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Cryoballoon Versus Radiofrequency Ablation In Persistent Atrial Fibrillation: Current Evidence And Predictors Of Recurrence

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ABSTRACT

Background: Persistent atrial fibrillation (AF) remains one of the most challenging arrhythmia subtypes to treat effectively. Catheter ablation has evolved as a cornerstone of rhythm-control therapy, with radiofrequency ablation (RFA) and cryoballoon ablation (CBA) being the two most widely adopted energy sources. Although both modalities aim to achieve durable pulmonary vein isolation (PVI), their relative efficacy, procedural performance, and predictors of recurrence in persistent AF continue to be debated.

Objective: To summarize and critically appraise the current evidence comparing CBA and RFA in persistent AF, emphasizing procedural characteristics, clinical outcomes, and independent predictors of arrhythmia recurrence.

Methods: A comprehensive review of randomized trials, observational studies, and meta-analyses published between 2010 and 2025 was performed, focusing on comparative outcomes between CBA and RFA in persistent AF.

Results: Both modalities achieve comparable arrhythmia-free survival at 12 months. CBA consistently demonstrates shorter procedure times and a simpler workflow but greater fluoroscopy exposure and contrast use. Predictors of recurrence include long-standing AF (>12 months), early recurrence during the blanking period, and markers of left atrial remodeling.

Conclusions: CBA and RFA provide equivalent efficacy for rhythm control in persistent AF. Early ablation, attention to atrial substrate, and close rhythm monitoring during the blanking period are key determinants of durable success. Emerging technologies such as pulsed-field ablation and imaging-guided substrate assessment may refine future strategies.

KEYWORDS: Atrial fibrillation; cryoballoon ablation; radiofrequency ablation; persistent AF; predictors of recurrence; electrophysiology; catheter ablation; outcomes.

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INTRODUCTION

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia worldwide and a major contributor to cardiovascular morbidity and mortality. Its prevalence continues to rise, affecting more than 33 million individuals globally and contributing substantially to the burden of stroke, heart failure, and all-cause mortality **[1]**. Persistent AF, defined as continuous AF lasting longer than seven days or requiring cardioversion, represents a more advanced disease stage characterized by structural remodeling, fibrosis, and electrical heterogeneity **[2,3]**. Achieving durable rhythm control in this population remains challenging despite advances in medical and interventional therapy **[4]**.

Catheter ablation is a cornerstone of rhythm-control management for symptomatic AF refractory to antiarrhythmic drugs **[4,5]**. The primary procedural goal is pulmonary vein isolation (PVI), based on the established role of pulmonary vein triggers in AF initiation **[4]**. Radiofrequency ablation (RFA) and cryoballoon ablation (CBA) are the two principal ablation modalities, each with distinct advantages and limitations **[5]**.

RFA delivers point-by-point radiofrequency energy using electroanatomic mapping, allowing precise lesion creation and substrate modification **[4,5]**. However, the technique is more operator-dependent and requires longer procedure time **[6]**. CBA utilizes a single-shot balloon system delivering cryothermal energy, enabling circumferential PVI with shorter procedure times and improved workflow reproducibility **[6,7]**. Second-generation cryoballoons have enhanced lesion durability and narrowed performance differences between the two modalities **[6,10,11]**.

In paroxysmal AF, trials such as **FIRE AND ICE** demonstrated the non-inferiority of CBA compared with RFA **[6]**. However, persistent AF represents a more complex substrate due to progressive fibrosis and non-pulmonary vein triggers, limiting direct extrapolation from paroxysmal AF data. Recent evidence from the STOP Persistent AF, CRRF-PeAF, and NO-PERSAF trials suggests that CBA achieves outcomes comparable to RFA in persistent AF **[7–9]**.

Predictors of recurrence after ablation include long-standing AF (>12 months), left atrial enlargement, and early recurrence during the 90-day blanking period **[16]**. These reflect underlying atrial remodeling and play a major role in the long-term durability of ablation regardless of energy modality **[16]**. Early identification and management of such predictors may improve patient selection and procedural success **[17,18]**.

Given the expanding evidence comparing CBA and RFA in persistent AF, this review synthesizes data from randomized trials, registries, and meta-analyses, integrates real-world observations, and highlights procedural outcomes, safety, and predictors of recurrence.

