Impact of Transcatheter Edge-to-Edge Mitral Valve Repair on Atrial Functional Mitral Regurgitation from the GIOTTO Registry

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Atrial functional mitral regurgitation (aFMR) has a peculiar pathophysiology that may have distinctive outcomes. We investigated the impact of transcatheter edge-to-edge repair in aFMR compared with other FMR etiologies. The GIOTTO (GIse registry Of Transcatheter treatment of MR) is a multicenter, prospective study enrolling patients with symptomatic MR treated with MitraClip up to 2020. We categorized patients with FMR as aFMR, ischemic FMR (iFMR), and nonischemic ventricular FMR (niFMR). The clinical end points were defined according to the Mitral Valve Academic Research Consortium. Of 1,153 patients, 6% had aFMR, 47% iFMR, and 47% niFMR. Patients with aFMR were older, mostly women, and had a higher atrial fibrillation rate. They had better left ventricular ejection fraction and smaller left ventricular volumes, with no difference in mitral effective regurgitant orifice area. The acute device and procedural success rates were similar among the groups. At the longest available follow-up (median 478 days, interquartile range 91 to 741 days), the rate of MR ≥2+ was similar among the groups. Patients with aFMR had a lower rate of cardiovascular death and heart failure than patients with iFMR (hazard ratio [HR] 0.43, p = 0.02) and niFMR (HR 0.45, p = 0.03). The aFMR etiology remained independently associated with the composite outcome, together with postprocedural MR ≤1+ (HR 0.63, p <0.01) and peripheral arteriopathy (HR 1.82, p = 0.003). The results of this GIOTTO subanalysis suggested that aFMR is less prevalent and associated with better outcomes compared with other causes of FMR treated by transcatheter edge-to-edge repair. Postprocedural MR >1+, peripheral vasculopathy, non-aFMR were independent predictors of worse outcomes. **(Am J Cardiol 2024;211:219−227)**

Keywords: functional mitral regurgitation, atrial fibrillation, MitraClip procedure, transcatheter edge-to-edge repair

Mitral valve (MV) regurgitation is the most common valvular disease and the second most frequent indication for heart valve intervention in the Western world after aortic stenosis.[1−3] Functional mitral regurgitation (FMR) is because of an imbalance between leaflets tethering and closure forces leading to poor coaptation without intrinsic

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structural valve changes.[2,4] The traditional etiologies of FMR include nonischemic cardiomyopathy and ischemic remodeling, leading to left ventricular (LV) dilatation, systolic disfunction, and global/regional LV abnormalities (ventricular FMR [vFMR]). More recently, a subtype of FMR has been described, the so-called atrial FMR (aFMR), because of left atrial (LA)/annulus enlargement, in combination with an insufficient adaptation of the mitral leaflets but with preserved LV geometry and function.[5,6] It has been shown that untreated severe aFMR is associated with increased 5-year mortality compared with age- and gender-matched controls without mitral disease.[7,8] In addition, aFMR—because of its peculiar pathophysiology—may require a different approach and have different outcomes compared with ventricular MR.[6,9] The current guidelines do not acknowledge this difference.[3] Previous studies on the therapeutic role of transcatheter edge-to-edge repair (TEER) in patients with aFMR are small, with heterogeneous definitions of aFMR, different echocardiographic cut-off values, and no further discrimination between ischemic and nonischemic etiologies.[10−17] Accordingly, we aimed to evaluate the clinical impact of TEER with the MitraClip system (Abbott Vascular, Santa Clara, California) for patients with aFMR compared with all the other FMR etiologies (ischemic vFMR, ischemic FMR [iFMR], and nonischemic vFMR [niFMR]) using the large, multicenter Italian prospective Gise Registry of Transcatheter treatment of mitral valve regurgitation (GIOTTO).

