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Catheter Ablation vs. Medical Therapy in Congested Hearts with AF

(CATCH-AF in Patients with impaired LV function)

An Early Ablation Strategy Study
Impact on Health Care Utilization

Cleveland Clinic Center for Atrial Fibrillation Investigators:
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Sponsor:	Cleveland Clinic Foundation
Protocol Number	6.0
Version Date	May 22, 2017

Primary Investigator Protocol Signature Page

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I, the undersigned, have read and approve this protocol and agree on its contents. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practice, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements.

Primary Investigator
Signature

Oussama Wazni, MD

7/17/2017
Date

Abbreviation of Term	Definition
AAD	Anti-Arrhythmic Drug
ACC	America College of Cardiology
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AF	Atrial Fibrillation
AFSS	Atrial Fibrillation Severity Scale
AHA	American Heart Association
ARB	Angiotensin Receptor Blocker
AVN ablation	Atrioventricular Node ablation
BP	Blood Pressure
CHF	Congested Heart Failure
CRF	Case Report Form
DC cardioversion	Direct Current cardioversion
ECG	Electrocardiogram
EF	Ejection Fraction
ESC	European Society of Cardiology
HF	Heart Failure
HR	Heart Rate
HRS	Heart Rhythm Society
ITT	Intent To Treat
LV	Left Ventricle
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PVI	Pulmonary Vein Isolation
RVR	Rapid Ventricular Response
SAE	Serious Adverse Event
SOC	Standard of Care

Study Synopsis

Title	**C**atheter **A**blation vs. Medical **T**herapy in **C**ongested **H**earts with **AF (CATCH-AF** in Patients with impaired LV function)
Protocol Number	6.0
Study Treatment	Strategy of Early Atrial Fibrillation Ablation compared to conventional Anti-Arrhythmic Drug management.
Indication	Chronically impaired LV function on optimal medical therapy with first encounter for new symptomatic AF diagnosis within 12 months.
Study Design	This study is a, multi-center, randomized, unblinded, clinical trial with the objective of enrolling 220 patients over approximately 18 months.
Study Objectives	• To determine if catheter-based atrial fibrillation (AF) ablation is superior to medical treatment in patients with impaired left ventricular function who have been diagnosed with symptomatic AF within the past 12 months • Hypothesis: AF ablation is better than medical therapy for patients with symptomatic AF and impaired LV function in terms of recurrent and total number of hospitalizations, recurrence of AF, EF, quality of life, and 6-minute walk distance.
Primary Endpoint	The primary endpoint is time to first hospitalization (>24hr) for heart failure, recurrence of AF or DC cardioversion after the treatment period
Secondary Endpoint	Secondary endpoints will include evaluation of the following: • Total number of cardiovascular hospitalizations during the trial period for each group • Time to Recurrence of AF lasting longer than 30 seconds • Change in distance walked in 6-minute walk test • Change in Rand 36-Item Health Survey (SF-36) during trial period • Change in EF during trial period
Duration of Treatment and Study Period	The time course for the trial is divided into a treatment period followed by the trial period. The treatment period will include the first 3 months post enrollment. The trial period will commence at end of treatment period and all outcome data will be collected over a 12 month period.

Inclusion Criteria	Patients must meet **all** of the following criteria: • Be ≥18 years of age • Provide signed written Informed Consent • Symptomatic AF documented by ECG or heart rhythm monitoring within 12 months. • Patients should be on optimal medical therapy for HF (heart failure) for three months prior to randomization. Adjustments to medications within this 3 month period are permitted. • Chronically impaired LV function defined as EF 20%-45% within the last 3 months by echocardiogram, nuclear imaging, MRI or cardiac catheterization • All patients should be on an optimal therapy for impaired LV function. Optimal therapy includes at least one ACE inhibitor or angiotensin receptor blockers (ARB) in ACE-intolerant patients along with beta blockers for at least 3 months. For those patients intolerant to ACE/ARB's, a combination of hydralazine and isosorbide dinitrate is recommended. NYHA class III patients may be prescribed spironolactone • Ability to complete 6 minute walk test • Be eligible for catheter ablation and anti-arrhythmic drugs

