



# Functional mitral regurgitation: structural modifications with percutaneous valve repair with MitraClip

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**Background:** Mitral regurgitation (MR) is one of the most prevalent valvular diseases in our society. Transcatheter mitral valve repair (TMVR) with the MitraClip<sup>®</sup> system is increasingly used for treating this condition. The aim of our study is to analyse morphological mitral valve changes related to the procedure and its correlation with the degree of regurgitation at mid-term follow-up and with the combined endpoint of heart failure and all-cause mortality.

**Methods:** A single-centre, prospective and observational study including consecutive patients admitted between October 2015 and October 2019 for TMVR was designed. The mitral valve annulus (MVA) was analyzed using the three-dimensional MVQ QLAB mitral valve quantification software (Philips; Amsterdam, The Netherlands). Clinical data was collected retrospectively.

**Results:** Eighty-two MitraClip<sup>®</sup> were implanted. Control echocardiograms showed a significant decrease in the three measures: annular diameters, perimeter and area. Patients with functional MR had greater left ventricular and mitral annular dimensions and experienced greater reductions in anteroposterior diameter and mitral valve area compared with organic MR patients. The anteroposterior diameter reduction (OR 0.90; 95% CI: 0.82–0.99), as well as posterior leaflet grasping (OR 0.94; 95% CI: 0.89–0.99) were associated with the probability of significant MR recurrence. Posterior leaflet grasping and left ventricle ejection fraction were associated with the combined endpoint of heart failure and any cause death.

**Conclusions:** MitraClip<sup>®</sup> implantation results in secondary changes in the mitral annular morphology. The magnitude of these morphological changes varies depending on the etiology of the mitral valve regurgitation. Posterior leaflet grasping and anteroposterior diameter reduction after clip are factors associated with relevant clinical and echocardiographic endpoints.

**Keywords:** MitraClip; percutaneous; mitral repair; functional; mitral regurgitation (MR)

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## Introduction

Mitral valve regurgitation (MR) is considered the second most prevalent valvulopathy in Europe and even the most prevalent one in the United States (1,2). During last

years, transcatheter mitral valve repair (TMVR) using the MitraClip<sup>®</sup> (Abbott Vascular, Menlo Park, California) system has gained increasing interest for treating high or prohibitive surgical risk patients with severe symptomatic

MR, as it implies a less invasive approach. As previously described (3,4), TMVR uses the edge-to-edge technique proposed by Alfieri in order to diminish MR grade. Different studies have proved its efficacy and safety and, recently, a randomized clinical trial has settled robust clinical evidence for its use in symptomatic patients with functional MR (5-8).

TMVR procedure may cause anatomical changes at the level of the mitral valve annulus (MVA) rather than just a simple edge approximation. A previous study suggested relevant changes in the antero-posterior MVA diameter only in functional MR cases (9), while other described global anteroposterior reductions with intercommissural diameter augmentation depending on the etiology of the dysfunction (10).

The aim of our study is to analyse the different morphological changes that take place at the MVA in patients undergoing TMVR, comparing the observations between MR etiologies and relating them to mid-term clinical events.

## Methods

This is a prospective and observational study performed at a tertiary-level hospital.

The aim of our study is to analyse morphological mitral valve changes related to the procedure and its correlation with the degree of regurgitation at mid-term follow-up and with the combined endpoint of heart failure and all-cause mortality.

### Patient selection

All patients with symptomatic, in spite of being under optimal medical therapy, moderate to severe (grade III/IV) or severe (grade IV/IV) MR were evaluated by a multidisciplinary Heart Team. Patients at high surgical risk and considered optimal for TMVR according to previous anatomical criteria (4,7) were included. Due to the limitations of annular anatomic changes assessment in patients with previous surgical mitral annuloplasty, those patients were excluded for this study. MR was categorized attending to its etiology: primary (organic) or secondary (functional). MR valves with combined etiology were reviewed by two experienced cardiologists in order to classify them into one of the two groups according to its main etiological component. All patients were given proper information about the procedure and signed an informed consent fulfilling Declaration of Helsinki statements.

