

## Implantation of More than One MitraClip in Patients Undergoing Transcatheter Mitral Valve Repair: Friend or Foe?

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### ABSTRACT

**AIM:** Mitral valve repair by means of cardiac surgery is effective yet associated with peri-operative complications. Transcatheter mitral valve repair (TMVR) with MitraClip is emerging as a safe and effective alternative in high-risk patients. There is uncertainty however on the outlook of patients requiring >1 MitraClip for TMVR.

**METHODS:** We retrospectively collected data on patients undergoing TMVR at three tertiary care centers. Subjects requiring a single MitraClip were compared with those requiring >1 MitraClip during the index procedure. Patients were followed after discharge for events and echocardiographic changes.

**RESULTS:** A total of 74 subjects were included, all but 1 achieving procedural success: 54 (74%) were treated with a single MitraClip,

and 19 (26%) required >1 MitraClip. Baseline and procedural features were similar in the groups, with the notable exclusion of female gender, which was less prevalent in those requiring >1 MitraClip ( $p=0.030$ ). Clinical outcomes were also similar in the groups, with a general trend toward fewer adverse events in the >1 MitraClip group. Notably, both groups showed similar improvements in MR severity during follow-up, which overall were evident in 68 cases (96%).

**CONCLUSIONS:** Minimally invasive valve repair with MitraClip for mitral regurgitation is equally safe and effective if a single or >1 MitraClip are required. As no clear-cut features predict the need for multiple MitraClip implantation, clinicians should maintain a high index of suspicion and be prepared to perform multiple MitraClip deployments in most cases.

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**Key words:** Heart failure; MitraClip; Mitral regurgitation; Mitral valve repair

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### INTRODUCTION

Mitral regurgitation (MR) has a significant morbidity and mortality burden worldwide<sup>[1]</sup>. Surgical repair still represents the gold standard treatment, but it may be associated with peri-procedural complications, especially in the elderly or those with other adverse features<sup>[2]</sup>. Accordingly, minimally invasive means, either surgical or based on transcatheter approaches, have been developed to treat MR, with the most robust and comprehensive data available for MitraClip (Abbott Vascular, Santa Clara, CA, USA), which is based on the transcatheter implantation of one or more clipping devices to perform a mitral valve repair according the Alfieri "edge to edge" technique<sup>[3-5]</sup>.

Among all patients with significant MR, those at high surgical risk and suitable valve anatomy (amounting to up to 20-25% of the whole set of patients at risk) may thus undergo transcatheter mitral valve repair (TMVR) with MitraClip, typically based on the implantation of a single MitraClip device<sup>[6-7]</sup>. Yet, some subjects require the implantation of >1 clipping device during the same procedure<sup>[8-9]</sup>. There are limited data concerning these patients, and specifically their baseline, echocardiographic and angiographic features. Indeed, it would be crucial to be able to recognize beforehand, if at all possible, those subjects requiring >1 MitraClip in order to optimally plan the procedure in advance and to identify more precisely which patients are truly eligible for TMVR and which ones are, at least in relative terms, unsuitable for a single MitraClip TMVR. This is so especially as it remains unclear whether the implantation of >1 MitraClip may have untoward short- or long-term impacts on patients<sup>[10]</sup>. Indeed, patients requiring >1 MitraClip might be at higher risk of device embolization, infection, or iatrogenic mitral stenosis. Conversely, having more than >1 MitraClip might protect from device fatigue and fracture and maintain valve competence even if one MitraClip has deteriorated or embolized. Accordingly, having the opportunity to predict beforehand which patients and valves will require >1 MitraClip would increase the safety, procedural success and long-term durability of the results of TMVR.

Indeed, a recent study on 43 patients has showed that >1 MitraClip is typically required in 48% of cases, and suggested that >1 MitraClip is required especially when vena contracta was >7.5 mm<sup>[9]</sup>. Yet, in this work there was no significant difference in short- or long-term clinical outcomes when comparing subjects receiving a single vs >1 MitraClip. However, uncertainty persists on these findings given the limited sample size, lack of independent core lab analysis, and risks of tautology or multiplicity.

We thus aimed to further clarify whether there are potential pre-procedural predictors of the need for multiple MitraClip implantation and to compare the outlook of these patients to those requiring a single MitraClip, by retrospectively pooling data from three centers performing MitraClip procedures.

## METHODS

This was a retrospective multicenter registry examining prospectively-collected data entered into administrative databases.

