TOPICS IN REVIEW

What clinical trials of ablation for atrial fibrillation tell us – and what they do not

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Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia in clinical practice. Radiofrequency and cryoballoon catheter ablation are therapeutic options in addition to antiarrhythmic drug therapy for the treatment of AF. Ablation is effective at reducing recurrent atrial arrhythmias and also in the reduction of AF burden. Besides arrhythmia control, improvement in quality of life and clinical outcomes are also desirable goals with AF treatment. Randomized clinical trials have evaluated ablation in several patient populations, including symptomatic patients as first-line or second-line therapy, asymptomatic patients, and patients with heart failure. These trials clarify the durability of ablation in arrhythmia control, clarify quality-of-life improvement, and identify patient populations in whom ablation may be expected to improve clinical outcomes. In this review, we summarize the major clinical trials involving ablation; discuss the strengths, weakness, and clinical implications of these trials; and highlight the knowledge gaps in our current understanding of AF ablation for future clinical studies.

KEYWORDS Atrial fibrillation; Catheter ablation; Clinical outcomes; Clinical trials

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and a major source of morbidity and mortality. Antiarrhythmic drugs (AADs) can suppress or delay recurrences of AF, but their efficacy is less than optimal in many patients. Haïssaguerre and colleagues[1] first identified pulmonary veins to be the main trigger source for AF. Pulmonary vein isolation (PVI) using either radiofrequency or cryoballoon ablation has since emerged as a safe and effective treatment modality in patients with AF, although patients with more advanced stages of AF often require adjunctive lesions in addition to PVI. The primary goal of AF ablation is to decrease or eliminate recurrences of AF, particularly those that are symptomatic and adversely affect quality of life (QOL). An important additional goal is to improve adverse clinical outcomes in patients with AF.

The purpose of this review is to summarize the results of the major clinical trials of AF ablation, examine what we have learned, and understand what questions remain unanswered. We discuss the definition of a successful procedure, options for monitoring of recurrences, the definition of AF burden and how to assess it, techniques used for ablation, complications, and expected success rates. We then review clinical trials that addressed ablation to prevent recurrences of AF after failure of medical therapy, ablation as the initial approach to treatment of AF, the effect of ablation on QOL, and the results of clinical trials that examined clinical outcomes after ablation. We consider the interrelationship between AF and heart failure (HF) and the effect of ablation on AF burden and heart function. Finally, we conclude with the major knowledge gaps in ablation of AF.

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Atrial fibrillation ablation: Approaches, efficacy, and safety

It is critical to have a consistent definition of what constitutes a successful procedure after AF ablation in order to evaluate the results of clinical trials. The 2017 expert consensus statement on catheter and surgical ablation of AF identified freedom from any atrial arrhythmia, defined as AF, atrial flutter, or atrial tachycardia, lasting for more than 30 seconds off AAD therapy, as the gold standard for reporting the efficacy of AF ablation.[2] Options for monitoring for recurrences of atrial arrhythmias after ablation include Holter monitors, longer-term monitoring such as 30-day event monitors, intermittent rhythm recording using devices such as the Apple Watch or Kardia Mobile, or insertable loop recorders (ILRs).[3–5] It is well recognized that symptoms alone are not sufficient to determine freedom from AF, as many patients have been demonstrated to have asymptomatic episodes after ablation. Major clinical trials will generally use either more extended monitoring or ILRs to detect recurrences of atrial arrhythmias.

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KEY FINDINGS

- Catheter ablation for atrial fibrillation (AF) is effective in preventing recurrences and reducing AF burden both as first-line and second-line therapy.
- Ablation improves quality of life in patients with symptomatic AF.
- Ablation may improve clinical outcomes in patients with recent-onset AF and cardiovascular comorbidities when offered as part of an early rhythm control strategy.
- Ablation reduces AF burden and improves clinical outcomes and cardiac function in patients with heart failure and reduced ejection fraction.

AF burden is another measure of the success of ablation, and it is defined as the total time in AF compared to the total duration of the monitoring period. It can be determined by continuous monitoring with an ILR or by an implanted cardiac device such as a pacemaker or an implantable cardioverter-defibrillator (ICD). AF burden is also recognized as an endpoint to assess the efficacy of ablation.

The foundation of AF ablation is isolation of the pulmonary veins. Point-by-point radiofrequency energy delivered via transvenous electrodes and circumferential cryoenergy lesions delivered by balloon-based systems are the most common sources of energy utilized to achieve PVI. Both techniques have a similar efficacy and safety profile.[6] Other energy sources that have been studied, but with limited clinical use, include a laser balloon ablation system, hot balloon ablation system using radiofrequency energy, and low-intensity collimated ultrasound ablation.

AF ablation is a complex electrophysiological procedure which can lead to life threatening complications. In-hospital mortality following ablation varies between 0.6 and 4 per 1000 patients.[7,8] Cardiac tamponade is the most frequent serious complication leading to death, while vascular complications are the most common adverse effect related to the procedure. Other complications include pulmonary vein stenosis, catheter entrapment, periprocedural embolic events, phrenic nerve injury, atrioesophageal fistula, vagal nerve injury, acute coronary artery injury, and pericarditis.

