

Radiofrequency Ablation Versus Cryoablation as First-Line Treatment

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Catheter ablation has been shown to be more effective at maintaining sinus rhythm and improving quality of life when compared to antiarrhythmic drugs. Radiofrequency and cryoablation are two effective methods.

catheter ablation

atrial fibrillation

1. Medical Management of Atrial Fibrillation

Antiarrhythmic drugs (AADs) are the first-line treatment of choice for restoring and maintaining sinus rhythm in patients with symptomatic atrial fibrillation (AF). In patients for whom rhythm control is not appropriate, rate control can be used instead by exerting a negative chronotropic effect to reduce the ventricular rate in combination with anticoagulation for stroke prevention. AADs have demonstrated debatable results with class 1 and 3A agents terminating 50% of AF episodes, whilst amiodarone is able to terminate only 70% of AF episodes ^[1]. They are also associated with significant side effects and can be proarrhythmic ^[2].

AF catheter ablation has become established as the superior alternative to maintaining sinus rhythm and achieving an improvement in quality of life. Catheter ablation also offers curative treatment in contrast to AADs, through electrical isolation of the pulmonary veins. Current guidelines recommend AF ablation in the event of AAD failure; however, the role of AF ablation as the first-line treatment option for AF is surfacing. At present, the European Society of Cardiology and American College of Cardiology guidelines provide a restricted recommendation for AF ablation as first-line therapy, limiting it to a highly selected patient group with symptomatic paroxysmal (class IIa) or persistent AF (class IIb) without major risk factors for AF recurrence such as left atrial size, AF duration, and renal dysfunction as well as consideration of patient preference ^{[3][4]}. Overall, these guidelines provide comprehensive information regarding indications to treatment strategies and relevant clinical data for patients with AF ^[3].

2. Radiofrequency Ablation as First-Line Treatment

The first catheter ablation in humans was performed in 1981 by Scheinman through the delivery of DC shocks to an electrode catheter ^[5]. This provided proof of principle for closed-chest catheter ablation for arrhythmias; in particular, AF. Scheinman's work was the foundation for the development of radiofrequency (RF) energy catheters allowing the delivery of precise lesions. Haissaguerre, a French electrophysiologist, later pioneered the use of RF catheter ablation in patients with AF by inserting the catheter into the pulmonary veins (PVs) of human hearts and mapping the triggers for AF ^[6]. He determined that the origin of these triggers was found in the PVs in 96% of

patients. Through mapping and ablating these foci in the PVs, 62% of patients had freedom from AF without the need for AAD therapy. Haissaguerre also then developed a new strategy for PV isolation (PVI). In contrast to his earlier work of mapping individual triggers, he used a multielectrode circular catheter placed at the junction of the PV and the left atrium to localise these. He then electrically isolated the entire PV from the atrium, leading to the development of PV isolation as an empirical treatment for AF. This led to the current use of catheter ablation as a standard treatment for AF.

Three key trials have addressed the relative differences in ablation and pharmacological therapy as first-line interventions in paroxysmal AF (PAF). The Radiofrequency Ablation versus Antiarrhythmic Drugs as First-line Treatment of Symptomatic Atrial Fibrillation (RAAFT-1) trial was the first to suggest the merits of catheter ablation as a first-line therapy for AF. In this trial, 70 patients with symptomatic PAF (96% PAF; mean age 54 years) were randomised to either catheter ablation or AAD therapy (**Table 1**). The ablation protocol comprised of PV antrum isolation confirmed by recordings from a circular mapping catheter. In this early trial, only non-irrigated tip ablation catheters (8 mm) were used. At the end of 1-year follow-up, 63% of patients assigned to AAD therapy experienced ≥ 1 recurrence of symptomatic AF, as compared with 13% of those assigned to the PV antrum isolation arm. These figures accounted for an 80% relative risk reduction with catheter ablation ($p < 0.001$). In addition, PV antrum isolation was associated with a significantly lower rate of hospitalisation (9% versus 54%; $p < 0.001$) and improved quality of life.

Table 1. Catheter ablation versus antiarrhythmic drugs in the treatment for PAF.

