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INNOVATIVE TECHNOLOGIES FOR TRANSCATHETER ABLATION OF ATRIAL FIBRILLATION IN PATIENTS WITH HEART FAILURE: THE NEW AGE AF-HF REGISTRY

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ABBREVIATIONS AND ACRONYMS:

AF = Atrial fibrillation.

CA= Catheter Ablation

ECG = Electrocardiogram.

TEE = Transoesophageal echocardiography.

ICE = Intracardiac echocardiography.

eGFR = Estimated glomerular filtration rate.

CKD-EPI = Chronic kidney disease epidemiology collaboration.

EF = Ejection fraction.

HF = Heart failure.

HFrEF = Heart failure with reduced ejection fraction.

HFmEF = Heart failure with mildly reduced ejection fraction.

HFpEF = Heart failure with preserved ejection fraction.

CKD = Chronic kidney disease.

MACCES = Major adverse cardiocerebrovascular events.

ACS = Acute coronary syndrome.

TIA = Transient ischemic attack.

EHRA = European Heart and Rhythm Association.

PV = Pulmonary vein.

PVI = Pulmonary vein isolation

MR = Magnetic resonance.

ESC = European Society of Cardiology.

CRT = Cardiac resynchronization therapy

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1. ABSTRACT:

Background:

Heart failure (HF) and atrial fibrillation (AF) frequently coexist, worsening each other's clinical course. Data on catheter ablation (CA) of AF using novel ablation technologies in patients with HF remain limited.

Methods:

We established a prospective, multicentre international registry including patients consecutively undergoing CA of AF using pulsed-field ablation (PFA), third-generation visually guided laser balloon (VGLB), or the latest-generation cryoballoon between 2020 and 2025. The study group comprised patients with HF diagnosed and subtyped (with reduced (HFrEF), moderately reduced (HFmrEF), and preserved ejection fraction (HFpEF)) per the European Society of Cardiology (ESC) 2021 guidelines; patients without HF served as controls. Primary endpoints were procedural time and the rate of procedure-related adverse events; secondary endpoints were 12- and 24-months freedom from AF recurrence beyond the 3-month blanking period and from major adverse cardiac and cerebrovascular events (MACCEs).

Results:

Among 1,047 enrolled patients, 180 (17.2%) had HF; 886 (84.6%) had follow-up, and 400 had adjudicated MACCE data. HF patients had longer procedural (median 93.5 (70–141) vs 75 (60–105) min, $p<0.001$) and fluoroscopy times (19.5 (8.5–32.2) vs 10 (6.4–18) min, $p<0.001$) with similar complication rates (1.7% vs 2.1%, $p=0.13$). Freedom from AF recurrence at 12 and 24 months was significantly lower in HF patients (74.0% vs 63.2% and 57.5% vs 50.5%, $p<0.001$). HF was the only independent predictor of AF recurrence (HR 1.50, $p=0.024$), driven by HFpEF (HR 2.28, $p=0.001$). HF patients also showed reduced 12- and 24-month freedom from MACCEs (99.0% vs 89.0%; 98.0% vs 83.5%; $p<0.001$). Independent predictors of MACCEs included HFrEF (HR 14.89, $p<0.001$), HFpEF (HR 11.07; $p=0.001$), and rhythm-control discontinuation at follow-up (HR 6.9, $p=0.002$).

Conclusions:

Novel ablation technologies were safe and effective for patients with HF, and outcomes were comparable to standard systems. While both HFpEF and HFrEF increased MACCE risk, only HFpEF predicted AF recurrence post-ablation, underscoring the need for tailored rhythm-control strategies across the HF spectrum.

Introduzione:

Lo scompenso cardiaco (HF) e la fibrillazione atriale (AF) coesistono frequentemente, e l'uno peggiora il decorso clinico dell'altro. La disponibilità di dati sull'ablazione transcatetere (CA) dell'AF mediante tecnologie di nuova generazione nei pazienti con HF è limitata.

Metodi:

Abbiamo istituito un registro internazionale, prospettico e multicentrico, che ha incluso consecutivamente tutti i pazienti sottoposti tra il 2020 e il 2025 ad ablazione transcatetere di AF mediante campi pulsati (PFA), pallone laser a guida endoscopica di terza generazione (VGLB) o pallone crio di ultima generazione. Il gruppo di studio comprendeva i pazienti affetti da HF a frazione di eiezione ridotta (HfrEF), moderatamente ridotta (HfmrEF) e preservata (HFpEF), diagnosticato secondo le linee guida ESC 2021; il resto dei pazienti costituiva il gruppo di controllo. Come endpoint primario, abbiamo confrontato i tempi e le complicanze procedurali tra i gruppi di studio. Come endpoint secondario abbiamo valutato la sopravvivenza a 12 e 24 mesi da eventi cardiocerebrovascolari maggiori (MACCEs) e da recidiva di AF oltre i 3 mesi post-procedura.

Risultati:

Tra i 1.047 pazienti arruolati, 180 (17,2%) presentavano HF; 886 (84,6%) disponevano di sufficiente follow-up, di cui 400 con valutazione sistematica dei MACCEs. Rispetto ai controlli, i pazienti con HF hanno mostrato tempi procedurali (93,5 (70–141) vs 75 (60–105) min, p<0,001) e di fluoroscopia (19,5 (8,5–32,2) vs 10 (6,4–18) min, p<0,001) più lunghi, ma tassi di complicanze procedurali simili (1,7% vs 2,1%, p=0,13). La libertà da recidiva di AF a 12 e 24 mesi è risultata significativamente inferiore nei pazienti con HF (74,0% vs 63,2% e 57,5% vs 50,5%, p<0,001). L'HF è risultato l'unico predittore indipendente di recidive di AF (HR 1,50, p=0,024), nello specifico nella forma a frazione di eiezione preservata (HFpEF) (HR 2,28, p=0,001). I pazienti con HF hanno inoltre mostrato una minore libertà da MACCE a 12 e 24 mesi (99,0% vs 89,0%; 98,0% vs 83,5%; p<0,001). Sia l'HFrEF (HR 14,89, p<0,001) sia l'HFpEF (HR 11,07, p=0,001), oltre all'interruzione del rhythm control al follow-up (HR 6,9, p=0,002), risultavano predittori indipendenti di MACCEs.

Conclusioni:

L'ablazione con tecnologie di nuova generazione si è dimostrata sicura ed efficace nei pazienti con HF, con risultati comparabili a quelli ottenuti con i sistemi tradizionali. Sebbene HFpEF e HFrEF aumentino il rischio di MACCE, solo HFpEF predice la recidiva di AF, evidenziando la necessità di strategie di rhythm control personalizzate per l'intero spettro dell'HF.

2. INTRODUCTION:

2.1 EPIDEMIOLOGY OF ATRIAL FIBRILLATION AND HEART FAILURE:

Atrial fibrillation (AF) is the most common chronic arrhythmia, and a 2019 estimation indicates a global prevalence of 59.7 million persons.[1] Every decade, incident cases of AF are doubling, and future increases are anticipated.[2]

As regards heart failure (HF), its prevalence in developed countries is approximately 1–2%, exceeding 10% among people of 70 years of age. The age-adjusted incidence still ranges from 3 (all-ages) to 5 (adults) cases per 1000 person-years, and the total number of new cases has increased by 12%[3].

AF and HF facilitate each other's occurrence and thus frequently coexist. In HF with preserved ejection fraction (HFpEF), the prevalence of AF ranges from 25% to 39%, while in HF with reduced ejection fraction (HFrEF), it ranges from 4.2% in New York Heart Association (NYHA) class I patients to 49.8% in NYHA class IV patients[4]. One-third of patients experiencing the first AF episode present HF[5]. The development of AF in patients with HF is associated with worse prognosis, and the converse is also true. [6]

Nevertheless, AF may be a distinct clinical entity in relation to the associated HF form, and some studies suggest a higher frequency and prognostic relevance of AF in patients with HFpEF.[7-9]

2.2 MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION AND HEART FAILURE:

The AF-CARE is a simplified approach to AF, provided by the European Society of Cardiology (ESC) 2024 AF guidelines[10].

However, management of patients with concomitant AF and HF is challenging. In the ESC 2021 HF guidelines, a specific algorithm for HFrEF (Figure 1) has been provided[11].

Regarding rhythm control in patients with chronic HF, several studies have compared this approach with rate control.

After initial encouraging results from small studies[12], the AF-CHF trial failed to show that pharmacological rhythm control improved rates of cardiac death compared with rate control[13].

The EAST-AFNET-4 trial compared a rhythm-control strategy with usual care for patients with AF diagnosed in the previous 12 months. A rhythm-control strategy could improve cardiovascular outcomes, and these results were consistent in the subgroup of patients with HF (28.6%). Compared with the AF-CHF trial, in EAST-AFNET-4, a significant proportion of patients (19.4%) underwent CA of AF[14].

2.3 CATHETER ABLATION IN HEART FAILURE:

In the last decade, CA of AF has proved to be a safe and effective strategy in patients with HF. The ESC 2024 AF guidelines indicate CA with a Class IIa recommendation, level of evidence B, in selected AF patients with HFrEF to improve survival and reduce HF hospitalization, and with a class I, level of evidence B in those HFrEF patients with a high probability of tachycardia-induced cardiomyopathy.[10]

In patients with HFrEF, initial small clinical trials have shown that, compared with conventional therapies, CA could improve left ventricular ejection fraction (EF), quality of life (QOL), and NYHA class.[15-18]

Two trials, AATAC and CASTLE AF[19,20], showed a benefit in hospitalization and mortality. These results were offset by those from two randomized clinical trials, i.e., AMICA and RAFT-AF.[21,22]

The AATAC trial compared CA to amiodarone and showed a superiority of CA in primary and secondary endpoints, including a positive effect on rates of death and hospitalization.[19]

The CASTLE-AF trial was the first trial sufficiently powered to evaluate hard endpoints in AF. It enrolled patients with symptomatic paroxysmal or persistent AF who had no response to, side effects from, or unwillingness to take antiarrhythmic drugs. Patients were on optimal medical therapy for HF. All had a NYHA class II-IV, EF ≤35%, and an implanted device. CA, compared to medical therapy (rate or rhythm control), led to a lower rate of a composite endpoint of death from any cause or hospitalization for worsening HF[20].

The AMICA trial included patients with persistent/long-standing persistent AF and EF≤35% and assigned them to a CA or a conventional therapy arm. At 1 year, patients in the CA arm

showed no significant improvement in EF or QOL. Results from the AMICA trial could be due to the study enrolling patients with more advanced HF (lower EF, worse NYHA class, or persistent/long-standing persistent AF) [21].

The recent RAFT AF compared ablation-based rhythm control and rate control in patients with high-burden AF and HFrEF. The study showed no difference in all-cause mortality or HF events between groups; however, there was a non-significant trend toward improved outcomes in the CA group[22].

Figure 2 presents trials comparing CA with other conventional therapies in patients with HFrEF.

As regards HFpEF, most of the data come from a few observational studies and retrospective analyses. These suggest that CA could be as safe and effective in maintaining sinus rhythm as in patients with HFrEF, but no prospective, randomized, long-term study has been performed so far[23-26].

