AtriCure

Combined Endoscopic Epicardial and Percutaneous Endocardial Ablation versus Repeated Catheter Ablation in Persistent and Longstanding Persistent Atrial Fibrillation

A randomized international multicenter trial comparing interventional treatment strategies in symptomatic patients with drug refractory atrial fibrillation

Revision: H Date: 11 Feb 2020

Sponsor:

AtriCure Europe BV.
De Entrée 260
1101 EE Amsterdam Z.O.
The Netherlands

Sponsor's Medical Monitor:

Timo Weimar, MD
Cardiac Surgeon

Coordinating Investigator:

Prof. Dr. Kai-Nicolas Doll, Stuttgart, Germany

This study will be performed in compliance with This Study will be conducted in accordance with the Declaration of Helsinki and EN ISO 14155:2012 (Clinical investigation of medical devices for human subjects - Good Clinical Practices.). In addition, the Study will comply with any applicable European or National regulations. The clinical investigation shall not begin until the required approval/favorable opinion from the EC or regulatory authority have been obtained, as appropriate.

AtriCure

Table of Contents

1. ABBREVIATIONS 5
2. SUMMARY 6
2.1. Protocol Synopsis 6
2.2. Schedule of Assessments 13
3. PROTOCOL APPROVAL PAGE 14
4. INTRODUCTION 15
4.1. Clinical Need 15
4.2. Current interventional Treatments 15
4.3. STUDY AIM 16
4.4. Study Hypothesis 16
4.5. Study Justification 18
5. STUDY DESIGN & ENDPOINTS 21
5.1. Overview 21
5.2. Investigational Sites requirements 22
5.3. Population 22
5.4. Treatment PROCEDURES 23
5.5. Effectiveness Endpoints 24
5.6. Safety Endpoints 25
6. SUBJECT ENROLLMENT 26
6.1. Identification of candidates 26
6.2. Informed Consent 26
6.3. Randomization procedure 26
6.4. Inclusion Criteria 26
6.5. Exclusion criteria 27
7. TREATMENT ARMS 28
7.1. Pre-treatment preparation 28
7.2. Catheter Ablation Arm 28
7.3. Hybrid Ablation Arm 28
7.3.1. STAGE 1 – Epicardial Endoscopic Ablation 28
7.3.2. STAGE 2 –Endocardial Procedure 29
7.4. Postprocedurale Care 30
7.4.1. ORAL ANTICOAGULATION 30
7.4.2. Antiarrhythmic Drug Regimen 31
7.5. Repeat ablation 32
8. STUDY ASSESSMENTS AND FOLLOW-UP VISITS 33
8.1. Schedule of visits and assessments 33
8.2. Study Duration 33
8.3. SCREENING AND CONSENT 34
8.4. RANDOMIZATION / INDEX PROCEDURE 35
8.5. FOLLOW UP VISITS 37

8.6. UNScheduleD VISITS 37
8.7. Trial exit 37
8.8. Patients withdrawn and lost to follow up 37
9. CLINICAL RISK BENEFIT EVALUATION 39
9.1. Expected Benefits 39
9.2. Potential Risks 39
10. STATISTICAL METHODS 40
10.1. Sample size computation 40
10.2. Randomization 40
10.3. Analysis Populations 40
10.4. Analysis of Study Endpoints 40
10.4.1. Effectiveness and Health Economic Analyses 41
10.4.2. interim analyses 42
10.4.3. Safety Analysis 42
10.5. Detailed Analysis Plan 43
11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS 43
11.1. Investigator Reporting Timelines 43
11.2. Adverse Event Definitions 44
11.2.1. Adverse Event (AE) 44
11.2.2. Adverse Device Effect (ADE) 44
11.2.3. Serious Adverse Event (SAE) 44
11.2.4. Serious Adverse Device Effect (SADE) 44
11.2.5. Anticipated and Unanticipated SADE (ASADE/USADE) 45
11.2.6. Device deficiency and malfunction 45
11.3. SAFETY MONITORING and reporting 45
11.3.1 SAFETY MONITORING 45
11.3.2. SAFETY REPORTING 45
12. STUDY RECORDS 45
12.1. Case Report Form (CRF) 45
12.2. Source documents 46
12.3. Investigator Study File 47
13. ETHICAL ASPECTS 48
13.1. Declaration of Helsinki 48
13.2. Sponsor duties and responsibilities 48
13.3. Ethics Committee (EC) Approval 49
13.4. Study suspension or termination 49
13.5. Responsibilities of Principal Investigators 50
13.5.5 Reporting Requirements 51
13.6 Confidentiality and patient data protection 51
14. STUDY OVERSIGHT 52
14.1 ECG/holter Core Laboratory 52
15. INVESTIGATOR REPORTS 52

15.1. Study progress reports 52
15.2. Publication Policy 52
16. QUALITY CONTROL AND QUALITY ASSURANCE 53
16.1. Compliance to Standards and Regulations 53
16.2. Data Recording 53
16.3. Quality Assurance and Monitoring 53
16.4. Quality Assurance and Data management 54
17. REFERENCES 54
18. LIST OF APPENDICES 56
18.1. Appendix I. Definitions according to 2012 HRS Consensus Statement 56
18.2. Appendix II. Modified Rankin Scale 56
18.3. Appendix III. SF-12v2™ Health Survey Scoring Demonstration 56

1. ABBREVIATIONS

AAD	antiarrhythmic drug
ADE	Adverse Device Effect
AE	Adverse Event
AF	atrial fibrillation
AFL	atrial flutter
ASADE	Anticipated Serious Adverse Device Effect
AT	trial tachycardia
ATA	atrial tachyarrhythmia
CA	catheter ablation
CE	Conformité Européenne
CFE	complex fractionated electrogram
CHA2DS2VASc	**C**ongestive heart failure – **H**ypertension – **A**ge$_2$ – **D**iabetes mellitus – prior **S**troke**2** – **V**ascular disease – **A**ge – **S**ex **c**ategory
CVA	Cerebrovascular Accident
CRF	Case Report Form
CTI	Cavotricuspid Isthmus
EC	Ethics Committee
ECAS	European Cardiac Arrhythmia Society
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
EP	electrophysiology
GCP	Good Clinical Practice
HRS	Heart Rhythm Society
ICU	intensive care unit
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IVC	inferior vena cava
LA	left atrium
LAA	left atrial appendage
LMWH	Low Molecular Weight Heparin
LOM	Ligament of Marshall
MRI	Magnetic Resonance Imaging
NSR	Normal Sinus Rhythm
OAC	oral anticoagulation
OR	Operation Room
PAF	Paroxysmal Atrial Fibrillation
PRBC	Packed Red Blood Cells
PV	pulmonary vein
PVI	pulmonary vein isolation
QUALY	QUality-Adjusted Life Years
RF	radiofrequency
RR	R wave-to-R wave
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SF-12	12-item Short Form Survey
SOC	Standard Of Care
SR	sinus rhythm
SVC	superior vena cava
SVT	supraventricular tachycardia
TEE	TransEsophageal Echocardiogram
TTE	TransThoracic Echocardiogram
TIA	Transient Ischemic Attack
USADE	Unanticipated Serious Adverse Device Effect

2. SUMMARY

2.1. PROTOCOL SYNOPSIS

Title	Combined **E**ndoscopic Epicardia**l** and Percutaneous **E**ndocardial Ablation versus Repeated **C**atheter Ablation in Persisten**t** and Longstanding Pe**r**sistent **A**trial Fibrillation [CEASE AF - Trial]
Clinical Need	Atrial fibrillation (AF) is the most common cardiac arrhythmia with a lifetime risk of developing AF of 1 in 4 people aged over 40. Besides hemodynamic compromises, AF increases the risk of stroke by 5-fold, and is associated with increases the odds ratio of death to 1.5 in males and 1.9 in females. Anti-arrhythmic drug (AAD) therapy remains the first line treatment for AF; however, it does not represent a cure for AF. All AAD therapies used for AF treatment have significant side effects and they are of marginal effectiveness in nearly all patient populations. Atrial pacing and defibrillators do not cure the arrhythmia and may not result in better quality of life.
Current Interventional Treatments	Catheter ablation has evolved as a standardized treatment option in paroxysmal AF supported by the current guidelines. Although pulmonary vein isolation (PVI) is the cornerstone of all interventional approaches for AF-treatment, no uniform concept in the setting of the non-paroxysmal forms currently exists. Especially in the setting of long-standing persistent AF, additional strategies apart from sole pulmonary vein isolation are required to achieve reasonable results regarding rhythm control. Due to the advanced electrical and structural remodeling of the atria, the results of a single catheter ablation for persistent and longstanding persistent AF are disappointing, and repeated endocardial procedures are required in most patients. Due to these shortcomings, minimally invasive endoscopic surgical techniques applied epicardially have gained attention with good results in this difficult to treat patient population. The combination of initial epicardial (surgical) ablation followed by endocardial (catheter) ablation **(staged hybrid ablation)** is expected to be most efficacious in avoiding lesion gaps and providing the most complete lesion set for effective treatment of the arrhythmia.
Study Aim	Currently, no robust clinical data are available comparing interventional ablation strategies in the setting of persistent AF with enlarged Atrium > 4 cm and longstanding persistent AF, which reflects a difficult to treat patient-subgroup. Thus, it is the aim of the present randomized study to compare the effects of combined epicardial endoscopic surgical and endocardial catheter techniques vs standard endocardial catheter ablation strategies with regard to safety, efficacy and quality of life. Also, effects on health economics of the two treatment strategies will be evaluated
Hypothesis & Justification	This study hypothesizes that the hybrid approach, combining minimally invasive surgical endoscopic ablation and trans catheter techniques in a two-staged fashion, provides superior **clinical effectiveness through 36 months** compared with repeated catheter ablation in patients with persistent AF and enlarged left atrium or long-standing persistent AF. This hypothesis is supported by recent prospective studies, indicating that hybrid ablation has high success rates without the need for further interventions.
Study Objective	This is an international, prospective, randomized multicenter trial to investigate the optimal treatment of Persistent AF with enlarged LA > 4cm or Longstanding Persistent AF referred for Radiofrequency (RF) ablation. The study objective is to compare the efficacy and safety of two interventional approaches (hybrid ablation versus standard catheter ablation), in preventing the recurrence of AF in symptomatic, drug refractory patients with the most difficult to treat types of AF. Definitions and endpoints in the CEASE-AF trial are derived from the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.
Study Design	A total of 210 eligible patients will be randomized (2:1 ratio) to the following

	treatment arms: • Hybrid ablation arm (n = 140 patients): a staged hybrid procedure consisting of endoscopic epicardial surgical ablation (first stage, index procedure) combined with endocardial catheter ablation (second stage) which will be performed between 91 and 180 days (6 months) after the surgical (index-) procedure. • Catheter ablation arm (70 patients): standard catheter ablation with PV isolation (minimum lesion set) and optional additional lesions (index procedure). When required due to AF recurrence, ablation may be repeated within 6 months after the index-procedure according to clinical indications and consistent with the HRS/EHRA/ECAS Consensus Statement. • Patients follow-up is divided into 3 phases; ○ **Phase 1 – Ablation Treatment**, including the period between the index procedure and 6 months. During these 6 months, patients will complete the hybrid ablation or receive repeated catheter ablation if indicated. ○ **Phase 2 - Outcomes through** 12 months. The follow-up period starts at 6 months (T0 = 180 days from the index procedure) and lasts for 3 years. Therefore, patients will be followed up at 3, 6 and 12 months from T0. Comparative and descriptive statistics will be used to summarize patient outcomes for the specified study endpoints. During this phase, cross-over or further catheter ablations are allowed if indicated. ○ **Phase 3 - Long-term outcomes.** Patients will be followed for an additional 24 months for a total of 36 months. During this phase, cross-over or further catheter ablations are also allowed if indicated.
Population	Patients with a history of persistent AF with a LA > 4cm or long-standing persistent AF who are symptomatic and have failed at least one antiarrhythmic drug class I or III. AF types are defined in accordance to the Heart Rhythm Society (HRS) AF Expert Consensus Statement (2012). Persistent AF: Continuous AF which is sustained beyond seven days, or lasting greater than 48 hours and less than seven days but necessitating pharmacologic or electrical cardioversion Longstanding Persistent AF: Continuous AF of greater than 12 months' duration
Treatment Arms	Catheter ablation will be performed using standard endocardial transvenous technique of PV isolation and possibly additional ablations on physician's discretion / center's strategy which are in accordance with current guidelines. Endoscopic surgery will include a minimum lesion set including a PV isolation by the means of a box lesion (right and left epicardial isolation of the PVs, superior and inferior connecting lines) and exclusion of the left atrial appendage if considered safe by the surgeon under general anesthesia. Additional lesions may be performed, based on standard practice at the interventional sites. *For details refer to section 7 of the Protocol.*
Effectiveness Endpoints	The **Primary Effectiveness Endpoint** is freedom from documented AF/AFL/AT episodes > 30 seconds through 12-months follow-up, in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed). The following scenarios shall constitute a failure of the primary effectiveness endpoint: 1. Any documented AF, atrial flutter, or atrial tachycardia lasting >30 seconds duration occurring between T0 and 12-months follow-up. 2. Any previously failed class I or III AAD administered at a dose higher

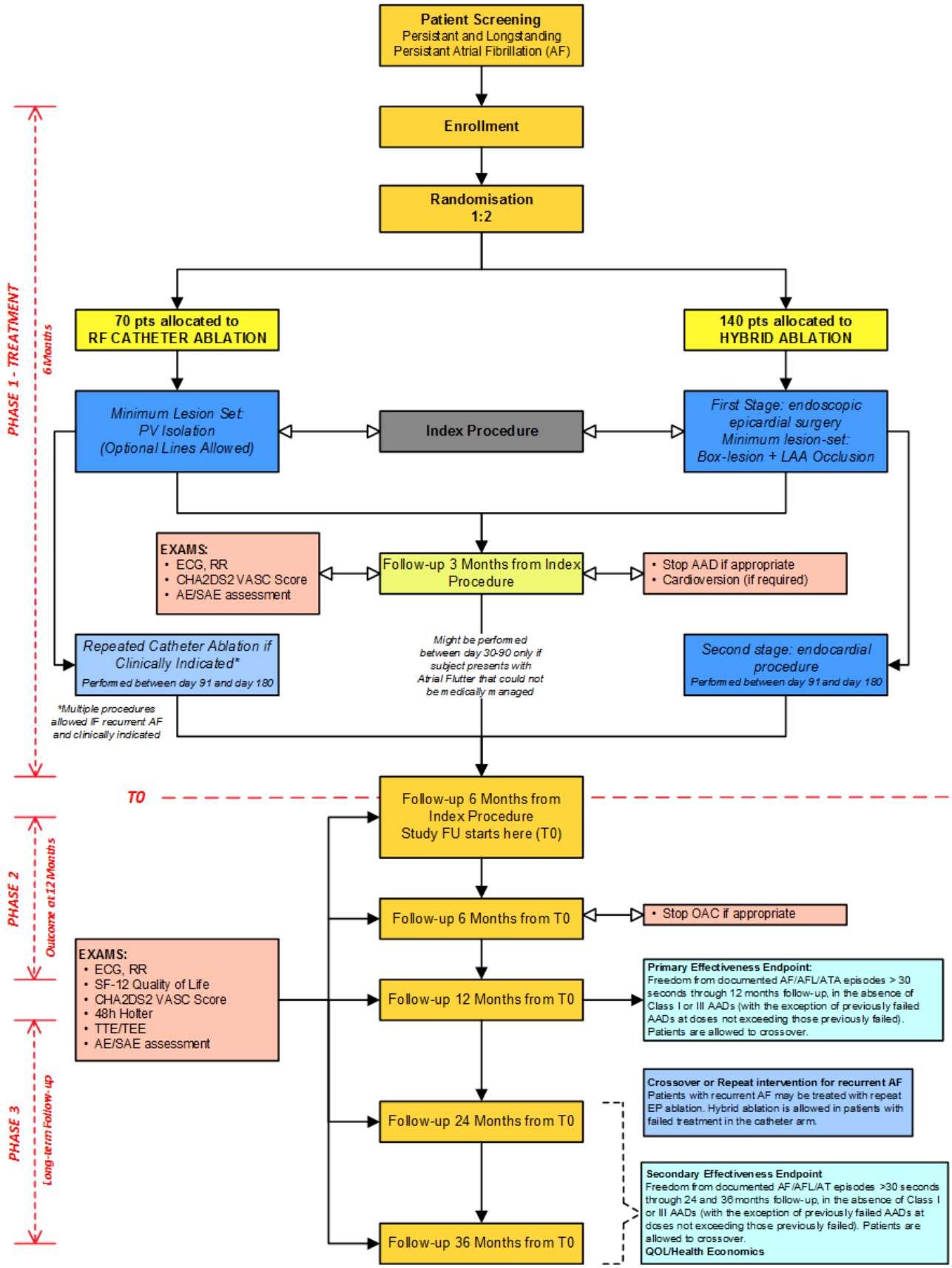
	than baseline and between T0 and the 12-month follow-up visit. 3. Any newly introduced class I or III AAD usage beginning at T0 and through the 12-months follow-up visit. 4. DC cardioversion for AF, atrial flutter, or atrial tachycardia that takes place between T0 and the 12-months follow-up visit. The **Secondary Effectiveness Endpoint** is freedom from documented AF/AFL/AT) >30 seconds through 24- and 36-months follow-up, in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed). The rhythm status used for evaluation of the Primary and Secondary Endpoint will be derived from regularly scheduled 48-hour Holter monitoring and any symptom driven monitoring performed. ECG recordings performed for symptom driven monitoring should have a (total) duration of at least 30 seconds.
Additional endpoints	Additional endpoints will be assessed and compared in the 2 study arms: Procedure and radiation exposure times, number and severity of AF symptoms (EHRA class), freedom from antiarrhythmic medications, quality of life scores SF-12, number of cardioversions and repeat ablations, number of hospital admissions due to AF recurrence. Exploratory health economic analysis will include potential differences in hospital and third party payer/societal economics. Formal economic models may be built from the clinical data captured and secondary data sources.
Safety endpoints	Composite major complications and adverse events will be analyzed during follow-up, comparing cumulative complication rates occurring during the repeated procedures in the 2 study arms. Adverse events may include the following: death, stroke, transient ischemic attack, myocardial infarction in the context of AF Ablation, pericarditis, bleeding, wound infection, atrio-esophageal fistula, esophageal injury, permanent phrenic nerve paralysis, permanent pacemaker, pulmonary vein (PV) stenosis of >70%, cardiac tamponade/cardiac perforation, empyema, superficial wound infections or vascular access complications, pneumonia, pneumothorax requiring intervention.
Patients screening and randomization	After signing an informed consent, patients referred for invasive treatment of AF will be screened for eligibility for the study according to the specified inclusion and exclusion criteria. For enrolled subjects, randomization will be performed centrally, so that 2:1 ratio of Hybrid to Catheter ablation is achieved.
Inclusion Criteria	1. Patient is between 18 and 75 years of age 2. Patient has a history of symptomatic Persistent AF and a LA > 4cm or Long Standing Persistent AF as defined by the HRS/EHRA/ECAS expert consensus statement 3. Patient is refractory to or intolerant to at least one antiarrhythmic drug (class I or III) 4. Patient is mentally able and willing to give informed consent 5. Patient is willing and able to receive all of the study related procedures, and attend the scheduled follow-up visits.
Exclusion Criteria	1. Patient has longstanding persistent AF > 10 years 2. Patient presenting with paroxysmal AF 3. Patient with persistent AF and a LA-diameter ≤ 4 cm 4. AF is secondary to electrolyte imbalance, thyroid disease, or other reversible or non-cardiovascular cause 5. Patient underwent previous ablation procedure or heart surgery 6. Patient needs other cardiac surgery procedures besides AF treatment (valve, coronary, others) 7. Contraindication for either catheter ablation or epicardial surgery (including, but not limited to: previous thoracic radiation, previous perimyocarditis, Previous cardiac tamponade, Pleural adhesions, Prior thoracotomy) 8. Body mass index > 35