Methods

The GIOTTO study is a single-arm, multicenter, prospective registry enrolling 2,005 patients with symptomatic and significant MR who underwent TEER with the MitraClip system in Italy between January 2016 and October 2020. The qualifying inclusion and exclusion criteria, echocardiographic selection and protocols used, and details of the MitraClip procedure, have been previously reported.[18−20] In particular, only patients who were eligible for MitraClip device, despite optimal medical therapy, according to the current guidelines and per the heart team and investigators, were included. Several generations of the device were used, from first generation to MitraClip NT, NTr, and XTr. For this study, we included patients with FMR. The cases presenting incomplete data for MV evaluations (n = 32, 1.6%) and primary or mixed MR etiologies (n = 820, 40.9%) were excluded. The FMR types were retrospectively classified depending on aFMR, iFMR, and niFMR etiologies on the basis of cardiac imaging and the clinical context, such as the presence of identified ischemic heart disease or cardiomyopathy. All echocardiographic data were analyzed by experienced investigators at each institution in accordance with the European Association of Cardiovascular Imaging guidelines.[5,7,21] Consistent with previous review documents, patients with aFMR met all the following criteria: (1) LV ejection fraction (LVEF) ≥50%, (2) indexed LV end-diastolic volume ≤74 ml/m^2 for men and £61 ml/m^2 for women or indexed left ventricle end-diastolic diameter ≤30 mm for men and ≤31 mm for women, and (3) indexed LA volume >34 ml/m^2 or indexed LA diameter >23 mm or history of atrial fibrillation (AF).[5,7,21]

A web−based electronic case report form was used for data collection. Follow−up data were obtained by means of inpatient or outpatient clinical visits and/or telephone calls scheduled at 1 month, 1 year, and yearly thereafter. Transesophageal echocardiography was assessed before and during the index procedure, and transthoracic echocardiography was performed at discharge, 1 to 3 months up to 1 year, and then yearly.

The study complied with the Declaration of Helsinki and was approved by the local ethics committee at each site. All patients included in the study were deemed unsuitable for surgery according to the standard of care,[22] eligible to receive the MitraClip device per the currently approved indications for use, and have signed written informed consent.

All outcomes were defined according to the Mitral Valve Academic Research Consortium (MVARC)[23] criteria, including acute technical success (defined as successful access, delivery, and retrieval of the device delivery system and successful device deployment without procedural death or emergent surgery or reintervention), 30-day device success (defined as proper device deployment without procedural death or stroke or device- or access-related complications requiring surgery or reintervention and post-procedural MR reduction at least acceptable), and procedural success (defined as device success and absence of major device or procedure related serious adverse events). The primary outcome of interest was the composite of cardiovascular (CV) death (CVD) and hospitalization for heart failure (HF) up to the longest available follow-up. Other clinical outcomes included all-cause death, CVD, hospitalization for HF, and New York Heart Association (NYHA) class up to the longest available follow-up. Echocardiographic data included MR grade, LV dimension and function, LA dimension, and systolic pulmonary arterial pressure (sPAP) up to the longest available follow-up.

The analysis was stratified by FMR etiologies (aFMR vs iFMR vs niFMR). Descriptive statistics were reported as median (quartile 1 to quartile 3) for continuous variables and as absolute numbers (percentages) for categorical variables. The distribution of continuous and categorical variables was compared using the Wilcoxon Kruskal−Wallis and chi-square tests, respectively. The survival distribution at follow-up was evaluated using the Kaplan−Meier method, whereas the distribution of the composite outcome, HF hospitalization, and CV death at follow-up were evaluated using cumulative incidence functions to account for competing risks. The association between the study groups and the outcomes of interest at follow-up was evaluated using univariable Cox proportional hazard model. The results were reported as hazard ratio (HR), 95% confidence interval, and p value. Furthermore, a multivariable Cox proportional hazard model was estimated for the composite end point. Model selection was performed according to the Bayesian information criterion. The analyses were performed with R software, within the packages rms, survival, and glmulti.

Results

Up to October 2020, 2,005 patients who underwent to TEER with the MitraClip system were enrolled in the

GIOTTO Registry in 22 participating Italian centers. Of these, 1,153 patients (58%) had FMR and complete data for the MV anatomy assessments. According to FMR etiology, the subjects were divided into 3 study groups: aFMR (n = 71, 6.2%), iFMR (n = 541, 46.9%), and niFMR (n = 541, 46.9%) (Figure 1). The median follow-up duration was 478 days (interquartile range 91 to 741 days).

