Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial: Study Rationale and Design

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Abstract

The **C**atheter **Ab**lation Versus **A**nti-arrhythmic Drug Therapy for **A**trial Fibrillation (**CABANA**, NCT00911508)(1) trial is testing the hypothesis that the treatment strategy of percutaneous left atrial catheter ablation for the purpose of eliminating atrial fibrillation (AF) is superior to current state-of-the-art pharmacologic therapy. This international 140-center clinical trial was designed to randomize 2200 patients to a strategy of catheter ablation versus state-of-the-art rate or rhythm control drug therapy. Inclusion criteria include: 1) age > 65, or 65 with 1 risk factor for stroke, 2) documented AF warranting treatment, and 3) eligibility for both catheter ablation and 2 anti-arrhythmic or 2 rate control drugs. Patients were followed every 3 to 6 months (median 4 years) and underwent repeat trans-telephonic monitoring, Holter monitoring, and CT/MR in a subgroup of patient studies to assess the impact of treatment on AF recurrence and atrial structure.

With 1100 patients in each treatment arm, CABANA is projected to have 90% power for detecting a 30% relative reduction in the primary composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest. Secondary endpoints include total mortality; mortality or cardiovascular hospitalization; a combination of mortality, stroke, hospitalization for heart failure or acute coronary artery events; cardiovascular death alone; and heart failure death, as well as AF recurrence, quality of life, and cost effectiveness. At a time when AF incidence is rising rapidly,

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CABANA will provide critical evidence with which to guide therapy and shape health care policy related to AF for years to come.

Introduction and rationale

Atrial fibrillation (AF) is the most common clinically problematic arrhythmia, and perhaps the most difficult to treat.[2–7] Arrhythmia drug therapy, utilized over decades, has been relatively ineffective, is accompanied by side effects and pro-arrhythmic propensity, and showed little advantage in a series of rate versus rhythm control trials: AFFIRM,[8] RACE,[9] STAF,[10] PIAF,[11] and AF-CHF.[12] Still, it has been a long-held assertion that rhythm control should be more effective than rate control itself. The similarity of outcomes for rate versus rhythm control in these studies may be direct evidence against the importance of maintaining normal sinus rhythm, or may incompletely account for the side effects and pro-arrhythmic risks of rhythm control agents, as well as the relative inability of anti-arrhythmic agents to maintain normal sinus rhythm.

In part because of these issues, surgical intervention in the form of the Maze procedure was developed during the late 1980s and applied in many patients beginning in the early 90s. [13–20] A variety of largely observational studies suggested high efficacy in restoring and maintaining normal sinus rhythm.[13–20] However, no large clinical trials were ever conducted to compare the surgical approach to outcomes with antiar-rhythmic drug therapy. Furthermore, these studies, using a wide variety of different techniques, could not address the overarching question of impact on total mortality and stroke.

Subsequently, a series of hypothesis-driven, mechanistic studies by Allessie, et al.,[21] and Morillo and coworkers[22] and others, suggested a strong role for triggers or maintenance substrate as therapeutic targets for AF. Later, Haissaguerre, et al.,[23] demonstrated AF initiation in humans often emanating from the pulmonary vein (PV) muscle sleeves leading to adoption of catheter-based techniques, designed to isolate pulmonary veins as a less invasive method for eliminating AF compared to surgical techniques. Many investigators have reported high rates of short term control of AF but more variable long term outcomes. [24–27] Multicenter prospective observational studies including CACAF,[24] RAAFT,[25] APAF[26] and A4,[27] each provided information suggesting better efficacy with ablation versus drug therapy. Key limitations in these studies were the relatively small number of patients enrolled, limited representation of patients with significant cardiac comorbidities, largely paroxysmal AF, and the exclusion of more elderly patients. Typically patients were only followed for a period of 12 months, and studies were not powered to reveal possible beneficial effects of ablation on mortality, stroke, bleeding, or other important clinical outcomes.

In the early years of percutaneous AF ablation, the ability to design and conduct an adequately powered comparative outcome trial was limited by the absence of agreement among experts on which ablative approach should be used. In the early 2000s, many groups performed various combinations of pulmonary vein isolation (PVI), focal ablation, segmental isolation, wide area circumferential ablation, linear ablation and complex fractionated atrial electrograms (CFAE) directed ablation. At the Boston AF meeting in

2005,[28] AF ablation panelists agreed on the preeminence of PVI as the key ablation method, an opinion that was subsequently supported by other observational studies.[29–31]

In September of 2005, the National Heart, Lung, and Blood Institute (NHLBI) convened an AF Work Group, which was charged with the task of advising the NHLBI on the types of clinical studies the Institute should support or initiate to assess the role of catheter ablation for the treatment of AF. Specifically, the Work Group was asked to determine the opportunity and feasibility of a clinical trial to assess the long term clinical and public health benefits of AF ablation treatment in the broad population of patients affected by AF. The Work Group recommended, as top priority, a comparative study of ablation versus drug therapy for treating AF. This came with the recommendation of answering the higher-level questions regarding the impact of therapies on mortality. Following thereafter was the charge to assess impact on stroke and treatment efficacy in patients with underlying comorbidities, advancing age, and those with persistent or long-standing persistent AF. Subsequently, the Institute of Medicine of the National Academy of Sciences included in its first quartile of Initial National Priorities for Comparative Effectiveness Research, the need to "Compare the Effectiveness of Treatment Strategies for Atrial Fibrillation Including Surgery, Catheter Ablation, and Pharmacologic Treatment" (National Academy of Sciences, June 2009).[32]

