Treating symptoms and reversing remodelling: clinical and echocardiographic 1-year outcomes with percutaneous mitral annuloplasty for mild to moderate secondary mitral regurgitation

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Aims
To determine the effects of percutaneous mitral annuloplasty on symptoms, walk distance and left ventricular (LV) structure and function in patients with mild or moderate secondary mitral regurgitation (SMR).

Methods and results
This was a pooled analysis of patients (n = 68) who, despite guideline-directed medical therapy had symptomatic heart failure (HF) with mild (n = 25) or moderate (n = 43) SMR treated with percutaneous mitral annuloplasty as part of the TITAN, TITAN II, or REDUCE-FMR trials. Primary outcomes were changes in symptoms, 6-min walk distance, and quality of life assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) after 1 year. Secondary analyses included changes in LV structure and function. At 1 year, New York Heart Association class status was maintained (48%) or improved (46%) in most patients, mean KCCQ scores increased from baseline by 10 units [95% confidence interval (CI) 3 to 17; P < 0.01] and mean 6-min walk test distance increased by 34 m (95% CI 12 to 57; P < 0.01). SMR grade improved in 25% of patients and was maintained in 58% of patients with changes in mean regurgitant volume of −7 mL (95% CI −11 to −3; P < 0.001), vena contracta −0.11 cm (95% CI −0.20 to −0.02; P < 0.05), and effective regurgitant orifice area −0.03 cm² (95% CI −0.06 to −0.01; P < 0.05). There were non-significant improvements in LV ejection fraction and volumes. Survival over 1 year was 89% with no difference between mild (96%) and moderate (86%) SMR (log-rank P = 0.22). Progression-free survival was 70% (82% in mild vs. 63% in moderate SMR; P = 0.16). Freedom from HF hospitalization was 73% (87% in mild SMR vs. 66% in moderate SMR; P = 0.07).

Conclusion
Among patients with symptomatic HF and mild or moderate SMR on guideline-directed medical therapy, percutaneous mitral annuloplasty was associated with improvements in symptoms, SMR, a stabilization of LV structure and function, and high survival rates.

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Graphical Abstract

Mild-moderate SMR in HFrEF

Associated with progressive:
- Symptoms
- Exercise intolerance
- LV remodeling
- Hospitalisation risk
- Mortality risk

Future approach?

Associated with improvements in:
- Symptoms
- Exercise intolerance
- LV remodeling
- Hospitalisation risk
- Mortality risk

The adverse effects of untreated mitral regurgitation in patients with heart failure with reduced ejection fraction (HFrEF) and the possible effects with earlier percutaneous treatment. LV, left ventricular; SMR, secondary mitral regurgitation.

Keywords
- Carillon
- Heart failure
- Indirect mitral annuloplasty
- Mitral regurgitation
- Survival

Introduction

Secondary mitral regurgitation (SMR) in the presence of left ventricular (LV) systolic dysfunction is directly associated with adverse outcomes, including mortality.\(^1\) Even patients with mild SMR have a higher risk of hospitalization and mortality compared to those without SMR. However, despite this knowledge and consistent data that early medical and cardiac implantable electronic device treatment in heart failure with reduced ejection fraction (HFrEF) improves outcomes,\(^2\) patients with less severe mitral regurgitation (MR) have thus far received little attention regarding treatment.

There are specific challenges to studying and treating patients with milder forms of SMR, despite the recognition of increased risk. From a mechanistic perspective, those with mild SMR have less room for improvement. Moreover, the lesser degree of ventricular and atrial remodelling at baseline and slower progression means that showing improvement or even a stabilization of progression are both more difficult compared to patients with more severe SMR. Identifying a modification of disease progression in clinical trials addressing earlier stages of the disease therefore requires longer patient follow-up and a larger sample size, although this can be somewhat compensated for by true blinding. From a recruitment perspective, there may also be a lack of drive to enrol those less sick into a device study due to perceived procedural risk. Hence, the design of a study to explore the hypothesis that treating patients with mild SMR is a safe ‘preventative’ strategy for progressive disease requires a careful assessment of existing data to identify a population at risk of deterioration in whom any procedural risk might be more acceptable.

