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Left ventricular functional recovery after atrial fibrillation catheter ablation in heart failure: a prediction model

This is a pre print version of the following article:

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1927311> since 2023-12-06T08:33:26Z

Published version:

DOI:10.1093/eurheartj/ehad428

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(Article begins on next page)

Title: A new prediction model for left ventricular systolic function recovery after catheter ablation of atrial fibrillation in patients with heart failure: an external validation study

Short title: predicting LVEF recovery in HF patients undergoing AF ablation

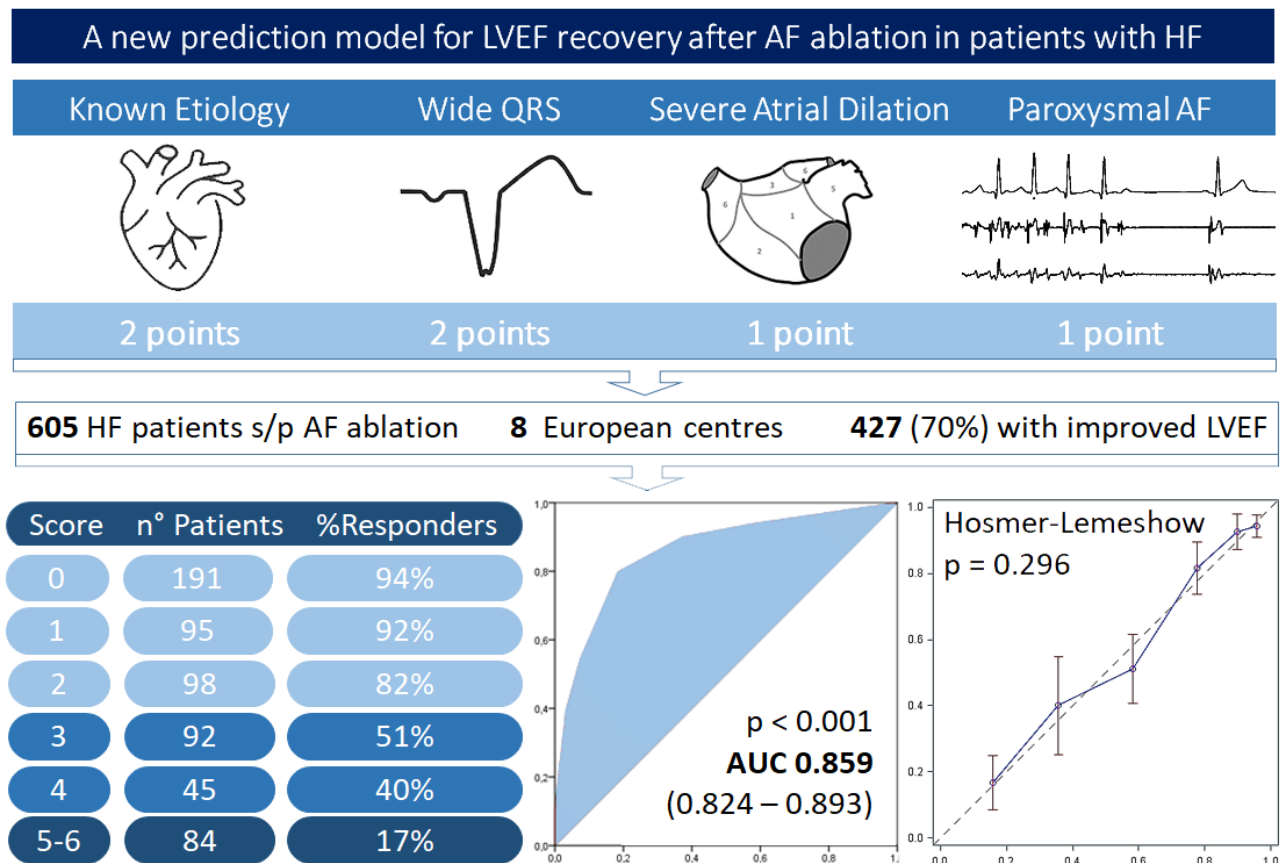


Figure Central Illustration: On the upper side, the 4 variables included in the score and their respective weight is shown. The score was evaluated in 605 heart failure (HF) patients with impaired (<50%) left ventricular ejection fraction (LVEF) undergoing atrial fibrillation (AF) ablation, recruited from 8 European centers. Based on the 2021 Universal definition of HF, 12 months post-procedural LVEF improvement was observed in 427 (70%) patients (Responders). In this external evaluation study, the score accurately predicted the response rate (area under the curve (AUC) 0.859, $p < 0.001$) with a good calibration ($p = 0.296$), as shown on the lower right side. In the lower left side, the specific response-rate stratified according to the score value is represented.