PVI is sufficient to eliminate AF in approximately 60%–70% of patients with paroxysmal AF at 12–18 months of follow-up with a single procedure and after a 3-month blanking period.[2,6] The success rate increases after repeat procedures, or with the addition of AADs, some of which may have previously been unsuccessful in controlling the arrhythmia. When repeat procedures are necessary, techniques such as left atrial roof lines, ablation of fractionated atrial electrograms, isolation of the left atrial appendage, and others are used, in addition to isolation of pulmonary veins that have reconnected. Success rates are lower in patients with enlarged atria or with HF with a reduced ejection fraction. Ablation is also performed in patients with persistent AF or even long-standing (>1 year) persistent AF, but success rates are progressively lower, typically around 50% after a single procedure for persistent AF and well below 50% with long-standing persistent AF.[9–11]

In addition to reducing or eliminating recurrences of AF, it is essential to know whether AF ablation is effective in improving important clinical outcomes such as QOL, HF, and mortality. Recent data help to clarify the role of AF ablation in improving hard clinical outcomes in several subgroups of patients and the durability of ablation in controlling the arrhythmia and improving QOL.

Ablation to prevent recurrent atrial arrhythmias

Table 1 lists major trials evaluating the efficacy of ablation in patients with AF who had failed therapy with at least 1 AAD. The trials used different techniques for ablation, various definitions for recurrent atrial arrhythmias, and several monitoring methods to detect recurrences. Ablation has been shown to be more effective than AADs in preventing recurrences in patients with both paroxysmal and persistent AF during a follow-up period of up to 1 year. A meta-analysis of these trials confirmed the efficacy of ablation in reducing the burden of recurrent atrial arrhythmias as a second-line therapy, with a 63% reduction in the risk of recurrence compared to drug therapy (risk ratio 0.37; 95% confidence interval [CI] 0.29–0.48; $P < .00001$).[12] The Cryoballoon vs Irrigated Radiofrequency Catheter Ablation: Double Short vs Standard Exposure Duration (CIRCA-DOSE)[13] trial was a multicenter, prospective, parallel-group, single-blinded randomized clinical trial designed to evaluate the comparative effectiveness of various ablation technologies in patients with drug-refractory paroxysmal AF. All patients had an ILR for continuous arrhythmia monitoring. Though the 1-year freedom from any atrial arrhythmia ranged from 51.7% to 53.9% depending on the ablation technology used, all the strategies were effective in lowering median AF burden by 98.40%–99.93% compared to the monitoring period prior to ablation. Thus, ablation has been shown to be significantly more effective than AADs in preventing recurrences of AF in patients who have failed medical therapy and also in drastically reducing AF burden. However, given that these trial designs generally randomized patients to either an approach that had already failed (AADs) or ablation, it is perhaps not surprising that ablation was superior.

Ablation as first-line management for atrial fibrillation

Given that many patients progress over time from paroxysmal to persistent to permanent AF, and that remodeling of the atria in AF may make restoration of sinus rhythm more and more difficult, there has been interest in exploring ablation as a first-line strategy for the management of AF. In addition, an early approach when no therapy has been tried already allows for a fairer comparison of AADs vs ablation.

Table 1 Clinical trials evaluating ablation in drug-refractory atrial fibrillation

Study	Methods	Definition of recurrent atrial arrhythmia	Monitoring methods	Freedom from recurrence	Results (primary outcomes)
Stabile et al[37] 2006	RFA with AADs vs AADs in pAF and persAF	>30 seconds after 1-month blanking	Transtelephonic and Holter	Ablation: 55.9% AADs: 8.7% (12-month follow-up)	Ablation with AADs is superior in preventing recurrences ($P < .001$)
Oral et al[38] 2006	Amiodarone with cardioversions during first 3 months alone or with RFA in chronic AF	>3 seconds, no blanking	Transtelephonic	Ablation: 74% Control: 58% (12-month follow-up)	Ablation is more effective in maintaining sinus rhythm without AADs compared to control group ($P = .05$)
Pappone et al (APAF)[39] 2006	RFA vs AADs in pAF	>30 seconds, 6-week blanking	Holter and event	Ablation: 86% AADs: 22% (12-month follow-up)	Ablation is more effective than AADs at preventing recurrences ($P < .001$)
Jaïs et al (A4)[21] 2008	RFA vs AADs in pAF	>3 minutes, 3-month blanking	Holter	Ablation: 89% AADs: 23% (12-month follow-up)	Ablation is superior to AADs at maintaining sinus rhythm ($P < .0001$)
Forleo et al[40] 2009	RFA vs AADs in diabetic patients with symptomatic AF	>30 seconds, 5-week blanking	Holter	Ablation: 80% AADs: 42.9% (12-month follow-up)	Ablation is more effective than AADs at preventing recurrences in diabetic subjects ($P = .001$)
Wilber et al (ThermoCool AF)[20] 2009	RFA vs AADs in pAF	No clear definition, 3-month blanking	Transtelephonic and Holter	Ablation: 63% AADs: 17% (9-month effectiveness period)	Ablation resulted in a longer time to treatment failure compared to AADs ($P < .01$)
Packer et al (STOP AF)[41] 2013	Cryoballoon vs AADs in pAF and persAF	Any detectable AF, 3-month blanking	Transtelephonic and Holter	Ablation: 69.9% AADs: 7.3% (12-month follow-up)	Ablation is more effective than AADs at preventing recurrences ($P < .001$)
Mont et al (SARA)[22] 2014	RFA vs AADs in persAF	>24 hours for primary outcome measure and >30 seconds for secondary outcomes, 3-month blanking	Holter	Ablation: 60.2% AADs: 29.2% (12-month follow-up, based on secondary outcome definition)	Ablation is superior to AADs for sinus rhythm maintenance ($P = .002$)
Hummel et al (TTOP-AF)[42] 2014	Phased RFA system vs AADs in persAF and longstanding persAF	≥10 minutes on Holter, blanking not specified	Holter	Not reported Effectiveness defined as ≥90% reduction in time of recurrent arrhythmia episodes Ablation: 55.8% AADs: 26.4% (6-month follow-up)	Ablation is more effective than AADs in reduction of atrial arrhythmias ($P < .0001$)
Natale et al (SMART-AF)[43] 2014	RFA using contact force–sensing catheter in pAF, nonrandomized trial comparing to performance goals	>30 seconds, 3-month blanking	Transtelephonic and Holter	Ablation: 72.5% (12-month follow-up)	Ablation with contact force–sensing catheter is safe and effective

