Reappraisal of Atrial Fibrillation: Interaction between HyperCoagulability, Electrical Remodeling, and Vascular Destabilisation in the Progression of AF - An observational exploratory study on pathophysiological mechanisms of AF progression AND on the role of LinQ/ CareLink guided patient tailored therapy in patients with AF (RACE V)

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2.2 Primary ObjectiveTo study clinical factors, (blood) biomarkers and genetic markers related to AF progression in patients diagnosed with recent onset self-terminating AF with special reference to hypercoagulability.2.3 Secondary Objectives1. To...

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

Summary

ID

NL-OMON50560

Source
ToetsingOnline

Brief title
RACE V

Condition

- Cardiac arrhythmias
- Dementia and amnestic conditions

Synonym
atrial fibrillation. Alzheimer□s disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Cardiovasculair Onderzoek Nederland (CVON),Medtronic B.V.

Intervention

Keyword: AF progression, atrial fibrillation, cognitieve functie, Cognitive function, Dementia, hypercoagulation

Outcome measures

Primary outcome

Progression of AF, defined as self-terminating AF proceeding into

non-self-terminating AF.

Secondary outcome

1. Feasibility of implementing changes in therapy in patients with

selfterminating AF using the LinQ/ Carelink system

2. AF burden

3. Number of AF episodes

4. Duration of AF episodes

5. MACCE (i.e. death, stroke, myocardial infarction);

6. First recurrent AF;

7. Duration and frequency of AF episodes;

8. Self-terminating AF turning into non-self-terminating AF;

9. Electrical AF complexity measured from AF waves in 12 lead ECG in patients with recurrent AF;

10. Rhythm control strategy chosen by treating physician, including:

• Rhythm control medication;

• Electrical/pharmacological cardioversion;

• Pulmonary vein isolation;

11. Echocardiographic parameters;

12. Cardiac CT parameters;

13. Prevalence and incidence of subclinical atherosclerosis and endothelial dysfunction;

14. Changes in blood biomarkers;

15. Prevalence of genotypes

16. Biomarkers in acute AF;

17. Biomarkers assessed locally in the atria;

18. Electrophysiological properties of the atria;

19. Quality of life;

Study description

Background summary

Atrial fibrillation (AF) commonly progresses from paroxysmal self-terminating to non-self-terminating persistent and permanent AF, which we call AF progression. The importance of AF progression is that it is associated with a significant disease burden, including increased cardiovascular hospitalisation and mortality due to heart failure, stroke and myocardial infarction. In order to find new strategies to prevent AF progression and to reduce major adverse

cardiac and cerebrovascular events (MACCE), we aim to elucidate the prevalence, mechanisms and markers of AF progression. The core hypothesis of our proposal links AF progression to vascular risks via hypercoagulability, i.e. activation of blood coagulation through thrombin. Hypercoagulability is an obvious, yet largely unexplored, disease mechanism in a disease like AF, with its well-known predisposition for stroke and other thromboembolic complications.

Study objective

2.2 Primary Objective
To study clinical factors, (blood) biomarkers and genetic markers related to AF progression in patients diagnosed with recent onset self-terminating AF with special reference to hypercoagulability.

2.3 Secondary Objectives
1. To study the feasibility of implementing changes in therapy in patients with selfterminating AF using the LinQ/ Carelink system
2. To study the number of patients with change in rate or rhythm control therapy because of an increase in AF burden (sum of all episodes X duration per episode) by 30% as assessed over successive 3 months periods.
3. To study the number of patients with change in rate or rhythm control therapy because an increase in number or duration of episodes of AF by more than 30% as assessed over successive 3 months periods.
4. To study the number of patients with short SCAF at baseline who show progression to SCAF/AF > 24 hours in whom anticoagulation is initiated.
5. To study the incidence of AF progression in patients diagnosed with self-terminating AF;
6. To study the cross-sectional relation between hypercoagulability and the cardiovascular and arrhythmia profile at inclusion;
7. To study changes in hypercoagulability between baseline and 2.5 years follow-up and relate these to cardiovascular and arrhythmia profiles at various time points in the study;
8. To study the clinical impact of AF progression on MACCE incidence;
9. To study gender differences in incidence of AF progression, clinical factors and (blood) biomarkers related to AF progression and occurrence of MACCE;
10. To study differences between systemic markers of hypercoagulability assessed at the moment of an acute episode of AF compared to remote from an AF episode during sinus rhythm;
11. To study differences between other biomarkers in acute AF versus sinus rhythm;
12. To study the cross sectional relation between biomarkers, the cardiovascular risk profile and arrhythmia profile at inclusion assessed at the moment of an acute episode of AF compared to remote from an AF episode in sinus rhythm;
13. To study differences between hypercoagulability assessed locally in the atria at the moment of an acute episode of AF as compared to sampled peripherally (femoral vein);

