ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3556

RESEARCH ARTICLE

Guideline-directed medical therapy for heart failure in arrhythmia-induced cardiomyopathy with improved left ventricular ejection fraction

Luis Manuel Domínguez-Rodríguez[1,2,3]*, David Dobarro[4], Carla Iglesias-Otero[4], María G. Crespo-Leiro[5,6,7], Sergio Raposeiras-Roubín[4,7,8], Jesús Álvarez-García[1,3,7], Manuel Barreiro-Pérez[4], Isabel Muñoz-Pousa[4], Angel Sánchez-Recalde[3], Ándrés Íñiguez-Romo[4], and José Luis Zamorano[1,2,3,7]

[1]Cardiology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain; [2]Universidad de Alcalá, Madrid, Spain; [3]Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain; [4]Cardiology Department, Hospital Universitario Álvaro Cunqueiro, Vigo, Spain; [5]Cardiology Department, Hospital Universitario de A Coruña, A Coruña, Spain; [6]Universidade de A Coruña, A Coruña, Spain; [7]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain; and [8]Universidade de Vigo, Vigo, Spain

Received 20 May 2024; revised 15 November 2024; accepted 29 November 2024

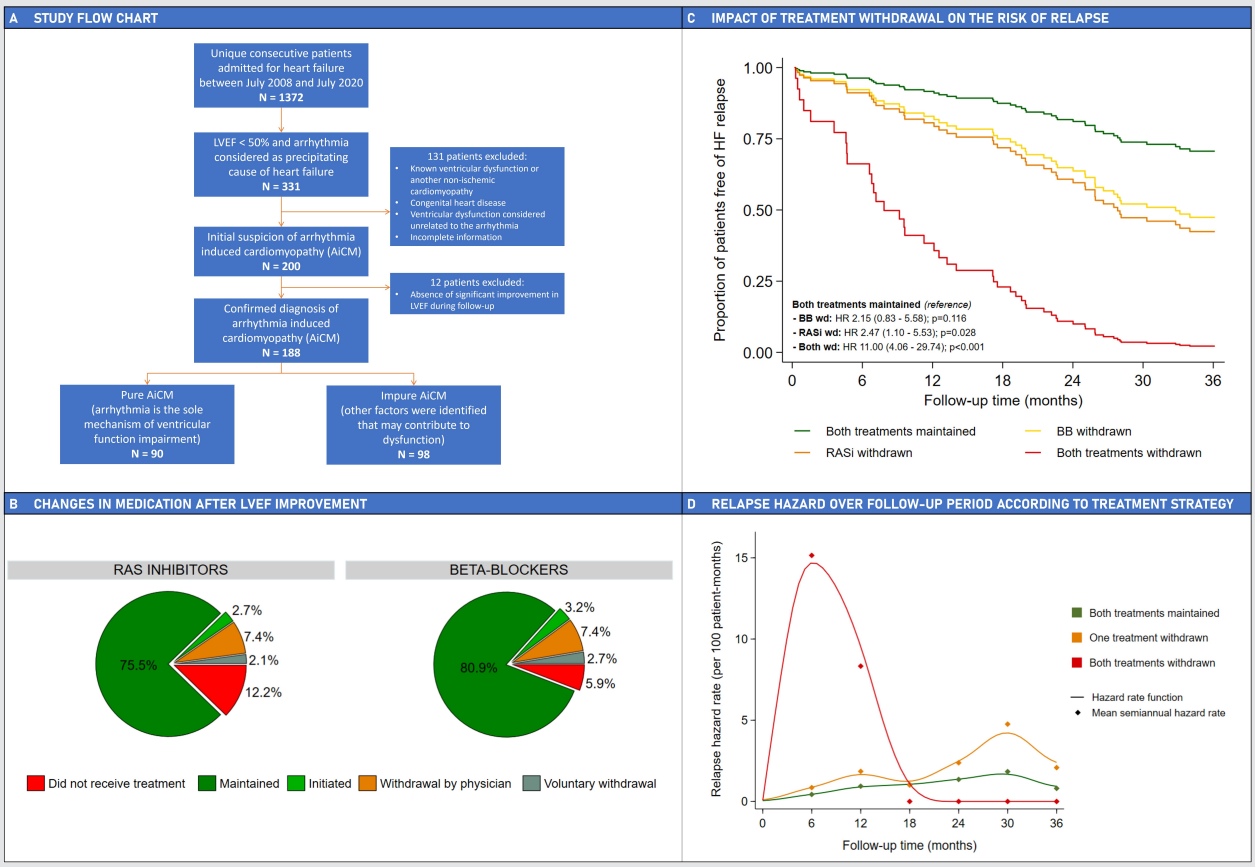
Aims No study has analyzed the impact of guideline-directed medical therapy in preventing heart failure (HF) relapse in patients with arrhythmia-induced cardiomyopathy (AiCM) following left ventricular ejection fraction (LVEF) improvement.

Methods and results We analyzed data from a single-center cohort of 200 patients admitted for HF, LVEF <50% and cardiac arrhythmia considered by cardiologists to be the precipitating cause of the episode. The primary endpoint was time-to-HF relapse, defined as the composite of readmission for HF, Emergency Department (ED) visit for HF, or significant decline in LVEF. Changes in medication were recorded and a time-varying multivariate Cox regression was performed. After a median follow-up period of 6.14 years, diagnostic confirmation was achieved in 188 out of the initial 200 patients with suspected AiCM. A total of 89 patients (47.3%) met the primary endpoint. RAS inhibitors (adjusted hazard ratio (HR) 0.50 [0.31–0.81]; $p = 0.005$) and beta-blockers (adjusted HR 0.48 [0.28–0.81]; $p = 0.006$) were associated with a lower incidence of relapse. Mineralocorticoid receptor antagonists were associated with a significantly lower incidence of ED visits for HF (adjusted HR 0.38 [0.15–0.95]; $p = 0.038$), but did not achieve statistical significance for the combined primary endpoint. Antiarrhythmic drugs did not show a significant impact on the primary endpoint.

Conclusion Maintaining RAS inhibitors and beta-blockers was associated with a significantly lower incidence of relapse in the setting of AiCM with improved LVEF.

