A randomized clinical trial of early invasive intervention for atrial fibrillation (EARLY-AF) - methods and rationale

Jason G. Andrade, MD,[a,b] Jean Champagne, MD,[c] Marc W. Deyell, MD, MSc,[b] Vidal Essebag, MD, PhD,[d] Sandra Lauck, PhD,[b] Carlos Morillo, MD,[e] John Sapp, MD,[f] Alan Skanes, MD,[g] Patricia Theoret-Patrick, RN, CCRP,[h] George A. Wells, PhD,[h] and Atul Verma, MD[i], for the EARLY-AF Study Investigators, *Montréal, British Columbia, Quebec, Calgary, Halifax, London, Ottawa, and Newmarket, Canada*

Background The ideal management of patients with newly diagnosed symptomatic atrial fibrillation (AF) remains unknown. Current practice guidelines recommend a trial of antiarrhythmic drugs (AAD) prior to considering an invasive ablation procedure. However, earlier ablation offers an opportunity to halt the progressive patho-anatomical changes associated with AF, as well as impart other important clinical benefits.

Objective The aim of this study is to determine the optimal initial management strategy for patients with newly diagnosed, symptomatic atrial fibrillation.

Methods/Design The EARLY-AF study (ClinicalTrials.gov NCT02825979) is a prospective, open label, multicenter, randomized trial with a blinded assessment of outcomes. A total of 298 patients will be randomized in a 1:1 fashion to first-line AAD therapy, or first-line cryoballoon-based pulmonary vein isolation. Patients with symptomatic treatment naïve AF will be included. Arrhythmia outcomes will be assessed by implantable cardiac monitor (ICM). The primary outcome is time to first recurrence of AF, atrial flutter, or atrial tachycardia (AF/AFL/AT) between days 91 and 365 following AAD initiation or AF ablation. Secondary outcomes include arrhythmia burden, quality of life, and healthcare utilization.

Discussion The EARLY-AF study is a randomized trial designed to evaluate the optimal first management approach for patients with AF. We hypothesize that catheter ablation will be superior to drug therapy in prevention of AF recurrence. (Am Heart J 2018;206:94-104.)

From the [a]Montreal Heart Institute, Université de Montréal, Canada, [b]University of British Columbia, Canada, [c]Department of Medicine, Université Laval, Quebec, Canada, [d]McGill University Health Centre and Hôpital Sacré-Cœur de Montréal, Montreal, Canada, [e]Department of Cardiac Sciences, University of Calgary, Calgary, Canada, [f]Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Canada, [g]University of Western Ontario, London, Canada, [h]University of Ottawa Heart Institute, Ottawa, Canada, and [i]Southlake Regional Health Center, University of Toronto, Newmarket, Canada.

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Reprint requests: Jason Andrade MD, 2775 Laurel St, Vancouver, BC V5Z 1M9, Canada.
E-mail: Jason.andrade@vch.ca
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Background

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice, affecting approximately 1–2% of the population.[1] Beyond stroke reduction the contemporary management of AF is centered on symptomatic improvement, with consequent reduction in AF-related emergency room visits and hospitalizations, as well as improved exercise capacity and quality of life.[2-5]

Contemporary guidelines recommend AADs as the "first-line" therapy for the maintenance of sinus rhythm. However, these medications have only modest efficacy at maintaining sinus rhythm.[6,7] Moreover, these agents are associated with significant non-cardiac side-effects, as well as the potential for pro-arrhythmia, heart failure, or organ toxicity.[8-11]

Conversely, the success rate of catheter ablation in maintaining sinus rhythm is universally superior to that of drug therapy when AADs have been ineffective, are contra-indicated, or cannot be tolerated (AF elimination in 66–89% with catheter ablation vs. 9–58% with AAD).[2,12-14] While catheter ablation has not been

definitively proven to improve survival, it has been shown to be superior to AADs for the improvement of symptoms, exercise capacity, and quality of life.[13,15]

Why consider early invasive intervention?

Given the universal superiority of ablation over AAD therapy, it is postulated that early invasive intervention with catheter ablation offers an opportunity to halt the progressive pathophysiological and anatomical changes associated with AF.[16] While catheter ablation has not been definitively proven to impact mortality in unselected patients, there are certain patient groups who may derive significantly benefit from ablation (e.g. younger patients, those with newly diagnosed AF, and those with heart failure).[15,17] In addition, early invasive intervention may result in a significant reduction in overall health care utilitization.[4,5,18,19]

The evidence supporting "first-line" catheter ablation (i.e. as an initial therapy prior to AAD) with radiofrequency (RF) energy is promising, but far from definitive. To date three key studies have been performed. The MANTRA-PAF Study and the RAAFT studies randomized patients to either first-line ablation or first-line AADs.[20-22] Despite disparate ablation techniques, these three studies collectively demonstrated an improved freedom from recurrent arrhythmia (37% reduction in AF recurrence vs. AAD therapy), an improved freedom from symptomatic AF (43% reduction in symptomatic AF vs. AAD therapy), and a reduction in the overall AF burden (50% reduction over AAD therapy). While the results of these previous studies suggest that ablation is more effective than AAD therapy as first-line treatment, a significant proportion of patients in the intervention group experienced arrhythmia recurrence, (mean 1.6 procedures in MANTRA-PAF, 1.2 procedures in RAAFT).