Exclusion Criteria	Patients must meet **none** of the criteria: • Women of childbearing potential (women will not be permitted to participate unless post-menopausal or surgically sterile) • Patients hospitalized for HF (heart failure) within the 3 months prior to randomization • Reversible causes of AF such as pericarditis, thyroid disorders, acute alcohol intoxication, recent major surgical procedures, or trauma • Recent Reversible LV impairment that may be attributed to AF with RVR and may improve with introduction of rate control. • Presently with Valvular Heart disease requiring surgical intervention • Presently with coronary artery disease requiring surgical or percutaneous intervention • Early Post-operative AF (within three months of surgery) • Previous MAZE or left atrial instrumentation (including ablation and Left Atrial Appendage exclusion) • History of AVN ablation • Hypertrophic Cardiomyopathy • Prolonged QT interval • Liver Failure • Renal Failure requiring dialysis • Social factors that would preclude follow up or make compliance difficult. History of drug, alcohol, or substance abuse as assessed by the investigator. • Contraindication to the use of anti-arrhythmic medications and/or appropriate anticoagulation therapy • Currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product or non-approved use of a drug or device or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. • Patients with severe pulmonary disease • Documented intra-atrial thrombus, tumor, or another structural abnormality which precludes catheter introduction • Unable or unwilling to comply with protocol requirements or deemed by the investigator to be unfit for the study.
Study Product, Dose, Route, Regimen	Patients will be randomized in a 1:1 fashion (based on EF stratification EF ≤35% and >35%) into treatment by AF ablation or AADs.
Statistical Methodology	Sample size is based on an expected 30-40% AF recurrence rate at 12 months in the ablation arm and a 60% AF recurrence rate at 12 months in the AADs. One hundred patients per treatment arm are needed to have 80% power at an alpha level of 0.05 to detect this difference. Assuming a 10% drop-out rate, a total of 220 patients will need to be enrolled. Randomization will be 1:1 based on EF stratification EF ≤35% and >35%. A Cox proportional hazards regression model adjusting for site and EF strata will be used to test for treatment group differences in the primary endpoint.

Study Assessments:

Procedure	Screening/ Baseline/ Randomization Visit	3-6 month Follow-up Visit (+/- 3 weeks)	12-15 month Follow-up Visit (+/- 3 weeks)
Confirm Inclusion/Exclusion Criteria	X		
Obtain Informed Consent	X		
Verify that females are not of childbearing potential [1]	X		
Randomization	X		
Record Medical History and Physical	X		
Record Vital Signs HR/BP	X	X	X
Record Medications	X	X	X
Record ECG	X	X	X
Record Echocardiogram	X		X
6 minute walk test	X	X	X
Record Routine Lab Assessments	X	X	X
Record Clinically Indicated Tests	X	X	X
Rand 36-Item Health Survey (SF-36)	X	X	X
AFSS QOL	X	X	X
Assessment NYHA	X	X	X
Arrhythmia Monitoring	X	X	X
Assessment of SAE/AE		X	X
Assessment of Hospitalization		X	X

1. **Verify that female subject is post-menopausal /surgically sterile following individual site standard of care process**

Note: Baseline assessments to be completed before assigned treatment initiated.

If the above assessments are collected as part of routine care, please record the information on the Case Report Form (CRF) at the study visit time points. For the ablation arm, record date of ablation and target areas on the CRF.

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1 Introduction

1.1 Background

AF is the most prevalent arrhythmia[i] (Kannel, 1982) and its optimal management remains unclear. AF frequently complicates the management of patients with heart failure (HF) and rate control only strategy is not always possible or practical in this population. Furthermore, it is well recognized that HF begets AF, vice versa and in this particular population AF begets more AF, leading to AF prevalence rates as high as 50% in an elderly population with CHF[ii]. The optimal treatment strategy for AF in this population, and clinical outcomes of these strategies, has not been well studied.

