Prognostic Value of Pre-operative Atrial Fibrillation in Patients With Secondary Mitral Regurgitation Undergoing MitraClip Implantation

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Limited data are available regarding the independent prognostic role of preoperative atrial fibrillation (AF) after transcatheter mitral valve repair with MitraClip. We sought to evaluate the impact of preoperative AF in patients with heart failure (HF) and concomitant secondary mitral regurgitation (MR) after MitraClip treatment. The study included 605 patients with significant secondary MR from a multicenter international registry. Patients were stratified into 2 groups according to the presence or absence of preoperative AF. Primary end point was 5-year overall death, secondary end points were 5-year cardiac death and first re-hospitalization for HF. To account for baseline differences, patients were propensity score matched 1:1. The overall prevalence of preoperative AF was 44%. At 5-year Kaplan-Meier analysis, compared with patients without AF, those with AF had significantly more adverse events in term of overall death (67% vs 43%; HR 1.84, log-rank p <0.001) and cardiac death (56% vs 29%; HR 2.11, log-rank p <0.001) and re-hospitalization for HF (63% vs 52%; HR 1.33, log-rank p = 0.048). Multivariate analysis identified AF as independent predictor of worse outcome in term of primary end point (HR 1.729, 95% C.I. 1.060 to 2.821; p = 0.028). After propensity score matching, patients with AF had higher rates of death and cardiac mortality but similar rates of re-hospitalization for HF. In conclusion, in patients with HF undergoing MitraClip treatment for secondary MR, preoperative AF is common and an unfavourable predictor of 5-year death and cardiac death. However, AF did not affect the frequency of re-hospitalization for HF. **(Am J Cardiol 2021;143:51−59)**

Secondary mitral regurgitation (MR) is a common finding in patients with heart failure with reduced ejection fraction. It results from geometrical distortion of the subvalvular apparatus secondary to enlargement and spherical remodeling of the left ventricle,[1,2] producing a vicious circle that worsens the prognosis.[3] Besides, in patients with long-standing atrial fibrillation (AF), atrial enlargement may lead to mitral valve (MV) annular dilatation which in turn may cause MR even in the presence of preserved ventricular function.[4] In the last few years, percutaneous MV repair using the MitraClip system has been developed to treat symptomatic patients with severe MR, who were considered by the heart team at high risk for surgery or inoperable.[5−7] Despite its role in symptoms improvement, there is still debate about which kind of clinical benefit to expect in patients with secondary MR.[6−8] This may be related to the presence of several co-morbidities, including AF, whose impact on outcomes after MitraClip treatment is largely unknown, with smaller scale studies reporting conflicting results.[9−12] The aim of this study was to evaluate the independent prognostic value of preoperative AF in patients with heart failure (HF) and concomitant significant secondary MR treated with MitraClip.

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Methods

The MiZüBr (Milan-Zürich-Brescia) registry is an observational ongoing study including HF patients with significant MR treated with MitraClip starting from October 2008 to May 2018 at San Raffaele Hospital of Milan, Spedali Civili of Brescia and University Heart Center of Zürich. Patients were considered suffering from chronic HF according to current guidelines.[13] Patients with both ischemic and non-ischemic secondary MR were included. Ischemic secondary MR was recognized when dilated cardiomyopathy was due to previous myocardial infarction or severe stable coronary artery disease, otherwise secondary MR was defined non-ischemic.[14] All patients were evaluated by the local Heart Team. Decision making for intervention was made by the Heart Team on the basis of both morphological suitability for MitraClip implantation as well as contraindication to surgery because of an elevated European System for Cardiac Operative Risk Evaluation (EuroSCORE) or severe co-morbidities or any contraindication to cardio-pulmonary by-pass. Before procedure, patients underwent transthoracic and transesophageal echocardiography to evaluate morphological suitability for MitraClip implantation and quantify MR, that was graded according to the European Association of Cardiovascular Imaging guidelines: 0+ (none), 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe), 4+ (severe).[15] All patients included had significant (≥ 3+) secondary MR and a history of HF despite optimal medical therapy. Patients were defined with right ventricular (RV) dysfunction if tricuspid annular plane systolic excursion (TAPSE) was <17 mm and/or systolic wave velocity at tissue doppler imaging was <9.5 cm/s, according to the American Society of Echocardiography guidelines.[16] In case of discrepancy, the systolic wave velocity at tissue doppler imaging was utilized as the discriminant value (90% sensitivity and 85% specificity to identify the presence of RV dysfunction).[17] Annular dilation was defined by an antero-posterior or a latero-lateral annulus diameter >35 mm.[1]

Patients were defined to be affected by paroxysmal, persistent or permanent AF according to current guidelines.[18] Particularly, AF was identified according to EKG interpretation in patients with permanent AF and to documented charts in those with pre-procedural paroxysmal or persistent. Chronic kidney disease as Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation-derived estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2.[19] Six-minute walking test (6MWT) was performed if patient status allowed.

The endovascular edge-to-edge mitral valve repair procedure with MitraClip has been previously described.[14] Technical, device and procedural success was defined as recommended by the Mitral Valve Academic Research Consortium.[20]

After discharge, patients were regularly followed at 6-month, 1-year, 2-year up to 5-year after MitraClip implantation. Clinical evaluation of New York Heart Association (NYHA) functional class, echocardiography assessment and 6MWT were performed at follow-up visits.