MECHANISTIC AND TECHNICAL CONSIDERATIONS

Catheter ablation for atrial fibrillation (AF) aims to achieve durable pulmonary vein isolation (PVI) by eliminating arrhythmogenic triggers originating predominantly from myocardial sleeves that extend into the pulmonary veins **[4]**. Although both radiofrequency ablation (RFA) and cryoballoon ablation (CBA) share this endpoint, the two energy sources differ substantially in lesion formation, workflow, safety, and procedural efficiency **[4,5]**.

2.1. Lesion Formation and Biophysics

Radiofrequency ablation (RFA) delivers high-frequency alternating current (350–500 kHz) producing resistive heating at the electrode–tissue interface, followed by deeper conductive heating. Lesion quality depends on contact force, power, irrigation, temperature, and duration. Optimal contact force (10–40 g) and power settings (25–50 W for irrigated catheters) are essential to create contiguous, transmural lesions while minimizing steam pops and collateral injury **[4,5]**.

Cryoballoon ablation (CBA) delivers cryothermal energy via a balloon catheter that occludes the pulmonary vein ostium. Rapid expansion of refrigerant (commonly nitrous oxide) cools tissue to −40°C to −60°C, inducing intracellular ice formation, membrane disruption, and microvascular injury. Lesion maturation occurs during the thawing phase. Preservation of extracellular matrix architecture may reduce thrombus formation and pulmonary vein stenosis **[4,5]**.

2.2. Procedural Workflow and Mapping Systems

RFA typically requires three-dimensional electroanatomic mapping systems (CARTO®, EnSite®, Rhythmia™) that facilitate detailed anatomical reconstruction, lesion placement, and assessment of conduction block **[4]**. This allows for customized lesion sets such as posterior wall isolation or linear ablation which may be helpful in persistent AF with extensive remodeling. However, this comes with increased complexity and longer procedure times **[6]**.

CBA employs a "single-shot" approach, isolating each pulmonary vein with one or more cryoapplications **[6,7]**. Real-time signal monitoring can be achieved using the Achieve™ catheter. Due to reliance on fluoroscopy and contrast to confirm vein occlusion, radiation exposure and contrast dose tend to be higher with CBA **[6,7]**. CBA is limited in addressing non-pulmonary vein triggers or diffuse atrial scarring **[4,16]**.

2.3. Safety and Lesion Durability

Both RFA and CBA have comparable safety profiles when performed by experienced operators **[6,7]**.

- RFA risks include esophageal injury, pericardial tamponade, and steam pops **[4]**.
- CBA-specific concerns include phrenic nerve palsy and contrast-induced nephropathy **[6,7]**.

Second- and third-generation cryoballoons have improved balloon compliance and cooling uniformity, reducing complications and enhancing lesion quality **[10,11]**.

Durability of PVI is crucial for long-term success. Chronic lesion transmurality is similar between optimized RFA and CBA **[6,10]**, but incomplete or non-transmural lesions can lead to pulmonary vein reconnection and recurrence **[16]**. Novel technologies including high-power short-duration RFA and pulsed-field ablation (PFA) may improve lesion durability and safety **[20–22]**.

2.4. Comparative Procedural Efficiency

Comparative studies consistently show that CBA reduces total procedure time by 30–60 minutes compared with RFA **[6–9,12–14]**. This advantage is largely due to the simplified single-shot workflow.
However:

- Fluoroscopy times are often higher with CBA (≈40–55 min) than RFA (≈25–40 min).
- CBA requires greater contrast use, which is relevant in renal dysfunction **[6,7]**.

CBA also has a shorter learning curve (≈20–25 cases vs. ≥50 for RFA) **[6]**, making it more accessible to newer ablation programs. RFA's strength lies in its flexibility for individualized lesion sets, advantageous in complex or long-standing persistent AF **[4,16]**.

EVIDENCE FROM CLINICAL TRIALS AND META-ANALYSES

The evolution of AF ablation has been shaped by multiple randomized controlled trials (RCTs), large observational cohorts, and meta-analyses comparing CBA and RFA **[6–15]**. While early research focused primarily on paroxysmal AF, contemporary investigations increasingly address persistent AF—a population with greater procedural challenges and substrate complexity.