AF ablation has emerged as a highly effective way to abolish the triggers that initiate AF and thus provides an important treatment option for patients intolerant of AF, or those whose AF is refractory to standard therapies. We and others have published analyses of patients with impaired LV function treated with ablation and found ablation to be an effective and safe therapeutic option for this patient population as well[iii]. However this strategy is not widely adopted. Studies have shown that rate control remains a safe and effective means of managing AF. The results of the rate-control vs. rhythm-control trials might lead to the conclusion that sinus-rhythm restoration is of comparable efficacy while allowing patients to remain in AF with a controlled ventricular rate[iv]. A limitation of all these trials is that the rhythm-control strategy was not efficacious. Furthermore, in an analysis of a study that evaluated predictors of mortality, sinus rhythm was associated with a 47% reduction in the risk of death, whereas use of antiarrhythmic drug therapy was associated with a 49% increase in mortality[v]. This suggests that the neutral results in the rate-control vs. rhythm-control trials might be explained by the fact that the benefits of antiarrhythmic drugs in restoring sinus rhythm were negated by offsetting detrimental effects of antiarrhythmic drug therapy. In theory, a therapy that restores and maintains sinus rhythm while avoiding the deleterious effects of antiarrhythmic drugs would improve survival. It is known that ablation and management of paroxysmal AF is much more successful than persistent AF. Also a longer history of AF and longer duration of AF episodes are associated with worse outcomes. In our practice it has also become more evident that early intervention with ablation may decrease the AF burden so that if ablation is performed early in the disease there is less opportunity for developing permanent AF with all its deleterious effects.

Medical Therapy for Atrial Fibrillation:
Anti-arrhythmic drugs (AADs) choice will be based on the treating physicians' preference but will be in accordance with HRS, ACC, AHA, ESC guidelines.

Detection of Atrial Fibrillation:
In the general population AF is usually detected during workup of palpitations or during routine physical exams/ECGs in patients with no symptoms of palpitations. Also it may be detected during workup of stroke or peripheral thromboembolism.
In the group intended for this study AF should be **symptomatic** for inclusion. However after treatment with PVI or AADs it is not unusual for patients to develop asymptomatic AF recurrence. As such implanted devices (already implanted for clinical indications) may be used to assess for recurrence of AF in conjunction with device and event monitoring.

2 Study Objectives

2.1 Objectives

- To determine if catheter-based atrial fibrillation (AF) ablation is superior to medical treatment in patients with impaired left ventricular function that has been diagnosed with symptomatic AF within the past 12 months.
- Hypothesis: In patients with an early diagnosis of AF, ablation is better than medical therapy for patients with symptomatic AF and impaired LV function in terms of recurrent and total number of hospitalizations, recurrence of AF, EF, quality of life, and 6-minute walk distance.

3 Study Endpoints

Timeframe to endpoints: After the 3 month treatment period, the endpoints will be assessed for 12 months

3.1 Primary Endpoint

Time to first hospitalization (> 24 hours) for Heart Failure, recurrence of AF or DC cardioversion after the treatment period

3.2 Secondary Endpoints

- Total number of cardiovascular hospitalizations during the trial period for each group
- Time to Recurrence of AF lasting longer than 30 seconds
- Change in distance walked in 6-minute walk test
- Change in the Rand 36-Item Health Survey (SF-36) during trial period
- Change in EF during trial period

4 Study Design

This will be a multi-center randomized, unblinded clinical trial comparing Ablation to Anti-arrhythmic treatments for patients with first encounter for new symptomatic AF diagnosis within 12 months. Up to 220 patients will be enrolled over approximately 18 months.

5 Subject Selection

5.1 Subject Screening and Enrollment

The study will enroll patients with chronically impaired LV function on optimal medical therapy with first encounter for new symptomatic AF diagnosis within 12 months. Before any study tests or procedures take place, the subject will be asked to read and sign the informed consent form (ICF) that has been approved by the Institutional Review Board (IRB) / Ethics Committee. Previously evaluated subjects that meet amended study eligibility can be reconsidered for the trial. The complete informed consent process will include giving the subject adequate information about the study and ensuring that there is a sufficient amount of time to comprehend the information in the consent form and have all questions answered before making a decision to participate in the study. Enrollment will occur when a subject signs and dates an informed consent form and provides authorization to use protected health information.

