Long-term clinical and haemodynamic results after transcatheter annuloplasty for secondary mitral regurgitation

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Abstract

Aims The study sought to investigate the long-term outcome after transcatheter mitral valve annuloplasty for secondary mitral regurgitation (MR).

Methods and results Consecutive patients with symptomatic secondary MR undergoing transcatheter mitral valve annuloplasty with the Carillon device at Leipzig University Hospital between 2012 and 2018 were studied prospectively. Left ventricular (LV) function and MR severity were quantified by standardized echocardiography. 33 patients were included. Mean age was 75 ± 10 years, and 20 patients were women. A Society of Thoracic Surgeons score of 8.1 ± 7.2% indicated high-risk status. In 24 patients, MR resulted from LV remodelling and dysfunction, eight suffered from left atrial dilatation, and one patient had MR due to combined primary and secondary aetiology. LV ejection fraction at baseline was (median) 38% [inter-quartile range (IQR) 30–49%]. During the mean follow-up time of 45 ± 20 months, 17 patients died, two patients withdrew consent, and four patients were lost. Of the remaining patients, four were hospitalized for decompensated heart failure. Two of these patients underwent additional transcatheter edge-to-edge mitral valve repair. At follow-up, New York Heart Association (NYHA) functional class improved from 95% in Class III/IV at baseline to 70% in Class I/II with no patients in NYHA Class IV (P < 0.0001). Mitral regurgitant volume was reduced from 27 mL (IQR 25–42 mL) to 8 mL (IQR 3–17 mL) (P = 0.018) and regurgitant fraction from 42% (IQR 34–54%) to 11% (IQR 8–24%) (P = 0.014). LV end-diastolic volume index [92 mL/m² (IQR 74–107 mL/m²)] vs. 67 mL/m² (IQR 46–101 mL/m²), P = 0.065] and end-systolic volume index [50 mL/m² (IQR 44–69 mL/m²)] vs. 32 mL/m² (IQR 20–53 mL/m²), P = 0.037] decreased. Total stroke volume remained unchanged [38 mL/m² (IQR 33–43 mL/m²)] vs. 33 mL/m² (IQR 26–44 mL/m²), P = 0.695], while LV ejection fraction increased [43% (IQR 35–49%) vs. 54% (IQR 46–57%), P = 0.014]. Forward stroke volume, heart rate, and forward cardiac output were not significantly altered.

Conclusions Among high-risk patients undergoing transcatheter mitral valve annuloplasty for symptomatic secondary MR, mortality was ~50% at 4 years. In the surviving patients, reduced MR severity was associated with reduced NYHA functional class, reverse LV remodelling, and improved LV function.

Keywords Secondary mitral regurgitation; Mitral valve repair; Annuloplasty; Heart failure

Introduction

Mitrail regurgitation (MR) is the most common valvular heart disease. While primary MR results from structural valve disease, secondary MR is caused by left ventricular (LV) dilatation and/or dysfunction, or left atrial (LA) dilatation. Secondary MR contributes to morbidity and mortality and impairs survival in chronic heart failure. Treatment of secondary MR is primary based on the underlying aetiology, that is, guideline-directed medical therapy for heart failure. However, severe secondary MR imposes a volume load on the LV and the LA, which contributes itself to haemodynamic
deterioration, that is, congestion, heart failure symptoms, and cardiac decompensation. This pathophysiological concept is the basis for structural interventions on the mitral valve for secondary MR to prevent the progression of heart failure. A frequent mechanism of secondary MR is mitral annulus dilatation, caused by either LV or LA dilatation, precluding central leaflet coaptation. Mitral annulus dilatation can be treated with annuloplasty. Prognostic data for surgical mitral annuloplasty are lacking. Thus, a majority of the patients with severe secondary MR are not referred for mitral valve surgery, probably because most of them are high-risk patients due to the underlying heart failure and extracardiac comorbidities. Therefore, transcatheter techniques for mitral valve annuloplasty have been developed.

The Carillon contour system is a transcatheter mitral valve annuloplasty (TMVA) fixed-length device with a double anchor, which is implanted in the coronary sinus surrounding the mitral annulus. Thereby, the annulus becomes strengthened and leaflet adaptation improved. Hence, it affects directly the underlying mitral annulus dilatation. Small studies and meta-analysis have demonstrated both short-term and midterm reduction of MR severity, functional improvement, and reverse LV remodelling. Survival has been reported up to 6 years after TMVA, but the long-term effects on symptoms, mitral valve, and LV function are unknown. The aim of the present study was to investigate the long-term clinical and haemodynamic outcome after TMVA in a real-world patient population.