The primary study end point was overall death after MitraClip up to 5-year in patients stratified for pre-operative AF. The secondary clinical end points were cardiac death and first re-hospitalization for acute HF up to 5-year. A composite clinical end point of Left Ventricular Assist Device (LVAD) implantation, need for conventional MV surgery, heart transplantation or redo MitraClip after the first treatment was also evaluated. Other secondary end points presented were functional end points: variation of NYHA class and 6MWT between baseline and long-term follow-up. Moreover, variation of MR grade, left ventricular ejection fraction, left ventricular end-diastolic volume, diameter, and right ventricular function were predefined as echocardiographic end points. All end points were evaluated and adjudicated independently by at least 2 physicians (C.G., A.S. and A.S. in Milan, M.A. and F.E. in Brescia, M.T. and F.M. in Zürich). In case of a suspected event, the medical records from the referring institution were systematically reviewed by the core members. In case of discrepancy or unclear data, the opinion of the referring physician was also required to reach an agreement.

The study was approved by the Hospital Ethics Committee of each centers and each patient provided written informed consent for the procedure, data collection and subsequent analysis. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Distribution of continuous data was tested with the Shapiro-Wilk test. Normally distributed variables were expressed as mean ± standard deviation, whereas non-normally distributed variables were presented as median and interquartile range. Categorical variables were reported as percentages. Continuous variables were then compared using an independent-sample Student's *t* test or Kolmogorov-Smirnov Z test, when appropriate; categorical variables were compared with Chi square test. Paired comparison between baseline and follow-up variables was performed with the paired-sample Student's t test or Wilcoxon signed-rank test. Data for patients lost to follow-up were censored at the time of the last contact. Event-free survival up to 5-year were evaluated according to the unadjusted Kaplan-Meier method and survivals among groups were compared using log-rank test (Cox-Mantel test). Cox proportional hazards regression analysis was used to determine significant predictors of primary and secondary clinical end points. Variables with a univariate statistical significance of <0.05 were selected for inclusion into the multivariable model. Multivariate analysis, using stepwise forward selection, was finally performed to analyze the association of baseline characteristics with study end points, expressed as hazard ratio (HR) with 95% confidence interval (CI) and p values. Finally, to assess the truthfulness of our results a propensity score matching was performed in order to minimize differences in terms of confounding variables among the 2 groups (AF vs no-AF). The propensity scores were obtained through a binary logistic regression model with AF as binary outcome and variables found to be significantly associated ($p < 0.05$) with AF as predictors (ie, age, gender, chronic kidney disease, left ventricular ejection fraction, previous coronary artery by-pass graft, cardiac resynchronization therapy, and systolic pulmonary artery pressure >60 mm Hg). A sensitivity analysis approach was allowed with inclusion of strong predictors for the primary end points, while variables unrelated to the end points were not included, even if

significantly different between the 2 populations, because they would have increased the variance of the estimated exposure effect without decreasing bias.[21] Patients of the 2 groups were matched 1:1 through a greedy algorithm based on a caliper defined to have a maximum width of 0.2 SD of the logit of the estimated propensity-score, in order to eliminate over 90% of the bias in the observed confounders.[22] The final caliper was 0.035. Hosmer-Lemeshow and c-statistic tests were used to assess the goodness of fit for logistic regression models and the predictive model discriminatory power, respectively. All statistical tests were 2-sided, and p values <0.05 were considered statistically significant. The statistical analyses were performed by 2 investigators (A.S. and C.A.P.), using SPSS software version 25.0.0 (SPSS Inc., Chicago, Illinois), STATA software version 14 (StataCorp, College Station, Texas) and GraphPad Prism software version 6 (GraphPad, Inc, San Diego, California).

Results

Six-hundred five patients with HF and significant secondary MR (mean age 71 ± 10 years; 77% male) were included in the study, Supplementary Appendix, Figure S1. According to AF we identified 2 groups, 267 (44%) patients with pre-operative AF and 338 (56%) patients without. Concerning AF group, 74 (29%) patients suffered from paroxysmal, 39 (16%) from persistent and 137 (55%) from permanent AF. 509 (84%) patients had HF with reduced left ventricular ejection fraction (LVEF) without

Table 1
Baseline clinical features in entire study and propensity score matched cohorts according to the presence or absence of atrial fibrillation (AF)