	9. LA Diameter > 6 cm 10. Left ventricular ejection fraction < 30 % 11. Severe mitral regurgitation (>II) 12. Patient unable to undergo TEE 13. Presence of LA thrombus by TEE, CT scan, MRI or angiography 14. History of cerebrovascular disease, including stroke or transient ischemic attack (TIA) within 6 months prior to enrollment 15. Active infection or sepsis 16. Other clinical conditions precluding inclusion (e.g., organ disease, disturbances of hemostasis) 17. Contraindication to anticoagulant therapy, or inability to comply with anticoagulant therapy 18. Pregnancy, planned pregnancy or breastfeeding 19. Life expectancy is less than 18 months 20. Patient is involved in another study involving an investigational drug or device
Follow-up visits	For each patient, the study duration will be 3.5 years (42 months). Subjects will be followed at discharge and at 3 and 6 months from the index procedure: during this interval, the study ablation treatment will be completed. The 6 months visit is the starting point of the follow-up period that lasts for additional 3 years and is defined as T0. During the follow-up period, patients will be evaluated at 6 and 12 months, and yearly thereafter, until 3 years after completion of the treatment phase. At follow-up visits after hospital discharge, patients will undergo the following non-invasive routine diagnostic tests, according to the schedule of assessments presented in section 2.2 of the protocol: • ECG, RR • SF-12 quality of life • EHRA class AF symptoms • CHA2DS2 VASC score • Echocardiogram (TTE/TEE) • 48-hour Holter (during follow-up visits) • AE/SAE assessment • Medications assessment: OAC medication, AAD medication
Patient Follow-up	Treated patients will be assessed for primary safety throughout the follow-up. Cumulative risk of events will be evaluated by assessing complications associated with the repeated ablation treatments performed during the course of the study. Treatment effectiveness will be assessed through 36 months post treatment (hybrid epi-endocardial ablation, or repeated endocardial ablation). All treated patients will be followed through 3 years.
Study Duration	Enrollment is expected to take approximately 18 months, the treatment phase is 6 months, and patient follow-up will be 36 months (3 years), for a total anticipated duration of the clinical investigation of approximately 60 months (5 years).
Study Timeline	First patient enrolled: November 2015 Last patient enrolled: November 2017 Last patient follow-up: November 2020
Investigational Sites Requirements	International sites are pre-selected based on their documented experience in interventional treatment of AF. The centers performing epicardial ablation must have already performed a minimum of 10 surgical ablation procedures in the prior 12 months. Sites must have high procedure volumes and adequate laboratory equipment and staffing to perform the study examinations.
Sample Size Computation	A total of 210 subjects (randomization ratio 2:1) will be enrolled in this trial, in order to evaluate the Primary Effectiveness Endpoint of freedom from documented AF/AFL/AT episodes > 30 seconds through 12 months follow-up

	without AADs. Historical rates of success for catheter ablation is estimated at 50% through 12 months, while success rate is expected to be at least 75% for the staged hybrid procedure. A two treatment group continuity corrected chi-squared test with an alpha = 0.05 two-sided significance level will have 80% power to detect the difference between a Catheter group failure rate of PC = 0.5 and a Hybrid group failure rate of PH = 0.25 when the sample sizes are 49 and 98, respectively (a total sample size of 147). Adjusting for loss to follow-up (anticipated 30% dropout rate at 12 months), the required total sample size will be 210 subjects (140 in the Hybrid group, and 70 in the Catheter group).
Statistical Analysis	For the interim analyses: The first interim analysis will be performed when 165 patients are randomized, and thereafter at 170, 180 and 210 patients. Each interim analyses will be performed by an independent statistician. Both sponsor Atricure and study team members other than the independent statistician will remain blinded to the primary effectiveness outcome of the study, with exception of being informed on one of the two decision options shared below. Based on the outcome of the interim analysis, one of the following two decisions will be made available by the independent statistician to Atricure and the study team with regard to the primary endpoint, either: 1. Continue enrolling patients; 2. Stop enrollment and follow all treated patients to 12-months (primary endpoint), at which time the primary analysis is conducted; The interim analyses will be performed using a Bayesian Adaptive Design method (27). The analyses will use all primary endpoint related patient data available in the study dataset and apply the following assumptions: Given current observed data, calculate both PPS_n which is defined as the predictive probability of success with current sample size and 12 months of follow-up on all patients and PPS_{max} which is defined as the predictive probability of success at N=210 with 12 months of follow-up on all patients Continue enrolling patients if $PPS_n < 0.95$ and $PPS_{max} \geq 0.30$: – Success with current sample size not certain – Interim observed effect close (or bigger) than observed effect needed for success at N=210 Otherwise stop enrollment and continue follow-up: – Either very likely or reasonably unlikely to succeed. The final analysis will be based on a Pearson's Chi-Squared test with an adjusted two-sided alpha significance level of 0.044. For the final analysis: Study endpoints will be summarized by treatment group. Continuous variables will be summarized by presenting the number of subjects, mean, standard deviation, median, minimum, maximum by procedure group (Hybrid or Catheter). Tabulation of categorical variables by group will include counts and percentages. 95% confidence intervals will be provided as appropriate. Additional analyses, analysis populations, covariates and summary tables and/or graphs will be generated as needed.

	In all analyses the null hypothesis will be a two-sided test of no treatment group difference. All statistical tests will use a two-sided significance level of alpha = 0.05. A Pearson's Chi-Squared test will be used to compare the primary effectiveness success rate through 12-months between the two procedure groups. Alternatively, a Fisher's Exact test will be used if justified by small cell counts (less than 5) and Clopper-Pearson (Exact) 95% CI will also be reported. The secondary effectiveness endpoints will be similarly summarized and analyzed at 24 and 36 months from T0. In addition, effectiveness success might also be analyzed using multiple logistic regression model with the proportion of success as the dependent variable and the following independent variables: sites (or clusters of sites), age, gender, CHA2DS2- VASc score and relevant interaction terms. A Pearson's Chi-Squared test will be used to compare the incidence of composite safety endpoint between the two procedure groups. Alternatively, a Fisher's Exact test will be used if justified by small cell counts (less than 5) and Clopper-Pearson (Exact) 95% CI will also be reported. Prior to database lock, a detailed statistical analysis plan will be developed if needed.

Protocol Flowchart



2.2. SCHEDULE OF ASSESSMENTS

Investigations and measurements performed according to the following flow-chart:

			Phase 1: Ablation Treatment		NOTE: Between day 91 and day 180 from Index Procedure, patients may (CATH arm) or have to (HYBRID arm) undergo repeat ablation.			**Phase 2**: Outcomes through 12 Months		**Phase 3**: Long-term Outcome
Procedure/ Test	Screening and informed consent	Randomization	Index Procedure	Post procedure	Discharge	3 months from Index	6 months from Index Procedure: start of FUP (T0)	6 months from T0[1]	12 months from T0	24,36 months from T0
Visit name	Screen	Pre			Vis 0	Vis 1	Vis 2	Vis 3	Vis 4	Vis 5,6
Window for performing test Relative to Vis 0						+ 7 days	+ 14 days	+ 14 days	+ 1 month	+ 1 month
History/events	X				X	X	X	X	X	X
Recording of medications		X			X	X	X	X	X	X
Physical exam EHRA Score		X			X			X		
ECG, RR	X[2]	X		X[3]	X	X	X	X	X	X
SF-12 Quality of Life		X					X	X	X	X
CHA2DS2 VASC score[6]		X			X	X	X	X	X	X
Echo (TTE or TEE)[4]		TTE[2]	TEE				TTE	TEE		
48-hour Holter	X						X	X	X	X
AE/SAE Assessment			X	X	X	X	X	X	X	X
Concomitant treatments[5]										
Procedure (study arms)			X			[X	X]			
OAC medication				start				stop[6]		
AAD medication (preferably Amiodarone)				start		Stop[7]				
Cardioversion (if required)				X	X	X				

[1]One year Follow-up: the starting date for 1-year follow-up is T0 = 6 months from the first ablation procedure (Index ablation).
[2]Results obtained within 4 weeks prior to signing informed consent may be used for screening purposes.
[3]12-lead ECG recorded on ICU within 2 hours after skin closure time.
[4]In case LAA management is planned a TEE is required during the Index procedure. If indeed a LAA occlusion or exclusion device is used the TEE should be repeated at Visit 3.
[5]Procedure: Catheter ablation or hybrid procedure
- Oral anticoagulation is continued for 6 months, at 6 months stop OAC if appropriate
- Antiarrhythmic drugs (class I or III) are continued for 3 months if needed, stop at 3 months if appropriate
- Pharmacological or electrical cardioversion is performed as needed for SR restoration until reaching T0.

[6]if CHA2DS2 VASC score >=2, continue anticoagulants.
[7]At the investigator's discretion.

AtriCure

3. PROTOCOL APPROVAL PAGE

This signature page shall be completed for each study center.

STUDY CENTER NAME: _____
STUDY CENTER #: _____

This Study will be conducted in accordance with the Declaration of Helsinki and EN ISO 14155:2012 (Clinical investigation of medical devices for human subjects - Good Clinical Practices.). In addition, the Study will comply with any applicable European or National regulations. The clinical investigation shall not begin until the required approval/favourable opinion from the EC or regulatory authority have been obtained, as appropriate.

PRINCIPAL INVESTIGATOR SIGNATURE
I have read and understood the Clinical Protocol and agree to follow the procedures and requirements.

Principal Investigator Name (print):

Principal Investigator Signature: _____ Date: _____

SPONSOR SIGNATURE
AtriCure Europe BV has reviewed and approved the full final version of the Clinical Protocol.

Sponsor Signature: Nfii K. Ndikintum, PhD, MBA (Feb 19, 2020) Date: Feb 19, 2020
Name/Title: Nfii K. Ndikintum
Vice President, Clinical Affairs and Biometrics

Sponsor Signature: Dr. Erik Fransen (Feb 19, 2020) Date: Feb 19, 2020
Name/Title: Dr. Erik Fransen
Director of Clinical Science, International

Sponsor Signature: Timo Weimar, MD (Feb 19, 2020) Date: Feb 19, 2020
Name/Title: Dr. Timo Weimar
Medical Director

4. INTRODUCTION

4.1. CLINICAL NEED

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a lifetime risk of developing AF of 1 in 4 people aged over 40. It is the most common rhythm disorder among patients hospitalized with a primary diagnosis of an arrhythmia. The prevalence of AF rises from 0.7% in the age group 55-59 to 17% for those aged 85 or above (1). Besides hemodynamic compromises stroke remains the most feared complication of AF with an increase in risk by 5-fold (2). Furthermore, the Framingham Heart Study has demonstrated that after correcting for concurrent risk factors, AF increases the odds ratio of death to 1.5 in males and 1.9 in females (3).

Anti-arrhythmic drug (AAD) therapy remains the first line of treatment for AF; however, it does not represent a cure for AF. All AAD therapies used for AF treatment have significant side effects and they are of marginal effectiveness in nearly all patient populations. Atrial pacing and defibrillators do not cure the arrhythmia and may not result in better quality of life.

4.2. CURRENT INTERVENTIONAL TREATMENTS

Catheter ablation has evolved as a standardized treatment option in paroxysmal AF supported by the current guidelines (4). Although, pulmonary vein isolation (PVI) is the cornerstone of all interventional approaches for AF - treatment, no uniform concept in the setting of the non-paroxysmal forms currently exists. Especially in the setting of long-standing persistent AF additional strategies apart from sole pulmonary vein isolation are required to achieve reasonable results regarding rhythm control (5). Due to the advanced electrical and structural remodelling the single procedural results of catheter ablation for persistent and longstanding persistent AF are rather disappointing without a proven superiority of any applied strategy compared to others. However, catheter ablation for persistent and longstanding persistent AF can achieve comparable results to patients treated with the paroxysmal form (PAF) requiring repeat procedures in most patients (6, 7).

Due to these shortcomings, minimally invasive endoscopic surgical techniques have gained attention with good results in this difficult to treat patient population (8, 9, 10). Regardless of the mechanism involved, the majority of the sites of origin of persistent AF are located in the posterior part of the left atrium, as this portion is easily encompassed by the box lesions created by surgical ablations [11]. As such, a staged approach may be a more suitable strategy, with use of percutaneous endocardial techniques only in case of failure of the surgical procedures.

The combination of epicardial and endocardial ablation is expected to be most efficacious in avoiding lesion gaps and providing the most complete lesion set. Currently, no robust clinical data are available in the setting of persistent and longstanding persistent AF comparing interventional treatment strategies. Thus, it is the aim of the present study to investigate both strategies in a randomized fashion with regard to safety, efficacy and quality of life.

4.3. STUDY AIM

Currently, no robust clinical data are available comparing interventional ablation strategies in the setting of persistent and longstanding persistent AF. Thus, it is the aim of the present randomized study to compare the effects of combined endoscopic surgical and catheter technique vs standard catheter ablation strategies with regard to safety, efficacy and quality of life.

4.4. STUDY HYPOTHESIS

Catheter ablation techniques are designed to isolate or ablate the atrial triggers that induce AF, and modifying the abnormal atrial substrate that sustains AF when indicated. Since the majority of paroxysmal atrial fibrillation (PAF) is induced by pulmonary vein triggers, catheter ablation is used most commonly to isolate the pulmonary veins in patients with PAF. **In the persistent forms of AF, it is essential to add other measures, such as linear lesions to modify the substrate responsible for sustaining AF.** While multiple catheter ablations have proven to be successful for PAF, catheter ablation has suffered substantially less success when used for the persistent forms (non-paroxysmal) AF (15, 16, 17).

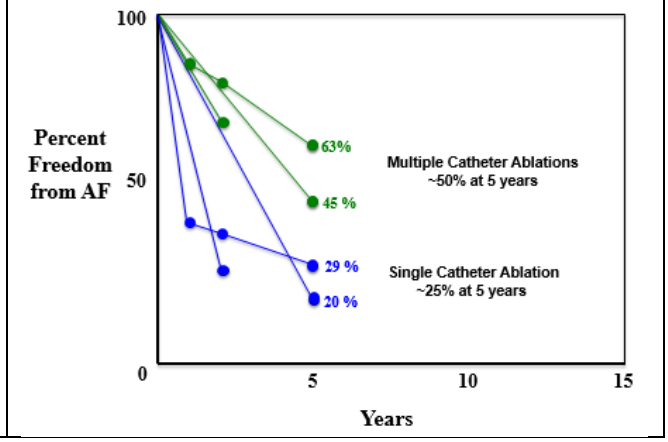
Three pivotal articles have reported the long term efficacy of catheter ablation of AF. Although freedom from AF in some studies reaches almost 90% at 1 year, rates of success drop below 50% at 5 years, even with multiple ablations (figure 1).

