Clinical and Hemodynamic Effects of Percutaneous Edge-to-Edge Mitral Valve Repair in Atrial Versus Ventricular Functional Mitral Regurgitation

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The present study aims to assess the clinical and hemodynamic impact of percutaneous edge-to-edge mitral valve repair with MitraClip in patients with atrial functional mitral regurgitation (A-FMR) compared with ventricular functional mitral regurgitation (V-FMR). Mitral regurgitation (MR) grade, functional status (New York Heart Association class), and major adverse cardiac events (MACE; all-cause mortality or hospitalization for heart failure) were evaluated in 52 patients with A-FMR and in 307 patients with V-FMR. In 56 patients, hemodynamic assessment during exercise echocardiography was performed before and 6 months after intervention. MR reduction after MitraClip implantation was noninferior in A-FMR compared with V-FMR (MR grade ≤2 at 6 months in 94% vs 82%, respectively, p <0.001 for noninferiority) and was associated with improvement of functional status (New York Heart Association class ≤2 at 6 months in 90% vs 80%, respectively, p = 0.2). Hemodynamic assessment revealed that cardiac output at 6 months was higher in A-FMR at rest (5.1 ± 1.5 L/min vs 3.8 ± 1.5 L/min, p = 0.002) and during peak exercise (7.9 ± 2.4 L/min vs 6.1 ± 2.1 L/min, p = 0.02). In addition, the reduction in systolic pulmonary artery pressure at rest was more pronounced in A-FMR: Δ SPAP −13.1 ± 15.1 mm Hg versus −2.2 ± 13.3 mm Hg (p = 0.03). MACE rate at follow-up was significantly lower in A-FMR versus V-FMR, with an adjusted odds ratio of 0.46 (95% confidence interval 0.24 to 0.88), which was caused by a reduction in hospitalization for heart failure. In conclusion, percutaneous edge-to-edge mitral valve repair with MitraClip is at least as effective in A-FMR as in V-FMR in reducing MR. However, the hemodynamic improvement and reduction of MACE were significantly better in A-FMR. **(Am J Cardiol 2021;161:70−75)**

Functional mitral regurgitation (FMR) is classically defined as mitral regurgitation (MR) secondary to underlying myocardial dysfunction.[1] Recently, a new etiology of FMR has been described in patients with a dilated left atrium or mitral annulus without obvious left ventricular (LV) systolic dysfunction, typically in the context of atrial fibrillation and/or heart failure (HF) with a preserved LV ejection fraction (LVEF).[2-4] This novel type of FMR has been recently recognized as atrial FMR (A-FMR) and is clearly distinct from classical ventricular FMR (V-FMR). Percutaneous edge-to-edge mitral valve repair by means of MitraClip has emerged as a promising treatment for symptomatic HF with reduced LVEF and severe FMR despite optimal HF treatment.[5-8] Reduction of MR has been shown to improve hemodynamics by reducing volume overload and by increasing forward stroke volume with improvement of functional status and prognosis.[9,10] However, outcome data of mitral valve intervention in A-FMR are limited. Surgical mitral annuloplasty has been reported in a small case series.[11,12] Recently, Nagaura et al[13] reported the first experience with MitraClip therapy in 38 patients with A-FMR and found similar acute MR reduction compared with 49 patients with V-FMR.[13] Whether this success was sustainable over time and whether it has a similar symptomatic and prognostic impact is currently unknown. Accordingly, this multicenter prospective observational study was designed to assess the clinical and hemodynamic impacts of edge-to-edge repair with MitraClip in patients with A-FMR compared with V-FMR. We hypothesized that the reduction in MR would be comparable between the 2 groups, but

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considering the different underlying mechanisms of FMR, the hemodynamic and clinical impacts would be different.

