PROSPECTIVE STUDY OF MEDICAL THERAPY AGAINST CRYOBALLOON ABLATION IN PATIENTS WITH SYMPTOMATIC RECENT ONSET PERSISTENT ATRIAL FIBRILLATION: METACSA

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BACKGROUND

Atrial fibrillation (AF) is the most common cardiac arrhythmia and causes significant morbidity and mortality. AF is not benign, as the mortality risk is doubled and the risk for stroke, left ventricular dysfunction and hospitalization are increased. The prevalence is 1-2%, and increases with age. [1] The health care burden is substantial. [2]

Treatment of AF is targeted on prevention of thrombo-embolic complications and the reduction of symptoms. Medication includes anticoagulation and anti-arrhythmic drugs (AAD) for either rhythm or rate-control. Although AAD are the first line of therapy, they have their shortcomings, as most AAD have been shown only to be 40-50% effective in maintaining sinus rhythm and may have serious side effects. Only amiodarone performs better, but its side effects are substantial, and it is withdrawn of treatment in about 20% of patients, which makes its efficacy comparable to that of propafenone. [3,4]

Ablation of the pulmonary veins (pulmonary vein isolation, further PVI) has proven to be a safe and effective treatment for AF with variable success rate, depending on the AF type, and the presence or absence of underlying disease. [5,6] Recent data show that non-repeated PVI with radiofrequency (RF) ablation, has only a limited effect at one year (50-60%). These results can be improved with a repeated ablation, and seem not

be maintained after 5 year. [7-11] These are some of the arguments that alternative techniques are still being investigated, inclusive minimal invasive surgical techniques.

Success rates, at least similar to RF ablation have been reported after 1-year follow-up and later with a freedom from AF of 69-77% in patients using a cryoballoon technology (CBA). [12-14]. CBA seems to be a reproducible technique, with the same outcome in different centers. It has theoretically less side effects than RF, and its only specific side effect is phrenic nerve paresis.

Results are better in paroxysmal patients, than for persistent AF, also for CBA. [13] Nevertheless, persistent patients with normal left atrial dimensions made up an important proportion of our group. [15] Differentiation between paroxysmal and short term persistent becomes almost impossible from a clinical point of view, as patients get early cardioversion, before they are spontaneously reverted to sinus rhythm. [16] Real longstanding persistent patients, however were excluded from our and all previous trials, as were patients with very large atria. Larger atria have more recurrences than smaller atria. Successful ablation results in a smaller left atrial volume, which was shown in several studies with RF, also for paroxysmal patients. [17] This volume reduction is antiarhythmic as well.

It has been hypothesized that early therapy prevents further progression of the disease. [16] This has never been proven for catheter ablation, while some pilot trials were promising. [18] Reduction of left atrial volume can be used as a substitute for antiarrhythmic efficacy and for less disease progression.

RATIONALE

Limited data indicate that ablation is better than AAD therapy. The 9 small randomized clinical trials as recently summarized by health care authorities with a correct methodology only included 971 patients, and only studied radiofrequency ablation. [19] However, there was substantial heterogeneity, with a majority of paroxysmal patients, but some had mixed groups. Endpoints in these trials were not always clear and variable as well. Side effects of ablation were somewhat neglected. Stop-AF only addressed paroxysmal patients (but included 22% cardioverted patients) and has recently been published. [14] This opens the perspective to organize a prospective trial comparing the efficacy and safety of CBA to standardized medication for treatment of paroxysmal AF and early onset persistent AF without structural heart disease. As elsewhere a trial is launched for first onset paroxysmal AF, we would like to focus in this protocol *on early onset persistent AF without structural heart disease*. The value of CBA in these patients has never been studied; the endpoints for persistent patients are much easier than for paroxysmal patients. Reduction in LA size can be compared versus patients on drug therapy and versus failing patients.

HYPOTHESIS

1. The results of CBA in early onset persistent AF are better compared to standard medical therapy with as endpoint maintenance of sinus rhythm after 1 year and an improved QOL in the ablation group.