Methods

Patient population and mitral valve intervention

Consecutive patients who underwent TMVA for symptomatic secondary MR with the Carillon system between 2012 and 2018 at the University Hospital Leipzig were included in the study for prospective follow-up. The indication for TMVA was consented by the interdisciplinary heart team based on the clinical history, symptoms, co-morbidities, and mitral valve morphology and regurgitation severity at the time of index admission for symptomatic heart failure. TMVA was performed under general anaesthesia and transoesophageal echocardiographic guiding, as described recently. Patients gave written informed consent. The investigation conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee (No. 488/18-ek).

Endpoints

Clinical endpoints were all-cause mortality, heart failure hospitalizations, and additional mitral valve procedures. The main echocardiographic endpoints were MR severity (measured as regurgitant volume and regurgitant fraction), LV remodelling (i.e. LV end-systolic and end-diastolic volume index), and LV function (LV ejection fraction, forward ejection fraction, and forward cardiac index) on latest available follow-up.

Echocardiography

Baseline echocardiography was performed using Vivid E9 or E95 (GE Vingmed Ultrasound, Horten, Norway) prior to TMVA in a compensated cardiorespiratory condition, determined by the absence of signs and symptoms of congestion (i.e. pulmonary rales, orthopnoea, jugular venous dilatation, and peripheral oedema). Follow-up echocardiography was performed 45 ± 20 months (mean ± standard deviation) after TMVA. Data acquisition was carried out by an experienced echocardiographer. Analysis was conducted offline using the EchoPAC software (GE Vingmed Ultrasound). Standardized echocardiographic analysis included parasternal short-axis and long-axis views; apical long-axis (three-chamber), four-chamber, and two-chamber views; and subcostal view with M-mode, 2D, colour Doppler, Doppler, and tissue Doppler techniques according to the current recommendations. Survival has been reported up to 6 years after TMVA, but the long-term effects on symptoms, mitral valve, and LV function are unknown. The aim of the present study was to investigate the long-term clinical and haemodynamic outcome after TMVA in a real-world patient population.
proximal isovelocity surface area (PISA) method were measured as recommended. Supporting Information, Figure S1 (Figure legend: Data S1) summarizes quantitative MR assessment. Echocardiographic analysis of the acute effects of TMVA in a subset of those patients was reported recently.  

Statistical analysis

Categorical data were presented as absolute (%) values and continuous variables as median (with inter-quartile range). Comparisons of continuous variables between two groups were performed using the paired Wilcoxon rank-sum test or the unpaired Mann–Whitney U test, as appropriate. Categorical variables were compared using the $\chi^2$ test. Survival between groups was compared with log-rank test. Hazard ratios for survival were examined using the Cox proportional regression analysis. Multivariable adjustment was performed for age, sex, and parameters with a $P$ value <0.1 in the univariable analysis. Statistical analysis was performed with SPSS Version 25 (SPSS, Chicago, IL) and GraphPad Prism Version 6 (GraphPad Software, La Jolla, CA). Statistical significance was considered at a two-sided $P$ value <0.05.

Results

Baseline characteristics

Thirty-three consecutive patients who underwent TMVA were included. The baseline characteristics of the patients are presented in Table 1. Mean age was 75 years, and 61% were women. One patient had combined primary and secondary aetiology of MR, and 32 patients suffered from secondary MR. Of those, eight were due to atrial remodelling and 24 due to LV remodelling and dysfunction. Patients were in New York Heart Association (NYHA) Functional Classes II–IV and had an elevated N-terminal pro-brain natriuretic peptide of (median) 7037 pg/mL (inter-quartile range 2341–29 152 pg/mL). The majority of patients were on guideline-directed heart failure therapy with beta-blockers, renin–angiotensin system inhibitors, and diuretics. High-risk status for mitral valve surgery was determined by a (mean) Society of Thoracic Surgeons score of 8.1% and a EuroSCORE II of 15.8%.

Atrial vs. ventricular mitral regurgitation

Table 2 shows the baseline echocardiographic parameters. Overall, left ventricles were dilated with increased LV mass and reduced LVEF and cardiac index. Both LA volume and systolic pulmonary artery pressure were elevated.