*Corresponding author. Cardiology Department, Hospital Universitario Ramón y Cajal, 100, Fuencarral-El Pardo, 28034 Madrid, Spain. Tel: 0034639825665; Email: luis-s-ma@hotmail.com

Graphical Abstract



Impact of guideline-directed medical therapy for heart failure after left ventricular ejection fraction (LVEF) improvement in arrhythmia-induced cardiomyopathy. (*A*) Study flow chart. (*B*) Changes in renin-angiotensin-system (RAS) inhibitors and beta-blockers (BB) prescriptions after LVEF improvement. (*C*) Time-to-relapse curves based on treatment strategies (*D*) Mean hazard rates of relapse (expressed in number of events per 100 patient-months) for each semester and treatment strategy. A Gaussian kernel local polynomial smoothing was employed for hazard function plotting. AiCM, arrhythmia-induced cardiomyopathy; BB, beta-blocker; LVEF, left ventricular ejection fraction; RAS, renin-angiotensin system; RASi, renin-angiotensin system inhibitor; wd, withdrawn.

Keywords Heart Failure • Arrhythmia-Induced Cardiomyopathy • Tachycardia-Induced Cardiomyopathy • Tachycardiomyopathy • Improved Ejection Fraction • Guideline-Directed Medical Therapy

Introduction

Arrhythmia-induced cardiomyopathy (AiCM) is defined as ventricular dysfunction resulting from an increased heart rate caused by an arrhythmia.[1,2] The diagnosis of AiCM is always deferred and can only be confirmed after a significant improvement of left ventricular ejection fraction (LVEF) is documented following rhythm or rate control strategies.[1] Although traditionally considered a benign condition, it has a high risk of recurrence and it has been demonstrated that myocardial structural abnormalities may persist in these patients even after improvement of LVEF.[3–7]

The management of these patients has primarily focused on controlling or suppressing the arrhythmia.[2,8–11] However, there is limited evidence regarding the role of pharmacological treatment for heart failure (HF) in this clinical scenario. While maintaining guideline-directed medical therapy (GDMT) after LVEF improvement is recommended for patients with dilated cardiomyopathy,[12] its benefits for those with AiCM are less documented.

In this context, the aim of this study was to assess the impact of GDMT on preventing HF relapse in patients with AiCM after improvement of LVEF.

Methods

Study design and population

This study analyses data from a registry of all consecutive patients admitted to the Cardiology Department of a tertiary, academic hospital in Vigo (Spain) for acute HF with LVEF <50% and cardiac arrhythmia considered by cardiologists as the precipitating cause of the episode, between July 2008 and July 2020. Patients with known ventricular dysfunction or a previous diagnosis of another cardiomyopathy were excluded. The study obtained approval from the hospital ethics committee and complies with the principles outlined in the *Declaration of Helsinki*.

The diagnosis of AiCM was confirmed only upon documentation of LVEF improvement during follow-up. LVEF improvement was defined as an improvement to ≥50% (complete improvement) or an increase of ≥10 points to an LVEF ≥40% (partial improvement).[13]

At the end of follow-up, patients were retrospectively classified into two groups: those in which the arrhythmia was the sole mechanism of ventricular function impairment (pure AiCM) and those in which other factors that may contribute to dysfunction were identified (impure AiCM). Inclusion and exclusion criteria, as well as those established for defining impure AiCM, are detailed in *Appendix S1*.

Given the retrospective nature of the study, all therapeutic decisions were made by attending physicians. We recorded prescriptions of beta-blockers (BB), renin–angiotensin system inhibitors (RASi; including angiotensin receptor–neprilysin inhibitor [ARNi], angiotensin-converting enzyme inhibitors [ACEi] and angiotensin II receptor blockers [ARB]), mineralocorticoid receptor antagonists (MRA), sodium–glucose cotransporter 2 inhibitors (SGLT2i), and antiarrhythmic drugs (AAD) at the time of LVEF improvement. Treatment modifications throughout the follow-up period were retrospectively recorded, including the date of each change.

Data collection and outcomes

All data related to medical history, prescriptions, and supplementary tests (e.g. laboratory analyses, cardiac imaging) were obtained by a cardiologist from each patient's electronic health record.

The primary endpoint was time-to-HF relapse, defined as a composite of (1) readmission for HF, (2) Emergency Department (ED) visit for HF, or (3) decline in LVEF (decrease to <50% in those with previous complete improvement or a decrease of ≥10 points in patients with partial improvement). The secondary endpoint was relapse-free survival, defined as the composite of HF relapse and all-cause mortality.

Statistical analysis

Categorical variables were expressed as number of patients and percentage and compared within AiCM types and treatment strategies using the chi-square test. Continuous variables were expressed as mean and standard deviation and compared using the Student's *t*-test. Time data were expressed as median and interquartile range (IQR).

The primary and secondary outcomes were assessed in a time-to-first-event analysis (single-failure-per-subject). As each event occurrence may have a direct impact on subsequent events and often resulted in modifications in medication, only the first event for each patient was considered and mortality was not evaluated as an individual endpoint. If two adverse events occurred simultaneously (e.g. readmission or ED visit for HF and decline in LVEF), both events were accounted in the analysis of individual endpoints.

Given the variability in drug prescriptions throughout the follow-up period, treatment variables were considered as time-varying covariates. Multiple records per patient were analysed, allowing patients to be assigned to different treatment groups in case there were any changes in prescriptions during follow-up.[14] Time-to-relapse curves were estimated using time-varying Cox proportional-hazards models,[15] based on treatment received, with adjustment for initial LVEF at admission, degree of LVEF improvement achieved before relapse (complete or partial), type of AiCM (pure or impure), and age. This Cox regression model was used to predict time-to-relapse curves, according to treatment strategy, in a population with mean values for the confounding covariates included in the model.

Sensitivity analyses were performed by repeating the calculations considering treatment variables as fixed covariates and including arrhythmia recurrence and creatinine levels at discharge from the initial hospital admission in the regression model.

Finally, we specifically analysed the subgroup of patients receiving both cornerstone treatments for HF (RASi and BB) to assess the risk of relapse associated with discontinuing one or both medications, as well as the timing of treatment withdrawal following LVEF improvement. This sub-analysis was conducted using Cox regression models with the same covariates included in the preceding models, considering treatment variables as fixed covariates (only one record per patient). Consequently, for patients with medication changes, the analysis was restricted to the period from treatment withdrawal until the occurrence of an event or the end of follow-up (censoring). Two additional sensitivity analyses were performed to evaluate the entire follow-up period from the time of LVEF improvement, with one considering treatment withdrawal as a fixed covariate and the other treating it as a time-varying covariate. The actuarial method was applied to estimate the mean hazard rates of relapse (expressed in number of events per 100 patient-months) for each treatment strategy and semester of follow-up. A Gaussian kernel local polynomial smoothing was employed for hazard function plotting.

