

Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation – the CAPTAF trial

a randomized multicentre study comparing atrial fibrillation ablation strategy with optimized conventional pharmacological strategy after 12 months follow-up.

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1 Committees and Boards

1.1 Steering Committee

The steering committee will provide scientific leadership for the conduct of the study. It is composed of a principal investigator, three co-chairs, and country centre investigators. The committee will oversee the conduct and execution of the trial, and set the agenda for the steering committee.

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1.2 Study Coordinators

1.3 Data Safety Monitoring Board (DSMB)

The DSMB will be responsible for patient safety but will not perform a regular monitoring of patient safety, except for serious adverse events, related to the different treatment allocations since all treatments used are regarded as clinical routine.

Members of the committee, see separate list.

1.4 Adjudication Committee

This committee is established for the blinded adjudication of the following secondary events: serious adverse events, hospitalization classifications, composite morbidity and its classification.

The committee will report to the steering committee. Records of all adjudication decisions and of adjudication committee minutes will be maintained. The committee will work under the principals of the PROBE-design (Prospective Randomized Open trial with Blinded Evaluation of outcomes).

The procedures used to reduce the potential for bias in the reporting and assessment of the primary and secondary outcome events are:

1. The primary and secondary outcomes of the study will be based on objective documentations.
2. Outcome events stated above are adjudicated by blinded adjudication experts. Each event will be evaluated by more than one adjudicator.

Members of the committee, see separate list.

2 PROTOCOL SYNOPSIS

Objectives To compare the efficacy of 2 treatment strategies, catheter ablation of atrial fibrillation (AF) versus optimized conventional pharmacological therapy, in pat with symptomatic AF.

Study design Randomized, prospective, controlled, open -label multicentre, parallel-group study.

Sample size 250 patients (125 per regimen)

Inclusion criteria • Patients aged 30-70 years with symptoms related to AF (diagnosed for more than 6 months and at least one AF episode documented on ECG during the previous 12 months), who have failed or been intolerant to at least one anti-arrhythmic drug (Vaughan Williams class I - III), with occurrence of at least one symptomatic paroxysmal AF episode during the previous 2 months or at least 2 symptomatic episodes of persistent AF in the previous 12 months (sinus rhythm maintained for at least 1 hour after cardioversion).

Exclusion criteria • Patients who have tested 2 or more anti-arrhythmic drugs for rhythm control, AF secondary to transient or correctable abnormality, uncontrolled hypertension, valvular disease requiring anticoagulation, planned valve surgery within 2 years, contraindication to treatment with anticoagulants, heart failure (NYHA class III o-IV) or LVEF \leq 35 %, left atrial diameter > 60 mm, unstable angina or acute myocardial infarction within the last 3 months, cardiac revascularization procedure within the last 6 months, prior cardiac surgery or planned cardiac corrective surgery within 1 year, prior AF ablation procedure, appropriate vascular access is precluded, renal failure requiring dialysis or liver function abnormalities, participant in another clinical trial, pregnancy, unwilling/unable to give informed consent or inaccessible for follow-up, predictable limited compliance and active abuse of alcohol or other drug.

Endpoints Primary endpoint: general health-related quality of life at 12 months follow-up

Secondary endpoints: morbidity and mortality as composite outcome (ischemic and hemorrhagic stroke, systemic embolic events, TIA, major bleeding, cardiovascular hospitalizations, pacemaker

implantation, all cause death), cardiovascular hospitalization, symptoms, left ventricular heart failure, left atrial and ventricular function and diameters, exercise capacity, health care economics, rhythm, successful versus failed treatment, warfarin treatment, further interventions, safety outcome parameters and frequency of withdrawals and “cross-overs” over time.

Treatment schedule Patients will be randomly assigned to receive: an antiarrhythmic drug (for rhythm or rate control) or undergo left atrial catheter ablation.

Evaluation of response is scheduled at 12, 24, 36 and 48 months of follow-up, while health economy will be evaluated at 24 and 48 months of follow-up. All endpoints will be evaluated at last visit before any cross-over. In case of documented disease progression or unacceptable toxicity, subjects will be switched to the alternative regimen.

Statistical analysis The main statistical analysis of the primary endpoint will be based on the intention-to-treat (ITT) population

Trial duration: 48 months.

3 ABBREVIATIONS

AC	Anticoagulants	LA	Left atrial
ACE	angio converting enzyme	Lab tests	Laboratory tests
AEs	Adverse Events	LA	Left atrial
ARB	angiotensin receptor blockers	LAA	Left atrial appendage
AV	Atrio-ventricular	Lad	Left atrial diameter
AVNRT	AV nodal reentry tachycardia	LF	Low Frequency
BNP	Brain natriuretic phactor	LOE	Level Of Evidence
BP	Blood pressure	LV	Left ventricular
bpm	beats per minute	LVEDd	LV End-diastolic diameter
BSA	Body Surface Area(m ²) = 0.007184 x Height(cm)0.725 x Weight(kg)0.425	LVESd	LV End-systolic diameter
CAGB	Coronary artery by pass surgery	LVH	Left ventricular hypertrophy
CRT	Cardiac resynchronization therapy	LVM	left ventricular mass
CS	coronary sinus	mo	Month
CT	Computer Tomography	MRI	Magnetic resonance imaging
CV	Cardioversions	ms	milliseconds
DAP	dose-area product	NYHA	New York Heart Association
DMP	Data Management Plan	PM	Pacemaker
DRSQ	Disease Related Symptom Questionnaire	PP	Per protocol
DVP	Data Validation Plan	PV	Pulmonary Vein
EBT	Exercise bicycle test	PVI	Pulmonary vein isolation
eCRF	electronic CRF	PWT	posterior wall thickness
ECG	Electrocardiogram	QoL	Quality of life
EF	Ejection fraction	RA	Right atrial
EHRA	European Heart Rhythm Association	RF	Radiofrequency
EHRA SC	EHRA symptom classification	SAB	Subarachnoidal bleeding
EQ 5D	EuroQol 5D	SAEs	Serious adverse events
ESC	European Society of Cardiology	SAP	Statistical Analysis Plan
FU	Follow up	SD	Standard Deviation
GI	Gastrointestinal	SF 36	Short Form-36
HF	Heart failure	SR	Sinus rhythm
HR	Heart rate	SSQ	Symptom Severity Questionnaire
HRV	Heart Rate Variability	SVT	Supraventricular tachycardia
ICDs	Implantable Cardioverter Defibrillators	TEE	Transesophageal echocardiograms
ICM	Implantable Cardiac Monitor	TIA	Transient ischemic attack
IECG	Intracardiac electrogram	TP	Total Power
INR	International normalized ratio	TSH	Thyroid stimulating hormone
ITT	Intention to treat	w	week
IVST	interventricular septal thickness	VW	Vaughan Williams

4 INTRODUCTION

4.1 Background

4.2 Previous therapy trials in patients with atrial fibrillation

4.3 Rationale for performing the study

See separate chapter

5 PATIENT SELECTION AND BACKGROUND POPULATION

5.1 Logbook

Patients fulfilling clinical criteria for catheter ablation but who are not eligible for the study will be monitored separately in a logbook, defining inclusion and exclusion criteria. The patients will undergo baseline evaluation parameters, and followed with regard to treatment strategy and rhythm by 12 lead ECG at 12 months.

5.2 Background population

In order to evaluate the size of the AF population that potentially would benefit from AF ablation, AF patients seeking acute medical care (at emergency rooms, outpatient clinics) or are referred for antiarrhythmic treatment of AF at hospitals will be monitored in a CAPTAF registry. Baseline parameters will be registered including symptoms (symptom severity score) and the EQ 5D questionnaire.

6 STUDY OBJECTIVES

The objective of the CAPTAF multicentre, randomized, open-label study is to compare the effects of two treatment strategies, catheter ablation of atrial fibrillation (AF) versus optimized conventional pharmacological therapy, in patients with symptomatic AF.

6.1 Primary objective

The primary hypothesis is that catheter ablation of atrial fibrillation is superior to optimized conventional pharmacological therapy, in improving general health-related quality of life (QoL) at 12 months follow-up, in patients with symptomatic AF.

6.2 Secondary objectives

The secondary objectives are to compare the two treatment strategies with respect to a number of prospectively defined variables. These are:

- 1) Quality of life determined by standardized questionnaires (SF 36, EQ 5D)
- 2) Symptoms (Symptom Severity Questionnaire, Disease Related Symptom Questionnaire, EHRA Symptom Classification)
- 3) Morbidity and mortality as composite outcome (ischemic and hemorrhagic stroke, systemic embolic events, TIA, major bleeding, cardiovascular hospitalizations, pacemaker implantation, all cause death).
- 4) Cardiovascular hospitalization
- 5) Successful versus failed treatment
- 6) Recurrence of episodes of atrial fibrillation

- 7) AF burden (symptomatic and asymptomatic episodes)
- 8) Left ventricular heart failure
- 9) Left ventricular function and diameters
- 10) Left and right atrial function and diameters
- 11) Exercise capacity.
- 12) Health economics
- 13) AF profile
- 14) Frequency of withdrawals and change of treatment group over time
- 15) Further interventions.
- 16) Safety outcome parameters.

Evaluated at 12, 24, 36 and 48 months of follow-up.

All endpoints will be evaluated at last visit before change of treatment.

A substudy (on treatment analysis) will determine whether sinus rhythm obtained by AF ablation is superior to sinus rhythm obtained by pharmacological therapy, and whether sinus rhythm obtained by either strategy is superior to atrial fibrillation with regard to QoL, exercise capacity, morbidity (as composite outcome), cardiovascular hospitalizations, safety and health economy.

Other substudies are detailed in Appendix I.

7 STUDY POPULATION

7.1 Inclusion criteria

1. Age: 30-70 years.
2. Patients with symptoms related to AF, who have failed or been intolerant to at least one drug used for either rate or rhythm control (Vaughan Williams class I, II, or III anti-arrhythmic drug) thus excluding digitalis and Ca channel inhibitors.
3. The first diagnosis of AF must have been first noted more than 6 months prior to consideration.
4. At least one AF episode documented on 12-lead ECG or 2-channel telemetry/Holter recording during the previous 12 months.
5. Paroxysmal AF (AF is self-terminating within 7 days of recognized onset) with occurrence of at least one symptomatic episodes (patient history) in the previous 2 months that merits non-pharmacological intervention (see classification), or
6. Persistent AF (AF is not self-terminating within 7 days or is terminated electrically or pharmacologically) with occurrence of at least 2 symptomatic episodes of AF in the previous 12 months, necessitating pharmacological or electrical cardioversions (CV), on or off antiarrhythmic drugs that merits non-pharmacological intervention. Upon cardioversion, it must be documented that sinus rhythm can be maintained for at least 1 hour, to distinguish from permanent AF. (see classification).

7.2 Exclusion criteria

1. Patients who have tested 2 or more anti-arrhythmic drugs for rhythm control at highest tolerable dosages (Vaughan Williams class I or III anti-arrhythmic drug; flecainide, propafenone, disopyramide, sotalol or amiodarone).
2. AF secondary to a transient or correctable abnormality including electrolyte imbalance, trauma, recent surgery, infection, toxic ingestion, and uncontrolled thyroid disease.

3. Atrial fibrillation episodes triggered by another uniform SVT, i.e. AVNRT, atrial flutter or atrial tachycardia, including those with preexcitation syndrome.
4. Untreated or uncontrolled hypertension
5. Valvular disease requiring chronic anticoagulation or planned valve surgery within 2 years.
6. Contraindication to treatment with Warfarin or other anticoagulants.
7. Heart failure with NYHA class III or IV or left ventricular ejection fraction (LVEF) $\leq 35\%$, which is not secondary to AF with inadequate rate control, according to the judgement of the investigator.
8. Left atrial diameter > 60 mm.
9. Unstable angina or acute myocardial infarction within last 3 months.
10. Cardiac revascularization procedure within last 6 months.
11. Prior cardiac surgery or planned cardiac corrective surgery within 1 year.
12. Prior AF ablation procedure
13. Implantable cardioverter-defibrillator, CRT device, Dual chamber- and VVI-pacemaker if needed for VVI pacing, as well as AV block II-III and sustained ventricular tachyarrhythmias.
14. Patients with intra-atrial thrombus, tumor, or another abnormality in whom transseptal catheterization or appropriate vascular access is precluded.
15. Renal failure requiring dialysis or abnormalities of liver function tests
16. Participant in investigational clinical or device trial.
17. Pregnant women.
18. Unwilling or unable to give informed consent or inaccessible for follow-up. Specify if ICM was not accepted by the patient to be implanted.
19. Psychological problem that might limit compliance.
20. Active abuse of alcohol or other substance which may be causative of AF and/or might affect compliance.

Note: AAI, DDD or VVI pacemaker are not exclusion criteria provided there is no need for VVI pacing.. Prior radiofrequency catheter ablation of other supraventricular tachycardia is not an exclusion criterion. A waiting period of at least 6 months is required after such procedure, before entry into the present trial.

All patients are required to sign an informed consent form approved by the local ethical committee.

