Keynote Lecture Series

Ablation or drug therapy for initial atrial fibrillation

Jason G. Andrade[1,2,3]

[1]University of British Columbia, Vancouver, Canada; [2]Center for Cardiovascular Innovation, Vancouver, Canada; [3]Montreal Heart Institute, Université de Montréal, Montréal, Canada

Correspondence to: Dr. Jason G. Andrade, MD. University of British Columbia, Vancouver, Canada; Center for Cardiovascular Innovation, Vancouver, Canada; Montreal Heart Institute, Université de Montréal, Montréal, Canada; Gordon and Leslie Diamond Health Care Centre, 9th Floor, 2775 Laurel Street, Vancouver, BC V5Z 1M9, Canada. Email: jason.andrade@vch.ca.

Atrial fibrillation (AF) is a chronic heart rhythm disorder, characterized by exacerbations interspersed with clinical remissions. Antiarrhythmic drugs (AADs) are traditionally considered to be the preferred initial therapy for the maintenance of sinus rhythm however, these medications have modest efficacy and significant adverse effects. Recent clinical trials have evaluated the role of catheter ablation as the initial therapeutic intervention, demonstrating that cryoballoon ablation significantly reduces atrial tachyarrhythmia recurrence and arrhythmia burden, produces clinically meaningful improvements in symptoms and quality of life, and significantly decreases healthcare resource utilization. In contrast to AADs, catheter ablation appears to be a disease modifying therapy, significantly reducing the progression to more advanced forms of AF. These findings are relevant to patients, providers, and healthcare systems, helping inform the decision regarding the initial choice of rhythm-control therapy in patients with treatment-naïve AF.

Keywords: Atrial fibrillation (AF); antiarrhythmic drugs (AADs); catheter ablation; cryoballoon; cryotherapy

Submitted Sep 18, 2023. Accepted for publication Nov 23, 2023. Published online Jan 23, 2024.
doi: 10.21037/acs-2023-afm-0159
View this article at: https://dx.doi.org/10.21037/acs-2023-afm-0159

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder observed in clinical practice. Current estimates suggest that AF affects 2–3% of the general population (1). In addition to being a common disorder, AF is associated with significant symptoms, resulting in significantly impaired quality of life, as well as significantly increased risk of major adverse cardiovascular outcomes (e.g., heart failure, stroke and systemic thromboembolism, as well as cardiovascular and non-cardiovascular mortality). Taken together, the major management goals for AF focus on improving arrhythmia-related symptoms and reducing the morbidity associated with AF by employing strategies that meaningfully reduce AF-associated healthcare utilization (2).

Ablation or drug therapy for initial AF

The initial management of AF has been one of great discussion for several years. Previous randomized trials performed in the late 1990s to early 2000s suggested that there was no significant difference in cardiovascular outcomes between patients treated with rate-control *vs.* rhythm-control strategy (3-5). Given this evidence base, the preferred strategy for initial AF management was perceived to be rate control, which has become foundational for all patients with AF to improve arrhythmia-related symptoms, exercise tolerance, and quality of life, as well to prevent tachycardiomyopathy. However, despite the evidence from these studies, it is known that restoration and maintenance of sinus rhythm can alleviate symptoms and improve exercise capacity/quality of life. More recently, the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) re-examined the utility of rhythm control, however, instead of focusing on patients with established AF, the EAST-AFNET 4 investigators focused on patients with newly diagnosed AF (specifically, within one year) (6). In contrast to the prior large rate control *vs.* pharmacologic rhythm control trials, the EAST-AFNET

