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Management and Outcome of Failed Percutaneous Edge-to-Edge Mitral Valve Plasty

Insight From an International Registry

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ABSTRACT

OBJECTIVES This study evaluated the incidence, management, and outcome of patients who experienced MitraClip (Abbott Vascular) failure secondary to loss of leaflet insertion (LLI), single leaflet detachment (SLD), or embolization.

BACKGROUND Transcatheter edge-to-edge repair with MitraClip is an established therapy for the treatment of mitral regurgitation (MR), but no data exist regarding the prevalence and outcome according to the mode of clip failure.

METHODS Between January 2009 and December 2020, we retrospectively screened 4,294 procedures of MitraClip performed in 19 centers. LLI was defined as damage to the leaflet where the MitraClip was attached, SLD as demonstration of complete separation between the device and a single leaflet tissue, and clip embolization as loss of contact between MitraClip and both leaflets.

RESULTS A total of 147 cases of MitraClip failure were detected (overall incidence = 3.5%), and these were secondary to LLI or SLD in 47 (31.9%) and 99 (67.3%) cases, respectively, whereas in 1 (0.8%) case clip embolization was observed. MitraClip failure occurred in 67 (45.5%) patients with functional MR, in 64 (43.5%) patients with degenerative MR, and 16 (10.8%) with mixed etiology. Although the majority of MitraClip failures were detected before discharge (47 intraprocedural and 42 in the hospital), up to 39.5% of cases were diagnosed at follow-up. In total, 80 (54.4%) subjects underwent a redo procedure, either percutaneously with MitraClip (n = 51, 34.7%) or surgically (n = 36, 24.5%) including 4 cases of surgical conversion of the index procedure and 7 cases of bailout surgery after unsuccessful redo MitraClip. After a median follow-up of 163 days (IQR: 22-720 days), 50 (43.9%) subjects presented moderate to severe MR, and 43 (29.3%) patients died. An up-front redo MitraClip strategy was associated with a trend toward a reduced rate of death at follow-up vs surgical or conservative management ($P = 0.067$), whereas postprocedural acute kidney injury, age, and moderate to severe tricuspid regurgitation were independent predictors of death.

CONCLUSIONS MitraClip failure secondary to LLI and SLD is not a rare phenomenon and may occur during and also beyond hospitalization. Redo MitraClip strategy demonstrates a trend toward a reduced risk of death compared with bailout surgery and conservative management. A third of those patients remained with more than moderate MR and had substantial mortality at the intermediate-term follow-up. (J Am Coll Cardiol Intv 2022;15:411–422) © 2022 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

AKI = acute kidney injury

LLI = loss of leaflet insertion

MR = mitral regurgitation

SLD = single leaflet detachment

TR = tricuspid regurgitation

Nowadays, the MitraClip (Abbott Vascular) system is considered a key tool to treat mitral regurgitation (MR).[1] This technological tool replicates the surgical edge-to-edge technique that has proven its efficacy and safety in the treatment of both degenerative and functional MR even in high-risk patients because of no need of cardiopulmonary bypass[2] and as a bridge to heart transplant or a left ventricular assist device.[3] Firstly approved for use in patients with degenerative MR at high risk for cardiac surgery, MitraClip has progressively expanded the spectrum of anatomies suitable for its use and has been demonstrated to improve patients' survival in a selected population with functional MR.[4,5] Even through MitraClip has proven safety and efficacy, a relapse of significant MR can be observed after the index procedure as result of multiple causes.[6] Loss of leaflet insertion (LLI) and single leaflet detachment (SLD) are possible complications after the implantation of MitraClip and can be responsible for MR relapse both acutely or at follow-up. However, no data are available regarding the prevalence and the outcome of patients with LLI or SLD after MitraClip procedures.

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METHODS

The FILM registry (Failed mItraclip Long-term follow-up and Management) is an international, multicenter registry including 147 consecutive patients recruited in 19 centers with a diagnosis of LLI or SLD after the treatment of MR with MitraClip. All patients were considered as high-risk surgical candidates because of comorbidities and were scheduled for percutaneous correction of MR after discussion in local heart teams. Grading of the severity of MR was assessed using a combination of semiquantitative and quantitative assessment as described by the American Society of Echocardiography guidelines and the European Association of Echocardiography guidelines. LLI and SLD were defined according to a modified classification from Kreidel et al[7] as follows:

- LLI: MitraClip is still attached at both leaflets but with a damage on it; the injury can result in a tear (disruption of leaflet integrity reaching the leaflet edge), perforation (disruption of leaflet integrity not reaching the leaflet edge), or shape distortion. The resultant regurgitant jet is typically parallel to the clip, with the flow convergence area in between the clip and the leaflet tip.
- SLD: complete loss of connection between the clip and 1 leaflet.
- Embolization: loss of contact between MitraClip and both leaflets.

The diagnoses of LLI and SLD were made after a comprehensive evaluation of transthoracic and/or transesophageal echocardiography using color Doppler imaging and tridimensional evaluation of the mitral valve. The echocardiographic evaluation was independently performed at each center.

