced systolic heart failure.[1,12–15] Despite optimal guideline-directed medical therapy, the prognosis remains poor.[13,14,16] Different transcatheter treatments of FMR have been, or are being, developed.[17,18] The MitraClip device has been evaluated in two large clinical trials with diametrically different results.[2,19] While the MITRA-FR study was neutral, the COAPT trial showed an important reduction in the rate of mortality and hospitalization for heart failure. Several differences in patients selection between these two studies have been pointed out to possibly explain the differences between the observed outcomes.[20–22] These theories remain speculative at this time, and it is unclear if the assumptions in those theories are translatable to devices other than MitraClip.

Table 4 12 month parameters comparing patients who survived from those who did not survive through 6 years post-procedure

	Group 1 survivors >6 years (n = 9)	Group 2 survivors <6 years (n = 5)*	P-value
NYHA at 12 months % (n)			0.05
I	22.2 (2)	0 (0)	
II	77.8 (7)	60.0 (3)	
III	0 (0)	40.0 (2)	
6MWD change from baseline (m)	82.5 ± 74.4	98.0 ± 109.4	0.77
LVEF change from baseline (%)	5.2 ± 8.7	2.9 ± 14.7	0.81
LVEDV change from baseline (mL)	−14.3 ± 13.4	−6.7 ± 9.0	0.44
EROA change from baseline (mm^2)	−9.0 ± 5.6	−1.7 ± 1.5	0.02
Regurgitant volume (mL)	−11.3 ± 10.3	−2.7 ± 6.6	0.25
MR Grade at 12 months % (n)			0.04
None or trace	25.0 (2)	0 (0)	
1+	25.0 (2)	0 (0)	
2+	50.0 (4)	50.0 (2)	
3+	0 (0)	50.0 (2)	
4+	0 (0)	0 (0)	

6MWD, 6 min walk distance; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; EROA, effective regurgitant orifice area; 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 antagonist; MR, mitral regurgitation; NYHA, New York Heart Association; SD, standard deviation.
Values are ±SD.
*One patient died prior to 12 month follow-up.

Figure 2 Patients comparing baseline and long-term follow-up echocardiography at 7 years post-procedure demonstrating significantly reduced mitral regurgitation and improved left ventricular function.



The main finding of our study is that 60% of severely symptomatic patients with heart failure and FMR treated by Carillon Mitral Contour System survived for at least 6 years after the procedure and were virtually free of mitral regurgitation at that long-term follow-up. This marked reduction in mitral regurgitation was associated with left ventricular reverse remodelling and clinical improvement as assessed by NYHA class. These results compare favourably with the outcomes of medically treated patients, reported in several recent studies. In several studies evaluating patients treated with medical therapy, the 3–5 year long-term mortality was over 50% in patients with moderate or severe FMR.[12,15,16] In COAPT

and MITRA-FR, the 2 year mortality rate in the medically treated patients were 46% and 34.2%, respectively, with a 55% mortality at 3 years in medically managed patients in COAPT.[2,19,20,23] Thus, the 40% 6 year mortality in the current study appears to be favourable. The observation of only residual mitral regurgitation in survivors at long-term follow-up seems to support the hypothesis that improving mitral regurgitation in FMR may break the vicious cycle of volume overload that the mitral regurgitation is contributing.

It is difficult to compare the outcomes of patients analysed in this study with those included in MITRA-FR and COAPT trials. Patients in this analysis presented with degrees of LV dilation and MR severity between those found in those studies, with larger ventricles on average than in COAPT and more severe MR than in MITRA-FR. In both of the MitraClip studies, the mortality rates remain high even in the treatment arms, suggesting that there may be a role to treat FMR earlier in the disease process. This has been addressed in the recent Carillon studies, and the ongoing CARILLON pivotal study, which include or included patients with 2+ as well as more severe MR.[24] The place of newer medical therapeutics also need to be evaluated in further studies. In particular, the use of angiotensin receptor-neprilysin inhibition was shown to reduce the degree of FMR in patients with heart failure.[25] In our study, 3 of 8 patients were on this drug at long-term follow-up visit. Other medical therapies showed a tendency for reduced medications with follow-up.