3.1. Randomized Controlled Trials

- **FIRE AND ICE (2016)** established CBA as non-inferior to RFA in paroxysmal AF, with comparable arrhythmia-free survival and safety **[6]**.
- **STOP Persistent AF (2020)** was the first multicenter RCT evaluating CBA exclusively in persistent AF, reporting 55% 12-month freedom from atrial arrhythmia **[7]**.
- **CRRF-PeAF (2025)** randomized 220 persistent AF patients to CBA vs. RFA and found similar 12-month arrhythmia-free survival (63.2% vs. 65.1%) with significantly shorter procedural time for CBA **[8]**.
- **NO-PERSAF Registry (2022)** reported 58% 2-year arrhythmia-free survival with CBA and identified AF duration >12 months as a predictor of recurrence **[9]**.

Table 1. Key clinical trials and registries evaluating cryoballoon versus radiofrequency ablation in persistent atrial fibrillation

Study	Year	Design	Population	Ablation modalities	Follow-up	Main outcomes
STOP Persistent AF	2020	Prospective multicenter	165 persistent AF	CBA	12 mo	55% arrhythmia-free; low complication
CRRF-PeAF	2025	RCT	220 persistent AF	CBA vs RFA	12 mo	63.2% vs 65.1%; shorter procedure with CBA
NO-PERSAF	2022	Registry	522 persistent AF	CBA	24 mo	58% freedom; AF >12m predicts recurrence
Ciconte et al.	2015	Observational	Persistent AF	CBA	12 mo	~65% arrhythmia-free
Tscholl et al.	2016	Prospective cohort	Persistent AF	CBA	24 mo	Sustained efficacy
FIRE AND ICE	2016	RCT	Paroxysmal AF	CBA vs RFA	12–30 mo	Non-inferiority (paroxysmal AF)
Meta-analyses	2020–25	Systematic reviews	Mixed cohorts	CBA vs RFA	Varied	Equivalent efficacy, shorter CBA time

3.2. Observational Studies and Real-World Evidence

Large multicenter experiences, including European and North American registries, demonstrate comparable efficacy between CBA and RFA, with CBA consistently providing shorter procedure times **[10,11]**. Advances such as contact-force sensing (RFA) and second-/third-generation cryoballoons have further improved outcomes **[10,11]**.

3.3. Meta-Analyses

Meta-analyses consistently report no significant difference in arrhythmia recurrence between CBA and RFA in persistent AF:

- Gao et al. (2025) found an OR = 0.96 (95% CI 0.78–1.15; p = 0.47) **[12]**
- Liu et al. (2020) and Kim et al. (2023) reported equivalent recurrence and complication rates **[13,14]**
- Amin et al. (2024) confirmed comparable efficacy across randomized trials **[15]**