Verma et al (STAR AF II)[10] 2015	RFA using PVI alone vs PVI and ablation of complex fractionated activity vs PVI and linear ablation of left atrial roof and mitral valve isthmus in persAF	>30 seconds, 3-month blanking	Transtelephonic and Holter	PVI alone: 59% PVI with complex electrogram ablation: 49% PVI with linear ablation: 46% (18-month follow-up)	No reduction in recurrent arrhythmias with additional ablation ($P = .15$)
Reddy et al (TOCCASTAR)[44] 2015	RFA using contact force catheter vs non–contact force catheter in pAF	>30 seconds, 3-month blanking	Transtelephonic and Holter	Contact force catheter: 67.8% Non–contact force catheter: 69.4% (Effectiveness evaluation at 12-month follow-up)	Ablation using the contact force catheter is noninferior to non–contact force catheter with respect to efficacy ($P = .0073$) and safety ($P = .0004$)
Dukkipati et al (HeartLight)[45] 2015	RFA vs visually guided laser balloon	Symptomatic AF ≥1 minute or atypical flutter or atrial tachycardia, 3-month blanking	Transtelephonic and Holter	RFA: 63.9% Visually guided laser balloon: 63.5% (12-month follow-up)	Visually guided laser balloon is noninferior to RFA with respect to efficacy ($P = .003$) and safety ($P = .002$)
Kuck et al (FIRE AND ICE)[6] 2016	RFA vs cryoballoon in pAF	>30 seconds, 3-month blanking	Transtelephonic and Holter	RFA: 76.9% Cryoballoon: 78.7% (12-month follow-up)	Cryoballoon is noninferior to RFA with similar safety profiles ($P < .001$)
Sohara et al[46] 2016	RFA using HotBalloon system vs AADs in pAF	>30 seconds, 84-day blanking	Holter	RFA: 59% AADs: 5% (9-month effectiveness period)	Ablation using the HotBalloon system is superior to AADs ($P < .001$)
Andrade et al (CIRCA-DOSE)[13] 2019	Contact force RFA vs 4-minute cryoballoon vs 2-minute cryoballoon in pAF	>30 seconds, 84-day blanking	Implantable loop monitor	RFA: 53.9% 4-minute cryoballoon: 52.2% 2-minute cryoballoon: 51.7% (12-month follow-up)	No significant differences between ablation strategies in reducing recurrences

AADs = antiarrhythmic drugs; pAF = paroxysmal atrial fibrillation; persAF = persistent atrial fibrillation; PVI = pulmonary vein isolation; RFA = radiofrequency ablation.

Table 2 Clinical trials evaluating ablation as first-line therapy for symptomatic paroxysmal atrial fibrillation

Study	Methods	Key inclusion and exclusion criteria	Definition of recurrent atrial arrhythmia	Monitoring methods	Primary endpoints
Wazni et al (RAAFT-1)[14] 2005	RFA vs AADs as initial therapy in symptomatic AF	Inclusion: age 18–75 years, symptomatic AF >3 months Exclusion: previous ablation or use of AADs	>15 seconds, 2-month blanking	Holter and event	Atrial tachyarrhythmia recurrence in 13% in ablation arm compared to 63% in drug arm ($P < .001$) at 12 months
Nielsen et al (MANTRA-PAF)[15] 2012	RFA vs AADs as initial therapy in paroxysmal AF	Inclusion: symptomatic AF for at least 6 months Exclusion: age >70 years, previous ablation or use of AADs, LA diameter > 5 cm	>1 minute, 3-month blanking	Holter	No significant difference in cumulative AF burden between the ablation and drug therapy arm ($P = .10$) over a period of 2 years
Morillo et al (RAAFT-2)[16] 2014	RFA vs AADs as initial therapy in paroxysmal AF	Inclusion: symptomatic AF for at least 6 months Exclusion: age <18 or >75 years, previous ablation or use of AADs, LA diameter > 5.5 cm	>30 seconds, 3-month blanking	Transtelephonic and Holter	Atrial tachyarrhythmia recurrence in 54.5% in ablation arm compared to 72.1% in drug arm ($P < .001$) at 24 months
Wazni et al (STOP AF First)[18] 2020	Cryoballoon vs AADs as initial therapy in paroxysmal AF	Inclusion: age 18–80 years Exclusion: treatment with AADs, left atrial size > 5 cm, previous LA procedure	≥30 seconds during ambulatory monitoring or ≥10 seconds on 12-lead ECG, three-month blanking	Transtelephonic and 24-hour Holter	Treatment success was 74.6% in the ablation arm compared to 45% in the drug therapy arm ($P < .001$) at 12 months No difference in serious events between groups
Andrade et al (Early AF)[19] 2020	Cryoballoon vs AADs in untreated symptomatic AF	Inclusion: age >18 years Exclusion: regular use of AADs	≥30 seconds, 3-month blanking	Implantable cardiac monitors	Atrial tachyarrhythmia recurrence in 42.9% in ablation arm compared to 67.8% in drug arm ($P < .001$) at 12 months