5.2 Inclusion Criteria

Patients must meet **all** of the following criteria:

1. Be ≥18 years of age
2. Provide signed written Informed Consent
3. Symptomatic AF documented by ECG or heart rhythm monitoring within 12 months
4. Patients should be on optimal medical therapy for HF (heart failure) for 3 months prior to randomization. Adjustments to medications within this 3 month period are permitted.
5. Chronically impaired LV function defined as EF 20%-45% within the last 3 months by echocardiogram, nuclear imaging, MRI or cardiac catheterization
6. All patients should be on an optimal therapy for impaired LV function. Optimal therapy includes at least one ACE inhibitor or angiotensin receptor blockers (ARB) in ACE-intolerant patients along with beta blockers for at least 3 months. For those patients intolerant to ACE/ARB's, a combination of hydralazine and isosorbide dinitrate is recommended. NYHA class III patients may be prescribed spironolactone
7. Ability to complete 6 minute walk test
8. Be eligible for catheter ablation and anti-arrhythmic drugs

5.3 Exclusion Criteria

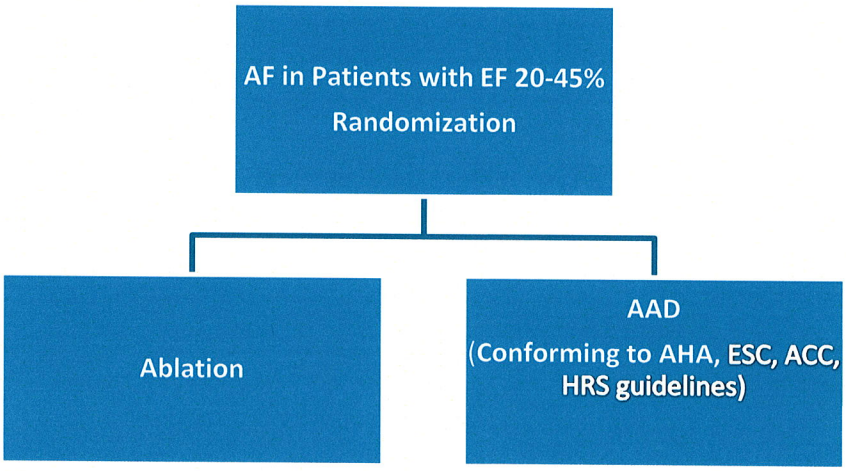
Patients must meet **none** of the criteria:

1. Women of childbearing potential (women will not be permitted to participate unless post-menopausal or surgically sterile)
2. Patients hospitalized for HF (heart failure) within the 3 months prior to randomization
3. Reversible causes of AF such as pericarditis, thyroid disorders, acute alcohol intoxication, recent major surgical procedures, or trauma
4. Recent Reversible LV impairment that may be attributed to AF with RVR and may improve with introduction of rate control.
5. Presently with Valvular Heart disease requiring surgical intervention
6. Presently with coronary artery disease requiring surgical or percutaneous intervention
7. Early Post-operative AF (within three months of surgery)
8. Previous MAZE or left atrial instrumentation (including ablation and Left Atrial Appendage exclusion)
9. History of AVN ablation
10. Hypertrophic Cardiomyopathy
11. Prolonged QT interval
12. Liver Failure
13. Renal Failure requiring dialysis
14. Social factors that would preclude follow up or make compliance difficult. History of drug, alcohol, or substance abuse as assessed by the investigator.
15. Contraindication to the use of anti-arrhythmic medications and/or appropriate anticoagulation therapy
16. Currently enrolled in, or discontinued within the last 30 days from a clinical trial involving an investigational product or non-approved use of a drug or device or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
17. Patients with severe pulmonary disease
18. Documented intra-atrial thrombus, tumor, or another structural abnormality which precludes catheter introduction
19. Unable or unwilling to comply with protocol requirements or deemed by the investigator to be unfit for the study.