Limitations

This study is observational in nature, and the data are being presented to support further and ongoing research. A strong association with favourable remodelling with drug and device therapy and subsequent mortality has been previously demonstrated,[7] and the data presented here are consistent with that finding. However, the numbers are small, and the comparator groups are historical. Patients who did not receive a device despite an attempt were not followed. Unlike patients in the blinded REDUCE FMR trial,[6] patients in this cohort were not blinded nor is there a concurrent control group. Nevertheless, these data support moving forward with the clinically powered CARILLON trial.[24] As noted earlier, changes in medical management could have played a role in the outcomes.

The comparisons of long-term echos in this study were based upon jet area measurements and were not based upon independent core lab measurements of quantitative parameters, although the core lab measurements were used for assessment of echos at baseline through 12 months. However, the long-term echos all demonstrated very mild amounts of residual MR, in a range in which quantitative measurements likely are of lesser importance.

Conclusions

The use of Carillon Mitral Contour System in symptomatic patients with reduced LV function and moderate FMR showed a tendency towards favourable long-term outcomes in terms of mortality, functional status, MR reduction, and LV remodelling as compared with the standard of care strategies from literature based reporting of outcomes.

These encouraging results support and inform the ongoing CARILLON[21] pivotal trial, which will be evaluating 2 year clinical events, including mortality.

Conflict of interest

J.L. has been a proctor for Cardiac Dimensions. T.S. received proctoring fees from Cardiac Dimensions. T.J., S.V., and M.S. are employees of Cardiac Dimensions. S.L.G. is a stockholder and consultant to Cardiac Dimensions, during the conduct of the study; he has received honoraria from Abbott, outside the submitted work.

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References

1. Sannino A, Smith RL 2nd, Schiattarella GG, Trimarco B, Esposito G, Grayburn PA. Survival and cardiovascular outcomes of patients with secondary mitral regurgitation: a systematic review and meta-analysis. *JAMA Cardiol* 2017; **2**: 1130–1139.
2. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ, Investigators C. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018; **79**: 2307–2318.
3. Lipiecki J, Siminiak T, Sievert H, Muller-Ehmsen J, Degen H, Wu JC, Schandrin C, Kalmucki P, Hofmann I, Reuter D, Goldberg SL, Haude M. Coronary sinus-based percutaneous annuloplasty as treatment for functional mitral regurgitation: the TITAN II trial. *OpenHeart* 2016; **3**: e000411.
4. Schofer J, Siminiak T, Haude M, Herrman JP, Vainer J, Wu JC, Levy WC, Mauri L, Feldman T, Kwong RY, Kaye