AF = atrial fibrillation; AADs = antiarrhythmic drugs; ECG = electrocardiogram; LA = left atrium; RFA = radiofrequency ablation.

Table 3 Clinical trials evaluating ablation and quality-of-life outcomes

Study	Methods and patient population	QOL measure	Follow-up	QOL outcome
Wazni et al (RAAFT-1)[14] 2005	Ablation vs AADs as first-line therapy in symptomatic AF	Short Form-36 health survey	6 months	Improvement in QOL in the ablation arm compared to AAD therapy ($P < .001$)
Oral et al[38] 2006	Amiodarone with cardioversions during first 3 months alone or with ablation in chronic AF	Symptom severity score	12 months	Reduction in severity of symptoms following maintenance of sinus after ablation ($P < .001$)
Jaïs et al (A4)[21] 2008	Ablation vs AAD in drug-refractory pAF	Short Form-36 health survey	12 months	Higher QOL score in the ablation arm compared to AAD therapy ($P = .01$)
Forleo et al[40] 2009	Ablation vs AADs in diabetic patients with symptomatic drug-refractory AF	Short Form-36 health survey	12 months	Higher improvement in QOL score with ablation ($P < .05$)
Wilber et al (ThermoCool AF)[20] 2009	Ablation vs AADs in drug-refractory pAF	Short Form-36 health survey AF symptom frequency and severity checklist	3 months	Higher QOL score and lower symptom frequency and severity scores compared to AAD therapy ($P < .001$)
Nielsen et al (MANTRA-PAF)[15] 2012	Ablation vs AADs as first-line therapy in pAF	Short Form-36 health survey	24 months	Higher improvement in the physical component of QOL score in the ablation arm compared to AAD therapy ($P = .01$)
Packer et al (STOP AF)[41] 2013	Cryoballoon vs AADs in drug-refractory pAF and persAF	Short Form-36 health survey	12 months	Significantly improved symptoms and QOL score with ablation
Mont et al (SARA)[22] 2014	Ablation vs AADs in drug refractory persAF	AF QOL questionnaire	12 months	No significant differences in QOL between groups
Morillo et al (RAAFT-2)[16] 2014	Ablation vs AADs as first-line therapy in pAF	EQ-5D (generic tool from EuroQol group)	12 months	Higher score change from baseline in the ablation group ($P = .03$) compared to AAD therapy
Hummel et al (TTOP-AF)[42] 2014	Phased RFA system vs AADs in drug-refractory persAF and longstanding persAF	AF symptom severity and QOL survey	6 months	Higher QOL score in the ablation arm ($P = .0052$)
Reddy et al (TOCCASTAR)[44] 2015	Ablation using contact force catheter vs non–contact force catheter in drug-refractory pAF	AF effect on QOL questionnaire	12 months	Significant improvement in QOL in both the ablation arms
Sohara et al[46] 2016	Ablation using HotBalloon system vs AADs in drug-refractory pAF	Short Form-36 health survey, version Japan	12 months	Significant improvement from baseline in most components of the QOL metric with ablation

AADs = antiarrhythmic drugs; AF = atrial fibrillation; pAF = paroxysmal atrial fibrillation; persAF = persistent atrial fibrillation; QOL = quality of life; RFA = radiofrequency ablation.

Table 4 Clinical trials evaluating the effect of ablation on clinical outcomes of morbidity and mortality

Study	Methods	Key inclusion and exclusion criteria	Median time since AF diagnosis	Previous treatment for AF	Interventions utilized	Primary outcome
Packer et al (CABANA)[26] 2019	Ablation vs AAD therapy in patients with symptomatic AF	Inclusion: age $\geq$65 years or $<$65 years with at least 1 risk factor for stroke Exclusion: prior ablation, failed more than 2 AADs Number of patients randomized: 2204	1.1 years	Ablation arm: 81.6% with 1 AAD AAD therapy arm: 82.2% with 1 AAD	Ablation arm: 90.8% underwent ablation AAD therapy arm: 88.4% received AAD therapy;27.5% crossed over to undergo ablation	No significant reduction in the composite of death, disabling stroke, serious bleeding, or cardiac arrest with ablation (hazard ratio 0.86, $P = .30$) over a median follow-up of 48.5 months
Kirchhof et al (EAST-AFNET 4)[27] 2020	Early rhythm control therapy vs usual care in patients with recent-onset AF	Inclusion: age $>$75 years or history of stroke or age $>$65 years with at least 1 additional risk factor for stroke Exclusion: prior ablation, therapy failure with amiodarone Number of patients randomized: 2789	36 days	No prior treatment with AADs (around 40% in both arms had previous cardioversion)	Early rhythm control arm: 19.4% underwent ablation and 45.7% received AAD Usual care arm: 7% underwent ablation and 7.6% received AAD (at 2 years of follow-up)	Significant reduction in the composite of death from cardiovascular causes, stroke, or hospitalization with worsening heart failure or acute coronary syndrome with early rhythm control therapy (hazard ratio 0.79, $P = .005$) over a median follow-up of 5.1 years

AAD = anti arrhythmic drug; AF = atrial fibrillation.