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Conflicts of interest:

MA is consultant for Biosense Webster and Boston Scientific, clinical proctor for Medtronic, and has received educational fees from Abbott.

Aims: Management of patients with atrial fibrillation (AF) and concomitant heart failure (HF) remains complex. In 2021 a prediction model based on 4 simple parameters (QRS>120msec [2 points], known etiology [2 points], paroxysmal AF [1 point], severe atrial dilation [1 point]) adequately estimated the probability of left ventricular ejection fraction (LVEF) recovery after AF ablation in a single-center cohort. The present study aims to externally validate this prediction model in a large European multicenter cohort.

Methods and Results: 605 patients (61.1±9.4 years, 23.8% females, 79.8% persistent AF) with HF and impaired LVEF (<50%) undergoing AF ablation in 8 European centers were retrospectively identified. Based on the 2021 Universal definition of HF, 12 months post-procedural LVEF improvement was observed in 427 (70%) patients (Responders). Responders experienced more often positive ventricular remodeling (OR 8.9, p<0.001), fewer heart failure hospitalizations (OR 0.09, p<0.001) and lower mortality (OR 0.11, p<0.001). External validation of the score yielded good discrimination (AUC 0.86 (95% CI 0.82–0.89), p<0.001) and good calibration (Hosmer-Lemeshow p=0.3). This result was consistent across the LVEF spectrum: LVEF<40% (AUC 0.86, Hosmer-Lemeshow p=0.3), LVEF 40-50% (AUC 0.86, Hosmer-Lemeshow p=0.9). Patients with a score < 2 had a 93% probability of LVEF recovery as opposed to only 24% in patients with a score > 3.

Conclusions: In our large multicenter cohort of patients, the new prediction model provided good prognostic information and discriminated patients who benefit most from the ablation procedure. These findings support the use of the score to standardize shared decision-making regarding AF ablation referral in the clinical setting and future clinical studies.

1 | BACKGROUND

Atrial fibrillation (AF) and heart failure (HF) frequently coexist with AF being both a consequence and a precipitant factor of HF. The border between these two conditions is subtle and the causal relationship is often elusive.

Five randomized controlled trials (RCTs) provided evidence that AF ablation is more effective than pharmacological therapy in improving left ventricular ejection fraction (LVEF), hospitalization and mortality.¹⁻⁵ However, two more recent large RCTs (AMICA and RAFT-AF trials) failed to show any benefit of catheter ablation.^{6,7} One of the reasons behind these contradictory results is that the outcomes of AF ablation in HF patients largely depend on the selection and characteristics of enrolled patients. Further evidence to help stratify and identify those patients who will most likely benefit from AF ablation is thus needed.

The ANTWOORD I Study developed in 2021 a novel prediction model for individualized assessment of patients with HF and reduced LVEF undergoing AF ablation.⁸ This study identified four clinical and echocardiographic variables (AF pattern, atrial dimension, HF aetiology, QRS duration) which were associated with LVEF recovery after AF ablation (Figure Central Illustration). The score based on these variables accurately predicted (C statistics 0.93, $p < 0.001$) LVEF recovery after AF ablation. An easily available and generalizable score for the identification of LVEF recovery after AF ablation would enable clinicians to identify patients who will most likely benefit from early intervention strategies. Moreover, it would lay the foundation to adequately stratify patients in randomized trials so to achieve more consistent results. Beyond improving patients' prognosis and quality of life, healthcare costs could be reduced through improved selection of patients and reduced need for additional diagnostic assessments (e.g. cardiac magnetic resonance (CMR)).

The model has been internally validated in a small single-center study.⁸ However, adequately powered external validation is still lacking. Ensuring the reproducibility and accuracy of the new prediction model in an independent patient population is crucial to confirm both usefulness and applicability. The aim of the present study is to conduct external validation of the published score in an adequately powered cohort.

2 | METHODS:

Study Design:

This is a multicenter, retrospective, study. The study was approved by the local ethics committees and data protection agency and conforms to the Declaration of Helsinki. All patients provided written informed consent. The study is in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement.⁹ The datasets generated and/or analyzed during the current study are not publicly available to maintain patient confidentiality but are available from the corresponding author on reasonable request, and after the agreement of all the co-authors.

Patient Population:

The study population was derived from 8 tertiary referral centers for AF ablation in Europe (Supplementary Table S1). No patient in the current cohort was present in the original derivation cohort. New patients from the center participating in the original study (University Hospital of Antwerp) were included. From each site consecutive patients who were (i) diagnosed with HF with impaired LVEF (<50%) and (ii) referred for AF ablation were screened.

The AF ablation procedure was performed according to operator's discretion and is described in the *Supplementary material online*.¹⁰ All patients received, prior to AF ablation, optimal heart-failure medical therapy according to current Guidelines.