Figure 1. Pivotal articles on Success Rate of Catheter Ablation for Stand-Alone AF

Long-term single procedure efficacy of catheter ablation of atrial fibrillation.
Cheema A, Vasamreddy CR, Dalal D, Marine JE, Dong J, Henrikson CA, Spragg D, Cheng A, Nazarian S, Sinha S, Halperin H, Berger R, Calkins H.
J Interv Card Electrophysiol. 2006 Apr;15(3):145-55. Epub 2006 Aug 5.

Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up?
Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, Lellouche N, Knecht S, Wright M, Nault I, Miyazaki S, Scavee C, Clementy J, Haissaguerre M, Jais P.
J Am Coll Cardiol. 2011 Jan 11;57(2):160-6. doi: 10.1016/j.jacc.2010.05.061.

Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy.
Tilz RR1, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck KH, Ouyang F.
J Am Coll Cardiol. 2012 Nov 6;60(19):1921-9. doi: 10.1016/j.jacc.2012.04.060. Epub 2012 Oct 10.

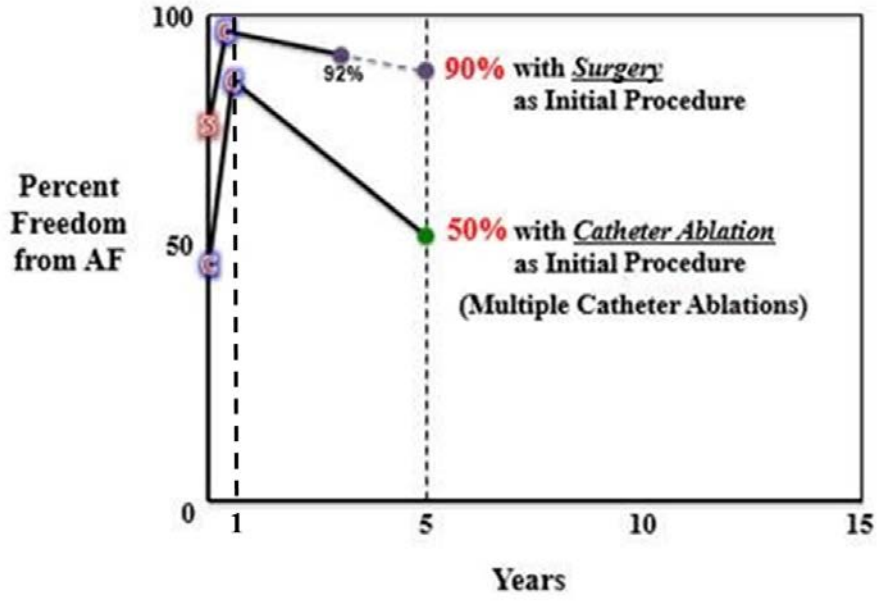


The *2012 HRS/EHRA/ECAS Guidelines* (Appendix 1) define hybrid procedures as:
"…. a joint AF ablation procedure performed by electrophysiologists and cardiac surgeons either as part of a single "joint" procedure or performed as two pre-planned separate ablation procedures separated by no more than six months of time".

This study hypothesizes that a two-staged hybrid approach, combining initial surgery with a minimally invasive surgical endoscopic ablation, followed by catheter ablation performed at a later stage, will have greater clinical effectiveness in a long-term follow-up compared with repeated catheter ablation in patients with persistent or long-standing persistent AF. This hypothesis is supported by literature, indicating that surgical ablation through bilateral thoracotomy demonstrates better results after a single procedure (Figure 2).

Based on the evidence, this study therefore hypothesizes that higher success rates will be obtained through 12 months and sustained through 3 years, with hybrid ablation. Prospective observational studies report a remarkable 92% of success with hybrid or staged procedures of surgical ablation coupled with catheter ablation at 30 months follow-up (13). Therefore, it is expected that with Hybrid therapy, fewer patients will be submitted to repeated ablations while remaining in sinus rhythm during a long-term follow-up.

Figure 2. Pivotal articles on Success Rate of staged Surgery/Catheter Ablation for Stand-Alone AF



Muneretto C, Bisleri G, Bontempi L, Curnis A. Durable staged hybrid ablation with thoracoscopic and percutaneous approach for treatment of long-standing atrial fibrillation: a 30-month assessment with continuous monitoring. J Thorac Cardiovasc Surg. 2012 Dec;144(6):1460-5

It is important therefore to consider the impact of these two treatments from a clinical viewpoint should take into consideration multiple factors

1) In regards to effectiveness, from the literature analysed, success rates have the tendency to progressively drop with time more significantly for single but even repeated catheter ablation than for a hybrid approach; the proposed CEASE-AF study will allow us to verify this hypothesis for the first time in a randomized fashion;

2) In regards to safety, patients exposed to multiple ablations will be subjected to a cumulative higher risk of complications, because increased numbers of adverse events will occur during multiple interventions. Therefore, cumulative safety of the treatment will be assessed considering the number of events occurring during all interventions that are required to successfully treat the arrhythmia;
3) In regards to clinical impact, although the primary effectiveness endpoint of this study is based on the HRS guidelines (30 seconds, off AADs), the study will also look at the patient's subsequent clinical course (including quality of life, number of hospital admissions, need for cardioversion, number of repeat ablations) and compare it in the two arms, to provide an accurate reflection of the clinical results of the two different ablation strategies for persistent and long-standing persistent AF.

The proposed study groups (staged hybrid ablation vs multiple clinically driven catheter ablations) are currently accepted standard of care therapies and considered Class II indications in the current European Society of Cardiology (5) and European Association of Cardiothoracic Surgery (14) guidelines for the treatment of persistent AF. As such, their comparison complies with the Declaration of Helsinki for the Ethical Principles of Medical Research in human subjects.

4.5. STUDY JUSTIFICATION

The Cox-Maze III surgical technique that was pioneered by Dr. James Cox in the 1980's has excellent long-term results but remains too invasive to be widely applied in all patients with AF, especially as a stand-alone procedure. It was based on intraoperative mapping studies that documented the presence of multiple relatively large (> 5cm diameter) macro-reentrant circuits in all patients during all episodes of AF. These large macro-reentrant circuits were unstable and often remained in one area for only 200 msec. However, by placing multiple lesions in the atria that were close enough together to prevent the macro-reentrant circuits from forming, the atria, by definition, could no longer fibrillate. Furthermore, by placing those lesions in the pattern of a maze, it was possible for the SA node to take over afterwards and have the resultant sinus impulse activate the entire myocardium of both atria except for the isolated pulmonary veins. **The success rates of the Cox-Maze III procedure were 98% at 5 years, 98% at 8.5 years, and 94% at 15 years. (17, 19, 20)**

The introduction of the AtriCure Bipolar System has led to the development of the Cox-Maze IV procedure, so-called because it is performed with an ablation device rather than by the "cut-and- sew" technique of the Cox-Maze III. **The ultimate goal is to perform a minimally invasive endoscopic lesion set compatible with the Cox-Maze IV pattern on the beating heart, without the need for cardiopulmonary bypass and with no incisions on the heart**.

- The surgical epicardial lesions include pulmonary vein isolation in pairs with the AtriCure Bipolar System plus roof and floor linear ablation lines that convert the pulmonary vein isolation lesions into a **"box" lesion of all 4 veins** and the intervening posterior left atrial wall as was done in the Cox-Maze III procedure.

- A “mitral line” extending from the “box lesion” down to the mitral valve annulus cannot be performed epicardially and thus should be added by the catheter ablation procedure.. *The cavo-tricuspid isthmus lesion will be added during the follow-up Endocardial EP Ablation Procedure as well.*

The Cox-Maze IV has been performed in an open chest setting on cardiopulmonary bypass with success rates as high as 95%. (21) However, the associated complications of being on bypass are still present. With the development of endoscopic ablation instruments and the use of videoscopic assisted techniques (VAT), the cardiac surgeon has the option to perform a limited maze procedure off bypass on the beating heart. Such minimally invasive thoracoscopic ablation have produced a wide range of results (35% to 90%) depending upon the lesion set and the definition of success (12).
Catheter ablation has been utilized to treat individuals with Persistent or Longstanding Persistent AF, however with less promising outcomes than surgery.

Although frequently used to isolate triggers such as the PVs in order to treat paroxysmal AF, catheter ablation for Persistent or Longstanding Persistent AF has been less effective due to the limitations of the current catheter technology to perform reliable transmural linear lesions (23). The results for a recent catheter ablation registry of more than 20,000 procedures reports success rates for the treatment of persistent forms of AF of less than 60% (24). Furthermore, Kuck recently published his 5-year results with single and multiple catheter ablations for the persistent forms of AF and found that the success rate at 5 years for single catheter ablation was 20% and for multiple catheter ablations was 45% (17).

In the CEASE-AF study, after the surgical ablation procedure, patients will return to the EP Laboratory to:

- Assess integrity of the Box lesion
- Eliminate gaps in the surgical lesions when found
- Complete the lesion set according to the Maze principle, including lesions to eliminate perimitral and peritricuspid flutter.
- Terminate fragmented potentials, if clinically appropriate under the discretion of the electrophysiologist

Upon completion of this EP procedure, integrity of the lesions is re-assessed just prior to withdrawing the EP catheters from the LA.

AtriCure’s Bipolar System is highly effective at creating reliable transmural ablation lines, the success rates for minimally invasive endoscopic ablation are challenged by sub-optimal mapping techniques and technologies for verification of conduction block and the inability of the surgeon to perform the valvular lesions associated with the Cox-Maze IV procedure. **A minimally invasive endoscopic ablation procedure combined with conventional catheter mapping and ablation techniques and technologies enables physicians to replicate the Cox-Maze IV procedure through a minimally invasive off pump approach.**

Consequently, the proposed hybrid treatment (staged epicardial and endocardial approach) is being developed as an opportunity to enhance patient outcomes. Working together, the cardiac surgeon and electrophysiologist can combine their techniques and technologies to offer Persistent and Longstanding Persistent AF patients who reflect the most difficult to treat patient subgroup a true minimally invasive Cox-Maze IV option with the anticipated highest success rates. During this epicardial surgical ablation and the endocardial catheter ablation approach, the endocardial catheter component of the procedure is introduced for mapping and confirmation of surgical ablation lines. The endocardial catheter can also be used for ablation to optimize a surgical lesion that may not have achieved conduction block and also to perform the cavo-tricuspid and mitral isthmus lesions which are key components of the Cox-Maze IV lesion set. **This procedure is currently being performed as standard practice by teams of surgeons and electrophysiologists** to improve on the efficacy in the treatment of Persistent and Longstanding Persistent AF patients which currently represents a group of patients with less effective treatment alternatives.

5. STUDY DESIGN & ENDPOINTS

5.1. OVERVIEW

This is a prospective, randomized (2:1) multicenter trial to investigate the optimal treatment of Persistent and Longstanding Persistent AF referred for Radiofrequency (RF) ablation.

The study objective is to compare the efficacy and safety of two interventional approaches, in preventing the recurrence of AF in symptomatic, drug refractory patients with persistent or longstanding persistent atrial fibrillation.

A total of 210 eligible patients will be randomized (2:1 ratio) to the following treatment arms:

- **Hybrid ablation arm** (n= 140 patients): a staged hybrid procedure consisting of endoscopic epicardial surgery (first stage, called index procedure here) combined with endocardial catheter ablation (second stage) performed after the blanking period of 3 months and within 6 months from the surgical epicardial ablation procedure. In other words: the endocardial ablation should be performed between day 91 and day 180 from the index procedure.

- **Catheter ablation arm** (n=70 patients): standard catheter ablation, followed by repeated catheter ablation(s) between 91 and 180 days from the index procedure if clinically indicated.

Repeated catheter ablation(s) or endocardial completion of the hybrid procedure may occur before 91 days after the index procedure only if patients present with Atrial Flutter that cannot be medically managed.

Patient follow-up is divided into 3 phases:

Phase 1 – Ablation Treatment, including the period between the index procedure (RF ablation or surgery) and 6 months. During these 6 months, patients will complete the Hybrid ablation or receive repeated Catheter ablation(s) as clinically indicated.

Phase 2 - Outcomes through 12 months (Primary Effectiveness Endpoint). The follow-up period starts at 6 months (T0 = 180 days from the index procedure) and lasts for 3 years. Patients will be followed up at 6 and 12 months from T0. Comparative and descriptive statistics will be used to summarize patient outcomes for the specified study endpoints. During this phase, patients in the Catheter Ablation Group with AF recurrence despite optimal AAD treatment (primary effectiveness failure) post T0, may crossover and undergo the Hybrid Procedure per the physician's recommendation. Similarly, patients in the Hybrid Ablation Group with AF recurrence may undergo additional catheter ablation(s) per the physician's recommendation. These patients will be entered as effectiveness failures in the database and will continue to be monitored per the study protocol. The Primary Effectiveness Endpoint is freedom from documented AF/AFL/AT episodes > 30 seconds through 12 months follow-up without AADs Class I or III (except at dosages not exceeding preoperative dosage of the same AAD).

Phase 3 - Long-term effectiveness (Secondary Effectiveness Endpoints). Patients will be followed up at 24 and 36 months from T0. The Secondary Effectiveness Endpoint is freedom from AF/AFL/AT through 24 and 36 months follow-up without AADs.

All definitions for the CEASE-AF trial are derived from the 2012 ***HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation*** (5).

For details see APPENDIX I of this protocol that includes the following definitions:

- Types and classification of AF (Table 1)
- Definitions of AF ablation outcomes (Table 5)
- Minimum AF documentation endpoints and success rates in clinical trials (Table 5)
- Definition of complications associated with AF ablation (Table 6)

5.2. INVESTIGATIONAL SITES REQUIREMENTS

Up to 20 International investigational sites will participate in this trial. A list of centers is provided in a separate document. Invited centers are selected based on the availability of a cardiac surgeon experienced in thoracoscopic AF ablation and an electrophysiologist with expertise in left atrial ablation.

Sites are pre-selected based on their documented experience in surgical treatment of AF, and in particular, the center performing the surgical procedure must have already performed a minimum of 10 endoscopic procedures in the prior 12 months. Sites performing the catheter ablations must have performed a minimum of 200 procedure in the prior 12 months. Sites must have adequate laboratory equipment and staffing to perform the study examinations. All clinical sites will be subject to a qualification process prior to site recruitment to evaluate the availability of proper patient volumes, staffing, resources and equipment for conducting the study.

5.3. POPULATION

Patients with a history of persistent AF or long-standing persistent AF who are symptomatic and have failed at least one antiarrhythmic drug class I or III.

Persistent or Long Standing Persistent Atrial Fibrillation are defined in accordance with the HRS/EHRA/ECAS 2012 AF Expert Consensus Statement (2012) (Appendix 1, Table1):

- Persistent AF: Continuous AF which is sustained beyond seven days, or lasting greater than 48 hours and less than seven days but necessitating pharmacologic or electrical cardio version.
- Long standing Persistent AF: Continuous AF of greater than 12 months' duration.

For definition details, see APPENDIX I, table 1 of this protocol.

5.4. TREATMENT PROCEDURES

Catheter ablation will be performed using standard endocardial transvenous technique of PV isolation and optional additional ablations on physician's discretion / center's strategy. When required due to AF recurrence, ablation may be repeated after 90 days (blanking period) according to clinical indications and consistent with the HRS/EHRA/ECAS Consensus Statement (5). Multiple ablations are allowed. Re-ablation in the Catheter arm needs to be completed within 6 months after the index procedure.

Endoscopic surgery will include a minimum lesion set including a box lesion with right and left epicardial isolation of the PVs, superior and inferior connecting lines, and exclusion or removal of the left atrial appendage under general anaesthesia. Additional lesions may be performed based on standard practice at the interventional sites.

The following AtriCure devices may be used for this surgical ablation procedure:

a. EMR2/EML2 Clamp
b. Isolator Long Pen TT (MAX5)
c. Coolrail Linear Pen (MCR1)
d. Isolator Linear Pen (MLP1)
e. RF Generator Model (ASU2/ASU3)
f. Switch Matrix (ASB3)
g. Glidepath Tape (GPT100) (accessory device)
h. Wolf Lumitip dissector (MID1) (accessory device)
i. AtriClip® PRO LAA Exclusion System (PRO1/PRO2)
j. Gillinov Cosgrove Selection Guide (CGG100) (accessory device)

The left atrial appendage should be managed using the AtriClip Pro (PRO1/PRO2). If the surgeon determines it is not feasible or safe to address the LAA, the appendage may be left intact.

All subjects should return between Day 91 – Day 180 to undergo the Stage-2 Endocardial EP Ablation Procedure performed by the electrophysiologist. The Endocardial Procedure may occur early if subject presents with atrial flutter that could not be medically managed.

Standard cardiac electrophysiological techniques will be used for mapping, ablation, and arrhythmia induction. RF based, irrigated, power controlled, ablation catheters for endocardial lesions must be used for endocardial left sided catheter ablation; no other device should be used for ablation purposes in the left atrium. The systems used in the catheter arm may vary, however, the used energy source is limited to radiofrequency, e.g. Celsius ThermoCool or NaviStar ThermoCool (Biosense Webster), TactiCath™ Quartz Contact Force (St. Jude). During ablation, it is recommended that power not exceed 50 watts and 35 watts, if the catheter is perpendicular to the tissue.