The CABANA investigators, having conceived the concept of such a trial 5 years earlier, submitted a Letter of Intent to the NHLBI in November 2005 and undertook the CABANA Pilot Study showing that enrollment of the patient population defined above was feasible and that ablation was more effective than drug therapy in eliminating AF.[33] The feasibility evidence from the CABANA Pilot Study combined with the likelihood that an extended long-term study would answer here-to-fore unaddressed issues led the NIH to approve funding for the 6-year CABANA trial on January 30, 2009 with additional financial support from industry partners, including St Jude Medical Inc., Biosense Webster Inc., Medtronic Corporation, and Boston Scientific Corporation. The first patient was enrolled at Mayo Clinic on November 13, 2009 after registering the trial as #NCT00911508 on the clinicaltrials.gov web site.[1]

Trial design and endpoints

The CABANA multicenter, prospective, randomized, open-label clinical trial design, informed by the experience of the CABANA Pilot Study,[33] was launched in over 140 centers during late 2009 and into 2010, with 126 centers enrolling patients. These centers included both academic and non-academic clinical centers with at least a 100 patient experience in catheter ablation of AF, 81 centers were in the United States, 15 were in Germany, 5 in the United Kingdom, 5 in China, 4 in Russia, 4 in Italy, 4 in Canada, 4 in the Czech Republic, 2 in South Korea, and 2 in Australia. The design dictated that one-half of the subjects be randomly allocated to treatment with catheter ablation and one-half to drug therapy for either rate or rhythm control as outlined in Figure 1.

Each patient was required to have untreated or incompletely treated AF that, in the opinion of the investigator, warranted therapy. Initially, it was intended that all CABANA patients would be enrolled and followed for a median of 3.0 years.

The trial organization is shown in Figure 2.

Primary endpoint

The initial hypothesiswas that percutaneous left atrial catheter ablation for the purpose of eliminating AF would be superior to current state-of-the-art therapy with either rate control or rhythm control drugs for reducing total mortality (primary endpoint) and decreasing the composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest (secondary endpoint) in subjects with untreated or incompletely treated AF warranting therapy. In early 2013, a predetermined review of the trial was undertaken by the study leadership and the Data Safety Monitoring Board (DSMB). Completely blinded to any treatment-specific outcome data, two major issues were identified and addressed by the leadership group: (1) a lower than expected aggregated event rate, and (2) a slower than projected accrual of study subjects. Careful consideration of these issues led to a decision to change the primary endpoint to the composite of totalmortality, disabling stroke, serious bleeding, or cardiac arrest, with the key secondary endpoint being total mortality. Because a longer enrollment period was expected, this allowed for a reduction in the sample size to 2,200 while remaining consistent with the choice of the new primary endpoint without limiting study power. This also allowed a 4 to 4. 5-year follow-up period.

Primary endpoint

The primary endpoint is the composite of total mortality, disabling stroke, serious bleeding, or cardiac arrest.

Secondary endpoints/objectives

1. Total mortality

2. Total mortality or cardiovascular hospitalization

3. Total mortality, stroke, or CV hospitalization (for heart failure or acute ischemic events)

4. Cardiovascular death

5. Cardiovascular death or disabling stroke

6. Arrhythmic death or cardiac arrest

7. Heart failure death

8. Freedom from recurrent AF

9. Cardiovascular hospitalization

10. Medical costs, resource utilization, and cost effectiveness

11. Quality of life

12. Composite adverse events

13. LA size, morphology, and function

The CABANA Clinical Events Committee provided a blinded adjudication of the events comprising the primary endpoint.

Inclusion and exclusion criteria

Eligible subjects were required to have new onset or under-treated paroxysmal, persistent, or longstanding persistent AF that warranted additional therapy in the judgment of the physician caring for the patient's AF. Complete inclusion and exclusion criteria are shown in Table I.

Randomization method

Eligible patients who gave written, informed consent and met all inclusion with no exclusion criterion were randomized in a ratio of 1:1 to a strategy of drug therapy for rate or rhythm control versus catheter ablation. Randomization was accomplished via telephone or internet using a centralized, interactive voice and web randomization system (IXRS). The randomization scheme was based on permuted block randomization with stratification by clinical site.

Patient drug and ablation treatment

Pharmacologic treatment

Patients randomized to the drug therapy strategy were to first receive rate control medication if appropriate. Anti-arrhythmic medication use was guided by the Guidelines for Management of Subjects with AF published in 2006 by the ACC/AHA/ESC.[34]

Ablative treatment arm

The NHLBI Work Group on AF Ablation, the AF Ablation Consensus document,[35] and the Venice Chart[36] documents all agreed that PVI should be the starting point for AF ablation for every patient in the trial, which has been subsequently adopted in three other large randomized clinical trials.[29–31] Adjunctive procedures such as enlarging the field of ablation for the targeting of complex fractionated atrial electrograms,[37] sites of apparent ganglia,[38] or the use of additional linear lesions was allowed as adjunctive therapy, but only after wider area or antral PVI was completed. The methods for each of these procedures are as outlined in the three AF Ablation Consensus Documents.[35,36]

Guidelines for anti-thrombotic therapy

Drug treated patients with risk factors for cerebral vascular accidents or peripheral thromboembolic events at the time of enrollment, treated with rate control agents alone, were to remain on active anticoagulation therapy with warfarin throughout the duration of the trial.[34] Unlike the AFFIRM trial, patients receiving rhythm control therapy were also required to receive warfarin anticoagulation for the duration of the trial. In the use of warfarin therapy, target INRs of 2 to 3 were required, unless higher INRs were mandated because of underlying disease.

