Prognostic Impact of Heart Failure History in Patients with Secondary Mitral Regurgitation Treated by MitraClip

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The aim of this study was to investigate the prognostic role of heart failure (HF) history in patients with secondary mitral regurgitation (SMR) underwent MitraClip. We retrospectively analyzed 186 patients with SMR undergoing MitraClip at 4 centres. HF history was defined as number or days of HF hospitalizations in the 12-month before MitraClip, or as time from last HF hospitalization to MitraClip, or time between first SMR diagnosis and MitraClip. More severe symptoms were observed in patients with >1 HF hospitalization compared with those with ≤1 HF hospitalizations, in those with ≥10 days versus <10 days of HF hospitalization and in those with shortest time from the last HF hospitalization. No significant differences were observed for procedural data in the population stratified according to the different definitions. In variables related with HF history, only the number of HF hospitalizations before MitraClip was associated with an increased risk of clinical events (hazard ratio 1.59; 95% confidence interval [1.09 to 2.12]; p = 0.015), whereas days of previous HF hospitalization, time from last HF hospitalization and from first diagnosis of SMR do not impact on prognosis. A significant decrease in the number and days of HF hospitalizations was observed in the 12-month after MitraClip compared with the 12-month before. In conclusion, in variables related with HF history, recurrence (>1) of HF hospitalizations before MitraClip was the most powerful predictor of prognosis. Latency of intervention did not affect outcomes. **(Am J Cardiol 2020;135:120−127)**

Percutaneous edge-to-edge mitral valve repair by MitraClip has become an established procedure for the treatment of patients with heart failure (HF) and secondary mitral regurgitation (SMR)[1−3] However, 2 recent randomized clinical trials with an apparently similar design, comparing Mitraclip and guideline-directed medical therapy (GDMT) to GDMT alone, have showed opposite results.[4,5] This further shows the need to identify predictors of outcomes after MitraClip in patients with SMR and HF to improve patient selection and long-term results. Several factors have been reported as associated to clinical events after MitraClip such as severe left ventricular dilatation, low left ventricular ejection fraction, right ventricular failure, advanced symptoms, high levels of neurohumoral markers, and co-morbidities.[6−11] HF history is a known predictor of poor outcomes in patients with HF.[12−16] However, its role in patients undergoing Mitraclip has never been investigated. To fulfil this evidence gap we aim at investigating the prognostic role of HF history in patients with SMR underwent MitraClip.

Methods

We retrospectively analysed 186 patients with significant SMR undergoing MitraClip between October 2010 and October 2018 at 4 European centres (Civil Hospitals of Brescia, University Hospital of Zurich and Hospital Puerta de Hierro-Majadahonda of Madrid and Hospital of Leon). For the purpose of the present analysis only SMR patients whose number and time of HF hospitalizations during the 12-month period before the intervention have been included.

A local multidisciplinary Heart Team discussed all cases at each centre.

The history of HF was assessed using 4 definitions. First, the number of HF hospitalizations during the 12-month period before MitraClip; second, the total days of HF hospitalization during the 12-month period before MitraClip; third, the time between the last HF hospitalization and MitraClip and, lastly, the time between the first diagnosis of significant SMR and MitraClip.

HF hospitalization was defined as admission to an inpatient unit or ward in the hospital for 24 ≥ hours in presence

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of both the following criteria: (1) Symptoms, signs and/or laboratory evidence of worsening HF; (2) Administration of intravenous HF therapies.

Significant SMR was defined as moderate-to-severe (3+) or severe (4+) SMR.[17,18]

The population was stratified according to the above definitions. The first stratification provided for 3 groups: patients who had not, patients who had one, and patients who had more than 1 HF hospitalization during the 12-month period before the procedure. According to the second definition of HF history, the population was divided into 2 groups: patients with ≥10 or <10 days of HF hospitalization during the 12-month period before MitraClip. The third and the fourth stratifications were made by the tertiles of the time between the last HF hospitalization and the procedure, and the time between the first diagnosis of significant SMR and the procedure, respectively.