8 STUDY DESIGN

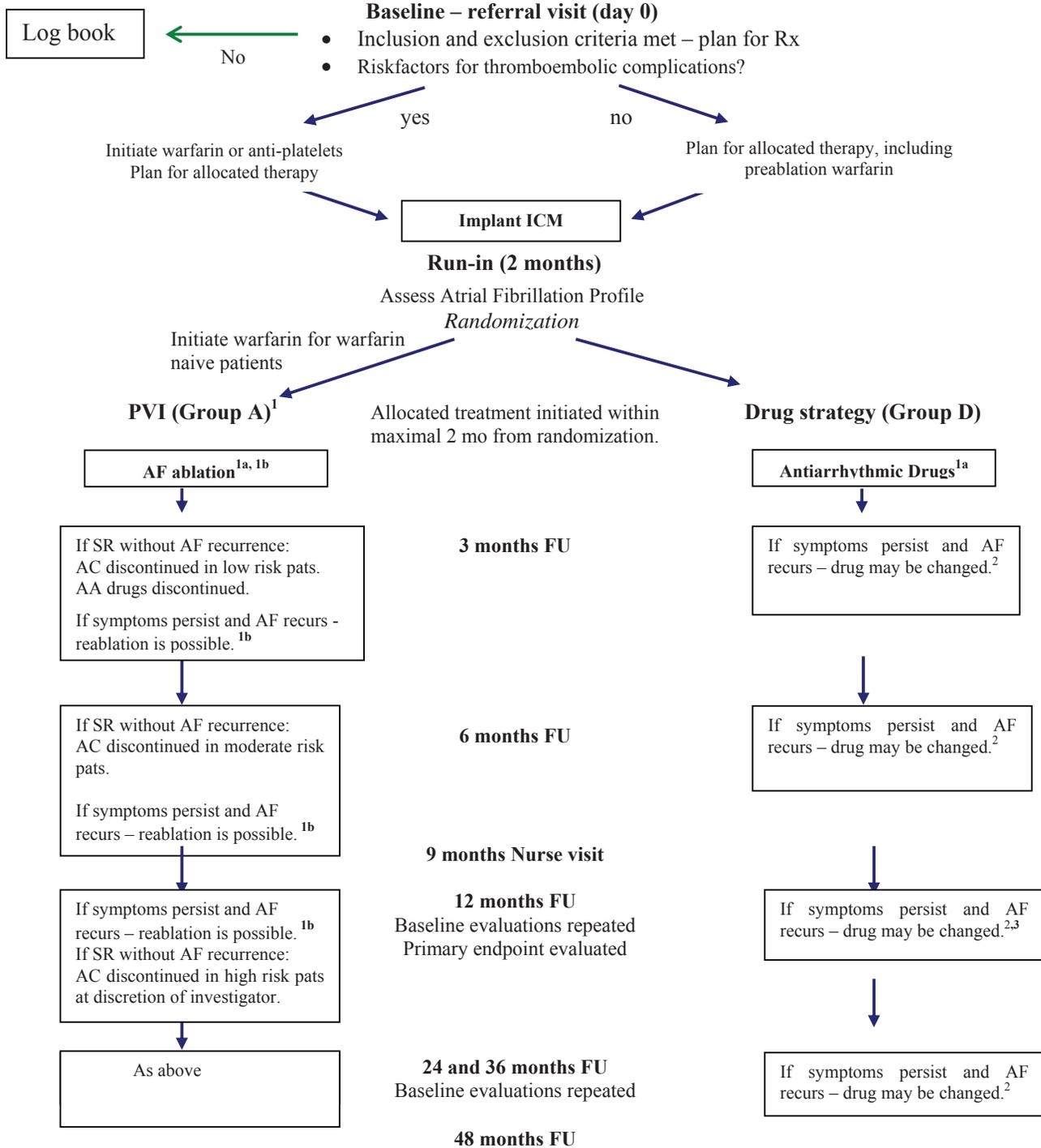
The study is a randomized, open-label, multi-centre trial in which patients with AF will be randomized to receive either catheter ablation of AF or conventional pharmacological therapy.

It is anticipated that 5 or more centres will enter this study. Each centre will register at least 20 patients for a total of 250 patients.

Patients who fulfil all the inclusion criteria and in whom there is no exclusion criterion will be randomized to one of the treatments.

In case of intolerable symptomatic atrial fibrillation despite allocated treatment, subjects will be switched to the alternative regimen, on patient's request.

Study Flow Chart



^{1a}Start allocated therapy within maximal 2 months after randomization.. ^{1b}Re-ablation within 4 weeks after decision for reablation, but earliest 3 months after latest procedure. ²If symptoms persists and worsens due to AF recurrence – antiarrhythmic drug may be changed at earliest 1 month after drug initiation, and for amiodarone at earliest 3 months after initiation. ³Anticoagulants may be discontinued in risk pats if maintenance of sinus rhythm is documented. Abbreviations: AC=Anticoagulants.

8.1 FLOW CHART OF EXAMINATIONS

SCHEDULE				Visit 0		ICM visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Hospital/Outpatients visits	Base-line 0	Start Run-in 0-1 w	Stop Run-in 8-9 w	Abl/Drug Rx starts max 2 m from random.	Dis-charge post abl /drug	4 weeks postabl. /post-drug	3 m ± 2 w	6 m ± 2 w	9 m [□] ± 2 w	12 m ± 2 w	18 m ± 2 w	24 m ± 2 w	30 m ± 2w	36 m ± 2 w	48 m ± 2 w
Medical history	X			X	X		X	X	X	X	X	X	X	X	X
Clinical events	X			X	X		X	X	(X)	X	X	X	X	X	X
Clinical evaluation	X						X	X		X	X	X	X	X	X
AF evaluation							#	#		#	#	#	#	#	#
#AF profile, CHADS2	#						#	#		#	#	#	#	#	#
#EHRA SC, #Pat estimate	#		#				#	#		#	#	#	#	#	#
Physical examination, (vital signs, physical examination)	X						X	X		X	X	X	X	X	X
Concom. & AF Medication	X				X		X	X	X	X	X	X	X	X	X
Informed Consent	X														
Inclusion/Exklusion	X														
Randomization			X												
Lab. tests*	X						X	X		X		X		X	X
12 lead ECG analysis	X			X	X		X	X	X	X	X	X	X	X	X
24 h Holter	X							X		X		X		X	X
Patient Event Report		X	X			X	X	X	X	X	X	X	X	X	X
ICM transmission, I=implantation		I [□]	2 mo		X [□] 3 y	X ^{□□}	□	□	□	□	□	□	□	□	
Exercise test	X									X		X		X	
Echocardiography	X									X		X		X	X
QoL-SF 36, EQ 5 D	X							X		X		X		X	X
DRSQ, SSQ	X							X		X		X		X	X
CT/MRI			A					A:6-12m							

Abbreviations: QoL=Quality of Life, SSQ=Symptom Severity Questionnaire, DRSQ=Disease Related Symptom Questionnaire, CT= Contrast Tomography, MRI=Magnetic Resonance Imaging, EHRA SC=EHRA symptom classification. Lab. tests=Laboratory tests, A=for group A patients only, ICM =Implantable Cardiac Monitor. □=nurse visit, mo=month, w = week, Pat = Patient. *Lab. tests include Hb, leukocytes, trombocytes, liver tests, thyroid tests. NT pro BNP, CRP and plasma sample for future use.

8.2 Run-in

All patients will be monitored during a two month “Run-in” period from which the basic AF burden will be defined, which will provide an objective basis to assess the efficacy of the randomized strategy. The EHRA SC and the patient estimate of frequency and duration of symptomatic episodes will also be assessed after the run-in period and at each follow-up visit. The assessments will refer to the immediate past follow-up period.

8.3 Randomization

Patients with symptomatic paroxysmal or persistent AF (=strata) will be randomized after run-in to one of two management strategies, either AF ablation, Group Ablation (A) or optimized pharmacological therapy, Group Drug (D). Randomization is chosen after run-in to eliminate effects on the run-in monitoring. Patients randomized to ablation therapy and who are not already on warfarin will be initiated on warfarin with INR values between 2 - 3 for at least 4 weeks prior scheduled ablation.

8.4 Allocated therapy

The allocated therapy should be initiated or performed within two months after randomization for all patients.

8.5 Follow-up

After initiation of randomized therapy, patients will be seen at 3, 6, 12, 18, 24, 30, 36 and 48 months, in the absence of interim events (see 8.1). A nurse visit will be scheduled at 9 months FU for recording of adverse events and retrieval of data from the ICM.

8.6 Definitions of withdrawals from study

- A supraventricular reentry tachycardia or a focal atrial tachycardia as the trigger mechanism of AF, not detected prior inclusion.
- Withdrawal of consent
- Patient lost to follow-up before 12 months
- Patients developing serious disease states or conditions that impose a discontinuation in the study as judged by the investigator. The decision of withdrawal should in these cases be discussed with the Steering committee.
- Violation of the protocol if a continued participation is medically unjustified. A withdrawal will, for example, be justified if a patient’s medical condition (other than atrial fibrillation) requires life-long anticoagulation therapy.

During visits, the QT interval on the ECG will be measured; if the QTc interval reach > 500 ms, or t1he QT prolongation exceeds 50 ms after drug initiation, the study drugs will be titrated downward. Inability to bring the QTc interval in a range < 500 ms will lead to the withdrawal of the drug, and recorded as adverse event.

Patients developing intolerable adverse reactions will be treated individually with dose reduction or change of drug. Temporary discontinuation of the allocated drug therapy is permitted for a period of 30 days, but permanent discontinuation is imposed if Torsades de Pointes, pulmonary toxicity, persistent liver function abnormalities, or heart failure or bronchospasm attributable to the study drugs develop in any patient. Patients who require coronary artery bypass surgery (CAGB) or pacemaker (PM), or patients who develop reduced thyroid function during the study, will be treated as deemed necessary and not withdrawn.

9 STUDY TREATMENTS

9.1 Left Atrial Catheter Ablation (Group A)

Catheter ablation will be performed at earliest convenience, but latest within two months after randomization. The ablation strategy will consist of pulmonary vein isolation (PVI) as follows:

- Transvenous catheter ablation of the left atrium for paroxysmal AF.
- Transvenous catheter ablation of the left atrium for persistent AF.
- Epicardial off-pump ablation may be offered after failed attempts of transvenous catheter ablation at earliest 3 months after latest procedure at the discretion of the investigator.

A linear lesion may be deployed at the LA roof in patients with AF recurrence after a first procedure or primarily for patients with persistent AF only. A 2nd transvenous ablation procedure may be undertaken at earliest 3 months after the first procedure, if symptoms persists or recurs. It should be performed without delay within the next 4 weeks. The follow-up schedule remains as planned for after the 1st ablation procedure, so that the time for follow-up will remain the same in both treatment groups.

Recurrence of atrial fibrillation should be documented on ECG and evaluated at earliest during the 3rd month after an ablation procedure. If the AV conduction during an atrial tachycardia is regular it should be confirmed on an ECG tracing with at least 2 leads.

In case the 2nd transvenous ablation procedure fails, patients may be offered i) a 3rd transvenous ablation procedure or ii) an epicardial off-pump PVI, according to the same rules for documentation of AF recurrence and time for intervention as defined for the 2nd procedure. In case the patient declines a 3rd intervention despite recurrence of AF, the patient should continue on the same anti-arrhythmic drugs. If new previously untested drugs are prescribed, the patient will be defined as a change of treatment (and failed ablation).

Epicardial off-pump procedures may not be repeated. If an epicardial procedure fails, patients may be offered i) repeat transvenous catheter ablation, or ii) anti-arrhythmic drugs as described above. Documentation of AF recurrence is required as described above.

9.1.1 Pre Ablation Management

All patient should be treated with warfarin for at least 4 weeks prior to the ablation procedure (INR > 2.0). Warfarin should be discontinued long enough before the procedure to anticipate an INR less than 1.8 at the time for catheterization. For most patients with a therapeutic INR of 2-3, this will mean stopping the warfarin approximately 3 days prior to the procedure.

Heparin or low-molecular heparin will be given 1-2 days prior to the ablation procedure when INR is anticipated to be < 2, and stopped 4 hours and 24 hours, respectively, prior to the intervention. Antiarrhythmic agents should be continued.

Preprocedure transesophageal echocardiograms (TEE) will be performed 1-2 days prior to the procedure, to exclude atrial mural thrombus or other structural contraindications to the procedure.

Contrast Tomography (CT) or Magnetic Resonance imaging (MRI) will be done prior to the ablation procedure to evaluate pulmonary vein diameters and esophagus anatomic position in relation to LA posterior wall.

Laboratory tests (Hb, leukocytes, trombocytes, CRP, electrolytes, creatinine, and INR), will be taken 1-2 days prior to the procedure, according to clinical routine.

9.1.2 Left Atrial Mapping and Ablation techniques

- Mapping Device: CARTO, NAVIX, LASSO-like or Basket catheter.
 - Energy source: Radiofrequency (RF) or cryo-energy,
 - Ablation Catheter: RF irrigated, 4 mm tip temperature control (thermocouple, thermistor; open or closed) or Freezer max/cryoballoon catheter.
 - Endpoint for ablation: Electrical isolation of all pulmonary veins
 - RF energy applications: Temperature-controlled mode, via distal electrode in unipolar fashion to a cutaneous ground patch.
Power limit of 25-35 W (25 W at LA posterior wall),
Temperature 50°C.
Irrigation rate of 20 ml/min (Cool Flow Pump)
Application duration: 20-30 seconds at each site (max 10 seconds posterior sites close to esophagus).
- at
- Cryo energy applications: Cryoduration of 4 - 5 minutes / application

A single linear lesion is comprised of a series of “standard” focal ablation lesions or using the dragging technique. Areas of the lesion suspected of being incomplete will be repeated after initial lesion assessment.

End points of ablation are complete entrance block into the pulmonary veins (PV). All PVs should be targeted for isolation. Preferably isolate the PV orifices by encircling them in pairs with one single complete linear lesion. A contiguous line of ablation lesions joining the superior PVs (LA roof line) may be performed if PAF recurs after a first procedure or primarily for persistent AF only.

Different mapping techniques are permitted. Each centre is requested to adhere to only one of the mapping techniques for each type of AF. The choice of ablation technique should be predefined at study start.

Briefly, 2-10 polar 5□6 F catheters are placed in the coronary sinus (cs) and right ventricular apex. Following transseptal puncture, intravenous heparin is administered and adjusted to maintain an activated clotting time 250-350 sec for the duration of the procedure. ACT levels should be checked every 30 minutes. Contrast injection to visualize the PV is optional.