What is different about this study?

The current trial differs from the previous studies in three significant respects.

First, the EARLY-AF trial will be undertaken utilizing a different ablation energy and toolset. The Cryoballoon system (Arctic Front; Medtronic CryoCath, Pointe Claire QC) is a purpose-built system designed specifically for the ablation of AF. When compared to RF energy, cryothermal energy offers several potential advantages:[23] 1) Freeze-mediated catheter adhesion facilitates catheter stability, which is advantageous in regions where stable radiofrequency ablation catheter placement is more difficult to achieve, such as the ridge between the left atrial appendage and left-sided pulmonary veins (PVs); 2) Cryothermal ablation results in a well-demarcated homogeneous lesion that is thought to be more durable and less arrhythmogenic than the more indistinct lesions associated with RF ablation. As such, cryoablation may decrease the incidence of focal or macro re-entrant LA tachycardia,[24] and may decrease repeat procedures;[25] 3) Cryoablation results in minimal endocardial surface disruption and may be less thrombogenic than the lesions produced with RF energy;[26] 4) The lesions resulting from cryothermal ablation have preserved ultrastructural tissue integrity which may lower the risk of severe complications such as cardiac perforation or PV stenosis.[24]

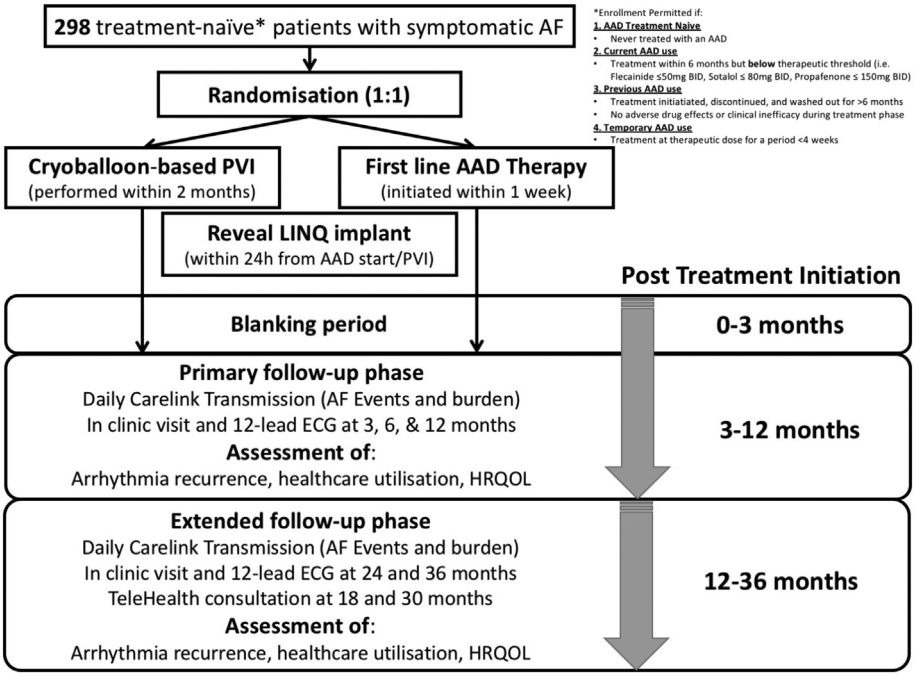
Second, the EARLY-AF study has elected to utilize an implanted cardiac monitor (ICM) with an automated AF detection algorithm (Reveal LINQ, Medtronic) to ascertain arrhythmia recurrence. While non-invasive intermittent rhythm monitoring remains the most widely utilized method of ascertaining ablation efficacy, it often fails to detect AF recurrence.[27] In addition to its superiority at arrhythmia detection, the use of an ICM will provide an accurate quantification of AF burden (hours in AF per day, and percentage of overall time in AF).[28] This allows for a more detailed examination of the relatively efficacy of the treatment approaches beyond that obtained with dichotomous event analyses such as "time-to-first-AF recurrence." Moreover, its usage can help correlate AF burden reduction to changes in quality of life and healthcare utilization. Participant compliance will also not be an issue with follow-up monitoring because of the use of automated home monitoring (Medtronic CareLink).

Third, the study is looking beyond the endpoint of arrhythmia recurrence through a comprehensive analysis of patient-reported outcomes (i.e. health-related quality of life - HRQOL), as well as an assessment of the economic impact of early intervention. The study will employ generic and disease-specific HRQOL instruments to determine the impact of a first line ablation approach from patients' perspectives. For each individual, the total direct costs (hospitalizations, emergency department visits, outpatient physician visits, and use of medications) will be recorded. A Quality Adjusted Life Years (QALYs) scores will be derived and used as a summary measure to inform subsequent healthcare resource allocation decisions.