	Entire study cohort			Propensity score matched cohort		
Variable	AF group (n = 267)	no-AF group (n = 338)	p value	AF group (n = 171)	no-AF group (n = 171)	p value
Age (years)	74 ± 8	69 ± 10	**<0.001**	72 ± 8	72 ± 8	0.881
Men	225 (84%)	244 (72%)	**<0.001**	140 (82%)	138 (81%)	0.782
AF type		n.a.	n.a.		n.a.	n.a.
paroxysmal	74 (29%)			49 (30%)		
persistent	39 (16%)			24 (15%)		
permanent	137 (55%)			86 (53%)		
EuroSCORE II (%)	11 ± 4	9 ± 4	**0.050**	10 ± 3.5	10 ± 4	0.400
NYHA class			0.114			0.430
I	5 (2%)	2 (1%)		3 (2%)	2 (1%)	
II	50 (19%)	82 (24%)		36 (21%)	38 (22%)	
III	171 (64%)	194 (57%)		108 (63%)	99 (58%)	
IV	41 (15%)	60 (18%)		24 (14%)	32 (19%)	
NT-proBNP (pg/mL)	3292 [2002; 7094]	3045 [1478; 7910]	0.494	3277 [1882; 5972]	3451 [1786; 8320]	0.952
eGFR (mL/min/1.73 m^2)	44 [31; 61]	53 [38; 81]	**<0.001**	48 [32; 67]	48 [33; 71]	0.161
6MWT distance (m)	223 ± 95	237 ± 116	0.371	222 ± 101	279 ± 116	**0.016**
Co-morbidities[†]						
Hypertension	158 (63%)	206 (65%)	0.643	99 (58%)	116 (68%)	0.057
Chronic kidney disease	151 (62%)	141 (46%)	**0.002**	91 (53%)	92 (54%)	0.605
Diabetes mellitus	72 (29%)	86 (27%)	0.686	48 (28%)	58 (34%)	0.228
Dyslipidemia*	114 (45%)	154 (48%)	0.470	71 (42%)	82 (48%)	0.232
Coronary artery disease	157 (62%)	171 (54%)	**0.037**	100 (59%)	105 (61%)	0.581
History of MI	126 (50%)	143 (45%)	0.219	80 (47%)	89 (52%)	0.330
Previous PCI	112 (42%)	167 (49%)	0.068	74 (43%)	93 (54%)	**0.040**
Previous CABG	85 (32%)	68 (20%)	**0.001**	45 (26%)	42 (25%)	0.710
COPD	58 (22%)	74 (22%)	0.945	33 (19%)	43 (25%)	0.183
Devices[†]						
ICD	108 (40%)	159 (47%)	0.105	64 (37%)	77 (45%)	0.153
CRT	84 (34%)	80 (26%)	**0.043**	53 (31%)	55 (30%)	0.814
Drugs[°]						
ACE-I/ARBs	104 (46%)	161 (55%)	0.060	64 (47%)	77 (53%)	0.311
Beta-blockers	161 (72%)	208 (71%)	0.718	95 (70%)	110 (75%)	0.301
K^+ savers	136 (61%)	171 (58%)	0.517	90 (66%)	91 (63%)	0.550
Digoxin	50 (22%)	33 (11%)	**0.001**	33 (24%)	16 (11%)	**0.005**
anticoagulant therapy	189 (79%)	70 (24%)	**<0.001**	128 (84%)	31 (21%)	**<0.001**
antiplatelet therapy	111 (63%)	203 (68%)	**0.002**	66 (63%)	109 (73%)	0.084

ACE-I: angiotensin-converting enzyme inhibitors. ARB: angiotensin 1 receptor blocker. CABG: coronary artery by-pass graft. COPD: chronic obstructive pulmonary disease. CRT: cardiac resynchronization therapy. EuroSCORE: European System for Cardiac Operative Risk Evaluation. eGFR: estimated glomerular filtration rate. ICD: implantable cardioverter-defibrillator. MI: myocardial infarction. NT-proBNP: N-terminal prohormone of brain natriuretic peptide. NYHA: New York Heart Association. PCI: percutaneous coronary intervention. 6MWT: 6-minute walk test.

Data are presented as n (%), mean ± SD or median [IQR].

*Previous lipid-lowering therapy or known total cholesterol >2.5 g/L.

[†] Values are avaible for ~ 90% of the entire study cohort.

[°] Values are avaible for ~ 80% of the entire study cohort.

significant differences between the 2 groups (p = 0.055). Compared with patients without AF, those with AF were older, more males, had higher surgical mortality risk, as assessed by the EuroSCORE II, and lower estimated glomerular filtration rate (44 [31; 61] mL/min/1.73 m^2 vs. 53 [38; 81] mL/min/1.73 m^2; p <0.001). Of note, there were no differences on HF drugs therapy, but, as expected, patients with AF were more often on digoxin and on oral anticoagulant therapy (including vitamin K antagonists and direct-acting oral anticoagulants). On the contrary, antiplatelet therapy was more frequent in no-AF group. Besides, patients without AF presented smaller left atrium, lower tricuspid regurgitation, and fewer right ventricular dysfunction.

After 1:1 propensity score matching, 342 patients (171 AF and 171 no-AF) were appropriately matched for patient-level and echocardiographic-level characteristics. Baseline clinical and echocardiographic characteristics of the 2 cohorts (entire study and propensity score matched cohorts) are reported in Table 1 and in Table 2, respectively.

Procedural success was achieved in 537 (89%) patients, without significant difference between overall patients with or without AF. Of the 68 patients with unsuccessful MitraClip implantation, 9 (2%) had in-hospital partial MitraClip detachment. Compared with those without AF, patients with AF presented significant higher mean number of implanted MitraClips. MR grade 1 or 2 at the end of implantation procedure characterized 77% of both groups. The in-hospital overall cardiac mortality was 2% (11 patients), without significant differences. Overall length of post procedural hospital stay was similar between the 2 groups.