### Percutaneous repair procedure

All TMVR procedures were performed using the MitraClip® system. This device had already received European conformity (CE mark) in 2018. Procedures were performed transoesophageally echo-guided and under general anaesthesia. Besides, they were all supervised by a technician specialized in MitraClip®. Decision regarding more than one clip implantation was taken according to the procedural team judgement. It was considered in those cases where at least one grade in MR decreased was not obtained, as long as the risk of iatrogenic mitral stenosis risk remained reasonably low.

### Echocardiographic study

Before and immediately after all procedures, 2 and 3 dimensional (3D) transoesophageal echocardiograms were performed using the late-generation ultrasound system EPIQ 7 (Philips; Amsterdam, The Netherlands). For this purpose, an extra effort was made to acquire images in similar afterload and haemodynamic conditions both before and after device implantation. Regarding three-dimensional MVA evaluation, the 3D images (Zoom 3D, Philips; Amsterdam, The Netherlands) obtained during the procedure were postprocessed with the mitral valve quantification software MVQ QLAB 10.0 (Philips; Amsterdam, The Netherlands).

Leaflet grasping analysis was calculated through the leaflet's length at the deployment plane before and after MitraClip® system implantation. Before clip, leaflet length was measured between the hinge point of the leaflet in the MVA and its free edge, whereas after clip it was measured between the aforementioned hinge point and the most distal leaflet point not yet involved between the clip arms.

Thus, absolute and relative grasping were calculated as follows:

- ❖ Absolute grasping (mm): leaflet length pre-clip – leaflet length post-clip.
- ❖ Relative grasping (%): [(leaflet length pre-clip – leaflet length post-clip)/leaflet length pre-clip] ×100.

### Study variables

#### Echocardiography

Technique success, device success and procedural success were defined according to the Mitral Valve Academic Research Consortium (11). Etiology and MR severity were

evaluated attending to the European Society of Cardiology and Echocardiography guidelines (12-14). Like in EVEREST clinical trial (4,7), severity of MR was classified into 4 different grades. All the measures were performed by only one senior Cardiologist specialist in structural imaging.

### Clinical

Functional status was evaluated by New York Heart Association (NYHA) scale. Heart failure admission was defined as a more than 24 hours hospitalization stay mainly driven by this syndrome. Follow-up main endpoints were MR grade III or IV recurrence and a combined endpoint of heart failure admission and all-cause death.

### Statistical analysis

Categorical variables are represented as absolute number and percentage, whereas quantitative ones as mean  $\pm$  standard deviation. T-Student pair test was used for the morphological evaluation of the MVA before and after device deployment. Xi-squared and T-Student test, as applicable, were used for between groups categorical and quantitative comparisons.

Binary logistic regression analysis was performed to evaluate MR grade III or IV recurrence, heart failure admission and death. A 0.05 alpha error was assumed for significance. All analysis has been performed with Stata 14 (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) software.

### Results

Between October-2015 and October-2019 a total of 82 TMVR using the MitraClip<sup>®</sup> system were performed, 20 of them (24.4%) on organic mitral regurgitation (MR) patients and 62 (75.6%) on functional ones. Mean age was 74.7 $\pm$ 7.8 and 31.7% were women. Baseline clinical and echocardiographic characteristics of the overall cohort and by etiology comparison are shown in *Tables 1* and *2*. Patients with functional MR have larger left ventricular and mitral valve annular dimensions. A total of 1.48 $\pm$ 0.6 clips were implanted per procedure. First generation clip was used in 43 (52.4%) patients, whereas late-generation clips were deployed in 39 (47.6%). A 100% of technical success was accomplished, whereas the procedural success achieved an 89% (73/82). From these nine considered unsuccessful procedures, 6 were due to post-clip MR (4 with grade III and 2 with grade IV), one due to a failed re-intervention

and 2 remaining cases presented partial detachment at 3-month follow-up.

Regarding morphological mitral valve analysis (*Table 3*), a significant overall reduction in annular diameter, perimeter and area was observed at both the two and three-dimensional analysis. Patients treated for functional MR experienced a greater relative reduction in terms of anteroposterior diameter (5.5% $\pm$ 8.4% organic *vs.* 9.8% $\pm$ 8.6% functional,  $P=0.04$ ) and three-dimensional area (0.4% $\pm$ 20.5% organic *vs.* 9% $\pm$ 13.5% functional,  $P=0.04$ ), as shown in *Table 4*. Nevertheless, there were no differences between groups in regard to absolute and relative grasping in neither the anterior nor the posterior mitral leaflet.

