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# The prognostic impact of frailty in patients undergoing percutaneous mitral valve repair

Tomás Benito-González<sup>1</sup>, Rodrigo Estévez-Loureiro<sup>2</sup>, Samuel del Castillo<sup>1</sup>, Carlos Minguito-Carazo<sup>1</sup>, Julio Echarte-Morales<sup>1</sup>, Carmen Garrote-Coloma<sup>1</sup>, Felipe Fernández-Vázquez<sup>1</sup>

<sup>1</sup>Department of Cardiology, University Hospital of León, León 24071, Spain.

<sup>2</sup>Department of Cardiology, University Hospital Alvaro Cunqueiro, Vigo 36213, Spain.

**Correspondence to:** Dr. Rodrigo Estévez-Loureiro, Department of Cardiology. University Hospital Alvaro Cunqueiro, c/Clara Campoamor 341, Vigo 36213, Spain. E-mail: roiestevez@hotmail.com

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## Abstract

**Aim:** Percutaneous mitral valve repair (PMVR) with MitraClip® has proven to be an effective therapy to reduce mitral regurgitation in patients at high risk for conventional surgery. This population is currently characterized by advance age and high prevalence of comorbidities. Our aim was to evaluate the prevalence of frailty in a cohort of patients undergoing PMVR and its impact on clinical outcomes during follow-up.

**Methods:** A prospective registry was performed including all consecutive patients who underwent elective PMVR between June 2014 and March 2018 in our institution. Frailty was evaluated at admission with the functional FRAIL scale. In-hospital and 30-day procedural outcomes were collected. Clinical follow up was carried out including New York Heart Association (NYHA) functional class, heart failure hospitalization and death.

**Results:** Overall, 70 patients were included (mean age  $75.3 \pm 9.9$  years, 65.7% male). Among them, 27 patients (38.6%) had a pre-procedural FRAIL score greater than 2, meeting frailty criteria. No differences between frail and non-frail patients were found in technical success ( $P = 1.0$ ) or 30-day device success ( $P = 0.739$ ). At six months follow up, both groups showed a significant improvement in NYHA functional class compared to baseline (frail:  $P = 0.002$ ; non-frail:  $P < 0.001$ ). During a median follow up of 675 (range 416-976) days, frailty patients had a higher incidence of HF admission and all-cause mortality ( $P = 0.013$ ). In multivariate COX regression analysis, FRAIL score greater than 2 was significantly related to the primary composite endpoint (HR = 2.45; 95%CI: 1.02-5.88;  $P = 0.044$ ).



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**Conclusion:** Frailty was common in patients undergoing PMVR in our institution. Despite post-procedural clinical improvement, frailty was related to adverse outcomes in our series.

**Keywords:** Percutaneous mitral valve repair, mitral regurgitation, frailty

## INTRODUCTION

In the last decade, percutaneous mitral valve repair (PMVR) with MitraClip® device (Abbot Vascular, Santa Clara, USA) has proven to be an effective therapy to reduce mitral regurgitation (MR), with a low incidence of complications in patients deemed as high-risk candidates or unfit for conventional surgery<sup>[1]</sup>. Risk stratification in these patients is challenging and it is usually based on non-dedicated risk scores developed in the surgery field, with a modest predictive value in this scenario<sup>[2]</sup>.

Frailty is a clinical syndrome related to aging and characterised by a decrease in so-called “biological reserve” against a stressful event, which implies a situation of vulnerability in the case of intercurrent disease or medical issues requiring hospitalization<sup>[3]</sup>. Current candidates for PMVR are characterized by advanced age and a high prevalence of cardiovascular and non-cardiovascular comorbidities<sup>[4,5]</sup>. All these factors have been commonly related to frailty. The main objective of our study was to assess the prevalence of frailty in a cohort of patients undergoing PMVR, and to assess its impact on clinical outcomes during follow-up.

## METHODS

### Study population

A prospective registry was performed including of all consecutive patients with symptomatic MR grade 3+ or 4+ who underwent elective PMVR in our center between June 2014 and March 2018. Those who received a MitraClip® as an urgent procedure ( $n = 15$ ), during an admission for decompensated heart failure (HF), were excluded from the analysis.