With 38 (6%) patients lost to follow-up, without significant differences between the 2 groups, 567 were followed for a median of 18 (IQR: 10-34) months. At 5-year Kaplan Meier analysis in the entire study cohort, compared with patients without AF, those with AF suffered more adverse events both in term of overall death (67% vs 43%; HR 1.84, log-rank p <0.001) and cardiac death (56% vs 29%; HR 2.11, log-rank p <0.001) as well as re-hospitalization for acute HF (63% vs 52%; HR 1.33, log-rank p = 0.048), Figure 1, panel A-C. Combined clinical end point (LVAD implantation, need for conventional MV surgery, heart transplantation or redo MitraClip) did not differ significantly between 2 groups (AF 9% vs. no-AF 10%; HR 1.02, log-rank p = 0.945) Figure 1, panel D. Primary and secondary clinical end points are shown in Table 3. Significant improvement in NYHA functional class (reduction of 1 or 2 classes) and in 6MWT was observed in both AF and no-AF groups, Figure 2, panel A and C. Similarly, significant reduction of mean MR grade was observed in both groups, Figure 2, panel E. Changes from baseline to follow-up of echocardiographic features in the 2 study groups are shown in Supplementary Appendix, Table S1, section A. At univariate Cox regression analysis, AF together with chronic kidney disease, NT-proBNP ≥10.000 pg/mL, NYHA functional class III/IV, LVEDVi ≤96 mL/m^2,

Table 2
Baseline echocardiographic features in entire study and propensity score matched cohorts according to the presence or absence of atrial fibrillation (AF)

Variables	Entire study cohort			Propensity score matched cohort		
	AF group (n = 267)	no-AF group (n = 338)	p value	AF group (n = 171)	no-AF group (n = 171)	p value
MR degree			0.303			0.247
1+ (mild)	0	0		0	0	
2+ (moderate)	4 (1%)	10 (3%)		2 (1%)	6 (4%)	
3+ (moderate-to-severe)	34 (13%)	48 (14%)		26 (15%)	26 (15%)	
4+ (severe)	228 (86%)	276 (83%)		143 (84%)	139 (81%)	
EROA (mm^2)	42 ± 15	40 ± 16	0.584	38 ± 14	37 ± 16	0.813
LVEDD (mm)	67 ± 10	68 ± 10	0.751	67 ± 10	68 ± 10	0.540
LVEDV (mL)	197 ± 74	208 ± 78	0.099	197.5 ± 81	219 ± 79	0.240
LVESV (mL)	140 ± 65	149 ± 67	0.132	142.5 ± 71	157 ± 69	0.870
LVEF (%)	31 ± 10.5	29 ± 10	**0.038**	30 ± 11	29.5 ± 10	0.780
LVEF <30%	146 (60%)	198 (65%)	0.221	107 (63%)	106 (62%)	0.911
LAV (mL)	137 ± 56	111 ± 38	**<0.001**	138 ± 57	113 ± 36	**0.001**
TR degree*			**0.004**			0.075
none	3 (1%)	14 (4%)		2 (1%)	7 (6%)	
1+ (mild)	68 (31%)	117 (42%)		44 (31%)	56 (44%)	
2+ (moderate)	81 (36%)	86 (31%)		50 (35%)	36 (28%)	
3+ (severe)	64 (32%)	70 (23%)		44 (31%)	28 (22%)	
RVEDD (mm)	37 ± 7.5	37.5 ± 9	0.904	36 ± 7	38 ± 9	0.299
RV dysfunction	79 (51%)	80 (39%)	**0.031**	54 (51%)	53 (42%)	0.160
sPAP (mmHg)†	46 ± 14	49 ± 17	**0.016**	47 ± 15	47 ± 15	0.961
sPAP >60mmHg	34 (15)	65 (24)	**0.012**	29 (17)	27 (16)	0.770

EROA: effective regurgitant orifice area. LAV: left atrial volume. LVEDD: left ventricular end-diastolic diameter. LVEDV: left ventricular end-diastolic volume. LVEF: left ventricular ejection fraction. LVESV: left ventricular end-systolic volume. MR: mitral regurgitation. RVEDD: right ventricular end-diastolic diameter. sPAP: systolic pulmonary arterial pressure. TR: tricuspid regurgitation.

Data are presented as n (%), mean ± SD.

*Values are avaible for ~ 80% of the entire study cohort.

† Values are avaible for ~ 90% of the entire study cohort.