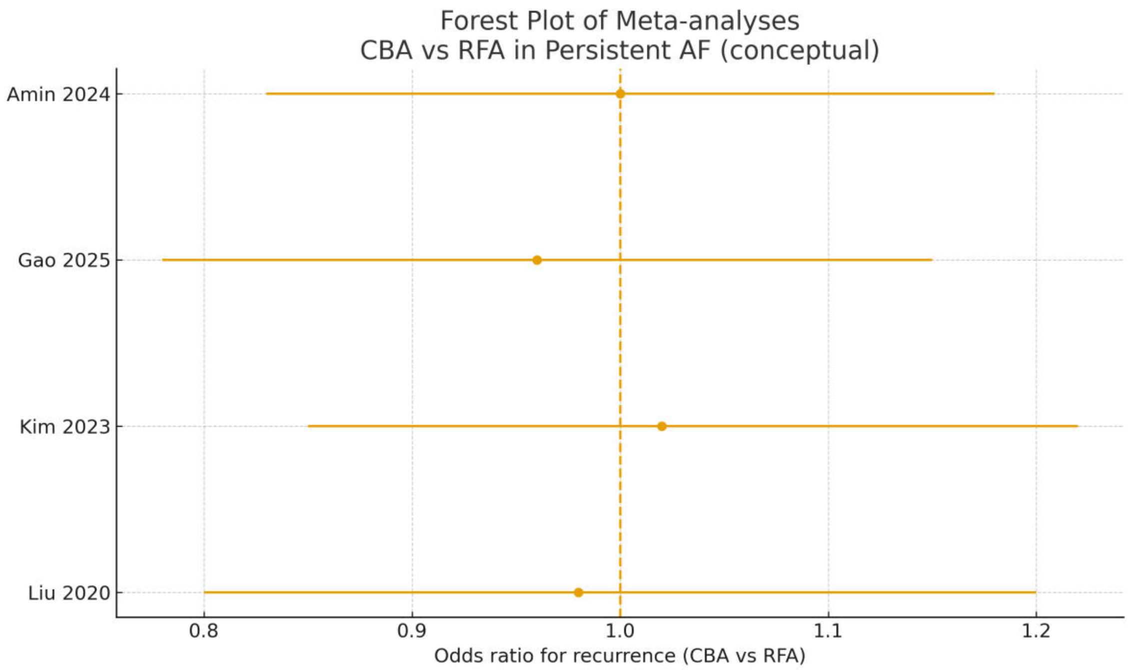

Chart A: Conceptual Kaplan–Meier curves comparing CBA vs RFA.

3.4. Predictors of Outcome Across Studies

Across trials and cohorts, predictors of recurrence remain consistent:

- Long-standing AF (>12 months)
- Enlarged left atrial volume
- Early recurrence during the blanking period
- Comorbidities such as hypertension, obesity, OSA, and diabetes **[16–18]**

These findings emphasize that **atrial substrate quality**, rather than energy modality, is the primary determinant of long-term success.

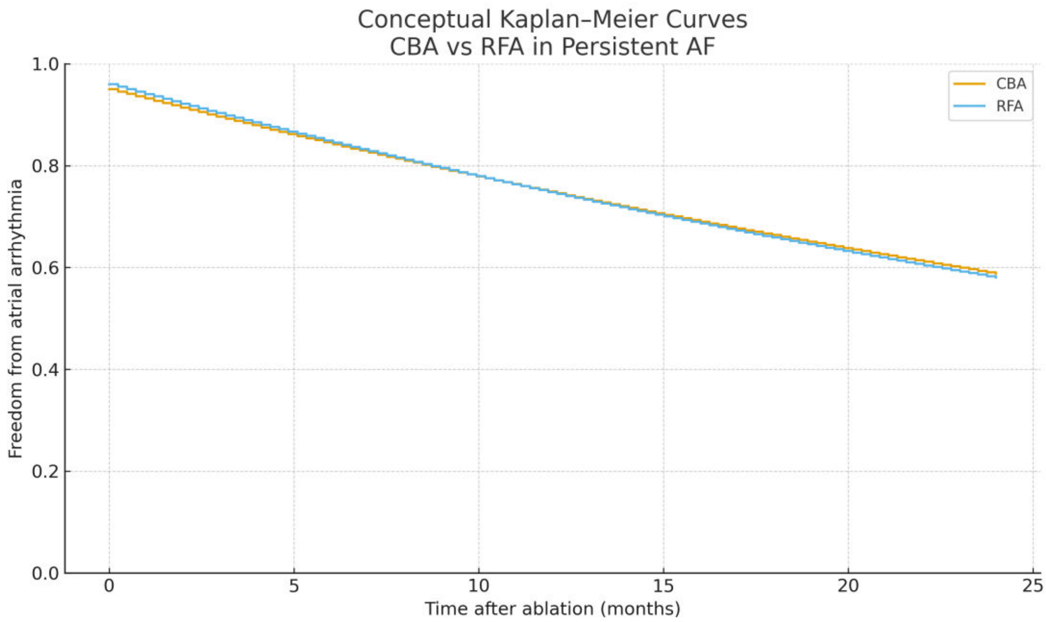

Chart B: Forest plot of meta-analyses comparing CBA vs RFA.

PROCEDURAL AND SAFETY OUTCOMES

4.1. Procedural Efficiency and Workflow

Cryoballoon ablation (CBA) consistently demonstrates **shorter procedure times** compared with radiofrequency ablation (RFA), typically reducing total procedural duration by **30–60 minutes** across comparative studies **[6–9,12–14]**. This efficiency stems from the single-shot nature of CBA, which simplifies pulmonary vein isolation and reduces dependence on extensive mapping **[6,7]**.

However, CBA is associated with:

- **Higher fluoroscopy time:** typically 40–55 minutes vs. 25–40 minutes for RFA
- **Greater contrast use:** often exceeding 100 mL, relevant for renal function **[6,7]**

CBA also has a **shorter learning curve** (≈20–25 cases) compared with RFA (≥50 cases) **[6]**, facilitating broader adoption. RFA remains advantageous in complex atrial substrates due to its flexibility in delivering tailored lesion sets **[4,16]**.