Data collection:

Data were collected independently by each of the participating centers using uniform definitions. A complete list of variables and their definitions can be found in *Supplementary material online*. Patients with >50% missing data or missing baseline LVEF and LVEF at one year after the procedure were excluded from the analysis. Patients in whom at least one of the score variables (AF pattern, etiology, left atrial size, QRS duration) was missing, were not included in the analysis.

Study Outcomes:

The primary outcome of the study was LVEF recovery 1 year after the index procedure. Patients were divided into Responders and Non-Responders according to the "Universal Definition and Classification of Heart Failure".¹¹ Responders were identified if: (i) in case of baseline LVEF between 40 and 50%: LVEF improvement to more than $\geq 50\%$; (ii) in case of baseline LVEF <40%: $\geq 10\%$ increase from baseline LVEF, and LVEF > 40%. Atrial arrhythmia recurrence-free survival, left ventricular remodeling, HF hospitalization and mortality were also collected (see *Supplementary material online* for definitions). During the first year, patients were evaluated at 3, 6 and 12 months following the AF ablation or if symptoms developed. At each visit, ambulatory 24-hour Holter monitoring and echocardiography were performed.

Predictor variables and risk calculator:

The same predictors as those selected in the published model were considered. These included: severe atrial dilation (left atrial volume index (LAVI) > 50 ml/m²), history of paroxysmal AF (See *Supplementary material online* for definitions), QRS > 120 ms, presence of known HF etiology (*Supplementary material online* for definitions). Each predictor variable was determined up to 3 months prior to the index AF ablation procedure, together with the baseline LVEF. The LVEF at follow-up was determined one year after the procedure (interval 9 to 15 months).

The score is calculated according to the following equation (Central Illustration):

$$\text{Known etiology (2 Points)} + \text{QRS} > 120 \text{ ms (2 Points)} + \\ \text{LAVI} > 50 \text{ ml/m}^2 \text{ (1 Point)} + \text{Paroxysmal AF (1 Point)}$$

Statistical analysis:

Continuous variables are presented as mean \pm standard deviation when normally distributed or otherwise median and interquartile range. Comparisons between groups were undertaken with parametric (Student's t-test) or non-parametric (Mann-Whitney U test) test, respectively and ANOVA

when appropriate. The comparison between categorical variables was performed with the χ^2 test and the Fisher Exact test, as indicated. Event-free survival probability was estimated using the Kaplan–Meier method. Logistic regression was used to estimate the association between the variable “Responders” and independent variables (e.g. heart failure hospitalization, mortality, LV remodeling, ecc.). Statistical analysis was performed using SPSS 23.0 (IBM Corp., Armonk, New York) and SAS (SAS Institute Inc., Cary, USA)).

Power calculation: Given a C statistics in the initial study of 0.9 and a prevalence of EF recovery of 0.5 (Cox-Snell R-sq = 0.4445) with 4 predictor parameters, the minimum **sample size** for external validation was estimated at 385 patients (assuming 0.05 acceptable difference in apparent & adjusted R-squared; assuming 0.05 margin of error in estimation of intercept).¹² Since we aimed to validate the score especially for HF_rEF, assuming a 60%/40% distribution (HF_rEF/HE_mrEF), a sample size of 640 patients was estimated to be sufficient.

Model Validation: The overall discriminative performance of the model was measured using Harrell’s C-statistic, and the model fit by calibration plot and Hosmer-Lemeshow p value. P value >0.05 was considered to signal no significant difference between predicted and observed value.

3 | RESULTS

The study population included 605 patients (61.1 ± 9.4 years of age and 23.8% females) with HF undergoing AF ablation between 2015 to 2021. Patients with HF_rEF accounted for 62.8% (n=380) of the study population. Seventy percent (n=427) of the patients reached during follow-up the criteria to be defined Responders. Other clinical and demographic characteristics are summarized in Table 1. The specific underlying etiology is presented in Supplementary Table S2. A comparison between the baseline characteristics of the different centers divided per geographical regions and divided into different score categories are presented in Supplementary Table S3 and Supplementary Table S4, respectively. A comparison between the derivation and validation cohort populations is presented in Supplementary Table S5.

AF ablation Outcomes:

AF ablation procedural data are reported in Supplementary Table S6. Overall, 3.5% (n=14) of the patients experienced complications, with no significant differences between Responders and Non-Responders. Half of the patients (51.4%, n=311) underwent PVI-only during the procedure, while the remaining underwent adjunctive left atrial ablation in addition to PVI.