Methods

We included 359 consecutive patients with symptomatic severe FMR referred for percutaneous mitral valve repair with MitraClip at 7 Belgian centers from 2011 to 2019. The clinical characteristics of the patients were extracted from the Belgian MitraClip database, which prospectively gathers information on all MitraClip procedures in Belgium. At the time of the evaluation, 555 patients with MitraClip were included in the database. A total of 196 patients were excluded because of degenerative or mixed valve disease. In the 359 patients with FMR, 52 patients (14%) had preserved LV function (LVEF ≥50%) with enlarged left atrium and were considered to have A-FMR, whereas the other 307 patients (86%) were considered to have V-FMR. The ethical committee of the Antwerp University Hospital approved the study protocol, and all patients provided written informed consent. The database is registered with ClinicalTrials.gov (NCT02506387).

All MitraClip procedures were performed under general anesthesia using transesophageal echocardiography and fluoroscopic guidance. A comprehensive description of the procedure has been previously described.[14,15] Procedural success was defined as a noncomplicated implantation of ≥1 clip together with a postprocedural (predischarge) estimated MR reduction to ≤grade 2. Device failure was defined as partial or complete detachment of the clip or any other technical issue precluding appropriate placement of the clip.

All patients underwent echocardiography by experienced operators using commercially available ultrasonography systems. MR severity was assessed before and 3, 6, and 12 months after MitraClip implantation and was graded according to the American Society of Echocardiography guidelines based on a validated multi-integrative method.[16] Both qualitative (color flow mapping) and quantitative measurements (proximal isovelocity surface area whenever feasible) were used to grade the MR severity from grade 0 to grade 4 (grade 0 = no/trace; grade 1 = mild; grade 2 = moderate; grade 3 = moderate to severe; grade 4= severe). The primary efficacy end point was the proportion of patients with MR grade ≤2 at 6 months.

LVEF was quantified by the modified Simpson's method in the apical 4- and 2-chamber view or by visual estimation in case of poor image quality. A-FMR was defined as FMR in the presence of LVEF ≥50% and left anterior volume index (LAVI) >34 ml/m^2 (or anterior-posterior left anterior dimension index >23 cm/m^2).[2]

In a subgroup of 56 patients (10 A-FMR and 46 V-FMR), hemodynamic assessment was performed before and 6 months after MitraClip implantation during symptom-limited exercise echocardiography. A protocol of 20 W with 10-W increments per minute was chosen for exercise testing, and acquisitions were made using a cardiovascular ultrasound system (Vivid 7 or Vivid E9, GE Healthcare or iE33). Peak exercise was defined as the highest workload (Watt) achieved. The echocardiographic data were analyzed offline (EchoPAC, version 112, GE Medical Systems, Horten, Norway). All measurements were averaged over 3 cardiac cycles for patients in sinus rhythm and 5 cycles for patients with atrial fibrillation. Cardiac output (CO) was derived from the product of forward stroke volume, measured in the LV outflow tract and the heart rate. Systolic pulmonary artery pressure (SPAP) was calculated as the sum of the maximal transtricuspid pressure gradient and an estimate of the right atrial pressure based on the inferior caval vein dimension and collapsibility, as recommended.[17] Chemla formula was used to calculate mean pulmonary arterial pressure.[18] Abnormal pulmonary vascular reserve was defined as mean pulmonary arterial pressure/CO slope >3 mm Hg/L/min by exercise echocardiography.[19] End-systolic left atrial volumes adjusted for body surface area were calculated offline by a single expert.

Clinical assessment was performed before, and 3 and 6 months, and yearly after the intervention. Functional evaluation was performed using the New York Heart Association (NYHA) classification and a 6-minute walk test. Results of a 6-minute walk test were available in 174 patients at baseline and 91 patients at follow-up (12 A-FMR and 79 V-FMR).

The clinical efficacy end point was freedom from major adverse cardiac events (MACE), defined as a combined end point of all-cause mortality and hospitalization for heart failure.

The safety end point at 30 days was freedom from major adverse events, defined as a composite of death, myocardial infarction, early (30 days) cardiac surgery, severe bleeding (VARC >2 including pericardial effusion) and stroke. All end points were assessed on an intention-to-treat basis and were obtained from patient records or from telephone calls with the patient.