The baseline demographic, clinical, and echocardiographic characteristics of the study population are listed in Table 1. Patients with aFMR were older, more often women, and more often overweight than those with iFMR and niFMR. They presented a lower prevalence of the common CV risk factors and co-morbidities, such as diabetes mellitus, peripheral artery disease, previous admission for HF, and better renal function, with a consistently lower surgical risk evaluated with the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, compared with other groups. Otherwise, they had a higher prevalence of arterial hypertension and AF. The NYHA classes and the degree of MR was similar among groups. Patients with aFMR had a better LVEF and smaller LV dimensions with enlarged LA and a smaller MV area. They showed a superior right ventricular function, with comparable sPAP and degree of tricuspid regurgitation compared with controls.

The procedural and 30-day outcomes are listed in Table 2. A mean number of 1.7 ± 0.7 devices per patient was implanted with no significant difference between groups. An optimal postprocedural MR reduction (less than moderate ≤1+) was achieved in the majority of patients without significant differences between the 3 groups. The overall MVARC technical success was 99%, device success was 89%, and procedural success was 86% without differences between the FMR etiologies subtypes. Furthermore, the MVARC procedural success rate were similar between different MitraClip iterations (86% for MitraClip, 88% for MitraClip NT, and 86% for MitraClip NTr/XTr, p = 0.07).

Echocardiographic characteristics are listed in Supplementary Figure 1, Supplementary Tables 1 and 2. At follow-up, the MR severity was significantly and sustainedly reduced after TEER in all etiologies and was reduced at least ≤2+ in more than 86% of all groups. The proportion of optimal MR reduction (≤1+) was about 50% and similar in all groups. The mean MV gradient was higher in patients with aFMR than others, also showing a slight decrease of LVEF without an LV dilatation compared with other groups. Conversely and in contrast from patients with iFMR, those with niFMR experienced a significant improvement of LVEF and indexed LV end-diastolic volume values at follow-up. No changes in LA volumes were observed in the groups. The aFMR cohort had a better right ventricular function, with a higher rate of moderate-to-severe tricuspid regurgitation than other groups. The sPAP was not different in the groups and improved consistently after TEER.

The unadjusted and adjusted event-free survival curves and relative risks of the combined and single digit events are shown Figure 2, Tables 3 and 4 and in the Central Figure 3, accordingly to FMR etiology; the frequencies of clinical events were reported in Supplementary Tables 2 and 3.

The patients with aFMR had a lower incidence of the composite of CVD and hospitalization for HF that was about half the rate observed for the iFMR and niFMR groups at the 3-year follow-up. Patients with aFMR had a significantly reduced risk of the primary outcome compared with both vFMR groups (aFMR vs iFMR: HR 0.43, aFMR vs niFMR: HR 0.45) because of a significant improvement of CV survival and a trend of lower rates of HF. At the adjusted analysis, the aFMR etiology remained independently associated with the composite adverse outcome compared with the niFMR and iFMR etiologies. The other independent predictors of the composite of CVD and HF were a postprocedural residual

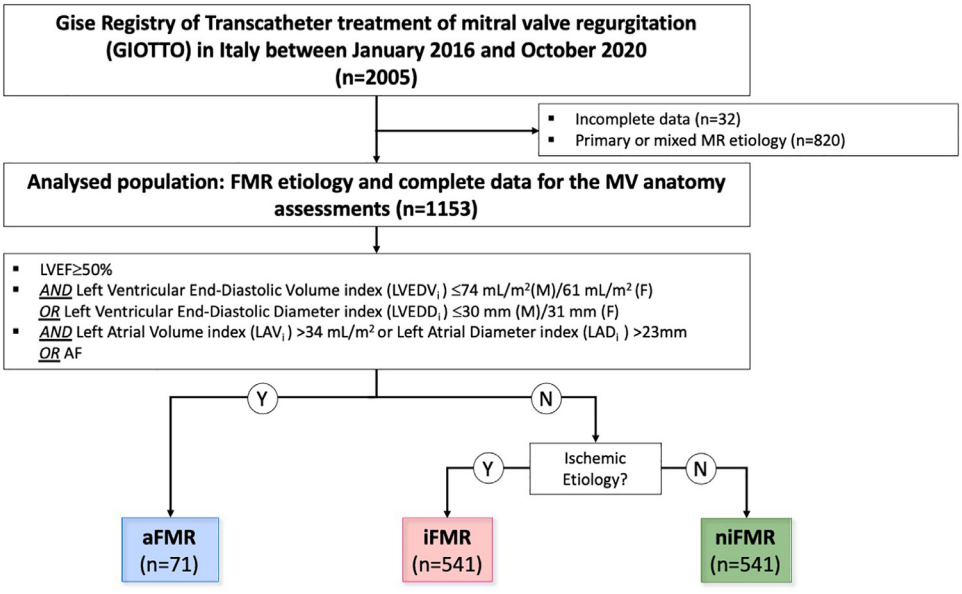

Figure 1. Study population flow alghoritm.