Patients were included if undergoing elective MitraClip implantation for moderate or severe ( $\geq 2+/4+$ ) MR, irrespective of underlying etiology or morphology. All patients were deemed at high surgical risk at heart team evaluation and were considered suitable candidates for TMVR on the basis of at least one year life expectancy and lack of anatomic contraindications to MitraClip implantation.

Procedures were performed by experienced operators under general anesthesia and through fluoroscopic and trans-esophageal echocardiographic (TEE) guidance. MitraClip implantation was performed according to established protocols after having accessed the right femoral vein with a 24 French sheath and having completed trans-septal puncture. All MitraClip implantations were attempted with the standard central clip concept<sup>[9]</sup>. After successful implantation of the first MitraClip, additional MitraClip implantation was attempted or envisioned only if TEE did not disclose a meaningful reduction ( $\leq 2+$ ) in mitral regurgitation. At the end of the procedure patients were first weaned and afterward extubated and then monitored for at least 24 hours. Subjects without an indication for oral anticoagulants continued aspirin plus clopidogrel for one month followed by aspirin alone for additional two months.

Control trans-thoracic echocardiography (TTE) was performed before discharge, one month, three months, and six months after the procedure, with subsequent follow-up exams every 6-12 months. Clinical follow-up was performed at the same time intervals by office visit or phone contact, if TTE had been performed elsewhere.

Outcomes of interest were procedural success (successful clip implantation with residual mitral regurgitation grade  $\leq 2+/4+$ ), improvement in mitral regurgitation grade at discharge, total hospital stay, and in-hospital events (death, myocardial infarction, major bleeding or acute kidney injury). In addition, we appraised the occurrence during follow-up of death, myocardial infarction, stroke, mitral valve surgery, rehospitalizations after successful discharge, mitral regurgitation grade, and New York Heart Association class.

Given our aim to compare patients undergoing implantation of 1 versus >1 MitraClip, statistical analysis was based on bivariate analyses using chi-squared tests for categorical variables belonging to a 2 by >2 contingency table, Fisher exact tests for categorical variables belonging to a 2 by 2 contingency table, and unpaired Student *t* tests for continuous variables. Statistical significance was set at the 2-tailed 0.05 level. Computations were performed with SPSS 20 (IBM, Armonk, NY, USA).

## RESULTS

A total of 74 subjects were included, in whom MitraClip implantation was envisioned. All but one achieving procedural success: 54 (74%) were treated with a single MitraClip, and 19 (26%) required >1 MitraClip. Specifically, one patient became unstable shortly after trans-septal puncture leading to discontinuation of the procedure. This subject, who had multiple severe comorbidities, died shortly afterwards of multi-organ failure, without any further attempt at MitraClip implantation. Thus, for the purpose of the present work, he has been excluded from the subsequent analyses (Table 1, 2, 3).

Baseline and procedural features were similar in the two groups of remaining patients, with the notable exclusion of female gender, which was less prevalent in those requiring >1 MitraClip [4 (21%) versus 28 (52%) in the single MitraClip group,  $p=0.030$ ]. Clinical outcomes, either in-hospital or at mid-term (six months), were similar in the groups, with a general trend toward fewer adverse events in the >1 MitraClip group. Specifically, after an average of six months after the index procedure, death had occurred in one (5%) patient in the >1 MitraClip group versus 9 (17%) in the single MitraClip group (0.437), with similar, albeit largely non-significant, trends in favor of the multiple MitraClip group for mitral valve replacement [0 versus 1 (2%),  $p=1.0$ ] and rehospitalizations after successful discharge [1 (8%) versus 4 (12%),  $p=1.0$ ]. In-hospital and follow-up echocardiography showed that both groups exhibited similar improvements in mitral regurgitation severity, which overall were evident in 68 cases (96%): 18 (95%) in the >1 MitraClip group and 50 (96%) in the single MitraClip group ( $p=1.0$ ). Specifically, MR was moderate or less than moderate ( $\leq 2+/4+$ ) in 15 (79%) of those receiving >1 Mitraclip versus 37 (69%) of those receiving a single MitraClip ( $p=0.307$ ).