The Radiofrequency Ablation vs Antiarrhythmic Drugs as First-line Treatment of Symptomatic Atrial Fibrillation (RAAFT-1),[14] Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF),[15] and Radiofrequency Ablation vs Antiarrhythmic Drugs for Atrial Fibrillation Treatment (RAAFT-2)[16] randomized trials compared radiofrequency ablation as first-line therapy against AAD therapy for symptomatic AF. Table 2 depicts the essential features of these studies. A meta-analysis[17] of these studies showed that radiofrequency ablation was associated with a greater freedom from recurrent AF, defined as episodes lasting 15 seconds to 1 minute in the various studies, as detected by Holter or event monitoring (risk ratio 0.63, 95% CI 0.44–0.92, $P = .02$). The analysis also concluded that radiofrequency ablation caused more severe adverse effects than AAD therapy.

Patients in the MANTRA-PAF trial were subjected to 7-day Holter monitoring at 3, 6, 12, 18, and 24 months during clinical follow-up. Although AF burden during each follow-up was lower than at baseline for both treatment groups ($P < .001$), there was no significant difference in the cumulative burden of AF between the groups over a period of 18 months of follow-up. However, at 24 months, AF burden was lower in the ablation group than in the drug therapy group (90th percentile, 9% vs 19%, $P = .007$) and more patients in the ablation group were free from any AF (85% vs 71%, $P = .004$), suggesting the durability of ablation in controlling the arrhythmia.

The Cryoballoon Catheter Ablation in Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation (STOP AF First)[18] and Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF)[19] trials were designed to evaluate cryoballoon ablation against AAD therapy as initial treatment for patients with symptomatic paroxysmal AF. Table 2 demonstrates the key features of both trials. The STOP AF First trial evaluated treatment success using patient-activated telephone monitoring and 24-hour Holter monitoring during follow-up, while the EARLY-AF trial used ILRs. Both trials demonstrated the superiority of cryoballoon ablation in preventing atrial arrhythmia recurrences at 1 year with a low risk of serious adverse effects. The EARLY-AF trial also demonstrated that mean AF burden was 3.3% lower in the ablation arm, although the median AF burden was extremely low, 0% in the ablation arm and 0.13% in the AAD arm. Both trials were underpowered to assess for cardiovascular outcomes and had follow-up data only for a year. Ablation is thus effective in reducing recurrences of atrial arrhythmias and in reducing AF burden when offered as first-line therapy in symptomatic patients. However, there is a similar reduction in AF burden with both ablation and AADs from baseline and no clinically meaningful difference in AF burden between groups up to 2 years of follow-up.

Ablation to improve quality of life

Table 3 summarizes the major randomized trials of catheter ablation that evaluated QOL in patients with symptomatic AF. Generic questionnaires such as the Short Form-36 health survey, EQ-5D from the EuroQol group, or AF-specific questionnaires like the AF symptom frequency and severity checklist were utilized. There was a significant improvement in QOL scores when ablation was offered as first-line therapy for paroxysmal AF[14,15,20] and also in patients with paroxysmal AF who had failed therapy with at least 1 AAD.[21] The benefit was seen up to 24 months of follow-up. However, in the Catheter Ablation vs Antiarrhythmic Drug Treatment of Persistent Atrial Fibrillation (SARA) study, no significant differences in QOL outcomes were detected in patients with drug-refractory persistent AF between the ablation and AAD therapy arms at 12 months of follow-up.[22] This finding was attributed to a lack of power to detect a statistically significant difference in the secondary outcome of QOL. Wokhlu and colleagues[23] prospectively studied the effect of AF ablation on QOL in 502 symptomatic patients. QOL was assessed using the Short Form-36 health survey. At 2 years of follow-up, ablation was associated with higher QOL scores in patients both with and without recurrence of atrial arrhythmias. Ablation is thus an effective tool in improving QOL in patients with symptomatic AF during a follow-up period of up to 2 years, as shown by both prospective observational and randomized trial data.

Rhythm control management and clinical outcomes in atrial fibrillation

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial investigated the impact of a rate vs a rhythm control strategy on mortality in patients with AF, with no significant difference found.[24] However, a sub-analysis showed that although maintenance of sinus rhythm led to better outcomes than AF, this improvement appeared to be offset by the adverse effects of AADs.[25] This finding engendered interest in exploring whether ablation could improve outcomes and control AF as well as if not better than AADs, while also avoiding the adverse effects of medical therapy.

It is clear from previous clinical trials that catheter ablation can reduce or eliminate recurrences of AF in many patients, greatly reducing symptoms and improving QOL. The impact of ablation on clinical outcomes such are HF or mortality has been investigated in the Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA)[26] trial and the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4).[27] Both were specifically designed to test contemporary rhythm control strategies (including ablation) on clinical outcomes such as morbidity and mortality. Table 4 summarizes the major differences between these trials.