Percutaneous mitral annuloplasty is a novel treatment for SMR in which a device is placed into the coronary sinus to reduce its diameter and allow approximation of the mitral valve leaflets\(^3\) to reduce SMR severity. Studies of percutaneous mitral annuloplasty for SMR are unique since in addition to patients with severe SMR, they also included patients with milder degrees of SMR. Three of these studies, TITAN,\(^4\) TITAN II\(^5\) and REDUCE FMR\(^6\) have follow-up to at least 1 year. The aim of this analysis was to present a post-hoc pooled analysis of the 1-year outcomes in patients with mild or moderate SMR treated with percutaneous mitral annuloplasty.

Methods

This is a pooled analysis of patients with mild or moderate SMR treated with a percutaneous mitral annuloplasty procedure utilizing the coronary sinus-based Carillon device (Cardiac Dimensions, Kirkland, WA, USA) in the TITAN, TITAN II, and REDUCE FMR trials. Ethics committees at each site approved the protocols of each trial, all patients provided written informed consent, and study procedures complied with the Declaration of Helsinki.

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Patient eligibility in these trials specified ongoing symptomatic heart failure with LV systolic dysfunction, despite guideline-directed medical therapy. Patients with class 1 indications for cardiac resynchronization therapy, or with an LV lead in place, were excluded due to the shared coronary sinus space used by mitral annuloplasty. All three trials targeted enrollment to patients with grade 2+ to 4+ MR. In TITAN and TITAN II the echo core laboratory pre-screened patients and excluded patients with 1+ SMR. REDUCE FMR was designed as a pragmatic trial and local investigators decided upon eligibility. Blinded core echocardiography laboratory analysis was undertaken only at study end, revealing that several enrolled patients actually had 1+ SMR. Additional inclusion criteria for all trials were LV enlargement defined as >5.5 cm LV end-diastolic diameter and reduced ejection fraction (<40% in TITAN and TITAN II; <50% in REDUCE FMR).

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. The protocols and complete eligibility criteria have been published previously.

The pooled dataset included baseline patient characteristics and secondary, echocardiographic, and vital status results at 1 year of follow-up. Baseline patient characteristics were summarized with the mean and standard deviation for continuous outcomes and counts and percentage for categorical outcomes. Changes in patient outcomes over 1 year relative to baseline were analysed with paired-samples t-tests and presented with 95% confidence intervals (CI). Fisher’s exact test was used for group comparison of categorical outcomes. Survival and freedom from heart failure hospitalization were analysed using Kaplan–Meier methods. Treatment success as a binary outcome variable was characterized by progression-free survival, defined as survival at 1 year without an increase in SMR grade. The association of baseline patient characteristics and echocardiographic results with progression-free survival was analysed with univariable logistic regression and reported as an odds ratio (OR) and 95% CI. Variables that entered the model at $P < 0.10$ were included in a multivariable model. Although this was a post-hoc analysis, we performed significance testing for information using a $P < 0.05$ to represent statistical significance. All tests were two-sided. Statistical analyses were performed using Stata v16 (StataCorp, College Station, TX, USA).

### Results

The pooled dataset of the three studies included 68 patients treated with percutaneous mitral annuloplasty (52 of whom had been part of REDUCE FMR, 7 had been in TITAN and 9 in TITAN II). Of these patients, 25 had mild and 43 moderate SMR. This represented 51% of device-treated patients enrolled in these trials. The mean patient age was 69 ± 9 years, 75% were male, and HFrEF was predominantly of ischaemic aetiology (68%). All patients were classified as New York Heart Association (NYHA) functional class II (35%) or III (65%). The mean LV ejection fraction at baseline was 32 ± 8% and LV end-diastolic diameter was 6.5 ± 0.8 cm (Table 1). Table 1 also shows medical therapy at baseline which was commensurate with guidelines for medical therapy for HFrEF at the time of studies.