For patients with AF at the beginning of the procedure electrical cardioversion or conversion with ibutilide infusion is desired.

9.1.2.1 Circular LASSO-like mapping and ablation

The 10-20 pole ring circular mapping catheter will be placed in the pulmonary veins and slowly dragged out, and its location while in the PV will be recorded. Electrograms from the circular catheter will be recorded at the ostia of the PVs.

The ablation catheter will be introduced either through the same or a separate transseptal puncture. The ablation catheter is placed 2 to 4 cm into each PV and slowly pulled back using fluoroscopy. The PV ostium/PV-LA junction is defined as the site where the ablation catheter tip “jumps” from its tract into the LA with the appearance of atrial potential.

9.1.2.1.1 Ablation

PV isolation should be performed by applying RF energy at ostial sites (at which the earliest bipolar PV potentials and/or unipolar electrograms with the most rapid intrinsic deflection are recorded) or as linear circumferential lines.

For patients who are in sinus rhythm, IECG should be recorded during continuous distal cs pacing at a cycle length of 500 to 600 ms for left PV analysis and during sinus rhythm or right atrial pacing for right PV analysis.

PV isolation should be confirmed by excitation analysis with block into veins and disappearance/dissociation of PV potentials.

9.1.2.2 Real-time 3D LA maps and ablation

The left atrial geometry will be mapped using a nonfluoroscopic navigation system (CARTO, Biosense Webster or NAVIX Endocardial Solution system).

The mapping /ablation catheter will be introduced into the left atrium via a transseptal approach. The ablation catheter will be placed in the PVs, slowly dragged out, and its location while in the PV will be recorded, and serve for the PV tags.

The mapping catheter is placed 2 to 4 cm into each PV and slowly pulled back, using fluoroscopy. The PV ostium/PV-LA junction will be defined as the site where the catheter tip “jumps” from its tract into the LA with the appearance of atrial potential, which will be marked on the map.

Mapping of the LA will be performed with care taken not to acquire locations within the PVs. The anatomical map is acquired as routinely done at each laboratory. Points will be acquired on the left lateral wall of the atrium including sites around the LA appendage.

For patients who are in sinus rhythm at the beginning of the procedure, maps should be acquired during continuous cs pacing at a cycle length of 500 to 600 ms.

For patients in AF, maps are acquired with a point sampling time that allows the technician to obtain a reliable anatomic map for lesion deployment.

9.1.2.2.1 Ablation

Circumferential lines are created with contiguous RF lesions at a distance >5 mm from the PV ostia. A single circular line around 2 ipsilateral veins is created until PV isolation is achieved. Lesion deployment will take place during sinus rhythm (SR) atrial pacing (CS) or atrial fibrillation. The ablation lines will be designed using the tagged map.

After completion of ablation, the pre-RF anatomic map is used to acquire new points, with the purpose of comparing pre-RF and post-RF maps.

The end goal of the ablation procedure is to achieve a complete PV antrum isolation of the left atrium.

Lesion completeness during applications may be judged by electrogram amplitude reduction or LAT block between contiguous points lying in the same axial plane across the line (see below).

9.1.3 Lesion Assessment Technique

It is critical that lesions be assessed for completeness.

9.1.3.1 Postablation control of PVI using electrical mapping

Following ablation of all PV, electrograms from each PV should be acquired. Lesions should be assessed during distal CS pacing for left PV and during SR/right atrial pacing for right PV.

The electrograms should be examined for conduction block/dissociation. A complete linear lesion will be defined by *documenting* PV entrance block in each vein using a circular mapping catheter.

9.1.3.2 Postablation control of PVI using anatomical mapping

Following the ablation the CARTO ReMAP feature may be activated. During re-mapping of the atrium, electrograms may be acquired from sites adjacent to the ablation line. Lesions

should, however, be assessed during atrial pacing and SR as described under 9.1.3.1. The electrograms should be examined for conduction block/dissociation. A complete linear lesion will be defined by *documenting* PV entrance block as described under 9.1.3.1.

9.1.3.3 Postablation control of complete roof line block

Evaluation of complete linear block should be performed after the restoration of sinus rhythm to allow pacing of the anterior LA adjacent to the line. Anterior LA pacing can be achieved by pacing the LA appendage or the distal CS advanced to the anterior aspect of LA. Linear block should be confirmed and documented by either i) demonstration by point-by-point mapping of an online corridor of double potentials along the entire length of the roof during pacing of the anterior LA; or ii) demonstration of an activation detour circumventing the right and left PVs to activate caudocranially the posterior wall with no conduction through the LA roof.

9.1.4 Reablation

Patients of Group A in whom therapy for AF failed will be offered a repeat ablation procedure. Lesions will be delivered only following re-mapping of the previously treated PV with a circular mapping catheter for assessing ablation line completeness.

9.1.5 Fluoroscopy exposure

The cumulative dose-area product (DAP, expressed in Gy.cm²) (defined at each centre) will be recorded for each plane in case a biplane lab is used. The extra exposure during an additive tricuspid isthmus ablation will be included but recorded separately, starting from the introduction of flutter catheters.

Effective dose calculations will also include any radiation resulting from pre- or post-cardiac or brain imaging.

9.1.6 Post Ablation Management

Activated clotting time levels should be checked and recorded prior to the withdrawal of the catheters to reduce bleeding complications. Patients will be monitored for at least 24 hours after the procedure. In the absence of contraindications, heparin or low-molecular heparin will be started after leaving the laboratory. The heparin infusion rate will be increased to a rate anticipated to provide full systemic anticoagulation (APTT 60-90 seconds). Heparin or low-molecular heparin will be maintained until an INR greater than 2 is reached with warfarin. Oral anticoagulation therapy – see specific heading.

All antiarrhythmic agents should be continued during and after the procedure.

CT or MRI (optional at follow-up but should be stated for each centre) at 6-12 months follow-up after last ablation procedure to visualize post-procedural PV stenosis.

9.1.7 Epicardial Off-pump pulmonary vein isolation technique

See appendix B.

9.2 Antiarrhythmic Drug therapy (Group D)

Anti-arrhythmic drugs remaining to be tested for rate and rhythm control should be defined at baseline, which may include previously tested tolerable antiarrhythmic drugs if dosages were inadequate. Study drug will be initiated within 2 months after the randomization.

The initiation and choice of anti-arrhythmic drug types and dosages should be according to published guidelines on atrial fibrillation (appendix A). Each study centre is obliged to use an adequate dosage of each anti-arrhythmic drug.

Optimized anti-arrhythmic drug therapy includes testing of all available anti-arrhythmic drugs at adequate dosages, including amiodarone 600 mg once daily for 7-10 days, and 100-200 mg once daily thereafter; sotalol: 80-160 mg twice daily; flecainide 100 to 150 mg twice daily or the entire dose as slow-release formula once daily; propafenone 300 mg twice daily; and disopyramide 250-375mg twice daily, and potentially new antiarrhythmic drugs commercially available during the study period. A change of drug regime should be guided by the patient's symptoms and undertaken at earliest one month after the initiation of last drug, except for amiodarone which should be evaluated for at least 3 months after initiation, to ensure adequate steady state and efficacy.

A previously not tested anti-arrhythmic drug may be initiated following cardioversion. In the case of a late recurrence of AF, the same antiarrhythmic drug regimen may be continued at the discretion of the investigator.

Rate control should be achieved with the administration of a beta-blocker, a nondihydropyridine calcium-channel blocker, or digitalis, alone or in combination. The target is a heart rate of 60-80 beats per minute at rest and 90 to 115 beats per minute at moderate exercise. If patients have intolerable symptoms due to atrial fibrillation, unacceptable adverse effects of atrioventricular-node-blocking drugs, or progressive left ventricular dysfunction despite treatment (i.e., tachycardia-induced cardiomyopathy), atrioventricular-node ablation and implantation of a pacemaker may be performed if preferred by the patient.

If symptoms worsen despite having tested all available and acceptable anti-arrhythmic drugs, patients, if requested, may undergo AF ablation following a minimum of 12 months anti-arrhythmic drug therapy. Physicians are, however, advised to keep patients in the same treatment arm during the advocated follow-up period. If in this case AF ablation is requested by the patient, all end-points will be evaluated prior to requested AF ablation.

9.3 Anticoagulation and other therapies (Both groups)

For patients not already receiving warfarin at baseline, but who have risk factors for thrombo-embolism, antithrombotic treatment should be initiated, including warfarin with a target international normalized ratio [INR] of 2 to 3.

For group D patients with risk factors for thrombo-embolic complications, warfarin therapy should be continued for at least 12 months following cardioversion of persistent atrial fibrillation or following initiation of prophylactic anti-arrhythmic agent where after it may be discontinued at the discretion of the investigator provided sinus rhythm has been maintained.

For group A patients anticoagulation with warfarin should be re-initiated the day after ablation.

Warfarin with an INR 2-3 must be maintained for at least 3 months after an ablation procedure. Decisions regarding the need for anticoagulation after this period will be guided by the success of therapy, i.e. maintenance of sinus rhythm, and thrombo-embolic risk profile according to published guidelines regarding anticoagulation for atrial fibrillation (Appendix A) as follows:

1. In patients without a primary clinical indication for antithrombotic therapy (i.e. absence of risk factors for thrombo-embolic complications), warfarin should be discontinued at 3 months post procedure, provided no re-ablation is planned.
2. In cases with a primary clinical indication for antithrombotic treatment, it should be continued for at least 6 months, and then discontinued at the discretion of the investigator if no atrial fibrillation is present and sinus rhythm is maintained.

All concomitant medications and changes will be recorded at each visit.

Cardioversion sessions should in general be performed within 48 hours after start of AF or AF symptoms. Patients should undergo electrical direct-current cardioversion using biphasic shocks at latest 2 weeks after AF onset. Adequate energy levels (with at least one cardioversion at maximum energy level if necessary) should be chosen.

9.4 Definition of change of treatment:

- A new previously untested antiarrhythmic drug (VW Class I or III) is prescribed to a Group A patient, who have undergone an ablation procedure.
 - An ablation is performed in a Group D patient, who have or have not tested all antiarrhythmic drugs.
- All endpoints will be evaluated at last visit before change of treatment.

10 PRE INCLUSION AND TREATMENT EVALUATION

Each patient will be evaluated by a cardiologist well familiar with the protocol.

10.1 Initial clinical evaluation

The *medical history* will be recorded at baseline as follows;

- AF history
 - Duration of AF since first detection
 - Patient estimate of frequency and duration of symptomatic episodes, during the last 12 months.
 - The AF profile (paroxysmal, persistent, type I or II) and the number and efficacy of previous cardioversions for atrial fibrillation.
- The past and present pharmacological therapy for rhythm and/or rate control with regard to efficacy/tolerability and adequacy in dosages.
- The past antithrombotic treatment and reason for discontinuation, including anticoagulation (vitamin K antagonists) and antiplatelets (aspirin, clopidogrel).
- The present antithrombotic (anticoagulation, antiplatelets), antihypertensive and heart failure treatment (ACEinhibitors, ARB, diuretics, etc).
- Thromboembolic History
 - History of ischemic stroke with acute loss of neurological function caused by an ischemic or hemorrhagic event with residual symptoms at least 24 hours after onset.
 - History of transient ischemic attack (TIA) consisting of acute loss of neurological function caused by an ischemic event with resolution of symptoms by 24 hours after onset.
 - History of systemic peripheral embolism with abrupt vascular insufficiency associated with clinical and radiological or pathological evidence of arterial occlusion in a vascular bed other than the cerebrovascular system in the absence of other likely mechanisms (e.g., atherosclerosis).
- Hemorrhagic History
 - History of intracranial hemorrhage including hemorrhagic conversion of a primary ischemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage, other (including subdural and epidural hematomas) or unknown.
 - History of other major bleeding
- Concomitant cardiovascular disease including coronary artery disease (prior documented myocardial infarction, coronary revascularization, or stenosis on angiography greater than or equal to 50%); hypertension; heart failure; valvular heart disease (documented history of moderate or severe stenosis or regurgitation); cardiomyopathy (left ventricular systolic dysfunction, LVEF < 0.45); and supraventricular tachycardia.

- Other diseases including diabetes mellitus; chronic lung disease; thyroid disease; chronic kidney disease; alcohol consumption/dependency; and smoking.

The present antiarrhythmic drug therapy will be maintained during the run-in period. If judged necessary dosages of anti-arrhythmic drug therapy including drugs for rate control will be optimized prior inclusion. An adequate dosage is defined as recommended by international guidelines (Appendix A).

The heart rate during AF should be evaluated for adequate rate control by exercise bicycle test (Appendix D), 24-hour Holter recording, stairs test, or a 6 minute walk test. Adequate rate control should be achieved by administering a beta-blocker, diltiazem, verapamil as well as digitalis, alone or in combinations, as deemed necessary to attain a target resting heart rate (HR) of 60 to 80 beats per minute (bpm), and with moderate exercise a heart rate of 90 to 115 bpm.

Patients with a history of congestive heart failure should be evaluated at adequate rate control of AF or during sinus rhythm to assess whether the heart failure is directly related to the atrial fibrillation. Patients with a history of hypertension should be judged only after optimization of medical therapy to exclude inadequate blood pressure control.

Prior to inclusion a search for correctable or primary causes of AF should be performed.

All screened patients who sign an informed consent and satisfy inclusion and exclusion criteria will undergo a *clinical evaluation* at baseline including;

- Symptoms and QoL,
- Physical examination including height, weight, BMI, blood pressure.
- Evaluation of heart failure including assessment of NYHA function.
- 12-lead electrocardiogram,
- Transthoracic echocardiography,
- Exercise bicycle test (EBT)
- 24-hour Holter recording
- Laboratory tests including NT pro BNP, serum-creatinine, CRP, natrium, kalium, calcium, albumin, bilirubin, ALP, ASAT, ALAT, LD, γ GT, glucose, TSH, T3, freeT4, Hb, leukocytes, trombocytes, APTT, and INR. And a sample saved for future use (biobank).