CABANA trial

The CABANA trial was a multicenter, international, open-label, controlled trial that randomized recently diagnosed symptomatic and inadequately treated patients with AF either to catheter ablation or to medical therapy. Key inclusion

Table 5 Clinical trials evaluating ablation in patients with atrial fibrillation and heart failure

Study	Methods	Definition of recurrent atrial arrhythmia	Monitoring methods	Freedom from recurrence	Results (primary outcomes)
Khan et al (PABA CHF)[47] 2008	PVI vs AVN ablation and BIV pacing in symptomatic, drug-resistant AF	>30 seconds, 2-month blanking	Loop event monitors	PVI: 88% BIV pacing arm: 0% (6-month follow-up)	Composite primary endpoint of improved HF questionnaire score, longer 6-minute walk distance, and higher EF favoring the PVI arm ($P < .017$)
Jones et al.[48] 2013	Ablation vs rate control in persAF	>30 seconds, 2-month blanking	Holter	Ablation: 88% Rate control: NA on account of persAF (12-month follow-up)	Improvement in peak oxygen consumption in ablation arm (difference +3.07 mL/kg/min, $P = .018$)
Hunter et al (CAMTAF)[49] 2014	Ablation vs rate control in persAF	>30 seconds, 3-month blanking	Holter	Ablation: 73% Rate control: 0% (12-month follow-up)	Absolute increase in EF of 8% in the ablation arm at 6 months ($P < .001$)
Di Biase et al (AATAC)[34] 2016	Ablation vs amiodarone in persAF	>30 seconds, 3-month blanking	Remote interrogation of ICD or CRT-D devices	Ablation: 70% Amiodarone: 34% (24-month follow-up)	Reduction in recurrent AF in the ablation arm ($P < .001$)
Prabhu et al (CAMERA MRI)[35] 2017	Ablation vs rate control in persAF	>30 seconds, 1-month blanking	Implanted loop recorder in ablation group and Holter in the rate control group	Ablation: 76% Rate control: 0% (6-month follow-up)	Improvement in LVEF by 18.3% in ablation arm vs 4.4% in the rate control arm ($P < .0001$)
Marrouche et al (CASTLE-AF)[36] 2018	Ablation vs medical therapy (rate or rhythm control) in symptomatic AF	>30 seconds, 3-month blanking	Remote interrogation of ICD or CRT-D devices	Ablation: 63.1% Medical therapy: 21.7% (60-month follow-up)	Composite primary endpoint of death or HF hospitalization occurred less frequently in the ablation arm (hazard ratio 0.62, $P = .007$)

AF = atrial fibrillation; AVN = atrioventricular node; BIV = biventricular; CRT-D = cardiac resynchronization therapy defibrillator; EF = ejection fraction; HF = heart failure; ICD = implantable cardioverter-defibrillator; NA = not applicable; persAF = persistent atrial fibrillation; PVI = pulmonary vein isolation.

Table 6 Current conceptualization of ablation for atrial fibrillation and knowledge gaps requiring further study

What Is Known
Ablation reduces recurrences of AF and improves quality of life
The foundational approach is PVI
Radiofrequency ablation and cryoablation have similar safety and efficacy with respect to PVI
Ablation of paroxysmal AF has a higher success rate than persistent or longstanding persistent AF
Ablation as first-line therapy results in greater freedom from AF than AAD therapy; AF burden tends to be low early in the course of AF and not greatly affected by ablation
Structural remodeling (LA enlargement and LV dysfunction) lowers success rates
Ablation improves clinical outcomes in select patient populations
Ablation in patients with HF lowers AF burden, improves LVEF, and reduces a composite of mortality or HF hospitalization
Knowledge Gaps
What are the mechanisms of AF beyond pulmonary vein triggers?
What ancillary approaches will eliminate AF if PVI is not sufficient?
In what circumstances is ablation futile and should not be pursued?
What is the effect of ablation on clinical outcomes in asymptomatic patients?
How are clinical outcomes different when ablation is offered to patients with and without HF?
Should we aim for a reduction in burden or elimination of all recurrences with ablation? If reduction of AF burden is sufficient, how much reduction is necessary to be clinically meaningful?
What kind of monitoring is ideal to assess outcomes in an ablation trial?
How do cardiac structure and function influence procedural and clinical outcomes with ablation?
How many patients with AF are truly cured with ablation vs just palliated? How does the underlying substrate affect long-term arrhythmia control?