A detailed description of both treatment arms is provided in Section 7 of the protocol.

5.5. EFFECTIVENESS ENDPOINTS

The **Primary Effectiveness Endpoint** is freedom from documented AF/AFL/AT episodes > 30 seconds through 12-months follow-up, in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed).

The following scenarios shall constitute a failure of the primary effectiveness endpoint:

1. Any documented AF, atrial flutter, or atrial tachycardia lasting >30 seconds duration occurring between T0 and 12-months follow-up.
2. Any previously failed class I or III AAD administered at a dose higher than baseline and between T0 and the 12-month follow-up visit.
3. Any newly introduced class I or III AAD usage beginning at T0 and through the 12-months follow-up visit.
4. DC cardioversion for AF, atrial flutter, or atrial tachycardia that takes place between T0 and the 12-months follow-up visit.

Secondary Effectiveness Endpoints are freedom from documented AF/AFL/AT episodes >30 seconds through 24- and 36-months follow-up, in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed).

The rhythm status used for evaluation of this endpoint will be derived from regularly scheduled 48-hour Holter monitoring and symptom driven monitoring performed during unscheduled hospital visits. For this, the patient should visit the hospital in case of symptoms, and an ECG of at least 30 seconds should be recorded.

In the **catheter ablation arm**, multiple interventions are allowed; any reintervention after 180 days after the index procedure will be counted as failure. At the physician's recommendation, the patient may crossover and undergo the hybrid procedure.

In the **hybrid arm**, a two-stage approach has to be completed within 180 days. Any reintervention after 180 days after the index procedure will count as failure. At the physician's recommendation, the patient may undergo additional catheter ablation(s).

Additional endpoints will be assessed and compared in the 2 study arms:

- Procedure times
- Radiation exposure times
- Number and severity of AF symptoms (EHRA class) (Appendix IV)
- Freedom from antiarrhythmic medications
- Preserved left atrial and cardiac function, and succesfull LAA exclusion (hybrid group only) using TEE
- Quality of life scores SF-12 (Appendix III)
- Number of cardioversions and repeat ablations
- Number of hospital admissions due to AF recurrence.

5.6. SAFETY ENDPOINTS

Cumulative risk of events will be evaluated by assessing complications associated with the repeated ablation treatments performed during the course of the study. This allows to verify whether the surgical procedure is associated with higher risk or instead, in the catheter ablation arm, a higher number of repeated interventions exposes the patient to greater overall risks. Therefore, composite major complications during follow-up (as presented in Table 6 of Appendix 1) will be compared in the two study arms, including:

- Death (regardless of cause)
- Stroke
- Transient ischemic attack (TIA)
- Cerebro Vascular Accident (CVA)
- Myocardial Infarction in the Context of AF Ablation
- Pericarditis resulting in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires a new hospitalization, or persists for more than 30 days following the ablation procedure
- Bleeding is defined as a major complication of endocardial catheter ablation if it requires and/or is treated with transfusion or results in a 20% or greater fall in hematocrit.
- Bleeding following cardiac surgery is defined as major complication if requiring reoperation or transfusion ≥ 2 units of PRBC within any 24 hours of the first 7 days following the surgical epicardial ablation procedure
- Wound infection at surgical site or puncture sites requiring re-operation for wound debridement
- Major vascular access complications, including the development of a hematoma, an AV fistula, or a pseudoaneurysm requiring intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires a new hospital admission
- Atrio-esophageal fistula (from the time of index procedure through 12 month follow-up visit)
- Esophageal injury
- Permanent phrenic nerve paralysis, defined as paralysis that remains unresolved at the 12-month follow-up visit
- Permanent pacemaker implantation that is a direct result of injury to the specialized conduction system (SA node or AV node).
- Pulmonary vein (PV) stenosis of >70%, as measured at any time after the endocardial catheter ablation procedure through the 12-month follow-up period
- Cardiac tamponade/cardiac perforation, defined as the development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure.
- Empyema
- Pneumonia
- Pneumothorax requiring intervention

6. SUBJECT ENROLLMENT

6.1. IDENTIFICATION OF CANDIDATES

All patients with symptomatic persistent or long-lasting persistent AF who are candidates for an interventional treatment can be approached for participation in this study. To minimize the potential for bias, all patients who may be suitable for this trial are to be screened based on the inclusion and exclusion criteria and a written informed consent must be obtained before performing any study-related examinations. A log book will record all eligible patients and document reasons for exclusion.

Point of enrollment: The point of enrollment is when all inclusion and exclusion criteria have been evaluated, the patient suitability for the intervention has been confirmed, and the patient has signed the written informed consent. Randomization will occur immediately after enrollment. Patients who may be found to violate the inclusion/exclusion criteria while in the operating room, but prior to the start of the index ablation (for example, due to pre-procedural detection of atrial thrombus by TTE/TEE), will be considered as “early withdrawals”. These patients withdrawn prior to the initiation of the index intervention, may be replaced, so that the total sample size of the study is unchanged.

In the Hybrid Group, subjects are considered “treated” upon initiation of pericardial access during the Epicardial Surgical Ablation Procedure.

In the Catheter Group, subjects are considered “treated” upon transseptal access with the ablation catheter.

6.2. INFORMED CONSENT

It is the responsibility of the treating physician to obtain written informed consent. The information is intended to give each participant a thorough understanding of the purpose and the nature of the trial, the cooperation required, anticipated benefits, and potential hazards of the study. The Investigator also explains that the patient is completely free to refuse or to withdraw from the trial and that if he/she does so, he/she receives standard treatment with the same degree of care. A local consent form (native language of participating countries) is available. The fact that informed consent was obtained is recorded in the Case Report Form.

6.3. RANDOMIZATION PROCEDURE

Patients referred for invasive treatment of AF will be screened for eligibility for the study according to the specified inclusion and exclusion criteria. All patients will be asked to participate in the study after reading the complete patient information sheet, including all the details of the procedures and specifying willingness to enter a randomization process for hybrid ablation or catheter ablation. Randomization will be performed centrally using the xClinical's MARVIN system.

6.4. INCLUSION CRITERIA

Subjects enrolled in this clinical study must meet the following criteria:

1. Patient is between 18 and 75 years of age
2. Patient has a history of symptomatic Persistent AF and a LA-diameter > 4cm (anteroposterior diameter in parasternal long-axis view > 4cm (LA > 4cm) (25) or Long Standing Persistent AF (as defined by the HRS/EHRA/ECAS expert consensus statement)
3. Patient is refractory to or intolerant to at least one antiarrhythmic drug class I or III

4. Patient is mentally able and willing to give informed consent.
5. Patient is willing and able to receive all of the study related procedures, and attend the scheduled follow-up visits.

6.5. EXCLUSION CRITERIA

Potential subjects will be excluded from the study if any of the following conditions apply:

1. Patient has longstanding persistent AF > 10 years
2. Patient presenting with paroxysmal AF
3. Patient with persistent AF and a LA-diameter ≤ 4 cm
4. AF is secondary to electrolyte imbalance, thyroid disease, or other reversible or non-cardiovascular cause
5. Patient underwent previous ablation procedure or heart surgery
6. Patient needs other cardiac surgery procedures besides AF treatment (valve, coronary, others)
7. Contraindication for either catheter ablation or epicardial surgery (including, but not limited to: previous thoracic radiation, previous perimyocarditis, Previous cardiac tamponade, Pleural adhesions, Prior thoracotomy)
8. Body mass index > 35
9. Left atrium anteroposterior diameter in parasternal long-axis view > 6cm
10. Left ventricular ejection fraction < 30 %
11. Severe mitral regurgitation (>II)
12. Patient unable to undergo TEE
13. Presence of LA thrombus by TEE, CT scan, MRI or angiography (*)

(*) It is possible that it is not known whether thrombus is present when determining suitability of the patient; in fact thrombus may be discovered by intraoperative imaging after the patient is randomized and undergoes intraoperative TEE, therefore patients withdrawn prior to the index intervention may be replaced, so that the total sample size of the study is unchanged.

14. History of cerebrovascular disease, including stroke or transient ischemic attack (TIA) within 6 months prior to enrollment
15. Active infection or sepsis
16. Other clinical conditions precluding inclusion (e.g., organ disease, disturbances of hemostasis)
17. Contraindication to anticoagulant therapy, or inability to comply with anticoagulant therapy
18. Pregnancy, planned pregnancy or breastfeeding
19. Life expectancy is less than 18 months
20. Patient is involved in another study involving an investigational drug or device

7. TREATMENT ARMS

7.1. PRE-TREATMENT PREPARATION

Patients can undergo catheter ablation under the anticoagulation regimen established at the investigational site.

Recommended anticoagulation

- Oral anticoagulation therapy (e.g., warfarin) stopped at least 2 days prior to surgery and international normalized ratio (INR) less than 1.5.
- Low molecular weight heparin (LMWH) (preventive) started at least 2 days prior to surgery.

Transoesophageal echocardiogram (TEE) is performed according to standard of care in all patients within 24 hrs prior to the ablation procedure in order to exclude left atrial thrombi.

(Note: TEE procedure may take place in the operating room (OR) prior to start of surgery. If a thrombus is present, the subject shall not have the surgical RF ablation procedure performed and will not continue in the trial and no further follow-up is required. In the event a subject has an adverse event related to the TEE they shall remain in the trial until the event is resolved.)

7.2. CATHETER ABLATION ARM

The percutaneous approach will be focused on the mechanisms involved in the initiation and maintenance of AF. The method and tools and energy source used may differ among the centers but need to be documented.

Access to the left atrium will be achieved by a transseptal puncture with the catheter(s) placed into the left atrium via the same puncture site. A single bolus of 50-100 U. per kg bodyweight of heparin will be administered after the transseptal puncture. The activated clotting time during the procedure will be kept between 300–400 sec.

The first step of the procedure is PV isolation; this is the minimum lesion-set and corner-stone that has to be performed. Additional ablations might be performed according to the current guidelines at the electrophysiologist's discretion but needs to be documented.

PV isolation must be confirmed by a circular mapping catheter in each PV to confirm exit and entrance block during sinus rhythm (right side) or coronary sinus pacing (left side).

Personnel resources needed to perform the procedure(s) need to be documented.

7.3. HYBRID ABLATION ARM

Preoperative oral anticoagulation therapy regimen is managed as established at the institutional site. Patients are intubated with a double-lumen endotracheal tube and external defibrillator-pads are placed. A transesophageal echocardiogram (TEE) has to confirm the absence of LAA-thrombus in all patients according to standard of care.

NOTE: During the procedure the TEE can be used to confirm successful placement of the AtriClip PRO.

7.3.1. STAGE 1 – EPICARDIAL ENDOSCOPIC ABLATION

The minimally invasive surgical radio-frequency (RF) ablation procedure is performed endoscopically on the beating heart and consists of the following general steps.

The procedure is performed under general anaesthesia, with a double lumen endotracheal intubation. Access is gained through small incisions or ports in the intercostal spaces. On the right side the pericardial sac is opened parallel to the phrenic nerve to expose the superior vena cava (SVC) and inferior vena cava (IVC). The pericardial reflections around the SVC and IVC are dissected in order to have access to the transverse and oblique pericardial sinuses.

The right PVs are isolated and the right-sided part of the roof and inferior line are created. On the left side a similar procedure is performed. Entry- and exit block are checked for the PVs and box-lesion if the patient is in SR. If the patient is in AF, the operator can decide to cardiovert the patient if this is considered safe. Excision or closure of the left atrial appendage should be performed.

The PV isolation with the so called **box-lesion**, consisting of PV isolation in pairs and a superior and inferior connecting lesion will be the epicardial lesion set in all patients regardless of the type of AF. Successful closure of the box, by proving bidirectional block using sensing and pacing technique using the Isolator Long Pen TT (MAX5) device.

Schematic of lesions sets created using endoscopic epicardial ablation. The „Box lesion“ (panel D) encompasses the left atrium around the 4 pulmonary veins.

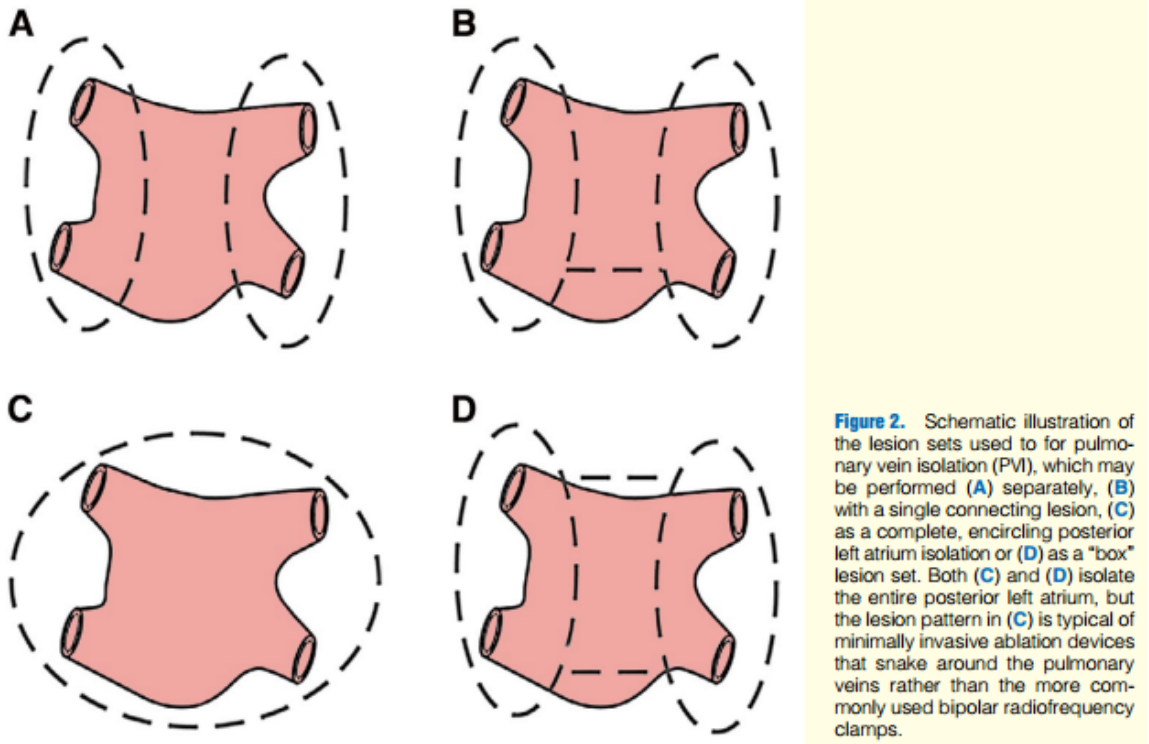


Figure 2. Schematic illustration of the lesion sets used to for pulmonary vein isolation (PVI), which may be performed (**A**) separately, (**B**) with a single connecting lesion, (**C**) as a complete, encircling posterior left atrium isolation or (**D**) as a "box" lesion set. Both (**C**) and (**D**) isolate the entire posterior left atrium, but the lesion pattern in (**C**) is typical of minimally invasive ablation devices that snake around the pulmonary veins rather than the more commonly used bipolar radiofrequency clamps.

7.3.2. STAGE 2 –ENDOCARDIAL PROCEDURE

The minimally invasive surgical ablation procedure is combined with a percutaneous endocardial procedure in a sequential step after 91-180 days from epicardial surgery.

During the endocardial approach isolation of the PV and the posterior box are checked and completed if necessary. If no gaps are detected this has to be documented. Locations of gaps should be determent and documented as well. Right and left isthmus lesions, CFE ablation can be added if wanted. Any additional ablation should be clearly described and justified.

If the patients are not in SR by the end of the procedure, they are positioned supine and given a

synchronized direct-current shock to establish sinus rhythm. Extubation is routinely performed in the operating room or at the ICU shortly after the procedure.

Patients experiencing atrial tachyarrhythmias (ATAs) on the postprocedural course should be started on class I or III antiarrhythmics and/or electrically cardioverted as needed.
Personnel resources needed to perform the procedure(s) need to be documented.

7.4. POSTPROCEDURALE CARE

7.4.1. ORAL ANTICOAGULATION

At the conclusion of the blanking period (3 months from the Index procedure), subjects should be managed on anticoagulation therapy according to the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation (26).

Link: http://circ.ahajournals.org/content/114/7/700.full

Antithrombotic Therapy for Patients With Atrial Fibrillation

Risk Category	Recommended Therapy	
No risk factors	Aspirin, 81 to 325 mg daily	
One moderate-risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)	
Any high-risk factor or more than 1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)*	
Less Validated or Weaker Risk Factors	Moderate-Risk Factors	High-Risk Factors
Female gender	Age greater than or equal to 75 y	Previous stroke, TIA or embolism
Age 65 to 74 y	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve*
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	
*If mechanical valve, target international normalized ratio (INR) greater than 2.5.		
INR indicates international normalized ratio; LV, left ventricular; and TIA, transient ischemic attack.		

Oral anticoagulation (OAC) therapy with warfarin or NOACs is started one day postprocedural. If patients are in sinus rhythm, antiarrhythmic drugs are discontinued after 3 months and rate-control medication is started at that point if appropriate.