### Study procedures

The indications for PMVR in each patient were discussed by an interdisciplinary Heart Team, including clinical and interventional cardiologists, cardiac surgeons, and imaging specialists. Pre-procedural transthoracic and transesophageal echocardiography was performed in all patients to assess the severity of MR and the anatomical suitability for clip implantation, following current recommendations from the European Association of Cardiovascular Imaging for valvular heart disease assessment<sup>[6]</sup>. PMVR was carried out under general anesthesia with guidance of fluoroscopy and transesophageal echocardiography.

Frailty was assessed according to functional FRAIL scale at admission for elective PMVR<sup>[7]</sup>. The FRAIL questionnaire includes 5 components (Fatigue, Resistance, Ambulation, Illness and Loss of weight) and scores range from 0 to 5, considering as frail patients with score of 3-5. Baseline characteristics, echocardiographic and biochemical findings were collected. Procedural and 30-day clinical and echocardiographic outcomes were collected. New York Heart Association (NYHA) functional class was documented at the 6-month scheduled outpatient clinic after discharge. Long-term clinical follow-up was performed including primary re-admission for heart failure (HF) and death from any cause.

### Study outcomes

Procedural results and adverse outcomes during follow-up were defined according to the “Mitral Valve Academic Research Consortium”<sup>[8]</sup>. Technical success was defined as the implantation of at least 1 clip in the absence of procedural mortality or the need for emergency cardiovascular surgery. Device success at

30 days was defined as the implantation of at least 1 clip with residual MR  $\leq 2+$  and transmitral valvular mean gradient  $< 5$  mmHg, in the absence of major adverse events (death, stroke, unscheduled cardiovascular intervention, or device detachment). Device-related complications such as fracture, migration, embolization or partial detachment were considered as structural device failure. Functional failure was defined as the suboptimal result of PMVR during follow up (residual or recurrent MR 3+ or 4+ and/or transmitral mean gradient  $\geq 5$  mmHg). Anemia was defined according to the World Health Organization as a concentration of serum hemoglobin  $< 12$  g/dL in women and  $< 13$  g/dL in men<sup>[9]</sup>. A composite primary endpoint of readmission for HF and all-cause death was established to define the prognostic impact of frailty in this series.

### Statistical analysis

Continuous variables were summarized as mean  $\pm$  standard deviation or as medians and interquartile range, and were compared using unpaired Student *t*-tests or the non-parametric Wilcoxon rank sum tests if the normal distribution of the variables could not be demonstrated. Derangement from the normal distribution was assessed with the Shapiro-Wilk test. Categorical variables were described as percentages and compared using Chi-square or Fisher exact tests accordingly to expected frequency over or below 5, respectively. Survival curves for time-to-event were constructed on the basis of all available follow-up data using Kaplan-Meier estimates, and comparisons between frail and non-frail PMVR patients were performed using the log-rank test. Cox regression multivariate analysis was performed to evaluate the prognostic impact of frailty as an independent predictor for HF hospitalizations and all-cause mortality. Variables found to be statistically significant in the univariate analysis as well as others with clinical interest were included as covariates in the multivariable model. A *P*-value  $< 0.05$  was regarded as statistically significant. Statistical analyses were performed using STATA software version 14.2.

## RESULTS

In the study period, 70 patients (age  $75.3 \pm 9.9$  years, 65.7% male) underwent elective PMVR in our center.

### Study population

Baseline characteristics of patients included in the study cohort are summarized in [Table 1](#), grouped by the presence of frailty criteria. Almost all patients (94.3%) had been admitted previously for HF, or were in advanced NYHA functional class III or IV. The etiology of the MR was predominantly functional, and patients were considered to be at high risk for conventional surgery according to surgical risk scales or Heart Team consensus. The prevalence of comorbidities was similar to other contemporary cohorts.

FRAIL questionnaire scores showed the following distribution in the cohort: score 0, 5.71%; score 1, 22.9%; score 2, 32.9%; score 3, 28.6%; score 4, 10.0%; score 5, 0%. Overall, 27 patients (38.6%) had a FRAIL score greater than 2, meeting frailty criteria. Patients classified as frail were older ( $P = 0.043$ ), and had lower body mass index (0.030), higher prevalence of low serum albumin  $< 4$  g/dL ( $P = 0.046$ ), and anemia (0.046), higher number of admissions for HF in the previous year ( $P = 0.044$ ), and worse prognosis estimated by Seattle HF risk score ( $P = 0.005$ ). Likewise, they presented worse pre-procedural NYHA functional class ( $P = 0.104$ ), higher levels of NT-proBNP ( $P = 0.070$ ), and higher surgical risk ( $P = 0.060$ ), as well as a higher prevalence of comorbidities (hypertension, advanced kidney disease, chronic obstructive pulmonary disease, or cognitive impairment), although this did not reach statistical significance.