AAD = antiarrhythmic drug; AF = atrial fibrillation; HF = heart failure; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; PVI = pulmonary vein isolation.

criteria included patients aged ≥65 years or <65 years with additional risk factors for stroke with paroxysmal or persistent AF deemed to warrant active therapy and eligible for catheter ablation and therapy with ≥2 rate and rhythm control drugs. Key exclusion criteria included AF in the setting of reversible causes, recent cardiac events, class IV angina or HF, failure to tolerate >2 AADs, prior catheter-based/surgical interventions for AF, and renal failure requiring dialysis. There were 1108 patients randomized to the ablation arm, of whom 1006 (90.8%) underwent ablation, and 1096 patients to the drug therapy arm, of whom 1092 (99.6%) received drug therapy, which was predominantly rhythm control therapy (969 patients, 88.4%). Both groups had approximately 14% of patients over the age of 75 years and 3.5% nonwhite, both populations not well represented in prior ablation trials. The median time since onset of AF was 1.1 years in both the groups. At the time of enrollment, 81.6% of patients in the ablation arm and 82.2% of patients in the drug therapy arm had current or past use of at least 1 AAD. Over a median follow-up of 48.5 months, the primary composite endpoint of death, disabling stroke, serious bleeding, or cardiac arrest occurred in 8% of the patients in the ablation arm vs 9.2% in the medical therapy arm (hazard ratio [HR] 0.85; $P = .3$), thus not meeting statistical significance in the intention-to-treat analysis. However, 301 (27.5%) patients in the drug therapy arm crossed over to the ablation arm during the follow-up period, potentially affecting the results. In the prespecified treatment-received analysis and per-protocol treatment comparisons, there was a suggestion of a statistically significant benefit with ablation with respect to the primary endpoint.

QOL outcomes were measured using the Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire and the Mayo AF-Specific Symptom Inventory (MAFSI).[28] At the 5-year follow-up, the mean AFEQT score was 3.4 points higher in the ablation arm compared to the drug therapy arm (95% CI 2.1–4.8; $P < .001$), with benefits across all the component scores of symptoms, daily activities, and treatment concerns. The mean difference in both the MAFSI frequency and severity score among all follow-up intervals was -1.4 (95% CI -1.9 to -0.9; $P < .001$) and -1.1 (95% CI -1.5 to -0.8), respectively, favoring catheter ablation. The benefits of catheter ablation on QOL assessed by the AFEQT and MAFSI summary scores were maximal at 12 months of follow-up, after which there was some reduction in benefit.

A subset of 1240 patients (56% of the CABANA population) was prospectively studied using a proprietary electrocardiographic monitoring system.[29] Symptom-driven 2-minute recordings, 24-hour autodetect triggered recordings for atrial tachyarrhythmias once per month in the first year followed by quarterly recordings, and biannual 96-hour Holter recordings for the period of the trial were used to determine AF recurrence and burden. Catheter ablation was associated with a significant reduction in the recurrence of symptomatic AF (HR 0.49; 95% CI 0.39–0.61; $P < .001$), any AF (HR 0.52; 95% CI 0.45–0.60; $P < .001$), and a composite of AF, atrial flutter, or atrial tachycardia (HR 0.53; 95% CI 0.46–0.62; $P < .001$) over a follow-up of 5 years. AF burden was significantly reduced in both randomized arms. However, AF burden was lower at 14.7% in the ablation arm compared to 20.8% in the medical therapy arm ($P \leq .01$). AF burden was significantly reduced in the ablation arm for both paroxysmal and persistent AF. The relationship between reduction in AF burden and improvement in QOL and other clinical outcomes was not reported. Thus, in symptomatic patients with AF and risk factors for stroke, catheter ablation was not associated with an improvement in clinical outcomes as compared to AAD therapy. However, ablation resulted in a durable improvement in QOL and reduction in atrial arrhythmia recurrence and AF burden over a follow-up period of 5 years.

EAST-AFNET 4 trial

The EAST-AFNET 4 study was an international, open-label, randomized trial with blinded outcome assessment that assigned patients with early AF (diagnosed within a year of enrollment) to early rhythm control or usual care. Patients at risk for cardiovascular events were enrolled, which

included patients >75 years of age or with a prior history of stroke or transient ischemic attack and patients with 2 or more of the following features of age >65 years, female sex, HF, hypertension, diabetes, chronic kidney disease stage 3 and 4, and left ventricular hypertrophy. Key exclusion criteria included limited life expectancy, severe renal disease, prior AF ablation, and previous therapy failure with amiodarone. A total of 2789 patients were enrolled a median of 36 days after the first diagnosis of AF and underwent randomization. About 30% of patients in both the groups did not have any symptoms attributable to AF at baseline. The trial was stopped for efficacy after a median of 5 years of follow-up. Patients in the rhythm control arm had received therapy with ablation (19.4%) or AAD therapy (45.7%) by 2 years of follow-up. Patients in the usual care arm mostly received rate control therapy (85.4% of patients at 2 years). The first primary composite endpoint of death from cardiovascular causes, stroke, or hospitalization with worsening of HF or acute coronary syndrome occurred less often in the early rhythm control arm (HR 0.79, 95% CI 0.66–0.94; $P = .005$). The second primary endpoint of nights spent in the hospital was not significantly different between the groups, and the primary safety endpoint event rate also did not differ significantly. Patients in the rhythm control arm were more often in sinus rhythm (82%) compared to the usual care arm (60.5%), as determined by electrocardiograms during follow-up visits. At 2 years of follow-up, most patients in both the groups (>70%) were asymptomatic.

EAST-AFNET 4 likely excluded patients very symptomatic from AF, as they could have had a perceived benefit from a rhythm management strategy. Only patients in the rhythm control arm were required to transmit a single-lead electrocardiogram twice per week and also when symptomatic. Recurrent AF triggered an in-person visit (15.4% of patients in the rhythm control arm) to escalate therapy as clinically indicated. The trial did not include detailed information on recurrent AF or AF burden.