Differences in the primary outcome between groups were assessed using adjusted hazard ratios (HR) with 95% confidence intervals (CI) and *p*-values derived from Cox regression. Statistical significance was defined as a *p*-value <0.05.

The statistical analysis was performed using STATA 18 (StataCorp LLC, College Station, TX, USA).

Results

Clinical characteristics of the study population

A total of 200 patients admitted for HF and ventricular dysfunction attributed to AiCM were evaluated. After a median follow-up of 6.14 years (IQR 4.18–8.03), 168 patients (84.0%) exhibited complete improvement of LVEF, 20 (10.0%) showed partial improvement and 12 (6.0%) did not demonstrate significant improvement in LVEF during follow-up, so they were subsequently excluded from the analysis. The flow chart of the study population is shown in the *Graphical Abstract*.

Among the 188 patients with confirmed diagnosis of AiCM, 90 (47.9%) were classified as 'pure AiCM' and 98 (52.1%) as 'impure AiCM'. Baseline characteristics of the patients are detailed in *Table 1*. The most frequent arrhythmia was atrial fibrillation (72.9%), followed by atrial flutter (17.6%). Compared to patients

Table 1 Baseline characteristics

Baseline characteristics	Overall population ($n = 188$)	Pure AiCM ($n = 90$, 47.87%)	Impure AiCM ($n = 98$, 52.13%)	*p*-value
Demographic characteristics and comorbidities				
Age, years	65.07 (10.5)	66.7 (10.3)	63.5 (10.4)	**0.035**
Male sex	128 (68.09)	47.0 (52.2)	81 (82.7)	**<0.001**
BMI, kg/m^2	29.9 (6.31)	30.1 (6.5)	29.6 (6.2)	0.283
Alcohol intake ≥80 g/day	26 (13.8)	0 (0.0)	26 (26.5)	**<0.001**
Tobacco use				
Never smoker	96 (51.1)	57 (63.3)	39 (39.8)	**0.004**
Former smoker	65 (34.6)	25 (27.8)	40 (40.8)	
Current smoker	27 (14.4)	8 (8.9)	19 (19.4)	
Arterial hypertension	106 (56.4)	51 (56.7)	55 (56.1)	0.940
Dyslipidaemia	101 (53.7)	37 (41.1)	50 (51.0)	0.173
Diabetes mellitus	44 (23.4)	19 (21.1)	25 (25.5)	0.477
CKD (eGFR <60 mL/min/1.73 m^2)	35 (18.6)	16 (17.8)	19 (19.4)	0.777
Dialysis	0 (0.0)	0 (0.0)	0 (0.0)	–
Coronary artery disease	22 (17.3)	0 (0.0)	22 (27.2)	**<0.001**
COPD	21 (11.2)	7 (7.8)	14 (14.3)	0.315
OSA	26 (13.8)	12 (13.3)	14 (14.3)	0.850
Previous cancer	26 (12.2)	13 (14.4)	10 (10.2)	0.375
Peripheral vascular disease	9 (4.8)	2 (2.2)	7 (7.4)	0.114
Electrocardiography at admission				
Type of arrhythmia				
Atrial fibrillation	137 (72.9)	58 (64.4)	79 (80.6)	
Atrial flutter	33 (17.6)	21 (23.3)	12 (12.2)	0.090
High density PVCs	4 (2.1)	2 (2.2)	2 (2.0)	
Other arrhythmias or combinations of more than 1 type	14 (7.4)	9 (10)	5 (5.1)	
Heart rate, bpm	134.2 (23.2)	136.4 (22.2)	132.2 (24.1)	0.211
Left bundle branch block	20 (10.6)	10 (11.1)	10 (10.2)	0.246
Non-specific interventricular conduction delay	12 (6.4)	2 (2.2)	10 (10.2)	**0.024**
Echocardiography at admission				
LVEF, (%)	30.5 (8.5)	33.1 (8.5)	28.2 (7.9)	**<0.001**
LVEDD, mm	57.3 (7.2)	54.2 (6.4)	60.1 (6.8)	**<0.001**
LA dimension, cm	4.5 (0.5)	4.4 (0.5)	4.7 (0.5)	**<0.001**
LA area, cm^2	28.9 (5.9)	27.5 (5.7)	30.3 (5.9)	**<0.001**
LA dilatation				**0.010**
Non dilated	13 (6.9)	11 (12.2)	2 (2.0)	
Mild dilatation	79 (42.0)	41 (45.6)	38 (38.8)	
Moderate dilatation	67 (35.6)	29 (32.2)	38 (38.8)	
Severe dilatation	29 (15.4)	9 (10.0)	20 (20.4)	
Significant mitral regurgitation (grade ≥3)	26 (13.8)	8 (8.9)	18 (18.4)	0.060
TAPSE, mm	17.0 (4.1)	17.9 (4.5)	16.3 (3.8)	**0.026**
RV dilatation	68 (36.2)	22 (24.4)	46 (44.9)	**0.001**
Severe tricuspid regurgitation	16 (8.5)	6 (6.7)	10 (10.2)	0.385

Values are given as *n* (%), or mean (standard deviation).
AiCM, arrhythmia-induced cardiomyopathy; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnoea; PVC, premature ventricular contraction; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

with pure AiCM, those with impure AiCM exhibited a higher proportion of males, were slightly younger and presented with a higher degree of biventricular dysfunction and dilatation at admission. The median time elapsed from hospital discharge to LVEF improvement was 10.0 months (IQR 3.4–18.9), and was significantly longer in patients with impure AiCM (12.9 vs. 7.5 months; $p = 0.007$). Complete LVEF improvement at the time of hospital discharge was documented in 20 patients (10.6%), occurring more