STUDY PROCEDURE AND DEVICE. The MitraClip procedure was performed with the patient under general anesthesia with transesophageal echocardiography and fluoroscopic guidance in the cardiac catheterization laboratory as previously described. During the procedure, deployment of additional MitraClip devices was permitted when a single device

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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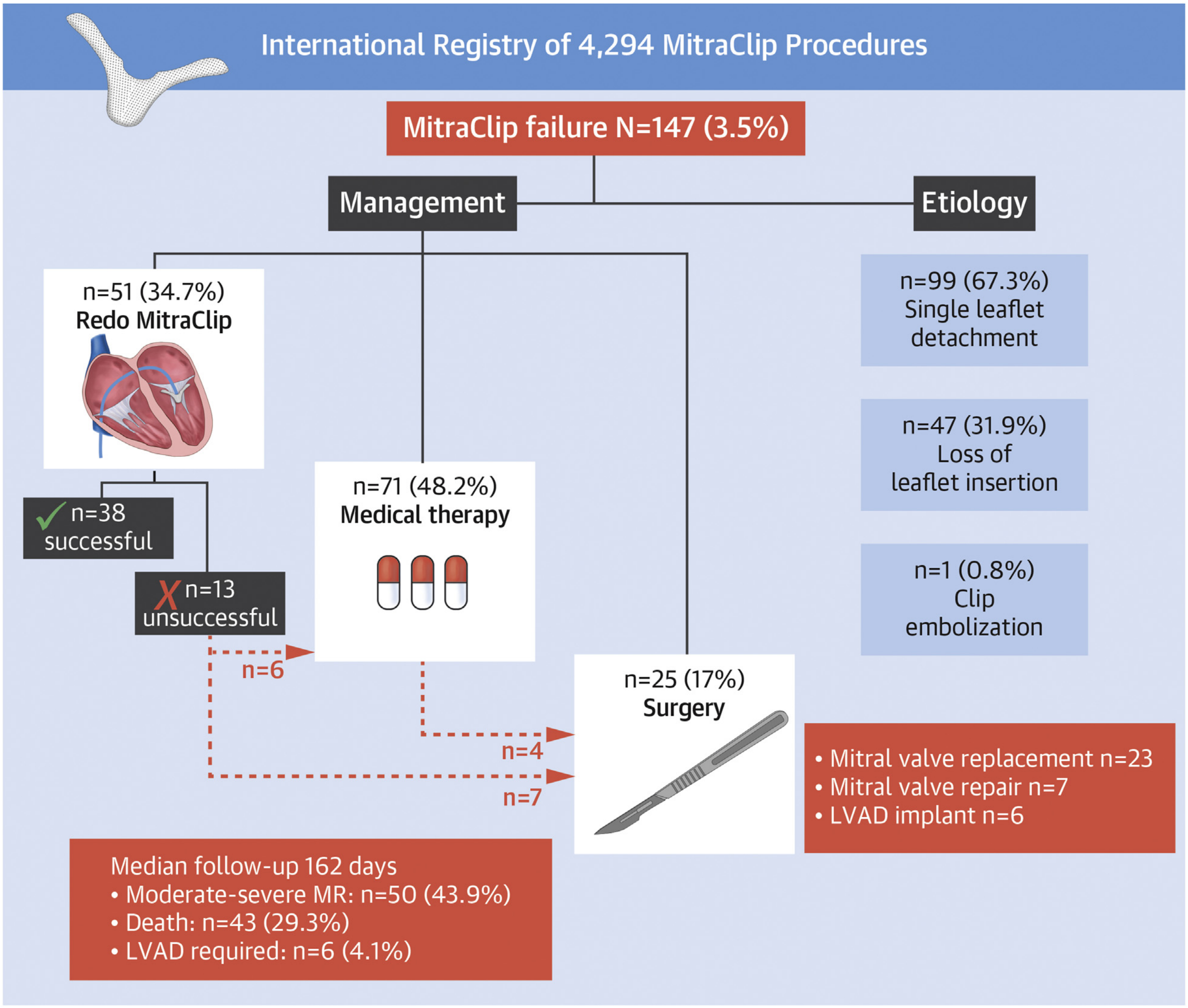
CENTRAL ILLUSTRATION The Failed MItraclip Long-Term Follow-Up and Management Registry Main Results



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LVAD = left ventricular assist device.

did not result in an adequate reduction in MR. In case of acute LLI or SLD during the index procedure, the acute management was left to the operator's decision according to the entity of MR and the patient's risk profile and hemodynamic status.[8] Each center also provided information on the total number of MitraClip cases performed every year along the study period as well as the model of MitraClip.

The investigators at each center were required to input the aforementioned data into a patient-level database and sent the anonymized data to the study coordinator (A.M.) for analysis. Source verification and query generation from the coordinating center to the participating sites were undertaken to partly account for the unavoidable bias of site-reported event adjudication. All the events reported are defined according to the Mitral Valve Academic Research Consortium.[9]

STATISTICAL ANALYSIS. Categoric variables were expressed as count (percentage) and compared with the chi-square or Fisher exact test. Continuous variables were expressed as mean ± SD or median (IQR); normality assumption was verified with the Shapiro-Wilk test. The Student's *t*-test, Mann-Whitney *U*