Table 1
Baseline demographic, clinical, and echocardiographic characteristics of the study population and according to study groups

	Total n=1153	aFMR n=71	iFMR n=541	niFMR n=541	*P*-value
Clinical characteristics					
Age (year)	73 [68−80]	79 [75−84]	73 [69−79]	72 [67−79]	<0.001
Female sex	339 (29)	41 (58)	111 (21)	187 (35)	<0.001
BMI (Kg/m^2)	25 [23−28]	27 [24−29]	25 [23−28]	25 [22−28]	0.006
Hypertension	843 (73)	60 (85)	422 (78)	361 (67)	<0.001
Diabetes mellitus	380 (33)	18 (26)	204 (38)	158 (29)	0.004
Dyslipidaemia	439 (53)	25 (46)	272 (66)	142 (39)	<0.001
Current or former smoker	213 (28)	9 (18)	133 (36)	71 (21)	<0.001
Severe CAD	643 (56)	23 (34)	519 (96)	101 (20)	<0.001
Peripheral artery disease	108 (15)	4 (8)	79 (23)	25 (8)	<0.001
Persistent/Permanent AF	576 (50)	54 (76)	232 (43)	290 (54)	<0.001
NYHA class					0.386
II	200 (17)	19 (27)	97 (18)	85 (15)	
III	825 (72)	46 (65)	381 (71)	398 (74)	
IV	123 (11)	6 (8)	59 (11)	58 (11)	
Prior admission for HF	763 (70)	33 (49)	374 (72)	356 (72)	<0.001
Prior cardiac surgery	292 (25)	16 (23)	204 (38)	72 (13)	<0.001
EuroSCORE II	5.7 [3.3−9.3]	4.2 [2.6−7.5]	6.7 [3.9−12.8]	5.1 [3.0−7.7]	<0.001
Haemoglobin (g/dL)	12.3 [11.0−13.6]	11.3 [10.3−12.6]	12.3 [10.9−13.5]	12.5 [11.3−13.8]	<0.001
Creatinine (mg/dL)	1.3 [1.1−1.8]	1.3 [1.0−1.6]	1.4 [1.1−2.0]	1.3 [1.0−1.8]	0.008
NT-proBNP (pg/mL)	1154 [389−3372]	545 [280−1271]	1170 [497−3047]	1428 [415−4285]	0.062
CRT (%)	259 (22)	-	99 (18)	160 (30)	<0.001
HF medical therapy					
ACE-I/ARB	387 (34)	24 (34)	183 (34)	180 (33)	0.946
Beta-blockers	956 (83)	56 (80)	435 (81)	465 (86)	0.08
MRA	631 (55)	28 (40)	316 (59)	287 (53)	0.006
CCBs	74 (6)	11 (16)	32 (6)	31 (6)	0.013
Inotropes	44 (4)	0 (0)	26 (5)	18 (3)	0.081
Diuretics	1071 (93)	63 (90)	503 (94)	505 (93)	0.5
Anticoagulant therapy					
VKA	314 (27%)	27 (38)	138 (26)	149 (28)	0.094
NOAC	241 (21%)	38 (54)	77 (14)	126 (23)	<0.001
Echocardiografic characteristics					
LV ejection fraction (%)	32 [26−40]	55 [52−59]	33 [27−40]	30 [25−35]	<0.001
LV end-diastolic volume index (mL/m2)	96 [74−117]	53 [44−60]	95 [76−114]	102 [81−125]	<0.001
LV end-diastolic diameter index (mm/m2)	35 [31−39]	28 [26−30]	35 [31−38]	36 [32−40]	<0.001
LV end-systolic diameter index (mm/m2)	28 [23−32]	19 [17−21]	28 [24−31]	29 [25−34]	<0.001
LA volume index (mL/m2)	55 [44−71]	52 [43−70]	52 [42−67]	59 [49−74]	0.004
LA diameter index (mm/m2)	28 [25−31]	28 [26−32]	27 [24−30]	28 [26−32]	<0.001
E-wave velocity (cm/sec)	105 [69−141]	115 [91−140]	106 [76−136]	100 [57−143]	0.06
e' velocity (cm/sec)	7 [3−11]	8 [5−11]	7 [2−12]	14 [4−24]	0.004
E/e' ratio	15 [6−24]	12 [6−18]	14 [6−22]	15 [5−25]	0.04
Mitral regurgitation					0.3
Moderate	13 (1)	2 (3)	6 (1)	5 (1)	
Moderate-to-severe	256 (22)	17 (24)	128 (24)	111 (21)	
Severe	884 (77)	52 (73)	407 (75)	425 (79)	
Effective Regurgitant Orifice Area (cm2)	0.33 [0.25−0.46]	0.37 [0.27−0.40]	0.32 [0.25−0.41]	0.36 [0.22−0.50]	0.6
Mitral valve area (cm2)	4.8 [4.0−6.0]	4.6 [4.0−5.5]	4.7 [4.0−5.5]	5.0 [4.0−6.2]	0.008
Mitral mean gradient (mmHg)	2.0 [1.0−2.5]	2.0 [1.9−3.8]	2.0 [1.0−2.0]	2.0 [1.0−2.7]	0.06
TAPSE (mm)	18 [15−21]	21 [17−22]	17 [14−19]	18 [15−21]	<0.001
Systolic PAP (mmHg)	45 [39−55]	44 [35−50]	45 [37−56]	46 [40−55]	0.3
Tricuspid regurgitation					0.188
None	36 (3)	1 (1)	18 (3)	17 (3)	
Mild	414 (37)	24 (34)	206 (39)	184 (35)	
Moderate	538 (48)	30 (42)	244 (46)	264 (50)	
Severe	142 (13)	16 (23)	60 (11)	66 (12)	