Finally, CA could play a role in HF candidates for Cardiac Resynchronization Therapy (CRT), a standard treatment for HFrEF and interventricular dyssynchrony. Most major trials excluded patients with AF, and data come only from observational studies, small trials, and meta-analyses[27,28]. AF patients have higher rates of non-response to CRT and mortality because CRT may be impaired by AF's irregular intrinsic conduction of AF[29]. An "Ablate and pace" strategy, based on atrioventricular node ablation and previous/subsequent CRT placement, showed good results for patients with permanent AF and systolic dysfunction who have uncontrolled ventricular rates despite medical therapy, but it results in partial or total pacemaker dependence[30].

The PABA-CHF trial compared CA of AF with an "ablate and pace" strategy in patients with AF and HFrEF. CA led to a superior improvement of EF, exercise capacity, and QoL[31]. This suggests that CA may also be a valid tool for CRT candidates with AF who have not responded to medical therapy.

2.4 CURRENT ABLATION TECHNIQUES AND LIMITATIONS:

Pulmonary vein isolation (PVI) is the cornerstone of CA of AF. This is based on the observation that initiation of FA usually arises from ectopic activity inside the pulmonary veins (PVs)[32].

Traditionally, PVI is accomplished by point-by-point radiofrequency ablation (RFA) to produce a circumferential lesion around the antrum of the PVs[33]. Cryoballoon ablation (CBA) is a more recent technology that uses a specific balloon placed in the antrum of a PV, creating a single circumferential lesion by cooling the distal section of the balloon. CBA showed similar arrhythmia-free survival, slightly shorter procedural times and complication rate in comparison to RFA[34].

Despite recent technological advances, the rate of PV reconnection during follow-up remains high, leading to AF recurrence and the need for re-ablation. This is mainly due to technical reasons, which lead to incomplete lesions at the PV ostia[35,36]. Further, a complication rate of around 3% associated with both RFA and CBA is non-negligible[37].

The ideal novel technology for CA of AF would enhance the rate of durable PVI while improving safety and efficacy[38].

2.5 NOVEL TECNOLOGIES: THIRD GENERATION LASER BALLOON, PULSED FIELD ABLATION, AND NEW GENERATION CRYOBALLOON:

Visually guided laser balloon (VGLB) ablation systems (LB; CardioFocus) were validated for clinical use for the first time in 2016[39].

This system consists of a compliant balloon which conform to the PV ostium, leading to its occlusion. The operator then has a real-time view of the PV ostia through a 2F endoscope inserted through the shaft. Thereby, the ablation substrate may be directly visualized. Ablation is performed with a 980-nm diode laser.

The first two generations of laser catheters used a point-by-point ablation system, with similar efficacy but longer procedural times compared to RF[40,41].

The latest generation of laser balloons (LB3; HeartLight X3) introduced a motor control system that enables uninterrupted, high-speed circumferential lesions at 13 W, resulting in significantly reduced procedure times and a shift from point-to-point to potentially single-shot.[42]

Pulsed field ablation (PFA) is the latest approved technology for CA of AF. It is based on high-voltage, short-duration pulses that create pores in the cellular membrane (microporation), leading to death of the target cells. Since myocardium has a lower injury threshold than other surrounding anatomical structures, PFA can uniquely ablate myocardium, reducing the risk of

damage to non-cardiac tissues. In addition, PFA requires only short applications to produce irreversible lesions.[44]

The most extensively studied PFA system is Farawave (Farapulse). This consists of a catheter with five splines, each containing four electrodes. It can be configured from a baseline linear configuration to a spherical (basket or biscuit) pose, and then to a fully deployed flower-petal configuration. The catheter is advanced to achieve circumferential contact of the splines with atrial tissue before energy delivery.[45]

Finally, a novel CB (POLARx, Boston Scientific) was recently introduced in clinical practice. A key innovation of the system is the constant internal pressure maintained during both positioning and freezing, which ensures stable tissue contact throughout the ablation[46]. In its latest version (POLARx FIT, Boston Scientific), the system has been further refined to include a variable-diameter balloon that improves anatomical conformity.[47]

Figure 3 shows images of all the novel technologies used for AF CA.

2.5.1 DIFFERENCE IN TISSUE LESIONS:

Radiofrequency uses tissue heating. However, 90% of the power is absorbed within the first 1-1.5 mm of the myocardium, which thus requires high heating to achieve a full transmural lesion.[48,49] Cryothermal lesions are based on freezing with subsequent necrosis and replacement fibrosis.[50]

VGLBA is based on photonic energy that can penetrate tissue beyond the endocardium. Here it is absorbed by water, causing deeper heating and necrosis. Nevertheless, the first layers of myocardium absorb most of the energy, reducing the charring of the endocardium and the subsequent thrombosis. Thus, lesions are well-defined, transmural, with no or minimal endocardial damage or charring,[51,52] as confirmed by cardiac magnetic resonance (MR) imaging studies. [53]

This lesion quality could result in a lower rate of acute PV reconnection and a better safety profile. PVs remapping studies conducted so far demonstrate a good lesion stability at one year. [55,56]

As regards PFA, this system causes selective tissue damage via microporation and, since the myocardium has one of the lowest injury thresholds, PFA could reduce the risk of non-target organ lesions and complications. Further, the impact on surrounding healthy atrial tissue seems

negligible. [44,45] Cardiac MR studies have demonstrated that, compared to thermal ablation (RF or CBA), PFA does not lead to oesophageal lesions, with no residual, ablation-related, atrial late gadolinium enhancement, and better left atrium functional parameters.[56]

2.5.2 EFFICACY AND SAFETY DATA:

Recently published multicentre prospective registries have demonstrated the excellent safety and efficacy of all three novel ablation technologies in unselected AF populations.[47,57,58]

Furthermore, a subanalysis of a PFA registry comparing patients with HF to those without HF already yielded promising results, showing favourable one-year arrhythmia-free survival and a reassuring safety profile. [59]

However, to date, no dedicated study has comprehensively evaluated the performance of these novel technologies across the full spectrum of HF or assessed their impact on major adverse cardiovascular outcomes.

3. METHODS:

3.1 STUDY DESIGN AND POPULATION:

We established an international, multicentre, observational, prospective registry designed to collect real-world data on the use of novel technologies—PFA, VGLB, and latest generation of cryoballoon—for CA of AF in patients with or without concomitant HF.

Between 2020 and 2025, we included all consecutive patients with symptomatic paroxysmal or persistent AF and an indication for CA according to the current ESC guidelines who underwent the procedure using one of the above-mentioned technologies at 11 participating high-volume centres.

HF diagnosis and classification into HFrEF, HFmrEF, and HFpEF subtypes were based on the 2021 ESC Heart Failure Guidelines. [11] Patients meeting the HF diagnostic criteria prior to ablation constituted the study group, while all others served as controls.

Exclusion criteria included previous AF ablation, any clinical condition associated with a life expectancy <1 year, or inability to provide informed consent.

The study complied with the Declaration of Helsinki and received approval from the Ethics Committees of all participating centres.

Patients could withdraw from the registry at any time, either at their own request or at the investigator's discretion.

3.2 PROCEDURE:

CA was performed using PFA, VGLB, or the latest generation cryoballoon, according to each centre's expertise, local availability, and clinical practice.

Procedures were performed according to the 2017 and 2024 ESC/HRS/APHRS/LAHRS consensus statements on AF ablation.[60,61] PVI was the primary procedural endpoint. Additional ablation lines (posterior wall, mitral isthmus, superior vena cava) were applied at the operator's discretion.

Ablation was performed under deep sedation or general anaesthesia. Intracardiac echocardiography (ICE) or transoesophageal echocardiography (TEE) was used when available according to local protocols.

3.3 DATA COLLECTION AND FOLLOW-UP:

Procedural data—including technology used, presence of left atrial anatomical variants, sedation protocol, and total procedural and fluoroscopy times—were recorded.

Baseline evaluation included medical history, physical examination, 12-lead electrocardiogram (ECG), transthoracic echocardiography, and main laboratory parameters.

Clinical history was used to calculate the CHA_2DS_2-VA thromboembolic risk score.

When known, HF aetiology was reported, and tachycardia-induced cardiomyopathy was identified according to a recent European Heart and Rhythm Association (EHRA) survey. [62]

Echocardiographic quantification of cardiac chambers and left ventricular function followed European Association of Cardiovascular Imaging recommendations.[63,64]

Serious procedure-related adverse events included transient ischaemic attack (TIA)/stroke (within two weeks post-ablation), major vascular complications (pseudoaneurysm, arteriovenous fistula, or groin haematoma requiring transfusion or prolonged hospital stay), cardiac perforation/tamponade, phrenic nerve injury, atrio-oesophageal fistula, PV stenosis, or procedure-related death.

Follow-up assessments were scheduled at 6-, 12-, and 24-month post-procedure via outpatient visits or structured phone interviews. Additional information was obtained from unplanned hospitalizations, emergency department visits, or cardiology consultations whenever documentation was available.

AF recurrence was defined as any symptomatic or asymptomatic AF episode documented by a 12-lead ECG, Holter monitoring, in-hospital telemetry, or wearable/patient-operated certified single- or multi-lead ECG devices. Asymptomatic events were adjudicated by an experienced physician at each enrolling centre.

Recurrences within the first three months post-ablation (blanking period) were not considered procedural failures. We evaluated procedure efficacy at follow-up based on recurrences occurring more than 3 months after the ablation.

Major adverse cardiac and cerebrovascular events (MACCEs) were defined as the composite of cardiovascular death, HF hospitalization, acute coronary syndrome (ACS), ischaemic stroke or TIA, peripheral embolism, or heart transplantation.

At follow-up, we also documented the clinicians' decisions to interrupt the rhythm-control strategy, thereby identifying AF as permanent.

3.4 ENDPOINTS:

The primary endpoint was to evaluate the safety and procedural performance of novel ablation technologies in patients with HF compared to controls.

Safety was defined as the composite rate of serious procedure-related adverse events.

Procedural performance was assessed through median procedural and fluoroscopy times.

Secondary endpoints included freedom from AF recurrence beyond the blanking period and from MACCEs, both evaluated through time-to-event analyses.

3.5 STATISTICAL ANALYSIS:

Continuous variables were assessed for normality using visual inspection of Q–Q plots and analysis of skewness and kurtosis. Normally distributed variables were expressed as mean ± standard deviation (SD), and non-normally distributed variables as median and interquartile range (IQR). Categorical variables were expressed as counts and percentages.

Between-group comparisons used the Student's t or Mann–Whitney U test for continuous variables and χ^2 for categorical variables.

Because only three of the twelve participating centres conducted systematic MACCE follow-up and adjudication, this endpoint was analysed using data from these centres only. To assess the generalisability of these data, baseline characteristics of included and excluded patients were compared using standardised mean differences (SMDs) for the most relevant variables; SMD <0.10 indicated a negligible difference, and SMD >0.30 indicated a meaningful difference.

We used univariate and multivariable linear regression to identify independent predictors of variation in procedural and fluoroscopy times.

Time-to-event outcomes were analysed using Kaplan–Meier curves, log-rank tests, and restricted mean survival time (RMST) analyses at the prespecified time points (τ) of 12 and 24 months.

We used Cox proportional hazards models to identify predictors of MACCEs and AF recurrence beyond the blanking period. Model adequacy for Cox regression was assessed using the global likelihood-ratio (LR) χ^2 statistic. The proportional hazards (PH) assumption was verified for the most relevant covariates and for the overall model using log–log survival plots and Schoenfeld residuals.

A Weibull proportional hazards regression model with a gamma-distributed shared frailty term was applied to account for unobserved centre-level heterogeneity in AF recurrence analyses.