TABLE 1 Baseline Characteristics

	Overall (N = 147)	Functional Etiology (n = 67)	Degenerative Etiology (n = 64)	Mixed Etiology (n = 16)	*P* Value
Age (y)	77.0 (71.0-83.0)	73.0 (67.0-80.3)	79.0 (74.0-84.5)	81.00 (74.0-84.5)	<0.001
Female	56 (38.1)	24 (37.5)	26 (41.3)	4 (25.0)	0.487
BMI (kg/m^2)	25.0 (22.0-27.9)	24.9 (22.0-27.2)	25.00 (22.0-28.3)	25.30 (23.7-27.2)	0.825
STS score	3.8 (2.0-5.6)	3.40 (2.3-5.9)	3.80 (1.8-5.1)	3.86 (3.5-5.4)	0.553
eGFR (mL/min/m^2)	50.7 (37.0-63.0)	48.9 (36.5-60.1)	55.25 (42.0-69.5)	37.40 (33.2-49.2)	0.035
Hypertension	113 (76.9)	48 (75.0)	46 (73.0)	15 (93.8)	0.210
Diabetes	32 (21.8)	15 (23.4)	12 (19.0)	2 (12.5)	0.591
Ischemic dilated cardiomyopathy	46 (31.3)	30 (46.9)	10 (15.9)	5 (31.2)	0.001
Nonischemic dilated cardiomyopathy	40 (27.2)	30 (46.9)	5 (7.9)	4 (25.0)	<0.001
Previous MI	40 (27.2)	22 (34.4)	11 (17.5)	6 (37.5)	0.063
Previous PCI	47 (32.0)	28 (43.8)	15 (23.8)	4 (25.0)	0.044
Previous CABG	18 (12.2)	8 (12.5)	7 (11.1)	3 (18.8)	0.713
Previous non-CABG cardiac surgery	13 (8.8)	2 (3.1)	9 (14.3)	1 (6.2)	0.072
Previous MV surgery	7 (4.8)	0 (0.0)	5 (7.9)	2 (12.5)	0.038
CRT-D	20 (13.6)	18 (28.1)	2 (3.2)	0 (0.0)	<0.001
ICD	20 (13.6)	17 (26.6)	1 (1.6)	2 (12.5)	<0.001
PPM	17 (11.7)	10 (15.9)	5 (7.9)	1 (6.7)	0.311
History of AF	77 (52.7)	32 (50.8)	35 (55.6)	6 (37.5)	0.431
Baseline severe MR	118 (80.3)	46 (71.9)	53 (84.1)	15 (93.8)	0.076
LVEF (%)	48.5 (30.0-60.0)	28.00 (21.0-35.0)	60.00 (52.5-65.5)	56.5 (47.5-60.2)	<0.001
EDV (%)	135.0 (107.0-208.0)	206.00 (132.0-243.0)	117.50 (92.5-144.0)	125.0 (111.5-136.5)	<0.001
LVEDD (mm)	59.5 (54.00-65.47)	65 (60.0-71.0)	54 (50.0-58.0)	59 (54.0-62.0)	<0.001
Vena contracta width (mm)	7.0 (6.24-8.00)	7.00 (6.0-8.0)	7.00 (6.24-8.00)	10.00 (8.5-10.0)	0.263
RVEDD (mm)	34.0 (28.00-40.00)	35 (31.0-40.0)	35 (28.0-39.0)	29.5 (26.5-32.0)	0.158
TAPSE (mm)	19.0 (16.0-22.00)	18.50 (16.0-21.0)	20.00 (16.00-22.00)	18.00 (15.0-24.8)	0.853
sPAP (mm Hg)	45.0 (35.0-60.0)	45 (36.3-60.0)	45 (33.5-60.0)	36,5 (35.0-48.5)	0.469
Fibroelastic deficiency	17 (13.0)	0 (0.0)	16 (27.6)	0 (0.0)	<0.001
Myxomatous disease	10 (6.8)	1 (1.6)	9 (14.3)	0 (0.0)	0.010
Annular calcifications	15 (11.9)	5 (9.4)	9 (15.5)	1 (7.1)	0.516
Leaflet calcifications	8 (6.4)	1 (2.0)	6 (10.2)	1 (7.1)	0.216
Mitral valve clefts	8 (6.4)	3 (5.9)	2 (3.4)	3 (21.4)	0.046
Baseline TR grade					0.489
0	10 (7.1)	6 (9.7)	2 (3.2)	2 (13.3)	
1	54 (38.3)	19 (30.6)	28 (44.4)	7 (46.7)	
2	45 (31.9)	23 (37.1)	18 (28.6)	3 (20.0)	
3	15 (10.6)	5 (8.1)	8 (12.7)	2 (13.3)	
4	17 (12.1)	9 (14.5)	7 (11.1)	1 (6.7)	
Baseline moderate to severe AS	4 (3.1)	2 (3.6)	2 (3.3)	0 (0.0)	0.774

Values are median (IQR) or n (%).

AF = atrial fibrillation; AS = aortic stenosis; BMI = body mass index; CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy defibrillator; EDV = end-diastolic volume; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LVEDD = left ventricular end-diastolic diameter; MI = myocardial infarction; MR = mitral regurgitation; MV = mitral valve; PCI = percutaneous coronary intervention; PPM = prosthesis-patient mismatch; RVEDD = right ventricular end-diastolic diameter; sPAP = systolic pulmonary artery pressure; STS = Society of Thoracic Surgeons; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

test, and analysis of variance tests were used as appropriate.

HRs and 95% CIs for all-cause death were estimated by fitting a Cox proportional hazard regression model and stratified according to the upfront management strategy (2 levels: redo MitraClip vs other strategies). Potential confounders and established risk factors were tested as a univariate predictor of death, and, if statistically significant, they were included together with clinically significant factors into a stepwise (both backward and forward) binary regression model to identify independent predictors

TABLE 2 Procedural Characteristics and Results

	Overall (N = 147)	Functional (N = 67)	Degenerative (N = 64)	Mixed (N = 16)	*P* Value
MitraClip number					0.567
1	61 (41.8)	30 (46.9)	22 (34.9)	8 (50.0)	
2	59 (40.4)	22 (34.4)	32 (50.8)	4 (25.0)	
3	19 (13.0)	8 (12.5)	7 (11.1)	3 (18.8)	
4	6 (4.1)	3 (4.7)	2 (3.2)	1 (6.2)	
5	1 (0.7)	1 (1.6)	0 (0.0)	0 (0.0)	
MitraClip model					0.046
MitraClip	45 (30.6)	18 (28.1)	21 (33.3)	5 (31.2)	
MitraClip NTr	59 (40.1)	33 (51.6)	18 (28.6)	5 (31.2)	
MitraClip XTr	33 (22.4)	11 (17.2)	16 (25.4)	6 (37.5)	
NTr and XTr	10 (6.8)	2 (3.1)	8 (12.7)	0 (0.0)	
Final MR grade (%)					0.421
0	3 (2.1)	2 (3.1)	0 (0.0)	1 (6.7)	
1	52 (35.9)	19 (29.7)	23 (36.5)	7 (46.7)	
2	53 (36.6)	22 (34.4)	25 (39.7)	6 (40.0)	
3	23 (15.9)	13 (20.3)	9 (14.3)	1 (6.7)	
4	14 (9.7)	8 (12.5)	6 (9.5)	0 (0.0)	
Final MV gradient (mm Hg)	3.00 (2.00-4.00)	3.50 (2.00-4.00)	3.00 (2.40-4.00)	3.00 (2.88-4.25)	0.933
Loss of leaflet insertion	46 (31.7)	21 (33.3)	18 (28.6)	6 (37.5)	0.737
Anterior leaflet	16 (23.9)	9 (31.0)	5 (17.9)	2 (22.2)	
Posterior leaflet	25 (37.3)	11 (37.9)	11 (39.3)	3 (33.3)	
Partial clip detachment	98 (68.1)	42 (67.7)	44 (69.8)	10 (62.5)	0.851
Anterior leaflet	29 (28.2)	16 (37.2)	12 (25.0)	0 (0.0)	
Both leaflet involved	2 (1.9)	0 (0.0)	2 (4.2)	0 (0.0)	
Posterior leaflet	67 (65.0)	26 (60.5)	30 (62.5)	10 (100.0)	
Clip embolization	1 (0.7)	1 (1.6)	0 (0.0)	0 (0.0)	
Timing					0.537
Intraprocedural	47 (32.0)	20 (31.2)	20 (31.7)	7 (43.8)	0.616
Intrahospital	42 (28.6)	25 (39.1)	12 (19.0)	4 (25.0)	0.042
Late at follow-up	58 (39.5)	19 (29.7)	31 (49.2)	5 (31.2)	0.064
Time to diagnosis (d)	6.00 (0.00-119.50)	3.50 (0.00-97.25)	31.00 (1.00-168.50)	1.50 (0.00-59.25)	