Anticoagulation before, during, and after the ablative intervention was to follow the guidelines of the AF Ablation Consensus Document.[35] Prior to the ablative intervention, patients with persistent and long-standing persistent AF were to receive at least one month of warfarin anticoagulation (INRs: 2,3), or have a TEE excluding intra-atrial thrombus at the time of the intervention. During the ablative intervention, maintaining an ACT between 300 and 400 seconds was strongly recommended. Following the ablative intervention, patients were to be started on IV heparin or subcutaneous injections of low molecular weight heparin beginning 4 to 6 hours after all sheaths were removed, and warfarin anticoagulation reinstituted the evening of the intervention.

Adoption of emerging new ablation or drug therapies

At the outset of the trial, the CABANA leadership expected that primary ablative intervention for AF would evolve over the course of this trial. In order to maximize the potential for the generalizability of CABANA findings to the broader area of AF ablation, newly evolving methods or devices were permitted, as approved by the Innovative Ablation Therapy and Executive Committees. New drug therapies, such as other antiarrhythmics or novel oral anticoagulants, were allowed as approved by the Innovative Drug Therapy and Executive Committees.

Patient follow-up

Follow-up in all patients occurred at 3, 6,12, and months following randomization and every 6 months thereafter, with clinic visits, phone follow-up, and other testing as described below. Quality of life (QOL) data collection included the SF-36,[39] Duke Activity Status Index (DASI),[40] Toronto Atrial Fibrillation Severity Scale, AF Effect on QOL (AFEQT),[41] EQ-5D-3 L,[42] Work Productivity and Activity Impairment Instrument (WPAI),[43] Stanford Presenteeism Scale,[44] and the Mayo AF Symptom Index (MAFSI).[45] All sites entered EQ-5D-3 L and MAFSI data during follow-up intervals. All other follow-up QOL data were collected by trained telephone interviewer staff from the Economics and Quality of Life Coordinating Center (EQOL CC) for patients enrolled in North America and by the Site Coordinator in sites outside North America.

Hospital bills for patients enrolled at US sites were collected throughout the trial by the EQOL CC economic team. The US Site Coordinators completed a one page Rapid Report Form (RRF) at each CABANA study visit documenting any interim hospitalizations (all cause) and ER visits since last contact, which were then faxed to the EQOL Coordinating Center to trigger requests for the relevant hospital bills.

As allowed within institutions or countries outside of the US, all study patients received a single 'CABANA Box' event recording system, a robust rhythm monitoring system provided by Medicomp Inc. (https://medicompinc.com) to be used for: 1) patient activated event monitoring (throughout the trial), 2) monthly autodetect event monitoring at one 24-hour period during year one and every 6 months thereafter, and 3) full disclosure Holter monitoring for 96 hours every 6 months throughout the study. All recordings were transferred via telephone download from the patient's home to Medicomp. The rhythm monitoring data were then sent from Medicomp to the Duke Clinical Research Institute

(DCRI), where a set of programmed rules were run to determine which rhythms should be submitted to the ECG core lab at the University of Washington in Seattle for review and adjudication. Following core lab review, the adjudicated results were electronically transmitted back to the DCRI for incorporation into analysis data sets. All recordings were also made available to the enrolling center for use in clinical practice. An equivalent monitoring system was required at centers unable to utilize the CABANA Box.

The CABANA primary hypothesis is that ablative intervention is superior to state-of-the-art drug therapy based on the composite endpoint of total mortality, disabling stroke, serious bleeding events, or cardiac arrest (primary endpoint), and total mortality (first secondary endpoint). Enrollment of patients was completed on April 4, 2016 with a final enrollment of 2,204 subjects, and follow up was completed on December 31, 2017. It is anticipated that the trial's primary results will be available in spring 2018.

Statistical analysis

Sample size and power calculations

CABANA was originally designed with an enrollment target of 3,000 patients, with a change to 2,200 patients for reasons noted above.

At trial inception, event-rate data for determining sample size were obtained for the drug arm from a combination of AF trials completed prior to the start of CABANA (AFFIRM,[8] RACE,[9] STAF,[10] PIAF,[11] and AF-CHF[12]), as shown in Table IIa. Based on this information, the 3-year event rate in the drug arm of CABANA was projected to be approximately 12% after 3 years of follow-up and up to 15% after 3.5 years of follow-up, the average duration of follow-up originally projected for CABANA. With the elevation of the first composite secondary endpoint as the new primary endpoint, the occurrence of the new primary endpoint was expected to be at least as high as the originally anticipated mortality rate.

A synthesis of information available on patients treated with ablation suggested that the event rate in ablation-treated patients would be less than 3% per year, which translated to a projected 3-year mortality rate of 8 to 9% or a 3.5-year rate of 10% or less (i.e., a reduction by one-third compared to the drug arm). For planning the CABANA sample size, the effect of ablation was projected to be a reduction of 30% in the primary composite endpoint.

The extent to which patients randomized to the drug arm would crossover to receive an ablation during the course of their follow-up was also considered. Although strict guidelines regarding changes to a patient's assigned therapy were established, allowance in the power projections was made for up to 25 to 30% of patients randomized to the drug arm to cross over to ablation at some point during follow-up.

Based on these assumptions, a sample size of 2,200 patients with an average follow-up of 4 to 4.5 years is adequate to achieve >90% power for detecting a 30% reduction in the primary endpoint, allowing for a 2% loss to follow-up. This sample size also provides acceptable power for detecting a 25% reduction in important secondary endpoints. A 25 to 30% reduction in clinical events will be highly important from a clinical and public health

standpoint, given the large population of patients in this country and throughout the world who suffer from AF. Additional subsequent studies (Table IIb) available at the time of the change in primary and secondary endpoints were used as an additional fail-safe review, although these studies published since the initiation of CABANA were not included in final sample size calculations. They simply provided support for the initially established power calculations based on data available at the beginning of the trial.