The primary end point was a composite of all-cause death and HF rehospitalizations at the longest available follow-up. The secondary end points were: all-cause death, cardiovascular (CV) death, and HF rehospitalization. We also evaluated the changes in the total number of HF hospitalizations and in the total days of HF hospitalization during the 12-month period before the procedure compared with the 12-month period after the procedure.

Device success was defined as postprocedural SMR ≤2 +.

The normal distribution of continuous variables was explored with Kolmogorov-Smirnov and the Shapiro-Wilk tests. Continuous variables following a normal distribution are reported as mean ± standard deviation and were compared using the Student *t* test or ANOVA test, whereas those not following a normal distribution are presented as median and interquartile range and were compared with the Mann-Whitney U or Kruskal Wallis test. Categorical variables are reported as counts and percentages and were compared using the Chi-square or Fisher exact tests, as appropriate. Comparison between dependent continuous variables at different time was performed with the Friedman test. Cumulative incidence of primary and secondary end points was estimated using the Kaplan-Meier curves and the differences between groups calculated using the log rank test. A multivariate Cox regression analysis, including variables differently distributed for the primary end point at an alpha level of 0.10, was performed to evaluate whether HF history was an independent predictor of all-cause death or HF rehospitalization. For this purpose 4 multivariable models were used according to the 4 considered definitions of HF history. Each result was expressed as hazard ratio (HR) and corresponding 95% confidence interval (CI). For all analyses, a 2-sided p <0.05 was considered to be significant. All statistical analyses were performed using the SPSS software, version 21 (SPSS Inc, Chicago, Illinois).

Results

Patients with more than 1 hospitalization during the 12-month interval before the procedure were more likely to be males and to have advanced symptoms compared with those with no-hospitalizations or 1 hospitalization (Table 1).

More advanced NYHA class and higher left ventricular end-diastolic diameter were noted in patients with ≥10 days versus <10 days of HF hospitalization during the 12-month period before MitraClip (Supplementary Table 1).

Shorter time between the last HF hospitalization and MitraClip was associated with more advanced NYHA class (Supplementary Table 2).

Table 1
Baseline characteristics of the population stratified by number of prior heart failure hospitalizations

Variable	No Hospitalization (n = 42)	1 Hospitalization (n = 74)	>1 Hospitalization (n = 70)	p-value
Men	23 (55%)	44 (60%)	56 (80%)	0.007
Age (Years)	68 ± 11	72 ± 8	71 ± 11	0.142
Body mass index (kg/m^2)	25.8 ± 6	25.7 ± 4	25.1 ± 4	0.604
Chronic kidney disease	25 (60%)	42 (57%)	42 (60%)	0.902
Diabetes mellitus	11 (26%)	22 (30%)	27 (39%)	0.333
Hypertension	21 (50%)	47 (64%)	38 (54%)	0.312
Atrial fibrillation	20 (48%)	37 (50%)	42 (60%)	0.345
Society of Thoracic Surgeons score (%)	3.0 (1.3−4.7)	4.0 (2.0−7.5)	2.5 (1.3−6.6)	0.250
New York Heart Association class				0.009
II	6 (14%)	7 (10%)	5 (7%)	
III	27 (64%)	46 (62%)	29 (41%)	
IV	9 (21%)	21 (28%)	36 (51%)	
Left ventricular ejection fraction (%)	33 ± 13	38 ± 14	33 ± 12	0.019
Left ventricular end-diastolic diameter (mm)	68 ± 9	64 ± 11	69 ± 10	0.053
Left ventricular end-diastolic volume (ml)	187 ± 77	173 ± 73	191 ± 75	0.390
Left ventricular end-systolic diameter (mm)	58 ± 11	56 ± 13	63 ± 10	0.042
Left ventricular end-systolic volume (ml)	132 ± 67	112 ± 60	135 ± 69	0.115
Left atrial diameter (mm)	44 ± 16	39 ± 17	38 ± 20	0.280
Systolic pulmonary artery pressure (mmHg)	46 ±14	48 ± 16	51 ± 14	0.302
Mitral regurgitation 4+	36 (86%)	67 (91%)	66 (94%)	0.331
Ischemic aetiology of mitral regurgitation	21 (50%)	43 (58%)	48 (69%)	0.190

Table 2
Procedural data of the population stratified by number of prior heart failure hospitalizations