Values are n (%) or median (IQR).
Abbreviations as in Table 1.

of death. Missing values were handled with multiple imputations using additive regression, bootstrapping, and predictive mean matching; the final model was tested in sensitivity analysis without multiple imputation.

The proportionality risk assumption was assessed by Schoenfeld's residuals and influential observations or outliers with dfbeta analysis. We tested for collinearity in the multivariable models using Martingale residuals plots. A minor violation in the proportional risk assumption for age was addressed by fitting a new model including this variable into quartiles (Supplemental Methods).

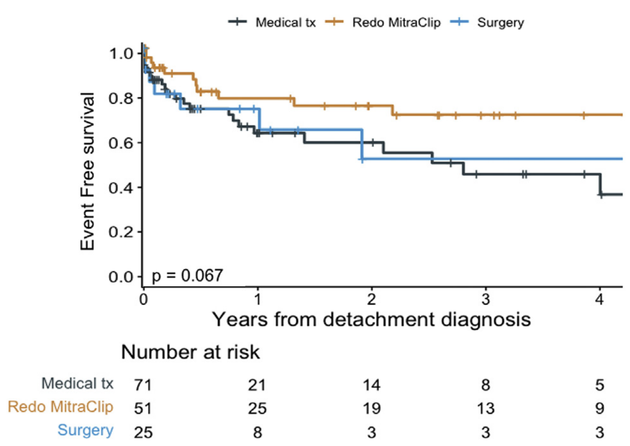
The relationship between the MitraClip volume per year and the number of MitraClip failures per year was tested with the Pearson correlation coefficient. A *P* value <0.05 was considered statistically significant for hypothesis testing. Data were analyzed in R environment 3.5.3 (R Foundation for Statistical Computing).

At some centers, data on patients undergoing MitraClip intervention were drawn from general prospective databases, which were approved by local ethics committees, with informed consent provided by patients. At other centers, the study complied with the rules and governance for retrospective studies of the local ethics committee.

RESULTS

Between January 2009 and December 2020, we screened 4,294 procedures of MitraClip performed in 19 centers from Europe, North America, and the Middle East (**Central Illustration**). A total of 147

FIGURE 1 Changes in MR Grading Over Time



The longest echocardiographic follow-up available was used for this analysis. MR = mitral regurgitation.

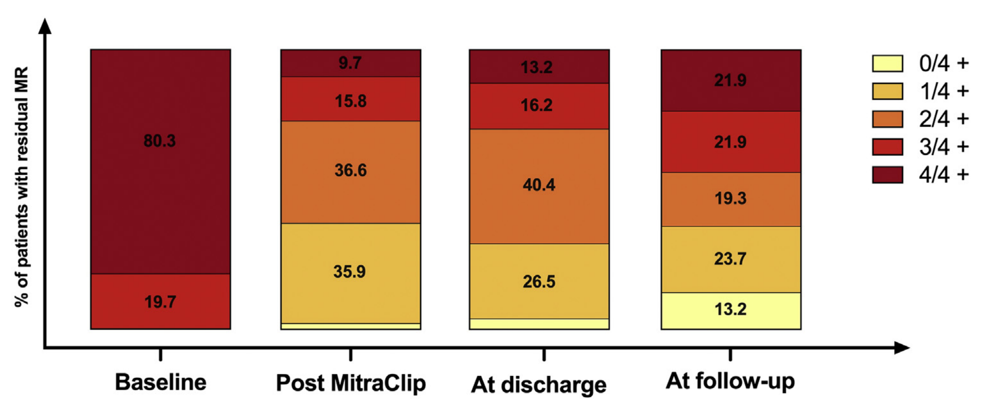
cases of MitraClip failure were detected (overall incidence = 3.5%); these were secondary to LLI or SLD in 47 (31.9%) and 99 (67.3%) cases, respectively, while in 1 (0.8%) case clip embolization was observed.

BASELINE AND ECHOCARDIOGRAPHIC FEATURES. The baseline clinical characteristics of our cohort of patients who experienced MitraClip failure are reported in Table 1. The median age was 77 years (IQR: 71-83 years), and 38.1% were female with a median Society of Thoracic Surgeons score of 3.8 (IQR: 2.02-5.55); 7 (4.8%) patients had previous mitral valve surgery, whereas a history of atrial fibrillation was present in 52.7% of the population. All patients underwent MitraClip for at least moderate MR. With regard to the etiology, MitraClip failure occurred in 67 (45.5%) patients with functional MR, 64 (43.5%) patients with degenerative MR, and 16 (10.8%) with mixed etiology. The baseline ejection fraction was 48.5% (IQR: 30.0%-60.0%), and patients with functional MR had a significantly lower ejection fraction ($P < 0.001$). Notably, 6.4% of all patients presented leaflet calcifications, whereas mitral annulus calcifications were present in 12% of our cohort.