For the samples that will be saved for the future, use an EDTA-tube (5mL) and a Natrium citrate- tube (5ml). These samples shall within short time (maximum 30 minutes) be centrifuged in 1300-1700g in 10 minutes. After the centrifuge the plasma shall be transferred to separate plastic tubes and then frozen in -70°C . Mark the tubes with EDTA and natrium citrate and the patients study number.

A standardized programmed stimulation study will be performed when indicated to exclude a supraventricular tachycardia as the underlying mechanism of AF (Appendix E).

The risk for thromboembolism will be classified with the ChADS2 score and published guidelines (Appendix A). Antithrombotic treatment will be initiated at baseline or immediately prior to the run-in period, if clinically indicated according to risk factors.

The date at which possible randomized allocation will be initiated (ablation or start of antiarrhythmic drug therapy) should be defined for all patients prior to run-in.

Anti-arrhythmic drugs remaining to be tested for rate and rhythm control should be defined at baseline, which may include previously tested and tolerable antiarrhythmic drugs if dosages were inadequate.

An Implantable Cardiac Monitor (ICM), Reveal XT, will be implanted in all included patients prior to run-in to record AF episodes prior to and after allocated treatment during follow-up. The heart rhythm will continuously be monitored and atrial fibrillation automatically detected by the ICM during the first 3 years of the study. The ICM is thereafter explanted and recordings retrieved. The rhythm is thereafter documented by 24-hour Holter monitoring on a yearly basis.

All patients will receive a diary, Patient Event Report Form, prior to run-in to record the start time and duration of all **symptomatic** episodes suggestive of an arrhythmia during the Run-in period and during the follow-up.

Patients will manually activate the ICM (Symptom mark button) for each symptomatic episode suggestive of an AF episode. The “Patient Assistant XT” will be used (Query button) by the patient to rule in or out arrhythmia cause for symptoms, which will be recorded in the Patient Event form.

Recordings from ICM and Patient Event Report will start immediately after ICM implantation and continue for 2 months run-in where after data are retrieved and the memory emptied. Recordings will then restart at discharge after initiation of allocated therapy.

10.2 Atrial Fibrillation profile

Five AF profiles are defined as follows:

AF Type	Pattern
Paroxysmal	Self-terminating symptomatic AF episodes.
Type I:	Short paroxysms of AF: 1 minute – 48 hours duration.
Type II:	Long paroxysms of AF: > 48 hours duration but \leq 7 days
Persistent	
Type I:	Mixed pattern with spontaneous conversions to SR and those necessitating cardioversion.
Type II:	Necessitates cardioversion. No spontaneous conversions.
	<i>Upon electrical or pharmacological cardioversion, sinus rhythm must be maintained for at least 1 hour for including a patient.</i>
Permanent	Atrial fibrillation does not convert to sinus rhythm upon electrical cardioversion or ongoing AF is accepted.

The outcome of cardioversion sessions should be assessed.

Definition of successful cardioversion

Cardioversion is successful when AF has been terminated and at least one beat of an atrial rhythm has been recorded.

Recurrences of AF after successful cardioversion and its timing should be documented.

For patients with paroxysmal AF, the AF profile is defined by the type and pattern of AF, and for those with persistent AF by the type, pattern and response to cardioversions. If electrical cardioversion (including maximal biphasic shock) is not successful (see above) the type of AF is defined as permanent AF.

The AF profile will be assessed at baseline, and at 3, 6, 12, 24, 36 and 48 months FU to determine the changes between AF profiles as an indirect measure of the procedural success and as criteria in conjunction with AF burden to determine the time for withdrawal of anti-arrhythmic and anticoagulation therapy.

10.3 Monitoring of AF episodes

The patient's rhythm will be monitored continuously and all atrial tachyarrhythmias (AF recurrences, left atrial tachycardias, and atrial flutter) automatically detected by the ICM during the run-in period and during follow-up for 3 years, starting 2 weeks after initiation of allocated therapy. If the ICM has to be explanted according to physician's discretion (for example infection, severe discomfort) the patient should continue in the study and the steering committee should be contacted for advice. For the continuous evaluation of AF after explantation of the ICM, the patients will carry either a 7 day (continuous) ECG recorder or a 14 day event recorder (with daily transmissions of 2 minutes and also when experiencing symptoms) at 6, 12, 18 and 24 months and then every year.

10.3.1 Symptomatic AF

Episodes of AF detected by the ICM that correlate in time and duration with recorded **symptomatic** episodes in the Patient Event Report Form will be defined as symptomatic AF episodes.

Manually stored symptomatic events by patient activation of the ICM will also be used to classify whether the AF episode is symptomatic.

10.3.2 Asymptomatic AF

Episodes of atrial tachyarrhythmias not identified as symptomatic by the patient ICM activation or Patient Event Report will be classified as asymptomatic.

All recorded AF episodes on the ICM will be saved on a diskette and transmitted to the core centre on a 3 months basis.

10.4 Definition of endpoints

10.4.1 Quality of life (QoL)

QoL is assessed by the Medical Outcomes Study Short Form-36 (SF-36) questionnaire. It contains 8 subscales: physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health. Scores range from 0 to 100, with lower scores representing a poorer QoL. The rhythm at the time of the evaluation will be recorded.

10.4.2 Symptoms

Symptoms are evaluated by a Symptoms Severity Questionnaire and a Disease Related Symptom Questionnaire, and classified by the EHRA Symptoms Classification. Patient's estimate of frequency and duration of symptomatic episodes will be recorded. The rhythm at the time of the evaluation will be recorded. (appendix C).

10.4.3 Morbidity

Composite outcome that sum up; stroke (ischemic and hemorrhagic), TIA, systemic peripheral embolic events, , major bleeding, cardiovascular hospitalizations, pacemaker implantation, all cause death.

- *Stroke* is an acute loss of neurological function caused by an ischemic or hemorrhagic event with residual symptoms at least 24 hours after onset. Ischemic and hemorrhagic stroke should be differentiated by CT/MRI scan, assessing intensity of anticoagulation at time of event, severity of stroke acutely and during follow-up. Cause of stroke should be classified according to TOAST criteria and its consequences evaluated 90 days after the event using the Rankin score (Appendix J). Extracerebral but intracranial bleeds (subdural or epidural hemorrhage) are not strokes, but should be reported as serious adverse events (SAEs), together with a statement whether they appear attributable to treatment.
- *TIA* consists of acute loss of neurological function caused by an ischemic event with resolution of symptoms by 24 hours after onset. It should be adjudicated for the presence of stroke by a neurologist, as a new definition that might classify such events as ‘stroke’ is under consideration at the World Health Organization.
- *Systemic peripheral embolism* is an abrupt vascular insufficiency associated with clinical and radiological or pathological evidence of arterial occlusion in a vascular bed other than the cerebrovascular system in the absence of other likely mechanisms (e.g., atherosclerosis). It should be confirmed by a surgeon.
- *Major bleeding* is present when one of the following criteria is met: Fatal outcome; clinically overt bleeding causing a fall in hemoglobin concentration of 20 g/l or more (for example from 130 to 110 g/l) or leading to transfusion of one or more units of whole blood cells; bleeding in areas of concern (e.g. retroperitoneal or intracranial hemorrhage, intraspinal or intraocular); or bleeding leading to treatment cessation and/or surgical intervention. Will also be reported as a safety outcome parameter.
- *Cardiovascular hospitalization* is the time (number of days) spent in hospital related to atrial fibrillation (eg any treatment or diagnostic procedure for AF that has to be performed in hospital such as cardioversions, medication, further AF ablations after AF recurrence, or adverse events related to AF or its treatment), thromboembolic complications (eg acute stroke), heart failure (eg hospitalization for acute heart failure), myocardial ischemic events (unstable angina, myocardial infarction, coronary artery revascularization); adverse events (eg. pacemaker implantation), including the relative contribution of the different causes of cardiovascular hospitalizations. Will also be analyzed separately.

10.4.4 Mortality

- Total mortality will be classified into different groups, which will also be evaluated separately. All-cause death will be classified in the following groups:
 - 1. Non-cardiovascular, including unknown, excluding sudden death.
 - 2. Cardiovascular death
 - a. cardiac
 - i. sudden (including arrhythmic, myocardial infarction)
 - ii. non-sudden
 - b. vascular (e.g. embolic, SAB, stroke, other)
 - i. sudden
 - ii. non-sudden
 - 3. AF-related

- 4. Treatment- or procedure-related (is also a SAE)

AF-related death are i) all cardiovascular deaths that do not have a clearly defined other cause (e.g. rupture of an aneurysm, pulmonary embolism, cardiac tamponade, myocardial infarction etc.) when AF was present in the days prior to death, and ii) all deaths that are a consequence of AF-related treatment (serious adverse event) which should also be reported in the primary safety outcome.

“Unknown” causes of death should be evaluated by best possible methods (autopsy, doctors` reports, read-out of ICDs/monitoring devices, Holter ECG recordings).

Cardiovascular deaths are all deaths without a clearly determined non-cardiovascular cause.

10.4.5 Health economics

This includes the number and costs of acute and scheduled ambulatory health care provision and the total duration of hospitalizations (days) to any type of health care provider categorized as for atrial fibrillation, thromboembolic complications, bleedings, heart failure, adverse events related to AF or its treatment, or other disease states. Each type of health care use and their costs will also be recorded, including number and timing of intervention (anesthesia, non-pharmacological treatment incl. cardioversions), diagnostic tests (including laboratory tests), devices (catheters, implants etc) type and duration of medication, time spent on sick-leave, and state of sickness insurance. AF-related health care use are: i) all health care uses that do not have a clearly defined other indication (e.g. diagnosis of rupture of an aneurysm, pulmonary embolism, myocardial infarction or bone fracture etc.) whenever AF may be the trigger or cause for the disease state leading to the health care use, and ii) all health care uses that are a consequence of AF-related treatment (serious adverse event). Costs will be calculated for each of these healthcare services and for state of sickness insurance, and related to type of employment. The duration and cost for not being at work will be retrieved from the sickness insurance institution, “Försäkringskassan”, by informed consent from the patient, if necessary. Care will be taken to consider cost reductions related to the advancement of technology. Calculation of costs related to involvement of family members will not be performed.

- As a measure of health status, the EuroQual instrument EQ5D will be used, and evaluated at identical intervals as QoL is measured.
- The costs will be evaluated at 24 and 48 months follow-up.
- A model will be made to calculate the life-time costs and the time for break even.

10.4.6 Other endpoints

1. Hospitalization for heart failure (heart failure defined as in ESC guidelines).
2. The presence of cardiac heart failure will be evaluated by assessing symptoms, NYHA function class, LVEF, NT pro BNP and pharmacological drug therapy required for heart failure. (ACE inh., ARB blockers, diuretics) (appendix G). The presence and number of CHF episodes will continuously be measured. NYHA will be analyzed separately.
3. Left ventricular function will be assessed by measuring EF using Simpsons technique, and LV endsystolic and enddiastolic diameters by 2-D echocardiography (Appendix F).
4. Right atrial (RA) and left atrial (LA) area and function will be assessed on 2D-echocardiography and LA diameter by M-mode as standard (appendix F).
5. Exercise capacity. The maximal exercise capacity will be assessed by a standardized bicycle exercise test, and defined as maximum work load and time reached. (appendix D).
6. Change in AF profile

- The AF profile, defined according to the AF type and AF pattern, will be assessed at baseline, run-in and at 3, 6, 12, 24, 36 and 48 months FU to determine the changes between AF profiles as an indirect measure of the procedural success.
7. AF burden (Appendix E)
 - Defined as the time spent in AF, i.e. duration of sustained AF episodes per month.
 - The number of AF episodes will be classified by their duration, thus the time spent in AF will be classified by duration as:
 - Number of paroxysms of AF duration < 1 minute per month.
 - Number of paroxysms of AF duration 1 minute to < 48 hours per month.
 - Number of paroxysms of AF duration \geq 48 hours per month.
 - The number of cardioversions per month will be calculated.

The AF burden during follow-up will be compared with that during run-in, apart from comparisons between treatment strategies.
The AF burden is retrieved from the ICM.
 8. Successful versus failed treatment will be recorded at 12, 24 36 and 48 months.
 9. Recurrence of atrial fibrillation (after 4 weeks stabilization period).
 - An AF episode lasting longer than 1 minute, documented on an ECG tracing and occurring 4 weeks after initiation of allocated therapy (ablation or anti-arrhythmic drug) will be defined and reported as an AF recurrence. Intra atrial tachycardias and flutter, not recorded prior ablation will be defined as recurrences. Any AF occurring within the first 4 weeks post-ablation or after anti-arrhythmic drug strategy initiation will not be defined as AF recurrence, and will be treated by cardioversion unless spontaneous conversion occurs within 48 hours.
 10. Frequency of warfarin treatment and antiarrhythmic drug therapy
 11. Frequency of withdrawals and “change of treatments” over time.
 12. Further interventions. Any procedure or change in therapy will be documented as “further intervention” eg. change in medical therapy (dose or drug), non-pharmacological procedure. Change in dosage related to dose titration will not be documented as further intervention.
 13. Safety outcome parameters. Type and frequency of adverse reactions will be recorded continuously and classified whether related to treatment, and whether serious.
 14. Laboratory tests.
 - For efficacy in addition to the safety test in 11.3.3, CRP, NT pro BNP (corrected for elevated creatinine), s-creatinine and an extra plasma sample for future analysis taken at each follow-up will be analyzed separately. The rhythm at the time for BNP test will be recorded.