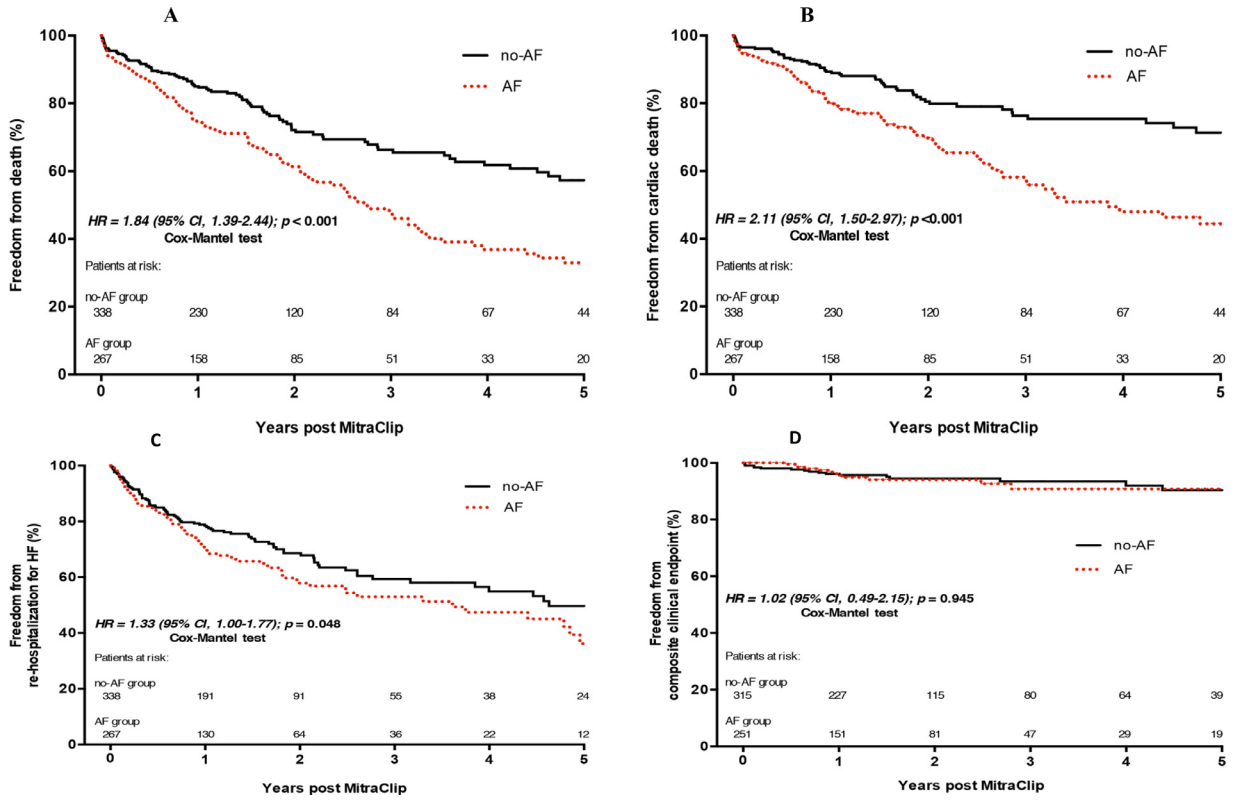

Figure 1. Entire study cohort 5-year Kaplan-Meier analysis of clinical end points according to the presence or absence of atrial fibrillation. Entire study cohort 5-year Kaplan-Meier analysis of survival free from *overall death* (panel A), *cardiac death* (panel B), first re-hospitalization for acute heart failure (panel C) and combined clinical end point [cardiac death, Left Ventricular Assist Device (LVAD) implantation, need for conventional mitral valve (MV) surgery, heart transplantation or redo MitraClip after the first treatment] (panel D) in patients stratified for pre-operative atrial fibrillation (AF) and no-AF.

LVEF ≤30%, RV dysfunction and procedural success were associated with a worse outcome in term of primary end point. Multivariate analysis identified AF as independent predictor of adverse outcome in term of primary endpoint (HR 1.729, 95% C.I. 1.060 − 2.821; $p = 0.028$). Other independent negative prognostic factors are shown in Table 4 and Figure 3. Many of these baseline features, including AF, have been identified as independent predictors of cardiac death, meanwhile AF was not able to predict neither re-hospitalization for HF nor composite clinical end point, as evidenced in Supplementary Appendix, Table S2.

Table 3
Clinical outcome in entire study and propensity score matched cohorts

	Entire study cohort					Propensity score matched cohort				
	AF group (n = 267)	no-AF group (n = 338)	HR	95% CI	p value	AF group (n = 171)	no-AF group (n = 171)	HR	95% CI	*P* value
Overall death	112 (67%)	87 (43%)	1.84	1.39-2.44	**<0.001**	69 (64%)	56 (50%)	1.46	1.03-2-08	**0.035**
Cardiac death	83 (56%)	56 (29%)	2.11	1.50-2.97	**<0.001**	51 (53%)	36 (35%)	1.68	1.10-2.58	**0.016**
Re-hospitalization for HF	93 (63%)	97 (52%)	1.33	1.00-1.77	**0.048**	54 (58%)	55 (56%)	1.10	0.76-1.61	0.592
Composite clinical endpoint	12 (9%)	16 (10%)	1.02	0.49-2.15	0.945	7 (10%)	11 (12%)	0.77	0.30-1.99	0.589
	3 (2.0%)	6 (3.0%)	0.68	0.17-2.7	0.592	2 (0.2%)	4 (3.4%)	0.57	0.10-3.16	0.527
LVAD implantation										
	4 (2.4%)	4 (1.5%)	1.40	0.35-5.63	0.627	1 (0.8%)	2 (1.6%)	0.56	0.05-6.27	0.640
MV surgery										
	3 (2.7%)	3 (3.1%)	0.86	0.20-3.60	0.836	2 (3.2%)	3 (4.8%)	0.08	0.13-4.82	0.810
MitraClip redo										
	2 (2.5%)	3 (3%)	1.09	0.18-6.60	0.919	2 (3.9%)	2 (2.7%)	1.31	0.18-9.35	0.785
Heart transplantation										

AF: atrial fibrillation. HF: Heart failure. LVAD: Left Ventricular Assist Device. Data are presented as n (%).

Composite clinical end point was defined as the composite of LVAD implantation, need for conventional mitral valve surgery, heart transplantation or redo MitraClip after the first treatment. All percentages are Kaplan−Meier estimates at the specific time point and thus do not equal the number of events divided by the total number of patients in the treatment group. p values have been derived from a Cox model comparing the incidence of each outcome in the AF versus no-AF group both in the entire study cohort and in the propensity score matched cohort.