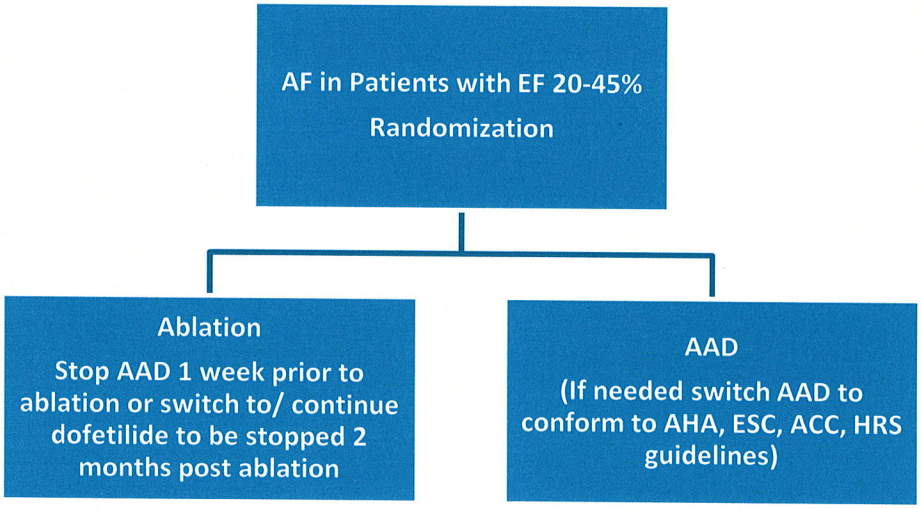
5.4 Randomization

Patients first encountered with recently diagnosed AF meeting the all of the inclusion criteria and none of the exclusion criteria and provided signed consent will be randomized in a 1:1 fashion (based on EF stratification EF ≤35% and >35%) into treatment by AF ablation or AADs. Patients already on dofetilide and randomized to ablation may continue taking dofetilide until 2 months post ablation. Other AADs will be stopped 1 week prior to ablation. Dofetilide may be initiated pre-ablation or post ablation but must be stopped 2 months post ablation.

Anti-Arrhythmic Drug (AAD) Naïve patients:



Patients already on AADs



6 Study Procedures

The time course for the trial is divided into a treatment period followed by the trial period. The treatment period will include the first 3 months post enrollment or post procedure during which repeat ablation can be performed and titration of AAD dosages can be performed. The follow-up trial period will commence at end of treatment period and all outcome data will be collected over a 12 month period.

6.1 AF Ablation

Experienced electrophysiologists will perform the electrophysiological studies, mapping and ablation for Atrial Fibrillation per guidelines and Standard of care. Ablation targets will be determined by the investigator. Patients already on dofetilide and randomized to ablation may continue taking dofetilide until 2 months post ablation. Other AADs will be stopped 1 week prior to ablation. Dofetilide may be initiated pre-ablation or post ablation but must be stopped 2 months post ablation. Oral anticoagulation will follow AHA/ACC guidelines and will be continued after the PVI procedure for at least 6 months.

Any repeat ablations occurring during the treatment period should be captured on the CRF. If a spiral CT scan was performed, information should be recorded on the CRF. Outcomes will be collected. Primary outcome data in the ablation arm will only be included in the analysis after the treatment period (three months post randomization).

6.2 AAD Treatment

Patients randomized to AAD will receive AADs per Physician and patient preference. Initiation and ongoing clinical evaluations of drug therapy must conform to HRS/ACC/AHA/ ESC guidelines. Oral anticoagulation will follow HRS/ACC/AHA/ESC guidelines. If a patient randomized to the AAD treatment arm has an ablation during the treatment initiation period, the date of ablation will be recorded on the CRF. Outcomes will be collected after the optimization of AAD.

6.3 Baseline Visit

Baseline visit assessments will be completed for both arms **before** initiation of treatment. These include:

1. Record vital signs (HR and BP)
2. Record demographic and medical history information
3. For female subjects: Verify that the subject is post-menopausal /surgically sterile following individual site standard of care process
4. Record use of select medications
5. Record 12 lead ECG results
6. Record Echocardiogram results
7. Perform 6 minute walk test
8. Collect Rand 36-Item Health Survey (SF-36)
9. Collect Atrial Fibrillation Severity Scale (AFSS)
10. Assessment of NYHA class
11. Record the data from remote arrhythmia monitoring and /or ECGs completed as a part of standard of care
12. Record results from routine lab assessment and clinically indicated tests completed as a part of standard of care; these may include but not limited to:
    - Laboratory assessments may include CBC, PT, PTT, INR if applicable, chest x-rays, pulmonary function test, spiral CT to assess pulmonary vein stenosis (only if in the ablation arm)