Primary statistical analysis

All major treatment comparisons between the randomized groups will be performed according to the principle of "intention-to-treat;" that is, subjects will be analyzed and endpoints attributed according to the treatment strategy to which subjects were randomized regardless of subsequent crossover or non-adherence to the assigned treatment. Statistical comparisons will be performed using 2-sided significance tests. Kaplan-Meier estimates of cumulative event rates as a function of follow-up time will be calculated and displayed.[46] Event (or censoring) times for all patients will be measured from the time of randomization (time zero). The primary statistical comparison will be a "time-to-event" analysis using the log-rank test. Relative risks will be expressed as hazard ratios with associated 95% confidence intervals derived using the Cox proportional hazards model.[47] The overall level of significance for the assessment of the primary endpoint will be $\alpha = 0.05$. An on-treatment analysis will also be performed as a sensitivity analysis on the primary results.

If the data provide evidence of an overall difference in outcome between treatment groups, an assessment will be made of whether the therapeutic effect is similar for all patients, or whether it varies according to specific patient characteristics. These analyses will utilize the Cox model by testing for interactions between treatment assignment and specific baseline variables. In addition to the formal assessment of treatment interactions, treatment effects characterized by a hazard ratio (with 95% confidence interval) will be calculated and displayed in forest plots for prospectively defined subgroups. For secondary composite endpoints in which all-cause mortality is a component, the log-rank test will be used for the assessment of treatment differences. For "time-to-event" secondary endpoints in which all-cause mortality is not a component, treatment comparisons will be performed using the competing risk methodology of Fine and Gray.[48]

Interim analyses

For ethical reasons, a pre-specified, interim examination of key safety and endpoint data was performed at selected intervals during the course of the trial. The primary objective of these analyses was to evaluate the accumulating data for an unacceptably high frequency of negative clinical outcomes in either treatment arm. In addition, the interim monitoring also involved a review of patient recruitment, compliance with the study protocol, status of data collection, and other factors which reflect the overall progress and integrity of the study. Interim analysis of the data was performed and reviewed by an independent DSMB appointed by the NHLBI. Any interim treatment comparisons of primary endpoint data were monitored with the use of 2-sided, symmetric O'Brien-Fleming boundaries generated with the Lan-DeMets α-spending function approach to group sequential testing.[49] The results of the interim analyses and status reports have been carefully and confidentially reviewed by

the DSMB which has reported its recommendations directly to the NHLBI Director or his designated representative.

Health economics analyses

The health economics analyses for CABANA will consist of two major parts: an empirical intention-to-treat cost comparison and a cost effectiveness analysis. Primary statistical comparisons between the two treatment arms of empirical costs will be performed by intention-to-treat. The patients enrolled outside the United States will be excluded from the primary cost analyses. Confidence limits around the observed cost differences will be constructed using bootstrap methods.

If the clinical comparisons of CABANA show an important clinical benefit for the ablation arm, cost effectiveness analysis will be performed to examine the economic efficiency of ablation over drug therapy in generating health benefits. The cost-effectiveness analysis will estimate the incremental cost required to add an extra life year with the investigational ablation arm relative to control medical therapy. In secondary analyses, utility weights to estimate the incremental cost per quality adjusted life year gained with ablation, relative to medical therapy will be incorporated. These analyses will be conducted from a societal perspective and will use a lifetime time horizon so that the estimated incremental cost-effectiveness and cost-utility ratios can be compared with societal benchmarks. The within-trial cost-effectiveness/cost-utility ratios will be calculated, although these ratios are limited in their value due to their failure to account for long-term benefits and costs and the absence of comparative benchmarks. Costs will be adjusted for inflation, and both costs and life expectancy will be discounted to present value at a 3% annual discount rate. Adjustments for censored data due to staggered entry will be made following published approaches.[50] Extensive sensitivity analyses will be performed.

Quality of Life (QOL) analyses

For each of the QOL measures examined in this study, data analysis will proceed in two stages. First, the CABANA trial will provide simple descriptive summaries and comparative analyses by intention-to-treat. Second, we will examine changes over time from baseline and identify the major determinants of those changes using regression analysis. Since there is currently no consensus in the statistical literature about the best way to deal with the multiple comparisons problem arising from testing each individual scale separately, we propose two complementary approaches. First, we have pre-specified two co-primary QOL endpoints, AF QOL assessed with the AFEQT and AF symptom burden assessed with the MAFSI and assigned all other comparisons to a secondary (exploratory) status. Based on our understanding of the effects of AF on QOL we believe the most direct and consequential QOL benefit from ablation will be on AF related symptoms with other QOL benefits derivative to those effects. Second, we have specified the 1-year follow-up point for primary comparison of the QOL endpoints with other time points assigned a secondary status. Mixed models will be used to make statistical comparisons while accounting for the repeated measures aspects of the QOL data and the problem of some missing values and will allow for testing at any follow-up point or averaging over all follow-up. Statistical power estimates

for this part of our analysis suggest that there will be >90% power to detect V standard deviation differences in the AFEQT scale.

Significance of the trial

This trial is of substantial importance at multiple levels. Clinically, the trial will establish whether the emerging role of aggressive catheter ablation in the treatment of AF is justified by patient outcomes. Catheter ablation is an expensive procedure, potentially complicated by life threatening events, which is now performed in thousands of patients without a full understanding of long-term benefit. The issues raised above have not been settled for "curative ablation." The impact of age, AF type, and underlying disease on the outcome of ablation and drug therapy remain unclear. This study will answer these questions, will document the effect of ablation on AF recurrence and specifically examine health care costs, cost effectiveness, and quality of life outcomes.