OAC is discontinued at six months depending on the CHA2DS2-VASc-score according to current guidelines if patients are free of ATAs confirmed by 48-hour Holter, and an echocardiogram (TEE) ruled out atrial stasis or thrombus formation or incomplete LAA occlusion or residual pouch (the latter two only if the LAA was managed).

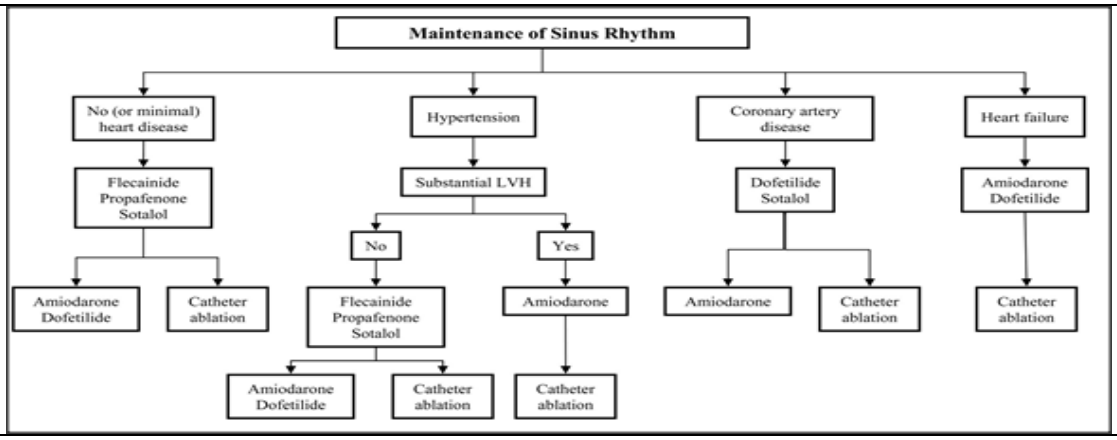
The first Holter is scheduled at 6 months. In selected patients with a low to moderate stroke risk (who would otherwise be treated with oral anticoagulants) and freedom from ATA as evidenced by an intense F/U strategy one might decide to stop anticoagulation on an individual basis.

7.4.2. ANTIARRHYTHMIC DRUG REGIMEN

The recommended AAD therapy dosing should follow the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation (see Figure below) and according to the drugs' approved labelling. Subjects receive AAD therapy, preferably Amiodarone unless contra-indicated, for 3 months beginning on the procedure day. Three months after the index procedure AAD should be stopped if the patient presents in stable NSR. However, continuation of AAD therapy beyond 3 months is at the investigator's discretion. The application of AAD type I or III at dosages exceeding preoperative dosage within 2 weeks before a core-lab holter monitoring is conducted is considered "on AAD". Rate control agents or AAD others than Type I or III may be prescribed at the investigator's discretion for all subjects throughout the entire follow-up period.

All AAD therapy will be recorded on the CRF.

Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation.
Within each box, drugs are listed alphabetically and not in order of suggested use. The vertical flow indicates order of preference under each condition. The seriousness of heart disease proceeds from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. LVH indicates left ventricular hypertrophy. See full text of the Guidelines for details.



7.5. REPEAT ABLATION

The **blanking period** is defined as early time period post-ablation, in which recurrent AF/AFL/AT is not considered a failure of AF ablation. This definition is in accordance with the "2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design".(5)

The blanking period will be 3 months (90 days) following the index procedure, during which Subjects will be monitored for AF recurrence. Any recurrence of AF will be recorded and documented, however, recurrences of AF during this time will not be considered as treatment failures.

Subjects may have their AAD medication dosage optimized during this time.

The time frame between the end of this blanking period (90 days) and 180 days after the index procedure is used to treat the patients with repeated catheter ablations if clinically indicated and to complete the hybrid procedure. Any recurrence of ATA after repeated interventions or completion of the hybrid procedure that occurs within 180 days after the index procedure will not be considered a failure and might be treated according to clinical practice. Any recurrence of ATA or any intervention after 180 days after the index procedure will be considered a failure.

When required due to AF recurrence, ablation may be repeated according to clinical indications and consistent with the HRS/EHRA/ECAS Consensus Statement (5). After T0, patients who have received 2 or more ablations («failures»), can be treated with Hybrid ablation.

8. STUDY ASSESSMENTS AND FOLLOW-UP VISITS

8.1. SCHEDULE OF VISITS AND ASSESSMENTS

Investigations and measurements performed according to the flowchart and schedule presented in section 2.2 of this protocol.

The starting point of the follow-up period is the date of first ablation procedure (catheter ablation or hybrid ablation first stage): all time points for follow-up visits are therefore calculated from this index procedure date.

For each patient the following visits are planned:

- Screening and Informed consent
- Randomization
- Index Procedure
  - Endoscopic epicardial surgery (Hybrid ablation arm)
  - Catheter ablation (Catheter ablation arm)
- Discharge
- Follow-up 3 months after the index procedure
- Repeat Procedure within 6 months
  - Endocardial catheter ablation (Second stage for patients in Hybrid ablation arm)
  - Repeated ablation procedure for patients with recurrent AF in Catheter Ablation arm
- T0: 6 months after the index procedure
- Follow-up 6 and 12 months from T0
- Follow-up 24 months from T0
- Follow-up 36 months from T0

For each patient, the study duration will be 3.5 years (42 months).

8.2. STUDY DURATION

It is estimated that it will take 18 months to enrol the patients, a maximum of 6 months to complete the treatment (two-staged) and a 36-months follow-up for all patients will be required. Effectiveness will be assessed through 36 months after the completion of the treatment (hybrid ablation or repeat catheter ablation). All treated subjects will be followed through 3 years.

The anticipated time schedule is presented in the table below.

CEASE-AF Time-schedule:

	2015		2016				2017				2018-2020			
Quarter	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Preparation of measuring instruments	X													
Preparation for screening patients	X													
Inclusion patients		X	X	X	X	X	X	X	X					
Intervention		X	X	X	X	X	X	X	X	X				
Data-gathering baseline and follow-up		X	X	X	X	X	X	X	X	X	X	X	X	X
Filling and cleaning databases			X	X	X	X	X	X	X	X	X	X	X	X
Literature research and preparing articles	X	X	X	X	X	X	X	X	X	X	X	X	X	X

8.3. SCREENING AND CONSENT

After signing an informed consent, patients referred for invasive treatment of AF will be screened for eligibility for the study according to the specified inclusion and exclusion criteria (see section 6.4 and 6.5)

Patients with a history of persistent AF or long-standing persistent AF who are symptomatic and have failed at least one antiarrhythmic drug class I or III will be considered eligible for the study.

Patient screening includes routine tests per Institution procedures. Patients older than 60 years of age and younger patients with an existing cardiovascular risk profile should receive a coronary angiogram or a cardiac CT-scan evaluating Ca^{++}-scores before surgery.

Pre-ablation procedures for all patients will follow standard hospital procedures and include:

- Medical history and physical examination
- Recording of medication
- 12-lead electrocardiogram
- Trans-Thoracic and Trans-Esophageal Echocardiogram (left atrial thrombus)
- Quality of Life Assessment SF-12
- CHA2DS2 VASC score (Appendix V)
- EHRA class of symptoms
- 48-hour Holter monitoring

8.4. RANDOMIZATION / INDEX PROCEDURE

Eligible patients will be randomized, see sections 6.1 and 6.3.

After the randomization, for the patients in the Hybrid Ablation arm the Endoscopic Epicardial surgery will be performed, while for patients in the Catheter Ablation arm a standard percutaneous catheter ablation will be conducted.

After the procedure, the following must be conducted and/or obtained:

- ECG
- Assessment of AE/SAE

Concomitant procedures to treat arrhythmia (i.e. cardioversion for subject in atrial fibrillation) may be performed if required on physician discretion.

Oral anticoagulation and antiarrhythmic drug medication should be administered.

See Section 7.3 for a complete description of the Hybrid Procedure.

At the time of discharge, the following must be conducted and/or obtained 2-3 days post Endoscopic Epicardial surgery procedure:

- Physical examination
- ECG, RR
- CHA2DS2 VASC score
- AE/SAE assessment
- Concomitant procedures to treat arrhythmia (i.e. cardioversion for subjects in atrial fibrillation), performed at physician‘s discretion
- Hospital Discharge date

After 3 months + 7 days from the Index procedure, a follow up visit is performed

-
- ECG, RR
- CHA2DS2 VASC score
- AE/SAE assessment
- Concomitant procedures to treat arrhythmia (i.e. cardioversion for subjects in atrial fibrillation), performed at physician‘s discretion

Generally, during the 3 months follow-up visit it is evaluated if a redo catheter ablation procedure is necessary in the catheter arm.
In case of atrial flutter that cannot be managed medically before reaching the 3 months follow up post index procedure visit, the endocardial catheter ablation might be performed on the physician’s discretion before the 3 months follow-up. The following will be conducted and/or obtained: (in both arms applicable).

- AE/SAE Assessment
- Heart Rhythm Assessment
- Medication review

All subjects should return between Day 91 – Day 180 to have the Endocardial Catheter Ablation Procedure (for Hybrid Ablation arm) or repeated endocardial catheter ablation for patients with recurrent AF (Catheter Ablation arm). Standard cardiac electrophysiologic techniques will be used for mapping, ablation, and arrhythmia induction.

After the second procedure, the patients will be scheduled for a visit at 6 months post index procedure, to assess their arrhythmia status. As indicated before at section 7.5, any recurrence of ATA that occurs within 180 days after the index procedure will not be considered a failure and might be treated according to clinical practice.

8.5. FOLLOW UP VISITS

Patient follow-up will be 36 months (3 years) in total after T0 (180 days (6 months) from the index procedure), During the follow-up visits (6 months, 12 months, 24 months, 36 months from T0), patients will undergo the following non-invasive routine diagnostic tests and evaluations, according to the schedule of assessments:

- Heart Rhythm Assessment (ECG, RR)
- Medication recording
- Physical examination (performed only for the 12 month Follow up)
- SF-12, EHRA class
- CHA2DS2 VASC score
- Echo (TTE or/ TEE)
- 48-hour Holter
- AE/SAE assessment

8.6. UNSCHEDULED VISITS

Unscheduled visits are defined as subject visits outside routine standard of care practice and outside of protocol defined visits, after a subject contacts the study sites and is asked to return to the study clinic specifically for a study-related concern. Additionally, all in-hospital events that occur outside of scheduled protocol visits should be captured as an unscheduled visit.

Symptom driven FU may be conducted as unscheduled visits. In case of symptoms the patient should contact the site coordinator and visit the site to record an ECG of at least 30 seconds.

Any ATA lasting > 30 seconds documented outside the scheduled visit due to symptoms of the patient will impact the effectiveness endpoints of success at 12, 24 and 36 months.

8.7. TRIAL EXIT

Once the subject has completed the final follow-up visit they can be exited from the trial provided they do not have any conditions that require continued follow-up.
At study exit the following must be collected.

- Study Exit Date
- Exit Reason

8.8. PATIENTS WITHDRAWN AND LOST TO FOLLOW UP

Subjects may withdraw from the study at any time for any reason, without prejudice or detriment to their medical care. Subjects may also be withdrawn from the study at any time at the discretion of the investigator as deemed appropriate for safety and/or if the subject's medical condition contraindicates further study participation.

If a subject prematurely terminates from the study, the reason for the termination will be recorded. For those who cannot be located for their follow-up visits, every reasonable effort (i.e. minimum two documented phone calls and one certified letter), will be extended to make contact. These subjects will be considered "lost to follow-up". Subjects who actively withdraw from the trial will be considered "withdrawals". If termination is a result of an adverse event or death, an Adverse Event Case Report Form will also be completed.

Subjects who prematurely terminate for any reason after treatment, will have their data evaluated until the time of their withdrawal. These data will be included only up to the time of withdrawal and removed from further analysis. All premature terminations will be tabulated and reported.

It should be understood that an excessive rate of withdrawals or lost to follow up could render the study difficult to interpret. Hence, unnecessary withdrawal of subjects should be avoided. Should a subject withdraw or is withdrawn, every effort must be made to collect any data from the subject that is available within their consent (e.g., a follow-up interview, even if it will be obtained outside the protocol follow-up window); and complete and report the observations as thoroughly as possible.

Subjects who withdraw or are withdrawn from the study should:
Have the reason(s) for their withdrawal recorded.

- Be seen by an investigator, whenever possible, and all final assessments should be performed and recorded.
- Be asked about the presence of any AEs. If an ongoing AE if present, the patient should be followed up until satisfactory clinical resolution of the event is achieved.
- In the event of pregnancy, the subject should be monitored until conclusion of the pregnancy and the outcome of pregnancy reported to the clinical monitor.

The patient is considered lost to follow-up when contact with the subject has been lost without completing the final visit assessment, and every attempt to contact has failed. Final documentation regarding all attempts to contact the subject requesting their return for the final visit should be documented.

9. CLINICAL RISK BENEFIT EVALUATION

9.1. EXPECTED BENEFITS

The hybrid approach is a relatively new method that combines minimally invasive, epicardial AF surgery, EP mapping and catheter-based endocardial ablation in an attempt to overcome the shortcomings of each technique.

- The surgeon may isolate the posterior LA, ablate the ganglionated plexus and ligament of Marshall (LOM), isolate the vena cava and begin a mitral isthmus line thoracoscopically.
- The addition of the endocardial step allows electrophysiologists to “touch-up” any gaps in epicardial lesions and create or complete lesions in areas that cannot be reached epicardially, such as the cavotricuspid and LA isthmus.

Theoretical advantages to the hybrid approach are (1) the ability to confirm conduction block across lesions, (2) the ability to close identified gaps that might result in postoperative arrhythmias or long-term failures, (3) minimization of surgical injury to structures not easily reached, (4) elimination of risk to the phrenic nerve and oesophagus from catheter ablation because the surgeon can protect these structures, (5) reduced risk of tamponade compared with catheter-based ablation alone because the pericardium is open and (6) reduced risk of embolism from coagulation caused by endocardial ablations because fewer endocardial ablations are needed.

Subjects’ persistent AF condition may improve with the proposed hybrid treatment as well as with the standard catheter ablation, and as such, subjects may benefit from participation in this trial.

9.2. POTENTIAL RISKS

All patients will be treated with routine standard of care procedures using approved CE-marked devices and techniques.
The risks associated with this study, are similar to risks posed by standard surgical and interventional cardiac procedures. Risks to the patient are minimized due to:

- The established, standard nature of the procedures and techniques to be used
- Selection of expert centers
- The use of state of the art equipment

The use of endoscopic surgical ablation is known to be safe and effective when used for the approved indications. Besides the usual risk of complications the following might occur: injury to the coronary arteries rarely, bleeding <2%, stroke or TIA, breathing problems due to injury to the phrenic nerve <3%, conversion to sternotomy <5%, postoperative infection <2%, renal insufficiency <1%, hyper or hypotension <1%, permanent pacemaker implantation <2%. These potential complications however are related to the procedure itself and not to any study specific activities. The EP diagnostic and ablation procedure and follow-up activities will be carried out in accordance with approved diagnostic techniques and standard operating procedures for the centers.
Nevertheless, the EP diagnostic and ablation procedure is an invasive procedure and as with any other routine invasive or surgical procedure it has some risks. Fewer than 5 percent of people who have the procedure develop any of the following problems: stroke or TIA <1%, cardiac tamponade <1%, pulmonary vein stenosis <1.5%, a fistula between the atrium and the esophagus rarely, phrenic nerve paralysis <10%, post procedure bleeding. The follow-up activities will be carried out in accordance with approved diagnostic techniques. Therefore, enrollment in this investigation does not pose any undue risks to the patients.

10. STATISTICAL METHODS

10.1. SAMPLE SIZE COMPUTATION

A total of 210 subjects (randomization ratio 2:1) will be enrolled in this trial, in order to evaluate the Primary and Secondary Effectiveness Endpoints of freedom from AF/AFL/AT >30 seconds through 12, 24 and 36 months follow-up, in the absence of Class I or III AADs (with the exception of previously failed AADs at doses not exceeding those previously failed).

A two treatment group continuity corrected chi-squared test with an α = 0.05 two-sided significance level will have 80% power to detect the difference between a Catheter group failure rate of PC = 0.5 and a Hybrid group failure rate of PH = 0.25 when the sample sizes are 49 and 98, respectively (a total sample size of 147). Adjusting for loss to follow-up (anticipated 30% loss at 12 months), the required total sample size will be 210 subjects (140 in the Hybrid group, and 70 in the Catheter group).

10.2. RANDOMIZATION

Upon enrolment subjects will be assigned a sequential identification number at each site using the xClinical MARVIN system. Subjects will be randomized 2:1 (2 Hybrid procedures to 1 Catheter procedure). Randomization sequences will be generated by an independent Statistician from Cardialysis using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and stratified by Site. A 2:1 randomization in favour of the Hybrid group, allows for important additional experience with this new procedure without substantially decreasing the power of the comparison with the Catheter group.

10.3. ANALYSIS POPULATIONS

The effectiveness, safety, health economic and Qualify of life analyses will be based on the Intent-To-Treat (ITT) Population. The ITT Population is defined as all subjects randomized to either the Hybrid or Catheter group and on whom the surgical procedure is attempted (even if the procedure is aborted).

An additional study population (per protocol) may be defined for effectiveness, health economic and Quality of life analyses. This population is defined by the ITT population but without any major protocol violations, that is, those that could potentially bias the results.