During a mean follow-up of 484 days (interquartile range, 182–744) there were 15 (18.3%) deaths: 5 (33.3%) due to heart failure, 1 (6.67%) because of acute coronary syndrome, 2 (13.3%) sudden cardiac deaths and 7 (46.67%) due to non-cardiovascular causes. Nineteen patients (23.17%) required hospitalization due to heart failure during follow-up, after procedural discharge. At the binary logistic regression analysis for the primary combined endpoint, after adjustment for different co-variables, left ventricle ejection fraction and relative posterior leaflet grasping were considered significant predictors (*Table 5*). At the proportional risk cox regression analysis, a trend toward a lower primary endpoint incidence was observed with higher posterior grasping, although without reaching statistical significance (hazard ratio 0.96; 95% CI: 0.92–1.01;  $P=0.08$ ). *Figure 1* shows Kaplan-Meier survival function of patients over and under the 50<sup>th</sup> percentile regarding posterior leaflet grasping percentage.

All patients were followed by periodical echocardiography, having 66 (80.5%) of them completed the 6-month follow-up transthoracic echocardiogram. From those patients, 10 (15.15%) presented a grade III or IV MR despite clip implantation (*Figure 2*). Logistic regression analysis searching for anatomical predictors of at least grade III out of IV MR was performed. Both the reduction obtained in anteroposterior mitral annular diameter after clip implantation and the magnitude of posterior leaflet grasping were predictors inversely correlated with a significant MR recurrence (*Table 6*).

A lineal regression analysis searching for anteroposterior diameter reduction predictors showed that percentual of posterior leaflet grasping was directly associated, maintaining its statistical significance after adjustment by MR etiology, with left ventricular volume, left atrial volume, basal mitral annular dimension and anterior leaflet grasping

**Table 1** Baseline overall cohort and by aetiology characteristics

Characteristics	Overall, 82 (100%)	Organic, 20 (24.4%)	Functional, 62 (75.6%)	P value
Age, years	74.7±7.8	76.9±1.6	75.3±1.1	0.46
Women	26 (31.7)	8 (40.0)	18 (29.0)	0.35
Weight, kg	76.7±19.3	77.1±3.2	76.5±2.1	0.91
Height, cm	163.4±13.1	162.6±9.8	163.7±14	0.76
Body surface area	1.85±0.23	1.86±0.19	1.85±0.24	0.84
Hypertension	62 (75.6)	14 (70.0)	48 (77.4)	0.5
Diabetes	32 (39.0)	10 (50.0)	22 (35.5)	0.24
Dyslipidaemia	43 (52.4)	13 (65.0)	30 (48.4)	0.19
Chronic kidney disease	27 (32.9)	4 (20.0)	23 (37.1)	0.24
Stroke	17 (20.7)	3 (15.0)	14 (22.6)	0.41
Ischaemic heart disease	42 (51.2)	10 (50.0)	32 (51.6)	0.9
PCI	27 (32.9)	6 (30.0)	21 (33.9)	0.75
CABG	11 (13.4)	4 (20.0)	7 (11.3)	0.32
Atrial fibrillation	56 (68.3)	13 (65.0)	43 (69.4)	0.8
MR severity				
III/IV	9 (11.0)	2 (10.0)	7 (11.3)	0.79
IV/IV	73 (89.0)	18 (90.0)	55 (88.7)	0.80
PASP, mmHg	43.8±13	44.3±11	43.6±11	0.60
COPD	21 (25.6)	7 (35.0)	14 (22.6)	0.37
Functional class				
NYHA III	58 (70.7)	15 (75.0)	43 (69.4)	0.83
NYHA IV	20 (24.4)	3 (15.0)	17 (27.4)	0.35
Euroscore II	5.65±4	5.5±4.1	5.7±5.1	0.87
STS mortality	5.19±3.2	5.88±4.8	4.9±2.1	0.27

Data are expressed as n (%) or mean ± SD. CABG, coronary artery bypass graft; COPD, Chronic obstructive pulmonary disease; MR, mitral regurgitation; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons.

( $\beta$  coefficient =0.17, 95% CI: 0.01–0.32, P=0.05). Hence, greater posterior grasping leads to a higher proportion of anteroposterior diameter reduction.