DM, Duffy SJ, Tubler T, Degen H, Brandt MC, Van Bibber R, Goldberg S, Reuter DG, Hoppe UC. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. *Circulation* 2009; **120**: 326–333.
5. Siminiak T, Wu JC, Haude M, Hoppe UC, Sadowski J, Lipiecki J, Fajadet J, Shah AM, Feldman T, Kaye DM, Goldberg SL, Levy WC, Solomon SD, Reuter DG. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN trial. *Eur J Heart Fail* 2012; **14**: 931–938.
6. Witte KK, Lipiecki J, Siminiak T, Meredith IT, Malkin CJ, Goldberg SL, Stark MA, von Bardeleben RS, Cremer PC, Jaber WA, Celermajer DS, Kaye DM, Sievert H. The REDUCE FMR trial: a randomized sham-controlled study of percutaneous mitral annuloplasty in functional mitral regurgitation. *JACC Heart Fail* 2019; **7**: 945–955.
7. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. *JACC Cardiovasc Imaging* 2011; **4**: 98–108.
8. 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.
9. Aimo A, Gaggin HK, Barison A, Emdin M, Januzzi JL Jr. Imaging, biomarker, and clinical predictors of cardiac remodeling in heart failure with reduced ejection fraction. *JACC Heart Fail* 2019; **7**: 782–794.
10. Lipiecki J, Kaye DM, Witte KK, Haude M, Kapadia S, Sievert H, Goldberg SL, Levy WC, Siminiak T. Long-term survival following transcatheter mitral valve repair: pooled analysis of prospective trials with the Carillon device. *Cardiovasc Revasc Med* 2020; **21**: 712–716.
11. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Shernan S, Thavendiranathan P, Thomas JD, Weissman NJ. 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**: 303–371.
12. Goliasch G, Bartko PE, Pavo N, Neuhold S, Wurm R, Mascherbauer J, Lang IM, Strunk G, Hulsmann M. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *Eur Heart J* 2018; **39**: 39–46.
13. Agricola E, Ielasi A, Oppizzi M, Faggiano P, Ferri L, Calabrese A, Vizzardi E, Alfieri O, Margonato A. Long-term prognosis of medically treated patients with functional mitral regurgitation and left ventricular dysfunction. *Eur J Heart Fail* 2009; **11**: 581–587.
14. De la Espriella R, Santas E, Minana G, Bodi V, Valero E, Paya R, Nunez E, Paya A, Chorro FJ, Bayes-Genis A, Sanchis J, Nunez J. Functional mitral regurgitation predicts short-term adverse events in patients with acute heart failure and reduced left ventricular ejection fraction. *Am J Cardiol* 2017; **120**: 1344–1348.
15. Kortlandt F, Velu J, Schurer R, Van den Branden B, Bouma B, Kelder J, Eefting F, Swaans M, Rensing B, Baan J Jr, Van der Heyden J. Impact of mitral valve treatment choice on mortality according to aetiology. *EuroIntervention* 2019; **14**: 1733–1739.
16. Goel SS, Bajaj N, Aggarwal B, Gupta S, Poddar KL, Ige M, Bdair H, Anabtawi A, Rahim S, Whitlow PL, Tuzcu EM, Griffin BP, Stewart WJ, Gillinov M, Blackstone EH, Smedira NG, Oliveira GH, Barzilai B, Menon V, Kapadia SR. Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine the potential role of MitraClip for this unmet need. *J Am Coll Cardiol* 2014; **63**: 185–186.
17. Feldman T, Mehta A, Guerrero M, Levisay JP, Salinger MH. MitraClip therapy for mitral regurgitation: secondary mitral regurgitation. *Interv Cardiol Clin* 2016; **5**: 83–91.
18. Klein P, Anker SD, Wechsler A, Skalsky I, Neuzil P, Annest LS, Bifi M, McDonagh T, Frerker C, Schmidt T, Sievert H, Demaria AN, Kelle S. Less invasive ventricular reconstruction for ischaemic heart failure. *Eur J Heart Fail* 2019; **21**: 1638–1650.
19. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie D, Nejjari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N, Investigators M-F. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018; **379**: 2297–2306.
20. 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. *JACC Cardiovasc Imaging* 2019; **12**: 353–362.
21. Pibarot P, Delgado V, Bax JJ. MITRA-FR vs. COAPT: lessons from two trials with diametrically opposed results. *Eur Heart J Cardiovasc Imaging* 2019; **20**: 620–624.
22. Praz F, Grasso C, Taramasso M, Baumbach A, Piazza N, Tamburino C, Windecker S, Maisano F, Prendergast B. Mitral regurgitation in heart failure: time for a rethink. *Eur Heart J* 2019; **40**: 2189–2193.
23. Mack M, Abraham WT, Lindenfeld J, Stone GW, Investigators TC. 3-year outcomes from a randomized trial of the MitraClip in patients with heart failure and severe secondary mitral regurgitation. *TCTMDorg* 2019.
24. NCT03142152 CgI. The CARILLON trial —assessment of the Carillon® Mitral Contour System® in treating functional mitral regurgitation associated with heart failure.
25. Kang DH, Park SJ, Shin SH, Hong GR, Lee S, Kim MS, Yun SC, Song JM, Park SW, Kim JJ. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. *Circulation* 2019; **139**: 1354–1365.