10.4. ANALYSIS OF STUDY ENDPOINTS

Study endpoints will be summarized by treatment group. Continuous variables will be summarized by presenting the number of subjects, mean, standard deviation, median, minimum, maximum by procedure group (Hybrid or Catheter). Tabulation of categorical variables by group will include counts and percentages. 95% confidence intervals will be provided as appropriate.

Additional analyses, analysis populations, covariates and summary tables and/or graphs will be generated as needed.
In all analyses described below, the null hypothesis will be a two-sided test of no treatment group difference. All statistical tests will use a two-sided significance level of α=0.05.

10.4.1. EFFECTIVENESS AND HEALTH ECONOMIC ANALYSES

To avoid any biases, the effectiveness endpoints from Holter data will be assessed in a blinded (no knowledge of the patient group) fashion by the core lab physician.

A Pearson's Chi-Squared test will be used to compare the effectiveness success rate through 12 months between the two procedure groups. Alternatively, a Fisher's Exact test will be used if justified by small cell counts (less than 5) and Clopper-Pearson (Exact) 95% CI will also be reported.

The secondary effectiveness endpoints will be similarly summarized and analyzed through 24 and 36 months from T0. In addition, effectiveness success might also be analyzed using multiple logistic regression model with the proportion of success as the dependent variable and the following independent variables: sites (or clusters of sites), age, gender, CHA2DS2- VASc score and relevant interaction terms.

Exploratory health economic analysis will include potential differences in hospital and third party payer/societal economics. Formal economic models may be built from the clinical data captured and secondary data sources.

Hospital economics assessed may include resource use variables such as ICU stay time, length of hospital stay, costs associated with serious adverse events and total procedure related costs examined over the study duration.
Variables also included for the hospital economics assessment will be:

- SF-12 (Brazier method)
- Interventional procedures performed (the initial endoscopic epicardial surgery, endocardial catheter ablation and any follow-up ablations or cardiac interventions related to initial interventions)
- Adverse events and treatments (minor/major IS, HS, major bleed, cost of care for minor stroke, cost of care for major stroke, pericardial effusion
- Readmission (AF related)
- Medication use (AF related)
- If stroke occurred, disability status using the Modified Rankin Scale (Appendix 2) (assessed during follow-up, and assessed if the patient became disabled as a consequence of AE originating from the trial interventions)

Third party payer/societal economics assessed may include total patient treatment costs during the study period, readmissions related to index and secondary treatment procedures, disability costs related to index procedures, stroke rehab costs, and cardiac related medication costs. The impact of LAA management during surgery on costs may be assessed if there is adequate sample size.

Formal economic models utilizing treatment effectiveness may be built with collected data and other secondary sources accounting for specific European country perspective and discounted appropriately. Cost data will be reported as both mean and median values and compared by 2 sample t tests. Regression modeling may be employed to assess patient and procedure predictive factors related to increased payer and hospital costs.

10.4.2. INTERIM ANALYSES

Although still subject to change the maturing study data indicate a lower occurrence of dropout during follow up than was assumed in the original sample size computation.

Several interim analyses will be performed to assess if the primary effectiveness outcome can be derived ahead of full patient enrollment.

The first interim analysis will be performed when 165 patients are randomized, and thereafter at 170, 180 and 210 patients.

Each interim analysis will be performed by an independent statistician. Both sponsor Atricure and study team members other than the independent statistician will remain blinded to the primary effectiveness outcome of the study, with exception of being informed on one of the two decision options shared below.

Based on the outcome of the interim analysis, one of the following two decisions will be made available by the independent statistician to Atricure and the study team with regard to the primary endpoint, either:

1. Continue enrolling patients;
2. Stop enrollment and follow all treated patients to 12-months (primary endpoint), at which time the primary analysis is conducted;

The interim analyses will be performed using a Bayesian Adaptive Design method (27). The analyses will use all primary endpoint related patient data available in the study dataset and apply the following assumptions:

Given current observed data, calculate bothPPS_n which is defined as the predictive probability of success with current sample size and 12 months of follow-up on all patients and PPS_{max} which is defined as the predictive probability of success at N=210 with 12 months of follow-up on all patients

Continue enrolling patients if $PPS_n < 0.95$ and $PPS_{max} \geq 0.30$:

- Success with current sample size not certain
- Interim observed effect close (or bigger) than observed effect needed for success at N=210

Otherwise stop enrollment and continue follow-up:

- Either very likely or reasonably unlikely to succeed.

The final analysis will be based on a Pearson's Chi-Squared test with an adjusted two-sided alpha significance level of 0.044.

10.4.3. SAFETY ANALYSIS

A Pearson's Chi-Squared test will be used to compare the incidence of composite safety endpoint between the two procedure groups. Alternatively, a Fisher's Exact test will be used if justified by small cell counts (less than 5) and Clopper-Pearson (Exact) 95% CI will also be reported.

In addition, composite safety endpoint might also be analyzed using multiple logistic regression model similar to the effectiveness endpoint described above.

10.5. DETAILED ANALYSIS PLAN

Prior to looking at the interim and final data and database closure, if needed, a detailed statistical analysis plan will be prepared and finalized to completely specify the statistical procedures to be applied to the data by the statistician who will conduct the analysis. The plan will amplify on the methods discussed in this protocol, will address any protocol changes that would affect the analysis, and will provide a rationale for any changes to the analysis.

11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1. INVESTIGATOR REPORTING TIMELINES

Adverse events and complications associated with AF ablation (as defined in Table 6 of the Consensus paper (Appendix I) will be identified and captured on the AE CRF throughout the duration of the study as they occur and will be followed until they are adequately resolved or explained.

Type, severity and duration of adverse events will be recorded, as well as withdrawal of treatment and evolution of these adverse events after withdrawal.

A description of the event, including the start date, resolution date, action taken, and the outcome should be provided, along with the investigator's assessment of the relationship between the AE and the AF ablation procedure and/or the devices used. The Investigational Site will provide relevant follow-up information to the Sponsor or Sponsor's designee upon request. All AEs must be recorded in the CRF database.

All Serious Adverse Events are to be reported to the Sponsor within a period of 24 hours after first knowledge of the event.

Notification of serious adverse events to the Sponsor may be done via entering the event in the electronic CRF (eCRF).
In the event of system outages or technical difficulties, serious adverse events may be submitted via e-mail to SafetyTeam@cardialysis.nl. Upon availability of the system or resolution of the technical difficulties, the event will be recorded in the Adverse Event eCRF.

The sponsor will determine whether the event requires immediate notification to other investigators participating in this trial to ensure the safety of the patients participating in the trial based on medical judgment, taking into account the profile of the devices and risk-benefit analyses based on cumulative safety data

- Serious concerns about subject's safety
- High rates of trial-related SAE(s)
- High rates of Unanticipated AEs
- New scientific or therapeutic development that may advisedly affect subject's safety or the ethical conduct of the clinical trial

In addition, Investigational Centers are responsible for reporting serious adverse events to their local Regulatory Bodies/EC in accordance with the applicable requirements.

11.2. ADVERSE EVENT DEFINITIONS

Adverse events are defined per ISO 14155:2011(E) Clinical Investigations of Medical Devices in Human Subjects- Good Clinical Practice, as summarized in table 1 below. Safety reporting is done in accordance with European Medical Vigilance reporting requirements (MEDDEV 2.12-1) and the reporting procedure during this clinical study is described below.

Table 1. ISO 14155:2011- Annex F - Adverse Event Categorization

Adverse Event	Non-Device Related	Device or Procedure Related
Non-Serious	Adverse Event **(AE)**	Adverse Device Effect **(ADE)**
Serious	Serious Adverse Event **(SAE)**	Serious Adverse Device Effect **(SADE)** • Anticipated Serious Adverse Device Effect **(ASADE)** • Unanticipated Serious Adverse Device Effect **(USADE)**

11.2.1. ADVERSE EVENT (AE)

An adverse event (AE) is defined in ISO 14155:2011 as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational device.

11.2.2. ADVERSE DEVICE EFFECT (ADE)

An adverse device effect is defined in ISO 14155:2011 as any adverse event related to the use of an investigational medical device. This definition includes:

- Adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- Any event resulting from use error or from intentional misuse of the investigational medical device.

11.2.3. SERIOUS ADVERSE EVENT (SAE)

A serious adverse event (SAE) is defined an adverse event that:

1. led to death,
2. led to a serious deterioration in the health of the subject, that either resulted in:
3. a life-threatening illness or injury, or
4. a permanent impairment of a body structure or a body function, or
5. in-patient hospitalization or prolonged hospitalization of existing hospitalization, or
6. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function.
7. led to a foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the investigational plan without serious deterioration in health, is not considered a serious adverse event.

11.2.4. SERIOUS ADVERSE DEVICE EFFECT (SADE)

A serious adverse device effect is defined as an adverse device effect that results in any of the consequences characteristics of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

11.2.5. ANTICIPATED AND UNANTICIPATED SADE (ASADE/USADE)

Anticipated adverse events are device or procedure related complications that are expected to occur, and that have been identified as potential risks in this investigational plan or in product labelling. If these events are deemed to be serious, they should be reported as Anticipated Serious Adverse Device Effects.

Unanticipated adverse device effect (USADE) is defined in ISO 14155:2011 as any serious adverse effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

11.2.6. DEVICE DEFICIENCY AND MALFUNCTION

Device deficiency is defined in ISO 14155:2011 as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Device deficiencies include malfunctions, use errors and inadequate labelling.

Device malfunction is defined in ISO 14155:2011 as a failure of an investigational device to perform in accordance with its intended purpose when used in accordance with the Instructions For Use.

11.3. SAFETY MONITORING AND REPORTING

11.3.1 SAFETY MONITORING

In order to assess the safety of the trial procedure, the Sponsor will generate tables summarizing the occurrence of procedure-related AEs. These reports will be summarized for review by the medical monitor with appropriate follow-up according to the Safety Monitoring Plan.

11.3.2. SAFETY REPORTING

A quarterly safety review will be conducted by the Medical Monitor or designee from the start of the trial (first subject enrolled) until database lock. Each review will follow with a written report and supporting documentation that includes a recommendation to the Clinical Project Manager as to whether or not the trial should continue without change, be modified, or terminated. The recommendation will be signed by the Medical Monitor. Recommendations regarding modification of the design and conduct of the trial may include, but are not limited to:

- Modifications of the trial protocol based upon the review of the safety data;
- Suspension or early termination of the trial because of serious concerns about subjects' safety;
- Increase or decrease in the number of trial centers; or
- Extension of the recruitment period when the incidence of primary trial outcomes is substantially less than expected.

12. STUDY RECORDS

12.1. CASE REPORT FORM (CRF)

For each randomized patient, a Case Report Form, which consists of a sequential set of instructions with provision for data recording, is provided. Electronic CRFs accessed via internet

will be used to record all information collected in the study.

It is anticipated that relevant sections of the CRF will be completed by the investigator or designee within 24 hours of the last data becoming available, but in no case later than 5 days. Similarly, when a subject completes a study, it is anticipated that all relevant CRF pages will be completed within 24 hours of the last data becoming available, but in no case later than 5 days.

During periodic monitoring visits, the study monitor will review the CRFs for completeness and accuracy at site or in-house. Errors detected or suspected will require clarification or correction of errors. This will be communicated to site via Data Clarification/Query. Any data correction must be documented and approved by the principal investigator.

Wherever possible the principal investigator should assist in clarification or correction of errors detected within 48 hours of their being brought to the attention of the investigator.

12.2. SOURCE DOCUMENTS

The investigator must maintain detailed source documents on all subjects who are enrolled or who undergo screening in the study. All information recorded on the CRFs must be traceable to these source documents. Source documents include subject medical records, hospital charts, clinic charts, investigator subject trial files, as well as the results of diagnostic tests (e.g., laboratory tests, hemodynamic studies).

1. The following minimum information should be maintained in the Source Documents:
2. The date the subject entered the study and the subject number;
3. The study protocol number and the name of the Sponsor;
4. The date that Informed Consent was obtained;
5. Evidence that the subject meet the trial eligibility requirements (e.g., medical history, trial procedures and/or evaluations);
6. The dates of all study related subject visits;
7. Evidence that required procedures and/or evaluations were completed;
8. Use of any concurrent medications;
9. Documentation of specific device used;
10. Occurrence and status of any adverse events;
11. The date the subject exited the trial and a notation as to whether the subject completed the trial or was discontinued, including the reason for discontinuation.

12.3. INVESTIGATOR STUDY FILE

The Investigators must maintain adequate and accurate records to document the conduct of the study and substantiate the study data. The essential documents required by clinical study regulations will be filed in an Investigator Study File. The investigator will be responsible for keeping the Investigator's Study File updated and ensuring that all required documents are filed. The essential documents, listed below, will be inspected during monitoring visits.

1. Signed protocol and amendments
2. EC Approval letter for original protocol and amendments, including a dated list of EC membership and members' affiliation
3. Informed consent form, approved by the EC
4. CV of investigator and co-investigator(s)
5. Correspondences with EC and Sponsor
6. Interim reports to EC including adverse events, protocol deviations and others
7. Patient enrollment / identity log
8. Site staff signature log
9. Monitor visit log
10. Other appropriate documents in accordance with GCP guidelines

12.4. RECORD RETENTION

All eCRF information, study records, reports and source documents that support the eCRF must be retained in the files of the responsible investigator according to national requirements following notification by the Sponsor or designee that all investigations have been completed, and will further be retained in accordance with local and international guidelines as identified in the Investigator Site Agreement. This documentation must be accessible upon request by international regulatory authorities or the Sponsor (or designee). The Sponsor or designee must approve archiving or transfer of the documentation for relocation purpose of premises, in writing, prior to the actual file transfer. The investigator must notify the Sponsor, in writing, of transfer location, duration, and the procedure for accessing study documentation. The investigator must contact the Sponsor, or designee, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

If the investigator retires, relocates, or for other reasons withdraws from assuming primary responsibility for keeping the study records, custody per written notice must be submitted to the Sponsor, or designee, indicating the name and address of the person accepting primary responsibility. The EC/IRB must be notified in writing of the name and address of the new custodian.

13. ETHICAL ASPECTS

13.1. DECLARATION OF HELSINKI

This study is conducted in full accordance with the principles of the "Declaration of Helsinki" (as amended in Fortaleza, Brazil, 2013) and with the laws and regulations of The Netherlands. The complete text of the “Declaration of Helsinki” is supplied to the Investigators upon request.

In addition, this study will be conducted in conformity with the principles set forth by the Good Clinical Practice (GCP) directives, the International Standard EN ISO 14155:2011, and the laws and regulations of each of the Countries involved.

13.2. SPONSOR DUTIES AND RESPONSIBILITIES

The Sponsor of this clinical study has the overall responsibility for the conduct of the investigation.
The Sponsor will select qualified investigators; obtain a signed Investigator’s Agreement, and provide the investigators with the information necessary to conduct the study.
The Sponsor will have certain direct responsibilities and will delegate other responsibilities for clinical research management/monitoring to a specialized organization:

Cardialysis
Westblaak 98
3012 KM Rotterdam
The Netherlands

The general duties of the Sponsor consist in submitting the clinical investigation notification to National Competent Authorities when required, obtaining or verifying the availability of Ethics Committee approvals prior to shipping the study materials, selecting qualified investigators, ensuring proper investigational site monitoring, and ensuring that informed consent is obtained. The Sponsor will evaluate circumstances where an investigator deviates from the investigational plan. The Sponsor retains the right to remove either the investigator or the investigational site from the study. The Sponsor will prepare written progress reports and a final report, as required.

For AF patients, all study treatments are part of standard routine care. The related insurance is comprised in the routine coverage for clinical and research activity of the Institution. All the products used for the study are CE marked and covered by product insurance policies.

In the coordinating center and other study centers, the staged hybrid procedure described in this protocol is already in routine clinical use.

13.3. ETHICS COMMITTEE (EC) APPROVAL

This investigational plan and the informed consent must be reviewed and approved by the appropriate Ethics Committee at each center where the trial will be conducted before enrollment of subjects. As per local regulation, changes to the investigational plan that may increase the risk or present new risks to the subject, or that may adversely affect the validity of the trial, must be approved in writing by the Sponsor and the Ethics Committee.

Prior to the subject enrollment, a signed copy of the Ethics Committee approval form or a signed copy of the Ethics Committee approval letter addressed to the investigator must be submitted to the Sponsor certifying this approval. Investigators are responsible for submitting and obtaining initial and continuing review of the trial by their Ethics Committee with the recurrence of at least once a year. All correspondence with the Ethics Committee should be filed in the Investigator's Study File and a copy forwarded to the Sponsor and the site monitor.

SAEs will be reported to the central Ethics Committees as a cumulative Line Listing on a 6-monthly basis. Only SAEs that have an impact on the conduct of the trial shall be reported promptly (within 2 business days).

13.4. STUDY SUSPENSION OR TERMINATION

The Sponsor reserves the right to terminate this study and remove all study materials from the study site at any time. The study may be suspended or terminated for any of the following reasons:

- It becomes apparent that patient enrollment is unsatisfactory with respect to quality or quantity
- Data recording is inaccurate and/or incomplete
- Violation or deviations from the signed protocol
- The incidence and/or severity of adverse events in this or in other studies indicate a potential health hazard caused by the treatment under study.