6.4 Follow Up (Month 3 through Month 15)

6.4.1 3-6 Months Post Randomization Visit (+/- 3 weeks)

1. Record data from office visit if completed as standard of care
2. Record vital signs (HR/BP)
3. Record use of select medications
4. Record 12 lead ECG results
5. Perform 6-minute walk test
6. Collect Rand 36-Item Health Survey (SF-36)
7. Collect Atrial Fibrillation Severity Scale (AFSS)
8. Assessment of NYHA class
9. Record the data from remote arrhythmia monitoring and /or ECGs completed as a part of standard of care
10. Record the results from routine lab assessment and clinically indicated tests completed as a part of Standard of care: these may include but not limited to:
    - Blood tests, chest x-rays, pulmonary function test, Spiral CT to assess pulmonary vein stenosis (only if in the ablation arm)
11. Assessment of Adverse Events (AE) and Serious Adverse Events (SAE)
12. Record any hospitalizations including short stays and hospital admissions.

6.4.2 12-15 Month Post Randomization Visit (+/- 3 weeks)

1. Record data from office visit if completed as standard of care
2. Record vital signs (HR/BP)
3. Record use of select medications
4. Record 12 lead ECG
5. Record Echocardiogram
6. Perform 6-minute walk test
7. Collect Rand 36-Item Health Survey (SF-36)
8. Collect Atrial Fibrillation severity Scale (AFSS)
9. Assessment of NYHA class
10. Record the data from remote arrhythmia monitoring and /or ECGs completed as a part of standard of care
11. Record the results from routine lab assessment and clinical indicated tests completed as a part of Standard of care: these may include but not limited to:
    - Blood tests, chest x-rays, pulmonary function test, Spiral CT to assess pulmonary vein stenosis (only if in the ablation arm only if clinically indicated)
12. Assessment of Adverse Events (AE) and Serious Adverse Events (SAE)
13. Record any hospitalizations including short stays and hospital admissions.

7 Statistical Analysis

A Cox proportional hazards regression model adjusting for site and randomization strata will be used to test for treatment group differences in the primary endpoint. Kaplan-Meier estimates and curves will also be created. Secondary endpoints will be analyzed using a two-sample t-test or Wilcoxon signed rank as appropriate. Depending on the distribution for the total number of hospitalizations it will be treated as a continuous variable or collapsed into categories (0-2, 3-5, 5-7, >7). The intent–to–treat population will be used for all analysis. Patients who drop-out before study completion due to cardiac causes will be considered as having an event at the time drop-out for the primary analysis. Patients who drop-out for other reasons will be treated as censored observations at the time of drop-out in the primary analysis. Analysis based on the protocol and safety populations will also be done. All statistical tests will be two-sided and an alpha of 0.05 or less will be considered statistically significant. Mean and

standard deviation or frequency and percent will be used to describe demographics, medical history and other baseline variables by treatment group. T-tests or chi-square tests as appropriate will be used to compare the baseline factors by treatment group.

Sample size is based on an expected 30-40% rate of hospitalization for recurrence of AF, heart failure or DC conversion at 12 months in the ablation arm and a 60% rate at 12 months in the AAD arm. One hundred patients per treatment arm are needed to have 80% power at an alpha level of 0.05 to detect this difference. Assuming a 10% drop-out rate, a total of 220 patients will need to be enrolled. Randomization will be 1:1 based on EF stratification EF ≤35% and >35%.

Safety population: All patients that received any ablation treatment **or at least 1 dose of AAD** will be included in the safety population.

7.1 Subject Population for Analysis

Analysis populations are defined as following:

Intent-to-treat population (ITT): All patients that are randomized to either the ablation treatment or antiarrhythmic treatment are included in the intention to treat population. ITT population is analyzed based on the treatments they are randomized to.
Per-protocol population: Patients that satisfy all the inclusion and exclusion criteria, and receive and stay within the randomized treatment during the treatment period are included in the per-protocol. The per-protocol population is analyzed based on the actual treatment they receive.
Safety population: All patients that received any ablation treatment **or at least 1 dose of AAD** will be included in the safety population.