| Table 1 Baseline patient characteristics |
|------------------------------------------|
| Characteristic                           |
| Demographics                            |
| Age (years) 69 ± 9                       |
| Male sex 75% (51/68)                     |
| Body mass index (kg/m²) 27 ± 5           |
| Medical history                          |
| Ischaemic aetiology 68% (46/68)          |
| Prior myocardial infarction 50% (34/68)  |
| Atrial fibrillation 46% (31/68)          |
| Diabetes mellitus 26% (18/68)            |
| Patients with a heart failure hospitalization in 12 months prior to enrolment 51% (35/68) |
| LV variables                            |
| LV ejection fraction (%) 32 ± 8          |
| LV end-diastolic diameter (cm) 6.5 ± 0.8 |
| LV end-systolic diameter (cm) 5.5 ± 0.9  |
| LV end-diastolic volume (mL) 175 ± 61    |
| LV ejection fraction (%) 32 ± 8          |
| LV end-diastolic volume (mL) 122 ± 53    |
| Mitral valve variables                   |
| Regurgitant volume (mL) 27 ± 14          |
| Vena contracta (cm) 0.42 ± 0.14          |
| EROA (cm²) 0.18 ± 0.09                   |
| MR grade                                 |
| 1 37% (25/68)                            |
| 2 63% (43/68)                            |

Values are mean ± SD for continuous variables and (n) or percentage (n/N) for categorical data.

SMR also had a lower prevalence of atrial fibrillation ($P = 0.03$), worse NYHA scores ($P = 0.009$), and lower ejection fraction ($P = 0.03$) (online supplementary Table S1).

Procedural device-related safety events occurred in two patients. In one patient, a branch of the circumflex artery was compressed by the device. The compression was judged to be non-significant at the time of procedure; however, the patient developed coronary spasm with electrocardiographic changes 1 day post-procedure. The patient continued in the study through 1-year follow-up with...
only one further occurrence of angina judged to be due to coronary spasm and treated with medical therapy. The other patient with a safety event had troponin elevation following the procedure, but without clinical evidence of myocardial infarction, which did not require intervention.

During the follow-up period, 7 patients died, and 4 withdrew consent, leaving 57 who returned for the 1-year follow-up visit. As appropriate for patients in whom optimal medical therapy was a requirement of enrolment, medical therapy was unchanged during follow-up in the majority of patients with only five patients either discontinuing or adding a drug category. Four patients discontinued any class of drug (two stopping their diuretic, one stopping their beta-blocker, and one stopping both beta-blocker and angiotensin-converting enzyme inhibitor). In one patient, previously deemed to be intolerant, a beta-blocker was added.

There were statistically significant decreases in regurgitant volume (−7 mL; 95% CI −11 to −3; \(P < 0.001\)) (Figure 1A), vena contracta (−0.11 cm; 95% CI −0.20 to 0.02; \(P < 0.05\)), and EROA (−0.03 cm²; 95% CI −0.06 to −0.01; \(P < 0.05\)). SMR grade improved in 25% of patients and was maintained in 58% of patients (Table 2). There was no progression in LV dysfunction; rather a trend to reverse remodelling and a significant reduction in LV end-systolic diameter relative to baseline (Table 2).

Functional status by NYHA classification significantly improved at 1 year from baseline (\(P < 0.001\)). Statistically and clinically significant improvements in both 6-min walk test distance and Kansas City Cardiomyopathy Questionnaire were also observed as soon as 1 month post-procedure and were maintained throughout follow-up (Figure 2 and Table 2). Relative to the mild SMR group, those with moderate SMR were more likely to experience an improvement in NYHA status (\(P < 0.01\)) and MR grade (\(P = 0.01\)) (online supplementary Table S2). LV structural and secondary changes are shown in Figure 1B–D.