4.2. Acute Efficacy

Acute procedural success, defined as complete pulmonary vein isolation (PVI) with entrance and exit block, exceeds **95%** for both CBA and RFA in contemporary practice **[6–11]**. Second- and third-generation cryoballoons achieve near-circumferential lesions comparable to contact-force RFA **[10,11]**.

Incomplete lesions remain the leading cause of pulmonary vein reconnection. Real-time PV potential monitoring (Achieve™ in CBA) and differential pacing (in RFA) enhance detection of residual conduction **[6,7]**.

4.3. Complications

Both modalities demonstrate **low complication rates**, typically **4–7%** in large datasets **[6–9]**.

Common complications (shared):

- Vascular access complications (1–2%)
- Pericardial effusion/tamponade
- Stroke/TIA
- Esophageal irritation (rare)

Modality-specific risks:

- **RFA:** slightly higher risk of tamponade due to mechanical contact and deeper thermal penetration **[4]**
- **CBA:** risk of **phrenic nerve palsy** (2–5%), especially in right-sided PVs; >90% recover spontaneously **[6,7]**

Pulmonary vein stenosis and esophageal injury are rare (<0.5%) with modern catheters **[4]**. Contrast-induced nephropathy remains a concern primarily with CBA **[7]**.

4.4. Long-Term Durability and Repeat Ablation

Durability of pulmonary vein isolation is the primary determinant of long-term success. Data from FIRE AND ICE and persistent AF cohorts show:

- **Similar long-term outcomes** between modalities
- **Comparable repeat-ablation rates**
- **Consistent lesion transmurality** on remapping **[6–11]**

Technological innovations—high-power short-duration RFA and third-generation cryoballoons—continue to improve lesion durability, safety, and efficiency **[10,11,20–22]**.

Table 2. Comparative procedural characteristics and safety of cryoballoon versus radiofrequency ablation

Parameter	CBA	RFA	Comment
Workflow	Single-shot balloon	Point-by-point mapping	CBA simpler
Procedure time	Shorter	Longer	Major advantage of CBA
Fluoroscopy	Higher	Lower	CBA uses contrast
Contrast use	Higher	Lower	Renal considerations
3D mapping necessity	Optional	Essential	RFA more customizable
Substrate modification	Limited	Flexible	RFA favored in complex AF
Acute PVI success	>95%	>95%	Both high
Phrenic nerve injury	Possible	Rare	CBA risk
Tamponade risk	Lower	Slightly higher	RFA mechanical contact
Learning curve	Shorter	Longer	CBA easier early

PREDICTORS OF SUCCESS AND RECURRENCE

5.1. Pathophysiological Basis

The degree of atrial remodeling strongly influences ablation outcomes. Persistent AF is sustained by fibrosis, conduction heterogeneity, and atrial dilation, all of which reduce the durability of PVI and increase recurrence risk **[16]**. Fibrotic disruption of cell-to-cell coupling promotes reentry and supports AF maintenance.

5.2. Clinical Predictors

Key predictors of recurrence include:

- **AF duration >12 months:** strong predictor of late recurrence **[16]**
- **Left atrial enlargement:** LA diameter >45 mm or indexed LA volume >48 mL/m² correlates with increased fibrosis burden and lower success **[16]**
- **Early recurrence (<90 days):** predicts long-term failure **[16]**
- **Comorbidities:** HTN, diabetes, obesity, OSA increase inflammatory and structural remodeling **[17,18]**
- **Left ventricular dysfunction:** reduced EF and elevated filling pressures increase atrial stretch **[16]**

Favorable predictors include short AF duration, preserved atrial function, and absence of structural disease **[17,18]**.

5.3. Procedural and Electrical Predictors

Durability of PVI is central to long-term rhythm maintenance. Early PV reconnection during re-do procedures predicts late recurrence in up to **80%** of cases **[16]**.
Technical factors:

- Variability in contact force (RFA)
- Incomplete vein occlusion (CBA) **[4]**

Adjunctive lesion sets (posterior wall, linear ablation) may improve outcomes in selected persistent AF cases, though evidence remains mixed **[4,16]**.
Inflammatory markers (CRP, IL-6) and autonomic factors also correlate with early recurrence **[16]**.