Study	Treatment Arms	Year	Patient Number	Median Follow-Up (Months)	AF Ablation Strategy	Paroxysmal AF Cases	Definition of Recurrence	Freedom from AF Recurrence: CA	Freedom from AF Recurrence: AAD	p-Value
RAAFT-1	RFA CA as first line therapy	2005	70	12	PVI	96%	AF recurrence lasting > 15 s	87%	37%	$p < 0.001$
MANTRA-PAF	RFA CA as first line therapy in PAF	2012	294	24	PVI + additional lesions as per physician preference	100%	AF recurrence lasting > 1 min	85%	71%	$p = 0.004$
RAAFT-2	RFA CA as first line therapy in PAF	2014	127	24	PVI + additional lesions as per physician preference	98%	>30 s of AF/AT/AFL occurrence	53%	41%	$p = 0.03$
STOP-AF	Cryoballoon CA as second line	2013	245	12	PVI	100%	>30 s of AF/AT/AFL occurrence	69.9%	7.3%	$p < 0.001$

Study	Treatment Arms	Year	Patient Number	Median Follow-Up (Months)	AF Ablation Strategy	Paroxysmal-AF Cases	Definition of Recurrence	Freedom from AF Recurrence: CA	Freedom from AF Recurrence: AAD	p-Value	
	therapy in PAF										
EARLY-AF	Cryoballoon CA as first line therapy in PAF	2021	303	12	PVI	95%	>30 s of AF/AT/AFL occurrence	57.1%	32.2%	$p < 0.001$	estimated, ons were the AAD
Cryo-FIRST	Cryoballoon CA as first line therapy in PAF	2021	218	12	PVI + additional lesions (if incomplete PVI or focal trigger identification)	100%	>30 s of AF/AT/AFL occurrence	82.2%	67.6%	$p = 0.01$	equency olation in Drugs as

First-Line Treatment of Paroxysmal Atrial Fibrillation (RAAFT-2) trial.

MANTRA-PAF randomised 294 patients with symptomatic PAF to either RFA or AADs. In contrast with the RAAFT trial, the ablation methods used were heterogeneous and varied from PV isolation guided by circular mapping catheter to circumferential PV ablation guided by a three-dimensional electroanatomic mapping system (CARTO Biosense Webster, Diamond Bar, CA, USA). The utilisation of different ablation methods was at the discretion of the enrolling cardiologist. The primary study endpoint was cumulative AF burden (symptomatic and asymptomatic) during 7-day Holter recordings after 3, 6, 12, 18, and 24 months of follow-up. Freedom from any AF after 24 months, quality of life, and burden of symptomatic AF were included among the secondary endpoints. The trial failed to meet its primary endpoint of a reduction in the cumulative burden of AF >2 years; however, it still demonstrated that CA was associated with a lower rate of AF recurrence compared with AAD (15% versus 29%, respectively; $p = 0.004$).

In contrast with RAAFT, the treatment failure of MANTRA-PAF in achieving its primary endpoint may be due to its discretionary use of circumferential ablation without confirmation of PV isolation with a circular mapping catheter. This strategy has shown inferiority to PV isolation confirmed by a circular mapping catheter [7]. It is also important to note that 36% of patients allocated to AAD crossed over to the RFA arm, as outcomes were analysed according to the intention-to-treat principle, and this may have further impacted the results.

The RAAFT-2 trial utilised similar inclusion criteria, endpoints, and ablation techniques as RAAFT; however, it had a significant exception with the utilisation of irrigated-tip ablation catheters. A total of 127 patients with symptomatic PAF were randomised to either RFA or AAD. After 2 years, AF/atrial tachycardia recurred in 54.5% of the RFA group compared with 72.1% of the AAD group ($p = 0.016$) at follow-up. The RAAFT-2 trial also had a substantial number of patients crossing over from AAD to RFA (26%).

These three studies used distinct ablation techniques; however, MANTRA-PAF and RAAFT-2 demonstrated an overall low level of success rates for freedom from atrial arrhythmias in the ablation arm. There was also no procedural standardisation between studies, and endpoints differed. AAD use also differed post-ablation in all studies: in RAAFT-1, beta blocker therapy was administered post-ablation as per physician preference. In RAAFT-

2, AADs were only administered during the 90-day blanking period post-ablation if required, and MANTRA-PAF allowed AADs in the initial 3 months post-ablation. Furthermore, the outcomes of point-by-point PVI by RF ablation are dependent on operator proficiency given the complexity of creating contiguous curvilinear ablation lesions using catheters initially developed for ablating focal arrhythmic targets [8].