All patients with atrial MR exhibited atrial fibrillation. Atrial MR patients had smaller LV end-diastolic and end-systolic volumes and preserved LVEF with a similar total stroke volume index compared with patients with ventricular MR. The regurgitant volume and regurgitant fraction were comparable between groups. Effective regurgitant orifice area was smaller in atrial vs. ventricular MR. Eight patients had eccentric MR jets, similarly distributed between ventricular and atrial MR. Posterior mitral annulus calcification was present in two patients.

Clinical outcome

At follow-up after (mean ± standard deviation) 45 ± 20 months, 17 patients (52%) were dead (Table 3 and Figure 1A). Of those, 13 patients had MR due to ventricular remodelling, three due to atrial remodelling and one due to combined aetiology. Mortality was similar in patients with atrial and ventricular MR (Figure 1B). Four patients were hospitalized for an episode of symptomatic heart failure; two of these
LV remodelling and systolic function
Blood pressure was similar at baseline and at follow-up. Both NYHA functional class and MR severity were improved at follow-up (NYHA functional class and MR severity were improved at follow-up (Figure 2)). Regurgitant volume and regurgitant fraction were reduced (Table 5). This was associated with decreased end-diastolic and end-systolic LV diameters and volumes (Table 5). Both LVEF (43% vs. 54%, \( P = 0.014 \)) and forward ejection fraction (23% vs. 45%, \( P = 0.006 \)) were increased, while forward cardiac index was similar to baseline. However, forward stroke volume index tended to increase (20 vs. 26 mL/m², \( P = 0.084 \)), while heart rate was numerically lower (84 vs. 69 b.p.m., \( P = 0.264 \)).

Predictors for mortality by univariable and multivariable Cox regression analysis are shown in Table 4. While there was an association of baseline total stoke volume and LA end-systolic volume with mortality in univariable analysis, no significant association was found after multivariable adjustment.

**Echocardiographic haemodynamics at follow-up**

Ten patients were available for echocardiographic follow-up. Blood pressure was similar at baseline and at follow-up. Both NYHA functional class and MR severity were improved at follow-up (Figure 2). Regurgitant volume and regurgitant fraction were reduced (Table 5). This was associated with decreased end-diastolic and end-systolic LV diameters and volumes (Table 5). Both LVEF (43% vs. 54%, \( P = 0.014 \)) and forward ejection fraction (23% vs. 45%, \( P = 0.006 \)) were increased, while forward cardiac index was similar to baseline. However, forward stroke volume index tended to increase (20 vs. 26 mL/m², \( P = 0.084 \)), while heart rate was numerically lower (84 vs. 69 b.p.m., \( P = 0.264 \)).

**Discussion**

This observational study is the first report of long-term clinical and haemodynamic results after TMVA. The data demonstrate that among high-risk patients undergoing TMVA...
for symptomatic secondary MR, mortality is ~50% at 4 years. In the limited number of patients available for follow-up echocardiography, reduction of MR was associated with reduced NYHA functional class, reverse LV remodelling, and improved LV function (Figure 3).

Ventricular vs. atrial mitral regurgitation

An important mechanism of secondary MR is mitral annulus dilatation, due to either ventricular or atrial dilatation. The subgroup analysis of ventricular vs. atrial remodelling showed that patients with ventricular MR exhibit typical features of heart failure with reduced ejection fraction, that is, LV dilatation and LV systolic dysfunction. In contrast, patients with atrial MR had concentric LV remodelling and preserved LV systolic function, while both absolute forward cardiac output and MR quantification were similar to patients with ventricular remodelling. LA volume tended to be larger in atrial MR, presumably due to atrial fibrillation, which was present in all patients. Because LV diastolic dysfunction and signs of elevated LV filling pressures were similar in both groups, patients with atrial remodelling resemble some characteristics of patients with heart failure with preserved ejection fraction.

Transcatheter approaches to treat secondary mitral regurgitation

From a pathophysiological point of view, a treatment approach directed to the predominant mechanism of secondary MR seems to be preferable, by either a surgical or interventional approach. The most widely used transcatheter edge-to-edge repair technique can be used to treat both primary and secondary MR. However, mitral leaflets are structurally affected by the clip, and increased post-procedural mitral valve gradients may occur and negatively impact the clinical benefit of this therapy. We recently demonstrated both short-term and long-term improved haemodynamics in patients undergoing transcatheter edge-to-edge repair. Two large, randomized clinical trials in secondary MR yielded conflicting clinical results of transcatheter edge-to-edge repair. Therefore, there is a need for further clinical studies to evaluate the effects of any mitral valve intervention in secondary MR.