trial demonstrated that early rhythm control was associated with significant reductions in the composite primary outcome of cardiovascular death, stroke, and hospitalization for worsening heart failure and acute coronary syndrome (from 5.0%/year to 3.9%/year) over a median follow-up of 5.1 years. Importantly, this result was driven by a significant reduction in cardiovascular death [1.0% *vs.* 1.3% per year; hazard ratio (HR) 0.72; 95% confidence interval (CI): 0.52–0.98] and a significant reduction in stroke (0.6% *vs.* 0.9%/year; HR 0.65; 95% CI: 0.44–0.97), with no significant difference observed in the rates of hospitalisation (6). Consistent with guidelines, rhythm control in the EAST-AFNET 4 trial was predominantly pharmacological, however, in contrast to the previous rate *vs.* rhythm control trials, the majority of patients in EAST-AFNET received Class Ic antiarrhythmic drug (AAD) therapy (*vs.* Class III agents in AFFIRM and AF-CHF) (7). Given this evidence, there has been renewed interest in an initial strategy of rhythm control, however the optimal first treatment for initial AF is still a matter of debate.

AAD therapy for rhythm control

The efficacy and safety of AAD therapy has been evaluated in multiple placebo-controlled trials, with several systematic reviews and meta-analyses having been published on the topic. Commonly used AADs include flecainide and propafenone (Class Ic use-dependent sodium channel blocking drugs), sotalol (Class III reverse use-dependence I_{kr} inhibition as well as beta-adrenergic receptor blocker), amiodarone (multichannel blocker and a non-selective beta-blocker), and dronedarone (multichannel blocker similar to amiodarone). The pooled rate of AF recurrence was noted to be between 64–84% at 1 year in controls, with antiarrhythmic therapy significantly reducing the recurrence rates by 45–80%. In network analysis, the most effective drug was amiodarone [odds ratio (OR) 0.22], followed by flecainide (OR 0.31), propafenone (OR 0.36), sotalol (OR 0.40), and dronedarone (OR 0.53) (8). Although superior to placebo in the prevention of arrhythmia recurrence, in absolute terms these agents have only modest efficacy at maintaining sinus rhythm (freedom from AF in the range of 30–50% at one year) (8,9). Moreover, AAD therapy is associated with significant side-effects. Compared to placebo, pro-arrhythmic events (ventricular or brady-arrhythmia) were significantly more frequent with sotalol (OR 6.44, 95% CI: 1.03–40.24, P=0.047) and propafenone (OR 4.06, 95% CI: 1.13–14.52, P=0.035). More concerningly, all-cause mortality was increased with long-term use of sotalol and amiodarone (OR 4.32 and OR 2.73, respectively) (8).

Catheter ablation for rhythm control

Over the last forty years these procedures have evolved significantly as we have gained a greater understanding of AF pathophysiology. Initial percutaneous catheter ablation procedures were designed based on the "multiple wavelet hypothesis", which was the dominant mechanistic theory of AF pathophysiology. This theory postulated that AF results from the presence of multiple independent coexisting wavelets that are occurring simultaneously and propagating randomly throughout the atria. This hypothesis postulated that AF could be initiated and then perpetuated indefinitely if the atrium had a sufficient area with adequately short refractory periods. As such, the early percutaneous procedures attempted to replicate the linear ablation of a surgical Cox maze procedure, aiming to decrease arrhythmia perpetuation by reducing the excitable mass of atrial tissue (e.g., compartmentalizing the atrium into smaller regions incapable of sustaining the circulating wavelets). This approach was associated with only moderate success, spurring interest in alternate interventional approaches.

In the late 1990's, Haïssaguerre and colleagues (10) demonstrated that AF was a triggered arrhythmia initiated by rapid discharges originating from the pulmonary veins (PVs). This led to percutaneous procedures focused on eliminating, or containing, the triggering foci within the PV. Over the past twenty years, the technique of PV isolation (PVI) has evolved significantly from focal ablation of discrete triggers within the PV musculature, to segmental ablation of the ostial pulmonary venous myocardial sleeves, to circumferential ablation of the left atrial (LA) myocardium outside of the tubular veins with a goal of circumferential electrical PVI (i.e., electrical conduction block into and out of the PVs). This contemporary approach not only targets the initiating triggers of AF (the PVs) but also the mass of electrically active LA tissue capable of perpetuating AF.

