Multimodality prediction of success of atrial fibrillation rhythm control strategy.

Published: 25-11-2013
Last updated: 22-04-2024

Primary objectivesTo show that a model incorporating the novel predictors BSPM, TE-ECG and SNPs is superior to existing models in predicting maintenance of sinus rhythm after successful DCC in patients with persistent AF.Secondary objectivesTo...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac arrhythmias
Study type	Observational invasive

Summary

ID

NL-OMON44772

Source
ToetsingOnline

Brief title
Multimodality prediction of AF rhythm control strategy.

Condition

- Cardiac arrhythmias

Synonym
Atrial Fibrillation

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: CTMM Cohfar

Intervention

Keyword: Atrial Fibrillation, Cardioversion, Rhythm control

Outcome measures

Primary outcome

Maintenance of SR after successful DCC.

Secondary outcome

1. Time to recurrence of AF in days

2. Failure of DCC

3. Cardiovascular mortality.

4. Hospitalisation for cardiovascular events

5. Stroke

6. Bleeding

Study description

Background summary

Atrial fibrillation (AF) affects 1-2% of the population, and its prevalence is estimated to double in the next 50 years. AF is related with increased mortality and morbidity.
There are different types of AF based on presentation and duration of the arrhythmia: paroxysmal, persistent, long-standing persistent and permanent AF. Paroxysmal AF is self-terminating within 7 days. Persistent AF lasts longer than 7 days or requires termination by cardioversion. Long-lasting persistent AF is present when AF lasts longer than 1 year and a rhythm-control strategy is adopted. Permanent AF is present when the arrhythmia is accepted by patient and physician.1
Long-term management of the arrhythmia can consist of a rate-control or rhythm-control strategy. In a rate-control strategy the goal is to control the ventricular rate adequately but not to restore sinus rhythm (SR). In a rhythm-control strategy the goal is to restore SR. Several large trials compared rhythm and rate-control strategy 2-3. The AFFIRM trial found no difference in all-cause mortality between the different strategies.2 The RACE

trial found rate control not inferior to rhythm control for prevention of cardiovascular mortality and morbidity.3 Therefor the ESC guidelines advocate a patient tailored therapy.1 The decision to choose between a rhythm or rate-control strategy is made by the patient and his cardiologist. Usually symptoms are the main reason to choose a rhythm-control strategy. A rhythm-control strategy can consist of anti-arrhythmic drug and direct current cardioversion (DCC). Anti-arrhythmic drugs can have potentially harmful side-effects and a DCC is a potentially dangerous procedure due to complications during anaesthesia. Therefore symptoms should not be the only reason to choose a rhythm-control strategy but also predictors for maintenance of SR after successful DCC should be taken into account. In patients unlikely to maintain SR a rate-control strategy might be a better solution.

Several predictors for maintenance of SR after DCC or ablation have been identified. Clinical predictors such as younger age and a shorter duration of AF predict maintenance of SR.4-7 Several parameters on a 12 lead ECG have been identified that predict maintenance of SR.8-15 Atrial dimension and function measured by echocardiography can predict maintenance of SR. Biomarkers of inflammation and cardiac specific markers have been investigated and show to be predictive in some studies.16-25 Recently common variants have been identified in patients with AF 26-28, presence of some of these variants on chromosome 4q25 predict recurrence after catheter ablation for AF.29-30 Recently a study showed these single-nucleotide polymorphisms (SNPs) to be predictive for recurrence after DCC in patients with persistent AF.31

To find patients likely to respond to rhythm control strategy we want to build a multimodality prediction model in patients with AF scheduled for DCC in order to restore SR. This model will include several known predictors stated previously and some additional diagnostic tools. An additional diagnostic tool included in this study is a transoesophageal electrocardiogram (TE-ECG). Preliminary results using ECG analysis software on a standard 12 lead ECG show a possible important role for left atrial complexity. TE-ECG recordings correspond to recordings within the left atrium.32 TE-ECG has been used in this hospital before, preliminary results confirm its correlation with left atrial complexity.