In the present dataset, survival was not significantly different between those with mild SMR (95.8%) and moderate SMR (85.6%) (log-rank \(P = 0.22\)) (Figure 3). Progression-free survival (survival at 1 year without an increase in MR grade), was 70% overall; 82% in those with mild SMR and 63% in those with moderate SMR (\(P = 0.16\)). Freedom from heart failure hospitalization was 73.3% over 1 year with no significant differences between the mild and moderate SMR groups (86.5% vs. 66.0%; log-rank \(P = 0.07\)).

The number of patients with any heart failure hospitalization in the 12-month period following device implant was significantly lower than those experiencing a heart failure hospitalization in the 12 months prior to the procedure (29.4% vs. 51.4%; \(P = 0.01\)).

In a univariable logistic regression model, baseline variables that were associated with better progression-free survival were lower NYHA class (\(P = 0.10\)), lower regurgitant volume (\(P = 0.02\), and lower EROA (\(P = 0.02\)). In the multivariable model, the

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Figure 1 Structural and functional changes over 1 year following implantation. Mean (95% confidence intervals) for (A) regurgitant volume, (B) left ventricular (LV) end-diastolic volume, (C) LV ejection fraction and (D) LV end-systolic volume at 1, 6 and 12 months after device implantation.
Table 2  Change in secondary and echocardiographic parameters with indirect annuloplasty at 1 year vs. baseline*

| Characteristic                  | NYHA class | Clinical status |
|---------------------------------|------------|-----------------|
|                                 | −0.5 (−0.7, −0.3)** | Improvement 46% (26/56) |
|                                 | −0.5 (−0.7, −0.3)** | No change 48% (27/56) |
|                                 | 5% (3/56) | Worsening 5% (3/56) |
| Left atrial variables           | 34 (12, 57)** | 6-min walk distance (m) |
| Left atrial volume (mL)         | 10 (3.17)** | KCCQ (units) |

| LV variables                    | 1 (−2, 4) | LV ejection fraction (%) |
|                                 | −0.1 (−0.3, 0) | LV end-diastolic diameter (cm) |
|                                 | −0.2 (−0.4, −0.1)** | LV end-systolic diameter (cm) |
|                                 | −6 (−19, 7) | LV end-diastolic volume (mL) |
|                                 | −5 (−16, 7) | LV end-systolic volume (mL) |

| Mitral valve variables          | −7 (−11, −3)** | Regurgitant volume (mL) |
|                                 | −0.11 (−0.20, −0.02)* | Vena contracta (cm) |
|                                 | −0.03 (−0.06, −0.01)* | EROA (cm²) |
|                                 | −0.1 (−0.3, 0.1) | MR grade |
|                                 | 25% (13/53) | Improvement 25% (13/53) |
|                                 | 58% (31/53) | No change 58% (31/53) |
|                                 | 17% (9/53) | Worsening 17% (9/53) |

Values are mean change (95% confidence interval) for continuous variables, or percentage (n/N) for categorical data.
EROA, effective regurgitant orifice area; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; MR, mitral regurgitation; NYHA, New York Heart Association.
*P < 0.05 for change vs. baseline.
**P < 0.001 for change vs. baseline.
***P < 0.01 for change vs. baseline.

Discussion

The present data provide the strongest data to date that, in patients with HFrEF with mild or moderate SMR, a transcatheter annular approach can safely reduce SMR and that doing this improves symptoms, exercise tolerance and quality of life and might also attenuate LV remodelling. This finding has potential implications for the large number of patients with less severe SMR that are currently not eligible for percutaneous leaflet clipping. Whether these improvements in surrogate endpoints translate to long-term modification of disease progression requires further work including larger studies and longer follow-up given the background that many other treatments for HFrEF, when applied early, are consistently associated with long-term benefits on outcomes.