### Procedural results

At least one clip was successfully implanted in all patients, and 28 cases (40%) were treated with 2 or more clips. No significant differences were found in the duration of the procedure ( $P = 0.749$ ), the time of fluoroscopy ( $P = 0.768$ ), or the number of clips implanted between frail and non-frail patients ( $P = 0.359$ , [Table 2](#)). One patient (1.4%) underwent emergency valve replacement due to rupture of the subvalvular

**Table 1. Baseline characteristics of patients included in the study cohort**

All patients (n = 70)	Frail (n = 27)	Non frail (n = 43)	P value	
Age (years)	75.3 ± 9.9	77.8 ± 9.0	73.7 ± 10.2	0.043
Male (%)	65.7	66.7	65.1	0.894
Body mass index (kg/m <sup>2</sup> )	27.2 ± 5.5	25.6 ± 4.3	28.2 ± 6.0	0.030
Serum albumin < 4 g/dL (%)	44.3	59.3	34.9	0.046
Smoking (%)	40.0	44.4	37.2	0.548
Hypertension (%)	65.7	77.8	58.1	0.092
Diabetes (%)	27.1	25.9	27.9	0.856
Chronic obstructive pulmonary disease (%)	30.0	40.7	23.3	0.120
Glomerular filtrate rate ≤ 60 mL/min (%)	47.1	59.3	39.5	0.108
Peripheral arteriopathy (%)	22.9	29.6	18.6	0.285
Stroke (%)	14.3	18.5	11.6	0.493
Cognitive impairment (%)	7.1	14.8	2.3	0.069
Anemia (%)	44.3	59.3	34.9	0.046
Ischemic cardiopathy (%)	48.6	48.2	48.8	0.955
Acute myocardial infarction	31.4	37.0	27.9	0.423
Coronary revascularization	40.0	40.7	39.5	0.920
Percutaneous coronary intervention	34.3	33.3	34.9	0.894
Coronary artery bypass grafting	14.3	18.5	11.6	0.423
Non-coronary cardiac surgery (%)	14.3	11.1	16.3	0.730
Implantable cardiac device (%)	31.4	22.2	37.2	0.189
Atrial fibrillation (%)	62.9	66.7	60.5	0.601
Left ventricular ejection fraction (%)	40.5 ± 16.3	41.1 ± 16.9	40.1 ± 16.1	0.597
Mitral regurgitation (%)				1.0
3+	10.0	11.1	9.3	
4+	90.0	88.9	90.7	
Etiology of mitral regurgitation (%)				0.298
Degenerative or mixed	27.1	33.3	23.3	
Ischemic functional	35.7	40.7	32.6	
Non-ischemic	37.1	25.9	44.2	
Severe pulmonary hypertension (%)	22.9	29.6	18.6	0.285
Prior heart failure admission within 12 months	1 [1-2]	2 [1-3]	1 [1-2]	0.044
NYHA functional class (%)				0.104
II	18.6	14.8	20.9	
III	67.1	59.3	72.1	
IV	14.3	25.9	7.0	
NT-pro brain natriuretic peptide (pg/mL)	2030.5 [1126.0-3428.0]	2962.0 [1525.0-9059.0]	2030.5 [1126.0-3428.0]	0.070
Euro score logistic (%)	17.4 [10.1-30.3]	21.6 [11.1-36.9]	16.0 [9.2-29.2]	0.151
Society of thoracic surgeons (%)	3.6 [1.9-5.4]	4.2 [2.4-6.1]	2.8 [1.2-5.4]	0.060
Seattle heart failure risk score (%)	16.6 [10.5-20.3]	19.8 [14.0-30.6]	15.4 [8.4-19.5]	0.005

NYHA: New York Heart Association

apparatus with massive residual MR after MitraClip® deployment. Overall, procedural technical success was 98.6%, with no differences between the two groups ( $P = 1.0$ ). Likewise, no significant differences in the incidence of major procedural complications were observed during hospitalization.