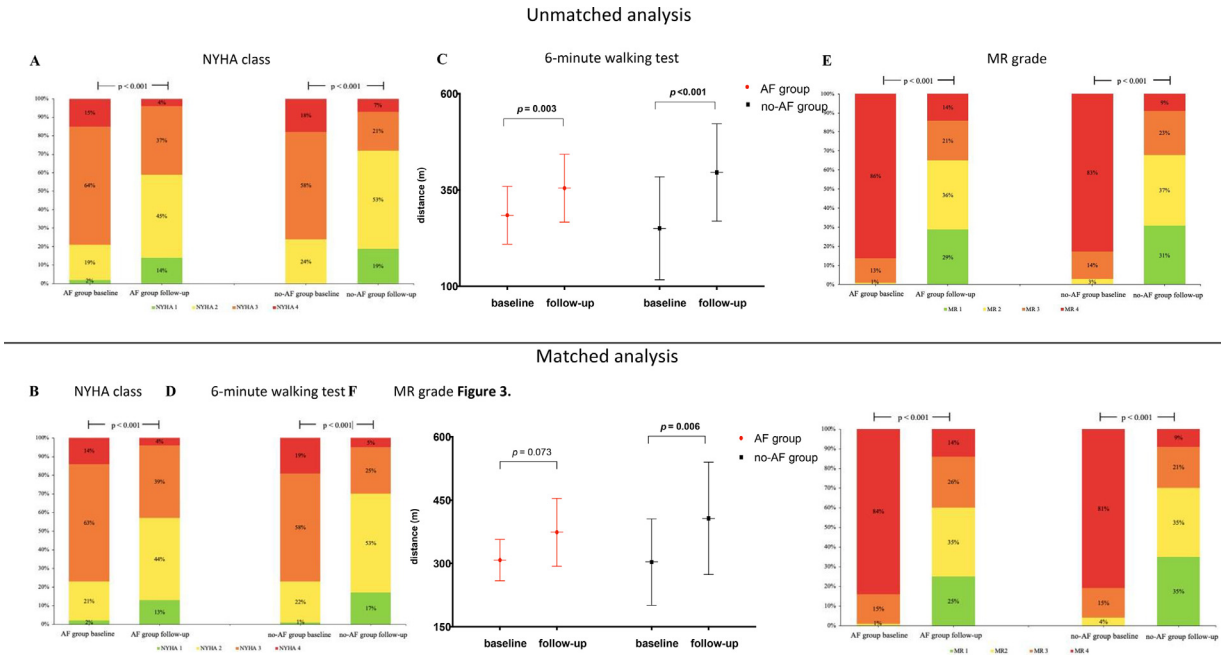

Figure 2. Variations from baseline to follow-up of clinical and echocardiographic features in patients stratified for atrial fibrillation and no-atrial fibrillation. Change from baseline to follow-up according to the presence or absence of atrial fibrillation (AF) in New York Heart Association (NYHA) functional class (panel A and B, entire study and propensity score matched cohort, respectively), mean 6-minutes walk test (6MWT) distance (panel C and D, entire study and propensity score matched cohorts, respectively) and mitral regurgitation (MR) grade (panel E and F, respectively).

After matching, statistically significant differences at 5-year Kaplan-Meier analysis were maintained regarding overall death (AF 64% vs. no-AF 50%; HR 1.46, log-rank $p = 0.035$) and cardiac death (53% vs. 35%; HR 1.68, log-rank p = 0.016), Figure 4, panel A-B. Conversely, there was no difference in term of re-hospitalization for acute HF (58% vs. 56%; HR 1.10, log-rank p = 0.592) and combined clinical end point (10% vs. 12%, HR 0.77, log-rank p = 0.589) between the 2 groups, Figure 4, panel C-D.

In both AF and no-AF patients there was improvement after the procedure of both functional evaluations, namely NYHA and 6MWT distance, Figure 2, panel B and D. Similarly, reduction of MR grade was observed in both population, Figure 2, panel F. Changes from baseline to follow-up of echocardiographic features in both groups are shown in Supplementary Appendix, Table S1, section B.

Discussion

In this propensity score-matched international multicenter analysis regarding the prognostic role of AF in patients with HF after MitraClip treatment of secondary MR we found that: (1) preoperative AF is common, affecting about 40% of patients, and (2) it is associated with worst 5-year outcome in terms of overall death and cardiac death, however, (3) after propensity score matching, there was no difference in HF re-hospitalization among patients with or without AF.

Actually, there is an open debate on the role played by AF after correction of secondary MR in patients with HF. Prior studies have reported conflicting findings as to whether pre-operative AF is an independent predictor of adverse outcome after MV repair, both in patients undergoing surgical MV repair[23,24] and percutaneous repair with MitraClip.[9,10,12]

Table 4
Primary endopoint-related univariate and multivariate Cox regression analysis in entire study cohort

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
AF	1.841	1.390 – 2.437	<0.001	1.729	1.060 – 2.821	0.028
CKD	2.378	1.685 – 3.355	<0.001	2.731	1.401 – 5.327	0.003
NYHA class III/IV	1.962	1.308 – 2.945	0.001	2.835	1.380 – 5.824	0.005
NT-proBNP ≥10000 pg/mL	3.221	2.232 – 4.649	<0.001	1.828	1.043 – 3.204	0.035
LVEDVi ≤96 mL/m^2	0.607	0.413 – 0.892	0.011			
LVEF ≤30%	1.613	1.182 – 2.201	0.003	1.986	1.137 – 3.468	0.016
RV dysfunction	1.541	1.077 – 2.206	0.018			
Procedural success	0.507	0.360 – 0.715	<0.001	0.533	0.304 – 0.935	0.028

AF: atrial fibrillation. CKD: chronic kidney disease. LVEDVi: left ventricular end-diastolic volume indexed. LVEF: left ventricular ejection fraction. NT-proBNP: N-terminal prohormone of brain natriuretic peptide. NYHA: New York Heart Association. RV: right ventricle.