Values are expressed as n (%) or median [interquartile range].

ACE-I = angiotensin-converting-enzyme inhibitors; AF = atrial fibrillation; aFMR = atrial functional mitral regurgitation; ARB = angiotensin-receptor blocker; BMI = body mass index; CAD = coronary artery disease; CCBs = calcium channel blockers; CRT = cardiac resynchronization therapy; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HF = heart failure; iFMR = ischemic functional mitral regurgitation; LA = left atrium; LV = left ventricle; MRA = mineralocorticoid receptor antagonist; niFMR = non-ischemic functional mitral regurgitation; NOAC = non-vitamin K oral anticoagulants; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PAP = pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; VKA = vitamin K antagonist.

Table 2
Procedural and 30-days outcomes after transcatheter edge-to-edge repair with the Mitra-Clip system of the study population and according to study groups

	Total n=1153	aFMR n=71	iFMR n=541	niFMR n=541	*P*-value
Procedural details					
General anesthesia	928 (97)	57 (97)	434 (95)	437 (98)	0.032
Device time (minutes)	55 [35−85]	50 [30−74]	55 [35−85]	60 [35−90]	0.2
Number of Clips per patient	1.71±0.66	1.54±0.56	1.69±0.64	1.76±0.69	0.09
MitraClip Model					0.45
1st generation	579 (29)	30 (28)	269 (29)	280 (30)	
NT	806 (41)	42 (39)	375 (41)	389 (41)	
NTr	260 (13)	17 (15)	106 (12)	137 (14)	
XTr	330 (17)	20 (18)	165 (18)	145 (15)	
Procedural and 30-days outcomes					
MVARC Technical Success*	1138 (99)	71 (100)	530 (98)	537 (99)	0.104
Post-procedural MR≤ 1	651 (56.5)	48 (67.6)	311 (57.5)	292 (54)	0.3
Post-procedural MR≤ 2	1051 (91.2)	69 (97.2)	493 (91.1)	489 (90.4)	0.4
Peri-procedural complications†	31 (3)	2 (3)	18 (3)	11 (2)	0.53
Peri-procedural Clip detachment	9 (0.8)	0 (0)	7 (1.2)	2 (0.3)	0.4
Peri-procedural Major Bleeding	24 (2)	1 (1.4)	17 (3.1)	6 (1.1)	0.4
MVARC Device Success ‡	1019 (89)	68 (97)	477 (88)	474 (88)	0.14
MVARC Procedural Success ‡	989 (86)	64 (91)	463 (86)	462 (86)	0.42