PROCEDURAL FEATURES. Procedural characteristics are reported in Table 2. Most of the patients with evidence of LLI or SLD received more than 1 MitraClip (57.8%), and in most cases a MitraClip NTr (Vascular Abbott) (40.1%) was used. The deployment location was central in 39.5% of cases. Of note, 62.2% of the population with MitraClip failure had a suboptimal final result with ≥ moderate residual MR; iatrogenic mitral stenosis was negligible, with a residual mean gradient of 3 mm Hg (IQR: 2-4 mm Hg).

PATTERN OF MitraClip FAILURE AND MANAGEMENT. The posterior leaflet was involved in most cases of LLI (80.6%) and SLD (69.8%). The only case of clip embolization was observed in a functional etiology. Although the majority of MitraClip failures were detected before discharge (47 intraprocedural and 42 in the hospital), up to 39.5% of cases were diagnosed at follow-up after a median time of 142 days (IQR: 60-243 days) (Table 4). Temporal trends of MitraClip failure are shown in Supplemental Figure 1.

FIGURE 2 Left Ventricular Ejection Fraction at Baseline and at Follow-Up



In each box and whisker plot, the median is represented as the **horizontal line within the box** and first/third interquartile range as the **bottom/top horizontal line**; **vertical lines** (whiskers) span to the lowest/highest value in the sample. The mean, SD, and *P* value for comparison (paired *t*-test) are shown.

TABLE 3 In-Hospital Outcome, Discharge, and Follow-Up

	Overall (N = 147)	Functional (n = 67)	Degenerative (n = 64)	Mixed (n = 16)	*P* Value
In-hospital					
Inotropic support	33 (24.1)	21 (34.4)	8 (14.0)	3 (20.0)	0.032
Mechanical support	15 (10.8)	13 (21.0)	1 (1.7)	1 (6.7)	0.003
In-hospital stay	7 (5.00-12.00)	8.50 (5.00-15.75)	7.00 (4.00-9.25)	6.50 (4.00-12.00)	0.150
In-hospital death	12 (8.3)	7 (10.9)	3 (5.0)	1 (6.2)	0.456
Stroke/TIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Bleedings					0.403
Major	3 (2.1)	2 (3.2)	1 (1.7)	0 (0.0)	
Extensive/life-threatening	1 (0.7)	0 (0.0)	1 (1.7)	0 (0.0)	
AKI stage					0.445
1	10 (7.0)	7 (11.1)	3 (5.1)	0 (0.0)	
2	8 (5.6)	4 (6.3)	2 (3.4)	1 (6.2)	
3	9 (6.3)	4 (6.3)	2 (3.4)	2 (12.5)	
Other serious in-hospital complication	17 (12.7)	7 (11.7)	7 (12.7)	2 (13.3)	0.977
Discharge					
LVEF (%)	50.00 (30.00-60.00)	0.00 (21.00-39.00)	60.00 (55.00-61.25)	56.50 (48.25-60.00)	<0.001
MR grade					0.076
0	5 (3.7)	2 (3.4)	1 (1.7)	2 (13.3)	
1	36 (26.9)	14 (24.1)	13 (22.4)	8 (53.3)	
2	55 (41.0)	22 (37.9)	28 (48.3)	4 (26.7)	
3	22 (16.4)	12 (20.7)	8 (13.8)	1 (6.7)	
4	16 (11.9)	8 (13.8)	8 (13.8)	0 (0.0)	
MV gradient (mm Hg)	4.00 (3.00-5.00)	4.00 (2.98-5.00)	4.00 (3.00-5.00)	4.00 (3.00-5.00)	0.818
Follow-up					
LVEF (%)	50.00 (33.00-60.00)	34.00 (20.25-45.00)	60.00 (53.00-64.00)	46.50 (41.00-53.00)	<0.001
MV gradient (mm Hg)	4.00 (3.00-5.75)	3.00 (3.00-4.70)	4.00 (3.00-6.00)	4.00 (3.50-4.88)	0.080
sPAP (mm Hg)	44.50 (31.50-55.25)	39.50 (29.75-50.00)	45.00 (35.00-58.00)	43.00 (38.00-45.00)	0.337

Values are n (%) or median (IQR).
AKI = acute kidney injury; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack; other abbreviations as in Table 1.

Interestingly, a progressive increase in the number of SLDs and LLIs was observed through the years (Supplemental Figure 2).

Among those with an intrahospital diagnosis of MitraClip failure, 34 (38.2%) needed either inotropic and/or mechanical circulatory support, whereas 43 (48.3%) underwent a redo intervention during their hospital stay. These included 14 redo MitraClip procedures and 15 surgeries; in 4 of these cases, a procedural conversion to surgery was necessary.

Of the 58 patients diagnosed with MitraClip failure at follow-up, 29 (50.0%) underwent redo MitraClip and 8 (13.8%) cardiac surgery, whereas the remaining 21 (36.2%) were managed with medical therapy alone.

In total, 80 (54.4%) subjects of our cohort underwent a redo procedure, either percutaneously with MitraClip (n = 51, 34.7%) or surgically (n = 36 [24.5%], including 23 cases of mitral valve replacement, 7 cases of mitral valve repair, and 6 cases of left ventricular assistance device) including 4 cases of surgical conversion of the index procedure and 7 cases of bailout surgery after an unsuccessful redo MitraClip procedure. In the other 6 cases of an unsuccessful redo MitraClip procedure, the patients were treated with medical therapy alone. Overall, 6 (4.1%) subjects needed left ventricular assist device implantation or a heart transplant.