Data are presented as hazard ratio (HR) with 95% confidence interval (CI) and p values.

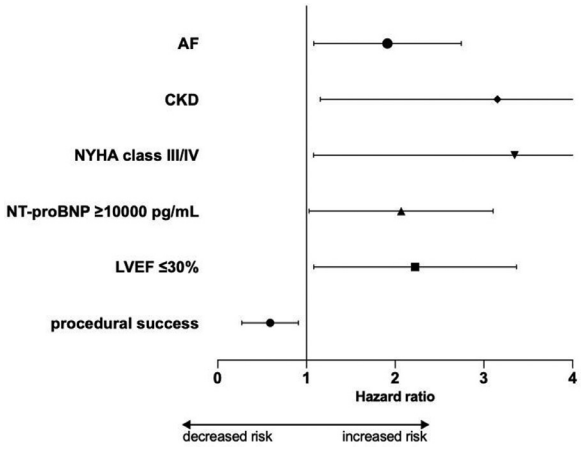

Figure 3. Forest plot showing results from multivariate Cox regression analysis regarding primary end point. AF: atrial fibrillation. CKD: chronic kidney disease. LVEF: left ventricular ejection fraction. NT-proBNP: N-terminal prohormone of brain natriuretic peptide. NYHA: New York Heart Association. Data are presented as hazard ratio (HR) with 95% confidence interval (CI).

Nevertheless, patients with AF are generally older, presenting more advanced HF disease, higher left ventricle and atrial volumes, more comorbidity, such as chronic renal failure and chronic obstructive pulmonary disease, compared with those without AF. Therefore, the conflict in study results may reflect different level of adjustment for several prognostic confounders, and AF might be just a marker of more advanced disease in sicker patients rather than an independent prognostic risk factor.

To our knowledge, this is the largest long-term analysis showing an association between pre-operative AF and worse survival in patients undergoing transcatheter repair of secondary MR in the contest of HF. In fact, none of the aforementioned studies evaluated the impact of preoperative AF only for secondary MR patients, mostly limiting the analyses at 1-year follow-up. Therefore, we try to partially cover these limitations, performing a propensity score matching analysis in a large series of patients with secondary MR followed up to 5 years. The present results are consistent with a meta-analysis across 23 studies enrolling 3.253 secondary MR patients undergoing MitraClip implantation which indicated AF negative prognostic value in term of survival, although limited to 1-year follow up.[25]

Several reasons might explain the impact on survival of AF after MitraClip treatment for secondary MR. First, patients with chronic HF and permanent AF have worse outcome than those in sinus rhythm, although this is largely explained by more advanced age and HF severity.[26,27] Second, AF is associated with annular dilatation that makes leaflets grasping with the clips more difficult and may result in worse long term efficacy, even after procedural success; besides, there is progressive annular dilation secondary to the arrhythmia that might impair procedural result at long-term follow-up. Third, patients with AF have additional