10.4.7 Definition of Procedural/ Anti-arrhythmic drug Success

To determine the procedural success with regard to symptoms, symptoms according to EHRA SC and Disease Related Questionnaire and present anti-arrhythmic drug therapy will be compared before and after the anti arrhythmic drug treatment / procedure at 12 months as defined below.

To compare the efficacy of the treatment with regard to rhythm, the atrial fibrillation burden will be assessed. Procedural success with regard to rhythm is defined as the absence of AF episodes duration > 1 minute after last therapy.

10.4.7.1 Success

1. No symptoms
 - a. SR is maintained at follow-up without antiarrhythmic drugs
 - b. SR is maintained at follow-up with previously ineffective antiarrhythmic drugs

- c. Atrial fibrillation recurrence with or without previously ineffective antiarrhythmic drugs
2. Symptoms improved with or without previously ineffective antiarrhythmic drugs, and with no patient desire to test a new antiarrhythmic drug or repeat ablation procedure, despite episodes of AF.

10.4.7.2 Failures:

1. Symptoms unchanged with or without previously ineffective antiarrhythmic drugs.
2. Symptoms worsened.
3. If the above Success criteria are met in group A with the addition of Class I or III antiarrhythmic drug therapy not previously tested the patient is defined as a change of treatment (and ablation failure).

In case other arrhythmia's appear following the procedure, success will be still be defined according to the definitions above.

An evaluation of symptoms and AF profile is undertaken at each follow up visit. Questionnaires on symptoms and QoL will be completed by the patient at the visits without interference from personels apart from assuring completeness.

Atrial flutter and post ablation intra atrial tachycardia (focal or intraatrial reentry) will be differentiated from AF by 12 lead ECG recordings whenever possible. In case an AF recurrence or left atrial tachycardia will be revealed following an ablation procedure or anti-arrhythmic drug therapy, the patient should undergo a cardioversion to terminate the arrhythmia at latest within 2 weeks without delay.

The primary endpoint will be assessed at 12 month follow-up (FU). An extension of the study for 48 months will be conducted to further assess the efficacy and health economy of AF ablation on long-term basis. The analysis will be performed according to the Intention to treat principle.

11 SAFETY ASSESSMENT / Reporting of Adverse Events

Complications are defined as acute if occurring within 1 week after initialized therapy, and late if occurring one week after initialized therapy.

11.1 Serious adverse event

All "Serious adverse events" should be documented on the "Adverse events Form" AND "Serious adverse events Form". All deaths events should be documented on the "DEATH REPORT FORM".

Serious aduers events

1. Death
2. Life-threatening pro-arrhythmic reactions (Sustained ventricular tachycardia/ Torsade de pointes and Ventricular fibrillation)
3. 1:1 atrioventricular conduction during atrial flutter causing syncope or hemodynamic compromise
4. Asystoli, requiring treatment, excluding transient episodes during RF application in the left atrium or reactions to painful stimuli
5. AV block III, excluding transient episodes during RF application in the left atrium

6. Heart Failure: NYHA class III and IV
7. Pulmonary oedema
8. Acute myocardial infarction or unstable angina pectoris
9. Cerebrovascular accident
10. Major Bleeding
11. Vascular injury requiring intervention
12. Injury to a cardiac valve that results in a significant change of valve function.
13. Pericardial effusion with or without tamponade, requiring treatment
14. Venous or systemic embolism
15. Pulmonary vein stenosis, significant if lumen reduction of $\geq 50\%$.
16. Permanent phrenic nerve paralysis
17. Atrio-esophageal fistula
18. Drug intoxications
19. Other events which require interventions or hospitalization, excluding those related to the treatment of AF recurrence, such as cardioversion or monitoring of antiarrhythmic drug effect. Included are all known side effects related to medical or interventional strategies that require treatment or hospitalisation.
20. Adverse reactions necessitating discontinuation of anti-arrhythmic drug therapy or interruption of catheter ablation.
21. Infection resulting in ICM explantation.

11.2 Adverse Event

All " Adverse events" should be documented in the "Adverse events Form".

All events which are part of performing a catheterization procedure will be reported.

Examples of exceptions are those which are an anticipated and inherent part of performing a catheterization procedure; vagal reactions with transient hypotension and bradycardia not requiring treatment, chest pain during RF applications which resolve without therapy, and haematoma at puncture sites not requiring observation. All serious unanticipated events whether or not they are considered to be related to the procedure but which have some association with the catheterization either by timing or physiology, will be reported.

Other bleedings than major bleeding events should be reported as minor bleeds.

All events related to pharmacological therapy will be reported.

Each adverse event will be classified according to the definitions provided below.

11.2.1 Definition of Procedural Complications

Procedural complications are defined as those arising during or within 1 month of the procedure, including death, major bleeding, vascular injury, cerebrovascular accident, myocardial infarction, pericardial effusion with or without tamponade, venous or systemic embolism, phrenic nerve paralysis, and heart block. Events occurring later than 1 month after the procedure and defined as related to the procedure are pulmonary vein stenosis, tamponade, retroperitoneal haematoma, and atrio-esophageal fistula (see below).

11.2.2 Relation to Device Procedure or drug

1. **Not related (none):** Any adverse event that is not associated with the traditional catheterization procedure - surgical procedure or antiarrhythmic medication by timing or pathophysiology
2. **Possibly related (possible):** Any adverse event determined to be possibly associated with the use of the ablation catheter, mapping system, catheterization, surgery or drug as above.

3. **Related (probable):** Any adverse event that is associated with the use of the ablation catheter, mapping system, catheterization, surgery or drug and the investigator believes was caused or contributed to by these procedures.

11.2.3 Intensity

All Adverse events should be classified according to the intensity of the event, as follows;

1. **Mild:** Any event which results in mild, awareness of sign or symptom, but easily tolerated.
2. **Moderate:** Any event which results in moderate, discomfort sufficient to cause interference with normal activity.
3. **Severe:** Any event which is incapacitating with inability to perform normal activity.

11.2.4 Outcome

The outcome or consequence of the Adverse event should be described as follows;

1. Resolved.
2. Not resolved.
3. Resolved with sequale
4. Fatal
5. Unknown

11.2.5 Action taken

The action taken due to the Adverse event should be described as follows;

1. None
2. Drug/ablation temporarily discontinued
3. Drug/ablation permanently discontinued
4. Other action, specify.....

11.3 Potential Risks to Patients

All side effects will be carefully monitored at each visit.

11.3.1 Ablation

<i>Side effects known to be related to ablation</i>	<i>Estimated risk</i>
Allergic reaction to the local anesthetic, sedatives, x-ray dye, heparin, or other agents administered during the procedure	< 1%
Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels	< 1%
Hemorrhage as a result of anticoagulation which would require transfusion	0.5%
Infection at the catheter insertion site or systematically, including endocarditis and septic emboli	0.5%
Intracardiac or intravascular thrombus formation which may cause embolization; pulmonary embolus, cerebrovascular accident, myocardial infarction, or other ischemic injury. The risk of thrombus formation is minimized by using anticoagulants and using a lower power approach detailed in the protocol above	1-4 %
Cardiac perforation, which may result in cardiac tamponade, and require percutaneous pericardial drainage or surgical repair.	1-2%.
Injury to a cardiac valve may result from catheter manipulation or the application of RF current.	< 1%
Pulmonary vein stenosis may occur. Significant pulmonary vein stenosis is defined as	1-5 %.

lumen reduction of $\geq 50\%$.	
Phrenic nerve paralysis related to ablation too far out of the right pulmonary veins.	1-5 %
Atrio-esophageal fistula related to RF application at the left atrial posterior wall may occur. Linear lesions are deployed at the LA roof, and limited to patients with AF recurrence or persistent AF only.	< 1 %.

11.3.2 Drug

<i>Side effects known to be related to anti-arrhythmic drugs</i>	<i>Estimated risk</i>
Allergic reactions	< 1%
Amiodarone specific: Photosensitivity, pulmonary toxicity, polyneuropathy, bradycardia, torsades de pointes (rare), hepatic toxicity, thyroid dysfunction, eye complications	< 1%-10%
Disopyramide specific: Torsades de pointes, Heart failure, glaucoma, urinary retention, dry mouth	0.5%-5%
Flecainide specific: Ventricular tachycardia, Heart failure, conversion to atrial flutter with rapid conduction through the AV node (Class C flutter)	0.5%-5%
Propafenone specific: Ventricular tachycardia, Heart failure, conversion to atrial flutter with rapid conduction through the AV node (Class C flutter)	0,5-5 %
Sotalol specific: Torsades de pointes, Heart failure, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease	0,5-5 %
Sinus node dysfunction, atrioventricular block (almost all drugs)	

11.3.3 Laboratory tests

Blood tests required for safety will be acquired from patients on amiodarone therapy according to clinical routine every 6 month (Hb, leukocytes, trombocytes, liver enzymes, TSH, T3, T4). INR values at the time for major bleeding or thromboembolic events will be recorded in all patients.

12 STUDY MONITORING AND AUDITING

12.1 Study monitoring

A monitor will verify that data recorded on the procedure forms are correct through quarterly communication, review of catheterization reports and medical records.

12.2 Source data verification and on-site audits

In accordance with applicable regulations, GCP, a monitor (study nurse from Uppsala) will contact the site prior to the start of the study to review with the site staff protocol, study requirements and their responsibilities to satisfy study requirements, if needed. When reviewing data collection procedures the discussion will also include identification, agreement and documentation of data items for which the CRF, patient files (paper or database), tracings of investigations, and questionnaires, will serve a source document. The investigator and the head of the medical institution agrees should allow the monitor direct access to all relevant documents whenever needed and in an event of an audit.

The monitor will monitor the study consistent with the demands of the study and site activity to verify the following:

1. Data are authentic, accurate and complete.

2. Safety and rights of subjects are being protected.
3. Studies conducted in accordance with the currently approved protocol and any other study agreements, GCP and all applicable regulatory requirements.

To ensure compliance for the GCP and study protocol the monitor may conduct a quality assurance audit. Such audits/inspections can occur at any time during or after completion of the study. If an auditor inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and relevant issues.

13 DATA MANAGEMENT

13.1 Data management

The Biometrics section at UCR will be responsible for the Data Management and will write a study specific Data Management Plan (DMP) and a Data Validation Plan (DVP), where further details will be specified.

All data will be recorded in the CRFs and entered via eCRF directly into a web based data capturing system except for electronically available data that will be loaded directly into the study database (ICM transmission). Patient Event Report data, data from Symptom Severity Q, Disease Related Symptom Q, EQ-5D and QoL SF-36 questionnaires will be recorded in separate documents attached to the CRFs.

Each investigational site will have authorized site personnel responsible for entering the data, as well as for changing and correcting the data according to instructions provided by Uppsala Clinical Research Centre (UCR) and the coordinating centre. All changes will be tracked by an audit trail. The entered data will be validated by a number of logical checks, both computerized and manual, as well as proof reading of specified variables. All inconsistencies detected during these procedures will be resolved by the monitor or site personnel.

The site specific investigator will sign the eCRF electronically when the data have been reviewed and edited, and Source Data Verification has been performed.

13.1.1 Source Data

Data reported on the CRFs that are transcribed from source documents must be consistent with the source documents. The source documents are filed at each Investigators site. Source data consists of:

- Signed copy of patient file (regarding hospitalizations, outpatient visits, health care provisions from other regions, study visits, adverse events etc)
- Investigation reports: ECG, Holter, Echo, Exercise test, ablation procedure, and so on, but not ICM transmission
- Patient questionnaires: Symptom Severity, Disease Related Symptom, EQ-5D and SF-36 (these forms will not be transcribed)
- Patient Event Reports
- Laboratory test results including local reference values.

For all other data the CRFs will constitute the source document.

13.1.2 Database Closure

The Database Closure will be performed in three steps, the first one when all data from the first 12 months are entered, the second one when all data from the 24 months period are entered and the third when the complete study period of 48 months are entered. The procedures below will be followed at all occasions but the randomization code will only be

loaded at the first occasion. All datasets used for the 12- and 24 months analyses will be locked separately.

Procedures: When all data are entered into the database and all queries solved, the Database Closure procedures will start. Decisions will be made how to classify patients into analysis populations, and how to handle protocol violations and deviating or missing data. Efforts will be made to maintain the blinding while these decisions are made. All decisions will be dated and documented in a Database Closure document. After that the database will be locked and the randomization code will be loaded.

14 STATISTICAL CONSIDERATIONS

The Biometrics section at UCR will be responsible for the statistical analysis and will write a study specific Statistical Analysis Plan (SAP) where further details will be specified. The analysis of Health Economics will be performed by Lars Åke Marké, SBU.

14.1 Objectives and Endpoints

The objective of this study is to compare the effects of two treatment strategies, catheter ablation of atrial fibrillation (AF) and optimized conventional pharmacological therapy.

14.1.1 Primary objective and endpoint

The primary objective of the study is to determine if the effects of the strategy catheter ablation of AF is superior to optimized conventional pharmacological therapy on the Quality of Life parameter General Health in patients with symptomatic AF.

Primary endpoint: Change in General Health, as measured by the SF-36 questionnaire, from baseline to 12 months after baseline ^(1,2).

14.1.2 Secondary objectives and endpoints

The secondary objectives of the study are to compare the effect of the two treatment strategies with respect to the following endpoints during the total study period of 48 months in patients with symptomatic AF at 6, 12, 24, 36 and 48months (if not otherwise specified, see 8.1).