Variable	No Hospitalization (n = 42)	1 Hospitalization (n = 74)	>1 Hospitalization (n = 70)	p-value
Number of clip				
1	20 (48%)	37 (50%)	33 (47%)	0.949
2	19 (45%)	30 (41%)	29 (42%)	
>2	3 (7%)	7 (10%)	8 (12%)	
Device success	40 (95%)	70 (95%)	67 (96%)	0.854
Intraprocedural death	1 (2%)	0 (0%)	0 (0%)	0.178
Mitral regurgitation at discharge				
0/1+	26 (62%)	34 (46%)	33 (47%)	0.347
2+	13 (31%)	28 (38%)	30 (43%)	
3/4+	3 (7%)	12 (16%)	7 (10%)	

Baseline characteristics of population stratified by the time between the first diagnosis of significant SMR and MitraClip are reported in Supplementary Table 3.

There were no significant differences with respect to number of clips used, device success, intraprocedural death, and MR degree at discharge in the population stratified by number of HF hospitalization (Table 2) as well as by using the other definitions of HF history (Supplementary Table 4, 5, and 6),

Median follow-up was 633 (interquartile range 257 to 1,132) days. Primary end point occurred in 101 patients (54%), 62 patients died (33%), 50 due to CV cause, and 69 were hospitalized due to HF (37%).

Cumulative incidence of primary end point was higher in patients having >1 HF hospitalization during the 12-month period before MitraClip compared with those who had not or had 1 HF hospitalization (70.5% vs 48.6% e 50.2%, log rank p = 0.008) (Figure 1). Similar results were observed