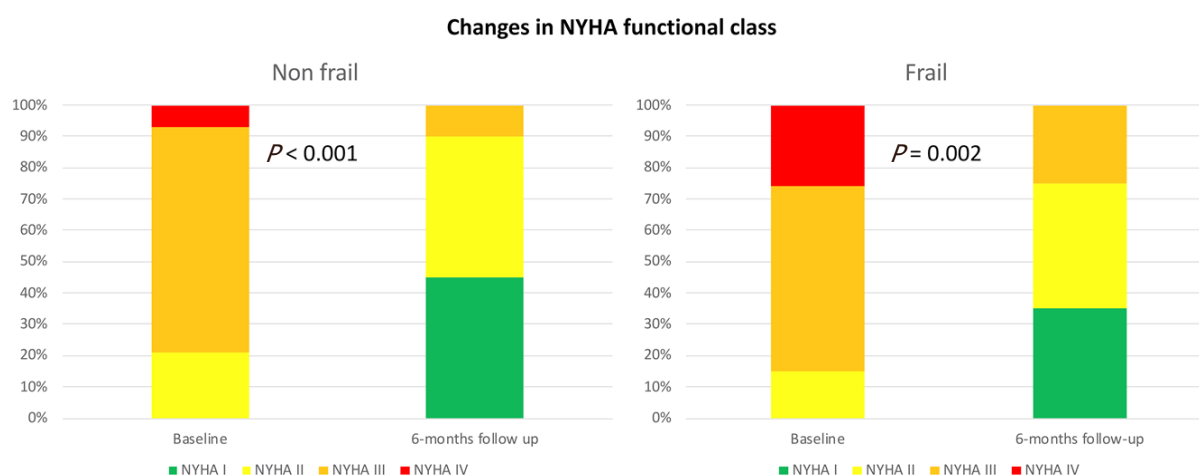
At 30-day echocardiographic follow-up, one patient (1.4%) had partial clip detachment with severe residual MR, and 6 patients (8.6%) had residual MR > 2+ and/or transmitral mean gradient ≥ 5 mmHg. One patient with very severe left ventricular dysfunction died within 30 days after discharge. Overall, device success rate at 30 days was 84.3%, with no differences between frail and non-frail groups ( $P = 0.739$ ).

### Clinical outcomes

At 6-month follow up, both groups of patients showed a significant improvement in NYHA functional class (frail:  $P = 0.002$ ; non-frail:  $P < 0.001$ ; [Figure 1](#)). During a median follow-up of 675 days (range 416-976), 22 patients (31.4%) were hospitalized due to HF and 16 patients (22.9%) died. The composite endpoint of readmission for HF or death from any cause occurred in 30 patients (42.9%).

**Table 2. Short-term procedural outcomes**

All patients (n = 70)		Frail (n = 27)	Non frail (n = 43)	P value
Procedure	Days of admission	4 [4-5]	4 [4-5]	0.625
	Device time (min)	62.5 [45.0-86.0]	70.0 [42.0-95.0]	0.749
	Fluoroscopy time (min)	40.8 [34.3-50.0]	43.4 [34.4-54.0]	0.768
	Number of clips	1 [1-2]	1 [1-2]	0.359
	Emergent cardiac surgery (%)	1.4	0	1.0
	Procedural death (%)	0	0	1.0
30-day	Technical success (%)	98.6	100	1.0
	Cardiovascular intervention (%)	4.3	0	0.279
	Stroke (%)	0	0	1.0
	Transient ischemic attack (%)	2.9	3.7	1.0
	Major vascular complication (%)	2.9	3.7	1.0
	Major structural complication (%)	0	0	1.0
	Major bleeding (%)	7.1	11.1	0.367
	Life-threatening or fatal bleeding (%)	0	0	1.0
	Acute kidney injury grade 2 or 3 (%)	0	0	1.0
	Death (%)	1.4	3.7	0.386
	Structural failure (%)	1.4	3.7	0.386
	Functional failure (%)	8.6	11.1	0.670
	Device success (%)	84.3	81.5	0.739