Sample size was calculated based on noninferiority of A-FMR compared with V-FMR of the primary efficacy end point (MR grade ≤2 at 6 months). With an estimated primary end point rate of 80% in both groups, a noninferiority margin of 15% and an expected proportion of 15% A-FMR, a sample size of 347 patients with FMR was calculated to prove noninferiority with a type I error of 0.05 and a type II error of 0.20. Continuous variables are presented as mean (SD) or median (with range), where appropriate. Categorical variables are presented as counts and percentages. Characteristics were compared between A-FMR and V-FMR using chi-square tests for categorical variables and *t* test or Mann-Whitney *U* test for continuous variables. Noninferiority of the proportion of patients with MR grade ≤2 at 6 months in the A-FMR group compared with the V-FMR group was shown in a one-sided *z*-test with noninferiority margin of 15%. Comparisons of pre- and post-MitraClip parameters (NYHA class, MR grade, hemodynamics) for the different study subgroups were performed using analysis of variance for repeated measurements. Cumulative event-free survival estimates were plotted using the Kaplan-Meier technique. The Cox proportional hazards model was applied to identify independent predictors of MACE. The following baseline factors were included in the model: age, gender, arterial hypertension, diabetes, peripheral vascular disease, EuroSCORE 2, renal failure (defined as glomerular filtration rate <60 ml/min/1.73 m^2), baseline

NYHA functional classification, etiology of FMR (atrial vs ventricular), and unsuccessful procedure (predischarge MR grade >2). Baseline LVEF was not included as a separate factor because it was used in the definition of A-FRM and was also incorporated in the EuroSCORE 2 calculation. A two-tailed p value <0.05 was considered statistically significant. Statistical analyses were performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

Results

Clinical and echocardiographic characteristics of 52 patients with A-FMR and 307 patients with V-FMR are listed in Table 1. Patients with A-FMR were older, more frequently female, and less likely to have impaired renal function. Along with preserved LV function, the LV dimensions were smaller in patients with A-FMR. However, the left atrium size was similar between the 2 groups.

Table 1
Baseline characteristics

Characteristics	A-FMR (n = 52)	V-FMR (n = 307)	p Value
Age (years)	79 ± 8	72 ± 10	<0.001
Women	28 (54%)	86 (28%)	0.0002
BMI (kg/m^2)	25 ± 5	26 ± 4	0.4
Atrial fibrillation	32 (62%)	151 (49%)	0.1
eGFR (ml/min/1.73 m^2)	50 ± 21	43 ± 21	0.04
eGFR <60 ml/min/1.73 m^2	28 (54%)	239 (78%)	0.0003
Arterial hypertension	41 (79%)	209 (70%)	0.16
Diabetes mellitus	11 (21%)	81 (26%)	0.4
Previous MI	15 (30%)	186 (62%)	0.0001
EuroSCORE 2	8 ± 10	13 ± 12	0.002
Functional capacity			
NYHA Class 2/3/4 (%)	14/71/15	13/65/22	0.5
6-minute walk test, meter	296 ± 88	303 ± 118	0.8
NT pro-BNP, μg/L (n=219)	2,425 ± 2,612	5,769 ± 6,014	0.008
Number of HF hospitalization during 1 y before MitraClip, n	0.8 ± 0.8	1.8 ± 3.6	0.06
Medication			
β-blockers	39 (78%)	247 (82%)	0.5
RAS inhibition	28 (56%)	190 (64%)	0.3
Aldosterone antagonist	19 (37%)	142 (47%)	0.2
Diuretics	39 (75%)	269 (89%)	0.007
Echocardiographic findings			
LVEF (%)	59 ± 7	31 ± 8	<0.001
MR grade 3/4 (%)	40/56	43/56	0.6
TR grade >2 (n = 202)	8 (27%)	47 (26%)	0.7
LV EDDi (mm/m^2)	30 ± 4	35 ± 5	<0.001
LAVi (ml/m^2)	72 ± 33	72 ± 21	0.9
LADi (mm/m^2)	28 ± 4	27 ± 5	0.6
SPAP (mm Hg)	48 ± 19	50 ± 17	0.4

Continuous data are presented as means ± standard deviation. Categorical data are presented as percentages.