3. Cryoablation as First-Line Treatment

Another approach to isolate PVs in AF involves the use of a cryoballoon. In contrast to PVI procedures, cryoballoon ablation is considered faster to perform compared to PVI since the point-by-point creation of individual lesions around each pulmonary vein may take longer to successfully achieve. Moreover, cryoballoon ablation is generally regarded as easier to learn and perform for electrophysiologists, as opposed to precise catheter manipulation and careful lesion creation in PVI. However, there is concern regarding higher radiation exposure during fluoroscopy. The introduction of cryoballoon technology in 1999 was a breakthrough invention as operators were able to achieve electrical isolation of the PVs with one single application, in contrast to the point-by-point lesion set delivered by RFA, thereby making it more appealing. The Arctic Front Balloon (Medtronic CryoCath) was the first cryoballoon technology used for ablation. This involved the use of the double-walled 10.5Fr cryoballoon catheter, which would inflate and fill with coolant (nitrous oxide) to deliver ablation lesions between the PVs and the LA. The 15Fr FlexCath Steerable Sheath was a deflectable delivery sheath that would allow introduction of the cryoballoon into the LA. The CryoConsole was the third component of the cryoballoon technology, which contained the coolant and mechanical components. The nitrous oxide would then be delivered to the double-walled balloon where it would undergo a liquid-to-gas transformation, delivering cooling temperatures of approximately -80°C .

There were three major randomised trials comparing cryoballoon ablation to AADs as first-line therapy of AF. These include the Catheter Cryoablation Versus Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation (Cryo-FIRST) trial [9], the Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF) trial [10], and the Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation (STOP-AF First) trial [11] (Table 1).

These three studies included a total of 724 patients in their intention-to-treat. Across them, the mean ages were 60 years (STOP-AF First), 60 years (EARLY-AF), and 52 years (CRYO-First). Most patients were male (61%, STOP-AF First; 68%, CRYO-First; 69%, EARLY-AF) and the majority of patients had normal left ventricular function and left atrial size. Although the patients had been enrolled at an early stage of diagnosis (median time from first AF diagnosis of 12 months), patients were mostly high symptomatic from their arrhythmia on the basis of their Atrial Fibrillation Effect on Quality-of-life (AFEQT) scores (mean score 60.1). Three-minute freezes were standardised in EARLY-AF, while they were recommended in STOP-AF First and Cryo-FIRST. Procedure duration was shortest in Cryo-FIRST (84 ± 29 min), moderate in EARLY-AF (106 min (IQR: 89–131 min)), and longest in STOP-AF First (139 ± 74 min; $p < 0.0001$). Class Ic AADs were the initial AAD of choice used in the antiarrhythmic drug group (first agent prescribed in 92% in Cryo-FIRST, 82% in EARLY-AF, and 79% in STOP-AF First). In EARLY-AF, 30% of the AAD group needed several antiarrhythmic drug trials to achieve suppression of AF on implantable monitoring.

Subtherapeutic antiarrhythmic drug dosing was observed in 7% in Cryo-FIRST, 0% in EARLY-AF, and 21% in STOP-AF First, with 18%, 0%, and 12% permanently discontinuing the study drug, respectively.

There was no crossover from AADs to ablation before the occurrence of a primary endpoint event in EARLY-AF, but it occurred in Cryo-FIRST (14%) and STOP-AF First (15%). STOP-AF and CRYO-FIRST assessed tachyarrhythmia occurrence with 12-lead electrocardiography at scheduled time points and 24 h Holter monitoring during months 6 to 12. Meanwhile, EARLY-AF monitored atrial tachyarrhythmias with continuous cardiac rhythm monitoring with an implantable cardiac device.

In contrast to the results of previous studies of first-line RFA, first-line cryoablation consistently demonstrated significant reductions in arrhythmia recurrence (**Table 1**). EARLY-AF demonstrated that after one year, atrial tachyarrhythmia recurrence occurred in 42.9% of the patients who underwent ablation versus 67.8% of the patients receiving drug therapy (HR 0.48, 95% CI 0.35–0.66, $p < 0.001$). Cryoballoon ablation was also associated with lower recurrence of symptomatic atrial tachyarrhythmia (11.0% versus 26.2%) and a significant reduction in AF burden. The rate of serious adverse events was similar in the two groups (3.2% versus 4.0%). STOP-AF showed that initial success of the ablation procedure was achieved in 97% of patients, and procedure-related serious adverse events were uncommon. The percentage of patients with treatment success at 12 months (freedom from initial failure of the procedure or atrial arrhythmia recurrence after day 90) was higher with ablation than with drug therapy (74.6% versus 45.0%; $p < 0.001$). CRYO-FIRST showed freedom from atrial arrhythmias was higher in patients who underwent cryoablation compared to the AAD treatment arm (82.2% of versus 67.6%, HR = 0.48, $p = 0.01$). The incidence rate of symptomatic palpitations was notably reduced in the cryoballoon compared to the AAD arm (7.61 days/year versus 18.96 days/year; IRR = 0.40, $p < 0.001$).