The international Steering Committee (see section 15.1) is responsible for periodic reviews of safety and efficacy. Should a determination be made that the study should be suspended or terminated at one or all sites, then:

1. Enrollment shall be suspended or terminated at one or all the sites
2. Currently enrolled subjects will be followed according to the protocol, which may be amended to accommodate study suspension or termination
3. The Sponsor shall promptly inform the investigators and Ethics Committees of the suspension or termination and the reasons for it.

Should the Sponsor decide to terminate the study, the investigator will complete the CRFs as far as possible. The completed CRFs and any study materials will then be collected by the Sponsor.

13.5. RESPONSIBILITIES OF PRINCIPAL INVESTIGATORS

13.5.1 Investigator Responsibility/Performance

Prior to starting enrolment of patients, the investigator must read and understand this study protocol, and must sign and date the Protocol Signature page. The Investigator Site Agreement documents agreement to all conditions of the study protocol and agreement to conduct the study accordingly. This study will be conducted in accordance the Declaration of Helsinki and other applicable regulatory requirements or any conditions of approval imposed by the EC/IRB or regulatory authorities.

13.5.2 Required Documents

The following documents must be submitted to Sponsor, or designee prior to patient enrolment:

- Signed Protocol Signature Page
- Recent (≤ 2 years old) signed and dated English Curriculum Vitae (CVs) of the Principal Investigator and co-investigators of the clinical site. These CVs should clearly show the investigator's and co-investigators' qualifications and experience.
- Copy of the written confirmation of the EC/IRB regarding approval of the protocol including version number and date, patient information sheet and informed consent form, including version and date and other adjunctive patient material.
- List of EC/IRB members, including name, title, occupation and any institutional affiliation of each member. If the EC/IRB member list is not available, the General Assurance or EC/IRB Recognition Number should be provided.
- Signed Investigator Site Agreement.

13.5.3 Ethics Committee (EC) / Institutional Review Board (IRB) Approval

According to the local regulations, the investigator must have all necessary approvals, including written approval from the EC/IRB of the clinical site or other accepted EC/IRB prior to enrolling patients in the study. A copy of the written approval must be provided to Sponsor and should include the following:

- Statement of EC/IRB approval for the proposed study at the clinical site
- Date the study was approved and the duration of the approval
- Listing of any conditions attached to the approval
- Identification of the approved Primary Investigator
- Signature of the EC/IRB chairperson
- Acknowledgement of the Co-Investigators
- EC/IRB approval of the informed consent form (if applicable)
- EC/IRB approval of the final protocol (if applicable).

Any substantial amendments to the protocol, as well as associated consent form changes, will be submitted to the EC/IRB and written approval obtained prior to implementation. Minor changes which do not affect the subject's safety will be subject to notification.

All Serious Adverse Event (SAE) reports (including device/procedure) will be submitted to EC/IRB and the sponsor by Cardialysis . Annual and final reports will be provided to the EC/IRB as required.

13.5.4 Informed Consent

Prior to study start, the investigator must obtain written EC/IRB approval for the informed consent form. A copy of the Patient Information and the signed and dated informed consent will be provided to the study patient. The original must be retained in the patient medical records at the study site. The study must be explained to the study subjects in lay language. Study patients will be assured that they may withdraw from the study at any time and for any reason and receive alternative conventional therapy as indicated.

13.5.5 Reporting Requirements

The investigator should notify the EC/IRB in writing within three months after completion, termination, or discontinuation of the study at the site. The same procedure will be applied to Competent Authority where required.

Site responsibilities for submitting data and reports:

Type of CRF/Report	Completed by Site Within	Process
Adverse Events	Ongoing Basis	Collected in the eCRF
Serious Adverse Event Notification eCRF (including death)	24 hours	Enter eCRF pages within 24 hours of knowledge of event
eCRF (Baseline, Follow-up visits, Patient Withdrawal)	Ongoing basis	Collected in the eCRF
Annual Reports	Forward as requested by EC/IRB	Copy to be provided to Sponsor and EC/IRB
Final Report	Forward within 3 months of study completion or termination	Copy to be provided to Sponsor and EC/IRB

13.5.6 Audits / Inspection

In the event that audits are initiated by the Sponsor (or its designee) or national/international regulatory authorities, the investigator allows access to the original medical records and provides all requested information. In the event that audits are initiated by a regulatory authority, the investigator will immediately notify the Sponsor.

13.6 CONFIDENTIALITY AND PATIENT DATA PROTECTION

All information and data concerning subjects or their participation in this trial will be considered confidential.
Only those working on the Sponsor's behalf, the independent Ethics Committee and regulatory authorities will have access to subject medical records and other study documents for verification of study procedures and data without violating the confidentiality of the subject. All data used in the

analysis and reporting of this evaluation will be de-identified.
The investigator must assure that the subject's anonymity will be maintained and that the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy of and confidentiality rules in accordance with applicable regulatory requirements (eg. GDPR).
Subjects must be pseudo-anonymized and identified only by their assigned study number (unique identification code) on all CRFs and other records and documents submitted to the Sponsor, the monitor, and other authorized parties. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity.
The investigator will keep a Patient Identification List with complete identification information (name, address, contact number) on each subject.
Documents not for submission to the Sponsor, such as subject's written informed consent, should be maintained by the investigator in strict confidence.

14. STUDY OVERSIGHT

14.1 ECG/HOLTER CORE LABORATORY

An independent ECG/Holter core laboratory will be utilized for assessment of the following data collected on subjects. The core laboratory will review and interpret submitted data :

- 12-lead ECG collected at follow-up study visits
- Continuous ECG monitoring recordings (48-hour Holter)
- Symptom driven monitoring during unscheduled hospital visits (in addition to the regular scheduled Holters)

All ECG monitoring shall be performed in accordance to the core laboratory's recommended protocol.

15. INVESTIGATOR REPORTS

15.1. STUDY PROGRESS REPORTS

Annual clinical progress report will be prepared and provided to each investigator. A final report will be provided at the completion of the trial. Copies of the final clinical progress report will be submitted by the CRO to the Sponsor, reviewing IRB/EC and the investigator. If applicable the investigator forwards the annual clinical progress report to their local IRB/EC.

15.2. PUBLICATION POLICY

The Sponsor and the co-primary investigators are committed to the publication and widespread dissemination of the study results. Prior to submission or presentation, the Sponsor will review the publication (abstract and manuscripts) within thirty (30) days after receipt to ensure technical accuracy of the information presented.
Authors of publications will include the participating investigators who have enrolled significant numbers of patients. Final author lists will be based on direct involvement in hypothesis generation, data analysis, patient recruitment, and composition of abstracts and manuscripts. The final decision about author lists will be the prerogative of the Sponsor and the International Scientific Board in accordance with guidelines to authors for each journal.
If a multicenter publication is not issued after 1 year from the conclusion of the CEASE-AF study (final database closure), single center results may be published with review by the Sponsor before 30 days of submission.

The Sponsor reserves the right of prior review of any publication or presentation of data from this study.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. COMPLIANCE TO STANDARDS AND REGULATIONS

The protocol, informed consent form and other study-related documents will be submitted to the Ethics Committee (EC) / Institutional Review Board (IRB). The study will be performed in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP).

The trial will only start at a clinical site after written approval of the study has been obtained from the appropriate national EC/IRB.

16.2. DATA RECORDING

It is the expectation of the Sponsor that all data entered into the eCRF has source documentation available at the clinical site. The site must implement processes to ensure this happens.

16.3. QUALITY ASSURANCE AND MONITORING

Monitoring the clinical investigation at the study site is the responsibility of the monitoring organization through trained and qualified Clinical Research Associates (CRAs).

The monitoring organization will discuss the investigator's patient enrollment prediction at the time of contracting.

Monitoring visits will be performed according to the monitoring plan. During on-site monitoring, the Informed Consent Forms will be checked and a sample of clinical data will be verified against eCRF data. Subject confidentiality will be maintained at all time. Emphasis will be on the complete reporting by the study staff of SAEs.

Each clinical site will be visited several times during the study to ensure a high degree of data quality. These site monitoring visits will be conducted to verify that the data are authentic, accurate and complete, that the safety and rights of subjects are protected, that the study is conducted according to the protocol, and that any other study agreements, GCP and all applicable regulatory requirements are met. The investigator and the head of the medical institution (where applicable) agree to allow the CRA direct access to all relevant documents. It is important that the investigator and the study staff are available during the monitoring visit and possible audits and that sufficient time is devoted to the process. Findings from the review and source documents will be discussed with the investigator.

Remote site monitoring will also be performed to ensure complete quality study data and patient adherence to the protocol. On a regular basis, the monitoring organization will contact each site to discuss the progress of the study with respect to patient enrollment, timely attendance of patients to their follow-up visits and other relevant study aspects such as data query resolution.

Each participating clinic will receive a close-out visit to resolve any outstanding issues and to perform the final source data verification.

There will be regular teleconferences between the Sponsor and the monitoring organization to discuss site management issues.

16.4. QUALITY ASSURANCE AND DATA MANAGEMENT

The data collection will be performed through an eCRF. The investigator or an authorized member of the investigational team must sign all completed eCRFs that require a signature by using an electronic signature (a password will be provided by the data management center at the start of the study).

Clinical data management will be performed in accordance with data cleaning procedures. This is applicable for data recorded in the eCRF as well as for data from other sources (e.g. Holter recordings, TEE/TTEs, ECGs, etc.). Appropriate computer edit programs will be run to verify the accuracy of the database. The investigator will be queried on incomplete, inconsistent or missing data.

17. REFERENCES

1. Heeringa J, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006 Apr;27(8):949-53..
2. Wolf PA, et al. Atrial Fibrillation as an Independent Risk Factor for Stroke: The Framingham Study. Stroke 1999;22:938-8.
3. Benjamin EJ, et al. Impact of Atrial Fibrillation on the Risk of Death: The Framingham Heart Study. Circulation 1998;98:946-52.
4. Camm AJ, Lip GY, De Caterina R et al. Focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J 2012 (doi10.1093/eurheartj/ehs253)
5. Calkins H, Kuck KH, Cappato R et al. HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace 2012, 2012:14528-14606.
6. Haissaguerre M, Hocini M, Sanders P et al. Catheter ablation of long-lasting persistent atrial fibrillation: Clinical outcome and mechanisms of subsequent arrhythmias. J Cardiovasc Electrophysiol 2005; 16: 1138 – 1147.
7. Rostock T, Salukhe TV, Steven D et al. Long-term single- and multiple - procedure outcome and predictors of success after catheter ablation for persistent atrial fibrillation. Heart Rhythm 2011; 8: 1391- 1397
8. Edgerton JR. Total thoracoscopic ablation of atrial fibrillation using the Dallas Lesion Set, partial autonomic denervation, and left atrial appendectomy. Oper Tech Thorac Cardiovasc Surg 2009;14:224-242.
9. Weimar T, Vosseler M, Czesla M, Boscheinen M, Hemmer WB, Doll KN. Approaching a paradigm shift: endoscopic ablation of lone atrial fibrillation on the beating heart. Ann Thorac Surg. 2012 Dec;94(6):1886-92.
10. Pison, L., La Meir, M., van Opstal, J., Blaauw, Y., Maessen, J.G., Crijns, H.J. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. J Am Coll Cardiol, 2012, 60 (1), 54-61.
11. Sherif HM: The developing pulmonary veins and left atrium: implications for ablation strategy for atrial fibrillation. Eur J Cardiothorac Surg 2013.
12. Muneretto C, Bisleri G, Bontempi L, Cheema FH, Curnis A: Successful treatment of lone persistent atrial fibrillation by means of a hybrid thoracoscopic-transcatheter approach. Innovations (Phila) 2012, 7:254-258.
13. Muneretto C, Bisleri G, Bontempi L, Curnis A. Durable staged hybrid ablation with thoracoscopic and percutaneous approach for treatment of long-standing atrial fibrillation: A 30-month assessment with continuous monitoring. J Thorac Cardiovasc Surg. 2012 Oct 11.
14. Dunning J, Nagendran M, Alfieri OR, Elia S, Kappetein AP, Lockowandt U, Sarris GE, Kolh PH, EACTS clinical guidelines committee: Guideline for the surgical treatment of atrial

fibrillation. Eur J Cardiothorac Surg 2013, 44:717-791.
15. Cheema A, Vasamreddy CR, Dalal D, Marine JE, Dong J, Henrikson CA, Spragg D, Cheng A, Nazarian S, Sinha S, Halperin H, Berger R, Calkins H. Long-term single procedure efficacy of catheter ablation of atrial fibrillation. J. Intervent Card Electrophy, 2006;15(3):145-55, Wpuv 2006 Aug 5.
16. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, Lellouche N, Knecht S, Wright M, Nault I, Miyazaki S, Scavee C, Clementy J, Haissaguerre M, Jais P Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up?. J Am Coll Cardiol. 2011 Jan 11;57(2):160-6. doi: 10.1016/j.jacc.2010.05.061.
17. Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck KH, Ouyang F Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy.. J Am Coll Cardiol. 2012 Nov 6;60(19):1921-9. doi: 10.1016/j.jacc.2012.04.060. Epub 2012
18. Cox, J.L., Boineau, J.P., Schuessler, R.B., Kater, K.M., Lappas, D.G.: Five-Year Experience With the Maze Procedure for Atrial Fibrillation. Annals of Thoracic Surgery 56:814-824, 1994.
19. Cox, J.L., Schuessler, R.B., Lappas, D.G., and Boineau, J.P.: An 8 ½ Year Clinical Experience With Surgery for Atrial Fibrillation. Annals of Surgery, 224(3);267-275, 1996.
20. Prasad SM, Maniar HS, Camillo CJ, Schuessler RB, Boineau JP, Sundt TM III, Cox JL and Damiano RJ Jr.: The Cox maze III procedure for atrial fibrillation: Long-term efficacy in patients undergoing lone versus concomitant procedures. Journal of Thoracic and Cardiovascular Surgery, 126:1822-27, 2003.
21. Damiano R, Rochus V. Surgical and minimally invasive ablation for atrial fibrillation. Current Treatment Options in Cardiovascular Medicine. 2006; 8: 371-376.
22. Mack M. Current results of minimally invasive surgical ablation for isolated atrial fibrillation. Heart Rhythm. 2009; 6: S46-S49.
23. Gillinov et al. Surgery for permanent atrial fibrillation: Impact of patient factors and lesion set. Ann Thorac Surg. 2006; 82: 502-514.
24. Han FT, Kasirajan V, Kowalski M, Kiser R, Wolfe L, Kalahasty G, Shepard RK, Wood MA, Ellenbogen KA. Results of a minimally invasive surgical pulmonary vein isolation and ganglionic plexi ablation for atrial fibrillation: single- center experience with 12month follow-up. Circ Arrhythm Electrophysiol. 2009 Aug; 2(4):370-7.
25. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39
26. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation. Europace 2006;8:651-745.
27. Broglio K, Connor J, Berry S; Not too big, Not too Small: A Goldilocks Approach to Sample Size Selection. J Biopharma Stats; Vol 24, 2014 P 685-705

18. LIST OF APPENDICES

18.1. Appendix I. Definitions according to 2012 HRS Consensus Statement
18.2. Appendix II. Modified Rankin Scale
18.3. Appendix III. SF-12v2™ Health Survey Scoring Demonstration
18.4 Appendix IV. EHRA class AF symptoms
18.5 Appendix V. CHA_2DS_2 VASc score

Appendix I

TABLE 1:

TYPES AND CLASSIFICATION OF ATRIAL FIBRILLATION**

Atrial Fibrillation Episode	An atrial fibrillation episode is defined as AF which is documented by ECG monitoring and has a duration of at least 30 seconds, or if less than 30 seconds, is present continuously throughout the ECG monitoring tracing. The presence of subsequent episodes of AF requires that sinus rhythm be documented by ECG monitoring between AF episodes.
Paroxysmal AF*	Paroxysmal AF is defined as recurrent AF (≥two episodes) that terminates spontaneously within 7 days. Episodes of AF of ≤48 hours' duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.
Persistent AF*	Persistent AF is defined as continuous AF that is sustained beyond seven days. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after ≥48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.
Longstanding Persistent AF	Longstanding persistent AF is defined as continuous AF of greater than 12 months' duration.
Permanent AF	The term permanent AF is not appropriate in the context of patients undergoing catheter or surgical ablation of AF, as it refers to a group of patients for which a decision has been made not to restore or maintain sinus rhythm by any means, including catheter or surgical ablation. If a patient previously classified as having permanent AF is to undergo catheter or surgical ablation, the AF should be reclassified.

** It is recognized that patients may have both paroxysmal and persistent AF. A patient's AF type should be defined as the most frequent type of AF experienced within six months of an ablation procedure.* Continuous AF is AF that is documented to be present on all ECG monitoring performed during a defined period of time.