BMI = body mass index; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; LADi = left atrium dimension index; LAVi = left atrium volume index; LV EDDi = left ventricular end-diastolic diameter index; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association; RAS = renin-angiotensin system; SPAP = systolic pulmonary artery pressure; V-FMR = ventricular functional mitral regurgitation.

Table 2
Periprocedural complications

Variable	A-FMR, n = 52	V-FMR, n = 307	p Value
Device failure	1.9%	3.7%	0.5
Early cardiac surgery	0%	1.5%	0.5
Myocardial infarction	0%	0.7%	0.5
Bleeding (VARC >2)	3.8%	3.3%	0.8
Stroke	1.9%	3.0%	0.6
30-d mortality	0%	3.30%	0.19

A-FMR = atrial functional mitral regurgitation; VARC = Valve Academic Research Consortium 2; V-FMR = ventricular functional mitral regurgitation.

The MR severity and functional status (NYHA classification and 6-minute walk test) were similar between the 2 groups. In contrast, the N-terminal pro B-type natriuretic peptide levels and the number of HF hospitalizations in the year preceding the intervention were lower in the A-FMR group.

The MitraClip procedure reduced MR successfully in 92% of the patients with A-FMR and V-FMR (p = 0.9). The number of clips implanted per patient was similar in both groups. Although the average predischarge mean transmitral gradient was higher in A-FMR, the presence of a mean transmitral gradient ≥7 mm Hg was comparable in both groups (7.1% vs 6.5%, p = 0.9). Device failure was observed in 1 patient with A-FMR (1.9%) and in 11 patients with V-FMR (3.7%) (p = 0.5). Other periprocedural complications did not differ significantly between both groups (Table 2).

Six months after MitraClip implantation, an MR grade ≤2 was observed in 94% of the A-FMR group and in 82% of the V-FMR group (p for noninferiority <0.001; p for superiority = 0.08). MR reduction was sustained during follow-up in both groups, as demonstrated in Figure 1.

Functional capacity improved similarly in both study groups, with a sustained reduction in NYHA class over time (Figure 2). At 6 months, 90% of patients with A-FMR were in NYHA class 1 to 2 compared with 80% for V-FMR (p = 0.2). Similarly, the 6-minute walk test increased by 50.2 ± 77 m for A-FMR versus 25.9±107 m for V-FMR (p = 0.4).

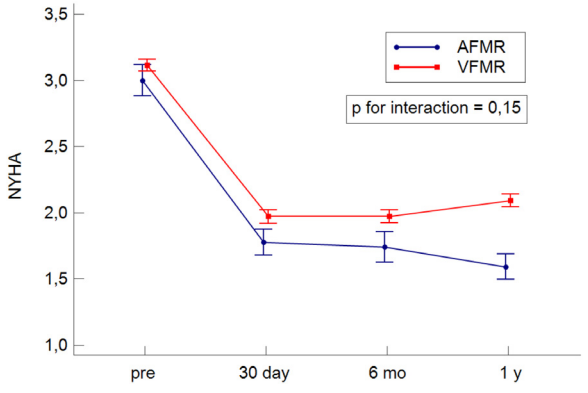

Figure 1. Clinical and hemodynamic effects of MitraClip treatment in A-FMR versus V-FMR.