ECHOCARDIOGRAPHIC OUTCOME. At discharge after the index procedure, moderate to severe MR was present in 38 patients (28.4%), including 20 with a diagnosis of MitraClip failure; of the 23 patients who survived an intrahospital surgical or percutaneous redo procedure, 9 (39.1%) were discharged with moderate to severe MR. After a median follow-up of 163 days (IQR: 22-720 days), 50 (43.9%) subjects presented moderate to severe MR (Figure 1). No significant difference was observed in terms of the left ventricular ejection fraction between baseline and follow-up ($P = 0.75$) (Figure 2).

OUTCOMES AFTER MitraClip FAILURE. The in-hospital complications are shown in Table 3. Twelve (8.2%) patients died, including 7 who had a redo surgery or MitraClip, 4 (2.7%) experienced Valve Academic Research Consortium major or life-

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TABLE 4 Baseline Characteristics and Outcomes According to Upfront Management Strategy

	Medical Management (n = 71)	Redo MitraClip (n = 51)	Surgery (n = 25)	*P* Value
Age, y	79.00 (71.50-85.00)	79.00 (70.50-83.00)	71.00 (70.00-75.00)	0.003
Female	28 (39.4)	23 (45.1)	5 (20.0)	0.101
BMI (kg/m^2)	25.00 (22.00-27.17)	23.90 (22.00-27.69)	26.10 (24.85-28.44)	0.342
STS score	4.15 (2.95-6.12)	2.95 (2.24-5.29)	2.27 (1.24-4.32)	0.026
eGFR (mL/min/m^2)	47.30 (36.00-62.58)	52.79 (39.00-62.00)	55.50 (43.50-78.00)	0.116
Hypertension	50 (70.4)	42 (82.4)	21 (84.0)	0.198
Diabetes	17 (23.9)	12 (23.5)	3 (12.0)	0.429
Ischemic dilated cardiomyopathy	28 (39.4)	11 (21.6)	7 (28.0)	0.102
Nonischemic dilated cardiomyopathy	16 (22.5)	16 (31.4)	8 (32.0)	0.468
Previous MI	26 (36.6)	9 (17.6)	5 (20.0)	0.045
Previous PCI	29 (40.8)	12 (23.5)	6 (24.0)	0.083
Previous CABG	10 (14.1)	6 (11.8)	2 (8.0)	0.721
Previous non-CABG cardiac surgery	7 (9.9)	3 (5.9)	3 (12.0)	0.620
Previous MV surgery	3 (4.2)	0 (0.0)	4 (16.0)	0.008
CRT-D	11 (15.5)	3 (5.9)	6 (24.0)	0.078
ICD	13 (18.3)	3 (5.9)	4 (16.0)	0.132
PPM	5 (7.1)	10 (20.0)	2 (8.0)	0.080
History of AF	35 (49.3)	28 (56.0)	14 (56.0)	0.720
Baseline severe MR	61 (85.9)	37 (72.5)	20 (80.0)	0.187
LVEF (%)	50.00 (25.00-60.00)	54.00 (35.00-65.00)	39.00 (28.00-55.00)	0.080
EDV (ml)	135.50 (109.25-223.50)	19.00 (93.25-168.25)	98.00 (131.50-243.50)	0.010
LVEDD (mm)	59.76 (9.94)	58.14 (9.40)	63.09 (7.05)	0.264
Vena contracta width (mm)	7.00 (6.16-8.00)	7.00 (6.30-8.00)	7.50 (7.00-9.50)	0.522
RVEDD (mm)	33.34 (7.25)	34.29 (8.04)	37.38 (8.98)	0.273
TAPSE (mm)	18.00 (16.00-21.00)	20.00 (15.50-23.00)	18.50 (16.75-21.00)	0.604
sPAP (mm Hg)	46.21 (16.27)	50.03 (16.54)	49.18 (16.91)	0.505
Fibroelastic deficiency	8 (12.7)	6 (13.3)	3 (13.0)	0.995
Myxomatous disease	3 (4.3)	5 (9.8)	2 (8.0)	0.479
Annular calcifications	10 (15.6)	4 (10.0)	1 (4.5)	0.347
Leaflet calcifications	5 (8.1)	2 (4.9)	1 (4.5)	0.751
Mitral valve clefts	4 (6.5)	0 (0.0)	4 (18.2)	0.019
Baseline TR grade				
0	5 (7.0)	3 (6.4)	2 (8.7)	
1	26 (36.6)	14 (29.8)	14 (60.9)	
2	22 (31.0)	19 (40.4)	4 (17.4)	
3	7 (9.9)	5 (10.6)	3 (13.0)	
4	11 (15.5)	6 (12.8)	0 (0.0)	
Baseline moderate to severe AS	1 (1.6)	2 (4.8)	1 (4.3)	0.604
Final MV gradient (mm Hg)	3.00 (2.00-4.00)	3.00 (2.00-4.00)	4.00 (3.00-5.00)	0.123
In-hospital stay (d)	10.89 (11.02)	8.21 (6.78)	15.20 (17.89)	0.051
Discharge LVEF (%)	47.00 (28.00-60.00)	50.00 (31.25-60.00)	49.00 (35.00-58.00)	0.319
Discharge MV gradient (mm Hg)	4.00 (3.00-5.00)	4.20 (3.00-5.00)	5.00 (3.00-7.00)	0.051
Outcomes at longest follow-up available				
Death (%)	25 (35.2)	11 (21.6)	7 (28.0)	0.260
MR grade (%)				<0.001
0	2 (3.6)	5 (12.8)	8 (40.0)	
1	8 (14.5)	14 (35.9)	5 (25.0)	
2	10 (18.2)	11 (28.2)	1 (5.0)	
3	20 (36.4)	5 (12.8)	0 (0.0)	
4	15 (27.3)	4 (10.3)	6 (30.0)	