5.4. Imaging and Electrophysiologic Markers

Advanced imaging enhances outcome prediction:

- **LGE-MRI fibrosis burden >30%** is strongly predictive of recurrence **[16]**
- **Low-voltage mapping** identifies scar and slow-conduction zones
- Electrophysiologic indices (cycle length, dominant frequency) may refine individualized strategies
- Integrating imaging with clinical predictors improves risk stratification.

5.5. Modifiable Risk Factor Control

Aggressive management of modifiable risk factors significantly improves ablation outcomes:

- Weight reduction
- Blood pressure control
- Glycemic optimization
- Treatment of sleep apnea

Large studies have demonstrated >50% reduction in AF burden and recurrence with structured risk-factor modification **[17,18]**.

Table 3. Predictors of atrial fibrillation recurrence after ablation in persistent AF

Domain	Predictor	Effect	Mechanism	Implication
Clinical	AF >12 months	Higher recurrence	Advanced remodeling	Early ablation advised
Clinical	LA enlargement	Higher recurrence	Fibrosis burden	Risk factor control needed
Clinical	OSA, obesity, HTN, DM	Higher recurrence	Fibrosis/inflammation	Manage comorbidities
Clinical	LV dysfunction	Higher recurrence	Atrial stretch	Optimize HF therapy
Procedural	Early recurrence	Predicts late failure	Gaps/inflammation	Close follow-up
Procedural	Durable PVI	Better success	Stable lesions	Improve lesion quality
Imaging	High fibrosis (LGE)	Higher recurrence	Scar substrate	Risk stratification

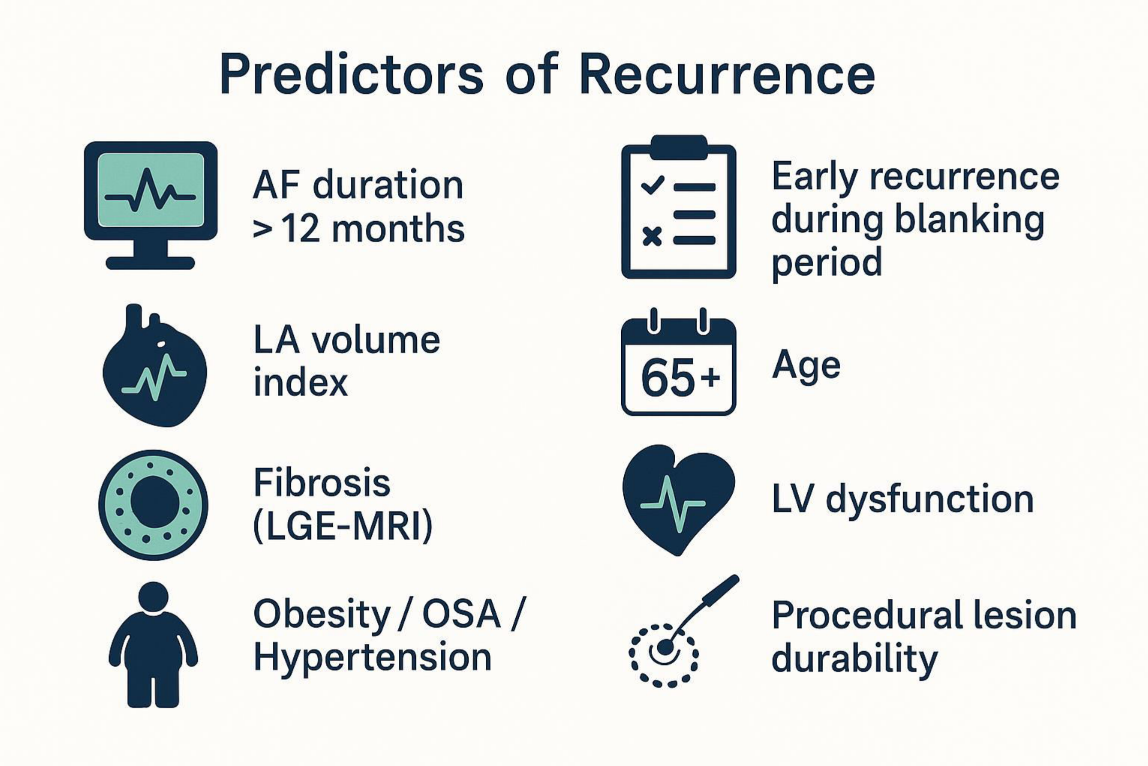

Figure 1. Predictors of atrial fibrillation recurrence.