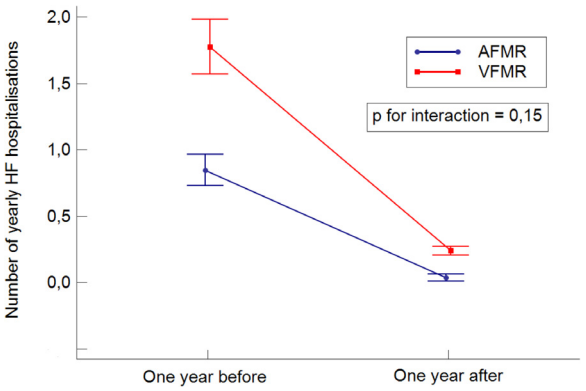

Figure 2. NYHA class before and after MitraClip treatment. Data plot showing the evolution of the NYHA classification at baseline and after intervention. Data are expressed as means ± SEM. mo = months; y = year.

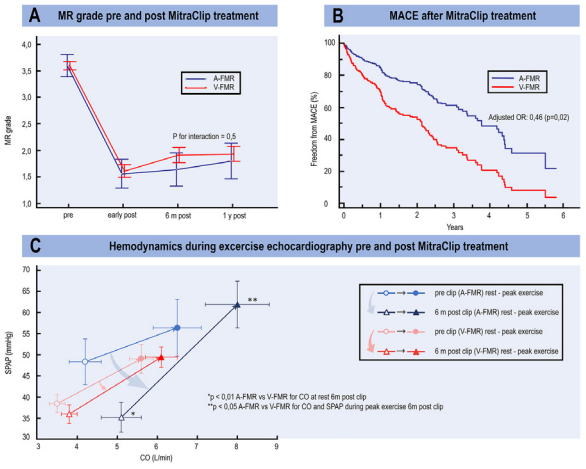

Figure 3. Heart failure hospitalization before and after MitraClip implantation. Data plot showing the number of hospitalizations for HF in the year before and after intervention. Data are expressed as means ± SEM.

Comparing the year before and after intervention, the number of hospitalizations for HF decreased with 95% in A-FMR versus 87% in V-FMR (p = 0.15, Figure 3).

Finally, during a follow-up period of 1.25 ± 1.16 years, MACE occurred in 161 patients (112 died and 97 were rehospitalized for heart failure). The MACE rate was significantly lower in A-FMR versus V-FMR (adjusted odds ratio [OR] 0.46, 95% confidence interval [CI] 0.24 to 0.88). This improved outcome was mainly caused by a lower rate of HF hospitalizations (adjusted OR 0.38, 95% CI 0.16 to 0.90), whereas all-cause mortality did not differ significantly (adjusted OR 0.8, 95% CI 0.4 to 1.67). MACE rate at 1 year was 15% in A-FMR versus 32% in V-FMR, with 1-year mortality rate of 10% and 13%, respectively. Beyond FMR etiology, NYHA class 4 before intervention and the success of the procedure were the other independent predictors of outcome (Table 3).

The hemodynamic impact of MitraClip intervention on CO and SPAP at rest and during peak exercise was assessed in a subgroup of 56 patients (10 A-FMR and 46 V-FMR). The baseline characteristics of these study subgroups were in line with those of the global study group (see Supplementary Table 1 in the online supplement). The main findings

Table 3
Predictors of MACE

	Odds ratio	95% CI	p Value
Age	0.99	0.97−1.01	0.6
Male	1.07	0.75−1.53	0.7
Arterial hypertension	0.75	0.50−1.12	0.16
Diabetes	0.98	0.67−1.45	0.9
Renal failure	1.16	0.76−1.78	0.5
PVD	0.87	0.57−1.34	0.5
EuroSCORE 2	1.01	0.99−1.02	0.16
NYHA Class 4	1.9	1.33−2.80	0.0005
A-FMR	0.46	0.24−0.88	0.02
Unsuccessful procedure	1.85	1.09−3.13	0.02

A-FMR = atrial functional mitral regurgitation; CI = confidence interval; NYHA, New York Heart Association; PVD = peripheral vascular disease.