Follow-up on atrial arrhythmia recurrences was available for 546 (90.2%) patients. After a mean follow-up of 440 (316-728) days, 204 (37.0%) patients experienced atrial arrhythmia recurrence. Data are reported in Table 2 and Figure 1. Responders experienced significantly fewer recurrences than Non-responders (HR 0.53, 95% C.I. 0.41-0.71, p<0.001), mainly driven by less persistent AF recurrences (HR 0.23, 95% C.I. 0.15-0.36, p<0.001), as shown in figure 1. A significantly greater number of patients in the Non-Responder group was reported in permanent AF at the end of the follow-up (3.5% vs. 12.5%, p<0.001).

HF Outcomes:

As depicted in Table 2, Responders experienced fewer deaths or heart transplantations (1.5% vs. 11.5%, $p < 0.001$); fewer HF hospitalizations (3.8% vs. 30.1%, $p < 0.001$); and more positive left ventricular remodeling (48.8% vs. 9.6%, $p < 0.001$), as compared to Non-Responders.

Mean time to EF recovery in the Responders group was 5.5 ± 3.5 months. After one year LVEDVi was 73.0 ± 27.0 mL/m² among Responders (7% [1.8-15%] decrease as compared to baseline) vs. 96.1 ± 44.9 mL/m² among Non-Responders (0% [-6 – 7%] change as compared to baseline). LGE data was available for 52 patients. LGE at CMR had good diagnostic yield in discriminating patients with and without subsequent recovery: 92% recovery rate in patients without LGE, 29% recovery rate in patients with LGE, AUC 0.841 (95% CI 0.726-0.957, $p < 0.001$).

External validation of the score:

Model validation revealed a Harrell C-index of 0.859 (95% CI 0.824–0.893, $p < 0.001$) (Figure 2). The calibration plot showed optimal calibration (Hosmer-Lemeshow $p = 0.296$) (Figure Central Illustration).

Subgroup analysis in patients with HF_rEF and HF_{mr}EF was consistent: AUC of 0.858 and 0.861, respectively (Figure 2) and good calibration plot (Hosmer-Lemeshow p of 0.298 and 0.937, respectively) (Figure 2). Sub-group analysis for each hospital, grouped into geographical regions is presented in Figure S1. In spite of the heterogeneous patient populations (Table S3), results were consistent among the centers with AUC ranging from 0.907 to 0.854 in the different regions.

The distribution of patients according to their score-derived probability of recovery is presented in Figure Central Illustration. In patients with score ≤ 2 and ≥ 5 90% recovery-rate and 14% recovery-rate is expected, respectively. In patients with intermediate score (3 or 4) (137 patients, 22.6%), the probability of recovery is intermediate (47%). In this subgroup, LGE was available in 17 patients and was present in 9/9 (100%) in Non-Responders and 4/8 50% in Responders.

4 | Discussion

The main findings of our study are as follows: (1) the novel prediction model accurately predicts with adequate discrimination and calibration the LVEF recovery in a multicenter cohort with large sample size. The overall performance of the novel risk calculator was comparable to what was reported in the initial cohort, with consistent results throughout the LVEF spectrum and in different geographical areas. (2) Responders achieved more positive ventricular remodeling, lower hospitalization rate and lower mortality as compared to Non-Responders. (3) AF recurrence rate among Responders was significant (30.6%), but lower than in Non-Responders and mainly paroxysmal in pattern.

Comparison between the internal and external validation populations

While based on the same inclusion criteria (i.e. heart failure with impaired LVEF and referral for AF ablation), the initial prediction model included only patients from a single center (University Hospital

of Antwerp (UZA)) with inherent selection bias due to preferential referral. As shown in Table S5, the derivation cohort had more advanced heart failure (lower LVEF, higher prevalence of CRT, broader QRS). Accordingly, the response–rate in the current “less advanced HF” validation cohort was higher (70% vs. 54%). (*Supplementary material online, Table S5*)

The initial study at internal validation derived from bootstrapping yielded a C-statistic of 0.93 (95% CI 0.88–0.97). In the current study, we obtained comparable results with a slightly lower C-statistic of 0.86 (95% CI 0.82– 0.89) but equally good discrimination and calibration (Hosmer-Lemeshow $p=0.296$), demonstrating no significant difference between predictions and observations. As illustrated in the calibration plot, this concordance between observations and predictions was consistent across the spectrum of LVEF (Figure 2).

The derivation study was designed to evaluate the overall performance of the score (AUC) more than to give definite information on the probability of recovery in each score-category. Despite these limitations and despite the differences in baseline characteristics between the derivation and validation cohort, we confirm the concordance in the recovery rate among patients with score ≤ 1 (90% derivation, 93% validation) and ≤ 2 (78% derivation, 90% validation). The same holds true for patients with score ≥ 5 (recovery rate 0% in the derivation, 14% in the validation). The main discrepancies concern the group of patients with score 3 and 4. This group was composed by only 15 (14%) patients in the derivation study, limiting the reproducibility of this data.