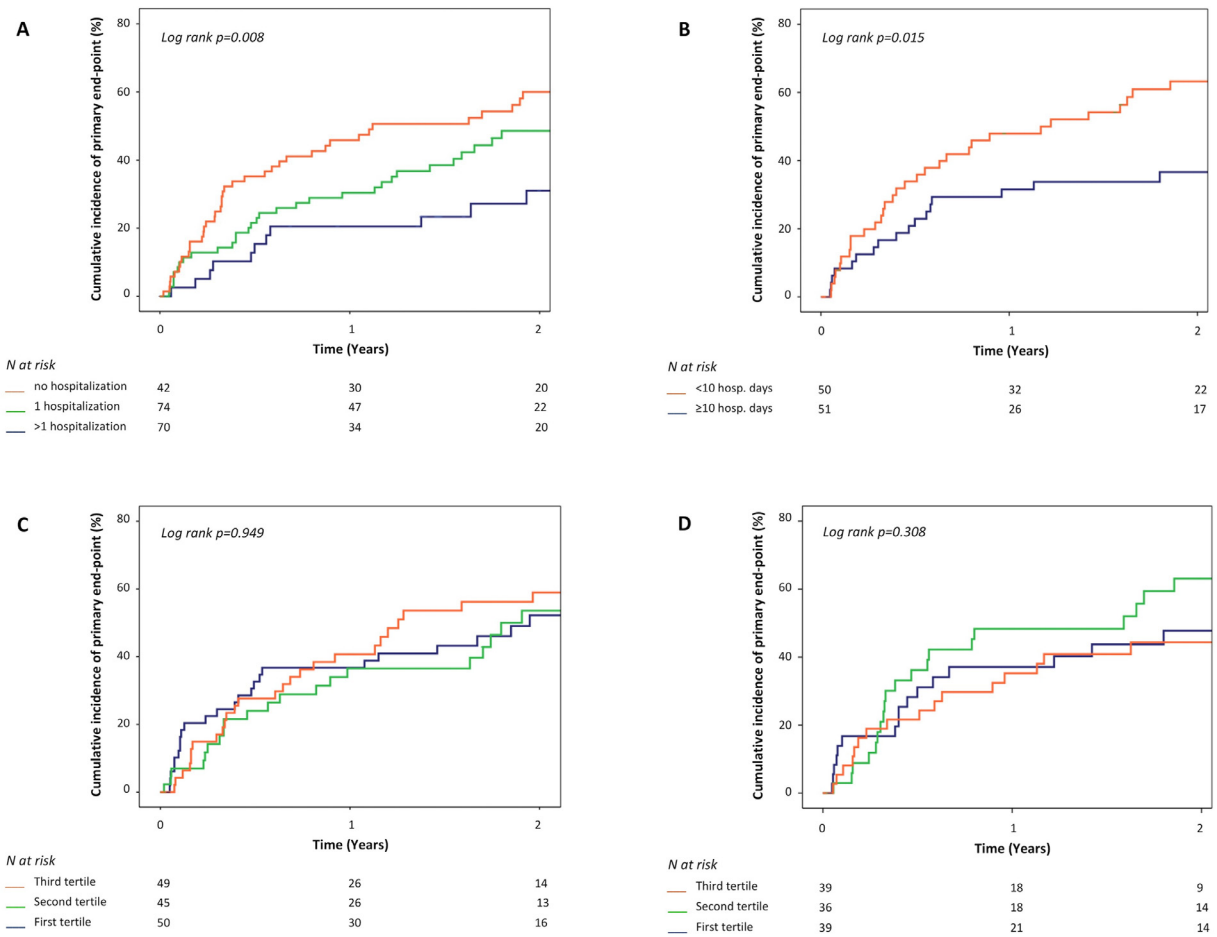

Figure 1. Cumulative incidence of primary end point by heart failure history. Kaplan Meier plots show cumulative incidence of all-cause death or heart failure (HF) rehospitalization in the population stratified by number of HF hospitalizations in the 12 months before MitraClip (*A*), days of HF hospitalizations in the 12 months before MitraClip (*B*), tertiles of time between last HF hospitalization and MitraClip (*C*), and tertiles of time between first diagnosis of significant secondary mitral regurgitation and MitraClip (*D*)

for the cumulative incidence of HF rehospitalizations (59.2% vs 40.9% e 35.6%, p log rank = 0.003). A trend toward a higher cumulative incidence of all-cause and CV deaths was observed in patients experiencing >1 HF hospitalization before MitraClip compared with the other 2 groups (44.5% vs 27.2% e 29.2%, log rank p = 0.083, and 41.7% vs 25.1% e 22.5%, log rank p = 0.086, respectively).

Cumulative incidence of primary was higher also in patients with ≥10 days compared with those with <10 days of HF hospitalization during the 12-month period before MitraClip (70.6% vs 51.5%, log rank p = 0.015) (Figure 1). Similar results were observed for the secondary end points (All-cause death: 49.2% vs 30.3%, log rank p = 0.029; CV death: 45.5% vs 22.8%, log rank p = 0.025; HF rehospitalization: 59.8% vs 39.9%, log rank p = 0.005).

No differences were observed in the population stratified by the time between the last HF hospitalization and the procedure and by the time between the first diagnosis of significant SMR and the procedure for both primary (Figure 1) and secondary end points (all-cause death: 35.4%, 47.7%, 39.5%, log rank p = 0.593; CV death: 30.8%, 41.3%, 37.2%, log rank p = 0.978; HF rehospitalizations: 38.9%, 67.6%, 43.4%, log rank p = 0.225; and all-cause death: 35.4%, 47.7%, 39.5%, log rank p = 0.593; CV death: 30.8%, 41.3%, 37.2%, log rank p = 0.978; HF rehospitalizations: 38.9%, 67.6%, 43.4%, log rank p = 0.225; respectively).

At univariate analysis, variables associated with an increased risk of the primary end point were: age, history of diabetes mellitus, NYHA class, MR degree at discharge, number of HF hospitalizations before MitraClip (>1 vs others), and number of HF hospitalization days before MitraClip (≥10 vs <10) (Table 3). In variables defining HF history, the number of HF hospitalization during the 12-month before the procedure (>1) was the only independent predictor of all-cause death or HF rehospitalization (Figure 2A).

Finally, A significant reduction in the total number of HF hospitalizations (146 vs 39; p <0.001) as well as in the total number of HF hospitalization days (1,655 vs 413; p <0.001) were observed in the 12-month period after MitraClip compared with the 12-month period before (Figure 2B).