Given the smaller number of centres with systematic MACCE adjudication, centre-level heterogeneity for this analysis was addressed by including the enrolling centre as a fixed covariate in multivariable Cox models.

Variables were selected for multivariable models based on clinical relevance or univariate association at $p<0.10$.

All tests were two-tailed, with $p<0.05$ considered statistically significant.

Statistical analyses were performed using Stata/SE 18.0 (StataCorp, College Station, TX, USA).

4. RESULTS:

BASELINE FEATURES:

Baseline features are reported in Table 1-3.

A total of 1,047 patients were enrolled in the registry. Table 4 summarizes the distribution of participants across enrolling centres and the corresponding prevalence of HF. A significant inter-centre variation was observed in the proportion of HF patients ($p < 0.001$).

The mean age was 63.4 ± 10.6 years, 327 (31.2%) patients were female, and 216 (24.6%) were obese.

657 (62.8%) patients had paroxysmal AF, 354 (33.8%) had persistent AF, and 36 (3.4%) had long-standing persistent AF.

177 (16.9%) patients showed a high risk (≥ 4) CHA2DS2-VA score (16.9%).

HF was present in 180 (17.2%) patients at baseline. Among these, 84 (46.7%) had HFrEF, 44 (24.4%) HFmrEF, and 52 (28.9%) HFpEF.

The most frequently observed structural heart diseases in HF patients were chronic coronary syndrome (47 (26.1%)) and dilated/hypokinetic non-dilated/ arrhythmogenic cardiomyopathy (47 (26.1%)).

45 (25%) HF patients showed a tachycardia-induced cardiomyopathy component, with or without a concomitant structural heart disease.

PROCEDURAL DATA:

Table 5 reports the main procedural data.

The median total procedural time was 75 minutes (IQR 60–111), and the median fluoroscopy time was 10.6 minutes (IQR 6.7–20.2).

Ablation was performed under general anaesthesia in 256 patients (29.8%) and deep sedation in 603 (70.2%).

Regarding ablation technology, VGLB, PFA, and cryoballoon ablation were performed in 597 (57.0%), 429 (40.6%), and 21 (2.0%) patients, respectively.

A variant anatomy was reported in 150 patients (14.5%), with 44 (29.3%) showing a middle PV, 91 (60.7%) a common ostium, and 15 (10%) both.

Procedural complications occurred in 21 cases (2%), including 7 (0.7%) phrenic nerve injury, 4 (0.4%) pericardial tamponade or cardiac perforation, 4 (0.4%) periprocedural strokes or TIA, 5 (0.5%) vascular access complications, and 1 (0.1%) coronary air embolism.

No procedure-related deaths, atrio-esophageal fistulae, or PV stenoses were reported.

FOLLOW-UP AND ATRIAL FIBRILLATION RECURRENCES:

Follow-up information is reported in Table 6.

Follow-up data were available for 886 patients (84.6%), with a median follow-up duration of 13 months (IQR 7–24).

591 patients (66.7%) had at least 12 months of follow-up, and 263 (29.7%) were followed for 24 months.

An early AF recurrence (≤3 months after the ablation procedure) occurred in 115 patients (13%), whereas 198 patients (22.3%) experienced a late AF recurrence (>3 months). Figure 1 reports the Kaplan-Meier survival curve for AF recurrence after the blanking period. The estimated freedom from AF was 71.9% (95% CI 67.9–75.5) at 12 months and 56.3% (95% CI 50.3–61.9) at 24 months.

In 47 patients (5.3%), rhythm-control therapy was discontinued, and AF was subsequently classified as permanent.

Redo procedures were performed in 33 patients (4.7%),

In the univariable Cox analysis, only HF (HR: 1.56, 95% CI: 1.16–2.09; p = 0.003) and severe left atrial enlargement (HR: 1.44, 95% CI: 1.01–2.08; p = 0.042) were significantly associated with AF recurrence beyond 3 months after ablation. Obesity (HR: 1.35, p = 0.079) showed a tendency to be associated with recurrences, while the other variables had no significant influence.

MAJOR ADVERSE CARDIOCEREBROVASCULAR EVENTS:

418 patients in our study underwent follow-up with systematic adjudication of MACCEs. Of these, 400 (95.7%) were sufficiently followed up to be included for event analysis.

Table 7 reports the results of the comparison between these patients and the remaining registry population using standardized differences.

Patients from MACCE-reporting centres had similar baseline characteristics compared with the rest of the cohort, except for a higher prevalence of HF (116 (27.8%) vs 64 (10.2%), standardized difference 0.46) and availability of a follow-up (400 (95.7%) vs. 486 (77.3%) months, standardized difference 0.55). Patients from the other centres had a higher frequency of CHA2DS2-VA scores above 3, indicating higher thromboembolic risk (143 (22.7%) vs 34 (8.1%), standardized difference 0.41).

During follow-up, 17 (4.2%) patients experienced a MACCE. Table 8 reports the MACCE analysis.

There were 12 decompensated HF episodes (3%), 3 ACS (1.2%), 1 stroke (0.2%), 6 cardiovascular deaths (1.5%), and 3 patients (1.2%) received a heart transplantation.

The median time to MACCE was 5 months (IQR 2–12).

31 (7.7%) patients were hospitalized for cardiovascular causes, and 68 (17%) required access to the emergency department or an unscheduled ambulatory visit during follow-up.

Figure 2 reports the Kaplan-Meier survival curve for MACCEs, and the estimated freedom from MACCEs was 96.3 % (95% CI 93.6–97.9) at 12 months and 93.9% (95% CI 89.9–96.3) at 24 months.

COMPARISON OF STUDY POPULATIONS:

A comparison of baseline characteristics between patients with and without HF is summarized in Table 9.

Patients with HF showed a higher prevalence of obesity (36.4% vs 23.1%, $p = 0.012$), a higher CHA_2DS_2-VASc score (2 (1–4) vs 2 (1–3), $p < 0.001$), and a higher prevalence of diabetes (22.2% vs 12.2%, $p < 0.001$).

Glomerular filtration rate was lower in the HF group (75.7 ± 21.3 vs 84.2 ± 16.6 mL/min/1.72 m^2, $p < 0.001$).

Patients with HF showed a lower mean left ventricular EF (42 (35–54) vs 58 (53–60), $p < 0.001$) and a higher prevalence of left atrial enlargement (83.4% vs 71.5%, $p = 0.018$).

The AF pattern was more often persistent in patients with HF (41.1% vs 32.3%, $p < 0.001$), and the median AF duration was significantly longer (35 (11–109) vs 26 (8–72) months, $p < 0.001$).

PRIMARY ENDPOINT: SAFETY AND EFFICIENCY:

The comparison of procedural characteristics is reported in Table 10.

PFA and VGLB were used with comparable frequencies, though HF patients underwent cryoballoon ablation slightly more often (4.4% vs 1.5%, $p = 0.036$). General anaesthesia was less common in the HF group (21.7% vs 31.6%, $p = 0.013$), whereas ICE was used more frequently (56.7% vs 23.6%, $p < 0.001$).

HF patients had significantly longer total procedural times (93.5 (70–141) vs 75 (60–105) min, $p < 0.001$) and fluoroscopy times (19.5 (8.5–32.2) vs 10 (6.4–18) min, $p < 0.001$).

This observation was confirmed in a multivariate linear regression analysis (Table 11 and 12). In the procedural time model (Table 11), HF showed a positive correlation with duration ($\beta = 0.088$, 95% CI 0.022–0.154, $p = 0.009$). Similarly, in the fluoroscopy time model (Table 12), HF remained a significant predictor of longer fluoroscopy use ($\beta = 0.169$, 95% CI 0.077–0.262, $p < 0.001$). General anaesthesia, ICE use, and ablation technology were also strongly associated with longer procedural and fluoroscopy times. The overall model fits were robust ($R^2 = 0.442$ and $R^2 = 0.566$, respectively), with both demonstrating strong explanatory capacity (F-test $p < 0.001$).

The overall rate of procedural complications did not differ significantly between groups (1.7% vs 2.1%, $p = 0.13$).

SECONDARY ENDPOINTS:

EFFICACY:

Table 13 summarizes the secondary endpoint analysis comparing AF recurrences between patients with and without HF.

Patients with HF had a significantly higher rate of follow-up availability (91.7% vs 83.2%, $p = 0.004$) and the proportion of patients followed for at least 12 months (76.4% vs 64.5%, $p = 0.004$) and at least 24 months (41.2% vs 27.0%, $p < 0.001$) was also higher among HF patients. Nevertheless, median follow-up duration did not differ between the two study groups (12 (6.5-24) vs 13 (8-24), $p = 0.54$)

Regarding arrhythmia outcomes, AF recurrence beyond the blanking period occurred significantly more often in the HF group (34.5% vs 19.5%, $p < 0.001$).

The decision to interrupt the rhythm control strategy occurred nearly three times more frequently in the HF group (11.5% vs 3.9%, $p < 0.001$).

The difference between the two groups in terms of AF recurrence rate beyond the blanking period was confirmed by survival analyses using the Kaplan–Meier curve (Figure 3) and log-rank testing ($\chi^2(1) = 9.00$; $p = 0.0027$). Freedom from AF at 12 months was 74.0% in patients without HF and 63.2% in those with HF; at 24 months, the corresponding values were 57.5%

and 50.5%, respectively. In the RMST analysis, patients with HF showed significantly shorter AF-free survival both at 12 months (RMST difference = –1.23 (95% CI –1.98 to –0.48), p = 0.001) and at 24 months (RMST difference = –2.41 (95% CI –4.24 to –0.58), p = 0.010).

In the multivariate Cox regression analysis (Table 14), HF was the only variable significantly associated with late AF recurrence (>3 months) (HR 1.50, 95% CI 1.06–2.13, p = 0.024). However, the global model fit was not statistically significant (LR $\chi^2(5) = 8.89$, p = 0.113), and the proportional hazards tests indicated a time-varying effect for HF (Schoenfeld p = 0.043, log-minus-log plot Figure 8).

When considering the different HF subtypes, the Kaplan–Meier curve (Figure 3) showed different AF-free survival by HF category, which was confirmed by a log-rank test (χ^2 (3) = 16.13; p = 0.0011). At 12 months, AF-free survival was 74.0% for patients without HF, 70.4% for those with HFrEF, 64.1% for HFmrEF, and 53.8% for HFpEF; at 24 months, these values declined to 57.5%, 60.9%, 58.8%, and 27.4%, respectively. Comparing the different types of HF, HFpEF was the only subtype with significantly shorter AF-free survival compared with patients without HF, both at 12 months (RMST difference = –1.96 (95% CI –3.32 to –0.61), p = 0.005) and at 24 months (RMST difference = –5.29 (95% CI –8.32 to –2.26), p = 0.001).

Also, when the multivariate analysis was stratified by HF subtypes (Table 15), HFpEF was the only subtype independently associated with AF recurrence (2.28 (1.44–3.62), p = 0.001). This model demonstrated significant overall fitness (LR $\chi^2(7) = 14.51$, p = 0.043) and no violation of the proportional-hazards assumption (global Schoenfeld p = 0.295, log-minus-log plot Figure 8).

In Weibull proportional hazards models including enrolling centre as a gamma-distributed shared frailty term, the variance component was minimal (θ = 0.012, p = 0.25), and the associations between HF or specific HF categories and AF recurrence remained unchanged (HF HR = 1.51, 95% CI 1.09–2.10, p = 0.014; categorical HF HR = 1.28, 95% CI 1.11–1.47, p = 0.001).