Scientifically, the trial will determine whether the attainment of normal sinus rhythm provides a mortality advantage. No trial to date has prospectively addressed this issue, nor will any currently envisioned study be sufficiently powered for this purpose. The trial will also provide outcomes-based evidence regarding the question of whether AF is a modifiable risk factor for increased morbidity and mortality or simply a risk marker. The trial will also establish the determinants of ablation outcome. The CT/MR Imaging Sub-study of a subset of the overall patient population will elucidate the structural abnormalities contributing to the occurrence of AF in a diverse population of patients and the modulation of those factors by drug or ablative intervention.

From a health policy standpoint, this trial will help establish the place for medical and non-pharmacologic therapies for this escalating national healthcare challenge. Aggressive intervention in an increasing number of patients and resulting mushrooming financial burden to society is already taking place at a time of increasingly constrained funding for health care. The quality of life and cost components of the trial will firmly establish whether AF ablation represents good value for the cost and is an efficient way of improving health in the affected population relative to alternative health care expenditures, especially in the rapidly expanding population over 65 years of age, which has the highest prevalence of AF. It will also allow much better estimation of the impact of the diffusion of ablation technology into the overall health care system. CABANA enrollment occurred during a critical window of opportunity, and the outcome of this landmark trial will likely shape therapy decisions and health care policy for years to come.

Acknowledgments

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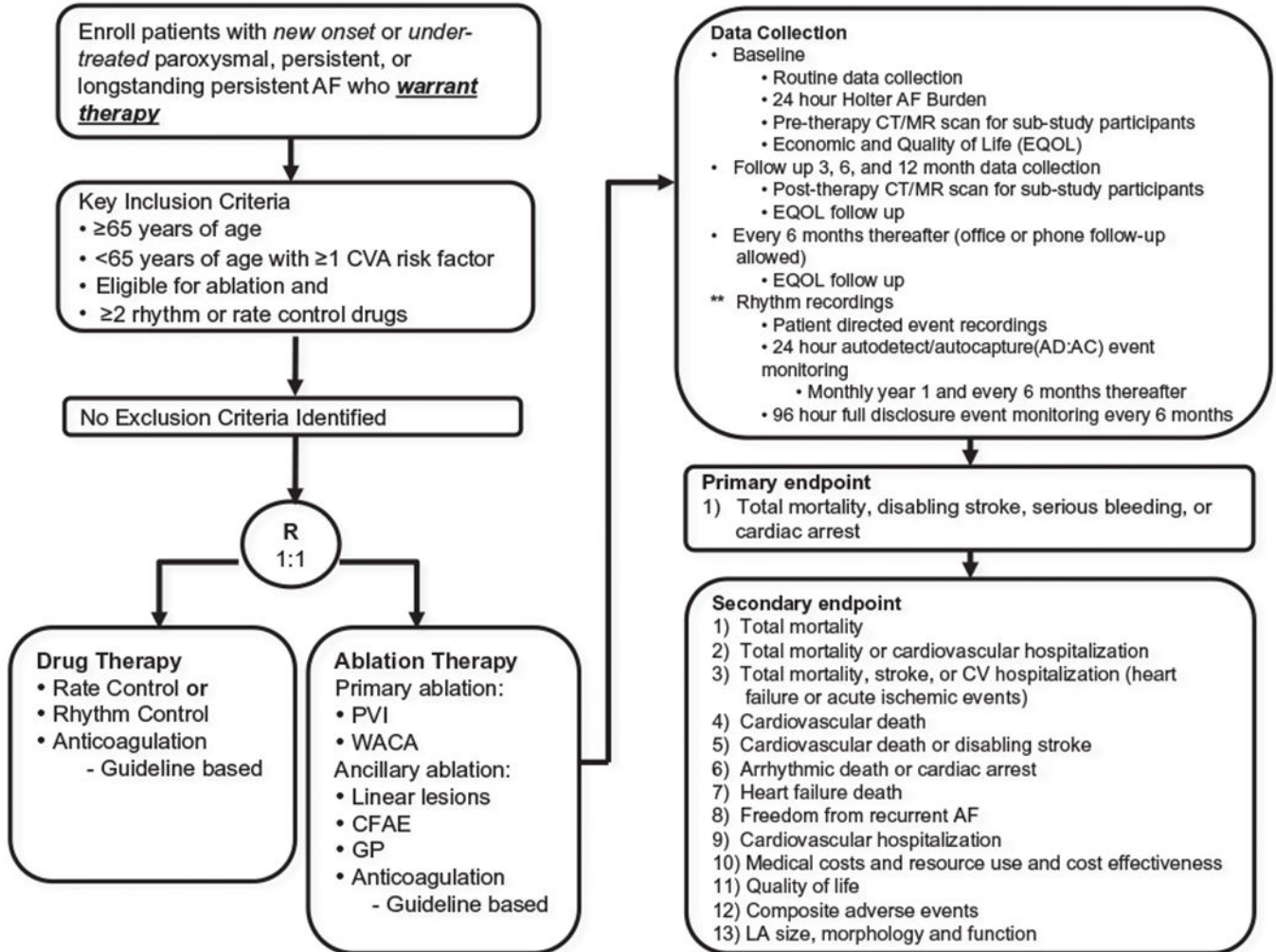
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CABANA Trial Design

Enroll patients with *new onset* or *under-treated* paroxysmal, persistent, or longstanding persistent AF who ***warrant therapy***

↓

Key Inclusion Criteria
- ≥65 years of age
- <65 years of age with ≥1 CVA risk factor
- Eligible for ablation and
- ≥2 rhythm or rate control drugs