are presented in Figure 1. Over a period of 6 months after MitraClip, CO increased and SPAP decreased in both groups (p values <0.01). Additional analysis revealed that CO at 6 months remained significantly higher in patients with A-FMR, both at rest (5.1 ± 1.5 L/min vs 3.8 ± 1.5 L/min, p = 0.002) and during peak exercise (7.9 ± 2.4 L/min vs 6.1 ± 2.1 L/min, p = 0.02). The differences in CO between both groups were mainly caused by a higher forward stroke volume in A-FMR (see Supplementary Table 2 in the online supplement). In addition, the reduction in SPAP was more pronounced in A-FMR with a Δ SPAP at rest of −13.1 ± 15.1 mm Hg versus −2.2 ± 13.3 mm Hg (p = 0.03). The postintervention systolic pulmonary and systemic pressure at peak exercise were higher in A-FMR than in V-FMR. Postintervention, an abnormal pulmonary vascular reserve was observed in 63% of A-FMR versus 65% in V-FMR (p = 0.9).

Discussion

To our knowledge, the present study is the first to document both clinical and hemodynamic benefits of percutaneous edge-to-edge mitral valve repair in A-FMR. MitraClip implantation resulted in a similar acute and sustained MR reduction in A-FMR compared with V-FMR. However, the procedure had a different impact on hemodynamics with a more pronounced decrease of pulmonary pressures and increased gain in CO in A-FMR. These findings may explain the more favorable postintervention clinical outcome noted in patients with A-FMR with particularly fewer hospitalizations for HF.

Significant (moderate or severe) A-FMR in the setting of atrial fibrillation or heart failure with preserved ejection fraction is not uncommon, with reported prevalence up to 40%.[4,20] The underlying mechanism of A-FMR is complex and relates to mitral annulus dilatation secondary to atrial remodeling, leaflet area reduction available for coaptation, and to tethering of the posterior leaflet by increasing the annulopapillary muscle distance.[2,21] As these mechanisms often coincide with V-FMR because of concomitant atrial remodeling (e.g., the atrial size was identical in both study groups), it was expected that the technical success of percutaneous edge-to-edge mitral valve repair would be similar in A-FMR compared with V-FMR.

Reduction of MR has been shown to improve hemodynamics by reducing volume overload, by reducing atrial and pulmonary filling pressures, and by increasing forward stroke volume with subsequent improvement of the functional status and prognosis.[9] Post hoc analysis of the COAPT trial demonstrated that a reduction in systolic pulmonary arterial pressure after the intervention was a strong independent predictor of improved long-term clinical outcomes.[22] In our hemodynamic study, we demonstrated that the reduction in SPAP was more pronounced in A-FMR than in V-FMR, which is probably a primary reason for the improved prognosis in A-FMR.

In addition, we observed a higher CO in patients with A-FMR both at rest and during peak exercise, which may also explain the better clinical outcome.

The observed favorable hemodynamics in A-FMR are most likely related to the preserved LV systolic function. In addition, preserved LV systolic function and LV dimensions prevent the development of afterload mismatch and LV adverse remodeling postintervention. Both maladaptive processes have been observed in patients with advanced cardiac dysfunction and have been linked to poor clinical outcomes after MitraClip implantation.[23–25] From that perspective, A-FMR resembles degenerative MR, a condition that is also associated with preserved LV function and good postintervention clinical outcomes.

Interestingly, we observed postintervention a significantly higher SPAP during peak exercise in A-FMR than in V-FMR. Higher vascular resistance due to high atrial filling pressure in the context of residual MR and/or diastolic dysfunction may play a role in exercise-induced pulmonary hypertension.[19] Indeed, the steep CO/SPAP slope postintervention, which is a marker of vascular pulmonary reserve, feeds the paradigm that heart failure with preserved ejection fraction is predominantly present in patients with A-FMR.