Values are expressed as n (%) or median [interquartile range].

aFMR = atrial functional mitral regurgitation; iFMR = ischemic functional mitral regurgitation; MR = mitral regurgitation; MVARC = Mitral Valve Academic Research Consortium; niFMR = non-ischemic functional mitral regurgitation.

* Measured at exit from the catheterization laboratory.

† including: major bleeding, myocardial infarction, major or disabling stroke, pulmonary embolism, malignant arrhytmia, cardiac tamponade, device and access related complication requiring reintervention or urgent surgery.

‡ measured at 30-day follow-up.

MR ≤1+ and the absence of peripheral arteriopathy. The device generation used was not associated with the primary composite outcome at the univariate analysis (p = 0.08). After TEER, all etiologies experienced a significant improvement in NYHA functional class at follow-up.

Discussion

The key findings of the present analyses on the large, multicenter Italian prospective GIOTTO Registry assessing the impact of TEER using the MitraClip system in patients with aFMR compared with other FMR etiologies are the following: (1) patients with aFMR were 6.2% of all the

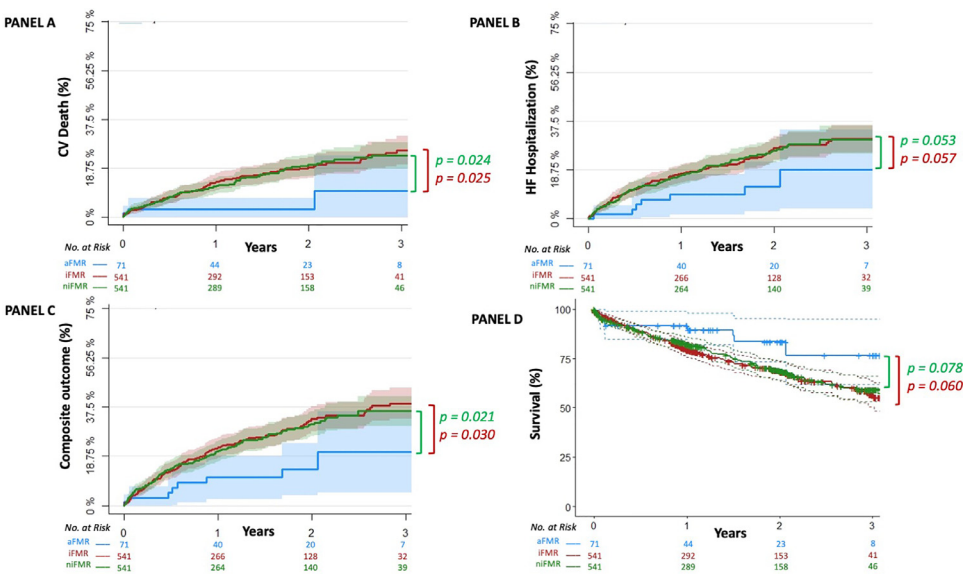

Figure 2. Time-to-event curves according to functional mitral regurgitation etiology for cardiovascular death (*A*), for heart failure hospitalization (*B*), for the composite of cardiovascular death and heart failure hospitalization (*C*), and for the overall survival (*D*).

Table 3
Results of the univariable analysis evaluating the association between the study groups and the outcomes of interest at follow-up (median 478 days, IQR [91-741])

	aFMR vs iFMR		aFMR vs niFMR	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Composite outcome of CV death and HF	0.43 (0.21−0.88)	0.021	0.45 (0.22−0.93)	0.03
HF	0.47 (0.22−1.01)	0.053	0.48 (0.22−1.02)	0.06
CV death	0.27 (0.09−0.85)	0.025	0.27 (0.09−0.84)	0.02
All-cause death	0.54 (0.28−1.03)	0.060	0.56 (0.30−1.07)	0.08

The table presents Hazard Ratios (HR) together with 95% Confidence Intervals, and p-values.

aFMR = atrial functional mitral regurgitation; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; iFMR = ischemic functional mitral regurgitation; IQR = interquartile range; niFMR = non-ischemic functional mitral regurgitation.