2. Successful CBA results in reduction of the LA volume.

INCLUSION/EXCLUSION CRITERIA

The total AF history is regarded for previous episodes, paroxysmal or persistent. ~~should be shorter than 24 months~~. Symptomatic patients can be included if they have had at

least 2 episodes in their total history, of which one within the last year. One episode in the entire history should have lasted more than 7 days ~~48 h~~, requiring electrical or pharmacological cardioversion or stopped spontaneously after more than 7 days. The duration of this episode should be shorter than 1 year. If one episode is paroxysmal it should have been lasting minimal 30 sec.

All patients eligible for the study will sign informed consent, have an echocardiogram prior to inclusion to exclude severe left ventricular dysfunction, to rule out significant valve abnormalities, left ventricular hypertrophy and to assess the left atrial (LA) volume and diameter.

Prior to randomization, and after inclusion it is suggested to the local investigators to perform an MRI-scan or CT scan of the LA and pulmonary veins (in both branches of the study) in eligible patients to assess the anatomy and the left atrial volume. The results should not influence the strategy of treatment.

Inclusion criteria

- > 21 years and legally capable
- history of 2 symptomatic AF epiodes more than 30 sec .
- At least one AF episode within the last year
- One episode cardioverted after more than 7 days or spontaneously terminated after more than 7 days; this episode should have been shorter than one year
- Eligible for at least one first step drug therapy (sotalol, propafenone, or flecainide) **and/or** for amiodarone

- Left ventricular ejection fraction estimated > 45%
- LA diameter < 50 mm (parasternal short axis) ~~**and**~~ **or** LA volume less than 100 ml (apical view, Area Length method)
- No previous CVA or TIA (the latter with documented deficit on CT scan)
- ~~CHADS2VASC ≤ XXXX~~
- Failed AAD strategy, or untreated with AAD
- No use of Amiodarone in the previous 6 weeks (except IV or oral for 7 days)
- Informed consent

Exclusion criteria

- Age **> = 80** yrs
- CHF
- Ischemic heart disease as known in the history
- (Severe) Left ventricular hypertrophy as shown on echo (IVSd or PWd > 14 mm)
- Uncontrolled Hyperthyroidism
- Congenital heart disease
- HCM, ARVC, channelopathies
- Contra-indications to AAD
- Long QT syndrome

- Received already adequately dosed all level 1 drugs (sotalol, propafenone, and flecainide) and >6 weeks amiodarone
- Pure (typical) atrial flutter as documented on one occasion

INVESTIGATION DESIGN

Type

Randomized study design. Experienced centres/operators with a load of > 50 cryoablations/year.

Randomization

1:1 at the time of inclusion

SAMPLE SIZE

The maximal expected 1 year success on AAD is 50% and minimal expected success of CBA is 72%.[3,14,15,20,21,22] With a power of 0.8 and a significance of 0,05, approximately 76 patients should be included in each arm. A total number of 167 patients need to be included in the study when anticipating that 10% of the patients will not be followed as required.

INTERVENTIONS

Run-in period (from month -1 till month 0)

Holter recording in the month after inclusion, preferably directly after inclusion to avoid extra visits.

MRI or CT scan to measure LA volume and PV sizes and anatomy is encouraged

(optional – if done it should be done in both branches)

Ablation arm (at month 0):

The ablation approach should be as standardised as possible, and will be discussed at the investigators meeting

After venous punctures, 5000 IE of heparin is administered and after the transseptal puncture (TSP) this is repeated. Hereafter, heparin infusion is started with a target ACT of at least 275-300 s. A multipolar catheter will be introducted into the coronary sinus. Single TSP will be performed (guided by X-ray and intracardiac echocardiography or transoesophageal echocardiography). The 12 Fr steerable sheath is introduced into the LA, and the second generation (large) cryoballoon with the Achieve catheter is introduced. Before ablation is started, the veins are checked for entrance and exit block. If there is conduction a balloon application is given during 300 s. The occlusion grade, maximal freezing temperature and time to isolation are noted. Every vein with potentials is ablated at least twice with at least one grade IV occlusion, except when PNP occurs at the right upper PV. If not isolated, a third application can be given. If after the third application the vein is still not occluded it is up to the physican to decide to do another balloon application or to use a freezer catheter.