Methods

Study design

The EARLY-AF study (ClinicalTrials.gov #NCT02825979) is a multicenter prospective, open label randomized clinical trial with blinded adjudication of endpoints (PROBE design). Patients with untreated AF will be randomized in a 1:1 ratio to either first-line antiarrhythmic therapy or first-line AF ablation using cryothermal energy. Randomization will be performed with concealed allocation using permuted block randomization according to a computer-generated sequence with a block size of 4 and 8 per site using web-based software (Dacima, Montreal, Canada). An independent, blinded statistician will generate the block randomization scheme. Outcomes will be adjudicated by personnel who are blinded to subjects' randomization status. All sites will obtain approval from their respective ethics committees, and the study procedures will be performed with the principles of Good Clinical Practice and the Declaration of Helsinki. The



Figure

Study Flow diagram.

authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of this paper and its final contents.

Study setting and timeline

This is a multicenter trial involving 18 AF ablation centers in Canada. As of December 31, 2017, 15 sites have been activated and 75 subjects enrolled. We aim to complete enrolment in 20 months and subjects will be followed for a minimum of 12 months.

Funding

The EARLY-AF study is funded by a peer-reviewed grant from the Cardiac Arrhythmia Network of Canada, which is a Networks of Centres of Excellence (NCE) program funded from a joint initiative of the Natural Sciences and Engineering Research Council, the Social Sciences and Humanities Research Council, the Canadian Institutes of Health Research, Industry Canada and Health Canada. In addition, the trial is supported by an unrestricted grant from Medtronic. The funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Study population

Written informed consent will be obtained from each subject. Patients aged ≥18 years with symptomatic, treatment naïve paroxysmal and early persistent AF will be screened for eligibility. At least 1 episode of AF must be documented on 12-lead electrocardiogram (ECG), transtelephonic monitor (TTM), or Holter monitor within 24 months of randomization (See Fig. 1). Inclusion and exclusion criteria are detailed in Table I.

Interventions

Loop recorder implant. All study participants will undergo the implantation of an ICM for the purpose of arrhythmia monitoring (Reveal LINQ™). The timing of the ICM implant will be no later than 24 hours after AAD initiation ("first-line" AAD therapy group), and no later than 24 hours after the ablation procedure ("first-line" cryoablation group). ICM programmed parameters are summarized in Table II. Participation in the trial is not possible without an ICM.

Anti-Arrhythmic Drug Therapy Group. Patients randomized to AAD arm will start regular (daily) AAD therapy within 1 week of randomization. The use of AAD therapy will be based on local clinical practice, and according to guideline-suggested management for symptomatic patients with paroxysmal AF.[4,5] Suggested AAD titration and monitoring protocols are provided in Appendix A.

During the titration phase, the ICM data will be reviewed by study personnel on a weekly basis, with AAD therapy progressively up-titrated to the maximum

Table I. Inclusion and exclusion criteria

Inclusion criteria
• Non-permanent atrial fibrillation documented on a 12 lead ECG, Trans Telephonic Monitoring (TTM) or Holter monitor within the last 24 months (Episodes of AF must be >30 seconds in duration to qualify as an inclusion criterion)
• Age of 18 years or older on the date of consent
• Candidate for ablation based on AF that is symptomatic
• Informed Consent
Exclusion criteria
• Regular (daily) use of a class 1 or 3 antiarrhythmic drug at sufficient therapeutic doses according to guidelines (defined as flecainide >50 mg BID, sotalol >80 mg BID, propafenone >150 mg BID, or dronedarone 40 mg BID)**
• Previous left atrial (LA) ablation or LA surgery
• AF due to reversible cause (e.g. hyperthyroidism, cardiothoracic surgery)
• Active Intracardiac Thrombus
• Pre-existing pulmonary vein stenosis or PV stent
• Pre-existing hemidiaphragmatic paralysis
• Contraindication to anticoagulation or radiocontrast materials
• Left atrial anteroposterior diameter greater than 5.5 cm by transthoracic echocardiography
• Cardiac valve prosthesis
• Clinically significant (moderately-severe, or severe) mitral valve regurgitation or stenosis
• Myocardial infarction, PCI / PTCA, or coronary artery stenting during the 3-month period preceding the consent date
• Cardiac surgery during the three-month interval preceding the consent date
• Significant congenital heart defect (including atrial septal defects or PV abnormalities but not including PFO)
• NYHA class III or IV congestive heart failure
• Left ventricular ejection fraction (LVEF) less than 35%
• Hypertrophic cardiomyopathy (septal or posterior wall thickness> 1.8 cm)
• Significant chronic kidney disease (CKD - eGFR <30 μMol/L)
• Uncontrolled hyperthyroidism
• Cerebral ischemic event (strokes or TIAs) during the six-month interval preceding the consent date
• Pregnancy
• Life expectancy less than one (1) year
• Currently participating or anticipated to participate in any other clinical trial of a drug, device or biologic that has the potential to interfere with the results of this study
• Unwilling or unable to comply fully with study procedures and follow-up

**Specific acceptable scenarios for enrolment:

A. Previous AAD use (trialed, discontinued, and washed out for >6 months).
   a. During the treatment phase with AAD the patient must not have experienced AAD failure (adverse drug effects or frequent AF episodes).
B. Treatment with an AAD within the past 6 months but the dose was below therapeutic threshold (listed above).
C. Temporary AAD use – treatment at therapeutic dose for a period <4 weeks.

tolerated dose with a goal of complete AF suppression. In the event of clinical inefficacy or intolerable side effects, a change to a second or to a third AAD will be undertaken, insofar as the patient remains within the blanking period. Once the blanking period has ended, any further changes made to AAD therapy for recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia (AF/AFL/AT) would be considered a primary endpoint (as defined below).