Long-term clinical outcome after transcatheter mitral valve annuloplasty

The randomized, sham-controlled REDUCED-FMR trial in patients with secondary MR demonstrated reduced regurgitant volume at 12 months after TMVA (the primary endpoint) as well as reverse LV remodelling. These data are similar to that of the previous TITAN trial, which showed improved functional status up to 24 months after TMVA. An individual meta-analysis of TMVR studies confirmed symptomatic and echocardiographic improvement at 12 months. Long-term follow-up of these patients revealed survival rates of 50–60% 5 years after TMVR. In our study, mortality steadily increases up to ~50% after 4 years. This slightly higher mortality may be attributed to an advanced stage of heart failure stage with high N-terminal pro-brain natriuretic peptide levels, 95% of patients in NYHA Classes III and IV, and low forward cardiac index, that is, a high-risk population.

Prognostic data about atrial MR are scarce. Our results suggest that prognosis of patients with atrial MR is similar to those with ventricular MR, thus requiring efforts to optimize treatment and prognosis. These data reflect the high burden of morbidity and mortality of patients with secondary
Assessment of mitral regurgitation

Mitral regurgitant volume and regurgitant fraction are suitable to quantify MR severity during mitral valve interventions, as demonstrated by others and our previous study. In contrast, the PISA method requires a well-defined proximal convergence zone, which can be small or undetectable in mild or even unreliable in eccentric jets, which occurs also in atrial MR. Because eccentric MR jets were distributed similarly in atrial and ventricular MR, the PISA method might underestimate MR severity in atrial MR because regurgitant volume and regurgitant fraction were similar between these entities. Thus, a quantitative approach seems preferable for grading MR severity and to monitor MR in patients undergoing mitral valve interventions. Our study provides important clinical and haemodynamic outcome in well-characterized patients with secondary MR.

Left ventricular remodelling and left ventricular function

Haemodynamic outcome beyond 12 months after TMVA is currently unknown. Our study shows that sustained reduction of MR at follow-up in the surviving patients was associated with reverse LV remodelling, that is, reduced LV
Table 5 Echocardiographic parameters at baseline and follow-up

| Variable                                      | Baseline (n = 10) | Follow-up (n = 10) | Difference (median) | P value |
|-----------------------------------------------|-------------------|--------------------|---------------------|---------|
| Vital parameter                               |                   |                    |                     |         |
| Heart rate (b.p.m.)                           | 84 (68–93)        | 69 (64–76)         | −4.5                | 0.264   |
| Systolic blood pressure (mmHg)                | 158 (122–165)     | 137 (121–161)      | −9.0                | 0.477   |
| Diastolic blood pressure (mmHg)               | 80 (70–90)        | 78 (66–96)         | −0.5                | 0.922   |
| LV remodelling and systolic function          |                   |                    |                     |         |
| LV end-diastolic septum thickness (mm)        | 12 (10–14)        | 12 (10–13)         | 0                   | 0.563   |
| LV end-diastolic diameter (mm)                | 60 (55–64)        | 55 (50–61)         | −0.3                | 0.012   |
| LV end-systolic diameter (mm)                 | 46 (39–57)        | 40 (33–46)         | −0.4                | 0.048   |
| LV end-diastolic volume index (mL/m²)         | 92 (74-107)       | 67 (46–101)        | −21.6               | 0.065   |
| LV end-systolic volume index (mL/m²)          | 50 (44–69)        | 32 (20–53)         | −15.2               | 0.037   |
| Total stroke volume index (mL/m²)             | 38 (33–43)        | 33 (26–44)         | −3.6                | 0.695   |
| LVEF (%)                                      | 43 (35–49)        | 54 (46–57)         | 4.9                 | 0.014   |
| Forward stroke volume index (mL/m²)           | 20 (19–26)        | 26 (21–35)         | 3.5                 | 0.084   |
| Forward cardiac index (L/min/m²)              | 1.7 (1.3–2.5)     | 1.9 (1.6–2.8)      | 0.4                 | 0.375   |
| Forward EF (%)                                | 23 (19–31)        | 45 (30–54)         | 17.5                | 0.006   |
| Diastolic LV function                         |                   |                    |                     |         |
| E wave (m/s)                                  | 1.1 (0.9–1.3)     | 1.0 (0.9–1.4)      | −0.1                | 0.748   |
| E’ mean (m/s)                                 | 0.07 (0.05–0.09)  | 0.07 (0.07–0.08)   | 0                   | 0.406   |
| E/e                                           | 17.8              | 14.4               | −2.5                | 0.232   |
| Left atrial end-systolic volume index (mL/m²) | 47 (41–56)        | 60 (39–69)         | 5.9                 | 0.275   |
| Systolic pulmonary artery pressure (mmHg)     | 67 (39–80)        | 49 (42–80)         | 3.5                 | 0.641   |
| Mitral valve function                         |                   |                    |                     |         |
| Regurgitation volume (mL)                     | 27 (25–42)        | 8 (3–17)           | −22.0               | 0.018   |
| Regurgitation fraction (%)                    | 42 (34–54)        | 11 (8–24)          | −33.9               | 0.014   |
| Effective regurgitation orifice area (cm²) PISA| 0.25 (0.18–0.33)  | 0.15 (0.10–0.28)   | −0.05               | 0.375   |
| Regurgitation volume (mL) PISA                | 42 (31–48)        | 26 (15–44)         | −20.5               | 0.156   |
| MV mean diastolic gradient                    | 2.4 (1.7–3.1)     | 1.6 (1.1–4.0)      | −0.9                | 0.688   |