## Discussion

Our first finding is that after MitraClip® system implantation important anatomical changes are observed at the MVA, either in diameters, perimeters or area. Functional MR valves have larger sizes than the organic ones, in terms of annular

measurements (excluding intercommissural diameter). This contrast is understandable based on the different underlying physiopathological mechanism of each condition. Remy *et al.* reported anteroposterior diameter reduction in the overall cohort, whereas only organic MR patients experienced a significant decrease regarding valve area (10). Other studies conducted exclusively in functional MR valves demonstrated a significant reduction in anteroposterior diameter (10,15–17). A recently published analysis of 60 clip recipients showed significant overall reduction in

**Table 2** Baseline echocardiographic characteristics

Characteristics	Overall	Organic	Functional	P value
LVEF	493.9±14.5	51.8±11.8	41.5±14.4	0.003
iTDLVV, mL/m <sup>2</sup>	77.3±33.3	58.4±32.4	83.8±31.2	0.001
iTDLVD, mm/m <sup>2</sup>	31.5±6.9	26.6±7.6	33.2±5.8	0.001
Index left atrial volume, mL/m <sup>2</sup>	58.5±30.6	54.2±27.7	60.1±31.7	0.47
ERO, cm <sup>2</sup>	0.39±0.13	0.43±0.16	0.36±0.11	0.05
Intercommissural diameter, mm	39.1±4.8	38.5±5	39.3±4.7	0.52
Anteroposterior diameter, mm	38.1±5.1	36.5±5.1	38.7±5	0.05
2D annular perimeter, mm	124.2±14.7	120.7±17.1	125.3±13.9	0.12
3D annular perimeter, mm	129.9±15.8	124.5±17	131.6±15.1	0.04
2D annular area, cm <sup>2</sup>	12.04±2.9	11.2±3.3	12.3±2.8	0.08
3D annular area, cm <sup>2</sup>	12.44±3.1	11.5±3.4	12.7±2.9	0.05
Anterior leaflet length, mm	25.3±3.1	24.4±2.7	25.7±3.2	0.13
Posterior leaflet length, mm	13.4±2.5	13±2.4	13.5±2.5	0.12
Tenting length, mm	10.1±3.9	7.8±3.9	10.6±3.8	0.01
Tenting area, cm <sup>2</sup>	2.47±1	1.9±1.2	2.6±0.9	0.01

Data are expressed as mean ± SD. 2D, 2 dimensions; 3D, 3 dimensions; ERO, effective regurgitant orifice; iTDLVD, index telediastolic left ventricular diameter; iTDLVV, index telediastolic left ventricular volume antero-posterior; LVEF, left ventricular ejection fraction.

**Table 3** Mitral valve annular changes and leaflet grasping

Variables	Overall	P value
Intercommissural diameter reduction, mm	2.3±5.5	0.001
Intercommissural diameter reduction, %	4.2±6.2	0.001
Anteroposterior diameter reduction, mm	6.5±4.3	0.001
Anteroposterior diameter reduction, %	8.7±7	0.001
2D perimeter reduction, mm	5.2±7.3	0.001
2D perimeter reduction, %	4.1±5.7	0.001
3D perimeter reduction, mm	4.2±6.5	0.001
3D perimeter reduction, %	6.1±5.1	0.001
2D area reduction, cm <sup>2</sup>	1.1±1.5	0.001
2D area reduction, %	8±12	0.001
3D area reduction, cm <sup>2</sup>	0.9±2	0.001
3D area reduction, %	6.8±11	0.001
Anterior leaflet grasping, mm	7.2±4	NA
Anterior leaflet grasping, %	27.8±12.4	NA
Posterior leaflet grasping, mm	4.5±1.9	NA
Posterior leaflet grasping, %	33.2±12.4	NA

Data are expressed as mean ± SD. 2D, 2 dimensions; 3D, 3 dimensions; NA, not applicable.