Table II. Implantable cardiac monitor programming

AF detection threshold	Balanced sensitivity
Ectopy rejection	Nominal
Episode storage threshold	All (record ECG of 2 minutes)

These parameters were chosen to optimize detection of AF (reported sensitivity of 96.1% with a positive predictive valve [PPV] of 73%), however al arrhythmia episodes will be independently adjudicated.[51,52]

Catheter Cryoballoon Ablation Procedure. Patients randomized to catheter cryoablation will undergo the procedure within 2 months of randomization.

The use of adjunctive pre-procedural cardiac magnetic resonance or computed tomographic imaging, and intraprocedural intracardiac echocardiography, pulmonary venography, or 3-dimensional electroanatomic mapping will be based upon physician preference.

Ablation may be performed under conscious sedation or general anesthesia (GA), per local practice. A multipolar catheter will be placed in the coronary sinus (CS) via central venous access. The LA will be accessed via trans-septal (TS) puncture or patent foramen ovale. Following left atrial access, IV heparin will be administered as sequential boluses and/or a continuous infusion to maintain an ACT >300 sec. Thereafter the TS sheath will be exchanged with a steerable 15 Fr sheath (Flexcath, Medtronic).

The 28 mm cryoballoon catheter (Arctic Front Advance, Medtronic) will be advanced through the steerable sheath into the LA with a 20-mm small-diameter circular mapping catheter (CMC) inserted in the central lumen of the CB and used as a guidewire. In exceptional circumstances the 23-mm cryoballoon may be used for PV diameters <20 mm (as assessed by pre-procedural imaging, or intra-procedural pulmonary venography) and based on physician judgment.[29-31]

Before ablation, the CMC will be positioned in the venous ostium to record baseline electrical activity. The CB will be positioned in the venous ostium and the degree of occlusion will be tested through the injection of 1:1 diluted contrast material, pulmonary vein pressure monitoring, intracardiac echocardiography, or other comparative methods.

Prior to ablation of right-sided PVs, a 5-Fr deflectable or non-deflectable catheter will be placed in the right subclavian vein or superior vena cava cranial to the right superior PV to pace the right phrenic nerve (10–20 mA at 1.0–2.0 msec pulse width at a cycle length of 1000 msec). Ablation will be immediately terminated upon any perceived reduction in the strength of diaphragmatic contraction or a 30% reduction in the diaphragmatic compound motor action potential (CMAP) amplitude as measured via diaphragmatic electromyography. Of note, if the procedure is performed under general anesthesia, paralytic agents will be discontinued

Table III. Schedule of enrolment, interventions, and assessments

	Enrolment	ABLATION Group only		FOLLOW-UP (Both Groups)					
	Baseline	Day 0	Discharge	1 week	3 month Visit	6 month Visit	12 month Visit	18, 30 month Visits	24, 36 month Visits
Consent	X								
Telephone Interview				X					
AF history	X								
AF symptoms status		X		X	X	X	X	X	X
Clinical examination	X		X		X	X	X		X
Medication Review	X		X	X	X	X	X	X	X
Adverse Event Review			X	X	X	X	X	X	X
Ablation Data		X							
Trans-septal Worksheet		X							
Laboratory test*		X*			X*	X*	X*		X*
Echocardiography*	X	X*			X*	X*	X*	X*is	X*
ECG	X	X	X		X	X	X		X
AFEQT/EQ5D-5 L QoL questionnaire	X				X	X	X		X
ICM Implantation	X								
ICM Interrogation					X*	X*	X*	X	X*
Cardiac CT* or MRI*	X*				X*	X*	X*	X*	X*
24 Hour Holter Monitor*	X*				X*	X*	X*	X*	X*
Re-Ablation (As needed)									

Legend – *CT* – computed tomography; *MRI* – magnetic resonance imaging; *QOL* – quality of life.
* if performed.

at least 30 minutes prior to planned phrenic nerve pacing.

Cryoablation with a minimum ablation duration of 3 minutes will be utilized. Lesions that fail to isolate the vein within 60 seconds (if real-time PV potential monitoring is feasible) or achieve a temperature colder than minus 35 °C after 60 seconds of ablation should be considered ineffectual and be terminated (except for common ostia). Thereafter the balloon and/or guidewire should be repositioned and a new lesion delivered. Once PVI has been achieved a single "bonus" application of 3 minutes will be delivered following the rewarming phase (to +20 °C). Should the operator fail to isolate the PV (excluding common ostia) after a minimum of 3 attempted cryoballoon applications then focal ablation with the 8 mm cryocatheter (Freezor Max) targeted to sites of LA-PV breakthrough will be permitted at operator discretion.