↓

No Exclusion Criteria Identified

↓

R 1:1

Drug Therapy
- Rate Control **or**
- Rhythm Control
- Anticoagulation
  - Guideline based

Ablation Therapy
Primary ablation:
- PVI
- WACA
Ancillary ablation:
- Linear lesions
- CFAE
- GP
- Anticoagulation
  - Guideline based

Data Collection
- Baseline
  - Routine data collection
  - 24 hour Holter AF Burden
  - Pre-therapy CT/MR scan for sub-study participants
  - Economic and Quality of Life (EQOL)
- Follow up 3, 6, and 12 month data collection
  - Post-therapy CT/MR scan for sub-study participants
  - EQOL follow up
- Every 6 months thereafter (office or phone follow-up allowed)
  - EQOL follow up
- ** Rhythm recordings
  - Patient directed event recordings
  - 24 hour autodetect/autocapture(AD:AC) event monitoring
    - Monthly year 1 and every 6 months thereafter
  - 96 hour full disclosure event monitoring every 6 months

↓

Primary endpoint
1) Total mortality, disabling stroke, serious bleeding, or cardiac arrest

↓

Secondary endpoint
1) Total mortality
2) Total mortality or cardiovascular hospitalization
3) Total mortality, stroke, or CV hospitalization (heart failure or acute ischemic events)
4) Cardiovascular death
5) Cardiovascular death or disabling stroke
6) Arrhythmic death or cardiac arrest
7) Heart failure death
8) Freedom from recurrent AF
9) Cardiovascular hospitalization
10) Medical costs and resource use and cost effectiveness
11) Quality of life
12) Composite adverse events
13) LA size, morphology and function

Figure 1.
CABANA Trial Design. *AF*, Atrial fibrillation; *CVA*, Cerebral vascular accident; *R*, Randomized; *PVI*, Pulmonary vein isolation; *WACA*, Wide area circumferential ablation; *CFAE*, Complex fractionated atrial electrograms (CFAE); *GP*, Ganglionated plexuses; *CT/MR*, Computed tomography/magnetic resonance; *EQOL*, Economic and Quality of Life; *AD:AC*, Autodetect/autocapture; *LA*, Left atria.

CABANA Trial Organization and Process Flow
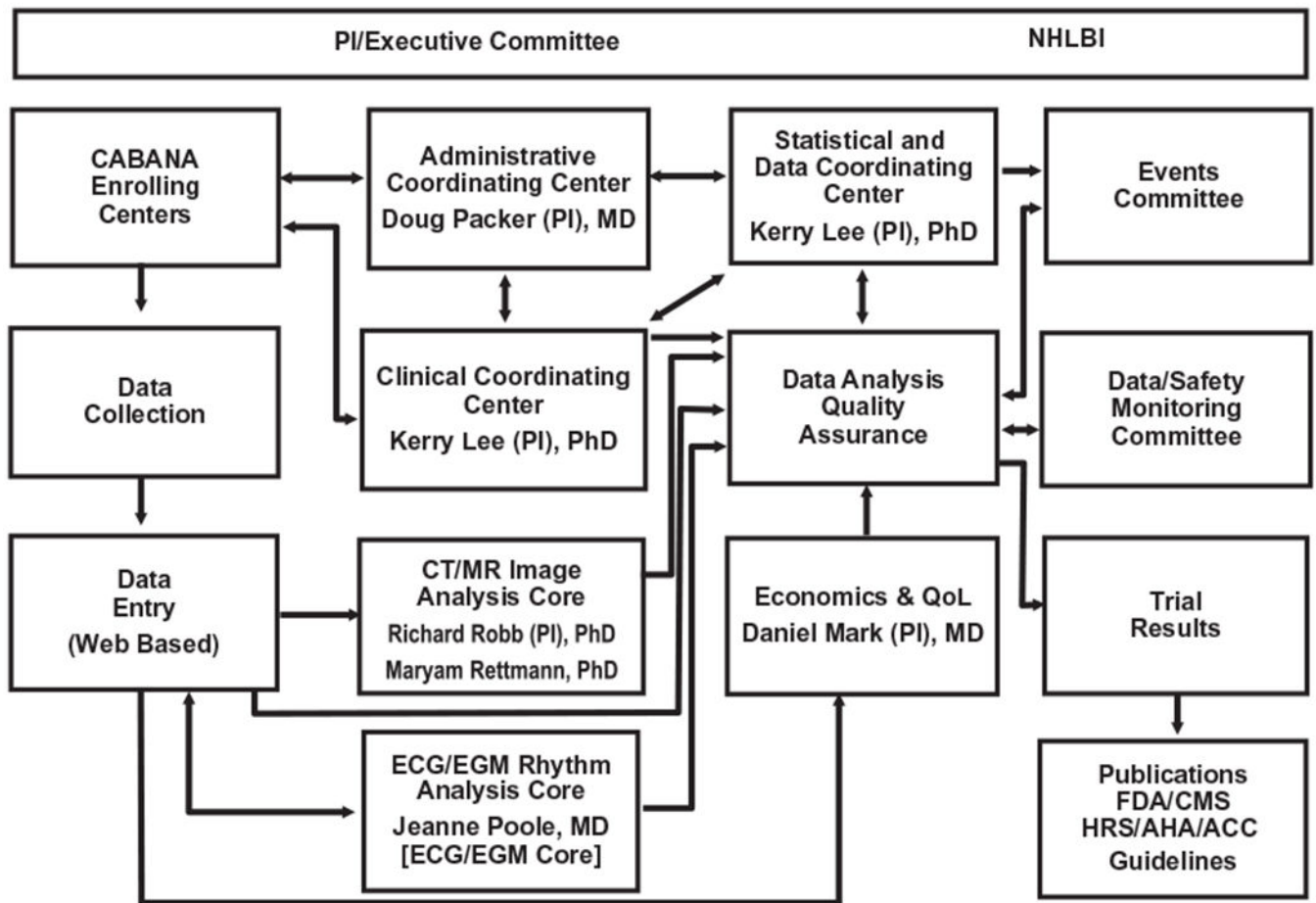
Figure 2.
CABANA Trial Organization and Process Flow. *PI*, Principal investigator; *NHLBI*, National Heart, Lung, and Blood Institute; *QoL*, Quality of Life; *ECG/EGM*, Electrocardiogram/ electrograms mapping; *FDA/CMS/HRS/AHA/ACC*, Food and Drug Administration/Centers for Medicare & Medicaid Services/Heart Rhythm Society/American Heart Association/ American College of Cardiology.