Rhythm control therapy (including ablation) offered early in the course of AF to symptomatic and asymptomatic patients with concomitant cardiovascular conditions is therefore associated with improved clinical outcomes. It does not appear to matter whether sinus rhythm is maintained by ablation or AADs, as long as rhythm is monitored and changes in therapy are made if AF recurs. It remains to be seen if the improvement in outcomes is related to a decrease in recurrence of AF or a reduction in AF burden.

Atrial fibrillation and heart failure

In the Framingham Heart Study, HF was associated with a markedly increased risk (odds ratio 4.5 for men and 5.9 for women) for developing AF during a 38-year period of follow-up.[30] Analysis of the Framingham cohort has confirmed the complex relationship between HF and AF. It has been established that new-onset/incident AF is associated with higher all-cause mortality in patients with both prevalent HF with a reduced ejection fraction and HF with a preserved ejection fraction as compared with a population with no HF.[31] AF has been shown to have an unfavorable effect on patients with chronic HF, with lower peak workload and peak oxygen uptake as assessed by graded bicycle ergometry.[32] The onset of AF in patients with HF is associated with worsening NYHA functional class, decrease in peak oxygen consumption and cardiac index, and an increase in the severity of mitral and tricuspid regurgitation.[33] Table 5 lists randomized controlled trials assessing the efficacy of ablation for AF in patients with HF, the definition of AF recurrences, the methods used to detect recurrent AF and AF burden, and the primary outcomes of the trials.

Effect of ablation on atrial fibrillation burden and ejection fraction in heart failure

The Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device (AATAC) trial established the superiority of ablation over amiodarone in achieving freedom from AF.[34] Although AF recurrence was evaluated based on remote monitoring of the implanted cardiac devices, formal information on AF burden was not reported. The CAMERA-MRI[35] study randomized 68 patients with persistent AF and idiopathic HF with a left ventricular ejection fraction (LVEF) $\leq$ 45% to catheter ablation or medical rate control therapy. At 6 months, LVEF as assessed by cardiac magnetic resonance imaging improved by 18% $\pm$ 13% in the ablation arm compared with 4.4% $\pm$ 13% in the medical arm ($P < .0001$). The average AF burden measured by loop monitors post catheter ablation was 1.6% $\pm$ 5%. The adequacy of rate control therapy in the medical arm was confirmed by serial Holter monitoring. The restoration of sinus rhythm with a low AF burden was hence associated with a significant improvement in LVEF at 6 months of follow-up. However, the study had a small sample size, had short-term follow-up, and was underpowered to detect clinical outcomes of morbidity and mortality.

Atrial fibrillation ablation and clinical outcomes in heart failure

The Catheter Ablation versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial was designed to test whether ablation of AF by PVI would improve the clinical endpoints of morbidity and mortality.[36] CASTLE-AF was an open-label, prospective, randomized, controlled, international, multicenter clinical trial. Patients 18 years or older with symptomatic paroxysmal or persistent AF, who had failed or were unwilling to take amiodarone therapy and with an LVEF $\leq$ 35%, were included in the study. Patients were also required to have a dual-chamber ICD or a cardiac resynchronization therapy defibrillator device with home monitoring capabilities. Patients with a left atrial diameter > 6 cm, contraindications to chronic anticoagulation therapy, previous ablation procedures, recent acute coronary syndromes

or cerebrovascular accidents, or cardiac assist devices or patients awaiting cardiac transplantation were the major exclusions. After a run-in period of 5 weeks during which HF management was optimized, patients were randomized to catheter ablation or medical therapy for AF.

After a median follow-up of 38.7 months, the composite endpoint of death or hospitalization for worsening HF occurred in 28.5% of patients in the ablation group compared to 44.6% of patients in the medical therapy group ($P = .006$). Patients who underwent catheter ablation had an increase in LVEF (8% vs 0.2%; $P = .005$), lower AF burden (27% vs 64%) and longer 6-minute walk distance at 12 months (41 meters vs 1 meter; $P = .001$). The mortality benefit in the ablation arm emerged after about 3 years, primarily driven by a lower rate of cardiovascular death. The study thus demonstrated that ablation was effective in lowering AF burden with an improvement in LVEF and clinical outcomes. Whether further reductions in AF burden would lead to additional improvement in clinical outcomes remains unanswered. The study had important limitations, including nonblinded randomization, which could have introduced bias; ablation performed by experienced high-volume operators, which could account for the low complication rates; baseline ICD and cardiac resynchronization therapy defibrillator therapy, which could have affected overall mortality; and a predominant rate control strategy in the medical therapy arm.

Summary and knowledge gaps

Trials of ablation in AF have focused on several broad patient groups: symptomatic patients who have failed medical therapy; clinical outcomes with ablation, potentially as first-line therapy, even in asymptomatic or minimally symptomatic patients; and patients with HF. While clinical trials have helped to clarify many factors associated with indications for and outcomes with ablation of AF, there remain many unanswered questions for further clinical studies. Table 6 summarizes our current understanding of ablation for AF and knowledge gaps that require further study. Key questions are the impact of ablation on clinical outcomes in asymptomatic and minimally symptomatic patients, how much reduction in AF is necessary to favorably impact clinical outcomes, and how a better understanding of mechanisms should dictate the timing and approach to ablation.

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Authorship

All authors attest they meet the current ICMJE criteria for authorship.

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