In accordance with the 2017 expert consensus statement on catheter and surgical ablation of atrial fibrillation, the ablation procedure will be considered acutely successful when PV isolation has been achieved, as confirmed by both entrance and exit conduction block between PV and LA. Entrance block is the stable absence of conduction into the PV from the LA and exit block is the stable absence of conduction from the PV into the LA (either spontaneous or during pacing from the each of the bipoles of the circular mapping catheter positioned at the ostium of the PV with documented local PV capture or at an acceptably high output [>10 mA]).[19] An observation period of 20 minutes following isolation of all PVs (i.e., at the end of the last ablation lesion) will be used to assess spontaneous recovery of conduction, which if present will undergo further targeted ablation. The use of adenosine testing to unmask dormant conduction is of limited utility with cryoballoon ablation, and thus is not mandated by this protocol. If adenosine testing is performed and dormant conduction is present then additional ablation should be delivered until this dormant conduction is eliminated.

Cavotricuspid isthmus ablation in the event of documented right atrial flutter is permitted with non-irrigated RF (8-mm or 10-mm tip), irrigated RF, or focal cryoablation at operator discretion. No prophylactic left atrial linear ablation lesions, or ablation of complex fractionated atrial electrograms (CFAE) are permitted in addition to PV isolation.

Barring complications, patients will be discharged within 24 hours of the index ablation procedure. Post-procedure evaluation at the end of hospital stay will permit the assessment of the nature and severity of all adverse events occurring during the immediate post-procedural phase.

Post therapeutic intervention (AAD or Ablation) "Blanking period". In accordance with 2017 expert consensus statement for reporting outcomes in AF ablation trials, a blanking period of 3 months is incorporated for both groups.[19] The rationale for the post-procedure blanking period is based on the observation that early recurrences of arrhythmias are common during the initial 3 month period post ablation, and is predicated on the assumption

that not all early recurrences of atrial tachyarrhythmias (AF/AFL/AT) will lead to later recurrences and, as such, does not necessarily represent treatment failure.[19,32] Correspondingly the 3-month "blanking period" in the AAD group will allow for drug titration and optimization. For this group the ICM data will be reviewed on a weekly basis to guide AAD titration during the blanking period.

For both groups, cardioversion may be utilized to treat sustained arrhythmia recurrence during the 3-month blanking period. In the ablation group AADs (with the exception of amiodarone) may be utilized to treat arrhythmia recurrence as outlined above. If utilized in the post-ablation period, the AADs must be discontinued within five (5) half-lives of the end of the 3-month blanking period. For patients in the AAD group it is recommended AAD therapy is uptitrated per protocol (see Appendix E) with a goal of complete AF suppression. In both groups, patients in persistent AF must undergo cardioversion before the end of the blanking period.

Anticoagulation. All patients will be systemically anticoagulated based on perceived stroke risk as per treatment guidelines and physician discretion. The decision to initiate oral anticoagulation (OAC) will be made based on the risk of stroke as per the CCS algorithm.[4] In patients <65 years of age and with a CHADS score of 0, aspirin alone or no specific antithrombotic therapy may be considered at treating physician discretion. For those >65 years of age, or with a CHADS score of 1 or more, OAC is strongly recommended.

In the ablation group, all patients >65 years of age, or with a CHADS score of 1 or more will remain anticoagulated with oral vitamin K antagonists (target INR between 2–3), low molecular weight heparin, or non-VKA oral anticoagulant medications (NOACs) for a minimum of 1 month prior to ablation and up to a minimum of 3 months post ablation. Thereafter, discontinuation of oral anticoagulation may be considered for patients <65 years of age and with a CHADS score of 0 (as above).

Minimization of Cross-Over. All efforts will be undertaken to avoid patients switching from their randomized group to the alternate treatment strategy. However, patients with documented symptomatic arrhythmia recurrence may "*change treatment strategy"* (e.g. from AAD to ablation, or vice versa) if the arrhythmia event occurs outside the 90-day blanking period (i.e. constitutes a primary endpoint for the study). A "cross-over" will be defined if the patient changes treatment strategy within the blanking period or in the absence of documented AF recurrence.

For patients to *"change treatment strategy"* from the AAD group to the ablation group or vice versa, the symptomatic sustained arrhythmia recurrence must occur outside the blanking period. In the AAD group, recurrence must occur despite a therapeutic dose of AAD therapy (defined as flecainide >50 mg BID, sotalol >80 mg BID, or propafenone >150 mg BID, or dronedarone 400 mg BID). The recurrence should be of sufficient clinical severity to warrant the performance of an ablation procedure, as per standard clinical practice. Prior to permitting a patient to *"change treatment strategy"*, an independent committee will review the rationale for change, the medication profile (to ensure adequate AAD dosing), and the arrhythmia episodes (which will have been independently adjudicated by the clinical events committee). Following this review, a change in treatment strategy may be permitted if the pre-specified criteria were met. If the patient is changing to ablation, the procedure should preferentially occur after the conclusion of the study follow-up but can occur sooner based on clinical necessity. The ablation procedure performed will preferably be a cryoballoon-based PVI (as outlined above).

All patients will be followed for a minimum of 12 months from the index abaltion procedure or the initiation of arrhythmic drug therapy, irrespective of cross-over or change in treatment strategy.