Secondary endpoints:

1. A composite of morbidity (stroke, systemic embolic events, TIA, major bleeding, cardiovascular hospitalizations, pacemaker implantation, all cause death) measured at each of the months as above.
2. Total number of hospitalization days due to AF and time to first event of hospitalization related to AF.
3. Total number of hospitalization days due to hospitalization for heart failure
4. Total number of hospitalization days due to cardiovascular reasons, and time to first event of hospitalization days due to cardiovascular reasons.
5. Frequency of morbidity (the components in 1 above).
6. All cause death, which will also be classified as in 10.4.4.
7. Success/failure (yes/no), with regard to symptoms and rhythm at 12, 24, 36, 48 months and so on.
8. Recurrence of episodes of AF lasting at least one minute (after four weeks stabilization period), obtained from the ICM continuously and 24 hour Holter recordings and extra visits related to AF cardioversion). Or in case of ICM explantation, recording with 7 day Holter or 14 day event recorder.

9. AF burden from ICM (5 variables: total time spent in AF per month, the number of AF episodes terminating spontaneously classified by their duration). Frequency of symptomatic respectively asymptomatic episodes of AF (AF events from ICM identified as symptomatic via patient event report and ICM). Or in case of ICM explantation, recording with 7 day Holter or 14 day event recorder.
10. Frequency of left ventricular heart failure (appendix G). The degree of left ventricular heart failure assessed by NYHA function class, LVEF, NT pro BNP and pharmacological drug therapy required for heart failure. (ACE inh., ARB blockers, diuretics).
11. NYHA function class.
12. Frequency of cardioversion sessions (electrical and pharmacological, respectively) per month.
13. Incidence, intensity and relationship of Adverse Events.
14. Frequency of withdrawals / 'cross-overs' over time.
15. Frequency of further interventions over time (drug or dose changes (titrations excluded), cardioversion sessions (electrical and pharmacological resp.), repeated ablations).
16. Frequency of warfarin and antiarrhythmic drug treatment

The following endpoints are defined as change from baseline to each of months 6, 12, 24, 36 and 48, if available.

17. Quality of Life (SF-36) all domains and time-points.
18. Quality of Life (EQ-5D) all domains and time-points.
19. Symptom Severity Questionnaire (see Appendix C1).
20. Disease Related Symptom Questionnaire (see Appendix C2).
21. EHRA Symptom Classification (see Appendix C3).
22. Patient's estimate of frequency and duration of symptomatic episodes.
23. AF profile: (5 types).
24. AF burden.
25. Left ventricular function and diameters (from Echocardiography and corrected for BSA).
26. Left atrial area and function (from Echocardiography and corrected for BSA).
27. Right atrial area and function (from Echocardiography and corrected for BSA).
28. Exercise/Physical capacity and % of predicted max. as well as duration.
29. Laboratory tests for efficacy: CRP and NT pro BNP. Laboratory tests for safety will be taken when applicable, and clinically significant values will be registered as AEs.
30. Covariate adjusted primary endpoint (analysis using following covariates at baseline: age, sex, background variables regarding social economic status, BMI, paroxysmal or persistent AF type I or II, coronary artery disease, hypertension, diabetes, congestive heart failure, failure of an antiarrhythmic drug class I or III prior to randomization, present medication and duration of AF).
31. Health care use and economy, including hospitalization and outpatient visits related to and not related to AF, treatment costs, and including corrections for background variables regarding social economic status, measured after 24 and 48 months (will be specified in a separate plan).
32. Logistic multiple regression analysis to identify baseline predictors for symptom-based response (symptom success) and rhythm-based response (rhythm success if absence of

AF episodes duration > 1 minute after last therapy), respectively (yes/no) by treatment group.

All endpoints will be evaluated at last visit before cross-over, see 14.3.1.

14.2 Statistical hypotheses

The null hypothesis (H_0) is that the difference in the mean change from baseline to 12 months after baseline in General Health between the two treatments is zero;

- mean change for the treatment group catheter ablation (μ_1)
- mean change for the treatment group optimized conventional pharmacological therapy (μ_2)

The alternative hypothesis (H_1) is that there is a non-null difference in the mean change from baseline to 12 months after baseline in General Health between the two treatments:

$$H_0: \mu_1 = \mu_2$$

$$H_1: \mu_1 \neq \mu_2$$

The test of the hypotheses will be two-sided and performed as an unpaired t-test at 5% significance level. The difference between the treatment groups with corresponding two-sided 95% confidence interval based on a normal approximation will be presented.

14.3 Statistical analysis

14.3.1 Analysis populations

Safety - All randomized patients will be included in the safety analysis. Only observed observations are used in the safety analysis.

Intention to treat (ITT) - All randomized patients.

Per protocol (PP) – All randomized patients completing the study treatment period of 12 months without any major protocol violation (for example ineligibility, early withdrawals, poor compliance).

The main analysis will be performed on the **ITT**-population. Missing values due to early termination or change of treatment will be imputed with the method of last observation carried forward (LOCF) up to 12 months. Thereafter these data will be considered as missing.

The PP-analysis will be regarded as supportive and only observed values will be used in this analysis.

14.3.2 Subgroups and explorative analyses

A subgroup analysis will determine whether sinus rhythm obtained by AF ablation is superior to sinus rhythm obtained by pharmacological therapy for rate and/or rhythm control.

In addition a comparison will be done between patients with sinus rhythm and patients with atrial fibrillation irrespective of allocated therapy.

Both analyses will be performed with regard to QoL, morbidity (composite, see secondary endpoint 1), cardiovascular hospitalizations, exercise/ physical capacity, safety, and health economy at 12 and 24 months.

Explorative analyses may be performed to further investigate relationships between treatments and endpoints, and between endpoints.

14.3.3 Statistical methods

All continuous variables will be presented per treatment group using descriptive statistics by mean, SD, max and min values, in addition medians, 25th and 75th percentiles will be presented when suitable.

The analysis of mean change in the primary endpoint will be two-sided and performed as an unpaired t-test at 5% significance level. The difference between the treatment groups with corresponding two-sided 95% confidence interval based on a normal approximation will be presented.

The continuous secondary endpoints will be analyzed in the same way as the primary endpoint, but the results will be interpreted descriptively.

Kaplan-Meier estimates and log-rank test will be used to determine the occurrence of the secondary endpoints over time.

All categorical secondary endpoints will be compared between treatment groups with frequency tables and Fisher's Exact Test including 95% confidence intervals where possible.

Adverse Events will be summarized per treatment group by body system/system organ class, preferred terms, intensity, seriousness and relationship.

Laboratory data for efficacy will be presented in mean change tables. Laboratory tests for safety will be done, and clinically significant deviations will be registered and presented as AEs.

14.4 Sample size considerations

Reason for amendment

Due to slow recruitment rate the CAPTAF trial inclusion period will be terminated prematurely. Recruitment of new patients will continue until December 31, 2012. Thereby, the expected total number of randomized patients in the study is changed from 270 to at least 140. Consequently, the current sample size calculation is not valid and the power to detect a difference of 7 units in the General Health is reduced from 80% to 53%. However, external studies (Wazni et al (2005), Forleo et al (2009)), indicate that the expected difference between treatment groups may be larger than assumed in the current sample size consideration. An updated sample size calculation has been performed based on the assumption that the expected difference in the primary endpoint (General Health) between treatment groups is at least 10.5 units (corresponding to an improvement of 15%).

Old text Sample size considerations

The primary endpoint is the change in General Health from baseline to 12 months after baseline. Based on historical data (^{1,2}), it is assumed that the variable is normally distributed and that the standard deviation for the change in General Health is about 20 units. To detect a difference of 7 units in General Health (corresponding to an improvement of 10%) between the two treatment groups with a power of 80 % and a type I error of 5 %, a sample size of approximately 125 subjects in each treatment group is required. Another 20 patients are added to ensure calculated number of patients for analysis at 12 months.

New text Sample size considerations

The primary endpoint is the change in General Health from baseline to 12 months after baseline. Based on external studies (Wazni et al (2005), Forleo et al (2009)), it is assumed that the variable is normally distributed with a standard deviation for the change in General Health of 20 units and an expected difference between groups of at least 10.5 units.

To detect a difference of 10.5 units in General Health (corresponding to an improvement of 15%, assuming a mean General Health of 70 units in the conventional pharmacological

therapy group) with a power of 80% and a type I error of 5% (two-sided alternative), a sample size of approximately 58 subjects in each treatment group is required, i.e. a total number of 116 patients. Another 20 patients are added to ensure calculated number of patients for analysis at 12 months. The power to detect a difference of 10.5 for 136 (116+20) and 140 (the minimum expected total number) patients is 85% and 86%, respectively.

Power	Diff	Diff (units)	SD	n1	n2	n-total
80%	15%	10.5	20	58	58	116
90%	15%	10.5	20	78	78	156
80%	20%	14	20	34	34	68
90%	20%	14	20	44	44	88

14.5 Randomization and blinding

A 1:1 block randomization will be used within each centre, stratifying patients between paroxysmal and persistent AF. The randomization code will be generated by UCR using validated software. Code envelopes will be used to avoid selection bias as far as possible.

Efforts will be made to maintain the blinding in the subjective evaluations regarding: Exercise tests, interpretations of 12-lead ECGs, of rhythm from implantable event recorders, rhythm from 24h Holter recordings by using core ECG laboratories, and of Echo measurements in core echo laboratories.

References

1. Lonnholm S, Blomstrom P, Nilsson L, et al. Effects of the Maze Operation on Health-Related Quality of Life in Patients With Atrial Fibrillation. *Circulation*. June 6 2000;101(22):2607-2611.
2. Singh SN, Tang XC, Singh BN, et al. Quality of Life and Exercise Performance in Patients in Sinus Rhythm Versus Persistent Atrial Fibrillation: A Veterans Affairs Cooperative Studies Program Substudy. *Journal of the American College of Cardiology*. 2006;48(4):721-730.

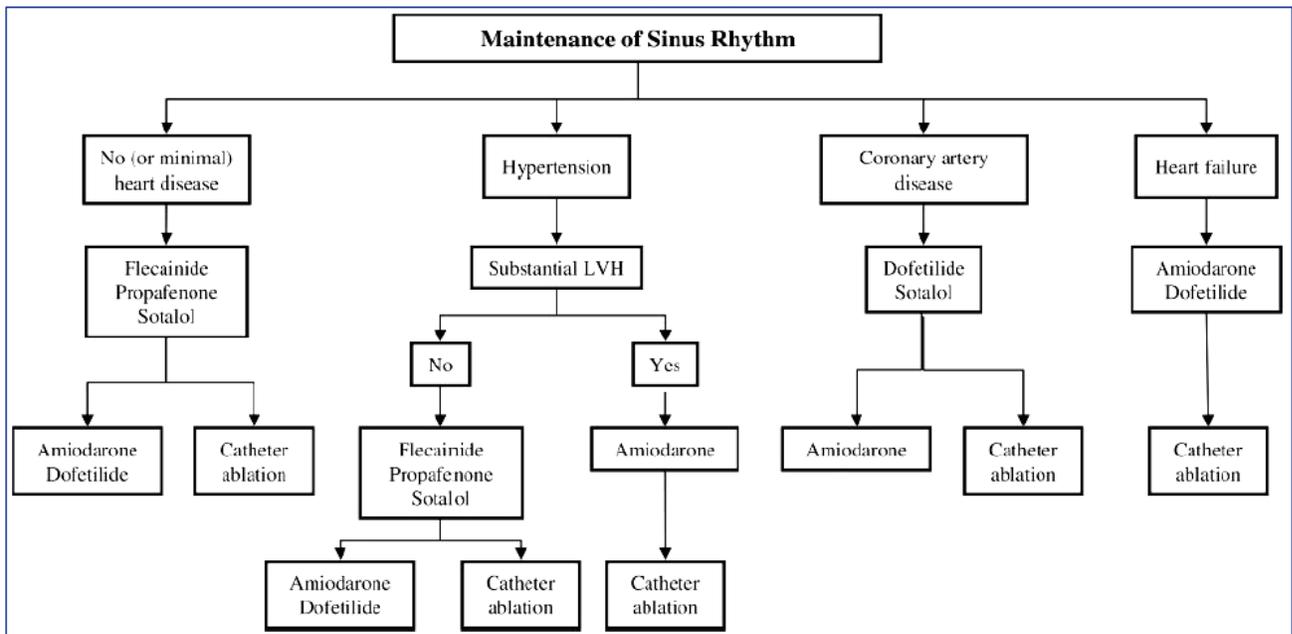
15 APPENDIX

15.1 Appendix A - Guidelines

15.1.1 Antiarrhythmic drug therapy

Patients should be hospitalized with telemetric monitoring during the initiation of sotalol, flecainide, propafenone and disopyramide. Treatment with amiodarone may be started on an out-patient basis. The choice of antiarrhythmic drug type and dosage should be according to published guidelines on atrial fibrillation.

Choice of antiarrhythmic drug type for rhythm control depending on underlying heart disease:



Typical Doses of Drugs Used to Maintain Sinus Rhythm in Patients With Atrial Fibrillation*

Drug†	Daily Dosage	Potential Adverse Effects
Amiodarone†	100–200 mg	Photosensitivity, pulmonary toxicity, polyneuropathy, GI upset, bradycardia, torsade de pointes (rare), hepatic toxicity, thyroid dysfunction, eye complications
Disopyramide	400–750 mg	Torsades de pointes, HF, glaucoma, urinary retention, dry mouth
Flecainide	200–300 mg	Ventricular tachycardia, HF, conversion to atrial flutter with rapid conduction through the AV node
Propafenone	450–900 mg	Ventricular tachycardia, HF, conversion to atrial flutter with rapid conduction through the AV node
Sotalol§	160 to 320 mg	Torsade de pointes, HF, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease

*Drugs and doses given here have been determined by consensus on the basis of published studies. †Drugs are listed alphabetically.

‡A loading dose of 600 mg per day is usually given for 1 week to 10 days..

§ s-creatinine should be assessed.

AF indicates atrial fibrillation; AV, atrioventricular; GI, gastrointestinal; and HF, heart failure.