The current data complement the results of previous studies demonstrating improvements in echocardiographic and clinical outcomes following percutaneous mitral annuloplasty in patients with, on average, moderate to severe SMR. However, SMR is associated with worse outcomes even when mild. Furthermore, the development of SMR is part of a vicious cycle, whereby SMR leads to further LV dilatation, which in turn results in worsening SMR. Arresting this cycle early on may interrupt a key component of cardiac...
Figure 3  Survival over 1 year with the Carillon device in patients with mitral regurgitation (MR) grade 1 or 2. The survival rate at 1 year was 89.3% [standard error (SE) 3.8%] among all patients and 95.8% (SE 4.1%) vs. 85.6% (SE 5.4%) comparing MR grades 1 vs. 2 (log-rank \( P = 0.22 \)).

Table 3  Association of baseline characteristics with progression-free survival at 1 year

| Variable                        | Unit of measure          | Odds ratio | 95% CI          | P-value |
|---------------------------------|--------------------------|------------|-----------------|---------|
| **Univariable analysis**        |                          |            |                 |         |
| Age                             | Per 5-year decrease      | 1.24       | 0.87, 1.76      | 0.24    |
| Sex                             | Female vs. male          | 1.24       | 0.34, 4.59      | 0.75    |
| Body mass index (kg/m\(^2\))   | Per 5 kg/m\(^2\) increase| 1.23       | 0.71, 2.11      | 0.46    |
| **Medical history**             |                          |            |                 |         |
| Ischaemic aetiology             | No vs. yes               | 3.08       | 0.77, 12.3      | 0.11    |
| Myocardial infarction           | No vs. yes               | 2.10       | 0.68, 6.47      | 0.20    |
| Atrial fibrillation             | Yes vs. no               | 2.20       | 0.70, 6.96      | 0.18    |
| Diabetes mellitus               | No vs. yes               | 1.23       | 0.35, 4.31      | 0.75    |
| **Functional status**           |                          |            |                 |         |
| NYHA class                      | II vs. III               | 2.89       | 0.81, 10.3      | 0.10    |
| 6-min walk distance             | Per 100 m increase       | 1.31       | 0.71, 2.41      | 0.39    |
| **Left atrial variables**       |                          |            |                 |         |
| Left atrial volume              | Per 50 mL increase       | 1.10       | 0.55, 2.23      | 0.78    |
| **LV variables**                |                          |            |                 |         |
| LV ejection fraction            | Per 5% increase          | 1.33       | 0.90, 1.95      | 0.15    |
| LV end-diastolic diameter       | Per 1 cm decrease        | 1.31       | 0.67, 2.59      | 0.43    |
| LV end-systolic diameter        | Per 1 cm decrease        | 1.28       | 0.70, 2.35      | 0.41    |
| LV end-diastolic volume         | Per 50 mL decrease       | 1.36       | 0.81, 2.29      | 0.24    |
| LV end-systolic volume          | Per 50 mL decrease       | 1.56       | 0.85, 2.84      | 0.15    |
| **Mitral valve variables**      |                          |            |                 |         |
| Regurgitant volume              | Per 10 mL decrease       | 1.84       | 1.12, 3.02      | 0.02    |
| Vena contracta                  | Per 0.1 cm increase      | 1.04       | 0.65, 1.66      | 0.87    |
| EROA                            | Per 0.1 cm\(^2\) decrease| 3.00       | 1.21, 7.39      | 0.02    |
| MR grade                        | 1 vs. 2                  | 2.62       | 0.74, 9.33      | 0.14    |
| **Multivariable analysis**      |                          |            |                 |         |
| EROA                            | Per 0.1 cm\(^2\) decrease| 3.00       | 1.21, 7.39      | 0.02    |