FUTURE PERSPECTIVES

6.1. Technological Advancements in Ablation

Atrial fibrillation (AF) ablation continues to evolve through innovations in energy delivery, catheter design, and real-time imaging. Despite comparable efficacy between cryoballoon ablation (CBA) and radiofrequency ablation (RFA), emerging technologies aim to enhance lesion durability, safety, and efficiency **[4,5]**.

Pulsed-field ablation (PFA) has emerged as a transformative modality. Using ultrarapid electrical fields to induce irreversible electroporation, PFA selectively ablates myocardial tissue while sparing adjacent structures such as the esophagus and phrenic nerve. Early randomized trials and real-world registries demonstrate high acute success and significantly lower complication rates compared with thermal ablation techniques **[20–22]**. PFA is poised to become the dominant technology for both paroxysmal and persistent AF.

6.2. Integration of Imaging and Mapping Technologies

Advances in imaging and electroanatomic mapping refine substrate assessment and improve targeting. High-density mapping identifies conduction gaps and low-voltage regions **[16]**. Integration of cardiac MRI or CT-derived 3D reconstructions enhances lesion planning and spatial accuracy **[16]**.

Intracardiac echocardiography (ICE) provides real-time visualization, reduces fluoroscopy exposure, and improves procedural safety. Artificial intelligence (AI)–assisted mapping and automated electrogram interpretation are emerging tools with the potential to standardize ablation workflows **[16]**.

6.3. Hybrid and Surgical Approaches

Hybrid AF ablation—combining minimally invasive epicardial ablation with endocardial catheter ablation—has shown promise in patients with long-standing persistent AF or markedly enlarged atria. The **CONVERGE trial** demonstrated higher arrhythmia-free survival at 12 months compared with catheter ablation alone **[23]**.

Thoracoscopic left atrial appendage occlusion and cryomaze procedures are also gaining traction, particularly for patients undergoing concomitant cardiac surgery **[23]**.

6.4. Patient Selection and Timing

Earlier AF ablation—before irreversible structural remodeling—has consistently been associated with superior outcomes **[16]**. Large randomized trials such as EAST-AFNET 4 underscore the benefits of early rhythm control in reducing cardiovascular events **[19]**.

Future risk-stratification tools may incorporate biomarkers, fibrosis quantification, and scoring systems to identify optimal candidates for early ablation **[16]**.

6.5. The Future of Precision Electrophysiology

The future of AF ablation is shifting toward precision and personalization. Combining advanced imaging, computational modeling, AI-driven decision support, contactless mapping, and real-time monitoring will allow patient-specific lesion strategies **[5,16]**. Long-term surveillance with wearable ECG devices and digital health platforms will further improve detection and management of arrhythmia recurrence **[19]**.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Cryoballoon ablation (CBA) and radiofrequency ablation (RFA) are established strategies for rhythm control in persistent atrial fibrillation (AF). Randomized studies, registries, and meta-analyses demonstrate **comparable efficacy and safety** when procedures are performed by experienced operators.

CBA offers procedural simplicity and shorter procedure times, making it attractive for high-volume centers and newer ablation programs. RFA offers greater flexibility for substrate modification and individualized lesion sets—particularly advantageous in long-standing persistent AF.

Predictors of long-term success include:

- Shorter AF duration
- Smaller left atrial size
- Absence of early recurrence
- Control of modifiable risk factors

Early recurrence during the blanking period, advanced atrial remodeling, and comorbidity burden strongly predict late failure.

Emerging technologies—particularly **pulsed-field ablation (PFA)**, ultra-high-density mapping, and AI-enhanced procedural planning—promise to improve safety, efficiency, and patient selection. The future landscape of AF ablation is moving toward a more personalized, substrate-guided approach.

In summary, both CBA and RFA remain essential tools. Procedural choice should be individualized based on patient characteristics, atrial substrate complexity, and institutional expertise. As technology advances, AF ablation is expected to become safer, faster, and more precise.

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