Re-evaluation of the association between HF and AF recurrences beyond 3 months in the MACCE subgroup (418 patients) yielded similar results. In the multivariate Cox analysis, HF was independently associated with late AF recurrence (HR 1.57, 95% CI 1.08–2.29; p=0.019). In the subgroup analysis distinguishing the different types of HF, HFpEF remained the only variable independently associated with recurrences (HR 2.42, 95% CI 1.35–4.33; p=0.003). Both models approached significance (LR χ^2 (4)=8.75, p=0.0675 and LR χ^2 (7)=13.31,

p=0.0649, respectively) and satisfied the proportional-hazards assumption (global Schoenfeld p 0.826 and 0.935, respectively).

MAJOR ADVERSE CARDIOVASCULAR EVENTS SUBANALYSIS:

Table 16 summarizes the comparison of MACCE-outcomes between patients with and without HF.

A significantly higher proportion of HF patients had follow-up data compared with non-HF patients (100% vs 94.0%, p = 0.007). Similarly, patients with HF had at least 12 and 24 months of follow-up more frequently (87.1% vs 75.4%, p = 0.009; and 49.1% vs 36.1%, p = 0.015, respectively). However, total follow-up duration did not differ among groups (13 (8–24) months vs 13 (7–24) months, p = 0.93).

During follow-up, MACCEs occurred more often among HF patients (12.1% vs 1%, p < 0.001). HF–related hospitalizations were more frequent in this group (10.6% vs 0%, p < 0.001), as were cardiac deaths (5.4% vs 0%, p < 0.001) and heart transplantations (2.7% vs 0%, p = 0.005). No significant differences were observed for ACS (1.7% vs 1.1%, p = 0.56) or stroke/TIA events (0.9% vs 0%, p = 0.11).

Median time to the first MACCE did not differ significantly between groups (4 months (2–12) vs 11 months (5–17), p = 0.23).

The difference between the two groups in terms of MACCEs was confirmed by survival analyses using the Kaplan–Meier curve (Figure 5) and log-rank testing (log-rank χ^2 (1) =29.67; p<0.0001). Freedom from MACCEs at 12 months was 99% in patients without HF and 89% in those with HF; at 24 months, the corresponding values were 98% and 83.5%, respectively.

In the RMST analysis, patients with HF showed significantly shorter MACCE-free survival both at 12 months (RMST difference = –0.71 (95% CI −1.172 to −0.242), p = 0.003) and at 24 months (RMST difference = –2.07 (95% CI −3.267 to −0.878), p = 0.001).

In the multivariate Cox regression adjusted for enrolling centre (Table 17), independent predictors of MACCEs were HF (HR 12.13, 95% CI 3.15–46.64; p<0.001), CHA_2DS_2-VA ≥3 (HR 3.31, 1.20–9.15; p=0.021), and lack of rhythm control at follow-up (HR 6.86, 2.03–23.15; p=0.002). The global model fit was significant (LR χ^2 (7) =51.15; p<0.0001), and proportional-hazards assumptions were satisfied (global Schoenfeld p=0.519 log-minus-log plot Figure 9).

When considering the different HF subtypes, the Kaplan–Meier curve (Figure 5) showed a progressive reduction in MACCE-free survival across HF categories, as confirmed by the log-rank test (χ^2 (3) = 50.45; p < 0.0001). At 12 months, MACCE-free survival was 99.1% in patients without HF, 83.2% in those with HFrEF, and 89.8% in those with HFpEF; at 24 months, these values declined to 98.2%, 77.3%, and 79.2%, respectively. Heart failure with mildly reduced ejection fraction (HFmEF) could not be included in the analysis, since no MACCE occurred during follow-up in this group.

The multivariate Cox regression stratified for HF subtypes (Table 18) confirmed that HFrEF (HR 14.89, 95% CI 3.95–56.13; p=0.000), HFpEF (HR 11.07, 2.67–45.83; p=0.001), a CHA_2DS_2-VA >3 (HR 3.53, 1.23–10.12; p=0.019), and evolution to permanent AF/rhythm-control discontinuation at follow up (HR 4.60, 1.39–15.26; p=0.013) were independently associated to MACCE occurence. Proportional hazards were met (global Schoenfeld p=0.361, log-minus-log plot Figure 9) and the model was globally statistically significant (LR χ^2 (6) =54.00; p<0.0001).

The result regarding HF subtypes was also confirmed by the multivariate Cox regression adjusted for enrolling centre (HF subtypes HR 1.7, 95% CI 1.1–2.5; p=0.008). (Table 19)

In the RMST analysis, patients with HFrEF showed significantly shorter MACCE-free survival both at 12 months (RMST difference = –1.22 (95% CI −2.10 to −0.34), p = 0.007) and at 24 months (RMST difference = –3.06 (95% CI −5.16 to −0.96), p = 0.004). Similarly, patients with HFpEF exhibited a reduction in MACCE-free survival at 24 months (RMST difference = –2.70 (95% CI −5.05 to −0.35), p = 0.024), while the difference at 12 months was not statistically significant (p = 0.140).

5. DISCUSSION:

We created a large registry of patients undergoing AF CA using novel technologies, including VGLB, the latest generation cryoballoon, and PFA.

Specifically, we collected the largest reported cohort of patients with HF treated with these ablation systems (180). Compared with patients without HF, the use of novel technologies proved equally safe, although procedures in the HF group required longer procedural (93 vs 75 min) and fluoroscopy time (19.5 vs 10 min).

In a multivariate linear regression, HF emerged as an independent predictor of prolonged procedural and fluoroscopy times (both p<0.001), irrespective of potential confounders known to influence procedural times, including left atrial anatomical variants, ablation technology, and procedural protocol.

Patients with HF present a higher comorbidity burden and a more advanced atrial cardiomyopathy, leading to challenging vascular access and complex cardiac anatomy, with subsequent difficulty during transseptal puncture and catheter manipulation in the left atrium. Furthermore, since HF patients exhibit higher rates of persistent AF and extensive atrial fibrosis, operators may perform additional ablation lesions (left atrial posterior wall isolation, mitral isthmus line, or superior vena cava isolation)[60,61].

The finding of longer procedural duration in patients with HF is consistent with prior evidence[58]. However, the ablation times and complication rates in our HF patients remain favourable compared with those reported in unselected cohorts in the contemporary literature.[47,57,58]

Regarding procedural success, the overall AF-free survival rate in our registry was satisfactory and consistent with contemporary literature.[47,57,58] Patients with HF experienced higher recurrence rates, though these remained comparable to those reported in HF populations treated with radiofrequency or earlier-generation cryoballoon technologies (freedom from AF at 12 months 74.0% vs 63.2%; at 24 months 57.5% vs 50.5%; p=0.0027)[15-26].

HF emerged as an independent predictor of AF recurrence beyond the blanking period, irrespective of other confounders (HR 1.50, p=0.024). However, this finding was based on a multiparametric Cox model with limited statistical significance, and the effect of HF on recurrence was observed mainly in the early months after ablation.

When HF subtypes were analysed separately within the same model (HFrEF, HFmrEF, and HFpEF), results changed substantially. Only HFpEF independently predicted AF recurrences (HR 2.28, p=0.001), and this model demonstrated significant statistical relevance, with the effect of HFpEF on AF recurrences constant over follow-up time.

The recurrence rate among HF patients in our registry did not differ across ablation technologies. Nevertheless, the observational design of our registry, the number of HF patients enrolled, and the absence of standardized protocols for adjunctive ablation in patients treated with PFA limit our ability to compare the effectiveness of specific technologies.

The MACCE rate was low in our registry (freedom from event at 12 and 24 months: 96,3% and 93,9%, respectively). Both HFpEF and HFrEF were confirmed as independent predictors of this outcome during follow-up (global HR 12.13, p<0.001). Furthermore, the decision to interrupt rhythm-control therapy after AF recurrence was also strongly associated with MACCE occurrence (HR 6.86, p=0.002). Although our study lacked a control group of HF patients not undergoing CA, overall MACCE-free survival in our HF cohort remained lower than that reported in the literature for unselected HF populations with concomitant AF (89.0% at 12 months and 98.0% vs 83.5% at 24 months)[3,6,11], and was comparable to the treatment arms of trials comparing CA with conventional technologies versus standard therapy in HF patients. [15-26]

HF and AF are interconnected, each promoting the onset and progression of the other[4-6]. Patients affected by both conditions have a worse clinical course than those with only one condition. However, this relationship may vary depending on the HF phenotype. While HFrEF and HFmrEF share common etiologies primarily affecting the ventricular myocardium, HFpEF represents a distinct pathophysiological entity involving both the atria and ventricles.[7,8]

In HFrEF and HFmrEF, atrial changes are frequently compensatory and evolve more slowly, with AF often appearing later in the disease course[7,8]. Conversely, in HFpEF, atrial pathology develops concomitantly with ventricular remodeling, driven by shared upstream mechanisms such as systemic inflammation, endothelial dysfunction, and microvascular disease. As a result, AF occurs earlier and more frequently, with an aggressive course. Moreover, the loss of atrial contraction has a greater hemodynamic impact in a stiff, preload-dependent ventricle.[7-9]

This pathophysiological mechanism may explain why, in our registry, AF recurrences after ablation were significantly more frequent among HFpEF patients and why this entity—traditionally considered “milder” than HFrEF[3,11]—was associated with MACCEs almost as strongly as HFrEF. The effect was particularly evident among patients who developed AF recurrence beyond the blanking period and were shifted to a permanent AF strategy (HR 4.60, 1.39–15.26, p=0.013).

Our findings highlight the importance of rhythm-control strategies across the entire HF spectrum and the need for tailored treatment in this population. The higher MACCE rate and risk of AF recurrence in specific HF subsets underscore the importance of optimized and comprehensive pre- and post-ablation therapy, selection of ablation technology, consideration of adjunctive substrate modification, and timely intervention.

Future studies should confirm our findings and further explore the optimal procedural strategy—including technology and lesion set selection—for the full spectrum of HF patients with AF, considering that this population continues to grow and remains challenging to manage.

6. STUDY LIMITATIONS:

There was heterogeneity among participating centres in both the number of patients enrolled and the proportion of those with HF. Moreover, adjudication of MACCEs was performed in only three centres, which limited the number of patients available for this analysis and may have introduced selection bias. A difference in follow-up completeness across centres was also evident: more patients with HF had follow-up data available than the rest of the cohort, which could have contributed to differences in event ascertainment.

To address these problems, specific statistical analyses were performed. A Weibull proportional hazards regression model with shared frailty by enrolling centre was used for AF recurrences beyond the blanking period, while a multivariate Cox regression including the enrolling centre as a fixed covariate was applied for MACCEs. The consistency of results across these approaches suggested that adjusting for enrolling centre did not materially alter the observed associations, partially mitigating concerns about bias arising from heterogeneous follow-up structures. Furthermore, the subgroup of patients included in the MACCE analysis had baseline characteristics comparable to those of the overall registry, as indicated by standardized differences.

For AF recurrences, unequal follow-up between HF and non-HF patients was addressed using complementary time-to-event methods — multivariate Cox regression, RMST analysis, and Kaplan–Meier survival estimates —which accounted for varying observation periods.

Nevertheless, both selection bias (related to inter-center heterogeneity in patient numbers) and information bias (related to differences in follow-up intensity and event ascertainment between HF and non-HF patients) cannot be entirely ruled out. Finally, the limited number of MACCE events and the relatively small sample size reduce the study's statistical power.