Continued on the next page

TABLE 4 Continued

	Medical Management (n = 71)	Redo MitraClip (n = 51)	Surgery (n = 25)	*P* Value
LVEF (mm Hg)	45.00 (29.00-58.00)	55.00 (45.00-64.00)	54.00 (34.50-60.00)	0.036
MV gradient (mm Hg)	4.00 (3.00-5.00)	4.00 (3.00-5.00)	4.75 (3.38-6.00)	0.364
sPAP (mm Hg)	44.50 (35.00-59.25)	44.50 (29.75-56.25)	42.50 (33.50-51.50)	0.715
Any redo (%)	4 (5.6)	51 (100.0)	25 (100.0)	<0.001
Any IH redo (%)	4 (100.0)	15 (88.2)	11 (100.0)	0.390
Any successful redo (%)	0 (NaN)	37 (100.0)	0 (NaN)	NA
Bailout surgery (%)	4 (5.6)	7 (13.7)	0 (0.0)	0.073

Values are median (IQR) or n (%).
IH = intra-hospital; NA = not applicable; other abbreviations as in Tables 1 and 3.

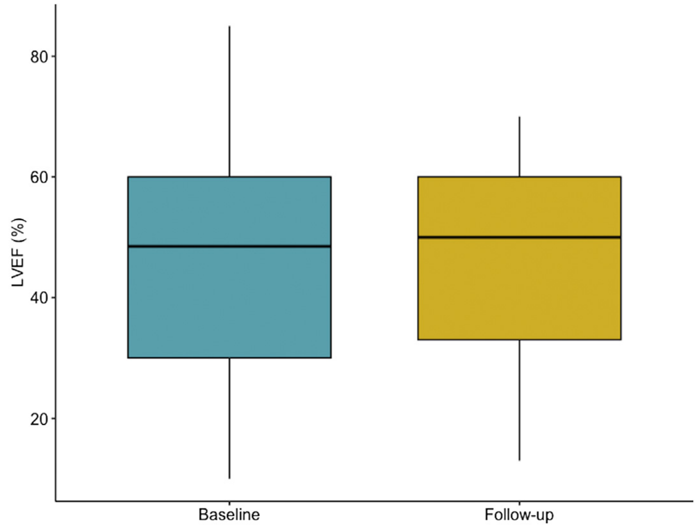
threatening bleedings, and 17 (11.6%) stage 2 to 3 acute kidney injury (AKI); no patients experienced stroke or transient ischemic attack. After a median follow-up of 163 days (IQR: 22-720 days) from MitraClip failure diagnosis, 43 (29.3%) patients died with no significant difference according to the type of failure (41.3% of those with LLI vs 24.5% with SLD, *P* = 0.31) (Supplemental Figure 3A). After MitraClip failure, patients were initially managed conservatively (n = 71) with a redo MitraClip (n = 51) or surgery (n = 25). The features of the 3 populations and the outcomes are reported in **Table 4**. An upfront redo MitraClip strategy demonstrates a trend toward a reduced risk of death vs bailout surgery or conservative management (*P* = 0.067) (**Figure 3**); no significant differences emerged at follow-up between patients who experienced LLI and those who had SLD (Supplemental Figures 3B and 3C). Multivariable predictors of death are shown in **Table 5**; age, moderate to severe tricuspid regurgitation (TR) (HR: 2.66; 95% CI: 1.37-5.20; *P* = 0.004), postprocedural AKI (HR: 2.91; 95% CI: 1.53-5.54; *P* = 0.001), and a MitraClip redo strategy (HR: 0.42; 95% CI: 0.22-0.83; *P* = 0.012) were independently associated with death. Univariate predictors of death are provided in Supplemental Table 1. The results of our multivariable model were confirmed in our sensitivity analysis without multiple imputation (Supplemental Table 2). We found no correlation between volume center and the rate of detachment (Supplemental Figure 4).

DISCUSSION

The main results of our analysis are as follows:

1. In high-volume centers, MitraClip failure is relatively uncommon (incidence = 3.5%), but it is associated with high rates of moderate to severe MR (43.9%) and death (29.3%) at follow-up.
2. An upfront redo MitraClip strategy was associated with a trend toward a reduced rate of death at follow-up vs surgical or conservative management (*P* = 0.067).
3. Age, AKI, and concomitant moderate to severe TR were found to be independent predictors of mortality.
4. We found no correlation between volume center and the number of MitraClip failures secondary to LLI and SLD; moreover, we found a temporal increase of SLD and LLI through the years.

FIGURE 3 Kaplan-Meier Curve for All-Cause Death



Subjects are stratified according to the upfront management strategy: redo MitraClip vs surgery or watchful waiting; the survival curve for the whole population is shown in light gray. The proportion of patients who died at follow-up for each group and log-rank *P* value are shown.

TABLE 5 Multivariable Model for Death

	HR	95% CI	*P* Value
Age			
<71 y	Ref	–	–
71-77 y	2.034	0.717-5.771	0.18
77-83 y	3.709	1.412-9.746	0.008
>83 y	3.796	1.404-10.262	0.009
Moderate to severe TR	2.980	1.534-5.791	0.001
Redo MitraClip	0.476	0.234-0.969	0.041
Postprocedural AKI	3.369	1.734-6.545	<0.001

Abbreviations as in Tables 1 and 3.