Table I

CABANA Inclusion/Exclusion Criteria

Inclusion	Exclusion
1. Over the preceding 6 months have:	1. Lone AF in the absence of risk factors for stroke in patients <65 years of age
a) 2 paroxysmal (*electrocardiographic documentation* of at least 1) AF episodes lasting 1 hour in duration: (that terminate spontaneously within 7 days or cardioversion is performed within 48 h of AF onset): or	2. Patients who in the opinion of the managing clinician should not yet receive any therapy for AF
b) *electrocardiographic documentation* of 1 persistent AF episode: (sustained for 7 days or cardioversion is performed more than 48 h after AF onset): or	3. Patients who have failed> 2 membrane active anti-arrhythmic drugs at a therapeutic dose due to inefficacy or side effects
c) *electrocardiographic documentation* of 1 longstanding persistent AF episode: (continuous AF of duration > 1 year)	4. An efficacy failure of full dose amiodarone treatment> 8 weeks duration at any time
2. Warrant active therapy (within the past 3 months) beyond simple ongoing observation	5. Reversible causes of AF including thyroid disorders, acute alcohol intoxication, recent major surgical procedures, or trauma
3. Be eligible for catheter ablation and 2 sequential rhythm control and/or 2 rate control drugs.	6. Recent cardiac events including MI, PCI, or valve or bypass surgery in the preceding 3 months
4. Be 65 yrs. of age, or <65 yrs. with one or more of the following risk factors for stroke: Hypertension (treated and/or defined as a BP >140/90 mmHg), Diabetes (treated and/or defined as a fasting glucose 126 mg/dl), Congestive heart failure (including systolic or diastolic heart failure), Prior stroke, TIA or systemic emboli, Atherosclerotic vascular disease (previous MI, peripheral arterial disease or aortic plaque), LA size> 5.0 cm (or volume index 40 cc/m²), or EF 35. Subjects <65 yrs. of age whose only risk factor is hypertension must have a second risk factor or LV hypertrophy to qualify.	7. Hypertrophic obstructive cardiomyopathy (outflow track)
	8. Class IV angina or Class IV CHF (including past or planned heart transplantation)
	9. Other arrhythmias mandating anti-arrhythmic drug therapy (i.e. VT, VF)
	10. Heritable arrhythmias or increased risk for torsade de pointes with class I or III drugs
	11. Prior LA catheter ablation with the intention of treating AF
	12. Prior surgical interventions for AF such as the MAZE procedure
5. Have the capacity to understand and sign an informed consent form.	13. Prior AV nodal ablation
6. Be 18 years of age.	14. Patients with other arrhythmias requiring ablative therapy
	15. Contraindication to appropriate anti-coagulation therapy
	16. Renal failure requiring dialysis
	17. Medical conditions limiting expected survival to< 1 year
	18. Women of childbearing potential (unless post-menopausal or surgically sterile)
	19. Participation in any other clinical mortality trial (Participation in other non-mortality trials should be reviewed with the clinical trial management center)
	20. Unable to give informed consent

AF, Atrial fibrillation; *yrs*, Years; *BP*, Blood pressure; *TIA*, Transient ischemic attack; *MI*, Myocardial infarction; *LA*, Left atrial; *EF*, Ejection fraction; *LV*, Left ventricular; *PCI*, Percutaneous coronary intervention; *CHF*, Congestive heart failure; *VT*, Ventricular tachycardia; *VF*, Ventricular fibrillation; *MAZE*, Cox maze procedure; *AV*, Atrioventricular node.

Table II

AE, Adverse Event.