Discussion

MitraClip is the most widespread device to treat SMR in HF patients. Data from many registries[1–3,6–11,18,19] and 2 recent randomized trials[4,5,20] support its use in carefully selected patients with significant SMR despite maximum GDMT, at an early stage of HF.[21] Several parameters have been identified to drive patient selection, such as SMR severity (i.e., effective regurgitant orifice area),[22] symptoms (i.e., NYHA class),[6–9] biomarkers (i.e., NT-proBNP),[11] comorbidities (i.e., renal insufficiency)[9,10], left ventricular dimension and function,[6–8] right ventricular involvement,[10,11] and concomitant tricuspid insufficiency.[23] Limited data are available regarding the prognostic role of HF history. Previous HF hospitalizations (6-month or 1-year before MitraClip) have been reported as associated with lack of left ventricular reverse remodeling,[8] HF re-admission and mortality up to 5-year follow-up after MitraClip.[6,7] However, details about HF hospitalization and other aspects of HF history, such as the time of SMR occurrence, have never been studied.

In the subgroup analysis of MITRA-FR and COAPT, variables related to HF history (previous >1 or at least 1 HF hospitalization respectively) did not modify the effect of therapies (MitraClip and GMDT vs GDMT) on clinical outcome.[4,5] These results may differ in randomized trails and clinical practice where study groups are less selected.

Table 3
Univariate analysis for the primary end point

Variable	Hazard Ratio	Confidence Interval 95%	p-value
Age	1.02	1.00–1.05	0.023
Men	1.30	0.85–1.99	0.234
Body mass index	1.00	0.96–1.04	0.996
Chronic kidney disease	0.99	0.99–1.00	0.086
Diabetes mellitus	1.51	1.01–2.27	0.045
Hypertension	1.42	0.95–2.14	0.089
Atrial fibrillation	1.44	0.97–2.14	0.075
Society of Thoracic Surgeons score	1.04	0.99–1.08	0.079
New York Heart Association class IV	2.26	1.52–3.35	< 0.001
Left ventricular ejection fraction (%)	1.00	0.98–1.01	0.706
Left ventricular end-diastolic volume (ml)	1.00	0.99–1.00	0.628
Left ventricular end-systolic volume (ml)	1.00	0.99–1.00	0.573
Left ventricular end-diastolic diameter (mm)	0.99	0.97–1.01	0.306
Left ventricular end-systolic diameter (mm)	1.00	0.99–1.02	0.782
Left atrial diameter (mm)	1.00	0.99–1.01	0.904
Systolic pulmonary artery pressure (mmHg)	1.00	0.99–1.02	0.338
Mitral regurgitation 4+ at baseline	1.23	0.66–2.28	0.517
Ischemic aetiology of mitral regurgitation	1.37	0.91–2.06	0.136
Mitral regurgitation 3/4+ at discharge	1.39	1.15–1.68	0.001
Number of heart failure hospitalization (>1)	1.34	1.10–1.63	0.004
Days of heart failure hospitalization (≥10)	1.88	1.12–3.14	0.016
Time from last heart failure hospitalization (Third tertile)	1.08	0.69–1.69	0.746
Time from first diagnosis of mitral regurgitation (Third tertile)	0.78	0.47–1.30	0.340