Assessments

All patients will be followed for a minimum of 12 months after the index ablation procedure or medication initiation. This duration is based on the 2017 expert consensus statement for reporting outcomes in clinical trials of AF ablation, as well as the knowledge that most recurrences transpire during the first year after ablation.[19,33-36]

Table III details the planned visits and procedures. For both groups, a one-week post treatment telephone call will occur followed by scheduled visits at 3, 6, and 12-months from index ablation procedure or medication initiation. A clinical evaluation and 12-lead ECG will be performed at each of the scheduled clinical encounters. A specific patient interview will be conducted at each clinical visit to ascertain symptomatic AF. Information regarding disease specific HRQOL (AFEQT), generic HRQOL (EQ-5D) and an AF symptoms score (CCS-SAF) will be assessed at each follow-up visit. In addition, information regarding health care resource use will be prospectively collected (emergent acute care visits, emergency department visits, hospitalizations, cardioversions, re-ablation, and planned/unplanned follow-up visits, and medication usage).

Automatic transmissions from the ICM will be obtained on a daily basis via CareLink. In addition, we have instructed patients to identify symptomatic episodes through the use of the loop recorder's patient activator.

The use of 24-hour Holter monitoring and cardiac imaging will be left to the discretion of the treating physician.

Primary outcome

Time to first recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia (AF/AFL/AT)

Table IV. Study endpoints

Primary endpoint
1) Time to first recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia (AF/AFL/AT) documented by 12-lead ECG, surface ECG rhythm strips, 24-hour ambulatory ECG (Holter) monitor, or on ICM between days 91 and 365 following AAD initiation or AF ablation.
Secondary endpoints
1) Time to first symptomatic recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia (AF/AFL/AT) documented by 12-lead ECG, surface ECG rhythm strips, 24-hour ambulatory ECG (Holter) monitor, or on ICM between days 91 and 365 following AAD initiation or AF ablation.
2) Arrhythmia burden (daily AF burden - hours/day; overall AF burden - % time in AF)
3) Proportion of patients experiencing an acute or adenosine provoked PV reconnection during the index ablation procedure
4) Proportion of patients requiring a repeat ablation procedure because of documented recurrence of symptomatic AF/AFL/AT
5) Number of ablation procedures required because of documented recurrence of symptomatic AF/AFL/AT
6) Proportion of patients prescribed AADs because of documented recurrence of symptomatic AF/AFL/AT;
7) Proportion of patients with AF/AFL/AT during the first 90 days post ablation
8) Emergency visit or hospitalization >24 h in a health-care facility (with a focus on events due to symptoms caused by documented atrial arrhythmias)
9) Frequency, type and associated cost of health care utilization at 12 months follow-up.
10) Major complications including death, stroke, TIA, Myocardial Infarction or systemic thromboembolism, PV stenosis, phrenic nerve palsy, pericarditis, pericardial effusion, cardiac perforation or tamponade, hematoma, AV fistula, pseudoaneurysm, esophageal injury and atrio-esophageal fistulae (both individually and as a composite endpoint)*
11) Trajectory of change in generic and disease-specific quality of life
12) Single and multiple procedure success (freedom from symptomatic or asymptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively
13) Single and multiple procedure success (freedom from symptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively.

A major complication is a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours. Because early recurrences of AF/AFL/AT are to be expected following AF ablation, recurrent AF/AFL/AT within 3 months that requires or prolongs a patient's hospitalization should not be considered to be a major complication of AF ablation.
*Complication definition as per 2017 expert consensus recommendations.[19] Acute peri-procedural complications will be defined as occurring within 30 days of ablation, with delayed complications occurring 31–365 days after ablation.

documented by 12-lead ECG, surface ECG rhythm strips, 24-hour ambulatory ECG (Holter) monitor, or on ICM between days 91 and 365 following AAD initiation or AF ablation. AF or atrial flutter/tachycardia will qualify as an arrhythmia recurrence if it lasts 30 seconds or longer on surface ECG rhythm strips or 24-hour ambulatory Holter monitor, or 120 seconds or longer on ICM (the minimum programmable episode interval on the ICM). All tracings will be independently adjudicated by a clinical events committee (CEC) blinded to treatment allocation. The primary end point and the 3-month blanking period adhere to the 2017 expert consensus statement recommendations for reporting outcomes in AF ablation trials.[19]

Secondary outcomes

Secondary outcomes are listed in Table IV. These outcomes focus on AF progression ("time to first episode of persistent AF (>7 days)") and AF burden ("% time in AF"), including examining the relationship between AF burden and healthcare utilization (e.g. "Emergency visit or hospitalization >24h in a health-care facility, with a focus on events due to symptoms caused by documented atrial arrhythmias", and "Frequency, type and associated cost of health care utilization at 12 months follow-up"), and the relationship between AF burden and HRQOL ("Trajectory of change in generic and disease-specific quality of life").

Planned analyses

Analysis of the primary and secondary endpoints will be based on the intention-to-treat principle according to the initial allocated strategy. Survival curves will be estimated by the Kaplan–Meier method and compared by the log rank test. An exploratory analysis of the primary endpoint will exclude patients with major deviations from the protocol.