It is important to note that each study employed different rhythm monitoring protocols, which could impact clinical outcomes. Intermittent non-invasive cardiac rhythm monitoring was used in Cryo-FIRST and STOP-AF, whereas EARLY-AF used implantable cardiac monitoring. Non-invasive monitoring is less sensitive in the detection of paroxysmal arrhythmias and can exaggerate the approximations of arrhythmia-free survival. EARLY-AF was the only study to provide AF burden data as it employed implantable cardiac monitoring, where it demonstrated a significant reduction in AF burden with ablation. However, the cardiac monitor was implanted when treatment was initiated so it did not evaluate change in AF burden from baseline. Additionally, continuous monitoring captured a higher AF recurrence.

These substantial randomised trials offer definitive evidence that AF ablation is superior to AADs as first-line treatment of patients with paroxysmal AF. The outcomes from the pivotal STOP-AF trial also formed the basis for the U.S Food and Drug Administration (FDA) approval for the Arctic Front CryoAblation Catheter system for the treatment of drug refractory PAF in 2010.

4. Radiofrequency Ablation Versus Cryoablation as First-Line Treatment

Two randomised studies directly compared both cryoablation and RFA for the treatment of drug-refractory PAF. These include FIRE AND ICE and CIRCA-DOSE. Both showed that these two approaches are comparable in terms of efficacy and safety.

In the FIRE AND ICE trial, a total of 762 patients were randomised to each arm with an average follow-up of 18 months (**Table 2**). The study did not find any significant difference between the two methods with regards to the efficacy endpoint. Additionally, both were comparable in terms of safety outcomes. A subsequent modified intention-to-treat analysis showed that cryoballoon was superior to RFA in the rate of repeat ablations, cardioversions, and cardiovascular re-hospitalisation during follow-up. Moreover, it demonstrated that in patients who underwent re-ablation, the number of electrical conduction relapses between the pulmonary veins and the left atrium was substantially reduced when the cryoballoon was used for the initial PV isolation at enrolment. This may be explained by cryoballoon catheters having a higher stability compared to RF catheters. Moreover, it is important to highlight that the adoption of new catheter technology was not uniform in the study. Specifically, the second-generation cryoballoon was used in 75.6% of patients in the cryoballoon arm, while only 24.7% of patients in the radiofrequency catheter group received advanced-generation catheters. This imbalanced use of second-generation cryoballoon technology versus advanced-generation catheters could have masked the true efficacy of the advanced contact-force sensing technology. Although the primary efficacy outcome did not show a difference between catheter generations, it remains essential to discern the impact of recently introduced technology on overall clinical outcomes, given the influx of new technologies in the field of AF ablation.

Table 2. Cryoablation and RFA for the treatment of PAF.

Study	Treatment Arms	Year	Patient Number	Median Follow-Up (Months)	Definition of Recurrence	Freedom from Recurrence (12 Months)	Outcome	Monitoring Method	Complications
FIRE AND ICE	RFA vs. cryoballoon PAF	2016	762	18	>30 s, with 3-month blanking period	RFA 76.9% Cryoballoon: 78.7%	Cryoballoon is noninferior to RFA with similar safety profiles	Holter monitor	RFA 12.8% versus CBA 10.2% ($p = 0.24$)
CIRCA-DOSE	Contact force RFA vs. 4 min cryoballoon vs. 2 min cryoballoon in PAF	2019	346	12	>30 s, with 84-day blanking period	RFA 53.9% 4 min cryoballoon: 52.2% 2 min cryoballoon: 51.7%	No significant differences between ablation strategies in reducing recurrences	Implantable loop monitor	RFA 2.6% versus CBA (4 min) 5.2% versus CBA (2 min) 6%

The cryoballoon was also shown to be more cost-effective due to lower resource utility post-ablation and lower payer cost than the RF arm. In summary the FIRE AND ICE trial confirmed the non-inferiority of the cryoballoon to RF ablation in patients with PAF. It also demonstrated a similar safety profile. Prior to this study, the European Society of Cardiology and the Heart Rhythm Society recommended radiofrequency energy as the leading ablation

CBA: cryoballoon ablation; PAF: paroxysmal AF; RFA: radiofrequency ablation.

energy source. Following the trial, both societies updated their consensus documents to advocate for both cryoablation and RFA as a safe and efficient modality for the treatment of AF.