**Table 4** Mitral valve annular change and leaflet grasping comparison among etiologies

Variables	Organic	Functional	P value
Intercommissural diameter reduction, mm	1.2±2.5	2.7±6.2	0.18
Intercommissural diameter reduction, %	2.9±6.6	4.6±6.1	0.18
Anteroposterior diameter reduction, mm	2±3.1	5.1±7.4	0.05
Anteroposterior diameter reduction, %	5.5±8.4	9.8±8.6	0.04
2D perimeter reduction, mm	4.3±6.4	5.5±7.6	0.28
2D perimeter reduction, %	3.3±5.5	4.3±6	0.27
3D perimeter reduction, mm	5±6.5	6.2±9.4	0.33
3D perimeter reduction, %	3.8±5.4	4.4±6.8	0.37
2D area reduction, cm <sup>2</sup>	0.6±0.9	1.1±1.5	0.13
2D area reduction, %	4.9±9	9±13.2	0.11
3D area reduction, cm <sup>2</sup>	0.2±2.2	1.2±1.8	0.03
3D area reduction, %	0.4±20.5	9±13.5	0.04
Anterior leaflet grasping, mm	6.9±4.1	7.3±4	0.71
Anterior leaflet grasping, %	29.9±13.3	27.2±12.2	0.43
Posterior leaflet grasping, mm	4.6±2.1	4.5±4.5	0.84
Posterior leaflet grasping, %	34.9±15.2	32.8±11.5	0.53

Data are expressed as mean ± SD. 2D, 2 dimensions; 3D, 3 dimensions.

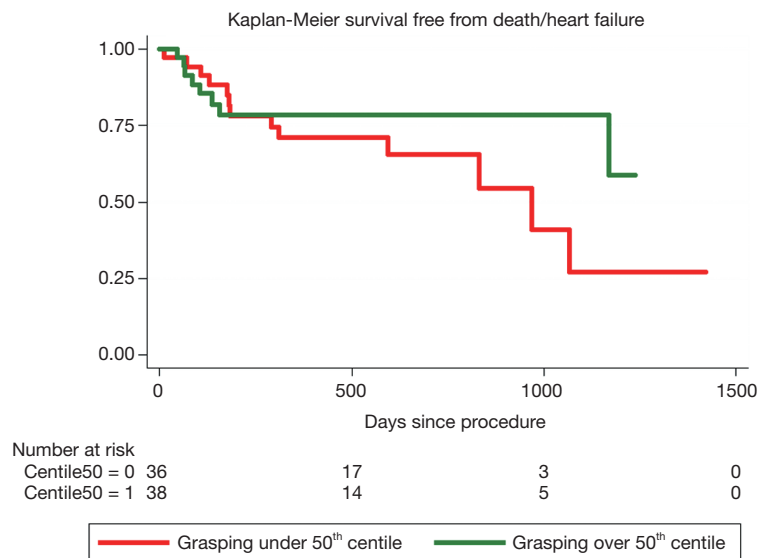
**Table 5** Binary logistic regression for the primary combined endpoint (death-heart failure)

Variables	OR	95% confidence interval	P value
Left ventricle ejection fraction	0.95	0.89–0.99	0.05
Posterior leaflet relative grasping	0.93	0.86–0.98	0.04
Tricuspid regurgitation grade pre-clip	1.08	0.49–2.41	0.31
Mitral regurgitation grade pre-clip	4.64	0.43–49.3	0.20
Anterior leaflet relative grasping	0.98	0.93–1.04	0.67
Relative anteroposterior diameter reduction	1.03	0.95–1.12	0.45
Ischaemic heart disease	1.72	0.45–6.52	0.42

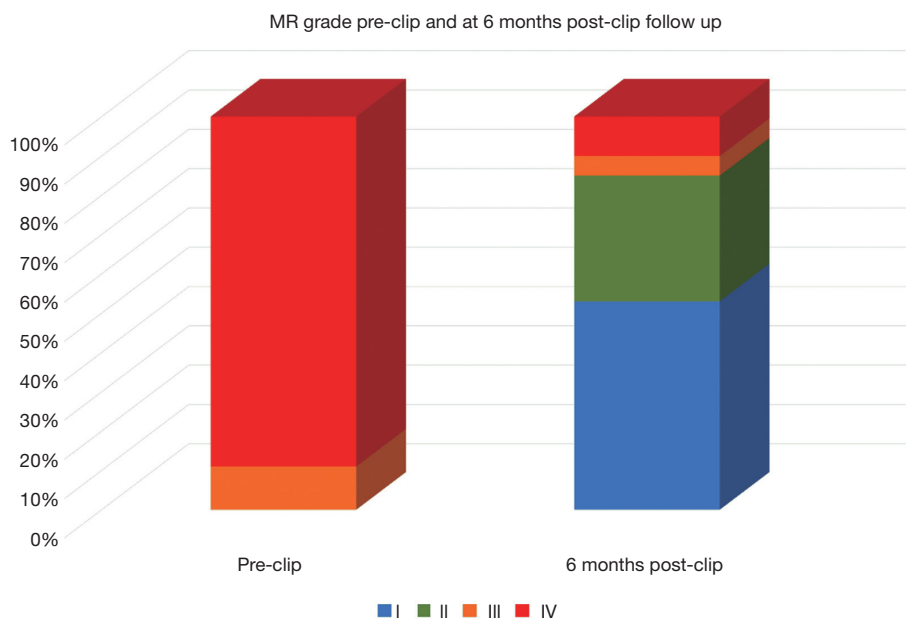
both diameter and perimeter, without differences between etiologies (16). In this study of a larger cohort, we confirmed the global geometrical changes, resulting significant in both etiological groups. However we did find differences between functional and organic valves results. In our cohort, geometrical remodelling after clip seems to be greater in functional MR patients than in organic MR ones.