Predicting LVEF recovery after AF ablation in patients with HF

The 2020 ESC Guidelines for the Treatment of AF carries a Class I indication for catheter ablation in patients with a suspected “tachycardia-mediated cardiomyopathy”, and a Class IIA recommendation for “selected” patients with heart failure for “improvement in survival and to reduce heart failure-related hospitalization”.¹³ Nonetheless, the tools to help clinicians to determine who exactly these “selected” patients should be and which patient has tachycardia-mediated cardiomyopathy are elusive and often subjective.

Multiple attempts have been made in the past years to identify factors associated with LVEF recovery after PVI.^{14–18} Overall the temporal relationship between AF and HF,¹⁴ the AF pattern,^{16,19} the etiology,³ the absolute value of LVEF,² the LV volume,^{2,16} and age² have previously been reported as predictors of LVEF recovery after AF ablation. In the ANTWOORD I study, although all the aforementioned variables were significantly associated with LVEF recovery at univariate analysis; in multivariate analysis only persistent AF, QRS duration, LA volume and etiology were associated with the primary endpoint.⁸ Remarkably, the ANTWOORD I was the first study to build a prediction model for individualized assessment of patients with AF and HF and to show a link between left atrial size and QRS duration to LVEF recovery.

We have now externally validated the proposed score in the current study. Patients with a low score (≤ 2) may benefit from early referral for catheter ablation (expected recovery $>90\%$). Patients with high score (≥ 5) and low expected recovery rate ($>20\%$) may benefit from initial aggressive rate control, followed by AV node ablation and physiologic pacing if ineffective. Patients in the intermediate zone (Score 3-4, expected recovery rate 47%) may benefit from further diagnostic tests such as MRI. Overall, we would like to strengthen the concept that an absolute cut-off score for referral to or exclusion from catheter ablation is not proposed. Our score should mainly be considered

as a tool for the clinician to discuss the advantages and disadvantages of the procedure in order to take a conscious and shared decision on AF ablation referral.

Finally, it should be noted, that LV systolic function recovery is not the only objective pursued with AF ablation. Symptoms caused by AF episodes (e.g. syncope, inappropriate ICD shock) may be additional factors to consider.

AF recurrence, LVEF Recovery, and Mortality: the chicken and egg dilemma

Recent literature supports the notion that AF ablation in HF patients resulting in >50% AF-burden reduction at 6-months is associated with a significant LVEF recovery, LV positive remodeling and decrease in death or hospitalization.¹⁹⁻²¹ Consistent with this concept, AF recurrence rate among Responders was 30% and mostly paroxysmal in pattern. Thus, the overall body of literature along with our study results suggest that in patients with AF and HF undergoing AF ablation, the aim should be AF burden control more than AF elimination.

In our study, Responders achieved a 10 times relative risk reduction of overall mortality, as compared to Non-Responders. This finding is associated but possibly not in a causal relation with the fact that Responders had lower AF recurrences and less persistent AF. Baseline clinical characteristics between responders and non-responders are significantly different. Responder patients are younger with less underlying structural heart disease and less dilated atrium and ventricles. Accordingly, during follow-up, AF recurrences, HF hospitalization and mortality were lower. A striking finding is the high mortality rate among non-responders; up to 10% of patients died within two years from the procedure. This data is in line with previous studies investigating different strategies of rate and rhythm control in HF and AF patients.^{2,22} The best treatment option for these high-risk patients still needs to be found. Whether a better AF ablation strategy could improve outcomes among non-responders or whether AF ablation is futile due to the underlying severe comorbidities is unknown. Further studies are needed to address different treatment options in the non-responder group.

Limitations:

There is an inherent selection bias in our cohort given that only patients already selected for catheter ablation are included. Real-world studies should investigate in an unselected cohort of HF patients with AF what proportion of patients belong in the different score categories. No information regarding NYHA class was collected at baseline and during follow-up. We did not perform BNP measurements in the current study. MRI data were available only for 52 patients. The absence of a pre-defined ablation strategy may influence ablation outcomes and thus potentially response rate. Another limitation of our study is the use of LVEF to classify between the two subgroups. LVEF is influenced by significant inter- and intra- observer variability and is a surrogate endpoint. However, it remains an important marker to guide treatment and predicts prognosis, as testified by the difference in hospitalization and mortality between the two groups during follow-up.

In this external validation study, we demonstrated that the published prediction model did accurately predict LV function recovery following AF ablation in HF patients. The prediction model is based on 4 readily available clinical and echocardiographic parameters (QRS duration, LA volume, AF pattern and underlying etiology). These findings support the use of the model to standardize shared decision-making regarding AF ablation referral in the clinical setting and in clinical studies.