The results of this study should be considered in the context of the following limitations. In this observational study, no control group was available to assess the effect of medical treatment on hemodynamics and clinical outcomes; however, we documented the effect of the intervention by comparing functional status and hospitalizations for HF before and after the intervention. In addition, the selection criteria for MitraClip implantation included the presence of symptoms refractory to optimal medical therapy. No external audit of data quality was performed in this national database. The steering committee of this national database organized regular meetings with the local investigators to ensure high quality of the data input, and we may assume that data quality is similar for A-FMR and V-FMR. The number of patients with A-FMR (particularly of the hemodynamic substudy) was limited and some parameters such as 6-minute walk test and Tricuspid regurgitation grade grade were incomplete precluding to make firm conclusions on these parameters.

In conclusion, percutaneous edge-to-edge mitral valve repair with MitraClip is able to reduce MR effectively in patients with A-FMR and seems to confer more clinical and hemodynamic benefits than in V-FMR, most likely related to the preserved LV function in A-FMR.

Disclosures

M. Claeys has received honoraria fees (<10,000 euro) from Abbott company. The remaining authors have nothing to disclose.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.08.062.

1. Piérard LA, Carabello BA. Ischaemic mitral regurgitation: pathophysiology, outcomes and the conundrum of treatment. *Eur Heart J* 2010;31:2996–3005.
2. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD, Vandervoort PM. Atrial functional mitral regurgitation: JACC review topic of the week. *J Am Coll Cardiol* 2019;73:2465–2476.
3. Gertz ZM, Raina A, Saghy L, Zado ES, Callans DJ, Marchlinski FE, Keane MG, Silvestry FE. Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. *J Am Coll Cardiol* 2011;58:1474–1481.
4. Pype L, Embrechts L, Cornez B, Van Paesschen C, Sarkozy A, Miljoen H, Heuten H, Saenen J, Van Herck P, de Heyning CMV, Heidbuchel H, Claeys MJ. Long-term effect of atrial fibrillation on the evolution of mitral and tricuspid valve regurgitation. *Acta cardiol* 2019:1–9.
5. Mendirichaga R, Singh V, Blumer V, Rivera M, Rodriguez AP, Cohen MG, O'Neill WW, Elmariah S. Transcatheter mitral valve repair with MitraClip for symptomatic functional mitral valve regurgitation. *Am J Cardiol* 2017;120:708–715.
6. 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, COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;379:2307–2318.
7. Foster E, Kwan D, Feldman T, Weissman NJ, Grayburn PA, Schwartz A, Rogers JH, Kar S, Rinaldi MJ, Fail PS, Hermiller J, Whitlow PL, Herrmann HC, Lim DS, Glower DD, EVEREST Investigators. Percutaneous mitral valve repair in the initial EVEREST cohort: evidence of reverse left ventricular remodeling. *Circ Cardiovasc Imaging* 2013;6:522–530.
8. Nasser R, Van Assche L, Vorlat A, Vermeulen T, Van Craenenbroeck E, Conraads V, Van der Meiren V, Shivalkar B, Van Herck P, Claeys 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.
9. Van De Heyning CM, Bertrand PB, Debonnaire P, De Maeyer C, Vandervoort PM, Coussement P, Paelinck BP, De Bock D, Vrints CJ, Claeys MJ. Mechanism of symptomatic improvement After percutaneous therapy for secondary mitral regurgitation: resting and exercise hemodynamics. *J Am Coll Cardiol* 2016;68:128–129.
10. Grayburn PA, Foster E, Sangli C, Weissman NJ, Massaro J, Glower DG, Feldman T, Mauri L. Relationship between the magnitude of reduction in mitral regurgitation severity and left ventricular and left atrial reverse remodeling after MitraClip therapy. *Circulation* 2013;128:1667–1674.