7. CONCLUSIONS:

New-generation technologies are a valid option for CA of AF in patients with HF, offering excellent safety, satisfactory procedural times, and recurrence rates comparable to those of standard technologies.

Both HFpEF and HFrEF emerged as independent predictors of MACCEs during post-ablation follow-up. However, only HFpEF was significantly associated with arrhythmic recurrences beyond the blanking period, and transition to a permanent AF management strategy during follow-up was an additional independent predictor of MACCEs.

These findings require validation in larger, randomized studies and underscore the need to improve and personalize rhythm-control and ablation strategies across the full spectrum of HF.

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9. TABLES

Table 1. Baseline Characteristics

	Patients with available information	
Age (years, mean ± SD)	1047	63.4 ± 10.6
Female sex (n (%))	1047	327 (31.2%)
BMI (kg/m², mean ± SD)	876	27.2 ± 4.3
Obesity (n (%))	876	216 (24.6%)
AF type	1047	
Paroxysmal (n (%))		657 (62.8%)
Persistent (n (%))		354 (33.8%)
Long-standing persistent (n (%))		36 (3.4%)
AF duration (months, median (IQR))	656	28 (9–80)
CHA_2DS_2-VA score	1047	
CHA_2DS_2-VA score 0 (n (%))		182 (17.4%)
CHA_2DS_2-VA score 1 (n (%))		269 (25.7%)
CHA_2DS_2-VA score 2 (n (%))		236 (22.5%)
CHA_2DS_2-VA score 3 (n (%))		183 (17.5%)
High risk CHA_2DS_2-VA score ≥4 (n (%))		177 (16.9%)
Creatinine (mg/dL, median (IQR))	572	0.9 (0.8–1.04)
eGFR CKD-EPI (mL/min/1.72 m², mean ± SD)	572	80.7 ± 19.7
Heart failure (n (%))	1047	180 (17.2%)

Abbreviations: AF = atrial fibrillation; BMI = body mass index; CHA2DS2-VA = Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years IQR = interquartile range; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; IQR = interquartile range; SD = standard deviation.

Table 2. Echocardiographic Characteristics

	Patients with available information	
LVEF (%; median (IQR))	827	55 (53–60)
Left atrial enlargement — any (n (%))	929	684 (73.6%)
Left atrial enlargement — mild (n (%))		158 (24.3%)
Left atrial enlargement — moderate (n (%))		161 (24.8%)
Left atrial enlargement — severe (n (%))		330 (50.8%)

Abbreviations: LVEF = left ventricular ejection fraction; LAE = left atrial enlargement; IQR = interquartile range.

Table 3. Heart Failure and Structural Heart Disease

Heart failure, n (%)	180 (17.2)
HFrEF, n (%)	84 (46.7)
HFmEF, n (%)	44 (24.4)
HFpEF, n (%)	52 (28.9)
Coronary artery disease, n (%)	47 (26.1)
Valvular/congenital heart disease, n (%)	12 (6.6)
Dilated/hypokinetic non-dilated/arrhythmogenic CMP, n (%)	36 (20.0)
Amyloidosis, n (%)	1 (0.6)
Hypertrophic CMP, n (%)	16 (8.9)
Tachycardia-induced cardiomyopathy, n (%)	45 (25.0)
Hypertensive heart disease, n (%)	14 (7.8)

Abbreviations: HFrEF = heart failure with reduced ejection fraction; HFmEF = heart failure with moderatly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; CMP = cardiomyopathy.

Table 4. Distribution of Heart Failure by Enrolling Center

.

Enrolling Center num	HF = 0	HF = 1	Total
1	152 (62.81%)	90 (37.19%)	242
2	106 (84.13%)	20 (15.87%)	126
3	44 (88.00%)	6 (12.00%)	50
4	18 (90.00%)	2 (10.00%)	20
5	77 (86.52%)	12 (13.48%)	89
6	44 (89.80%)	5 (10.20%)	49
7	336 (89.36%)	40 (10.64%)	376
8	30 (93.75%)	2 (6.25%)	32
9	5 (71.43%)	2 (28.57%)	7
10	41 (97.62%)	1 (2.38%)	42
11	14 (100.00%)	0 (0.00%)	14
Total	867 (82.81%)	180 (17.19%)	1047

Pearson Chi² = 96.40; Prob = 0.0000

Table 5. Procedural Characteristics

	Patients with available information	
Procedure time (min; median (IQR))	1033	75 (60–111)
Fluoroscopy time (min; median (IQR))	1012	10.6 (6.7–20.2)
Procedural sedation	859	
General anesthesia (n (%))		256 (29.8%)
Deep sedation (n (%))		603 (70.2%)
Procedural Echo guidance	859	
TEE guidance (n (%))		135 (15.7%)
ICE guidance (n (%))		255 (29.7%)
No echo guidance (n (%))		469 (54.6%)
Ablation technology	1047	
Visually guided laser balloon (n (%))		597 (57.0%)
Pulsed-field ablation (n (%))		429 (40.6%)
Cryoballoon (n (%))		21 (2.0%)
Variant anatomy — any (n (%))	1032	150 (14.5%)
Middle pulmonary vein (n (%))		44 (29.3%)
Common ostium (n (%))		91 (60.7%)
Both (n (%))		15 (10.0%)
Procedural complications — any (n (%))	1047	20 (1.9%)
Phrenic nerve injury, n (%)		7 (0.7)
Cardiac Perforation/Tamponade, n (%)		4 (0.4)
Stroke/TIA, n (%)		4 (0.4)
Vascular access complications, n (%)		5 (0.5)
Death, Atrio-esophageal fistula, PV Stenosis n (%)		0 (0)

Abbreviations: PFA = pulsed-field ablation; TEE = transesophageal echocardiography; ICE = intracardiac echocardiography; PV = pulmonary vein; IQR = interquartile range.

Table 6. Follow-up and Atrial Fibrillation Recurrences

Patients with follow up	886 (84.6)
Follow-up duration (months; median (IQR))	13 (7–24)
Followed ≥12 months (n (%))	591 (66.7)
Followed = 24 months (n (%))	263 (29.7%)
AF recurrence ≤3 months (n (%))	115 (13.0)
AF recurrence >3 months (n (%))	198 (22.3)
Paroxysmal, n (%)	113 (57)
Persistent, n (%)	85 (42.9)
Permanent AF with rhythm-control withdrawal (n (%))	47 (5.3)
Redo procedure (n (%))	33 (4.7%)
Ablate and Pace, n (5)	2 (0.2)
Typical atrial flutter during follow-up (n (%))	27 (3.0%)

Abbreviations: AF = atrial fibrillation; IQR = interquartile range.

Table 7. Baseline Characteristics — MACCEs-Reporting Centers vs. Others

	Other Centers	MACCEs-reporting Centers	Std. Diff.
Age at Procedure, mean ± SD (years)	64.5 ± 10.7	61.9 ± 10.3	0.24
Male sex, %	427 (68)	293 (65)	0.05
Hypertension, n (%)	443 (70.4)	234 (50.6)	0.303
Diabetes, n (%)	99 (11.2)	47 (15.7)	0.132
Coronary Artery Disease, n (%)	98 (11.2)	47 (15.6)	0.127
CKD-EPI eGFR, mean ± SD (mL/min)	82.96 ± 18.0	82.03 ± 18.1	0.05
Obesity, n (%)	172 (28.7)	44 (16.7)	0.29
Heart Failure, n (%)	64 (10.2)	116 (27.8)	**0.46**
CHA_2DS_2-VASc ≥ 4, n (%)	143 (22.7)	34 (8.1)	**0.41**
Left Ventricular EF (mean ± SD, %)	55.82 ± 11.24	54.37 ± 7.07	0.15
Anatomic variant, n (%)	79 (12.6)	71 (17.6)	0.14
Follow-up duration, median (IQR), months	13.7 (8.2)	15.2 (7.4)	0.19
Follow-up availability, n (%)	486 (77.3)	400 (95.7)	**0.55**

Abbreviations: CHA2DS2-VA = Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years; CKD-EPI = chronic kidney disease epidemiology collaboration; EF = ejection fraction; eGFR = estimated glomerular filtration rate; MACCE = major adverse cardiocerebrovascular event; IQR = interquartile range; SD = standard deviation.

Table 8. Major Adverse Cardiocerebrovascular Events (MACCEs)

Patients with available information	400
Any MACCE (n (%))	17 (4.2)
Median Time to MACCE, (months, median (IQR))	5 (2-12)
Heart failure hospitalisation (n (%))	12 (3)
Acute coronary syndrome (n (%))	3 (1.2%)
Stroke/TIA (n (%))	1 (0.2%)
Cardiovascular death (n (%))	6 (1.5%)
Heart transplantation (n (%))	3 (1.2%)
Hospitalization for cardiovascular cause (n (%))	31 (7.7%)
Emergency/unscheduled visits (n (%))	68 (17.0%)

Abbreviations: MACCE = major adverse cardiocerebrovascular event; TIA = transient ischemic attack; IQR = interquartile range.

Table 9. Comparison of Baseline Features: HF vs No-HF

	HF	No HF	P Value
Age, Mean±SD (years)	63.4 ± 10.5	63.3 ± 10.6	0.46
Female sex, n (%)	48 (26.7)	279 (32.2)	0.14
Body mass index, Mean±SD	28.2 ± 5.2	27.0 ± 4.0	**0.004**
Obesity, n (%)	47 (36.4)	169 (23.1)	**0.012**
Atrial fibrillation type			**<0.001**
Paroxysmal, n (%)	91 (50.7)	566 (65.3)	
Persistent, n (%)	74 (41.1)	280 (32.3)	
Long standing persistent, n (%)	15 (8.3)	21 (2.4)	
Atrial fibrillation duration, median (IQR) (months)	35 (11–109)	26 (8–72)	**<0.001**
CHA2DS2-VA score, median (IQR)	2 (1–4)	2 (1–3)	**<0.001**
High-risk CHA2DS2-VA (≥4), n (%)	49 (27.2)	128 (14.8)	**<0.001**
Hypertension, n (%)	116 (64.4)	561 (64.7)	0.94
Dyslipidemia, n (%)	114 (63.3)	500 (57.7)	0.16
Diabetes, n (%)	40 (22.2)	106 (12.2)	**<0.001**
Glomerular filtration rate (CKD-EPI), Mean±SD (mL/min/1.72 m²)	75.7 ± 21.3	84.2 ± 16.6	**<0.001**
Ejection fraction, median (IQR) (%)	42 (35–54)	58 (53–60)	**<0.001**
Left atrial enlargement, n (%)	136 (83.4)	548 (71.5)	**0.018**
Mild, n (%)	23 (17.0)	135 (26.3)	
Moderate, n (%)	31 (23.0)	130 (23.5)	
Severe, n (%)	81 (60.0)	249 (48.4)	

Abbreviations: CHA2DS2-VA = Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years; CKD-EPI = chronic kidney disease epidemiology collaboration; HF = heart failure; EF = ejection fraction; SD = standard deviation; IQR = interquartile range.