8 Safety and Adverse Event Reporting

8.1 Adverse Event

An ***adverse event*** (AE) is any new symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- Is associated with a serious adverse event
- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Is considered by the investigator to be of clinical significance

8.1.1 Unavoidable Adverse Event

Defined as an adverse event inherent to an invasive intervention that is expected to occur for a projected duration in all patients. Unavoidable adverse events are **not** reportable. The adverse events listed are considered unavoidable if the onset occurs within the time frame.

Unavoidable Event Description	Time Frame (after ablation)
Anesthesia related nausea/vomiting	24 hours
Mild to moderate bruising/ecchymosis of catheter puncture site	72 hours
Back pain related to laying on table	72 hours

8.1.2 Anticipated Adverse Event

An anticipated adverse event is an adverse event of which the nature, severity or degree of incidence is known and identified in applicable product labeling, published literature, or the Investigational Plan.

8.1.3 Unanticipated Adverse Event

An unanticipated adverse event is an advent of which the nature, severity or degree of incidence of which is not known nor identified in applicable product labeling, published literature.

8.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- Fatal
- Life-threatening
- Requires or prolongs hospital stay
- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.3 Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from time of informed consent to the end of the study treatment follow-up.

8.4 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.5 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

8.6 Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any

death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

8.7 Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

8.8 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

- Hospitalization for worsening of HF should not be reported as an SAE for this trial.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery is reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

8.9 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, the appropriate adverse event module of the case report form (CRF) and per sponsor guidelines. Events meeting the definition of serious adverse event (SAE) should be recorded within 24 hours of the sites knowledge of the event. All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.10 MedWatch Adverse Event Reporting and Product Complaint Reporting

The PI and Institution will be responsible for reporting adverse event information in accordance with FDA regulations for commercially marketed products following standard institutional policy.
If a death or serious injury occurs as a result of a Biosense Webster device malfunction used during the conduct of this study, a MedWatch form should be completed and filed with the FDA per standard institutional reporting policy for commercially marketed medical devices. The PI and institution will simultaneously notify Biosense Webster and C5Research within 24 hours of MedWatch form submission to the FDA. The PI is required to notify Biosense Webster of any and all complaints involving devices used and/or other Biosense Webster products used in the study.

For the purpose of this study, serious injury is defined as an unanticipated adverse device effect and definition of complaint is defined in Appendix (A.).

9 Safety Monitoring Plan

An independent Safety Medical Monitor will be appointed to monitor the study by reviewing the case report forms, SAE and AE forms at specified intervals throughout the study and will be responsible for the oversight of safety.

10 References

[i] Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. *N Engl J Med.* 1982;306(17):1018-1022

[ii] Van den Berg MP, Tuinenburg AE, Crijns HJ, Van Gelder IC, Gosselink AT, Lie KI. Heart failure and atrial fibrillation: current concepts and controversies. *Heart.* 1997;77(4):309-313.

[iii] Chen MS, Marrouche NF, Khaykin Y, Gillinov AM, Wazni O, Martin DO, Rossillo A, Verma A, Cummings J, Erciyes D, Saad E, Bhargava M, Bash D, Schweikert R, Burkhardt D, Williams-Andrews M, Perez-Lugones A, Abdul-Karim A, Saliba W, Natale A. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. *J Am Coll Cardiol.* Mar 17 2004;43(6):1004-1009.

[iv] Wyse DG. Some recent randomized clinical trials in the management of atrial fibrillation. *J Interv Card Electrophysiol.* Oct 2003;9(2):223-228.

[v] Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, Josephson RA, Kellen JC, Klein RC, Krahn AD, Mickel M, Mitchell LB, Nelson JD, Rosenberg Y, Schron E, Shemanski L, Waldo AL, Wyse DG. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation.* Mar 30 2004;109(12):1509-1513.

Appendix A: Adverse Event and Complaint Definitions

Reporting serious adverse events for a marketed device:

Reportable adverse events include death or serious injuries. Serious injuries is defined in FDA regulation as "an injury or illness that: (a) is life-threatening, or (b) results in permanent impairment of a body function or permanent damage to a body structure or (c) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure" 21CFR803.3.

Reporting device complaints

A device complaint is defined by the FDA regulation as "any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution" 21CFR820.3(b).