These percutaneous PVI procedures have evolved from an "experimental therapy" to becoming the standard of care for the maintenance of sinus rhythm when AADs have been ineffective, are contraindicated, or cause intolerable adverse effects. This evolution has been predicated on the results of multiple studies examining the outcomes of catheter

ablation versus AAD therapy or rate-control agents. Both large-scale observational studies, as well as multiple randomized controlled trials have demonstrated that the success rate of catheter ablation in maintaining sinus rhythm is universally superior to that of drug therapy (11). In addition, catheter ablation has been shown to be superior to AADs for the improvement of symptoms, exercise capacity, and quality of life. However, these "second-line" trials focused on patients who had already failed AAD therapy. By design these trials preselected a population in whom AADs have already proven to be ineffectual, and thus biasing the results towards those patients randomized to catheter ablation. As such, it was not known whether early intervention (i.e., ablation performed prior to AAD failure) would offer similar benefits in preventing arrhythmia, improving quality of life, and reducing healthcare utilization.

Catheter ablation as a first-line therapy

Three randomized trials of "first-line" focal point-by-point radiofrequency ablation were performed in the early 2000s. These included the Radiofrequency Ablation *vs.* Antiarrhythmic Drugs as First-line Treatment of Symptomatic Atrial Fibrillation (RAAFT-1) trial, the Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) trial, and the Radiofrequency Ablation *vs.* Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation (RAAFT-2) trial (12-14). In aggregate, these three studies demonstrated that initial radiofrequency ablation was more effective than AADs at preventing arrhythmia recurrence, however there was no clinically meaningful improvements in quality of life or healthcare utilization. As a result, these studies had only a modest impact on clinical practice.

More recently three multicenter randomized clinical trials examined the role of first-line cryoballoon ablation. These included the Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF), the Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation (STOP-AF First), and the Catheter Cryoablation Versus Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation (Cryo-FIRST) trials (9,15,16). These three trials included a total of 724 relatively young and healthy patients with treatment-naïve paroxysmal AF.

The primary outcome for each of these trials was the recurrence of any atrial tachyarrhythmia (defined as AF, atrial flutter, or atrial tachycardia) at one year following treatment initiation, with catheter ablation resulting in a reduction in the absolute rates of atrial tachyarrhythmia recurrence ranging from 15% (Cryo-FIRST and STOP-AF First) to 25% (EARLY-AF). Despite differences in the trial design and arrhythmia monitoring, the relative benefit of first-line cryoablation was consistent between studies [HR 0.50 in Cryo-FIRST, 0.57 in STOP-AF First, and 0.63 in EARLY-AF; pooled relative risk (RR) 0.61] (17,18). In addition, the EARLY-AF trial demonstrated that the recurrence of symptomatic atrial tachyarrhythmia was significantly reduced with first-line ablation (absolute difference in symptomatic AF of 15.2%; RR 0.42), as was the reduction in AF burden (mean difference in the percentage time in AF of 3.3%±1.0% between the ablation and antiarrhythmic groups, respectively) (9).

Examination of the patients enrolled in these cryoballoon studies demonstrate that they had a significantly impaired quality of life at baseline [mean Atrial Fibrillation Effect on Quality-of-Life (AFEQT) score of 60]. At one year following treatment initiation, both groups experienced a significant improvement in quality of life, however, those randomized to catheter ablation achieved a significantly greater improvement in quality of life compared to those randomized to initial AAD therapy (9,15,17).

Significant reductions in healthcare utilization were observed for patients randomized to first-line cryoablation at one year following treatment initiation (absolute reduction 9%, RR 0.71), which was driven by significant reductions in all-cause hospitalization (RR 0.38), and numerical reductions in emergency department consultations (RR 0.78) and cardioversion (RR 0.60) (17).