Explicit comparative analysis of baseline, procedural and echocardiographic features did not disclose any significant difference between the two groups of interest, including age ( $p=0.821$ ), presence/etiology of cardiomyopathy ( $p=0.202$ ), EuroSCORE II (an established risk score to quantify operative risk,  $p=0.925$ ), MR severity ( $p=0.926$ ), type of MR ( $p=0.068$ ), end-diastolic volume ( $p=0.742$ ), end-systolic volume ( $p=0.966$ ), coaptation length ( $p=0.616$ ), vena contracta ( $p=0.479$ ), or effective regurgitant orifice area ( $p=0.436$ ). Even procedural time and radiation exposure were

<b>Table 1</b> Baseline features.				
	Single MitraClip (N=54)	>1 MitraClip (N=19)	Total (N=73)	P value
Age (years)	74.8 ± 75.2	75.2 ± 5.4	74.9 ± 6.2	0.821
Height (cm)	162.4 ± 5.7	162.6 ± 9.1	162.4 ± 6.9	0.941
Weight (kg)	72.3 ± 10.1	66.3 ± 11.9	70.1 ± 11.0	0.149
Female gender	28 (51.9%)	4 (21.1%)	32 (43.8%)	0.030
Hypertension	42 (79.2%)	15 (78.9%)	57 (79.2%)	1.0
Diabetes mellitus	14 (26.0%)	8 (42.1%)	22 (30.1%)	0.095
Prior myocardial infarction	20 (37.0%)	10 (52.6%)	30 (41.1%)	0.235
Prior percutaneous coronary intervention	14 (25.9%)	8 (44.4%)	22 (30.6%)	0.140
Prior coronary artery bypass grafting	12 (23.1%)	7 (38.9%)	19 (27.1%)	0.226
Prior PM, ICD or CRT implantation				0.815
No	35 (74.5%)	14 (77.8%)	49 (75.4%)	
PM	4 (8.5%)	2 (11.1%)	6 (9.2%)	
ICD	8 (17.0%)	2 (11.1%)	10 (15.4%)	
CRT	0	0	0	
Cardiomyopathy				
No	14 (25.9%)	4 (21.1%)	18 (24.7%)	0.229
Dilated	29 (53.7%)	11 (57.9%)	40 (54.8%)	0.202
Ischemic	14 (25.9%)	6 (31.6%)	20 (27.4%)	0.205
New York Heart Association class				0.221
I-II	0	0	0	
III	41 (75.9%)	11 (57.9%)	52 (71.2%)	
IV	12 (22.2%)	8 (42.1%)	20 (27.4%)	
Atrial fibrillation	25 (46.3%)	10 (52.6%)	35 (47.9%)	0.188
Renal failure	19 (35.2%)	6 (31.6%)	25 (34.2%)	0.215
Chronic obstructive pulmonary disease	14 (25.9%)	3 (15.8%)	17 (23.3%)	0.178
EuroSCORE II	10.4 ± 16.1%	10.0 ± 14.8%	10.2 ± 15.7%	0.925
Society of Thoracic Surgery score	6.9 ± 6.1%	5.9 ± 6.0%	6.7 ± 6.1%	0.540

CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; PM: pace-maker.

<b>Table 2</b> Procedural and echocardiographic features.				
	Single MitraClip (N=54)	>1 MitraClip (N=19)	Total (N=73)	P value
Baseline echocardiography				
MR degree				0.926
Moderate	3 (5.6%)	1 (5.3%)	4 (5.5%)	
Moderate-severe	20 (37.0%)	8 (42.1%)	28 (38.4%)	
Severe	31 (57.4%)	10 (52.6%)	41 (56.2%)	
Type of MR (Carpentier classification)				
I	40 (74.1%)	12 (63.2%)	52 (71.2%)	0.151
II	10 (18.5%)	7 (36.8%)	17 (23.3%)	0.068
IIIa	13 (24.1%)	6 (31.6%)	19 (26.0%)	0.189
IIIb	2 (3.7%)	1 (5.3%)	3 (4.1%)	0.437
LV ejection fraction (%)	39.7±11.8	41.9±11.1	40.3±11.6	0.486
LV end-diastolic volume (mL)	149±55	141±48	147±53	0.742
LV end-systolic volume (mL)	46±7	36±10	44±6	0.966
Coaptation length (mm)	5.7±3.1	7.0±2.8	6.0±2.9	0.616
Vena contracta (mm)	9.2±2.8	8.7±2.8	9.1±2.8	0.479
Effective regurgitant orifice area (mm <sup>2</sup> )	9.1±3.3	8.2±3.2	8.8±3.2	0.436
Moderate-severe or severe AR	0	1 (5.3%)	1 (1.4%)	
Systolic pulmonary artery pressure (mm Hg)	50±15	47±16	49±15	0.347
Procedural success	54 (100%)	19 (100%)	73 (100%)	1.0
Procedural time (minutes)	131±69	148±71	135±69	0.374
Radiation dose (Gy cm <sup>2</sup> )	218±152	210±125	215±138	0.926
Follow-up echocardiography				
MR degree				0.307
Less than moderate	37 (68.5%)	15 (78.9%)	52 (71.2%)	
Moderate	13 (24.1%)	1 (5.3%)	12 (16.4%)	
Moderate to severe	1 (1.9%)	2 (10.5%)	3 (4.1%)	
Severe	1 (1.9%)	0	1 (1.4%)	
Improvement in MR severity	50 (96.2%)	18 (94.7%)	68 (95.8%)	1.0
Change in vena contracta (mm)	5.8±3.5	5.5±3.8	5.7±3.6	0.833
Change in effective regurgitant orifice area (mm <sup>2</sup> )	3.8±3.3	3.3±2.7	3.7±3.1	0.698
Change in LV ejection fraction (%)	0.8±5.5	0.6±9.3	0.8±6.6	0.875
Change in LV end-diastolic volume (mL)	-5.1±55.2	-4.3±33.9	-4.9±50.7	0.962
Change in LV end-systolic volume (mL)	-7.9±40.9	-0.2±20.7	-6.1±37.2	0.531
Change in systolic pulmonary artery pressure (mm Hg)	12±13	6±16	10±14	0.175
Moderate-severe or severe AR	0	0	0	1.0