Table 10. Procedural Data and Primary Endpoint: HF vs No-HF

	HF	No-HF	p value
Total procedural time, median (IQR), min	93.5 (70–141)	75 (60–105)	**<0.001**
Total fluoroscopy time, median (IQR), min	19.5 (8.5–32.2)	10 (6.4–18)	**<0.001**
Ablation technology			**0.036**
Laser balloon, n (%)	99 (55)	498 (57.4)	
Pulsed field ablation, n (%)	73 (40.6)	356 (41.1)	
Cryoballoon, n (%)	8 (4.4)	13 (1.5)	
Anesthesia during ablation			**0.013**
General anesthesia, n (%)	34 (21.7)	222 (31.6)	
Deep sedation, n (%)	123 (78.3)	480 (68.4)	
Echo-guidance			
No echo-support, n (%)	45 (28.7)	424 (60.4)	**<0.001**
TE, n (%)	23 (14.7)	112 (15.9)	0.16
ICE, n (%)	89 (56.7)	166 (23.6)	**<0.001**
Other arrhythmias treated, n (%)	19 (11.6)	67 (9)	0.16
Variant anatomy, n (%)	31 (17.7)	119 (13.9)	0.19
Procedural complications, n (%)	3 (1.7)	17 (1.9)	0.13
Phrenic nerve injury, n (%)	0 (0)	7 (0.8)	1.4
Cardiac perforation/tamponade, n (%)	1 (0.6)	3 (0.3)	0.17
Stroke/TIA, n (%)	1 (0.6)	3 (0.3)	0.17
Vascular access complications, n (%)	1 (0.6)	4 (0.5)	0.06
Death, atrio-esophageal fistula, PV stenosis, n (%)	0 (0)	0 (0)	1.0

Abbreviations: HF = heart failure. ICE = intracardiac echocardiography; IQR = interquartile range. PV = pulmonary vein; TE = transesophageal echocardiography; TIA = transient ischaemic attack.

Table 11. Multivariate Linear Regression — Total Procedural Time

	β (Coeff.)	95% CI	p-value
Heart failure	0.088	0.022 – 0.154	**0.009**
Anatomical variant	0.061	-0.011 – 0.134	0.096
General anaesthesia	0.206	0.147 – 0.266	**<0.001**
ICE	0.499	0.429 – 0.569	**<0.001**
CHA_2DS_2-VASc	0.059	-0.007 – 0.124	0.080
Technology	0.220	0.163 – 0.278	**<0.001**

N = 836 | R^2 = 0.442 | F-test = 109.453 (p < 0.001) | AIC = 625.2 | BIC = 658.3

Abbreviations: CI = confidence interval. ICE = intracardiac echocardiography; CHA2DS2-VA = Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years.

Table 12. Multivariate Linear Regression — Total Fluoroscopy Time

	β (Coeff.)	95% CI	p-value
HF	0.169	0.077 – 0.262	**<0.001**
Anatomical variant	-0.006	-0.108 – 0.096	0.908
General anaesthesia	0.410	0.289 – 0.531	**<0.001**
ICE	1.041	0.940 – 1.142	**<0.001**
CHA_2DS_2-VASc	0.040	-0.053 – 0.132	0.399
Technology	0.250	0.156 – 0.345	**<0.001**

N = 829 | R^2 = 0.566 | F-test = 153.049 (p < 0.001) | AIC = 1168.6 | BIC = 1206.4

Abbreviations: CI = confidence interval. ICE = intracardiac echocardiography; CHA2DS2-VA = Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years.

Table 13. Secondary Endpoint — Atrial Fibrillation Recurrences: Heart Failure vs No-HF

	HF	No-HF	p Value
Patients with Follow-up, n (%)	165 (91.7)	721 (83.2)	**0.004**
At Least 12 Months, n (%)	130 (76.4)	465 (64.5)	**0.004**
At Least 24 Months, n (%)	68 (41.2)	195 (27)	**< 0.001**
Median Follow-up Duration, median (IQR), months	13 (8-24)	12 (6.5-24)	0.54
AF Recurrence ≤3 Months post-Ablation, n (%)	35 (21.2)	80 (11.1)	**< 0.001**
AF Recurrence >3 Months after Ablation, n (%)	57 (34.5)	141 (19.5)	**< 0.001**
Paroxysmal, n (%)	27 (47.4)	86 (61)	0.052
Persistent, n (%)	30 (52.6)	55 (39)	0.052
Permanent AF and Interruption of Rhythm Control, n (%)	19 (11.5)	28 (3.9)	**< 0.001**
Median Time to AF Recurrence >3 Months, median (IQR), months	6 (4-9)	6 (4.7-10)	0.29
Redo Procedure, n (%)	10 (6.6)	32 (4.4)	0.38

HF, heart failure. AF, atrial fibrillation; TE, transoesophageal echocardiography; ICE, intracardiac echocardiography; p5e, median; IQR, interquartile range.

Table 14. Multivariate Cox Regression —Atrial Fibrillation Recurrences

	HR (95% CI)	p-value
Heart failure (HF)	1.50 (1.06–2.13)	**0.024**
Anatomical variant	1.09 (0.77–1.56)	0.613
CHA_2DS_2-VA ≥4	1.03 (0.69–1.56)	0.872
Obesity	1.23 (0.87–1.74)	0.238
Technology	1.08 (0.77–1.51)	0.659

n = 652. Global model fit: LR $\chi^2(5) = 8.89$, p = 0.113. Global Schoenfeld test: p = 0.043.

Abbreviations: HR = hazard ratio; CI = confidence interval.

Table 15. Multivariate Cox Regression — Atrial Fibrillation Recurrences (Heart Failure Categories)

	HR (95% CI)	p-value
HFrEF	1.05 (0.59–1.87)	0.865
HFmEF	1.26 (0.69–2.30)	0.447
HFpEF	2.28 (1.44–3.62)	**0.001**
Anatomical variant	1.11 (0.78–1.58)	0.562
CHA_2DS_2-VA ≥4	1.08 (0.71–1.62)	0.724
Obesity	1.23 (0.87–1.75)	0.234
Technology	1.07 (0.76–1.50)	0.705

n = 652. Global model fit: LR $\chi^2(7) = 14.51$, p = 0.043. Global Schoenfeld test: p = 0.16.

Abbreviations: HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with moderately reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction.HR = hazard ratio; CI = confidence interval.

Table 16. Secondary Endpoints — Major Adverse Cardiovascular Events: Heart Failure vs. No Heart Failure

	HF	No-HF	p Value
Patients with follow-up, n (%)	116 (100.00%)	284 (94%)	**0.007**
At least 12 months, n (%)	101 (87.1%)	214 (75.3%)	**0.009**
At least 24 months, n (%)	57 (49.1%)	109 (36.1%)	**0.015**
Total follow-up duration, median (IQR), months	13 (8–24)	13 (7–24)	0.93
Time to first MACCE, median (IQR), months	4 (2–12)	11 (5–17)	0.23
MACCEs, n (%)	14 (12.1%)	3 (1%)	**< 0.001**
Heart failure hospitalization, n (%)	12 (10.6%)	0 (0.00%)	**< 0.001**
Acute coronary syndrome, n (%)	2 (1.7%)	3 (1%)	0.56
Stroke/TIA, n (%)	1 (0.9%)	0 (0.00%)	0.11
Cardiac death, n (%)	6 (5.4%)	0 (0.00%)	**< 0.001**
Heart transplant, n (%)	3 (2.7%)	0 (0.00%)	**0.005**
Cardiovascular hospitalization, n (%)	19 (16.4%)	12 (4.2%)	**< 0.001**
Unscheduled ER/clinic visit for CV causes, n (%)	32 (27.6%)	36 (12.7%)	**< 0.001**

HF = heart failure; CV = cardiovascular; ER = emergency room; IQR = interquartile range; MACCEs = major adverse cardiovascular and cerebrovascular events. TIA = transient ischaemic attack.

Table 17. Multivariate Cox Regression — Major Adverse Cardiocerebrovascular Events

	HR (95% CI)	p-value
Heart failure	12.13 (3.1–46.6)	**<0.001**
CHA_2DS_2-VA ≥3	3.31 (1.2–9.1)	**0.021**
AF type	0.9 (0.4–1.9)	0.72
AF recurrence >3 months	1.3 (0.4–4.3)	0.066
Interruption of Rhythm Control	6.9 (2.0–23.1)	**0.002**
Enrolling centre	5.1 (1.2–21.8)	**0.029**

n = 400. Global model fit: LR $\chi^2(5) = 51.15$, $p < 0.001$. Global Schoenfeld test: p = 0.519.

Abbreviations: AF = atrial fibrillation; HR = hazard ratio; CHA2DS2-VA = Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years; HR = hazard ratio; CI = confidence interval.

Table 18. Multivariate Cox Regression — Major Adverse Cardiovascular and Cerebrovascular Events

Heart Failure Categories

	HR (95% CI)	p-value
HFrEF	14.89 (3.9–56.1)	**<0.001**
HFmrEF	–	–
HFpEF	11.07 (2.67–45.83)	**0.001**
CHA_2DS_2-VA ≥3	3.53 (1.23–10.12)	**0.019**
AF type	1.03 (0.50–2.12)	0.934
Interruption or Rhythm Control	4.60 (1.39–15.26)	**0.013**
AF recurrence >3 months	1.37 (0.42–4.46)	0.603

n = 400. Global model fit: LR $\chi^2(6) = 54.00$, $p < 0.001$. Global Schoenfeld test: p = 0.361.

Abbreviations: AF = atrial fibrillation; CHA2DS2-VA = Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years; CI = confidence interval. HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with moderately reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio.

Table 19. Multivariate Cox Regression — Major Adverse Cardiovascular and Cerebrovascular Events

Heart Failure Categories (Adjusted for Enrolling Centre)

	HR (95% CI)	p-value
HF category (overall)	1.7 (1.1–2.5)	**0.008**
CHA_2DS_2-VA ≥3	4.4 (1.6–12.0)	**0.004**
Lack of rhythm control at follow-up	5.8 (1.7–19.1)	**0.004**
AF type	1.1 (0.5–2.4)	0.767
AF recurrence >3 months	1.2 (0.4–4.1)	0.721
Enrolling centre	2.7 (0.7–11)	0.164

n = 400. Global model fit: LR $\chi^2(6) = 39.59$, $p < 0.001$. Global Schoenfeld test: $p = 0.289$.

Abbreviations: AF = atrial fibrillation; CHA2DS2-VA = Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years; CI = confidence interval. HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with moderately reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio.

10. FIGURE LEGEND:

Figure 1: ESC 2021 HF guidelines algorithm for management of AF in patients with HFrEF[11].

Figure 2: Trials comparing CA to other forms of conventional therapy in patients with HFrEF.

Figure 3: Structure of the catheter of the novel Cryoballoon (PolarX (Boston Scientific)), PFA (Farapulse, Farawave, middle), and VGLB ablation (HeartLight X3, Heartlight, right)[43,45,46].

Figure 4: Kaplan-Meier survival curve for atrial fibrillation recurrences >3 months after ablation.

Figure 5: Kaplan-Meier survival curve for Major Adverse Cardiocerebrovascular Events.

Figure 6: Left: Kaplan-Meier survival curve for atrial fibrillation recurrences >3 months after ablation in relation to the presence of heart failure. Right: Kaplan-Meier survival curve in relation to heart failure subtype.

HF = heart failure. HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with moderately reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction.

Figure 7: Left: Kaplan-Meier survival curve for Major Adverse Cardiocerebrovascular Events in relation to the presence of heart failure. Right: Kaplan-Meier survival curve in relation to heart failure subtype.

HF = heart failure. HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with moderately reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction.

Figure 8: Left: Log-minus-log survival plot for atrial fibrillation recurrences according to the presence of heart failure. Right: Log-minus-log survival plot for atrial fibrillation recurrences in relation to heart failure subtype.