Table 2 Events during follow-up

Events during follow-up	Overall population ($n = 188$)	Pure AiCM ($n = 90$, 47.87%)	Impure AiCM ($n = 98$, 52.13%)	p-value
LVEF improvement				**<0.001**
Partial improvement (LVEF 40–49%)	20 (10.6)	0 (0.0)	20 (20.4)	
Complete improvement (LVEF ≥50%)	168 (89.4)	90 (100.0)	78 (79.6)	
Time from discharge to LVEF improvement, months	10.0 (3.4–18.9)	7.5 (2.0–15.4)	12.9 (5.7–26.8)	**0.007**
Complete LVEF improvement at discharge	20 (10.6)	15 (16.7)	5 (5.1)	**0.010**
Primary endpoint (heart failure relapse)	89 (47.3)	33 (36.7)	56 (57.1)	**0.015**
Readmission for heart failure	40 (21.3)	15 (16.7)	25 (25.5)	0.139
Emergency department visit for heart failure	65 (34.6)	27 (30.0)	38 (38.8)	0.206
Decline of LVEF	64 (34.0)	17 (18.9)	47 (48.0)	**<0.001**
Minor relapse (LVEF >40%)	15 (23.4)	6 (35.3)	9 (19.1)	
Minor relapse (LVEF ≤40%)	49 (76.6)	11 (64.7)	38 (80.9)	
Time from LVEF improvement to heart failure relapse, months	26.5 (16.8–48.0)	26.5 (18.7–48.0)	26.3 (15.3–47.5)	0.965
Secondary endpoint (heart failure relapse or all-cause mortality)	109 (58.0)	46 (51.1)	63 (64.3)	0.068
Arrhythmia relapse[a]	85 (45.2)	40 (44.4)	45 (45.9)	0.839
Mortality (all-cause)	37 (19.7)	18 (20.0)	19 (19.4)	
Cardiovascular	7 (18.9)	2 (11.1)	5 (26.3)	0.916
Non-cardiovascular	24 (64.9)	11 (61.1)	13 (68.4)	
Sudden death	3 (8.1)	2 (11.1)	1 (5.3)	0.190
Unknown	3 (8.1)	3 (16.7)	0 (0.0)	
Time from LVEF improvement to death, months	37.5 (19.6–66.4)	26.0 (11.3–68.5)	37.6 (25.4–57.5)	0.321

Values are given as *n* (%), or median (interquartile range).
AiCM, arrhythmia-induced cardiomyopathy; LVEF, left ventricular ejection fraction.
[a]Arrhythmia relapse was defined as the reappearance of the initial arrhythmia (or another unknown arrhythmia) before heart failure relapse in patients who had previously restored sinus rhythm.

frequently in patients with pure AiCM (16.7% vs. 5.1%; $p = 0.010$) (*Table 2*).

Outcomes

A total of 89 patients (47.3%) met the primary endpoint of HF relapse, with a median time between LVEF improvement and the event of 26.5 months (IQR 16.8–48.0). A total of 40 patients (21.3%) were readmitted due to HF, 65 patients (34.6%) required ED visits for HF, and in 64 (34.0%), a decline in LVEF was documented, mostly to or below 40% (76.6%). Arrhythmia relapse was documented in 85 patients (45.2% of the total sample) who had restored sinus rhythm before experiencing HF relapse. At the end of follow-up, a total of 37 patients (19.7%) had died, primarily from non-cardiovascular causes (64.9%), with a median time from LVEF improvement to death of 37.5 months (IQR 19.6–66.4). Compared to patients with pure AiCM, those with impure AiCM exhibited a higher risk of HF relapse (57.1% vs 36.7%; $p = 0.015$) and decline in LVEF (48.0% vs 18.9%; $p < 0.001$); however, the median time-to-HF relapse (26.5 vs. 26.3 months; $p = 0.965$) and mortality risk (19.4% vs 20.0%; $p = 0.916$) were similar in both groups. Events throughout follow-up are detailed in *Table 2*.

Prognostic impact of guideline-directed medical therapy

Treatment prescriptions and its changes during follow-up are illustrated in *Figure 1*. At the time of LVEF improvement, RASi were prescribed in 85.1% of patients, BB in 91.0%, MRA in 60.1% and AAD in 40.4%. Prescription of SGLT2i in this cohort was minimal (4.3%). In most cases, RASi and BB were maintained following LVEF improvement and were discontinued only in 11.3% and 11.1% of those patients who were previously receiving them. However, discontinuation rates of MRA and AAD were higher, at 31.0% and 55.3%, respectively. Although isolated cases of patient-initiated treatment discontinuation were recorded, in most cases, medications were withdrawn at the discretion of the attending physician.

Treatment with RASi (adjusted HR 0.50, 95% CI 0.31–0.81; $p = 0.005$) (*Figure 2A*) and BB (adjusted HR 0.48, 95% CI 0.28–0.81; $p = 0.006$) (*Figure 2B*) was significantly associated with a lower incidence of the primary endpoint, primarily due to fewer HF readmissions and less decline in LVEF with RASi (*Figure 3A*), and fewer HF readmissions with BB (*Figure 3B*). Both treatments were associated with better outcomes for the secondary endpoint of relapse-free survival (adjusted HR 0.61, 95% CI 0.39–0.96; $p = 0.032$ for RASi and adjusted HR 0.52, 95% CI 0.32–0.85; $p = 0.008$ for BB, (*Figure 3A,B*)).

No significant interaction was observed in the subgroup analysis (*Figure 3*) between types of AiCM (interaction $p = 0.926$ for RASi; interaction $p = 0.350$ for BB) and degree of LVEF improvement before relapse (interaction $p = 0.572$ for RASi; interaction $p = 0.238$ for BB). Sensitivity analyses provided additional support for the significant association between BB and RASi and a lower incidence of relapse (*Appendix S2*).