A Cox proportional hazards model will also be used to test the consistency of the group effect while accounting for clinically important baseline characteristics, which will include: ablation site, age, gender, race, weight, LA size, and AF duration. The proportional hazard assumption will be assessed by visual inspection of the log-negative-log plot and through a formal test of the interaction term "group x time" at $\alpha = 0.05$. Should this assumption fail, a stratified Cox model will be fitted in order to correct for non-proportional hazards if possible or, if ineffective, time-dependent variables will be introduced. Should these corrective techniques fail, logistic regression will be used instead.

Dichotomous secondary endpoints expressed as time-to-event will be analyzed similarly using Kaplan–Meier

survival curves and a log rank test. Continuous variables, such as arrhythmia burden, will be analyzed using an analysis of variance (ANOVA). If the data are not normally distributed, then the non-parametric Wilcoxon Signed Rank test will be used. Health-related quality of life scores will be compared by analysis of covariance, adjusting for baseline values to reduce the error mean squares. In the event of missing data, a multiple imputation approach using SAS procedures PROC MI and PROC MIANALYZE will be considered. All tests will be conducted at an alpha level of 0.05.

Planned subgroup analyses

Adequate sample sizes permitting, subgroup analyses to investigate heterogeneity in overall effects for the primary endpoint will be performed using Cox proportional hazards models including terms for the factor defining the subgroups, the group, and the factor-by-group interaction. The factor-by-group interaction will be tested and used to determine the consistency of the group effect across subgroups. Subgroups based on the following variables will be considered: ablation experience (high volume vs. low volume centers as defined by procedure volume above/below the median), LA size (above/below median), AF duration from diagnosis (above/below median).

Economic evaluation

The purpose of the economic evaluation is to calculate incremental cost effectiveness ratio (ICER) for one QALY gain (primary economic outcome) or with one additional recurrence-free patient at the end of follow-up (one year after randomization). The analysis will adopt a data-driven approach (using trail-generated data without decision-analytic modeling). For each individual, total direct costs during the follow-up period as well as QALY will be calculated. A binary variable will also record whether patient has had any symptomatic AF during follow-up. Costs are sum-product of all resource use items with their corresponding cost units. QALYs will be calculated using the trapezium rule from the baseline and follow-up disease specific (generic in the sensitivity analysis) instruments. Follow-up time will be divided into 4 three-month periods. A nested cycle of imputation and bootstrapping will be performed to, respectively, impute the missing outcomes for a period (if the patient withdrew before/within the period) and to fully capture uncertainty around the outcomes, as has been performed in our previous RCT-based evaluations. The point estimate of the ICER, its 95% credible interval, cost-effectiveness plane and acceptability curve will be generated for both effectiveness outcomes.

Data collection and management

The Cardiovascular Research Methods Centre (CRMC) at the University of Ottawa Heart Institute will coordinate the study. The support staff at the CMRC will be composed of a full-time study coordinator, data manager, and biostatistician. The center will specifically be responsible for the randomization process, and for receiving, editing, processing, analyzing, and storing data generated in this trial.

A unique subject number not derived from personal identifiers will be utilized for subject identification. Study information using this unique subject number will be collected using case report forms, which will be entered into a secure online platform (DACIMA, Montreal). All electronic data are encrypted, password protected and stored on a secure network within the coordinating center.

All study endpoints will be adjudicated by a blinded clinical events committee. The seven-member committee will be composed of a cardiac electrophysiologist as Chairperson, and six (6) cardiologist reviewers with expertise in clinical event adjudication. The CEC members are independent from the sponsor and investigators, blinded to the study allocation, and have no conflicts of interest relevant to the trial. Two reviewers will be assigned to review each endpoint and SAE. If both reviewers agree, the chairperson will be provided with the reviewer's Forms and he will ratify the adjudication. If the reviewers are in disagreement, the chairperson will review the event and will serve as the third reviewer. If there is still disagreement between all three reviewers, a meeting will be scheduled to discuss the event.

Sample size calculation

The sample size was estimated using data from previous studies and from Steering Committee experience. From RAAFT Study[21] we know that 1-year freedom from any recurrence of symptomatic AF or asymptomatic AF lasting longer than 30 seconds was 37% in AAD arm and 87% in RF ablation arm. Both Namdar et al[37] and Tanner et al[38] showed that freedom from any documented episode of AF, atrial flutter or atrial tachycardia of $\geq$30 s duration on average of 15 months of follow-up was 78% in patients undergoing to cryoablation or RF ablation respectively as first-line therapy. As such we assumed a one-year recurrence-free survival for atrial fibrillation, atrial flutter and atrial tachycardia in the AAD arm of 50% and a recurrence-free survival of 70% in the ablation arm, using a 120 second minimum episode duration cut-off on ICM.

Sample size was estimated for two-sample comparison of survivor function using the log-rank test according to Freedman method.[39] The null hypothesis is Ho: S1(t) = S2(t) and the following parameters have been used for sample size estimation:

- Type I error (alpha) = 0.05 (two-sided)
- Power (1 - ß) = 0.90
- 1:1 randomization between groups
- 15% drop-out

Based on these assumptions and parameters, 88 independent events are needed to achieve 90% power

to demonstrate a 20% reduction in rate to first event for a total of 298 patients (149 per group).