11. Takahashi Y, Abe Y, Sasaki Y, Bito Y, Morisaki A, Nishimura S, Shibata T. Mitral valve repair for atrial functional mitral regurgitation in patients with chronic atrial fibrillation. *Interact Cardiovasc Thorac Surg* 2015;21:163–168.
12. Balogh Z, Mizukami T, Bartunek J, Collet C, Beles M, Albano M, Katbeh A, Casselman F, Vanderheyden M, Van Camp G, Van Praet F, Penicka M. Mitral valve repair of atrial functional mitral regurgitation in heart failure with preserved ejection fraction. *J Clin Med* 2020;9:3432.
13. Nagaura T, Hayashi A, Yoshida J, Ikenaga H, Yamaguchi S, Utsunomiya H, Rader F, Siegel RJ, Kar S, Shiota T. Percutaneous edge-to-edge repair for atrial functional mitral regurgitation: a real-time 3-dimensional transesophageal echocardiography study. *JACC Cardiovasc Imaging* 2019;12:1881–1883.
14. Tamburino C, Ussia GP, Maisano F, Capodanno D, La Canna G, Scandura S, Colombo A, Giacomini A, Michev I, Mangiafico S, Cammalleri V, Barbanti M, Alfieri O. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. *Eur Heart J* 2010;31:1382–1389.
15. Vandendriessche T, Kotrc M, Tijskens M, Bartunek J, Delesie M, Paelinck BP, De Bock D, Penicka M, Stockman B, De Maeyer C, Vrints C, Vanderheyden M, Claeys MJ. Percutaneous mitral valve repair in high-risk patients: initial experience with the MitraClip system in Belgium. *Acta Cardiol* 2014;69:265–270.
16. 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.
17. 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;23:685–788.
18. Chemla D, Castelain V, Humbert M, Hébert JL, Simonneau G, Lecarpentier Y, Hervé P. New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure. *Chest* 2004;126:1313–1317.
19. Lewis GD, Bossone E, Naeije R, Grünig E, Saggar R, Lancellotti P, Ghio S, Varga J, Rajagopalan S, Oudiz R, Rubenfire M. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation* 2013;128:1470–1479.
20. Saito C, Minami Y, Arai K, Haruki S, Yagishita Y, Jujo K, Ashihara K, Hagiwara N. Prevalence, clinical characteristics, and outcome of atrial functional mitral regurgitation in hospitalized heart failure patients with atrial fibrillation. *J Cardiol* 2018;72:292–299.
21. Silbiger JJ. Mechanistic insights into atrial functional mitral regurgitation: far more complicated than just left atrial remodeling. *Echocardiography* 2019;36:164–169.
22. Ben-Yehuda O, Shahim B, Chen S, Liu M, Redfors B, Hahn RT, Asch FM, Weissman NJ, Medvedofsky D, Puri R, Kapadia S, Sannino A, Grayburn P, Kar S, Lim S, Lindenfeld J, Abraham WT, Mack MJ, Stone GW. Pulmonary hypertension in transcatheter mitral valve repair for secondary mitral regurgitation: the COAPT trial. *J Am Coll Cardiol* 2020;76:2595–2606.
23. Jogani S, Van de Heyning CM, Paelinck BP, De Bock D, Mertens P, Heidbuchel H, Claeys MJ. Afterload mismatch after MitraClip implantation: intraoperative assessment and prognostic implications. *J Invasive Cardiol* 2020;32:88–93.
24. Brouwer HJ, Den Heijer MC, Paelinck BP, Debonnaire P, Vanderheyden M, Van De Heyning CM, De Bock D, Coussement P, Saad G, Ferdinande B, Pouleur AC, Claeys MJ. Left ventricular remodelling patterns after MitraClip implantation in patients with severe mitral valve regurgitation: mechanistic insights and prognostic implications. *Eur Heart J Cardiovasc Imaging* 2019;20:307–313.
25. Debonnaire P, Heyning CMV, Haddad ME, Coussement P, Paelinck B, de Ceuninck M, Timmermans F, De Bock D, Drieghe B, Dujardin K, Vandekerckhove Y, Kedhi E, Claeys M, Van der Heyden J. Left ventricular end-systolic dimension and outcome in patients With heart failure undergoing percutaneous MitraClip valve repair for secondary mitral regurgitation. *Am J Cardiol* 2020;126:56–65.