HF = heart failure. HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with moderately reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction.

Figure 9: Left: Log-minus-log survival plot for Major Adverse Cardiocerebrovascular Events according to the presence of heart failure. Right: Log-minus-log survival plot for Major Adverse Cardiocerebrovascular Events recurrences in relation to heart failure subtype.

HF = heart failure. HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with moderately reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction.

11. FIGURE:

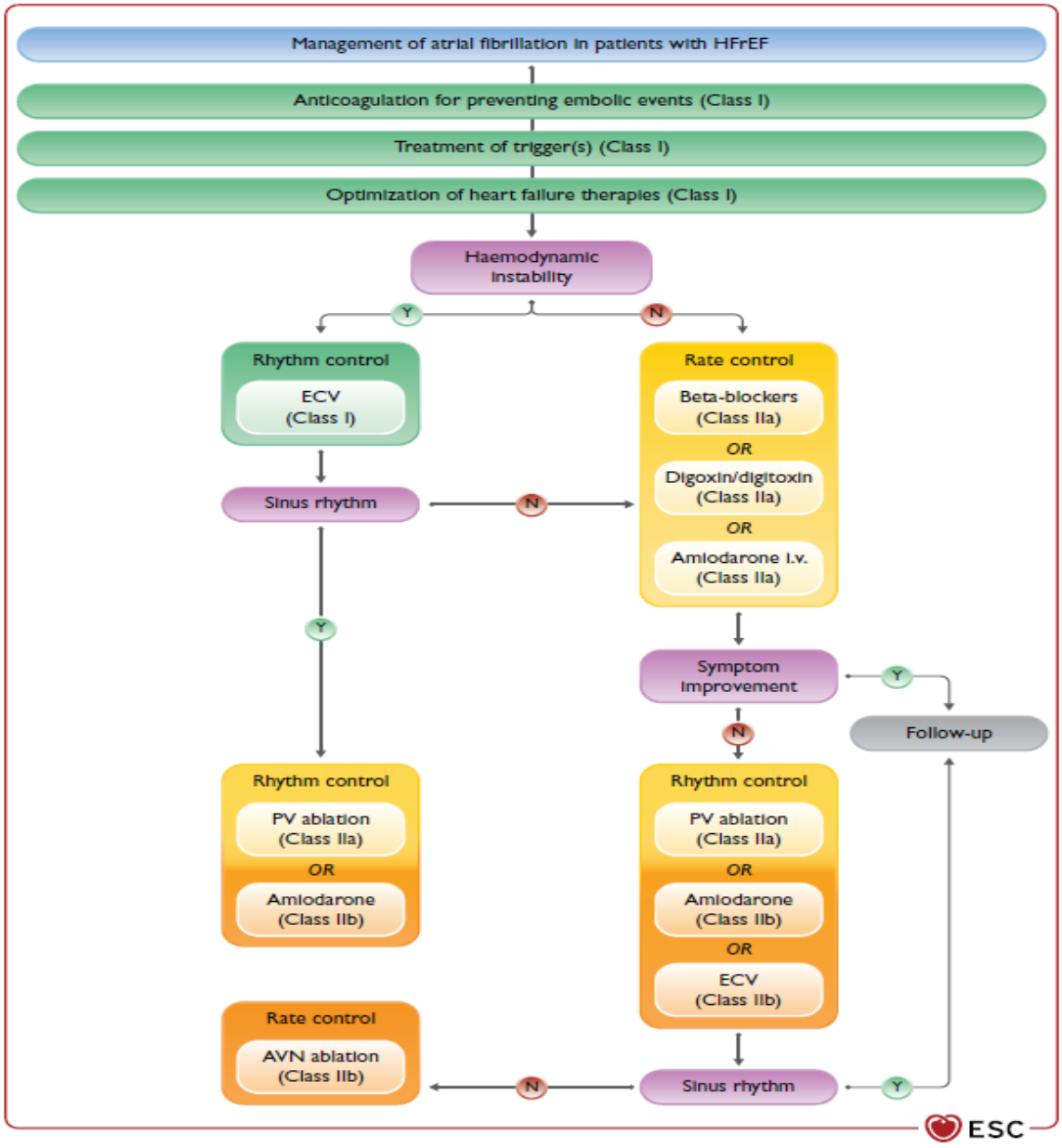

Figure 1

Study	Sample size, n	AF/device	Comparison arm	Follow-up, months	Primary end point	Primary results
PABA-CHF (20)	81	Paroxysmal, Persistent	Ablation vs AVN ablation with biventricular pacing	6	Composite of LVEF, 6MWD, and MLWHF score	CA was superior to AVN ablation with biventricular pacing.
MacDonald et al (12)	41	Persistent	CA vs rate control	6	LVEF change with CMR	No significant differences between treatment groups.
ARC-HF (13)	52	Persistent	CA vs rate control	12	Peak VO2	CA improved peak VO2.
CAMTAF (14)	50	Persistent	CA vs rate control	12	LVEF change	CA improved LV function compared with rate control.
AATAC (16)	203	Persistent/ ICD, CRT-D	CA vs amiodarone	36	AF recurrence	Ablation was superior to amiodarone in terms of rhythm control and improvement in LV dysfunction.
CAMERA-MRI (15)	68	Persistent	CA vs rate control	6	LVEF change	Ablation resulted in improvement in LVEF.
CASTLE-AF (17)	363	Persistent/ ICD, CRT-D	CA vs medical therapy (rate control or AADs)	60	Composite of all-cause mortality and HF hospitalization	CA was superior to conventional medical treatment of either rate or rhythm control.
AMICA (18)	202	Persistent, Long-Standing Persistent	CA vs medical treatment	12	LVEF change	No significant differences between treatment groups.
RAFT-AF (19)	411	Paroxysmal, Persistent	CA vs rate control	24	Composite of all-cause mortality and all HF events	No significant differences between treatment groups