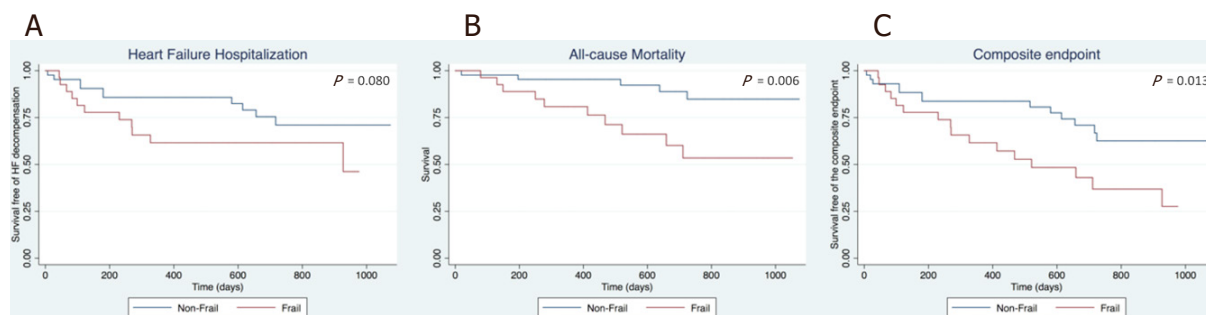
**Figure 1.** Changes in NYHA functional class according to frailty status. NYHA: New York Heart Association

Frail patients had a non-significantly higher rate of HF hospitalization (log-rank test:  $P = 0.080$ , [Figure 2A](#)), and a lower survival (log-rank test:  $P = 0.006$ , [Figure 2B](#)), compared to non-frail patients. Survival free of the composite endpoint was significantly lower in the group of frail patients (log-rank test:  $P = 0.013$ , [Figure 2C](#)), with a probability of survival with no HF re-admission at one-year follow up of 61.6% vs. 83.7% in frail and non-frail patients, respectively.

In Cox regression analysis, frailty was significantly related to the composite endpoint in the univariate analysis (HR = 2.59; 95%CI: 1.24-5.41;  $P = 0.011$ ). This association was not significantly modified (HR = 2.45; 95%CI: 1.02-5.88;  $P = 0.044$ ) after adjusting in a multivariate model including the following variables: age, diabetes mellitus, advanced chronic kidney disease (stage IIIb-V), pre-procedural NYHA functional class, high Seattle HF risk score, and atrial fibrillation.

## DISCUSSION

This study analyzed the prevalence of frailty in a single-center cohort of patients undergoing elective PMVR, and its impact on clinical outcomes during a median follow-up over 1 year. The main findings of



**Figure 2.** Kaplan-Meier curves displaying survival free from heart failure or death. A: Heart failure rehospitalizations. Frail patients experienced higher prevalence during follow-up; B: All cause mortality. Frail patients showed higher death rate than non frail patients; C: Composite end-point (death/readmission due to heart failure). Frail patients showed worse outcome.

our report were the following: (1) the prevalence of frailty in this series was high (about 2 out of 5 patients); (2) no differences in procedural outcomes and short-term device success rates were observed between frail and non-frail patients; (3) NYHA functional class significantly improved in both groups at 6-months follow-up after PMVR; and (4) frailty was significantly related to a higher risk of HF readmission or death from any cause during long-term follow-up.

Prevalence of frailty among patients with cardiovascular disease ranges between 25% to 50%, depending on the scales used and the clinical setting<sup>[10]</sup>. In addition, many reports have shown a higher incidence of adverse events in frailty patients with ischemic heart disease, HF, or those undergoing cardiac surgery, or percutaneous intervention for either coronary or structural heart disease<sup>[11-14]</sup>. In the latter scenario, several studies have pointed out that patients deemed as frail who undergo percutaneous aortic valve replacement have worse prognosis than those that do not meet frailty criteria<sup>[14,15]</sup>. Similar findings have been reported in patients undergoing PMVR. In this regard, Metzke *et al.*<sup>[16]</sup> observed a prevalence of frailty according to the FRIED score of 45.5% in a cohort of more than 200 patients who received MitraClip®. In this series, device success rates were similar among frail and non-frail patients, and a significant improvement was observed in both groups in the NYHA functional class, 6-min walk test, and quality of life questionnaires. However, frailty was significantly related to a higher probability of readmission for HF or death from any cause during a median follow-up of more than 1 year. Likewise, in our study, the presence of frailty according to the FRAIL score was associated with a more than two-fold increase in the incidence of the composite endpoint, despite similar short-term procedural results and functional improvement.

Multiple frailty scales have been validated in different clinical settings<sup>[3]</sup>. Some, such as the FRIED score, focus on physical strength and walking speed. This “uni-dimensional” approach has a higher predictive value in some scenarios of cardiovascular disease, although their use in daily practice is limited by its greater complexity and time demands<sup>[17]</sup>. On the other hand, the “multidimensional” approach, including the FRAIL scale, considers that frailty is an accumulation of comorbidities, deficits and symptoms involving one or more domains of human functioning. These scores are based on clinical questionnaires and the subjective judgment of the healthcare provider. The advantages of this approach are that it is simple to perform and can be used in patients with any stage of disability as a screening test. To the best of our knowledge, this is the first study to evaluate the prognosis impact of the FRAIL score in PMVR.