We will also record a 5 minute ECG with 5 additional surface leads. A previous study advocated at least 4 additional leads which contain the most independent information about the atrial electrocardiogram.33 In a previous study conducted in this hospital we performed body surface potential mapping (BSPM) in this patient population. Due to the promissing results (unpublished) we will also use the BSPM in this study.

In this study we aim to build a model to predict the maintenance of SR after successful DCC incorporating standard predictors such as echocardiographic parameters, clinical parameter and 12-lead ECG parameters and new parameters, including BSPM, TE-ECG and SNPs. Using this novel integrated prediction model will help in the identification of patients who will maintain SR after cardioversion. Another innovative aspect of our study is the use of daily rhythm monitoring using a versatile device (MyDiagnostick®). The clinical impact this study will have is that it helps the cardiologist to make a patient

tailored strategy in the treatment of AF as advocated by the guidelines and to prevent exposing patients not likely to maintain SR to the potentially harmful side-effect of a rhythm-control strategy.

Study objective

Primary objectives

To show that a model incorporating the novel predictors BSPM, TE-ECG and SNPs is superior to existing models in predicting maintenance of sinus rhythm after successful DCC in patients with persistent AF.

Secondary objectives

To assess the predictive value of new predictors (the TE-ECG, BSPM and SNPs) for maintenance of SR after successful DCC separately.
To assess the predictive value of new predictors (the TE-ECG, BSPM and SNPs) for time to recurrence of AF.
To assess the predictive value of predictors with respect to complete failure of cardioversion.
To assess the predictive value of predictors with respect to cardiovascular morbidity.

Study design

Patients with persistent AF scheduled for DCC will be included in this study.
At inclusion clinical characteristics of the patients will be recorded.
Clinical characteristics include medical history as well as physical examination before DCC. Physical examination will focus on vital signs and signs of heart failure.
Patients will receive an echocardiography, if not performed within the last six months. Echocardiography is standard care in patients with AF. Echocardiography will be performed to evaluate left ventricular systolic and diastolic function, valve function as well as left and right atrial dimensions.
At the day of cardioversion 24.5 ml additional blood will be drawn for biomarkers and DNA-analysis (if additional consent is obtained). This will be divided in 10 ml EDTA, 10 ml serum and 4,5 ml citrate. This will be incorporated in the regular blood examination before cardioversion, no additional venous puncture is needed. The routine blood examination focusses on potassium, renal function and coagulation. Additional blood examination focusses on inflammation (i.e. serum high sensitivity C-reactive protein, interleukin-6, tumor necrosis factor alpha, transforming growth factor beta-1), cardiac ischemia (Hs-TnT), cardiac specific biomarkers (ANP, NT-proBNP) and fibrosis. These blood samples will be processed and stored at -80 *C. The additional analysis will be done at a later stage, this means that these parameters won*t be used for patient treatment. These parameters are described

in detail in table 3.

At the 1 month visit an additional 24.5 ml blood will be drawn, the same as at the day of cardioversion. This additional venous puncture is needed to study the kinetics of biomarkers in an AF population. Furthermore, we will look more detailed into the dynamics of proteomics (i.e. change in composition due to the electrical and possible structural remodelling that occurs due to the cardioversion). There is more and more evidence for a role of proteomics in the prognoses of a successful rhythm strategy in patients with AF.43 This additional blood collection is for both the patients in AF and in SR at that time.

DNA-analysis will focus on SNPs identified in a meta-analysis of genome-wide association studies associated with AF.34 These SNPs are located near different genes involved in pacemaking activity, single transduction and cardiopulmonary development. Besides theses SNPs 2 other SNPs have been identified that predict recurrence of AF after ablation or DCC.29-31 The SNPs that will be determined in the patients and closest genes are represented in table 4. Patients won*t receive the results of the DNA-analysis about these SNPs, in line with the METC azM/UM protocol about DNA-research. This DNA-analysis will not have any consequences for the patients regarding future insurances.