Additionally, we report that Responders achieved more positive ventricular remodeling, lower hospitalization rate and lower mortality as compared to Non-Responders. AF recurrence rate among Responders was close to 30%, reinforcing the concept that AF ablation in the setting of HF, should be considered as an “anti-HF” treatment (i.e. burden-control), rather than a tool to eliminate AF completely.

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Table 1

Table 1: Baseline clinical characteristics of the study population				
Characteristic	Total n=605	Responders n=427 (70%)	Non Responders n=178 (30%)	p value
Age – mean (SD), yr	61.1 ± 9.4	60.4 ± 9.6	62.8 ± 8.9	0.016
Female Sex – no.(%)	144 (23.8%)	92 (21.5%)	52 (29.2%)	0.047
Hypertension	357 (59.0%)	254 (59.5%)	103 (57.9%)	0.720
Diabetes	107 (17.7%)	73 (17.1%)	34 (19.1%)	0.560
TIA / Stroke	57 (9.4%)	32 (7.2%)	25 (14.0%)	0.015
Obstructive sleep apnea	55 (9.1%)	32 (8.6%)	23 (12.9%)	0.06
Severe chronic kidney disease	65 (10.7%)	36 (8.8%)	29 (16.4%)	0.010
Years since first episode of AF	2 (1-5)	2 (1-5)	2 (1-4)	0.077
Years since first episode of HF	2 (1-4)	1 (1-4)	3 (2-5)	<0.001
Cardiac resynchronization therapy (CRT)	37/540 (6.1%)	19/374 (5.1%)	18/166 (10.8%)	0.025
Implantable cardiac defibrillator (ICD)	94/540 (17.4%)	31/374 (8.3%)	63/166 (38.0%)	<0.001
Left ventricular ejection fraction (LVEF)	37.3 ± 8.4	37.2 ± 8.7	37.2 ± 7.8	0.78
LVEF < 40 %	380 (62.8%)	268 (62.8%)	112 (63.3%)	0.93
LVEDVi, mL/m ²	81.6 ± 41.7	74.6 ± 35.6	96.9 ± 49.2	<0.001
Left Atrial Volume Index (Echo), mL/m ²	46.2 ± 14.0	43.7 ± 13.8	52.7 ± 12.9	<0.001
Severe Atrial Dilatation (LAVI >50 ml/m ²)	218 (36.0%)	109 (25.5%)	109 (61.2%)	<0.001
QRS, ms	109.5 ± 25.2	102.3 ± 20.3	126.9 ± 27.2	<0.001
QRS > 120 ms	180 (29.8%)	66 (15.5%)	114 (64%)	<0.001
Known Etiology*	243 (40.2%)	113 (26.5%)	130 (73.0%)	<0.001
Paroxysmal AF	122 (20.2%)	64 (15%)	58 (32.6%)	<0.001
Score	2 (0-3)	1 (0-2)	4 (3-5)	<0.001
Presence of late gadolinium enhancement (LGE)	24/52 (46.2%)	7/33 (21.2%)	17/19 (89.5%)	<0.001
Continuous variables are shown as Mean ± Standard Deviation (SD) or Median and (Inter Quartile Range) (IQR). Discrete variables are presented as numbers and percentages (%).				
**“Known Etiology” was defined as the presence of an established etiological diagnosis explaining the reduced LVEF other than AF. Heart failure (HF) etiologies are identified and defined in accordance with the 2021 “Universal definition and classification of heart failure” as follows: ischemic, valvular, infiltrative, peri-partum cardiomyopathy, chemotherapy-, alcohol- and viral myocarditis-induced, genetically-determined cardiomyopathy.				
Abbreviation List: AF atrial fibrillation, AML anterior mitral line, BMI body mass index, EF ejection fraction, EVM electroanatomical voltage map, LAVI left atrial volume index, LVZ Low Voltage Zone, SD standard deviation, TIA transient ischemic attack.				
Severe chronic kidney disease is defined as eGFR < 30 ml/min				