Choice of antiarrhythmic drug type for rate control depending on underlying heart disease:**NON-ACUTE SETTING and CHRONIC MAINTENANCE THERAPY¶***Heart rate control*

Metoprolol†	Class I, LOE C	Same as maintenance dose	4 to 6 h	25 to 100 mg tw orally
Propranolol†	Class I, LOE C	Same as maintenance dose	60 to 90 min	80 to 240 mg daily doses, orally
Diltiazem	Class I, LOE B	Same as maintenance dose	2 to 4 h	120 to 360 mg divided doses; if available, orally
Verapamil	Class I, LOE B	Same as maintenance dose	1 to 2 h	120 to 360 mg divided doses; if available, orally

Heart rate control in patients with heart failure and without accessory pathway

Digoxin	Class I, LOE C	0.5 mg by mouth daily	2 days	0.125 to 0.375 mg orally
Amiodarone‡	Class IIb, LOE C	800 mg daily for 1 wk, orally 600 mg daily for 1 wk, orally 400 mg daily for 4 to 6 wk, orally	1 to 3 wk	200 mg daily,

15.1.2 Antithrombotic therapy

The choice of anticoagulants and INR levels should be according to published guidelines on atrial fibrillation. INR should be 2-3.

Risk Factors for Ischemic Stroke and Systemic Embolism in Patients With Nonvalvular AF

TABLE 13. 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.		

15.1.3 CHADS₂ Index

The Chads2 risk criteria should be evaluated at baseline.

CHADS ₂ Risk Criteria	Score	Pat's score
Nil	0	
C (recent Cardiac Heart failure)	1	
H (Hypertension)	1	
A (Age \geq 75 years)	1	
D (Diabetes mellitus)	1	
S ₂ (prior Stroke or TIA)	2	
Total patient score:		

Adjusted Stroke Rate (%/y)* (95% CI)	CHADS ₂ Score
1.9 (1.2 to 3.0)	0
2.8 (2.0 to 3.8)	1
4.0 (3.1 to 5.1)	2
5.9 (4.6 to 7.3)	3
8.5 (6.3 to 11.1)	4
12.5 (8.2 to 17.5)	5
18.2 (10.5 to 27.4)	6

15.2 Appendix B - Thoracoscopic off-pump epicardial PV isolation

Bilateral video-assisted thoracoscopic off-pump epicardial pulmonary vein isolation and exclusion of the left atrial appendage.

Studies before the procedure

Each patient will undergo the same investigations (TEE and CT/MRI) and follow the same strategy for warfarin pretreatment and antiarrhythmic drugs as patients scheduled for left atrial ablation.

Low-molecular heparin is given (instead of fractionated heparin) when $INR \leq 2.0$ is reached, at a dosage of 200 Units/BW once daily (max 18 000 units). Last dosage is given 24 hours prior surgery. Warfarin is reinitiated the evening prior surgery and then given daily to reach INR values 2.0 – 3.0.

Surgical Ablation Technique

Instruments: A bipolar RF clamp and RF generator system should be used.

The tissue temperature at some distance (mm) from the electrode (within the clamped section), and the conductance of the tissue clamped between the device jaws, should be available.

Linear ablation lesions are performed using RF energy delivered between 2 electrodes embedded in the jaws of the clamp. When the conductance of the tissue decreases to a certain cut-off limit, typically after 8 seconds, an audible signal is automatically generated to indicate that the lesion is transmural. Ablation lines are visible on the epicardial surface.

Confirmation of PV isolation

PV conduction block is assessed by pacing each pulmonary vein from the outside at twice diastolic thresholds and 2 ms pulse width after completion of RF ablation of each pair of veins.

Procedure

The procedure is conducted under general anesthesia administered with a double-lumen endotracheal tube. Transesophageal echocardiography is performed in the operating room to verify the adequacy of LAA excision at the end of the procedure.

The right pulmonary veins are accessed first. The patient is positioned with the left side down and the right arm abducted above the head. The right lung is deflated, and a 10-mm trocar is introduced in the sixth intercostal space in the anterior axillary line. A 10-mm 30° thoracoscope is introduced through this port. Insufflation is delivered at approximately 8 mm Hg to assist in resorptive atelectasis. A 6-cm access port in the third intercostals space just anterior to the anterior axillary line provides direct visualization. The pleural space is entered, and a soft tissue retractor is placed without spreading the ribs.

Blunt dissection of the right pulmonary veins is accomplished under thoracoscopic guidance through the access port and lower port site. First, the pericardium is incised from the superior vena cava to the inferior vena cava 3 cm anterior and parallel to the phrenic nerve. Stay sutures in the posterior pericardial edge are brought through the skin and anchored. Blunt dissection is used to enter the oblique sinus behind the heart.

An articulated lighted dissector is then introduced into the chest through a port and passed into the oblique sinus beneath the right inferior pulmonary veins. While the superior vena cava is distracted medially, dissection around the pulmonary veins is completed with the lighted dissector. The dissector is exchanged for an 18F red rubber catheter to secure the path beneath the right pulmonary veins. The bipolar clamp, with its lower jaw placed in the end of the red rubber catheter, is introduced through the port incision. The red rubber catheter is then used to guide the lower jaw of the clamp behind the left atrial cuff adjacent to the right pulmonary veins as the

upper jaw passes in front of the veins. The red rubber catheter is then removed. Correct positioning of the clamp on the atrium and not on the pulmonary vein is verified by means of direct inspection of the device after closing the jaws of the clamp.

Once the position of the jaws has been confirmed, bipolar RF energy is applied to electrically isolate the right pulmonary veins; 2 or more overlapping lesions are created to ensure isolation. Right PV conduction block is confirmed by pacing as described above.

A 20F chest tube or Blake silicone drain (Ethicon) is placed, the right lung is reinflated, and the port sites are closed. No heparin is used during the procedure because the clamp is only in place for a maximum of 20 seconds. The patient is repositioned with the right side down and the left arm above the head.

The technique is repeated on the left side with the addition of division of the ligament of Marshall. As on the right side, a red rubber catheter is placed beneath the left pulmonary veins and is used to guide the bipolar clamp into place to ablate the left atrial cuff adjacent to the left pulmonary veins. Left PV conduction block is confirmed by pacing.

The LAA is then excised by stapling it with an EZ 45 stapler (Ethicon Endosurgery), which is introduced through one of the inferior port sites. The LAA exclusion is verified on transesophageal echocardiography. The pericardium is closed on the left side. If the patients are not in sinus rhythm 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.

Postprocedure and Follow-up.

Warfarin is given daily to reach INR from 2.0 to 3.0.

If patients experience atrial fibrillation postoperatively and the episode terminates spontaneously within 12 hours, the present medications are continued.

If patients experience more than one episode of postoperative AF, the AF is terminated with electrical cardioversion or pharmacologically with either ibutilide or amiodarone infusion. The present oral antiarrhythmic drugs are replaced by oral amiodarone treatment for 1 month.

In patients with no AF or only one postoperative AF, and no risk factors, antiarrhythmic drug therapy and anticoagulation therapy will be withdrawn after 3 months, provided sinus rhythm has been maintained without relapse according to the monitoring schedule. The same schedule as for transvenous ablation regarding discontinuation of anticoagulation and anti arrhythmic drugs will be followed.

Vagal denervation

Pacing at 800 bpm, 9.9 ms pulse width and 12 V for 5 seconds. A vagal reaction is defined as an arterial blood pressure (invasive) reduction of $\geq 50\%$. Diathermia performed at prespecified locations around each right and left pulmonary vein pairs, until the vagal reaction is abolished.

16 Appendix C

16.1.1 C1 Symptom Severity Questionnaire (SSQ)

Severity of Symptoms

On a scale of 1 to 5 (1= none, 5= most severe), please rate the severity of the following symptoms:

1. Palpitations

1 2 3 4 5

2. Fatigue

1 2 3 4 5

3. Shortness of breath

1 2 3 4 5

4. Lightheadedness or dizziness

1 2 3 4 5

5. Lack of energy during exertion or exercise

1 2 3 4 5

16.1.2 C2 Disease Related Symptom Questionnaire (DRSe Q)At baseline:

Which symptoms or problems are associated with your arrhythmia disturbance (atrial fibrillation)?

If you experience more than one symptom or problem, rank them in order, starting with the most important first:

1.
2.
3.
4.
5.
6.

The original ranking should be available at follow-ups.

At follow-up after treatment:

For each of the symptoms or problems indicate whether the treatment has resulted in a change:

- a) Improved
- b) Not changed
- c) Worsened

- | | | | |
|---------|-----------------------------------|--------------------------------------|-----------------------------------|
| 1. | <input type="checkbox"/> Improved | <input type="checkbox"/> Not changed | <input type="checkbox"/> Worsened |
| 2. | <input type="checkbox"/> Improved | <input type="checkbox"/> Not changed | <input type="checkbox"/> Worsened |
| 3. | <input type="checkbox"/> Improved | <input type="checkbox"/> Not changed | <input type="checkbox"/> Worsened |
| 4. | <input type="checkbox"/> Improved | <input type="checkbox"/> Not changed | <input type="checkbox"/> Worsened |
| 5. | <input type="checkbox"/> Improved | <input type="checkbox"/> Not changed | <input type="checkbox"/> Worsened |
| 6. | <input type="checkbox"/> Improved | <input type="checkbox"/> Not changed | <input type="checkbox"/> Worsened |

16.1.3 C3 EHRA symptoms classification

	Symptom severity	Definition
EHRA I	“no symptoms”	
EHRA II	“mild symptoms”	normal daily activity not affected
EHRA III	“severe symptoms”	normal daily activity affected
EHRA IV	“disabling symptoms”	normal daily activity discontinued

The classification is performed by the investigator.

The following items *during presumed arrhythmia episodes* are checked to determine the score:

Palpitations, fatigue, dizziness, dyspnea, chest pain, anxiety.

16.1.4 Patient's estimate of frequency and duration of symptomatic episodes:

- Frequency: patient estimate of average interval between symptomatic episodes
 - hours; days; weeks; months
- Duration: patient estimate of duration of most usual symptomatic episodes:
 - < 1 minute.
 - 1 minute to < 48 hours.
 - ≥ 48 hours.
 - Cardioversion required

16.1.5 C4: EQ-5D**Your own health state today**

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

1. Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

2. Self-care

- I have no problems with self-care
- I have some problems washing and dressing myself
- I am unable to wash and dress myself

3. Usual activities (eg. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

4. Pain/discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

5. Anxiety/depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

6. General health state

Compared with my general health state during the last 12 months, my health state today is:

- Better
- unchanged
- Worse

16.1.6 C4: Background variables för EQ-5D

1. Prolonged disease
 - a. Have you any prolonged disease, inconvenience after accident cases, disability or any other weakness?
 - i. yes,
 - ii. no,
 - iii. no information
2. General health conditions
 - a. How do you judge your health condition at present? Is it
 - i. very good,
 - ii. good,
 - iii. acceptable,
 - iv. poor
 - v. very poor
 - vi. no information
3. Education
 - a. What is your highest achieved level of education?
 - i. Primary school education (9 years or shorter)
 - ii. Upper secondary school 2 years (upper-secondary education maximum 2 years)
 - iii. Upper secondary school 3-4 years (upper-secondary education for maximum 3-4 years or post-secondary education shorter than 3 years)
 - iv. University/college of higher learning (3 years or longer)
 - v. no information
4. Employment
 - a. What is your main employment?
 - i. At presently employed (employee or own entrepreneurs)
 - ii. Unemployed,
 - iii. Pension or disability pension
 - iv. Other including students (students, service free for studies or households deals, other)
5. Smoking habits
 - a. Do you smoke daily?
 - i. Smokes daily
 - ii. Does not smoke daily
 - iii. no information
6. In cash margin
 - a. If you suddenly would end up in an unforeseen situation, where you within a week must get forward 1.500 Euro, would you be able to clear it?
 - i. Always or for most of it
 - ii. Never or for most of it not
 - iii. No information

16.2 Appendix D - Bicycle exercise test

Maximal symptom limited exercise test with stepwise increase of 10 W (women), 10-15 W (men) every minute.

Predicted maximal heart rate = $220 - \text{age in year}$.

Predicted maximal working load will be calculated according to Nordenfeldt's normal values (Nordenfeldt I et al: Reference values for exercise tests with continuous increase in load. Clin Physiol 1985; 5: 161-172).

Parameters to be assessed:

1. Baseline HR (beats per minute):
2. a) HR at maximal working load (beats per minute)
b) Predicted maximal heart rate (beats per minute)
c) % of predicted maximal heart rate reached
3. a) Maximal working load reached (W)
b) Predicted maximal working load
c) % of predicted maximal working load reached
4. Maximal time reached (minutes)
5. Baseline blood pressure (systolic/diastolic mmHg)
6. Blood pressure at maximal working load (max systolic/diastolic mmHg)
7. ECG before and during exercise with regard to rhythm, bundle branch block and signs of myocardial ischemia.

16.3 Appendix E - Arrhythmia definitions and analysis

Rhythms are classified as atrial fibrillation, isthmus dependant atrial flutter, left atrial tachycardia, sinus rhythm, or indeterminate.

Heart rhythm and rate will be assessed on 12 lead ECG, 24 h Holter monitoring, and Implantable Cardiac Monitors. Each episode will be correlated to the presence of symptoms.

Atrial flutter and post ablation intra atrial tachycardia assessed on Holter monitoring and ICMs will be confirmed on 12 lead ECGs if possible.

All rhythm tracings will be interpreted blindly to the treatment by a physician.

A core ECG analysis laboratory will be used.

16.3.1 Definitions

Atrial fibrillation is defined by the absence of consistent P waves before each QRS complex and an irregular ventricular rate. An arrhythmia has to last ≥ 1 minute to be classified as sustained atrial fibrillation or atrial flutter.