If isolated, the veins are checked after 30 minutes again for entrance and exit block. The left sided veins are ablated while pacing from the distal CS electrodes and when ablating the right sided veins the phrenic nerve is stimulated to prevent phrenic nerve palsy (PNP). When all veins are isolated AF induction is preformed, 5 s of pacing with CL 200 ms from the distal CS, LA roof (twice) en the HRA. Procedure times , X-ray times, and the radiation dose (mGy) are noted.

Ablation should be scheduled 4 weeks after cardioversion/inclusion. All patients should

be anticoagulated for at least 4 weeks prior to ablation. Antiarrhythmic drugs are maintained after cardioversion. One day before or the day of ablation a TEE will be made to exclude a LAA thrombus. Anticoagulation can be continued if this is the protocol of the participating centre, and the local protocol per ablation should be followed.

Proposed first level:

A: propafenone 300 mg BID / 150 mg QID if < 70 years and > 70 kg

propafenone 150 mg TID if ≥ 70 years or < 70 kg

B: sotalol 120 mg BID if men ≤70 years, cr ≤ 1,5mg/130 µmol, > 70kg;

80 mg TID if men ≥ 70 years, cr > 1,5mg/130 µmol, < 70kg;

if women ≤ 70 years; cr ≤ 1,2/110 µmol

80 mg once if women > 70 years or cr > 1,2 mg/110 µmol

C: Flecainide : Apocard Retard 100 mg/day as startdosis 4 to 5 days

Further 200 mg/day

Tambocor 100 mg BID if preferred

Proposed second level:

Amiodarone: loading 14 days with 600 mg/day

One week 400 mg/day

Maintenance 200 mg/day

Drug arm:

Anticoagulation should be continued per protocol (4 weeks) after the cardioversion. If the CHADS2VASC is ≤ 2, anticoagulation is left at the discretion of the physician. A first level antiarrhythmic drug regimen is started at the month -1, time of the inclusion and

an adequate dosage is prescribed. If the patients` condition requires so, a reduced dosage can be used during the first (5-7) days.

If at month 0, at the first clinical visit, the drug therapy does not look sufficient, another

Level 1 treatment can be used. This can be repeated if the clinical condition requests so.

The second slevel antiarrhythmic drug therapy is only allowed after failure of at least one level 1 drug. As this is amiodarone, its final efficacy can only be judged 6 months after its initiation.

FOLLOW UP : see flow charts Is in agreement with proposal in ref 23.

- 24 hour Holter:
    - after inclusion (month -1) and repeated at months 3 .This will be done with the study Holter without necessarily influencing the therapy (so called blanking period)
- 48 hour Holter: with a clinical device
    - at the end of 6 months .
- 7 days Holter: with a clinical device
    - at the end of 12 months .
- Clinical visits :

should be performed by the study nurses/supervised by the investigators

- At months 3, 6, and 12 months after ablation
- Additionally at month 0 for the drug arm, while the ablation group is admitted

- Office ECG ;

° at month 3, 6 and 12

- Drug management:
  - AAD: After 3 months stop AAD in the ablation arm in those patients free of AF episodes.
  - OAC: After 6 months consider stopping oral anticoagulation, or replacing them with antithrombotic medication in patients free of AF episodes if the scores allow so.
- Echocardiogram:
  - At month 12 a new echocardiogram is obtained to assess the LA volume and diameter.
- QOL with disease specific questionnaire (AFQOL 18)
  - At baseline and at month 12
- Blood samples
  - At baseline and at months 6 and 12
  - Thyroid tests (TSH), liver function (AP, SGOT, SGPT), creatinine

- Drug diary
    - At baseline, at month 0 and at months 6 and 12 for all patients in both arms
- Cost calculation: data should be prospectively collected in CRF at the time of scheduled and unscheduled visits, based on costs as foreseen in the reimbursement of the RIZIV/INAMI and additional drug costs.

CROSS OVER

Is allowed after 6 months. This implies that at 12 months we will be able to do not only ITT but also OTA.

SERIOUS ADVERSE EVENTS

SAE`s are expected to happen in 7% in the ablation arm, and at a rate of 12-15% in the drug arm, because of side effects and 3% because of proarrhythmia (20).