Table 2

Table 2: Endpoints						
	Responders	Non-Responders	HR	Lower 95%CI	Upper 95% CI	p value
Arrhythmia recurrence						
AF or AT recurrences	118/385 (30.6%)	86/167 (51.5%)	0.53	0.40	0.71	<0.001
<u>Paroxysmal AF</u> recurrence >30 s	81/385 (21.0%)	29/167 (17.4%)	1.18	0.76	1.82	0.47
<u>Persistent AF</u> recurrence	37/385 (9.6%)	57/110 (34.1%)	0.23	0.15	0.36	<0.001
	Responders	Non-Responders	OR	Lower 95%CI	Upper 95% CI	p value
Permanent AF	12/340 (3.5%)	19/152 (12.5%)	0.26	0.12	0.54	<0.001
Death or Heart Transplantation	5/342 (1.5%)	18/156 (11.5%)	0.11	0.04	0.31	<0.001
Heart Failure Hospitalization	13/342 (3.8%)	47/156 (30.1%)	0.09	0.05	0.18	<0.001
Positive Left ventricular remodeling	79/162 (48.8%)	11/114 (9.6%)	8.91	4.45	17.84	<0.001
Univariate COX regression (upper part) and logistic regression (lower part) analysis for predictors of AF recurrence after catheter ablation, comparing anterior mitral line (AML) and non-AML group.						
Abbreviation List: AF atrial fibrillation, AT atrial tachycardia, CI confidence interval, HR hazard ratio, OR odds ratio.						
Positive remodeling was defined as > or = 15% reduction in left ventricular end-systolic volume (LVEDV)						

Figure 1

Kaplan Meier analysis showing lower atrial fibrillation (AF), atrial flutter (AFL) and atrial tachycardia (AT) recurrence rate, between Responders and Non Responders (upper portion). In the central and lower side, the AF pattern-specific analysis is depicted. In the central portion, no significant difference is found when comparing paroxysmal AF recurrence. In the lower side, a significant difference is found when comparing persistent AF recurrence.