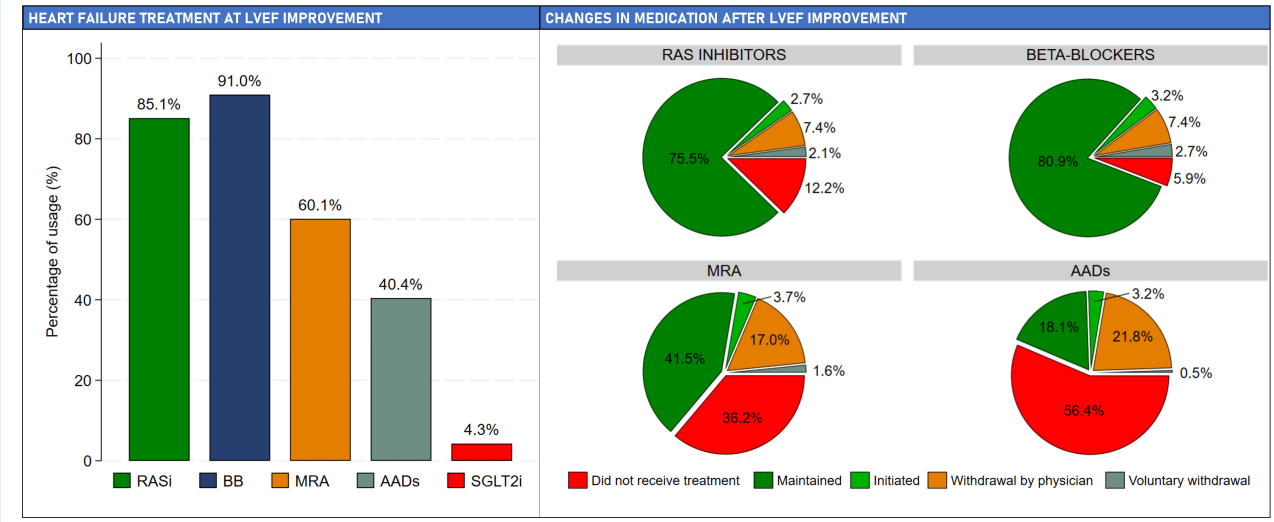


Figure 1 Treatment at left ventricular ejection fraction (LVEF) improvement and changes during follow-up. Medication prescriptions and their changes during follow-up are expressed as a percentage of the total sample size (188 patients). AAD, antiarrhythmic drug; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin system; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Mineralocorticoid receptor antagonists were associated with a significantly lower incidence of ED visits for HF in an individual endpoint analysis (adjusted HR 0.38, 95% CI 0.15–0.95; $p = 0.038$) (*Figure 3C*), but did not achieve statistical significance for the combined primary or secondary endpoints (*Figures 2C* and *3C*).

Treatment with AAD had no significant impact on the incidence of the primary or secondary endpoints (*Figures 2D* and *3D*).

Prognostic impact of discontinuation of renin–angiotensin system inhibitors and beta-blockers

To assess the impact of GDMT withdrawal, a subgroup analysis was conducted on 147 patients (78.2% of the total cohort) who were concomitantly undergoing treatment with BB and RASi at the moment of LVEF improvement. Among this subgroup, RASi were discontinued in only 18 patients (12.2%), BB were discontinued in 18 patients (12.2%), and both treatments were discontinued in 8 patients (5.4%) (*Appendix S3*). Patients in whom any treatment was withdrawn tended to be younger and exhibited significantly earlier LVEF improvement compared to those in whom both medications were maintained. However, no significant differences were identified in any other aspect.

The isolated withdrawal of RASi (adjusted HR 2.47, 95% CI 1.10–5.53; $p = 0.028$), or BB (adjusted HR 2.15, 95% CI 0.83–5.58; $p = 0.116$) was associated with a more than two-fold higher risk of relapse during follow-up compared to patients who maintained both drugs. However, discontinuation of both drugs demonstrated an exponential increase in the risk of relapse (HR 11.0, 95% CI 4.06–29.73; $p < 0.001$) (*Figure 4A*). The sensitivity analysis evaluating the entire follow-up period using a time-varying Cox regression model maintains the association between treatment discontinuation and a higher risk of relapse. However, statistical significance is lost when treatment is considered as a fixed covariate from the time of LVEF improvement (*Appendix S2*).

Mean hazard rates of relapse for each treatment strategy and semester of follow-up are depicted in *Figure 4B*. Patients who discontinue both treatments exhibit a very high risk of relapse in the first semester after withdrawal (15.15 ± 6.04 relapses per 100 patient-months), the period in which most patients under observation experienced relapse. Compared to patients who maintain both treatments, discontinuation of a single drug has also been associated with a higher risk of relapse throughout follow-up, with a peak incidence between months 24 and 30 (4.76 ± 2.72 relapses per 100 patient-months).

The time elapsed between LVEF improvement and drug discontinuation did not significantly influence the risk of relapse. No differences were found in the subgroup of patients who discontinued medication within the first year after ventricular function improvement compared to those who discontinued later (*Figure 4C*).

Discussion

The current study presents data from a cohort of 188 patients with confirmed diagnosis of AiCM, for which strict diagnostic and classification criteria have been established. This cohort is one of the largest described in the literature for this condition and the one with the longest follow-up period. Our results show that these patients remain at high risk of events despite LVEF improvement, and that RASi and BB are associated with a lower risk of HF relapse. To the best of our knowledge, this study is the