FMR, (2) patients with aFMR were older and more often women, with a higher rate of AF, but with a lower co-morbidity status compared with other etiologies of FMR, (3) TEER with MitraClip was safe and effective, with sustained MR reduction and significant functional improvement in all types of FMR at follow-up, (4) patients with aFMR had better outcomes in terms of CV mortality and/or HF than patients with iFMR/niFMR, and (5) aFMR, along with residual MR ≤1+ and the absence of peripheral arteriopathy, remained the major predictor of favorable outcomes.

The occurrence of FMR in AF and/or HF with preserved ejection fraction (HFpEF) has been a less studied etiology of MV disease. In contrast with the ischemic and nonischemic causes of FMR, patients with aFMR have an isolated impaired atrial or mitral annular sizes and dynamics, increased LA pressure, and inadequate leaflet adaptation, with normal LV size and systolic function.[2,5,9,24,25] The current guidelines do not recognize these differences and no specific recommendations on the management of aFMR are available yet.[2,3,5,6,9] Even the real proportion of patients with FMR with atrial etiology is not clearly known. To note, in the original article of Carpentier, nearly all reported cases of the type I disease (normal leaflet motion) were organic.[26] Currently, considering that the incidence of AF and HFpEF is growing epidemically,[1] it is likely that type I MR might include aFMR etiology. In previous studies, relevant aFMR has been reported in at least 4% to 7% cases with persistent AF or referred for AF ablation, in 4% of HFpEF cases, and up to 27% cases of a community-based data set.[7,27,28] From our data, aFMR was encountered in 6% of patients with FMR treated with the MitraClip. Notwithstanding, in other studies, the rate of patients aFMR treated with TEER has been higher (up to 36%). This difference is mainly explained by the discrepancies in definition (e.g., including patients with AF only) and the tricky overlap between aFMR with those patients with a certain degree of myxomatous leaflets degeneration and/or annular disjunction and the use of heterogeneous echocardiographic cutoffs (e.g., LA and LV dimensions).[10,11,13−15,29]

Table 4
Multivariable Cox Proportional Hazard model of predictors of the composite outcome of cardiovascular death and heart failure after transcatheter edge-to-edge repair with the Mitra-Clip system at midterm follow-up

	HR (95% CI)	*P*-value
Post-procedural mitral regurgitation ≤1+	0.63 (0.46−0.87)	0.01
FMR etiology aFMR vs iFMR	0.40 (0.16−1.02)	0.05
FMR etiology aFMR vs niFMR	0.37 (0.15−0.91)	0.03
Dyslipidemia	0.92 (0.67−1.27)	0.63
Current or former smoker	0.83 (0.57−1.17)	0.27
Peripheral arteriopathy	1.83 (1.23−2.71)	0.01
Prior myocardial infarction	1.04 (0.66−1.65)	0.85

The table presents Hazard Ratios (HR) together with 95% Confidence Intervals, and p-values.

aFMR = atrial functional mitral regurgitation; FMR = functional mitral regurgitation; iFMR = ischemic functional mitral regurgitation; niFMR = non-ischemic functional mitral regurgitation.

With respect to baseline clinical profile and consistent with previous reports,[10−12,14,16] our aFMR population were less sick and had a lower surgical risk profile and better biventricular function and smaller cavities than patients with other causes of FMR, being, instead, older and more often female, with arterial hypertension, and history of AF in up to 76% of patients.