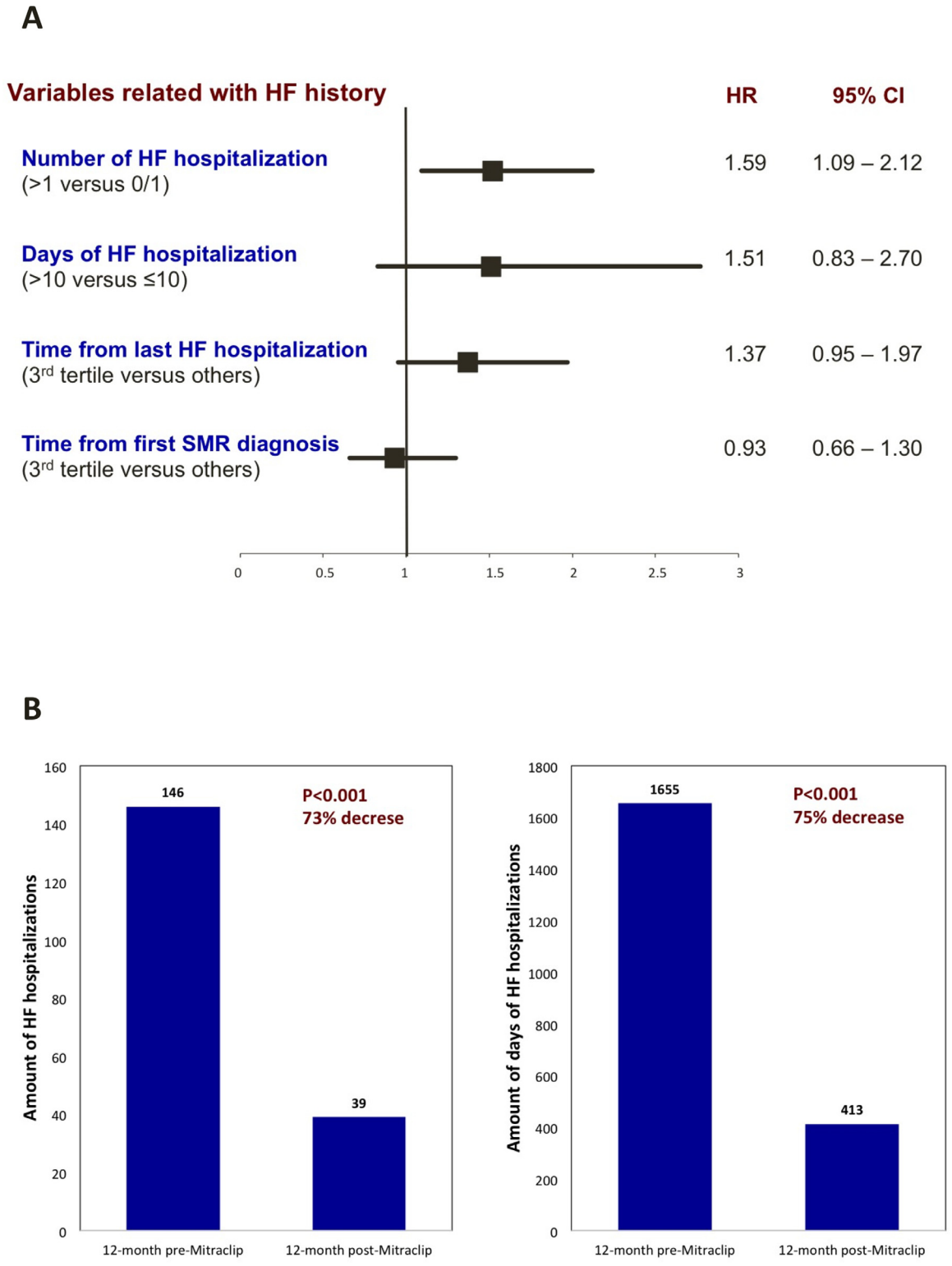

Figure 2. Impact of heart failure history on primary end point and changes in heart failure hospitalizations after MitraClip. The adjusted relative risk of all-cause death or heart failure (HF) rehospitalization is reported for all variables describing HF history (*A*). Total number of HF hospitalizations during the 12-month period before MitraClip compared with that occurred during the 12-month period after MitraClip, and total days of HF hospitalizations during the 12-month period before MitraClip compared with that observed during the 12-month period after MitraClip are showed (*B*).

To our knowledge this is the first study addressing specifically the impact of previous HF hospitalizations and SMR duration on outcomes of MitraClip candidates.

The main findings of the present analysis are: (1) patients with moderate to-severe or severe SMR having >1 HF hospitalization during the 12-month period before

MitraClip had a 59% increased risk of clinical events at mid-term follow-up compared with those who had only 1 or no HF hospitalizations; (2) patients spending ≥10 days of HF hospitalization during the 12-month period before MitraClip had a higher incidence of clinical events compared with those with <10 days; (3) time between last HF hospitalization and MitraClip and between first diagnosis of significant SMR and MitraClip were not associated with clinical events; (4) MitraClip was associated with a reduction in number and days of HF hospitalizations in the 12-month period after the procedure compared with the 12-month period before.