Atrial flutter is defined by a regular atrial activity with a regularly blocked ventricular rate or 1:1 AV conduction. The AA interval may range from 240-280 ms. All recordings with suspected flutter or macro-reentrant atrial tachycardia, and post ablation left atrial tachycardia will be evaluated by 2 investigators, blinded to the randomization.

Cavotricuspid isthmus-dependent flutter circuits are electrocardiographically defined as follows; Counterclockwise atrial flutter: dominant negative flutter waves in the inferior leads and a positive flutter deflection in lead V1 with transition to a negative deflection in lead V6.

Clockwise isthmus-dependent flutter: opposite pattern (ie, positive flutter waves in the inferior leads and wide, negative flutter waves in lead V1, transitioning to positive waves in lead V6)

No attempts will be made to differentiate isthmus dependant atrial flutter from post ablation left atrial tachycardia unless a 12 lead ECG is available.

Left atrial tachycardias are characterised by negative P waves in lead aVL.

An SVT is defined as a narrow and regular QRS complex tachycardia with three or more consecutive beats with a heart rate above or equal to 100 bpm.

(*An SPB* is defined as a narrow QRS complex occurring with 20% prematurity or more and differentiated from sinus arrhythmia on the basis of P wave morphology, cyclic changes in preceding R-R intervals, or both).

Bradycardia is defined as a three-interval heart rate less than 50 bpm.

A VPB is defined as a broad QRS complex occurring with 20% prematurity or more.

16.3.2 12 lead ECG

Recorded at a paper speed of 50 mm/s including a rhythm strip at paper speed 25 mm/s (1 page).

The parameters to be assessed are:

1. Heart rate in beats per minute
2. Rhythm: sinus rhythm, nodal rhythm, atrial fibrillation, isthmus dependant flutter, left atrial tachycardia, right atrial tachycardia, multifocal atrial tachycardia, atrial pacing.
 - a. AA intervals will be calculated if atrial tachycardia or atrial fibrillation is present.
3. PQ interval (ms)
4. QRS duration (ms),
5. Bundle branch block – type
6. Signs of myocardial infarction
7. QT interval (ms)
8. QTc interval according to automated analysis (ms)

16.3.3 Implantable Cardiac Monitor

Implantable Cardiac Monitor (ICM) will automatically record all episodes of atrial fibrillation. *Symptomatic* episodes of atrial fibrillation will be evaluated from the Patient Event Report and the patient activations of the ICM, by correlation with events automatically recorded on the ICM, so that the proportion of symptomatic versus asymptomatic AF episodes can be made. Patients will be asked to activate the device whenever they experience symptoms suggestive of an arrhythmia. Recurrence of asymptomatic episodes of atrial fibrillation will be evaluated automatically from the ICM.

16.3.3.1 AF burden will be analysed:

- Defined as the time spent in AF, i.e. duration of sustained AF episodes per month.
 - retrieved from the ICM AF summary
- The time spent in AF will be classified by duration, which will be retrieved from the ICM AF summary:
 - Number of paroxysms of AF duration < 1 minute per month (j.)
 - Number of paroxysms of AF duration 1 minute to < 48 hours per month
 - (c+d+e+f+g+h).
 - Number of paroxysms of AF duration \geq 48 hours per month (a+b)).

The mode of onset of AF is studied with regard to presence of an early atrial contraction or a VPB, atrial flutter or a regular SVT at the onset of AF.

The following parameters retrieved from the ICM: will be recorded.

16.3.3.2 AF summary since last session

- % of time in AF (n Hours over n days)
- Average AF time/day (ex. 15.1 hours/day)
- Average AF episodes (ex. 4.8 per day)

16.3.3.3 AF durations

	Duration	No of episodes
a	> 72 h (3d)	
b	48 – 72 (2-3d)	
c	24 – 48	
d	12 – 24	
e	4 – 12	
f	1 – 4	
g	10 min – 1 h	
h	1 min – 10 min	
i	< 1 min	

16.3.3.4 Ventricular rate

- Average ventricular rate during day and night (bpm)
- Ventricular rate during AF: max rate/day and average rate/day (bpm)

16.3.3.5 Heart rate variability

The SDNN index calculated for an interval of 5 minutes will be recorded at each visit.

16.3.3.6 Patient activity

The patient activity will be recorded in relation to baseline.

16.3.4 24 hour Holter monitoring

A standard two-three-channel digital recorder will be used. The recorders are controlled annually by the manufacturer and checked before use. The use of inferior leads II or III, will enhance the differentiation of AF from atrial flutter.

The following parameters will be assessed.

16.3.4.1 Heart rate

Mean heart rate (HR), Minimal HR and Maximal HR (bpm))

16.3.4.2 Atrial fibrillation episodes

- Number of short paroxysms of AF \geq 1 minute – 24 hours duration.
- Number of atrial tachycardias other than AF
- Total time spent in AF/24 hour (hours; minutes)
- The mode of onset of AF is studied with regard to presence of an early atrial contraction or a VPB, atrial flutter or a regular SVT at the onset of AF.

16.3.4.3 Heart Rate Variability – see substudies

16.3.5 Invasive electrophysiological study

A standardized programmed atrial stimulation study will be performed to exclude underlying supraventricular tachycardia as underlying mechanism of AF in patients with a history of regular sudden onset tachycardia and in all young patients (aged < 40 years). The programmed stimulation will be undertaken at the time for the ablation procedure or as a separate procedure prior to inclusion, except in cases where other trigger mechanisms have been revealed at the initiation of AF.

The protocol includes at least double extra-stimuli at a basic cycle length of 500 ms from the high right atrium or coronary sinus. Additional stimulation procedures will be added depending on the clinical history of the patient's arrhythmia.

16.4 Appendix F - 2-D echocardiography

Echocardiographic examinations will be made by experienced technicians familiar with the protocol. A 2.5-MHz transducer will be used for most of the examinations. The results are digitally recorded.

All recordings should be made at normal heart rates (50 – 100 beats per minute) during sinus rhythm, if possible, or atrial fibrillation. Recordings should include at least 5 cardiac cycles. Measurements will be done by one experienced physician or technician under supervision. Measurements should be averaged over 3 beats, or over 5 beats if the rhythm is irregular. Absolute values and values corrected for body surface area, using the Boyd formula, will be calculated.

16.4.1 Left ventricular function, diameters and wall thickness

Left ventricular function will be assessed by measuring LVEF (%) using modified Simpsons technique.

Left ventricular cavity diameters (cm) will be assessed by measuring LV endsystolic (LVESd) and enddiastolic diameters (LVEDd).

The presence of left ventricular hypertrophy will be determined by assessing the left ventricular mass (LVM). According to recommendation from American Society of Echocardiography a commonly used, well-validated formula for calculating LV mass is shown below. Two methods are available for calculating LV mass from 2D echocardiography: the biplane area-length method and the truncated ellipsoid method. In both methods the LV wall volume is derived by subtracting intracavitary (endocardial) LV volume from the entire (epicardial) LV volume including LV walls and ventricular septum. Myocardial mass is equal to the product of the volume and the specific gravity of the myocardium, 1.04g/mL. LV mass can also be estimated from measurements of LV dimension and wall thicknesses on 2D or M-mode echocardiograms. Without measuring the major axis of the LV, LV mass is obtained from the LV short-axis dimension and a simple geometric cube formula. The following equation provides a reasonable determination of LV mass in grams:

$$1.04[(LVID + PWT + IVST)^2 - LVID^2] \times 0.8 + 0.5$$

where LVID is the internal dimension (=LVEDd), PWT is posterior wall thickness, IVST is interventricular septal thickness, 1.04=specific gravity of the myocardium, and 0.8 is the correction factor. All measurements are made at end-diastole (at onset of the electrocardiographic R wave) excluding the endocardial echoes from the septal and posterior wall thickness, in centimeters.

16.4.2 Right atrial (RA) and left atrial (LA) size and function

Maximal right (RAmaxArea) and left atrial cavity areas (LAmxArea) will be obtained by two-dimensional echocardiographic examinations in the apical four-chamber view using tracing of endocardial contours by planimetry at the end of systole (defined as the last frame prior to mitral valve opening), and minimal right (RAminArea) and left atrial area (LAminArea) will be obtained at end diastole (at the time of the R wave on the ECG). Areas in cm².

Left atrial function will be assessed as the “fractional area change”;

$$\text{“fractional area change”} = \frac{(\text{max area} - \text{min area})}{\text{max area}}$$

16.4.2.1 LA diameter

Left atrial diameter (LAd) in cm will be calculated by M-mode as standard, for the assessment of exclusion criterion.

16.4.3 Transmitral inflow velocities

Pulsed-Doppler echocardiography will be used to assess the transmitral flow velocities from an apical four-chamber view with a sample volume from the tip of the mitral leaflets during diastole. Peak velocities of the early filling (E) wave and atrial filling (A) wave, will be measured and averaged, and the E/A ratios will be calculated. Also the E²/E-quota, deceleration time and MI grade will be evaluated. The mitral A wave on pulsed Doppler echo reflects atrial contraction during sinus rhythm.

Maximal A wave velocity (cm/s), Maximal E-wave velocity (cm/s) and the E/A ratios will be measured for left atrial contractility.

16.5 Appendix G - Heart failure

Definition

- I. Symptoms of heart failure (at rest or during exercise) and
 - II. Objective evidence (echocardiography) of cardiac dysfunction (systolic and/or diastolic) (at rest) and (in cases where the diagnosis is in doubt)
 - III. Response to treatment directed towards heart failure
- Criteria I. and II. should be fulfilled in all cases.

It will be evaluated by assessing NYHA function class, LVEF, NT pro BNP and pharmacological drug therapy required for heart failure. (ACE inh., ARB blockers, diuretics).

16.5.1 NYHA Functional Capacity

1. Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina.
2. Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
3. Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina.
4. Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

16.5.2 NT pro BNP:

Sample should be taken after 15 minutes of rest. The Rhythm should be recorded. S-creatinine should be analysed.

16.6 Appendix H - Stroke

16.6.1 TOAST criteria for classification of stroke

Etiology of ischemic strokes can be classified in five categories by clinical and imaging criteria. These are:

1. large-artery atherosclerosis
2. cardioembolism
3. small-vessel occlusion
4. stroke of other determined etiology (e.g. large vessel dissection)
5. stroke of undetermined etiology.

16.6.2 Rankin score for stroke severity

Grade I. No significant disability: able to carry out all usual duties

Grade II. Slight disability: unable to carry out some of previous activities but able to look after own affairs without assistance

Grade III. Moderate disability: requiring some help but able to walk without assistance.

Grade IV. Moderate severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance

Grade V. Severe disability: bedridden, incontinent and requiring constant nursing care and attention

16.7 Appendix I - Substudies:

16.7.1 1. Evaluation of thrombusformation in the left atrium

Transesophageal echocardiography.

All patients randomized to ablation will be evaluated by TEE for the presence of thromboembolism in the left atrium, prior to the ablation procedure.

All patients randomized to ablation will be evaluated by CT/MRI for the assessment of PV dimensions.

TEE features associated with thromboembolism in patients with nonvalvular AF, include:

- LA/LAA thrombus,
- LA/LAA spontaneous echo contrast (SEC),
- reduced LAA flow velocity,
- aortic atheromatous abnormalities.

The purpose of this study is to compare the sensitivity of TEE versus CT /Contrast enhanced MRI for the detection of thrombus.

Thromboembolism after conversion to sinus rhythm has been reported even when TEE did not show thrombus. For patients with AF of greater than 48-h duration, a TEE-guided strategy or the traditional strategy of anticoagulation for 4 wk before and 4 wk after elective cardioversion resulted in similar rates of thromboembolism (less than 1% during the 8 wk).

16.7.2 2. Heart Rate Variability - HRV

The heart rate variability (HRV) will be assessed at 6, 12, 24, 36 and 48 months visits using a 24 hour Holter monitoring.

HRV will be used as a measure of the autonomic balance, and comparisons are made before and after intervention.

The following time domain components will be calculated:

SDNN: the standard deviation (SD) of all normal R-R intervals of an entire 24-hour ECG recording,

SDNN-index: the mean of the SD of all normal R-R intervals for all 5-minute segments of a 24-hour ECG recording

RMSSD: square root of the mean of the sum of the squared differences between adjacent normal R-R intervals over the entire 24-hour ECG recording.

The power spectrum of frequency domain is divided into four different frequency bands:

1. the total power (TP), 0.0033 - 0.40 Hz (ms^2),
2. the very low-frequency (VLF), 0.0033 - 0.04 Hz (ms^2),
3. the low-frequency (LF), 0.04 - 0.15 (ms^2) and
4. the high-frequency (HF), 0.15 - 0.40 Hz (ms^2). And then also
5. the LF/HF ratio

In the neural regulation of circulatory function, the power of the HF component and the RMSSD, supposed to correspond to the HF component, are used as markers of modulation of vagal efferent outflow. The power of the LF component is used as a marker of both sympathetic and parasympathetic modulation. The instantaneous balance between sympathetic and vagal nerve activities was measured by a single ratio, the LF/HF ratio, which is used to mirror the sympathovagal balance.

16.7.3 2. Evaluation of benefit of sinus rhythm.

Determine whether sinus rhythm obtained by AF ablation is superior to sinus rhythm by pharmacological therapy for rate and/or rhythm control.

Determine whether sinus rhythm is superior to atrial fibrillation irrespective of allocated therapy,

with regard to:

1. QoL
2. Exercise capacity, Morbidity (composite as 1 in secondary endpoints),
3. Cardiovascular hospitalizations,
4. Safety
5. Health economy.

Superiority with regard to rhythm assessed by ICM *and including a stabilization period of 1 months. Evaluated at 12 and 24 months.*

Amendment p 58: *stabilization period changed to 1 month*