Moreover, we found an association between the percentual reduction in anteroposterior diameter after

procedure and the probability of at least moderate MR recurrence during follow-up. Some previous studies did not associate this finding with any clinical or echocardiographic significant endpoints (16). Hidalgo *et al.* demonstrated a positive correlation between anteroposterior diameter reduction and effective regurgitant orifice decrease (9). Schueler *et al.* found that, exclusively in functional MR patients, the anteroposterior diameter reduction was associated with clinical response at 6 months follow-up (15).



**Figure 1** Kaplan-Meier survival function of patients over and under the 50<sup>th</sup> percentile regarding posterior leaflet grasping percentage.



**Figure 2** Mitral regurgitation pre-clip and at 6 months of follow-up.

To our knowledge, this is the first study establishing the correlation between anteroposterior diameter reduction and significant echocardiographic endpoints like MR severity at mid-term follow up.

Regarding technical modifiable aspects which may play a role in patients’ evolution, we realized that percentual posterior leaflet grasping is a significant landmark to

be focused on. This not only predicts the grade of anteroposterior diameter change obtained after clip, but also the MR recurrence. Moreover, it was associated with the main combined endpoint. Regarding to this, we think posterior leaflet grasping should play a key role during the procedure and a goal in the final result, specially in cases with posterior leaflet retraction.

**Table 6** Binary logistic regression for grade III or IV MR at 6-month follow up

Variables	OR	95% confidence interval	P value
Indexed left ventricular telediastolic volume	1.01	0.99–1.03	0.88
Indexed left atrial volume	0.99	0.97–1.02	0.97
Intercommissural diameter reduction	1.01	0.90–1.11	0.97
Anteroposterior diameter reduction	0.90	0.82–0.99	0.04
3D perimeter reduction	0.89	0.79–1.01	0.07
3D area reduction	0.95	0.90–1.02	0.15
Anterior leaflet length	1.01	0.84–1.23	0.88
Anterior leaflet grasping	0.98	0.93–1.03	0.42
Posterior leaflet length	0.96	0.75–1.23	0.75
Posterior leaflet grasping	0.94	0.89–0.99	0.05

MR, mitral regurgitation; 3D, 3 dimensions.

### Limitations

Our study has different limitations. Firstly, it is an observational study with its inherent probability of bias. Secondly, it is a single-centre analysis, what may preclude general extrapolation of our findings. Regarding this subject, we think that new studies focused on mitral valve morphology and involving a greater number of MitraClip® patients should be encouraged. Thirdly, our number of organic MR patients was modest. Thus, we declined to perform a by-etiology separated search for predictors of MR recurrence or the primary endpoint. Recently, similar prognosis was reported between different etiologies of TMVR patients in a big Spanish cohort (18). Nevertheless it was not focused on mitral valve morphological changes.

The intra-observer variability should be considered in the interpretation of the results.

### Conclusions

MitraClip® implantation results in secondary changes in the mitral annular morphology. The magnitude of these morphological changes varies depending on the etiology of the mitral valve regurgitation. Posterior leaflet grasping and anteroposterior diameter reduction after clip are factors associated with relevant clinical and echocardiographic endpoints.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the corresponding IRB (reference number: 2020/026). Written informed consent was obtained from all patients.

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