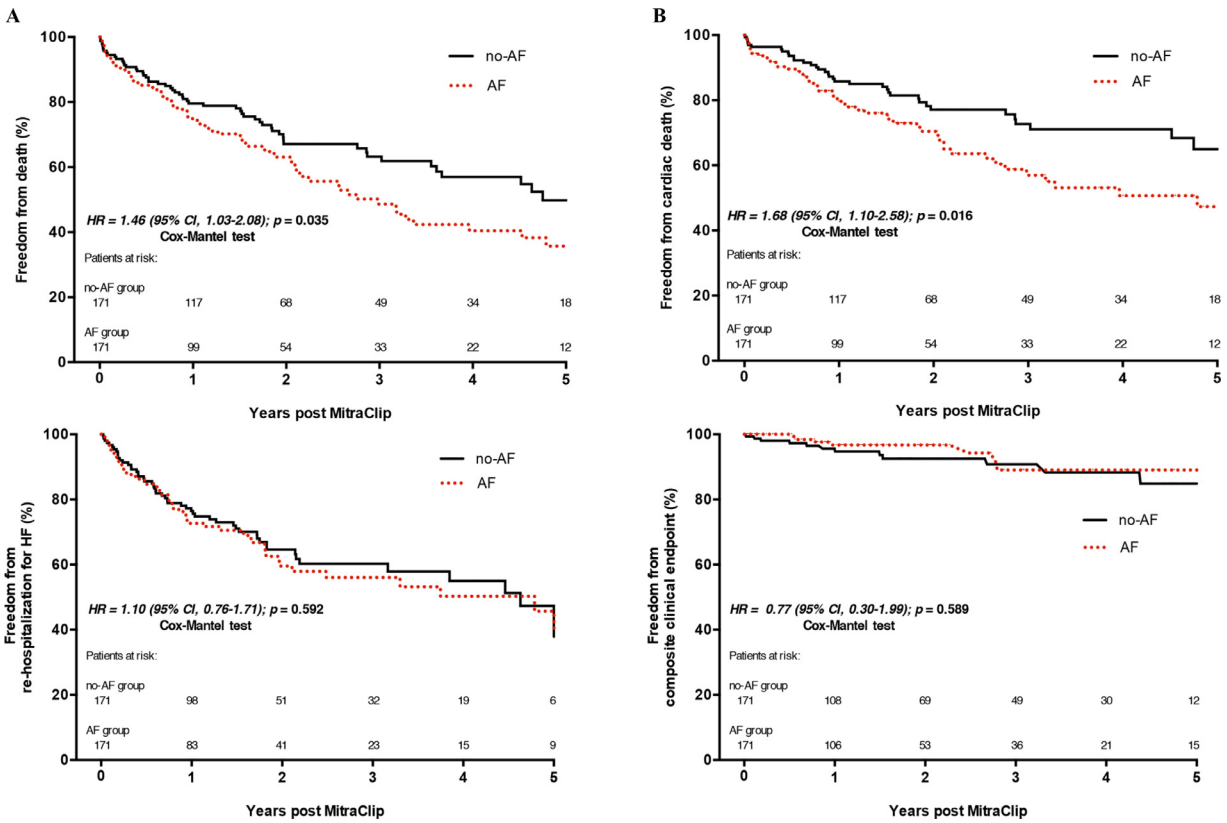

Figure 4. Propensity score matched cohort 5-year Kaplan-Meier analysis of clinical end points according to the presence or absence of atrial fibrillation. Propensity score matched cohort 5-year Kaplan-Meier analysis of survival free from *overall death* (panel A), *cardiac death* (panel B), first re-hospitalization for acute heart failure (panel C) and combined clinical end point [cardiac death, LVAD implantation, need for conventional MV surgery, heart transplantation or redo MitraClip after the first treatment] (panel D) in patients stratified for atrial fibrillation (AF) and no-AF.

risks related to both cardioembolic ischemic events (such as stroke) and hemorrhagic events (related to anticoagulant therapy). Fourth, the risk of sudden death is reported to be higher in patients with AF.[28,29] Finally, AF is also a major risk factor for cognitive impairment in the elderly,[30] which in turn is associated to an increased risk of falls and severe infections that contribute to worsening the prognosis of these patients.

Although MitraClip implantation in patients with secondary MR and AF has worse prognosis then in patients without AF, it doesn't seem futile in terms of re-hospitalization for HF, symptoms improvement, functional capacity. In fact, after matching for baseline confounders, the rate of re-hospitalization for HF at 5-year Kaplan-Meier analysis was equal between AF and non-AF groups (58% vs 56%; HR 1.10, $p = 0.592$). Actually, there is still debate about which kind of clinical benefit to expect from percutaneous MV repair in patients with secondary MR, and mostly, which kind of benefit to accept as still useful (symptoms and/or survival improvement) for each patient within the broad spectrum of HF presentation. We believe that a multiparametric patient assessment, which takes into account baseline clinic conditions (eg, age, NYHA class, renal function, chronic obstructive pulmonary disease etc.), echocardiographic (eg, grade of MR, left ventricular remodeling, RV function) and laboratory variables (eg, N-terminal prohormone of brain natriuretic peptide values), will be necessary for a personalized preprocedural evaluation of the possible clinical benefits after percutaneous MV repair in the contest of HF.[3] The present results regarding the prognostic role of pre-operative AF could be also integrated in this benefit-risk assessment.

The propensity score-matched analysis is a valuable tool for comparative effectiveness between treatment strategies but cannot replace a randomized trial. Therefore, our findings should be considered as hypothesis generating. Finally, we didn't account for AF developing after the procedure, therefore our findings should be limited on evaluating the prognostic role of pre-operative AF.

In conclusion, in this large 5-year propensity score matched analysis of patients with HF undergoing MitraClip treatment for significant secondary MR, preoperative AF is common and associated with higher rates of both overall- and cardiac-death. However, pre-operative AF did not affect the benefit of MitraClip procedure in term of re-hospitalization for HF.

Credit Author Statement

Cosmo Godino: Conceptualization, Methodology, Writing - Review & Editing, Visualization; Antonio Sisinni: Formal analysis, Writing - Original Draft, Visualization; Carlo Andrea Pivato: Formal analysis, Writing - Review & Editing; Marianna Adamo: Investigation; Maurizio Taramasso: Investigation; Antonio Parlati: Investigation; Leonardo Italia: Investigation; Davide Voci: Investigation; Andrea Scotti: Investigation; Andrea Munafò: Investigation; Nicola Buzzatti: Investigation; Paolo Denti: Investigation; Francesco Ancona: Investigation; Giorgio Fiore: Investigation; Alessandra Sala: Investigation; Pasquale Vergara: Supervision; Francesca Bodega: Investigation; Martina Maria Ruffo: Investigation Salvatore Curello: Supervision; Alessandro Castiglioni: Supervision; Michele De Bonis: Supervision; Ottavio Alfieri: Supervision; Eustachio Agricola: Supervision; Francesco Maisano: Supervision; Marco Metra: Supervision; Antonio Colombo: Supervision; Alberto Margonato: Supervision

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

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All authors have participated in the work and have reviewed and agree with the content of the article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.043.

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