Currently, the interplay between aFMR and treatment outcomes is largely unsettled. By the available data, aFMR seems to be with better outcomes compared with other FMR etiologies treated conservatively.[30−33] Conflicting short-term outcomes have been reported after surgical annuloplasty.[27,34,35] Moreover, recent studies on aFMR treated with TEER have shown a benefit of MitraClip on MR reduction and symptom and early outcomes improvement similar to patients with vFMR.[11−13,15] Notwithstanding, the reported major adverse events rates at short follow-up times and the absence of a comparison between all different types of FMR (e.g., ischemic vs niFMR) limit the knowledge that is thus far available on this topic. In our study, we confirmed the favorable procedural results and sustained MR reduction shown previously; interestingly, we focused the clinical evaluation on CV-related outcomes, extending them at a longer follow-up and providing comparisons with other FMR etiologies.[11,13,14,16,36] The peculiar clinical risk profile of patients with aFMR might explain their event-free CVD and HF advantage at the long term compared with both vFMR groups; in addition, MR reduction and significant functional improvement was not statistically different.[5] In other cases, such as in a recent meta-analysis, the different survival and HF incidence shown in the ventricular causes of FMR could be related to the unbalanced distribution of the patients with aFMR in the 2 ischemic versus nonischemic groups.[37]

Finally, in addition to aFMR and regardless of FMR etiology, postprocedural MR ≤1+ was a major favorable predictor of late outcome in our cohort. This finding is in line

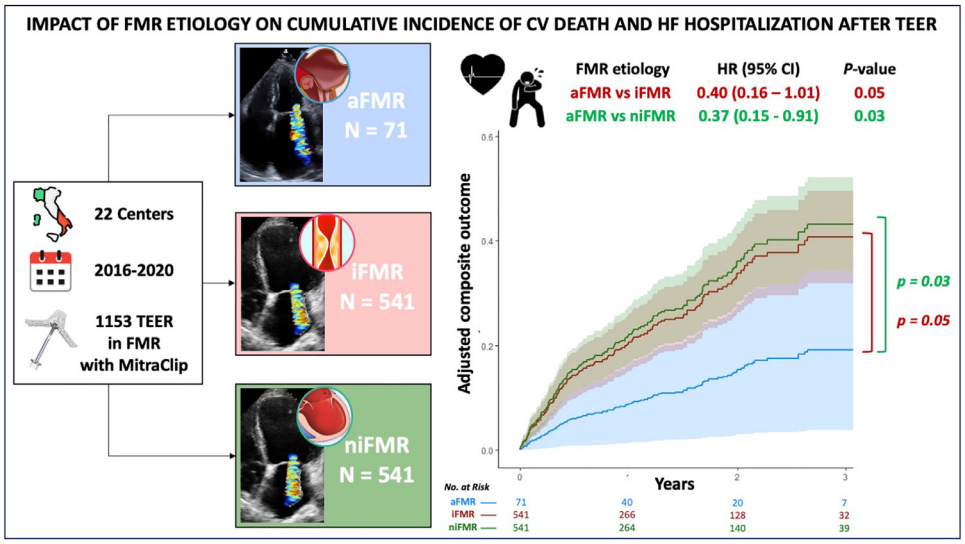

Figure 3. (Central illustration). Adjusted cumulative incidence of the composite of cardiovascular death and heart failure hospitalization according to functional mitral regurgitation etiology.

with previous evidence on the role of optimal procedural result after TEER. Thus, all effort should be made in terms of TEER optimization, and further studies are needed to find the best trade off with final transvalvular gradient and residual MR.[15,18,38,39]

This study has limitations. First, this is an observational, nonprespecified analysis of a multicenter, single-arm, prospective registry on TEER, with the inherent limitations of unmeasured confounders, study power, and the lack of comparison with alternative management. Second, our definition of aFMR is based on a recent consensus document that is not clearly validated in prospective studies.[5,7,11,13,15,21] Moreover, the percentage of aFMR treated by TEER was relatively smaller than in other series; however, the widespread lack of core laboratory evaluation and detection of screening failures does not allow further speculation on this point compared with other studies.[13,15] Finally, the conclusion of this study cannot be extended to the newer MitraClip iterations and different TEER devices.

The results of this GIOTTO subanalysis suggests that aFMR is the least prevalent cause of FMR but associated with better clinical outcomes after TEER than patients with vFMR. Postprocedural MR >1+, peripheral vasculopathy, and non-aFMR etiologies were independent predictors of worse outcomes after TEER with the MitralClip.

Declaration of Competing Interest

Drs. Giuseppe Tarantini, Bedogni, Grasso, Paolo Denti (PD), Tamburino, Petroni, Montorfano declared speaker fees from Abbott Vascular. The remaining authors have no competing interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.11.007.

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