At one year follow-up, the rate of serious adverse events was comparable between those randomized to first-line cryoballoon ablation and AAD therapy, however first-line cryoballoon ablation was associated with a slightly lower incidence of any adverse event at one year follow-up (RR 0.70; 95% CI: 0.54–0.89) (17).

Taken together, these randomized clinical trials demonstrated that an initial invasive strategy of cryoballoon catheter ablation resulted in significant and meaningful improvements in arrhythmia outcomes, patient-reported outcomes, and healthcare resource utilization. These studies, although clinically impactful, only followed patients for twelve months following treatment initiation. Longer-term follow-up would provide more information regarding the durability of intervention, downstream

healthcare utilization, and could provide novel insight into the natural history of AF (e.g., disease progression). Given the population with treatment naïve AF is relatively young, a comprehensive assessment of longer-term clinical effectiveness is important to inform decision-making and enabling patient empowerment regarding the choice of initial treatment.

Cryoballoon ablation as a first-line therapy: longer-term outcomes

Of the three first-line cryoballoon studies, only the EARLY-AF study program was designed as a pragmatic multi-phase platform, with the EARLY-AF trial designed to evaluate the effect of initial rhythm control treatment on short-term atrial tachyarrhythmia recurrence and healthcare utilization, and the PROGRESSIVE-AF study designed to evaluate the effect of initial rhythm control treatment on disease progression at 36 months of follow-up as assessed by an implantable continuous rhythm monitor (9,19,20).

Consistent with the one-year results, arrhythmia recurrence and AF burden at 36 months was significantly lower after initial cryoballoon ablation (56.5% recurrence after ablation *vs.* 77.2% with AAD therapy, HR 0.51; and mean difference in absolute AF burden of –1.9±0.7 favoring ablation) (19). In addition, patients randomized to initial cryoballoon catheter ablation achieved a significantly greater quality of life improvement [mean 7.4±2.2 point between-group difference in the AFEQT score, and mean 0.05±0.02 point between-group difference in the EuroQol-5 dimension (EQ-5D) score at 36 months], and were significantly less likely to report symptoms of AF at 36 months (RR 0.28; 95% CI: 0.13–0.61). Likewise, healthcare utilization was significantly lower in patients randomized to initial cryoballoon catheter ablation. At three years, 5.2% of the patients in the ablation group and 16.8% of those in the AAD group had been hospitalized (RR 0.31; 95% CI: 0.14–0.66). However, in contrast to the one-year data, adverse events were significantly less likely to have occurred in those patients randomized to initial cryoballoon catheter ablation at three years of follow-up (serious adverse events: 4.5% *vs.* 10.1%, and any adverse events: 11.0% *vs.* 23.5%).

Ablation as a first-line therapy: disease progression

AF is a chronic progressive disease. Although typically categorized on the basis of arrhythmia duration as paroxysmal (predominantly self-terminating episodes of AF lasting <7 days) or persistent AF (e.g., episodes lasting longer than 7 days), it is important to recognise that the underlying disease process is dynamic. Specifically, AF usually manifests as an isolated electrical disorder, initiated by sustained rapid pulmonary venous firing, that is maintained through secondary disorganization into fibrillatory waves. Initially, the episodes of AF are self-limited, these isolated AF episodes tend to induce maladaptive electrical and structural changes, which promotes the evolution to longer-lasting forms of AF. Clinically, the progression from paroxysmal to persistent AF has been associated with increasing rates of stroke, heart failure, and mortality, as well as increased rates of hospitalization and healthcare utilization (5).