The CIRCA-DOSE also directly compared both ablation modalities and its findings were in support of the FIRE AND ICE trial. However, there were two main differences. First, both RF and cryoablation were performed with the latest-generation catheter (contact force catheter and cryoballoon). CIRCA-DOSE further compared two cryoablation regimens (4 min versus 2 min freezes) to the use of contact-force-guided RF to isolate the PVs in patients with PAF. Secondly, all patients underwent implantation of a loop recorder. There were no significant differences between the two different ablation approaches in terms of recurrent atrial arrhythmias' occurrence in the first year. However, it did show an overall >98% reduction in arrhythmic load, but with no significant difference between the different ablation methods in the intention-to-treat analysis.

Furthermore, no significant difference in 1-year efficacy was seen between the 2 min and the 4 min freeze procedures; however, procedure duration was significantly reduced with the 2 min freeze protocol. Overall, the CIRCA-DOSE trial demonstrated that PVI completed either by cryoballoon or contact-force-guided RFA resulted in comparable freedom from atrial arrhythmias, as observed by implantable cardiac monitoring.

References

1. Roy, D.; Talajic, M.; Dorian, P.; Connolly, S.; Eisenberg, M.J.; Green, M.; Kus, T.; Lambert, J.; Dubuc, M.; Gagne, P.; et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N. Engl. J. Med.* 2000, 342, 913–920.
2. Kirchhof, P.; Camm, A.J.; Goette, A.; Brandes, A.; Eckardt, L.; Elvan, A.; Fetsch, T.; van Gelder, I.C.; Haase, D.; Haegeli, L.M.; et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N. Engl. J. Med.* 2020, 383, 1305–1316.
3. Hindricks, G.; Potpara, T.; Dagres, N.; Arbelo, E.; Bax, J.J.; Blomström-Lundqvist, C.; Boriani, G.; Castella, M.; Dan, G.-A.; Dilaveris, P.E.; et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur. Heart J.* 2021, 42, 373–498.
4. January, C.T.; Wann, L.S.; Calkins, H.; Chen, L.Y.; Cigarroa, J.E.; Cleveland, J.C., Jr.; Ellinor, P.T.; Ezekowitz, M.D.; Field, M.E.; Furie, K.L.; et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J. Am. Coll. Cardiol.* 2019, 74, 104–132.

5. Scheinman, M.M.; Morady, F.; Hess, D.S.; Gonzalez, R. Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias. *JAMA* 1982, 248, 851–855.
6. Haïssaguerre, M.; Jaïs, P.; Shah, D.C.; Takahashi, A.; Hocini, M.; Quiniou, G.; Garrigue, S.; Le Mouroux, A.; Le Métayer, P.; Clémenty, J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N. Engl. J. Med.* 1998, 339, 659–666.
7. Khaykin, Y.; Skanes, A.; Champagne, J.; Themistoclakis, S.; Gula, L.; Rossillo, A.; Bonso, A.; Raviele, A.; Morillo, C.A.; Verma, A.; et al. A randomized controlled trial of the efficacy and safety of electroanatomic circumferential pulmonary vein ablation supplemented by ablation of complex fractionated atrial electrograms versus potential-guided pulmonary vein antrum isolation guided by intracardiac ultrasound. *Circ. Arrhythmia Electrophysiol.* 2009, 2, 481–487.
8. Providencia, R.; Defaye, P.; Lambiase, P.D.; Pavin, D.; Cebon, J.P.; Halimi, F.; Anselme, F.; Srinivasan, N.; Albenque, J.P.; Boveda, S. Results from a multicentre comparison of cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: Is cryoablation more reproducible? *Europace* 2017, 19, 48–57.
9. Kuniss, M.; Pavlovic, N.; Velagic, V.; Hermida, J.S.; Healey, S.; Arena, G.; Badenco, N.; Meyer, C.; Chen, J.; Iacopino, S.; et al. Cryoballoon ablation vs. antiarrhythmic drugs: First-line therapy for patients with paroxysmal atrial fibrillation. *Europace* 2021, 23, 1033–1041.
10. Andrade, J.G.; Wells, G.A.; Deyell, M.W.; Bennett, M.; Essebag, V.; Champagne, J.; Roux, J.F.; Yung, D.; Skanes, A.; Khaykin, Y.; et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. *N. Engl. J. Med.* 2021, 384, 305–315.
11. Wazni, O.M.; Dandamudi, G.; Sood, N.; Hoyt, R.; Tyler, J.; Durrani, S.; Niebauer, M.; Makati, K.; Halperin, B.; Gauri, A.; et al. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. *N. Engl. J. Med.* 2021, 384, 316–324.

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