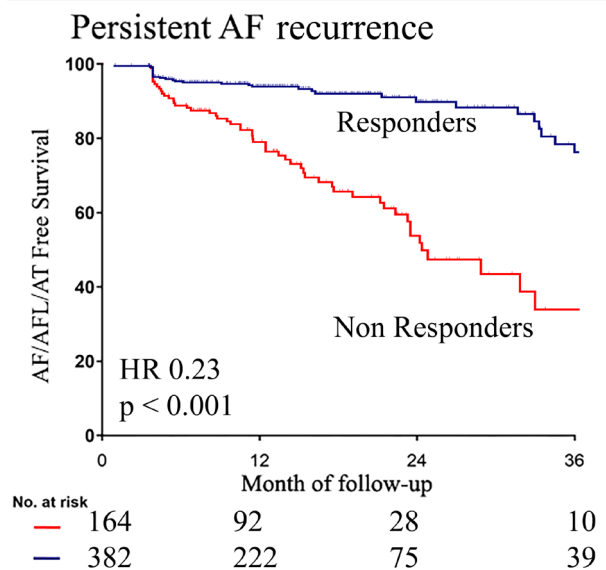
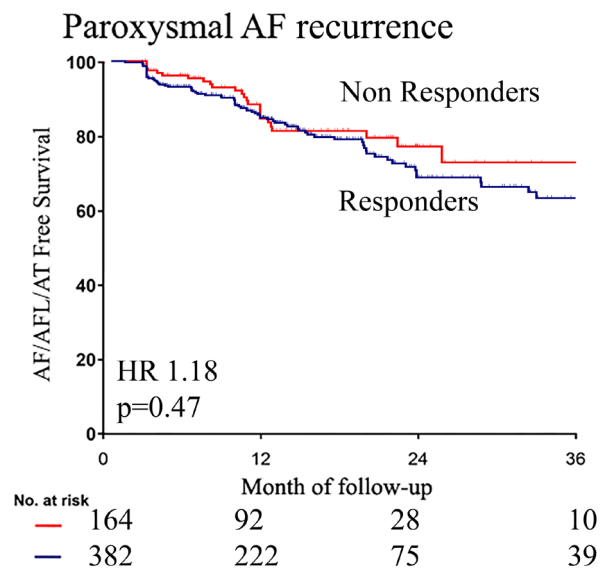
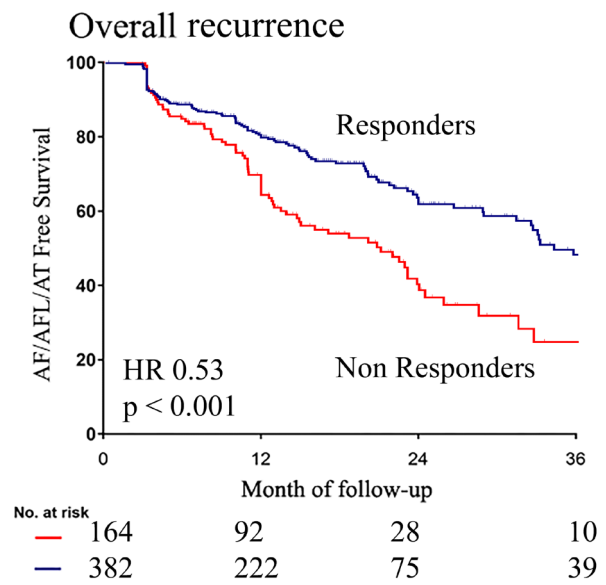
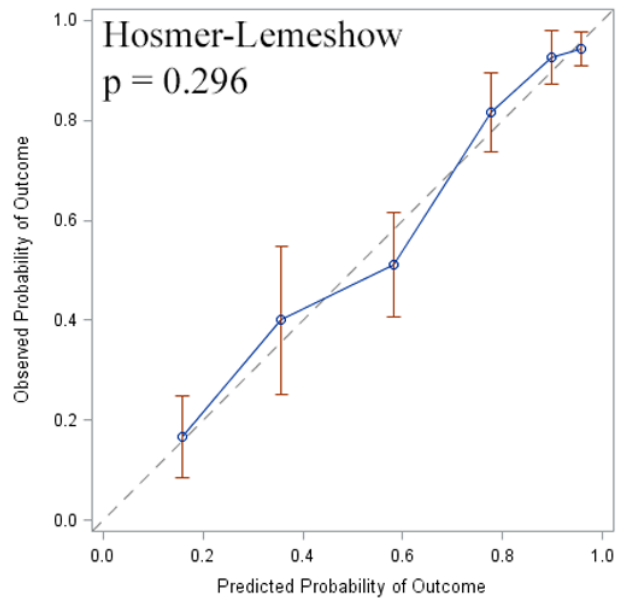
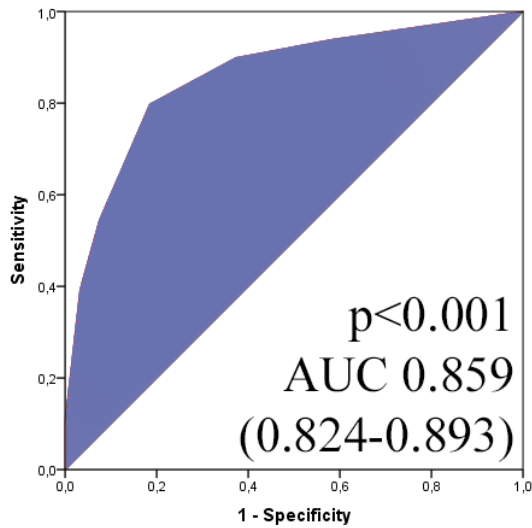
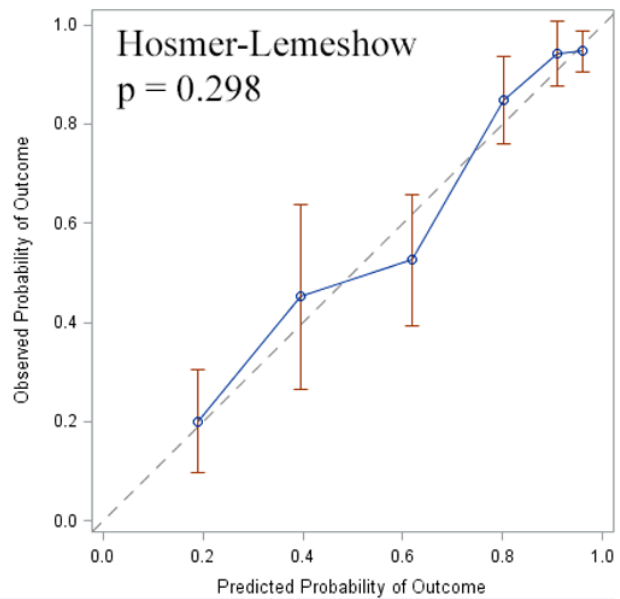
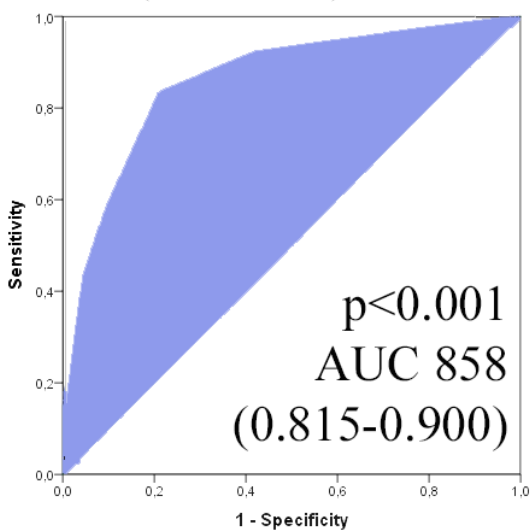


Figure 2: Area under the curve (AUC) and Calibration plot in the overall population and in different LVEF categories showing good prediction and good calibration.

Overall Population, n=605



HFrEF (EF < 40%) n=381



HFmrEF (EF 40-50%) n= 224