EF, ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; MV, mitral valve; PISA, proximal isovelocity orifice area. Data are presented as absolute values (%) or median (inter-quartile range), as appropriate. Statistically significant results are presented in bold.

Figure 3 Long-term clinical and haemodynamic outcome in patients with secondary mitral regurgitation treated with transcatheter mitral valve annuloplasty. Transcatheter mitral valve annuloplasty with Carillon device implantation in the coronary sinus (echo rich on biplane transthoracic parasternal views, yellow arrows) reduced mitral regurgitation severity. After a mean follow-up of 45 months, mortality was 52%. In the remaining patients—including two patients undergoing additional edge-to-edge mitral valve repair—reduced regurgitation fraction in the long-term was associated with reduced left ventricular (LV) end-diastolic volume index (LVEDVi) and LV end-systolic volume index (LVESVi) and increased LV ejection fraction (LVEF), that is, reverse LV remodelling and improved LV function.
volumes and diameters and improved LV function. Both LVEF and forward ejection fraction, which is a more accurate parameter of LV function than LVEF in MR,\textsuperscript{28,37} were increased after TMVA. While forward cardiac index remained similar at follow-up, forward stroke volume numerically increased while heart rate decreased (without statistical significance, probably due to the small number of patients). These changes can be interpreted as sign of a haemodynamic improvement.

In case of persistent or recurrent MR after TMVA, the transcatheter edge-to-edge repair offers an additional approach to obtain an optimal result of long-term MR reduction. The transcatheter treatment resulted reduced MR severity and improved LV parameters at follow-up in all but one patient. This observation was consistent in patients with and without event during follow-up.

In summary, these data demonstrate a favourable long-term effect of TMVA on MR severity, which is associated with reverse LV remodelling and improved LV function (Figure 3).

Limitations

This is an observational study of patients who underwent TMVA. The lack of a control group is a limitation for the interpretation of the clinical and echocardiographic outcome measures. This applies particularly for NYHA functional class, which is prone to bias. Unfortunately, the causes of mortality are not available from our study. The number of patients available for follow-up was small, primarily because of high mortality, and represents a selected population due to survival bias. The small sample size of the study is a limitation for Cox regression and subgroup analysis, which should be interpreted as hypothesis generating. However, the data may provide important insights into this area with very limited published data available. Optimal medical treatment is the mainstay of therapy for chronic heart failure.\textsuperscript{6} Increased doses of renin–angiotensin system inhibitors at follow-up may have contributed to reduced MR severity and improved LV function.\textsuperscript{6,38,39}

Conclusions

This report on long-term results of patients treated with transcatheter annuloplasty for secondary MR showed a significant mortality (~50%) at 4 years. Despite the limited number of patients available for follow-up, reduction of MR was associated with reverse LV remodelling and improved cardiac haemodynamics. The study provides important long-term data from a real-world population, which may help to design randomized controlled trials powered for clinical endpoints.