Patients will routinely receive a 10 second 12 lead ECG before DCC. In the time needed for the regular blood analysis we will perform a 5 minute 17 lead ECG, TE-ECG and Tissue velocity imaging (TVI). In total this will take about 30 minutes.
A BSPM is a 184-lead surface ECG containing unipolar surface leads on the front and the back of the thorax. These BSPMs have been used in a previous study to predict recurrence after DCC and success of pharmacological cardioversion for AF. This 184-lead ECG will cause no additional discomfort for the patient compared to a regular 12-lead ECG.
The TE-ECG is a 7 French catheter containing 4 unipolar leads for oesophageal ECG monitoring. This catheter needs to be swallowed and held into place for 2 minutes. After these 2 minutes the catheter will be removed. The swallowing of the catheter is discomforting for the patient.
TVI is an echocardiographic technique used for noninvasive quantification and timing of local myocardial wall motion. TVI can be used to determine AF cycle length (AFCL) and the velocity of the local atrial fibrillatory wall motion (AFV).35 There is a strong correlation between the AFCL measured by TVI and the AFCL determined during electrophysiology studies.36 Unpublished data show that both AFCL and AFV measured by TVI can predict recurrence of AF after DCC for persistent AF.
During DCC continuous rhythm monitoring will take place to assess initial therapy success. After cardioversion another 12-lead ECG will be made to assess success after one hour, this is part of routine clinical practice.
Patients in whom SR sustains for at least one hour will receive a MyDiagnostick. The MyDiagnostick has been used previously in the study with

study number 124038. The MyDiagnostick is a stick patients need to hold in their hands for one minute. After this minute the stick will indicate whether AF is present. In the PERFORMAF study the MyDiagnostick had a sensitivity of 100% and a specificity of 95.7% in decting AF, this study has been submitted. Patients are asked to hold the stick during one minute once daily. When the Mydiagnostick indicates AF recurrence patients will receive a 12 lead ECG to confirm AF. To minimize problems with compliance and to standardise follow-up, patients will receive a 12 lead ECG after 1 month (standard care) and 6 months. When the main study endpoint is met thus AF confirmed by 12 lead ECG or patients completed the initial 6 months follow-up the daily rhythm follow-up off the study is completed. If the main study endpoint is not met within the first 6 months an additional rhythm follow-up will take place 12 months after ECV. After a maximum duration of 12 months the study is completed. Further follow-up as indicated by the patients cardiologist. The additional 24,5 ml of blood drawn at one month is for both the patients in AF and SR at that time. The study ends after this time point if the patients are in AF. If patients are still in SR after 12 months the study will end also for those patients.

Daily rhythm monitoring is used to detect recurrence of AF as soon as possible. Recurrence of AF will be detected at an earlier stage and therefor additional rhythm control treatment can be initiated earlier, if necessary. This treatment strategy will be discussed with the referring cardiologist, further follow-up as indicated by the referring cardiologist.

Study burden and risks

Patients in whom SR sustains for at least one hour will receive a MyDiagnostick. The MyDiagnostic is a stick patients need to hold in their hands for one minute. After this minute the stick will indicate whether AF or SR is present. Patients are asked to hold the stick during one minute once daily with a maximum period of 6 months. If the stick indicates AF patients will have to make 1 extra hospital visit for an ECG. Furthermore, an additional rhythm follow-up moment at 12 months will be performed.
The investigations at the day of cardioversion will take about 30 minutes.
The recording of a TE-ECG is often being used in other studies without reporting of complications. We will use a commercial available electrode, Osypka TO 4-electrode 7F catheter CE1275. As part of another study (METC 03-071) we did this examination in 30 patients without any problems. As an extra safety measurement we will exclude patients with known oesophageal disease. In large studies with these catheters no complications occurred.
Patients will receive an additional venous puncture after one month to draw additional blood.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients with persistent atrial fibrillation scheduled for direct current cardioversion.

Exclusion criteria

1. Atrial flutter at time of DCC.
2. Patients with known oesophageal disease.
3. Patients with previous operation on throat or oesophagus.
4. Postoperative atrial fibrillation.
5. Patients with previous ablation for AF.
6. Patients on anti-arrhythmic drugs (AAD).
7. Patients with pacemakers unable to detect AF and with a regular paced rhythm during AF.

8. Planned ablation for AF.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-05-2014
Enrollment:	220
Type:	Actual

Ethics review

Approved WMO Date:	25-11-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-01-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-12-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL45118.068.13