AR: Aortic regurgitation; LV: Left ventricular; MR: Mitral regurgitation; TAPSE: Tricuspid annular plane systolic excursion.

**Table 3** Outcomes.

	Single MitraClip (N=54)	>1 MitraClip (N=19)	Total (N=73)	P value
In-hospital follow-up				
Total hospital stay (days)	6.7 ± 3.3	6.1 ± 2.0	6.6 ± 3.0	0.429
Final disposition				
Death	1 (1.9%)	0	1 (1.4%)	
Discharge home	53 (98.1%)	18 (94.7%)	71 (97.3%)	0.110
Transfer to other facility	0	1 (5.3%)	1 (1.4%)	
Myocardial infarction	0	0	0	1.0
Stroke	0	0	0	1.0
Major bleeding	0	1 (5.3%)	1 (1.4%)	0.260
Acute kidney injury	0	2 (10.5%)	2 (2.7%)	0.065
Long-term follow-up				
Follow-up duration (months)	6.2 ± 6.5	4.5 ± 5.8	5.7±6.3	0.346
Death	9 (16.7%)	1 (5.3%)	10 (13.7%)	0.437
Myocardial infarction	0	0	0	1.0
Stroke	0	0	0	1.0
Mitral valve replacement	1 (1.9%)	0	1 (1.4%)	1.0
Rehospitalization after successful discharge	4 (11.8%)	1 (8.3%)	5 (10.9%)	1.0
Rehospitalization or death after successful discharge	12 (22.2%)	2 (10.5%)	14 (19.2%)	0.159
New York Heart Association class				
I-II	22 (64.7%)	5 (41.7%)	27 (58.7%)	
III	11 (32.4%)	6 (50.0%)	17 (37.0%)	
IV	1 (2.9%)	1 (8.3%)	2 (4.3%)	

not significantly different in the groups ( $p=0.374$  and  $p=0.926$ , respectively).

## DISCUSSION

This real-world registry, pooling data from three tertiary care centers with extensive experience with surgical and TMVR, suggests that minimally invasive valve repair with MitraClip for MR is equally safe and effective if a single or >1 MitraClip are required. As no clear-cut features predict the need for >1 MitraClip implantation, clinicians should maintain a high index of suspicion and be prepared to perform >1 MitraClip deployment in most cases. While theoretically implanting >1 MitraClip may lead to heightened risks of infection, embolization and mitral stenosis, cardiologists should not consider the occurrence of multiple MitraClip implantation as an ominous event, as it is not associated with significant increases in procedural duration, procedural risk, or suboptimal results at follow-up<sup>[9]</sup>.

Mitral regurgitation is a common valve disease with an increasing incidence and prevalence over the last few decades given the concurrent epidemics in degenerative and functional mitral insufficiency<sup>[1]</sup>. Surgical management, either with valve replacement or repair, is universally considered the referencetreatment, as it combines several important technical aspects, including annuloplasty and sub-valvular apparatus intervention (e.g. with neochordae)<sup>[2-11]</sup>. However, it has an obvious invasiveness and indications, notwithstanding recent developments in port-access and video-assisted mitral minimally invasive surgery<sup>[12-13]</sup>.