Figure 2

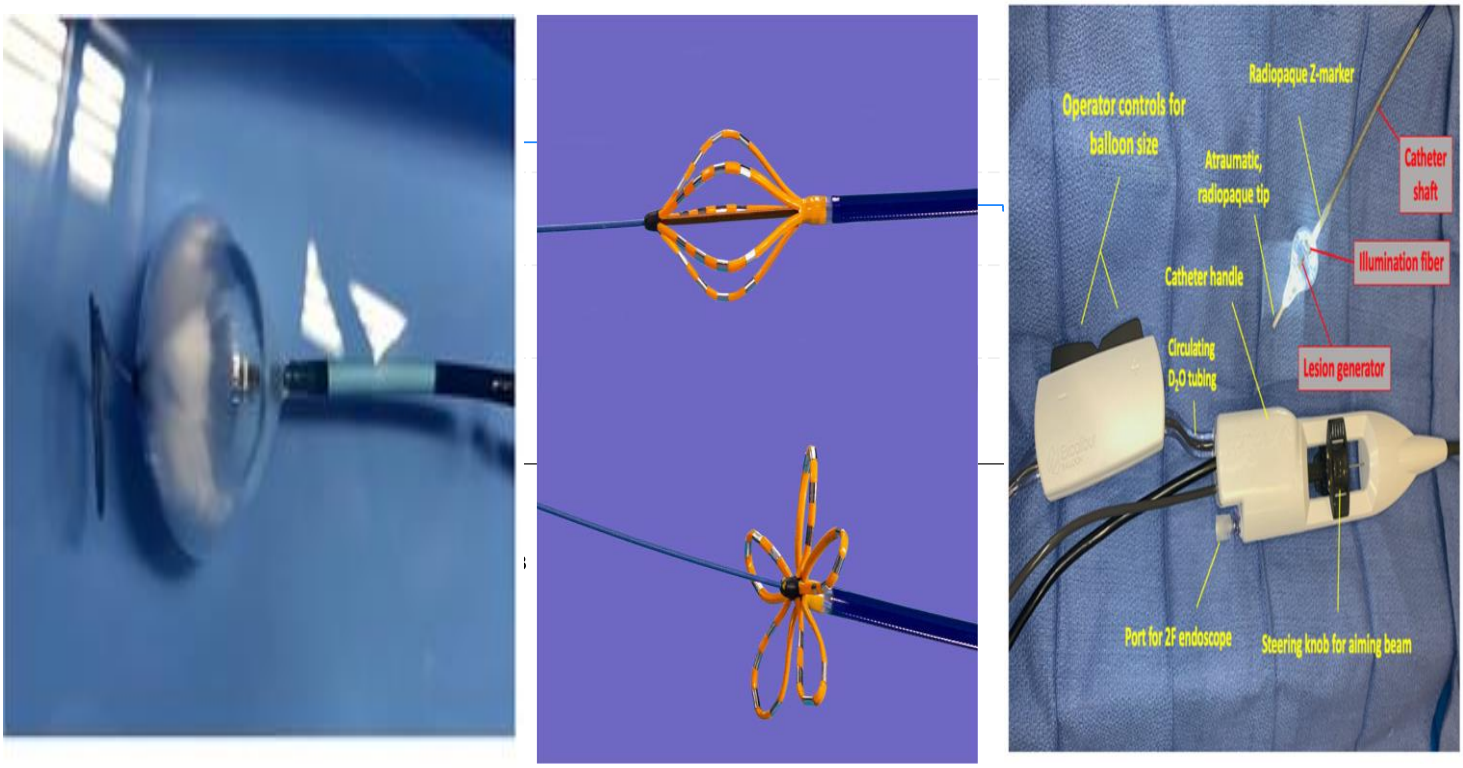

Figure 3

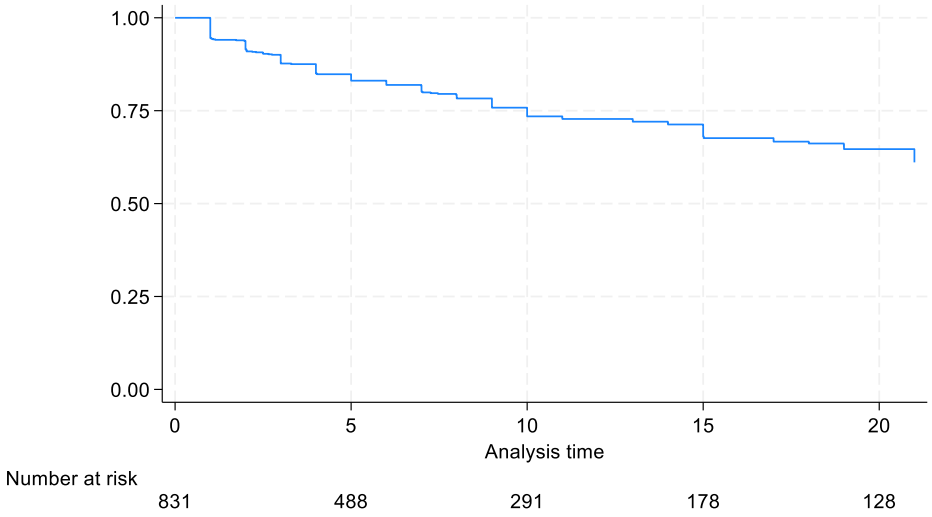

Figure 4

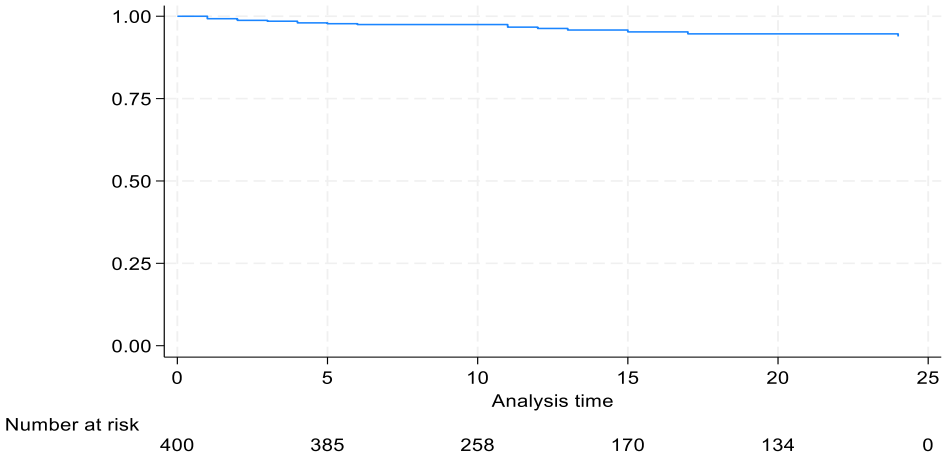

Figure 5

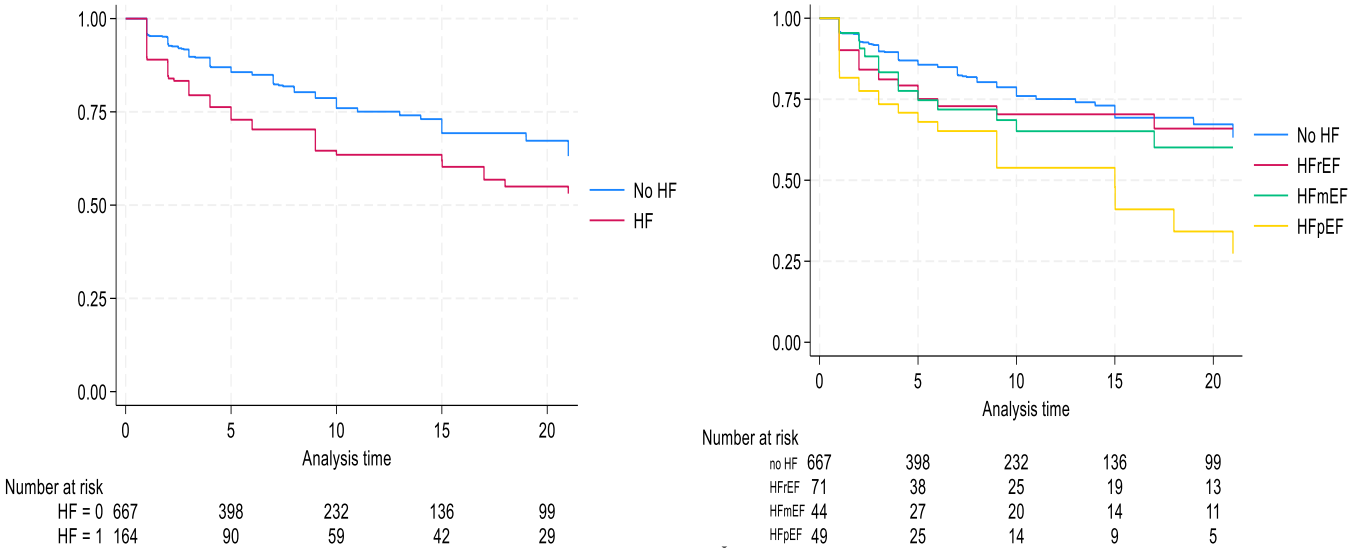

Figure 6

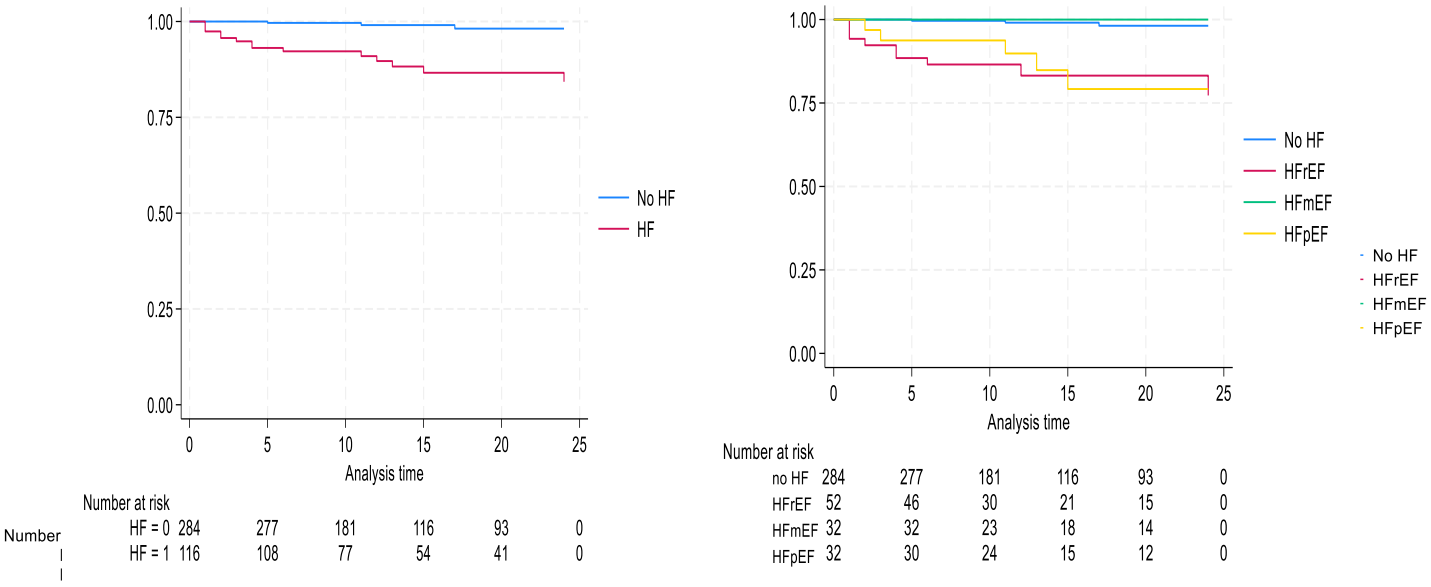

Figure 7

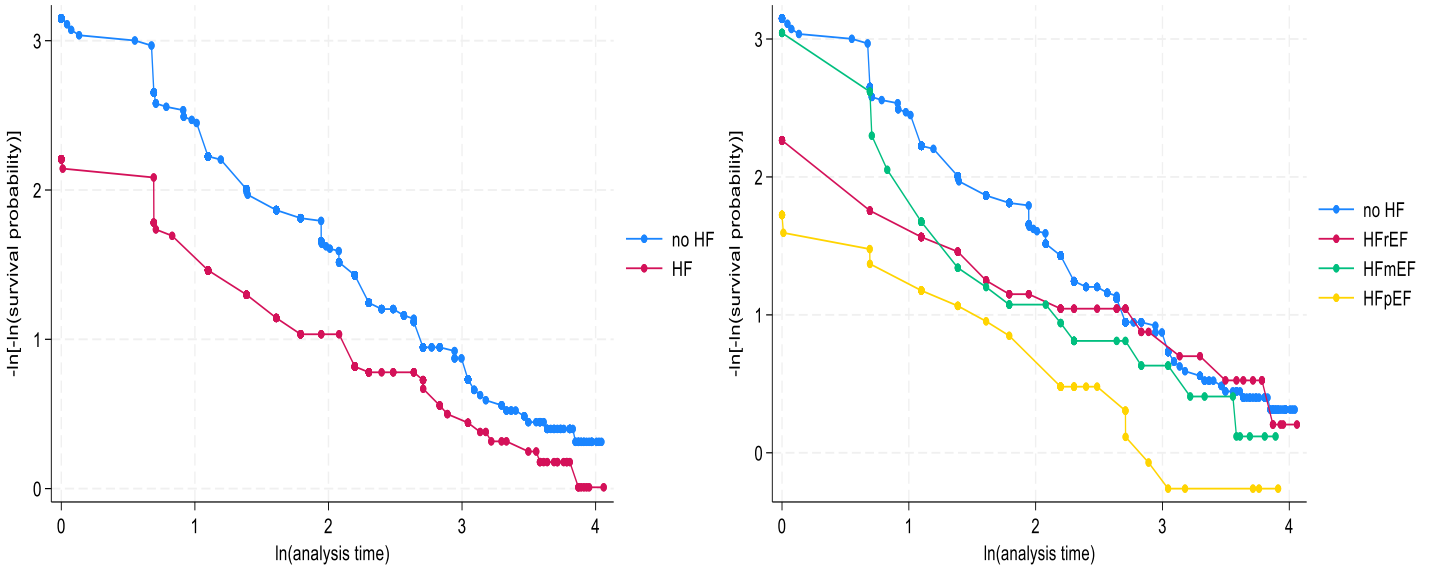

Figure 8

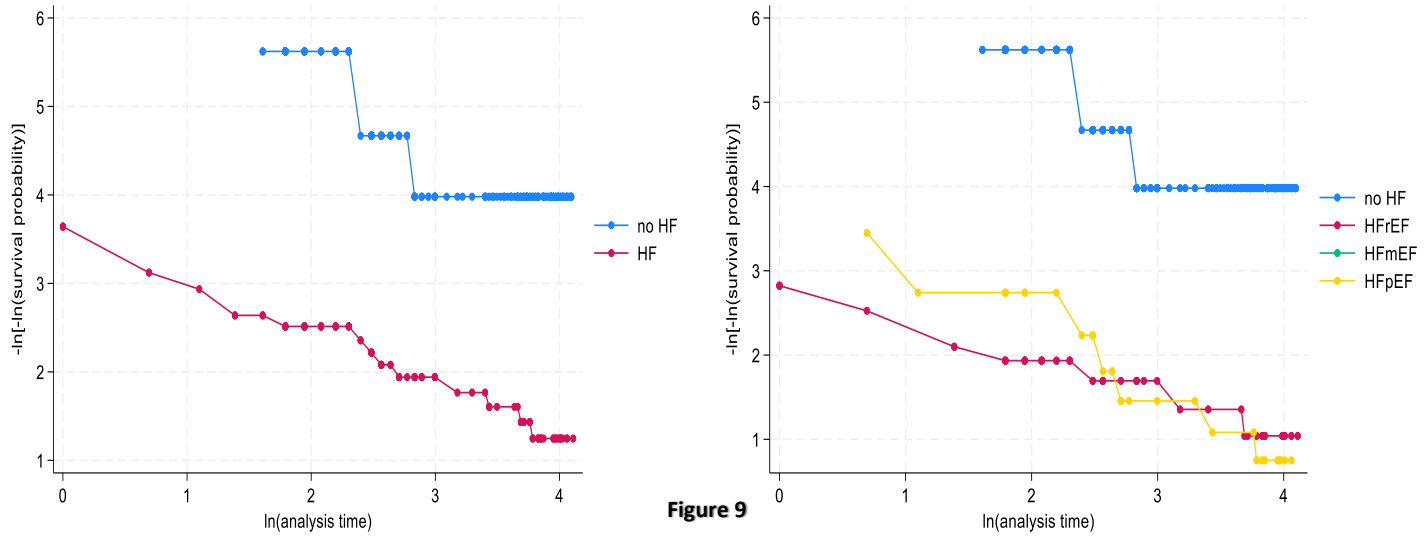

Figure 9