Discussion

Despite the presence of three prior trials comparing first-line AAD to ablation therapy for AF, the magnitude of benefit of ablation in this setting is still unknown. RAAFT-2 showed a significant reduction in AF recurrence in the ablation arm [HR 0.56; 95%CI 0.35–0.90; $P = .02$], but the magnitude in difference between the 2 groups was not clinically impactful [17.6% reduction in arrhythmia recurrence from 72.1% in the AAD group to 54.5% in the ablation group].[21] Furthermore, the MANTRA PAF trial did not show any benefit of first-line therapy over AAD in the primary endpoint of AF burden as measured by serial 7 day Holter monitors.[20] It was only in secondary analyses that freedom from AF was seen in more patients at 24 months in the ablation arm compared to the AAD arm.[20,40] Thus, the issue of first-line ablation remains an open question. This is reflected in current guidelines. In the recent 2017 Consensus Statement, ablation of symptomatic paroxysmal AF refractory to AAD is considered a class I indication with level of evidence A.[19] Primary ablation of symptomatic paroxysmal AF, on the other hand, is considered class IIa with a level of evidence of B. The CCS guidelines suggest that primary AF ablation only be considered in "selected patients" and the ESC guidelines state that "as first-line treatment for paroxysmal AF, randomized trials showed only modestly improved rhythm outcome with catheter ablation compared to antiarrhythmic drug therapy."[4,5] Further research is required before first-line catheter ablation can be considered routine for most patients with symptomatic paroxysmal AF.

By employing newer cryothermal ablation technology, the EARLY-AF study has the potential to demonstrate a more pronounced difference in AF recurrence between AAD and ablation. The cryoballoon consistently yields isolation in the antral region of the pulmonary veins. This process not only isolates the arrhythmogenic muscular PV sleeves but also extends the circumferential lesion into the regions around the PVs responsible for arrhythmia perpetuation.[41,42] Recently published data have examined short- and long-term success with the second-generation cryoballoon. Studies of planned re-mapping procedures have demonstrated that the durability of PVI at three months post index ablation procedure was improved at 91% with the second-generation cryoballoon, compared to 67% of PVs with standard (non-contact force) radiofrequency.[43-48] Clinically this has translated into a one-year freedom from recurrent AF of 82% with the second generation cryoballoon (11 studies; 1725 patients).[27] The improved safety profile was also highlighted in the introductory section. As such, it is possible that the favorable efficacy and safety profile associated with cryoballoon ablation will result in improved outcomes for patients with early AF undergoing first-line catheter ablation.

There is also a poor understanding of the correlation between AF burden and improved patient quality of life and reduction in health care utilization. The 30 second endpoint of most AF ablation trials is a good standard benchmark but presumes that the goal of ablation should be arrhythmia elimination. It is known, however, that many patients may report improvement in their function and a reduction in emergency visits post-ablation as long as the AF has been significantly reduced as opposed to eliminated.[17] Limited data shows that patients may experience improved HRQOL despite upwards of 4 hours of recurrent AF per month.[17,49,50] Since the EARLY-AF study will have ICM data on all patients post-AAD or ablation, more detailed analyses can be performed assessing the relationship between AF burden, HRQOL, and health care utilization. We intend to extend follow-up to 3 years in order to examine post-ablation changes in AF burden and their correlation to HCU and HRQOL.

In these ways, the outcomes of the EARLY-AF study have the potential to fundamentally change the way in which we approach early atrial fibrillation, and in particular, the timing of invasive catheter ablation procedures. On an individual level, early ablation may result in a reduction in AF recurrences and overall AF burden, with subsequent improvement in arrhythmia related symptoms, quality of life, physical health, mental health, and work performance. The societal benefits would be expected through a reduction in the economic burden of AF care (direct cost due to emergency room visits and hospitalizations) as well as a reduction in days of work missed due to illness resulting in increased productivity (indirect cost).

In conclusion, The EARLY-AF study is a multicenter, parallel-group, randomized trial designed to determine the optimal first treatment approach for patients with atrial fibrillation.

Competing interests

Dr. Andrade reports grants and personal fees from Medtronic, grants from Baylis, personal fees from Biosense-Webster; Dr. Champagne has nothing to disclose; Dr. Deyell reports grants from Biosense-Webster; Dr. Essebag reports personal fees from Biosense, Abbott, and Medtronic; Dr. Lauck has nothing to disclose; Dr. Morillo personal fees from Abbott (SJM), Boston Scientific, Bayer, Daiichi Sankyo, Medtronic, grants from Bayer, Pfizer; Dr. Sapp reports grants from Biosense-Webster, personal fees from Biosense-Webster, grants from Abbott (SJM), personal fees from Abbott, personal fees from Medtronic Inc.; Dr. Skanes reports grants from Medtronic and Biosense-Webster; Dr. Wells has nothing to disclose; Dr. Verma reports grants and personal fees from Medtronic, Bayer, and Biosense-Webster.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.05.020.

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