Transcatheter mitral valve repair holds the promise of achieving results similar to those of surgery in terms of efficacy, but with fewer adverse events<sup>[14]</sup>. However, surgery still appear to have the winning hand, especially in terms of complete repair and durability. Nonetheless, very favorable results have been so far reported on the MitraClip approach. Based on the ingenious Alfieri double-orifice stitching technique, the MitraClip device enables the transcatheter deployment of 1 or more nitinol clips fix together the regurgitant mitral valve leaflets. Four-year follow-up data stemming from the pivotal EVEREST II trial have confirmed prior more preliminary data<sup>[15]</sup>, showing that MitraClip can indeed provide favorable results in terms of safety and efficacy for patients requiring mitral

valve repair for significant regurgitation, albeit not matching yet the outcomes offered by surgery<sup>[3,15]</sup>. Thus, while awaiting for new devices and percutaneous techniques enabling transcatheter annuloplasty (possibly in combination with MitraClip implantation), it is important to focus on how best exploit the MitraClip device and maximize its yield. Indeed, achieving procedural success and discharge mitral regurgitation grade are indeed very important goals of any MitraClip procedure, as they are the main prognostic factor in patients candidate for transcatheter mitral valve repair<sup>[16]</sup>.

Several different methodological papers have focused on different approaches to perform MitraClip implantation, and go from the non-central repair approach to the zipping technique<sup>[8,17]</sup>. More pragmatically, we often asked ourselves whether a single MitraClip was always the best choice, and what was the fate of patients requiring >1 MitraClip because the first, despite being successfully implanted, had not provided a meaningful reduction in mitral regurgitation as recently highlighted by Alegria-Barrero and colleagues<sup>[9]</sup> in a cohort of 43 patients who underwent MitraClip implantation (albeit successful in 93%). More than one MitraClip was required in 48% of them, and this occurrence was more common in this registry in subjects with larger vena contractas or people with two broad jets. Conversely, this event was less frequent in patients with a restricted posterior mitral valve leaflet. Nonetheless, at multivariable analysis only vena contracta appeared as a significant predictor of >1 MitraClip implantation. Notably, in this relatively small series, mid-term survival was lower, albeit non-significantly, in the >1 MitraClip group (84% versus 95% in the single MitraClip group)<sup>[9]</sup>.

Our larger series, while focusing on the same topic, is at odds with the above work for three main reasons. First, in our experience >1 MitraClip is required in only 26% of cases. Second, we did not identify any variable meaningfully associated (either at baseline clinical examination or at echocardiographic assessment) with the need to implant >1 MitraClip. Accordingly, operators should maintain a high index of suspicion and consider any case as a potential one for >1 MitraClip implantation. Finally, echocardiographic and clinical results of subjects receiving >1 MitraClip are, counterintuitively, at least as good as those of patients receiving only 1 MitraClip. Thus, these findings may suggest that in the future a more liberal use of >1 MitraClip, if proven capable of further reducing MR severity without

increasing complication rates, could provide additional clinical benefits.

Indeed, we cannot exclude that implantation of a single MitraClip might not be insufficient to achieve and maintain long-term a meaningful reduction in mitral regurgitation. In addition, >1 MitraClip implantation could reduce the mechanical stress on valve leaflets and minimize the risk of clip detachment or leaflet damage. Additionally, in case of clip detachment, another MitraClip already in place might safeguard the patient from sudden recurrence of severe mitral regurgitation. However, >1 MitraClips also have their, at least theoretical, drawbacks, which include the risk for restrictive valve physiology and the potential additional hurdles created by extensive valve scarring in case surgical valve repair is ever considered after transcatheter mitral valve repair<sup>[18]</sup>. Last, the economic aspect of multiple MitraClip implantation faced to conventional surgery could challenge the entire aspect of the procedure.

Limitations of this work include the retrospective observational design, the lack of explicit, uniform and pre-hoc criteria guiding implantation of >1 MitraClip, and the follow-up limited to mid-term. As only larger series and prospective studies (despite being obviously problematic) will be able to definitely clarify which, if any, features can predict the need for >1 MitraClip implantation, and whether this occurrence may have favorable or unfavorable clinical consequences, further studies exploiting dedicated criteria for >1 MitraClip implantation and ensuring a longer follow-up time are warranted.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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