In our cohort, patients with more than 1 HF hospitalization during the year before MitraClip had a worse prognosis compared with the others. This variable, in those defining HF history, was the only independent predictor of the primary end point. The recurrence of HF hospitalization might be considered a surrogate of advanced disease. Therefore our results confirm the importance of a timely intervention to obtain a prognostic benefit from SMR reduction.

Of note, patients with 1 HF hospitalization before MitraClip had an occurrence of clinical events lower compared with those with >1 HF hospitalization, but higher compared with those without HF hospitalization. These data may be interpreted as showing that we do not have to necessarily wait for the first HF decompensation before treating SMR patients, as these patients not previously hospitalized are those with the best outcomes.

This concept is reinforced by the association between the number of days of previous HF hospitalization and prognosis. Even if this variable is not related to the outcomes after appropriate adjustments, we found an increased rate of death and HF rehospitalization in patients who spent more days (≥10) in hospital in the year before the procedure.

Our results might also partially explain the different results between MITRA-FR, where previous HF hospitalization was a mandatory criterion for enrolment, and COAPT, whose population had a previous HF hospitalization in about half of cases.

Conversely to that reported for some HF drugs (i.e., sacubitril/valsartan),[12] time between last HF hospitalization and MitraClip was not associated with prognosis in our cohort. Moreover, we did not find any correlation between the time from the first diagnosis of significant SMR to MitraClip and clinical outcomes. Thus, we could speculate that MitraClip should be definitely performed as soon as possible before HF hospitalization recurrence regardless of SMR or HF duration. Definitely, GDMT optimization included CRT if indicated, as first line approach in patients with SMR and HF remains mandatory.[21]

Finally, we found a significant reduction in the total number of HF hospitalizations and the total number of days of HF hospitalization in the 12-month after MitraClip compared with the 12-month before. This result has already been reported in other studies[24,25] and supports the use of MitraClip to improve quality of life and to potentially reduce health costs.[26]

This study presents several limitations. First, the sample size is limited and dividing our population in subgroups, the statistical comparisons could have been affected by a type II error. Second, the retrospective, non-randomized and non-controlled design of the study allows considering the results as hypothesis generating only. Third, time from first diagnosis of significant SMR to MitraClip may be influenced by multiple variables and is difficult to be ascertained.

In conclusions, HF history has to be carefully evaluated in patients with SMR underwent MitraClip. In particular, recurrent (>1) HF hospitalizations during the 12-month before the procedure increase the risk of clinical events at mid-term follow-up, whereas time from last HF hospitalization and from first diagnosis of significant SMR do not impact on prognosis. MitraClip is associated with a significant reduction in HF hospitalizations.

Authors contribution

Marianna Adamo: conceptualization, methodology, formal analysis, writing original draft.

Mara Gavazzoni: conceptualization, methodology, formal analysis, writing (review and editing).

Assunta Castiello: formal analysis, resources, data curation.

Rodrigo Estevez-Loureiro: writing (review and editing), resources, data curation.

Maurizio Taramasso: writing (review and editing), resources, data curation.

Laura Lupi: writing (review and editing), resources, data curation.

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Tomas Benito: writing (review and editing), resources, data curation.

Salvatore Curello: writing (review and editing), supervision.

Francesco Maisano: writing (review and editing), supervision.

Marco Metra: writing (review and editing), supervision.

Declaration of Interests

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

Disclosures

M. Metra received consulting honoraria for participation to steering committees or advisory boards or for speeches from Abbott, Amgen, Astra-Zeneca, Bayer, Edwards Ther., Fresenius, Novartis, Servier. F. Maisano received grant and/or research support from Abbott, Medtronic, Edwards Lifesciences, Biotronik, Boston Scientific Corporation, NVT, Terumo; consulting fees and honoraria from Abbott, Medtronic, Edwards Lifesciences, Swissvortex, Perifect, Xeltis, Transseptal solutions, Cardiovalve, Magenta Royalty Income/IP Rights from Edwards Lifesciences (FMR surgical annuloplasty); shareholder of Cardiovalve, Magenta, SwissVortex, Transseptalsolutions,Occlufit, 4Tech, Perifect. M. Taramasso is consultant for Abbott Vascular, Boston Scientific, 4tech, CoreMedic, and

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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.2020.08.037.

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