In between both scores, a modified FRAIL scale has been recently suggested, adding a rapid physical test (e.g., the ability to get up from the chair), a questionnaire to address cognitive impairment, and two laboratory parameters (serum albumin and hemoglobin) to the traditional score<sup>[14]</sup>. This “Essential Frailty Toolkit” demonstrated a greater predictive value for adverse events compared to other scales in patients with severe aortic stenosis undergoing either surgical or percutaneous valve replacement. Further studies

are needed to assess its usefulness in patients undergoing other structural interventional procedures.

PMVR with MitraClip® has proven to persistently reduce MR with low rates of procedural complications in patients at high surgical risk<sup>[18]</sup>. Furthermore, observational registries have shown a significant improvement in functional class, 6-minute walk test and quality of life<sup>[19]</sup>. More recently, data from randomized controlled trials suggest that there might be a survival benefit of MitraClip® compared to stand-alone medical therapy in patients with functional MR<sup>[20-22]</sup>. Nevertheless, selection of patients in order to find those who will benefit the most from PMVR and avoid futility is still extremely challenging. In this regard, pre-procedural evaluation of frailty might help to identify those patients with very poor short-term prognosis and those at a higher risk of non-cardiovascular mortality<sup>[23]</sup>. Although there is extensive evidence of the prognosis impact of frailty in cardiovascular disease, some aspects should be taken into account. First, frailty, in the absence of advanced disability, is a potentially reversible and treatable condition, so that a pre-procedural intervention could hypothetically improve the clinical prognosis of patients at high risk<sup>[24]</sup>. Second, the latest recommendations of the geriatric societies do not consider frailty as a contraindication to any invasive treatment but, on the contrary, as an important assessment element to establish an individualized plan of care<sup>[3]</sup>. Therefore, frailty should be an additive point to address by the multidisciplinary Heart Team when considering a potential candidate for MitraClip®, never a single tool for decision making. Risk stratification of patients undergoing PMVR is currently based on non-dedicated scales developed in the surgical field with a modest power of discrimination in this scenario<sup>[2]</sup>. The implementation of frailty scales might improve selection of patients<sup>[25]</sup>. Finally, despite an worse prognosis, frail patients showed a significant clinical improvement in the short-term and, therefore, this therapy might be considered for symptomatic relief in the absence of other reliable alternatives, even in the absence of consistent survival benefit.

### Limitations

This study has some limitations. First of all, it is a single center small cohort of patients. Second, no dedicated test has been included to assess physical frailty, such as pressure force or gait speed. Third, frailty was not re-evaluated during follow up.

In conclusion, frailty was a frequent finding among patients undergoing PMVR. The presence of this syndrome did not impact procedural success. Despite symptomatic improvement in this patient group after PMVR, frailty was associated with an increase in adverse outcomes during follow-up. Further studies are needed to validate our results, and to assess whether any intervention to improve this syndrome can modify the prognosis of this patient group.

### DECLARATIONS

#### Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Benito-González T, Estévez-Loureiro R

Performed data acquisition, as well as provided administrative, technical, and material support: del Castillo S, Minguito-Carazo C, Echarte-Morales J, Garrote-Coloma C

Drafted the paper: Benito-González T, Estévez-Loureiro R, Garrote-Coloma C

Reviewed critically: Fernández-Vázquez F

Gave final approval: Benito-González T, Estévez-Loureiro R, del Castillo S, Minguito-Carazo C, Echarte-Morales J, Garrote-Coloma C, Fernández-Vázquez F

#### Availability of data and materials

Data of this work can be provided in case of formal request and under a legitimate cause.

### Financial support and sponsorship

None.

### Conflicts of interest

Benito-González T received an unrestricted research grant from Abbot Vascular not related to this report; Estévez-Loureiro R and Garrote-Coloma C are proctors for MitraClip®.

### Ethical approval and consent to participate

This research has been conducted in accordance with the Declaration of Helsinki and approved by University Hospital of Leon ethics committee. All participants gave informed consent.

### Consent for publication

Not applicable.

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