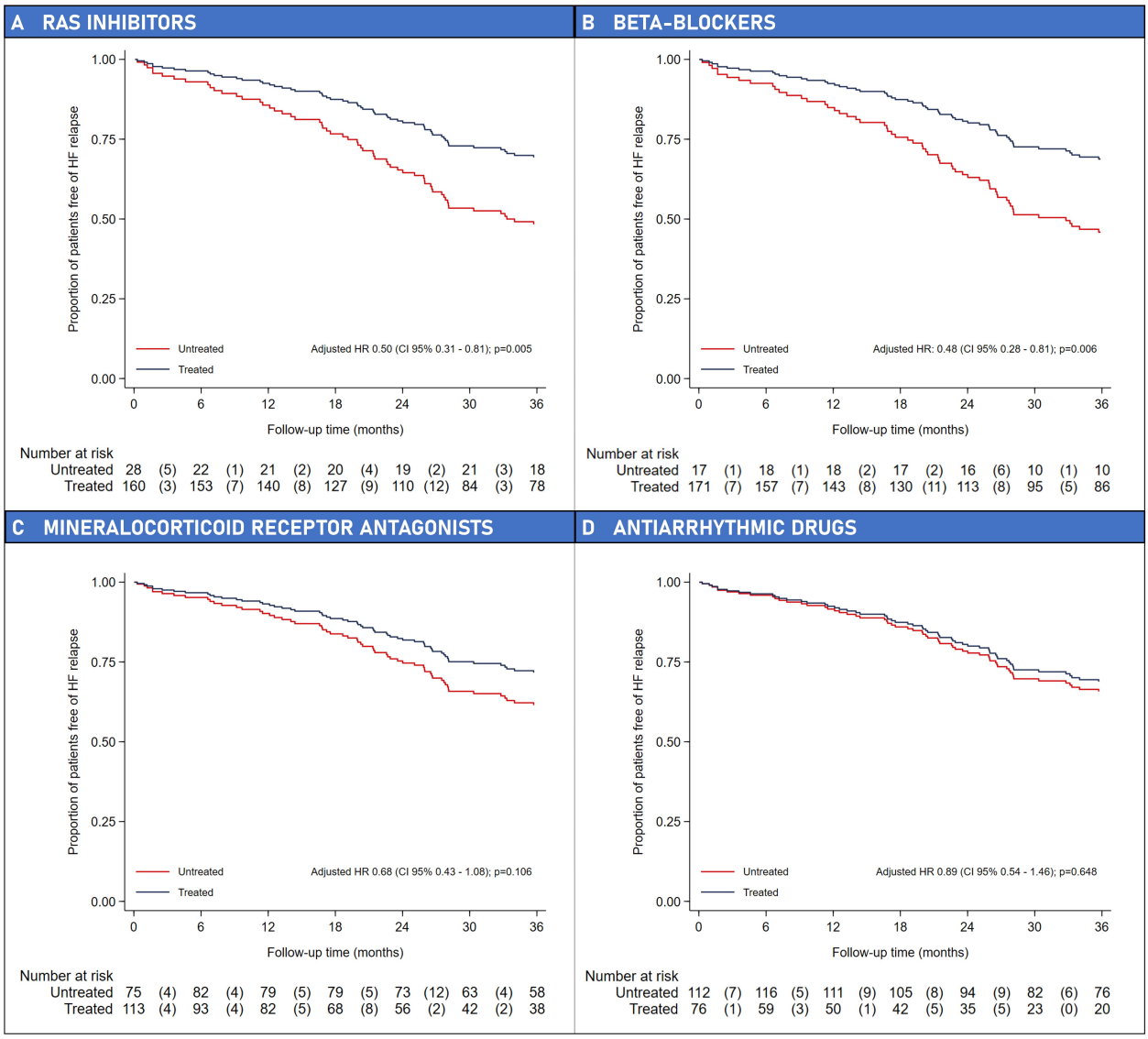


Figure 2 Primary composite endpoint, according to treatment received: (*A*) renin–angiotensin system (RAS) inhibitors; (*B*) beta-blockers, (*C*) mineralocorticoid receptor antagonists, and (*D*) antiarrhythmic drugs. The primary endpoint was time-to-heart failure (HF) relapse, defined as a composite of (1) readmission for HF, (2) Emergency Department visit for HF, or (3) decline in left ventricular ejection fraction (LVEF). Time-to-relapse curves were estimated using time-varying Cox proportional-hazards models based on treatment received, with adjustment for initial LVEF at admission, degree of LVEF improvement achieved before relapse (complete or partial), type of arrhythmia-induced cardiomyopathy (pure or impure), and age. 'Time 0' corresponds to the date when LVEF improvement is documented. The number of patients at risk at each follow-up time point is displayed in the risk table. The number of patients experiencing relapse is shown in parentheses. Since time-dependent covariates were used, patients may be assigned to different treatment groups in case there were any changes in prescriptions during follow-up. In example, a patient who discontinues a treatment is considered at risk in the treated group up to the withdrawal date, and in the untreated group from the moment of withdrawal until the occurrence of an event or censoring. Differences in the primary outcome between groups were assessed using adjusted hazard ratios (HR) with 95% confidence intervals (CI) and two-sided *p*-values derived from Cox regression. RAS, renin–angiotensin system.

first to evaluate the role of neurohormonal treatment in patients with AiCM beyond LVEF improvement.

Several findings from our study deserve special attention. First, it is noteworthy that the incidence of adverse events in patients with AiCM is high. Despite the majority of patients receiving appropriate treatment for HF and low rates of drug discontinuation, nearly half of the patients met the primary endpoint of HF relapse. The high mortality rate observed in these patients may be a consequence of a prolonged follow-up period, with a median exceeding 6 years. Although in most cases death was due to non-cardiovascular

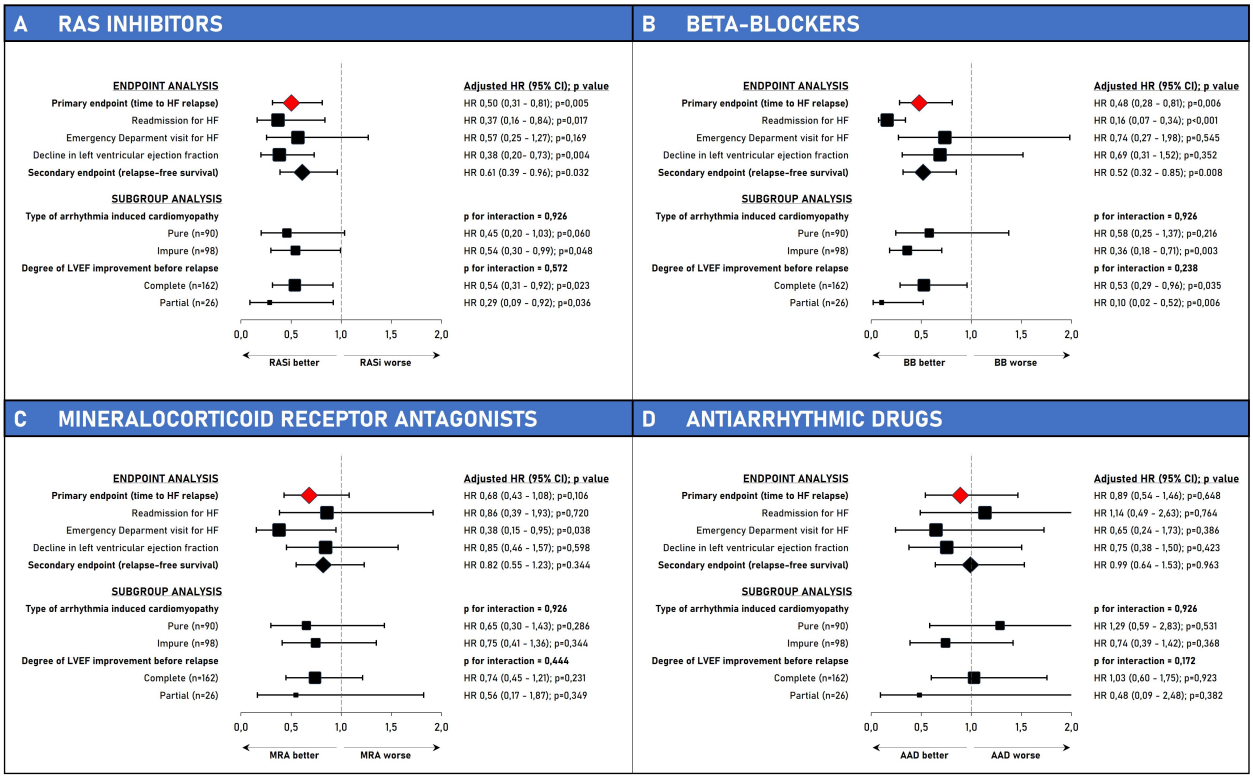


Figure 3 Endpoint and subgroup analysis, according to treatment received: (*A*) renin–angiotensin system (RAS) inhibitors; (*B*) beta-blockers, (*C*) mineralocorticoid receptor antagonists, and (*D*) antiarrhythmic drugs. Only the initial event for each patient was considered in the analysis of individual endpoints. If two adverse events occurred simultaneously (e.g., readmission or emergency department visit for heart failure [HF] and decline in left ventricular ejection fraction [LVEF]), both events were accounted. Differences in the primary outcome between groups were assessed using adjusted hazard ratios (HR) with 95% confidence intervals (CI) and *p*-values derived from Cox regression. The *p*-value for interaction was calculated for each subgroup analysis. AAD, antiarrhythmic drug; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin system; RASi, renin–angiotensin system inhibitor.