ENDPOINTS

Primary endpoints

- Sinus rhythm at clinical visit at 1 year after the ablation, or with AAD
- Freedom of AF with all measurements

Secundary endpoints

- Reduction of LA volume in successfully treated patients
- Number of cardioversions
- Percentage of patients on AAD after 6 and 12 months

- Vascular complications
- Stroke, TIA
- SAE in both groups
- Number of cross-overs (with OTA)

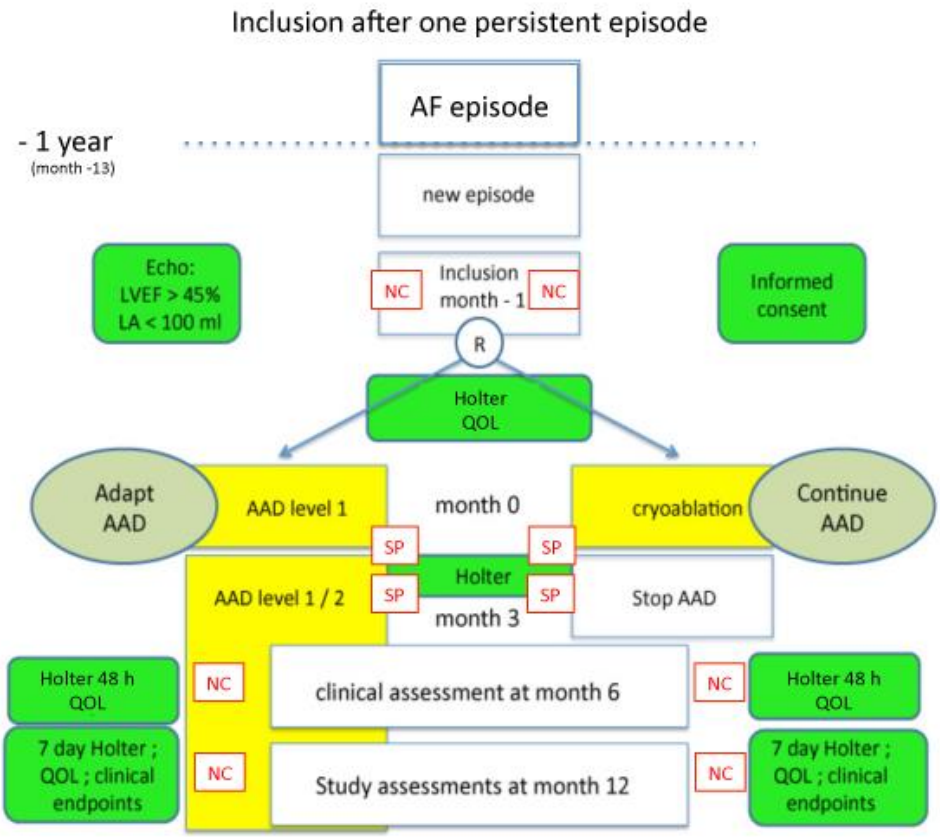

Figure 1. AAD **:** antiarrhythmic drugs; LA: left atrial; QOL: quality of life; R: randomization

STUDY ORGANISATION

Steering committee : L. Jordaens, GB Chierchia, F. Van Heuverswyn, M. De Pauw

DMSB : Dr Duytschaever, Dr. Bhagwandien, L. Deroy

One central study coordinator (University Hospital Ghent) – Pieter Vervaet

eCRF: electronic CRF will facilitate on line data management

Central data analysis of ECGs, 24 hour , 48 hr and 7 day Holters at central site ~~via software based (GEM-MED)~~

Analysis of echo in University Hospital Ghent

QOL data analysis

Cost efficacy (Belgian data) and MRI substudies will be encouraged.

STUDY SITES

Ghent University Hospital as primary Belgian site (METC submission);

~~Liege University Hospital~~

Sint Jan, Brussels

UCL - St Luc Brussels

UZ, VUB

Roeselare,

Liège, Citadelle

Luxembourg

Time line

METC submission: Sept 2013 (B); approval **3-5-2013** ; First inclusion November 2015; Inclusion completed April 2018; Follow-up completed April 2019.

Advisors:

Prof Dr Luc Deroy; Dr J; Schaar; Prof Dr Roland Stroobandt

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