To the best of our knowledge, the FILM registry is the largest report on MitraClip failure and the first to describe the outcome of patients according to the mechanism of failure (SLD vs LLI). Over 19 centers worldwide and 4,294 MitraClip procedures were included, with an overall rate of failure of 3.5%, which is sensibly lower than recently reported in a real-world single-center cohort (7.6%)[10] but higher than reported in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial, which documented an overall rate of SLD of 0.8% with no mention of LLI in a cohort of only functional MR and no degenerative MR. Notably, all the SLD cases in the COAPT trial occurred in close proximity to the index procedure with no cases of late leaflet detachment reported in the extended 3-year follow-up.[11] Conversely, we reported 58 cases of MitraClip failure diagnosed at follow-up, a result that is line with the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) Investigational Device Exemption program, which reported a rate of MitraClip SLD of 1.3% at 30 days and 3.2% at a 1-year follow-up. Because the COAPT trial included selected functional anatomies treated with optimal medical therapy, we can speculate that our real-world registry has a higher rate of late SLD or LLI due to an improper optimization of guideline-directed medical therapy that favored an increase of left ventricular volumes, tension on the leaflets, and possible late detachment or tear. This hypothesis is endorsed by animal models that highlight that MitraClip exerts tension in particular on the posterior leaflets in case of progressive ventricular dilatation.[12] This finding is not surprising because the anterior leaflet is broader than the posterior one, comprises one third of the annular circumference, and has a clear and rough zone so that it is easier to be efficiently grasped with the MitraClip. As a matter of fact, in our registry, MitraClip failure secondary to LLI and SLD predominantly occurred on the posterior leaflet both in functional and degenerative anatomies. These results suggest that the suspicion of failure should be raised early, during or immediately after the procedure, if significant features are evident, such as a suboptimal echocardiographic result or a technical difficulty to grasp the posterior leaflet. Nonetheless, in almost 40% of cases, a MitraClip failure is diagnosed at follow-up, often for a sudden worsening of heart failure symptoms; therefore, attention should not decrease over time.

In our registry, MitraClip failure was associated with a high rate of death both in the hospital (8.2%) and at the intermediate-term follow-up (29.3%) with a nonstatistical trend toward worse outcomes with LLI than SLD. Overall, 43.9% of subjects with MitraClip failure presented with moderate to severe MR at follow-up. As a matter of fact, the mortality rate of our population is higher compared with other real-world experiences, which report a mortality between 17.3% and 20.3% at a 1-year follow-up.[13-16] These results pose a serious warning about the outcome of failed MitraClip. In this regard, it is important to highlight what the current strategies are toward MitraClip failure and to highlight any potential advantage. In our registry, the most common management strategy was conservative (48.3%), whereas 34.7% and 17.0% of our patients underwent a repeat MitraClip or surgery, respectively. An upfront strategy of repeat MitraClip (including those converted to surgery) showed a trend toward a lower occurrence of death vs other upfront strategies such as deferred interventions or medical management ($P = 0.067$); moreover, redo MitraClip was an independent predictor of increased survival at follow-up (HR: 0.42; 95% CI: 0.22-0.83; $P = 0.012$). Such a trend was evident for both LLI and SLD, although our analysis was not sufficiently powered to detect significant differences in these subgroups. Considering the observational nature of our study, we recognize that patients who underwent repeat MitraClip might have had a lower risk than those who were managed conservatively, but conceivably repeat MitraClip seems a viable first-line strategy in most patients with LLI or SLD. Importantly, as demonstrated by Kreidel et al,[7] the possibility of a redo percutaneous MitraClip should be carefully evaluated on the basis of mitral anatomy because the presence of a laceration, perforation, or tear, which mostly occur in the presence of leaflet insertion, dramatically reduces the possibility of success.

We found that other independent predictors of death were age, moderate to severe TR, and postprocedural AKI, and clinical attention should be directed toward these factors to target early subjects at higher risk of a worse outcome.

Finally, we also explored the relationship between annual MitraClip volume and MitraClip failure in each center, and we were unable to find any correlation. Moreover, we observed a significant increase of LLI and SLD through the years. We can speculate that imaging refinements and improved sonographic technologies have led to an improvement of the diagnostic power. Moreover, we can speculate that progressive operator confidence and the introduction of MitraClip with larger and wider arms have led to an increase of challenging anatomies, thus resulting in an increase of the prevalence of SLD and LLI.

STUDY LIMITATIONS. This was a multicenter retrospective study with a relatively low number of patients. Because of the design of the study, the prevalence of leaflet insertion and SLD was not systematically searched at follow-up. Moreover, the diagnosis of leaflet insertion and SLD is highly influenced by the imaging techniques used because 3-dimensional echocardiography gives an additive diagnostic value; we cannot exclude that the use of 2-dimensional echocardiography in the first year of experience could have led to an underestimation of the MitraClip failure rate. In our analysis, we found that redo MitraClip is associated with a better outcome compared with redo surgery and medical therapy. However, a selection bias could not be excluded because the management of patients with failed MitraClip could have been influenced by underlying clinical conditions and anatomic features not considered in our analysis. Furthermore, echocardiography data were site reported without central core laboratory assessment, and echocardiographic acquisitions were performed without a systematic and reproducible protocol. Lastly, the reported percentage of SLD and LLI can be potentially underestimated because of the lack of systematic echocardiography at follow-up. In this study, a comparison between patients with and without mechanical MitraClip failure has not been performed.

CONCLUSIONS

MitraClip failure secondary to LLI and SLD is not a rare phenomenon and may occur during the index hospitalization or beyond. Redo MitraClip strategy demonstrates a trend toward a reduced risk of death compared with bailout surgery and conservative management. A third of those patients remained with more than moderate MR and had substantial mortality at the intermediate-term follow-up.

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PERSPECTIVES

WHAT IS KNOWN? MitraClip is an established treatment for MR, but data on the prognosis of patients with MitraClip failure are scarce and the modes of failure are poorly descripted.

WHAT IS NEW? Cumulatively, SLD, LLI, and clip embolization are relatively uncommon in experienced centers, but they are associated with recurrent significant MR and increased death at follow-up. In such cases, a repeat MitraClip seems to be associated with improved survival vs other approaches.

WHAT IS NEXT? These findings highlight the importance of a prompt diagnosis, even beyond hospital discharge, and of appropriate treatment by a multidisciplinary expert team.

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KEY WORDS cardiac surgery, MitraClip, mitral regurgitation, mitral valve

APPENDIX For an expanded Methods section and supplemental tables and figures, please see the online version of this paper.