*** We recommend that the term "chronic AF" not be used in the context of patients undergoing ablation of AF as it is ambiguous, and there is no standardized definition of this term.*

TABLE 5:

DEFINITIONS FOR USE WHEN REPORTING OUTCOMES OF AF ABLATION AND IN CLINICAL TRIALS OF CATHETER OR SURGICAL ABLATION OF AF

Acute Procedural Success	Acute procedural success is defined as electrical isolation of all pulmonary veins. A minimal assessment of electrical isolation of the PVs should consist of an assessment of entrance block. If other methods are used to assess PV isolation, including exit block and/or the use of provocative agents such as adenosine or isoproterenol, they should be pre-specified. Furthermore, it is recommended that the wait time used to screen for early recurrence of PV conduction once initial electrical isolation is documented be specified in all prospective clinical trials.
One Year Success*	One year success is defined as freedom from AF/AFL/AT off antiarrhythmic drug therapy as assessed from the end of the 3 months blanking period to 12 months following the ablation procedure.
Clinical/Partial Success*	Clinical/partial success is defined as a 75% or greater reduction in the number of AF episodes, the duration of AF episodes, or the % time a patient is in AF as assessed with a device capable of measuring AF burden in the presence or absence of previously ineffective antiarrhythmic drug therapy.
Long Term Success*	Long term success is defined as freedom from AF/AFL/AT recurrences following the 3-month blanking period through a minimum of 36 months follow-up from the date of the ablation procedure in the absence of Class I and III AAD therapy.
	**When reporting outcomes of AF ablation, the development of atrial tachycardia or atrial flutter should be included in the broad definition of recurrence following AF ablation. All studies should report freedom from AF, atrial tachycardia, and atrial flutter. These endpoints can also be reported separately. All studies should also clearly specify the type and frequency of ECG monitoring as well as the degree of compliance with the prespecified monitoring protocol.*
Recurrent AF	Recurrent AF/AFL/AT is defined as AF/AFL/AT of at least 30 seconds' duration that is documented by an ECG or device recording system and occurs following catheter ablation. Recurrent AF/AFL/AT may occur within or following the post ablation blanking period. Recurrent AF/AFL/AT that

	occurs within the post ablation blanking period is not considered a failure of AF ablation.
Early Recurrence of AF	Early recurrence of AF is defined as a recurrence of atrial fibrillation within three months of ablation. Episodes of atrial tachycardia or atrial flutter should also be classified as a “recurrence.”
Recurrence of AF	Recurrence of AF post ablation is defined as a recurrence of atrial fibrillation more than 3 months following AF ablation. Episodes of atrial tachycardia or atrial flutter should also be classified as a “recurrence.”
Late recurrence of AF	Late recurrence of AF is defined as a recurrence of atrial fibrillation 12 months or more after AF ablation. Episodes of atrial tachycardia or atrial flutter should also be classified as a “recurrence.”
Blanking Period	A blanking period of three months should be employed after ablation when reporting efficacy outcomes. Thus, early recurrences of AF/AFL/AT within the first 3 months should not be classified as treatment failure. If a blanking period of less than 3 months is acceptable and if is chosen, it should be pre-specified and included in the methods section.
Detectable AF	Detectable AF is defined as AF of at least 30 seconds' duration when assessed with ECG monitoring. If other monitoring systems are used, including implantable pacemakers, implantable defibrillators, and subcutaneous ECG monitoring devices, the definition of detectable AF needs to be pre-specified in the clinical trial based on the sensitivity and specificity of AF detection with the particular device. We recommend that episodes of atrial flutter and atrial tachycardia be included within the broader definition of a detectable AF/AFL/AT episode.
Entrance Block	Entrance block is defined as the absence, or if present, the dissociation, of electrical activity within the PV antrum. Entrance block is most commonly evaluated using a circular multielectrode mapping catheter positioned at the PV antrum. Entrance block also can be assessed using detailed point-by-point mapping of the PV antrum guided by an electroanatomical mapping system. The particular method used to assess entrance block should be specified in all clinical trials. Entrance block of the left PVs should be assessed during distal coronary sinus or left atrial appendage pacing in order to distinguish far-field atrial potentials from PV potentials.

Enrolled Subject	An enrolled subject is defined as a subject who has signed written informed consent to participate in the trial in question.
Exit Block	Exit block is defined as the inability to capture the atrium during pacing at multiple sites within the PV antrum. Local capture of musculature within the pulmonary veins and/or antrum must be documented to be present to make this assessment. Exit block is demonstrated by a dissociated spontaneous pulmonary vein rhythm.
Non-ablative Strategies	The optimal non-ablative therapy for patients with persistent and longstanding persistent AF who are randomized to the control arm of an AF ablation trial is a trial of a new class 1 or 3 antiarrhythmic agent or a higher dose of a previously failed antiarrhythmic agent.
Non-Inducibility of Atrial Fibrillation	Non-inducibility of atrial fibrillation is defined as the inability to induce atrial fibrillation with a standardized pharmacologic or electrical stimulation protocol. The stimulation protocol should be pre-specified in the specific clinical trial. Common stimulation approaches include a high dose isoproterenol infusion protocol or atrial burst pacing.
Patient Populations for Inclusion in Clinical Trials	It is considered optimal for clinical trials to enroll patients with only one type of AF: paroxysmal, persistent, or longstanding persistent. If more than one type of AF patient is enrolled, the results of the trial should also be reported separately for each of the AF types. It is recognized that “early persistent” AF responds to AF ablation to a similar degree as patients with paroxysmal AF and that the response of patients with “late persistent AF” is more similar to those with longstanding persistent AF.

CARDIOVERSION AND SURGICAL ABLATION-RELATED DEFINITIONS	
Failed Electrical Cardioversion:	Failed electrical cardioversion is defined as the inability to restore sinus rhythm for 30 seconds or longer following electrical cardioversion.
Successful Electrical Cardioversion	Successful electrical cardioversion is defined as the ability to restore sinus rhythm for at least 30 seconds following cardioversion.
Immediate AF Recurrence Post Cardioversion	Immediate AF Recurrence post cardioversion is defined as a recurrence of AF within 24 hours following cardioversion. The most common time for an immediate recurrence is within 30–60 minutes post cardioversion.

Early AF Recurrence Post Cardioversion	Early AF recurrence post cardioversion is defined as a recurrence of AF within 30 days of a successful cardioversion.
Late AF Recurrence Post Cardioversion	Late AF recurrence post cardioversion is defined as recurrence of AF more than 30 days following a successful cardioversion.
Hybrid AF Surgical Ablation Procedure	Hybrid AF surgical ablation procedure is defined as a joint AF ablation procedure performed by electrophysiologists and cardiac surgeons either as part of a single "joint" procedure or performed as two pre-planned separate ablation procedures separated by no more than six months of time.
Surgical Maze Ablation Procedure	Surgical Maze ablation procedure is defined as a surgical ablation procedure for AF which includes at a minimum the following components: (1) line from SVC to IVC, (2) line from IVC to the tricuspid valve, (3) isolation of the PVs, (4) isolation of the posterior LA, (5) line from MV to the PVs, (6) management of the LA appendage.

MINIMUM AF DOCUMENTATION, ENDPOINTS, AND SUCCESS RATES IN CLINICAL TRIALS	
Minimum Documentation for Paroxysmal AF	The minimum AF documentation requirement for paroxysmal AF is: (1) Physician's note indicating recurrent self-terminating AF; and (2) one electrocardiographically documented AF within 6 months of the ablation procedure.
Minimum Documentation for Persistent AF	The minimum AF documentation requirement for persistent AF is: (1) Physician's note indicating continuous AF ≥7 days but no more than one year; and (2) two electrocardiograms (from any forms of rhythm monitoring) showing continuous AF, with electrocardiograms taken at least 7 days apart.
Minimum Documentation for Longstanding Persistent AF	The minimum AF documentation requirement for longstanding persistent AF is: physician's note indicating at least one year of continuous AF plus a 24-hour Holter within 90 days of the ablation procedure showing continuous AF. The performance of a successful cardioversion (sinus rhythm >30 seconds) within 12 months of an ablation procedure with documented early recurrence of AF within 30 days should not alter the classification of AF as long-standing persistent.

Minimum Effectiveness Endpoint for Patients with Symptomatic and Asymptomatic AF	The minimum effectiveness endpoint is freedom from symptomatic and asymptomatic episodes of AF/AFL/AT recurrences at 12 months following ablation, off antiarrhythmic drug therapy including a prespecified blanking period.
Minimum Chronic Acceptable Success Rate: Paroxysmal AF at 12-month follow-up	If a minimum chronic success rate is selected as an objective effectiveness endpoint for a clinical trial, we recommend that the minimum chronic acceptable success rate for paroxysmal AF at 12-month follow-up is 50%.
Minimum Chronic Acceptable Success Rate: Persistent AF at 12-month follow-up	If a minimum chronic success rate is selected as an objective effectiveness endpoint for a clinical trial, we recommend that the minimum chronic acceptable success rate for persistent AF at 12-month follow-up is 40%.
Minimum Chronic Acceptable Success Rate: Longstanding Persistent AF at 12-month follow-up	If a minimum chronic success rate is selected as an objective effectiveness endpoint for a clinical trial, we recommend that the minimum chronic acceptable success rate for longstanding persistent AF at 12-month follow-up is 30%.
Minimum Follow-up Screening for Paroxysmal AF Recurrence	For paroxysmal AF, the minimum follow-up screening should include: (1) 12-lead ECG at each follow-up visit; (2) 24-hour Holter at the end of the follow-up period (e.g. 12 months); and (3) event recording regularly and at the time of symptoms with an event monitor from the end of the 3-month blanking period to the end of follow-up (e.g. 12 months).
Minimum Follow-up Screening for Persistent or Longstanding AF Recurrence	For persistent and longstanding persistent AF, the minimum follow-up screening should include: (1) 12-lead ECG at each follow-up visit; (2) 24-hour Holter every 6 months; and (3) symptom-driven event monitoring.

TABLE 6:

DEFINITIONS OF COMPLICATIONS ASSOCIATED WITH AF ABLATION

Major Complication:	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.
Serious Adverse Device Effect:	A serious adverse device effect is defined as a serious adverse event that is attributed to use of a particular device.
Atrio Esophageal Fistula:	An atrio esophageal fistula is defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT scan or MRI scan are the most common methods of documentation of an atrial esophageal fistula.
Bleeding:	Bleeding is defined as a major complication of AF ablation if it requires and/or is treated with transfusion or results in a 20% or greater fall in HCT.
Bleeding Following Cardiac Surgery:	Excessive bleeding following a surgical AF ablation procedure is defined as bleeding requiring re-operation or ≥2 units of PRBC transfusion within any 24 hours of the first 7 days following the index procedure.
Cardiac Perforation:	We recommend that cardiac perforation be defined together with cardiac tamponade. See Cardiac Tamponade/Perforation
Cardiac Tamponade:	We recommend that cardiac tamponade be defined together with cardiac perforation. See Cardiac Tamponade/Perforation.
Cardiac Tamponade/Perforation:	Cardiac tamponade/perforation is defined as the development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure. A significant pericardial effusion is one which results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1-cm or more pericardial effusion as documented by echocardiography. Cardiac tamponade/perforation should also be classified as “early” or “late” depending on whether it is diagnosed during or following initial discharge from the hospital.
Deep Sternal Wound Infection/Mediastinitis Following Cardiac Surgery:	Deep sternal wound infection/mediastinitis following cardiac surgery requires one of the following: (1) an organism isolated from culture of mediastinal tissue or fluid; (2) evidence of mediastinitis seen during operation; (3) one of the following conditions: chest pain, sternal

	instability, or fever (>38 °C), in combination with either purulent discharge from the mediastinum or an organism isolated from blood culture or culture of mediastinal drainage.
Esophageal Injury:	Esophageal injury is defined as an erosion, ulceration, or perforation of the esophagus. The method of screening for esophageal injury should be specified. Esophageal injury can be a mild complication (erosion or ulceration) or a major complication (perforation).
Gastric Motility/Pyloric Spasm Disorders:	Gastric motility/pyloric spasm disorder should be considered a major complication of AF ablation when it prolongs or requires hospitalization, requires intervention, or results in late disability, such as weight loss, early satiety, diarrhea, or GI disturbance.
Mediastinitis:	Mediastinitis: is defined as inflammation of the mediastinum. Diagnosis requires one of the following: (1) An organism isolated from culture of mediastinal tissue or fluid; (2) evidence of mediastinitis seen during operation; (3) one of the following conditions: chest pain, sternal instability, or fever (>38°C), in combination with either purulent discharge from the mediastinum or an organism isolated from blood culture or culture of mediastinal drainage.
Myocardial Infarction in the Context of AF Ablation:	The universal definition of myocardial infarction (Thygesen JACC 2007) cannot be applied in the context of catheter or surgical AF ablation procedures because it relies heavily on cardiac biomarkers (troponin and CPK), which are anticipated to increase in all patients who undergo AF ablation as a result of the ablation of myocardial tissue. Similarly, chest pain and other cardiac symptoms are difficult to interpret in the context of AF ablation both because of the required sedation and anesthesia and also because most patients experience chest pain following the procedure as a result of the associated pericarditis that occurs following catheter ablation. We therefore propose that a MI, in the context of catheter or surgical ablation, be defined as the presence of any one of the following criteria: (1) detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB) that persist for more than one hour; (2) development of new pathological Q waves on an ECG; (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Pericarditis:	Pericarditis should be considered a major complication following ablation if it results in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization, or persists for more than 30 days following the ablation procedure.
Phrenic Nerve Paralysis:	Phrenic nerve paralysis is defined as absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis is considered to be permanent when it is documented to be present 12 months or longer following ablation.

Pulmonary Vein Stenosis:	Pulmonary vein stenosis is defined as a reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as mild <50%, moderate 50%–70%, and severe ≥70% reduction in the diameter of the PV or PV branch. A severe PV stenosis should be considered a major complication of AF ablation.
Silent Cerebral Embolism:	Silent cerebral embolism is defined as an occlusion of a blood vessel in the brain due to an embolus that does not result in any acute clinical symptoms. Silent cerebral embolism is generally detected using a diffusion-weighted MRI.
Stroke or TIA Post Ablation:	We agree with the definition for stroke and TIA published by Leon *et al.* in JACC as a standardized definition from the Valve Academic Research Consortium.732
Unanticipated Adverse Device Effect:	Unanticipated adverse device effect is defined as complication of an ablation procedure that has not been previously known to be associated with catheter or surgical ablation procedures.
Vagal Nerve Injury:	Vagal nerve injury is defined as injury to the vagal nerve that results in esophageal dysmotility or gastroparesis. The vagal nerve injury is considered to be a major complication if it prolongs hospitalization, requires hospitalization, or results in ongoing symptoms for more than 30 days following an ablation procedure.
Vascular Access Complication:	Vascular access complications include development of a hematoma, an AV fistula, or a pseudoaneurysm. A major vascular complication is defined as one which requires intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.

*Stroke diagnostic criteria as described in: Leon MB, Piazza N, Nikolsky E, et al. . Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol. 2011;57(3):253-269. Jan 18.

- Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
- Duration of a focal or global neurological deficit ≥24 hours; OR <24 hours if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death
- No other readily identifiable nonstroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)∧
- Confirmation of the diagnosis by at least one of the following: neurology or neurosurgical specialist; neuroimaging procedure (MR or CT scan or cerebral angiography); Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage)
- Stroke definitions
    - Transient ischemic attack: new focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), always within 24 hours; neuroimaging without tissue injury
    - Stroke: (diagnosis as above, preferably with positive neuroimaging study);

- Minor—modified Rankin score <2 at 30 and 90 days
- Major—modified Rankin score ≥2 at 30 and 90 days

∧Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.

From: 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. Reference number 5.

AtriCure

Appendix II

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____

Rater Name: _____

Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

References

Rankin J. "Cerebral vascular accidents in patients over the age of 60."
Scott Med J 1957;2:200-15

Bonita R, Beaglehole R. "Modification of Rankin Scale: Recovery of motor function after stroke."
***Stroke* 1988 Dec;19(12):1497-1500**

Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. "Interobserver agreement for the assessment of handicap in stroke patients."
***Stroke* 1988;19(5):604-7**

AtriCure

Appendix III

SF-12v2™ Health Survey Scoring Demonstration

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

---

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

---

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
b	Climbing <u>several</u> flights of stairs	○	○	○

---

3. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	<u>Accomplished less</u> than you would like	○	○	○	○	○
b	Were limited in the <u>kind</u> of work or other activities	○	○	○	○	○

---

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	<u>Accomplished less</u> than you would like	○	○	○	○	○
b	Did work or activities <u>less carefully than usual</u>	○	○	○	○	○

AtriCure

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

---

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Have you felt calm and peaceful?	○	○	○	○	○
b	Did you have a lot of energy?	○	○	○	○	○
c	Have you felt downhearted and depressed?	○	○	○	○	○

---

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

Thank you for completing these questions!

Score the survey | Reset the survey form

Appendix IV

Modified EHRA (mEHRA) classification

mEHRA score	Symptoms	Description
1	None	
2a	Mild	Normal daily activity not affected, symptoms not troublesome to patient
2b	Moderate	Normal daily activity not affected but patient troubled by symptoms
3	Severe	Normal daily activity affected
4	Disabling	Normal daily activity discontinued

Underlined text represents the modification to the original descriptions of EHRA classes.

From: The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P, Gupta D. Europace. 2014 Jul;16(7):965-72.

Appendix V

CHADS2 – VASc Score		
C	Congestive Heart Failure	1
H	Hypertension (>140/90 mmHg)	1
A	Age ≥ 75	2
D	Diabetes Mellitus	1
S_2	Prior TIA or stroke	2
V	Vascular disease (MI, aortic plaque etc)	1
A	Age 65-74	1
Sc	Sex category (Female = 1 pt)	1

From: Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Chest. 2010 Feb;137(2):263-72.