Trial	Groups	n	Follow Up*	Death	Anticipated Mortality at 4, 5 yr.	Cardiac Death	Arrhythmia Death	CNS Death	Any CVA	Disabling Stroke Total	Thrombo Embolic Events	Major Bleed (not cns)	CNS Hemor	Hosp	Endpoint Composite
a. Event Rates in Atrial Fibrillation Trials Used In Power Calculations															
AFFIRM	Rate	2017	3.5 yr.	*310 (15%)	21.3 @ 5 yr.	130 (10%)	79 (3.9%)	28 (1.4%)	105 (7.4%)	77 (3.8%)	86 (6.0%)	107 (7.7%)	29 (1.9%)	1,220 (73%)	416§ (32.7%)
NEJM 2002;347:1825–33	Rhythm	2033	3.5 yr.	*356 (18%)	23.8 @ 5 yr.	129 (9%)	77 (3.9%)	28 (14%)	106 (8.9%)	80 (3.9%)	87 (7.5%)	96 (6.9%)	29 (2.1%)	1,374 (80%)	445§ (32%)
RACE	Rate	256	2.3 yr.	18 (7%)	7.0	18 (7.0%)	8 (3.1%)	0 (0%)	-	-	14 (5.5%)	12 (4.7%)	-	-	44‖ (17.2%)
NEJM 2002;347:1834–40	Rhythm	266	2.3 yr.	18 (7%)	6.8	18 (6.8%)	8 (3.0%)	6 (2.3%)	-	-	21 (7.9%)	9 (3.4%)	-	-	60‖* (22.6%)
STAF	Rate	100	1.7 yr.*	8 (8%)	8 (4.5/yr.)	8 (8%)	4 (4%)	-	-	1:0.6%/yr. (1%)	2 (2%)	8 (8%)	-	26 (26%)	10π (10%)
J Am Coll Cardiol. 2003; 41:1690–96	Rhythm	100	1.7 yr.*	4 (4%)	4 (2.9/yr.)	3 (3%)	2 (2%)	-	-	5: 3/yr. (5%)	5 (5%)	11 (11%)	-	54 (54%)	9π (9%)
PIAF	Rate	125	1 yr.*	2 (2%)	1.6	1 (1%)	0 (0%)	0 (0%)	-	-	-	-	-	30 (24%)	-
Lancet 2000;356:1789–94	Rhythm	127	1 yr.*	2 (2%)	1.6	2 (1.6%)	2 (1.6%)	0 (0%)	-	-	-	-	-	87+ (69%)	-
HOT CAFÉ	Rate	101	1.7 yr.	1 (<1%)	-	-	-	-	-	0 (0%)	-	-	-	-	-
Kariol Pol 2003;59:1–16	Rhythm	104	1.7 yr.	3 (3%)	-	-	-	-	-	3 (2.9%)	-	-	-	-	-
META ANALYSIS	Rate	2609	-	339 (13%)	13	-	-	-	-	78 (3.5%)	-	-	-	-	-
	Rhythm	2630	-	383 (15%)	14.6	-	-	-	-	88 (3.9%)	-	-	-	-	-
AF CHF	Rate	694	3 yr.*	228 (33%)	32.9	175 (25.2%)	-	-	25 (3.6%)	-	-	-	-	-	318 (45.8%)
NEJM.358:25–2667–77	Rhythm	682	-	217 (32%)	31.8	182 (26.2%)	-	-	18 (2.6%)	-	-	-	-	-	291 (42.7%)
PAPPONE	Abl.	589	2.5 yr.	38 (6%)	6.5	16 (2.7%)	0 (0%)	2 (0.3%)	4 (0.6%)	6 (1%)	5 (10.8%)	2 (0.3%)	2 (0.3%)	-	-
	Drug	582	2.5 yr.	83 (14%)	14	45 (7.7%)	12 (2.1%)	14 (14%)	15 (2.3%)	22 (3.8%)	18 (3.1%)	7 (1%)	7 (1%)	-	-
b. Event Rates in Atrial Fibrillation Trials †,‡															
ATHENA	Dronedarone	2301	1.8 yr.*	116 (5%)	2.5 @ 2 yr.	63 (2.7%)	26 (1.1%)	-	46 (2.0%)	-	-	-	-	675 (29%)	-
N Engl J Med 2009;360:668–78	Rate	2327	1.8 yr.*	139 (6%)	3.0 @ 2 yr.	90 (3.9%)	24 (2.1%)	-	70 (3%)	-	-	-	-	859 (37%)	-
PALLAS	Dronedarone	1619	0.29 yr.	25 (4.7%)	-	21 (4.0%)	13 (2.5%)	-	23 (4.4%)	-	19 (3.2%)	-	-	113 (22.5%)	43 (8.2%)#
N Engl J Med 2011; 365:2268–2276	Placebo	1617	0.29 yr.	13 (4.7%)	-	10 (1.9%)	4 (0.8%)	-	10 (1.9%)	-	9 (1.7%)	-	-	59 (11.4%)	19 (3.6%)#
RE-LY	VKA	6022	2 yr.*	487 (8%)	-	317 (5.3%)	-	-	199 (3.3%)	-	1.69%	397 (6.6%)	0.38%	2458 (41%)	-
N Engl J Med 2009; 361:1139–1151															
ROCKET	VKA	7133	2 yr.*	250 (4%)	8.8 @ 4 yr	-	-	-	306 (4.3%)	-	241 (2.2%)	386 (5.4%)	0.70%	-	-

Trial	Groups	n	Follow Up [*]	Death	Anticipated Mortality at 4, 5 yr.	Cardiac Death	Arrhythmia Death	CNS Death	Any CVA	Distabling Stroke Total	Thrombo Embolic Events	Major Bleed (not cns)	CNS Hemor	Hosp	Endpoint Composite
N Engl J Med 2011; 365:883–891															
ARISTOTLE	VKA	9081	1.8 yr	669 (7%)	7.1% @ 1.8 yr	-	-	-	250 (2.8%)	-	1.15%	462 (5.1%)	0.80%	-	-
N Engl J Med 2011; 365:981–992															

Abbreviations: *anox*, Anoxic; *CA*, Cardiac arrest; *CHF*, Congestive heart failure; *CNS*, Central nervous system; *CPR*, Cardio pulmonary resusitation; *CV*, Cardiovascular; *CVA*, Cerebral vascular accident; *enceph*, Encephalopathy; *Hemor*, Hemorrhage; *Hosp*, Hospital; *N*, Number; *PM*, Pulmonary event; *periph*, Peripheral; *TE*, Thromboembolic event; *Yr*, Year.

[*] reported in terms of months,

[†] used as confirmatory data after interim analysis,

[‡] not used in trial power calculations,

[§] death, disabl CVA, anox enceph, major bleed, CA;

[||] CV death, CHF, TE events, bleeding, PM, Severe AE;

[π] Death, CPR [like CA], CVA, periph TE;

[#] composite of stroke, myocardial infarction, systemic embolism, or CV death.