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Conflict of interest

D.L. received speaker honoraria from Cardiac Dimensions. J. B., T.S., S.S., and U.L. declared no conflicts of interest. A.H. received speaker honoraria from Cardiac Dimensions.

Supporting information

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

Figure S1: Quantitative assessment of mitral regurgitation.
Figure S2: Heart failure medication at baseline and at follow-up
Data S1. Supporting information

References

1. Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet 2009; 373: 1382–1394.
2. Lavall D, Hagendorff A, Schirmer SH, Böhm M, Borger MA, Laufs U. Mitral valve interventions in heart failure. ESC Heart Fail 2018; 5: 552–561.
3. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Mu DR, Rosenhek R, Sjögren J, Mas PT, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, Agewall S, Ahlsson A, Barbato E, Bueno H, Collet JP, Gaemperli O, Habib G, Harringer W, Haude M. 2017 ESC/EACTS guidelines for the management of valvular heart disease. The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2017; 38: 2739–2791.
4. Rossi A, Dini FL, Fagginello P, Agricola E, Cicioir A, Frattini S, Simionnic A, Gullace M, Ghio S, Enriquez-Sarano M, Temporelli PL. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. Heart 2011; 97: 1675–1680.
5. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral
regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001; 103: 1759–1764.

6. Ponikowski P, Voors AA, Anker SD, Cleland JGF, Coats AJS, Falk V, Jankowski EA, Nihoyannopoulos P, Pieske B, Rutten FH. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016; 37: 2129–2200.

7. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. Lancet 2006; 367: 356–367.

8. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol 2015; 65: 1231–1248.

9. Mirabel M, Jung B, Baron G, Messika-Zeitoun D, Détaillat D, Vanoverschelde JI, Butchart EG, Ravaud P, Vahanian A. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? Eur Heart J 2007; 28: 1358–1365.

10. MB, Johnson T, Vogt S, Stark MA, Siminiak T, Fajadet J, Shah AM, Feldmann KM, Kaye DM, Goldman 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.

11. Schofer J, Siminiak T, Haude M, Herrmann JP, Vainer J, Wu JC, Levy WC, Maeder P, Relan T, Kwong RY, Kaye DM, Duffy SJ, Tübler 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.

12. Ruf TF, Kreidel F, Tamm AR, Geyer M, Hahad O, Zirbs JC, Schwidral BL, Beiras-Fernandez A, Witte KK, Münzel T, von Bardeleben RS. Transcatheter indirect mitral annuloplasty induces annular and left atrial remodelling in secondary mitral regurgitation. ESC Heart Fail 2020; 7: 1400–1408.

13. Stoëte S, Kreyer K, Lavall D, Laufs D, Hagendorff D. Echocardiographic analysis of acute effects after treatment of functional mitral regurgitation by percutaneous mitral annuloplasty. ESC Heart Fail 2020; 7: 1645–1652.

14. Witte K, Lipicjki J, Siminiak T, Mere-dith IT, Malkin CJ, Goldman SL, Stark MA, von Bardeleben RS, Cremer PC, Jaber WA, Celermayer 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.

15. Siminiak T, Wu JC, Haude M, Hoppe UC, Sadowski J, Lipicjki J, Fajadet J, Shah AM, Feldmann KM, Kaye DM, Goldman 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.

16. Giallauria F, Di Lorenzo A, Parlati A, Testa C, Bobbio E, Vigorito C, Coats AJS. Individual patient data meta-analysis of the effects of the CARILLON™ mitral contour system. ESC Heart Fail 2020; 7: 3383–3391.

17. Lipicjki J, Kaye DM, Witte K, 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.

18. Lipicjki J, Fahrat H, Monzy S, Cailiot N, Siminiak T, Johnson T, Vogt S, Stark MA, Goldberg SL. Long-term prognosis of patients treated by coronary sinus-based percutaneous annuloplasty: single centre experience. ESC Heart Fail 2020; 7: 3329–3335.

19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015; 16: 233–271.

20. Naghieh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Paposcu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016; 17: 1321–1360.

21. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn R, Han Y, Hung J, Lang RM, Little SA, Nishimura RA, 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.

22. Hagendorff A, Knebel F, Helfen A, Stoëte S, Doenst T, Falk V. Disproportionate mitral regurgitation: another myth? A critical appraisal of echocardiographic assessment of functional mitral regurgitation. Int J Cardiovasc Imaging 2021; 37: 183–196.