causes, the rate of sudden death (3 cases; 8% of total deaths) is not negligible. These findings are consistent with those described in previous studies.[16–18] It has been demonstrated that in patients with AiCM, histopathological abnormalities in myocardial cells, diffuse myocardial fibrosis, ventricular dilatation and hypertrophy may persist even after normalization of LVEF.[3–7] Such observations could potentially justify the high risk of relapse and sudden death in patients with AiCM.

Second, treatment with BB and RASi following LVEF improvement is associated with a lower risk of HF relapse and better outcomes for relapse-free survival, primarily by less rehospitalizations in the case of BB and less rehospitalizations and decline in LVEF in the case of RASi. MRA showed a significantly lower incidence of ED visits for HF, but failed to achieve significance for the primary endpoint, probably due to lack of statistical power. AAD, widely used in AiCM to prevent arrhythmia recurrences, had no significant impact on the outcomes. The TRED-HF study is the only clinical trial to demonstrate that maintaining GDMT is associated with a lower risk of relapse in patients with dilated cardiomyopathy and improved LVEF.[12] Based on the results of this trial, some authors have proposed extending this strategy to patients with AiCM after LVEF improvement.[8,19] However, the absence of specific recommendations in clinical practice guidelines[20,21] means that decisions on the management of these patients are usually made on an individual basis according to the physician's judgment. Our findings support indefinite continuation of GDMT in patients with AiCM and improved LVEF, a clinical scenario in which specific evidence is currently lacking.

Third, our results suggest that treatment impact may be independent of the type of cardiomyopathy (pure or impure) or the degree of LVEF improvement (complete or partial). Consequently, patients with pure AiCM and no other comorbidities contributing to dysfunction could equally benefit from maintaining GDMT. This finding may challenge the perception of AiCM as a benign entity, emphasizing the need for caution when using the term 'cure' in this condition.

Fourth, discontinuing BB or RASi in previously treated patients was associated with a pronounced increase in the risk of relapse, which not only was exponentially higher but also occurred earlier (within the first year) among patients from whom both pharmacological groups were withdrawn. This trend mirrors the findings from the TRED-HF study, in which 45.7% of the withdrawal