CI, confidence interval; EROA, effective regurgitant orifice area; LV, left ventricular; MR, mitral regurgitation; NYHA, New York Heart Association.
deterioration in patients with cardiomyopathy and may play a major role in stabilization of the disease process. Current guidelines, based upon the available evidence, focus on patients with severe SMR stating that mitral valve repair or replacement may be considered for severely symptomatic patients. Due to lacking data, there is little discussion regarding the potential for disease modification and the prevention of progression in patients with lesser degrees of SMR, despite the worse prognosis compared to patients with no SMR. Whether a diagnosis of mild or moderate MR warrants transcatheter or surgical treatment is a topic of debate. What is clear is that early medical and cardiac implantable electronic device treatments demonstrate accumulating benefits over time, primarily in a slowing of progression in patients when treated early, which suggests that early treatment for SMR deserves careful study as well. A key question is to identify those patients in whom SMR is likely to contribute to longer-term deterioration. This will require carefully collected large longitudinal observational datasets, as well as evidence that early treatment is feasible, safe, and delays deterioration. This is therefore the first dataset to explore this hypothesis of the potential benefits of targeted early treatment prior to clinical deterioration.

Our analysis suggests that percutaneous mitral annuloplasty in patients with mild or moderate MR is feasible and safe. After 12 months of follow-up, there were improvements in NYHA class and 6-min walk distance, and quality of life. There were also reductions in MR as evidenced by changes in regurgitant volume, vena contracta, and EROA. As anticipated, the magnitude of these changes was less in those with mild vs. moderate SMR but, judging by the concurrent improvements in patient-oriented endpoints, seem nonetheless clinically significant. Given the modest improvements in MR yet equivalent improvements in clinical variables compared to previous datasets, it is possible that especially in this population the device limits exercise-induced worsening of MR. These results suggest that percutaneous mitral annuloplasty may be an effective treatment to provide symptomatic relief in even mild or moderate MR. These data, including the presented survival data, may be used for hypothesis generation in the design and statistical powering of future studies.

The challenge with any treatment for HFrEF is the balance of the risks of interventions to reduce SMR with the risks of untreated SMR over the patient’s lifetime. The advent of percutaneous treatments with lower upfront risk, has facilitated explorations of the potential lifetime benefits of earlier treatment. Future study designs need to consider the lower event rate in patients with lesser degrees of SMR and the need therefore for high levels of safety of the device, larger sample sizes with longer follow-up, and true blinding. The definitive studies will also need to focus on clinical outcomes consequent to disease progression rather than improvements of surrogate endpoints.

**Limitations**

This is the first study to describe the outcomes of patients with mild or moderate MR treated with a device to reduce SMR. There are, however, several limitations beyond the uncontrolled, observational nature of the data. First, these results represent data collected at 1 year of follow-up and extended follow-up is needed to characterize the long-term safety and effectiveness of this treatment approach in patients with less severe SMR. Second, comparisons of these results to those with other therapies in patients with mild or moderate MR should be made cautiously owing to possible differences in indications, patient characteristics, and echocardiographic protocols. Third, the sample size in each group was small such that the results should be considered primarily as hypothesis-generating for planning future prospective controlled studies. Fourth, of the included studies, only the randomized, sham-controlled REDUCE PMR study had an untreated (control) arm including 18 patients fulfilling the criteria for inclusion in this post-hoc analysis. An exploratory analysis of outcomes in this group described survival at 1 year of 80.8% compared with a 1-year survival of 89.3% in those allocated the device (data not shown). Such a survival analysis is only hypothesis stimulating but could help power future studies in this group. Fifth, given the pragmatic design of the studies and their focus on structural changes and patient-oriented outcomes, we did not routinely measure plasma-based biomarkers. Finally, MR assessment was undertaken at rest. Stress echocardiography was not performed during these studies. Future studies in those with milder forms of MR could explore whether patients with stress-induced worsening of MR have a greater gain from intervention than those in whom mild MR does not deteriorate with stress.

**Conclusions**

Among patients with HFrEF and mild or moderate SMR who were symptomatic despite guideline-directed medical therapy, and would not be indicated for currently approved percutaneous treatments, percutaneous mitral annuloplasty is associated with few complications, and could lead to improvements in clinical status and SMR parameters, and a stabilization of LV remodelling.

**Supplementary Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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