It has been proposed that catheter ablation may be a disease modifying therapy. In effect, catheter ablation is designed to modify the mechanism of AF initiation and perpetuation through trigger suppression (pulmonary venous isolation), substrate modification (predominantly at the pulmonary venous-LA junction), and autonomic nervous system modulation (e.g., vagal denervation). However, there had been no randomized evidence to support the hypothesis that ablation may alter the progressive pathophysiological changes associated with AF until the recent publication of the long-term follow-up from EARLY-AF trial. Specifically, this study demonstrated that patients randomized to an initial strategy of catheter cryoballoon ablation experienced a lower incidence of persistent AF compared to those randomized to AADs (HR 0.25; 95% CI: 0.09–0.70) (19). Importantly, these findings were observed despite enrolling a population of patients who were at objectively low risk for progression.

Perspective

AF is a major public health concern, imposing a significant burden on patients and healthcare providers. In addition to reductions in both functional status and quality of life, AF is associated with a significant risk of stroke (increased five-fold over the general population), ventricular dysfunction (increased five-fold over the general population), and through a combination of altered hemodynamics, atrio-ventricular dysynchrony, and progressive atrial and ventricular mechanical dysfunction, AF is associated with premature mortality (increased two-fold over the general population). As outlined previously, these risks are increased in the presence of more advanced forms

of AF. Unfortunately, the treatment options for more advanced forms of AF are relatively unsatisfactory. Invasive intervention is associated with lower rates of treatment success and higher rates of complication when performed for more advanced forms of AF. Given the recent recognition that AF is a chronic progressive disease, it is likely that the early management of AF has the potential to drastically change the long-term impact of the disease. In addition to being more effective when performed early in the disease, catheter ablation has the potential to avert the negative long-term outcomes associated with more advanced forms of AF.

Conclusions

Ablation as first-line therapy for AF is associated with significant improvements in arrhythmia-related outcomes, symptoms and quality of life, and lower rates of adverse events. In addition, catheter ablation is associated with significantly lower rates of disease progression suggesting that it is a disease modifying intervention.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: J.G.A. reports grants and personal fees from Medtronic, grants from Baylis, personal fees from Biosense-Webster.

References

1. Andrade J, Khairy P, Dobrev D, et al. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res 2014;114:1453-68.
2. Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. Can J Cardiol 2020;36:1847-948.
3. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33.
4. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834-40.
5. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667-77.
6. Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. N Engl J Med 2020;383:1305-16.
7. Cheung CC, Nattel S, Macle L, et al. Management of Atrial Fibrillation in 2021: An Updated Comparison of the Current CCS/CHRS, ESC, and AHA/ACC/HRS Guidelines. Can J Cardiol 2021;37:1607-18.
8. Freemantle N, Lafuente-Lafuente C, Mitchell S, et al. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. Europace 2011;13:329-45.
9. Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. N Engl J Med 2021;384:305-15.
10. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-66.
11. Calkins H, Reynolds MR, Spector P, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol 2009;2:349-61.
12. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med 2012;367:1587-95.
13. Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA 2014;311:692-700.
14. Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA 2005;293:2634-40.
15. Kuniss M, Pavlovic N, Velagic V, et al. Cryoballoon

ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. Europace 2021;23:1033-41.
16. Wazni OM, Dandamudi G, Sood N, et al. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. N Engl J Med 2021;384:316-24.
17. Andrade JG, Wazni OM, Kuniss M, et al. Cryoballoon Ablation as Initial Treatment for Atrial Fibrillation: JACC State-of-the-Art Review. J Am Coll Cardiol 2021;78:914-30.
18. Aguilar M, Macle L, Deyell MW, et al. Influence of Monitoring Strategy on Assessment of Ablation Success and Postablation Atrial Fibrillation Burden Assessment: Implications for Practice and Clinical Trial Design. Circulation 2022;145:21-30.
19. Andrade JG, Deyell MW, Macle L, et al. Progression of Atrial Fibrillation after Cryoablation or Drug Therapy. N Engl J Med 2023;388:105-16.
20. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275-444.

Cite this article as: Andrade JG. Ablation or drug therapy for initial atrial fibrillation. Ann Cardiothorac Surg 2024;13(1):71-76. doi: 10.21037/acs-2023-afm-0159