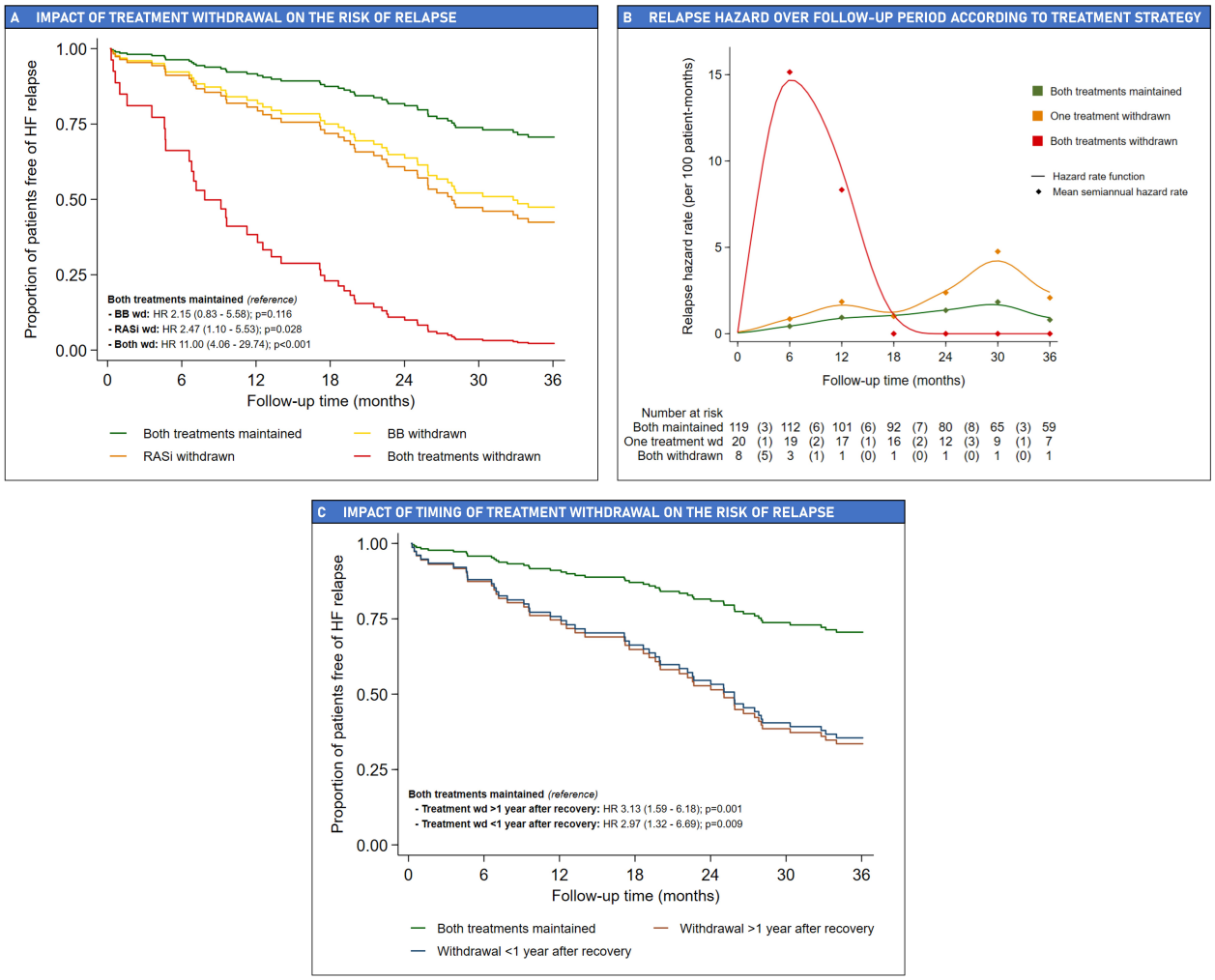


Figure 4 Impact of treatment withdrawal on the risk of relapse. (*A, C*) Time-to-heart failure (HF) relapse curves were estimated using Cox proportional-hazards regression models based on treatment received, with adjustment for initial left ventricular ejection fraction (LVEF) at admission, degree of LVEF improvement achieved before relapse (complete or partial), type of arrhythmia-induced cardiomyopathy (AiCM) (pure or impure), and age. Treatment variables were considered as fixed covariates (only one record per patient). Consequently, for patients with medication changes, the analysis was restricted to the period from the change until the occurrence of an event or the end of follow-up (censoring). (*B*) The actuarial method has been applied to estimate the mean hazard rates of relapse (expressed in number of events per 100 patient-months) for each treatment strategy and semester of follow-up. A Gaussian kernel local polynomial smoothing was employed for hazard function plotting. The number of patients at risk at each follow-up time point is displayed in the risk table. The number of patients experiencing relapse is shown in parentheses. (*A, B*) Define 'time 0' as the date of LVEF improvement for patients maintaining both treatments. For patients who discontinued one drug, 'time 0' corresponds to the date of that drug's withdrawal. For those who discontinued both drugs, 'time 0' is the date the last drug was withdrawn. (*C*) Defines 'time 0' as the date of LVEF improvement for patients maintaining both treatments; however, for patients who discontinued either of the two drugs, 'time 0' is the date the first drug was withdrawn. wd, withdrawn. BB, beta-blocker; HR, hazard ratio; RASi, renin–angiotensin system inhibitor.

group experienced relapse within the first 6 months following cessation of medication. Discontinuation of treatment may result from the physicians' belief that it was no longer beneficial, or because the patient was unable to tolerate the medication, possibly due to worsening health, which in turn could lead to subsequent adverse events. Similarly, the initiation of these medications during follow-up might reflect the physicians' response to a worsening of the patients' condition, which may also result in a later relapse. These factors represent a source of confounding that is difficult to control through statistical analyses and may result in an overestimation of the treatment benefits in reducing adverse events.

Fifth, the median time from LVEF improvement to relapse was approximately 2 years. Patients in whom medication was discontinued after 1 year without events showed a similar risk of relapse compared to those who ceased treatment within the first year. These findings imply that there is no period free from events

following LVEF improvement beyond which it is safe to withdraw medication.

The statistical methods applied in the study require specific attention. Regression analysis in the presence of covariates that vary over the follow-up period, such as changes in medical prescriptions, is complex and requires meticulous data collection and processing. The most recommended method in this scenario is the use of time-varying Cox regression models.[14] These models allow the same patient to be assigned to different treatment groups if there were changes in prescriptions during follow-up. For example, a patient who discontinues a treatment is considered at risk in the treated group up to the date of withdrawal, and in the untreated group from the moment of withdrawal until the occurrence of an event or censoring. This method was used to analyse the impact of each drug individually on the incidence of the primary endpoint (*Figures 2 and 3*).

Additionally, to specifically assess the impact of the suspension of BB and RASi, a subanalysis was conducted on the 147 patients who were receiving both medications at the time of LVEF improvement. Patients were divided into four cohorts: those who continued both medications, those who discontinued only BB, only RASi, or those who discontinued both (*Figure 4A*). In this case, to focus on patients' progression following treatment discontinuation, only the follow-up period after withdrawal was analysed. Although this approach may be simpler and easier to interpret, it could lead to overly favourable results. Focusing only on the period after the medication change could overestimate the drug's benefits due to the shifting of the 'time 0' point, especially since the withdrawal might have occurred in response to worsening conditions.

This is why additional sensitivity analyses were performed to evaluate the entire follow-up period from the time of LVEF improvement. Interestingly, when treatment withdrawal is considered as a fixed covariate from that time, the observed increase in relapse risk does not reach statistical significance (*Appendix S2*). However, this approach has methodological limitations and is not recommended due to its inconsistency with the time-varying Cox regression model,[14] which is the preferred method in this context and whose results clearly maintain statistical significance (*Appendix S2*).

The main limitation of using fixed covariates throughout the entire follow-up is that both patient cohorts are predefined from 'time 0' (the date when LVEF improvement is documented), without considering the time of medication withdrawal, which in many cases does not occur until years later. Such an analysis would assess the risk of relapse in the profile of patients in whom treatment was discontinued, rather than evaluating the actual impact of treatment withdrawal. The fact that the results do not show statistical significance might reinforce the idea that the primary determinant of relapse is the treatment received, rather than the characteristics of the patient in whom it is withdrawn.

Despite a careful statistical analysis, the complexities associated with time-varying covariates may still lead to substantial confounding, making the design of randomized clinical trials essential to confirm the hypotheses posed by our study.

Limitations

This study has several limitations. Due to the retrospective design of the study, the possibility of treatment bias cannot be ruled out, and the analytical challenges in presence of time-varying covariates may have influenced our results, leading to an overestimation of the benefits of medication. Our findings should be interpreted as hypothesis-generating only and should be confirmed in subsequent clinical trials. Despite being the largest single-centre cohort of AiCM described in the literature, the sample size is still relatively small. As a single-centre registry, caution is needed when extrapolating our findings to the general population diagnosed with AiCM. Only patients admitted for HF were included, excluding those diagnosed on an outpatient basis. However, by exclusively including hospitalized patients, we target those at higher risk and for whom evidence is crucial for clinical decision-making. Finally, the inclusion period from 2008 to 2020 resulted in a low use of SGLT2i and higher deprescription rates of GDMT than might be observed in current clinical practice, as most patients were enrolled before the publication of the TRED-HF study.

Conclusions

This study emphasizes that treatment with RASi and BB is associated with a lower risk of HF relapse and better outcomes for relapse-free survival. MRA were associated with a significantly lower incidence of ED visits for HF and a non-significantly lower rate of the primary endpoint of HF relapse. AAD had no significant impact on the outcomes. These findings support the recommendation for indefinite maintenance of GDMT in patients with AiCM and improved LVEF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

The authors gratefully acknowledge Dr. García-Pavía (Hospital Universitario Puerta de Hierro, Madrid, Spain) for his valuable advice and guidance on the study design, and the *PUBLIbeCA* program within the Spanish Society of Cardiology for providing statistical and medical writing support (Medical Science Consulting, Valencia, Spain).

Funding

The study was conducted without any external funding.
Conflict of interest: none declared.

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