23. Hagendorff A, Doenst T, Falk V. Echocardiographic assessment of functional mitral regurgitation: opening Pandora’s box? ESC Heart Fail 2019; 6: 678–685.

24. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685–713.

25. Tribouilloy C, Shen WF, Key JL, Adam MC, Lesbre JP. Mitral to aortic velocity-time integral ratio: a non-geometric pulsed-Doppler regurgitant index in isolated pure mitral regurgitation. Eur Heart J 1994; 15: 1335–1339.

26. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD, Vandervooort PM. Atrial functional mitral regurgitation: JACC review topic of the week. J Am Coll Cardiol 2019; 73: 2465–2476.

27. Mauri L, Foster E, Glower DD, Apruzzese P, Massaro JM, Herrmann HC, Hermiller J, Gray W, Wang A, Pedersen WR, Bajwa T, Lasala J, Low R, Greyburn P, Feldman T. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. J Am Coll Cardiol 2013; 62: 317–328.

28. Lavall D, Reil JC, Segura Schmitz L, Mehrer M, Schirmer SH, Böhm M, Laufs U. Early hemodynamic improvement after percutaneous mitral valve repair evaluated by noninvasive pressure-volume analysis. J Am Soc Echocardiogr 2016; 29: 888–898.

29. Lavall D, Mehrer M, Schirmer SH, Reil JC, Wagenpfel S, Böhm M, Laufs U. Long-term hemodynamic improvement after transcatheter mitral valve repair. J Am Soc Echocardiogr 2018; 31: 1013–1020.

30. Neuss M, Schau T, Isotani A, Pilz M, Schöpp M, Butter C. Elevated mitral valve pressure gradient after MitraClip implantation deteriorates long-term outcome in patients with severe mitral regurgitation and severe heart failure. JACC Cardiovasc Interv 2017; 10: 931–939.

31. Lavall D, Scheller B, Werner C, Buob A, Mahfoud F. Mitral valve pressure gradient after percutaneous mitral valve repair: every beat counts. ESC Heart Fail 2018; 5: 193–196.

32. Obadia J-F, Messika-Zeitoun D, Leurent G, Jung B, Bonnet G, Pirou N, Lefèvre T, Piot C, Rouleau F, Carrière D, Nejiari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu J-N, Cormier B, Armoiry X, Bouttie F, Maucoet-Bouclh D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018; 379: 2207–2216.

33. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopala V, Sarembock LJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ.
Mack MJ. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018; 379: 2307–2318.

34. Mele D, Pestelli G, Molin DD, Trevisan F, Smarrazzo V, Luisi GA, Fucili A, Ferrari R. Echocardiographic evaluation of left ventricular output in patients with heart failure: a per-heat or per-minute approach? *J Am Soc Echocardiogr* 2020; 33: 135–147.

35. Foster E, Wasserman HS, Gray W, Homma S, Di Tullio MR, Rodriguez L, Stewart WJ, Whitolw P, Block P, Martin R, Merlino J, Herrmann HC, Wiegens SE, Silvestre F, Hamilton A, Zunamon A, Kraybill K, Gerber IL, Weeks SG, Zhang Y, Feldman T. Quantitative assessment of severity of mitral regurgitation by serial echocardiography in a multicenter clinical trial of percutaneous mitral valve repair. *Am J Cardiol* 2007; 100: 1577–1583.

36. Kagiyama N, Mondillo S, Yoshida K, Mandoli GE, Cameli M. Subtypes of atrial functional mitral regurgitation: imaging insights into their mechanisms and therapeutic implications. *JACC Cardiovasc Imaging* 2020; 13: 820–835.

37. Kamperidis V, Marsan NA, Delgado V, Bax JJ. Left ventricular systolic function assessment in secondary mitral regurgitation: left ventricular ejection fraction vs. speckle tracking global longitudinal strain. *Eur Heart J* 2016; 37: 811–816.

38. Nasser R, Van Assche L, Vorlat A, Vermeulen T, Van Craenenbroeck E, Conraads V, Van der Meiren V, Shivalkar B, Van Herck P, Claeyss MJ. Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction. *JACC Heart Fail* 2017; 5: 652–659.

39. 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: PRIME study. *Circulation* 2019; 139: 1354–1365.