14. To study differences between other biomarkers assessed locally in the atria at the moment of AF as compared to sampled peripherally;
15. To study the cross sectional relation between biomarkers and the cardiovascular risk profile and arrhythmia profile at inclusion assessed locally in the atria at the moment of an acute episode of AF compared to sampled peripherally;
16. To study in patients included in the scene of calamity substudy the electrophysiological properties of the atria using an electro-anatomical mapping system.
17. To study the association between the electrophysiological properties of the atria with hypercoagulability, clinical characteristics, echocardiographic parameters of atrial remodeling, AF burden and other phenotypic information.
18. To study differences in AF progression rate and MACCE in patients on dabigatran, FXa inhibitors and VKA versus controls;
19. To study hidden associations between hypercoagulability, atrial remodelling, vascular disease and AF progression, using unbiased, hypothesis-free latent class clustering modelling;
20. To construct a novel risk prediction model for AF progression based on the most important phenotypic information (clinical and biomarker data) using data from the latent class clustering modelling;
21. To construct a multimarker genetic risk score with the independently associated genetic mechanisms, and study whether the multimarker genetic risk score is associated with progression of AF.

Study design

This study is a multi-center, prospective registry. A total of 750 patients with paroxysmal AF will be included. In addition to routine clinical practice, we will perform deep phenotyping and continuous rhythm monitoring. Eligible patients will be asked to participate in two substudies. In the *time of calamity* (TOC) substudy, patients with an acute episode AF will undergo one extra vena puncture. In the *scene of calamity* (SOC) substudy, extra blood collections in the left atrium will be performed in patients who undergo catheter ablation of AF as part of their clinical care.
For the HBC-x substudy, an MRI will be taken from the brain for the patients to be included, and an extensive NPO examination will be done. At the end of the study all patients will receive a shortened version of the NPO.

Study burden and risks

AF progression is a harbinger of MACCE. By continuous atrial monitoring AF progression can be carefully assessed. We expect our approach to change the clinical diagnostic approach towards patients with AF. Using continuous atrial rhythm monitoring, the early detection of AF and of AF progression will become primary diagnostic goals. Biomarking in patients reporting with an acute AF episode will emerge, comparable to the clinical routine in acute coronary

syndrome (*diagnosis before shock*). Our research will also generate new prediction rules, which should distinguish susceptible patients from resilient patients more efficiently in terms of AF progression. These results will be generated through robust clinical-epidemiological techniques, but also through cutting-edge novel analysis techniques that are able to find the hidden associations between hypercoagulability, atrial remodelling, vascular disease, and AF progression.
Risks include complications associated with implantation of the ILR, being extremely low (i.e. <0.3%) and include infection and bleeding. These potential complications are easily treatable. No additional study visits are necessary. Patients will be seen according to routine follow-up protocols. Blood sampling via vena punctures will be performed twice (at baseline and 2.5 years of follow-up), and one phone call at the end of life of the device. Complications of vena punctures are rarely reported.

In a subgroup of 100 patients blood sampling will be performed at the moment of an episode of AF (*time of calamity* or TOC). This requires one extra vena puncture. In another group of 100 patients undergoing pulmonary vein isolation, blood sampling will be performed in the atria, at the *scene of calamity* (SOC). This requires no extra puncture, will be done via catheters in situ during the procedure.

In another subgroup of 150pts (with early onset self-terminating AF) and 50pts (which also undergo CABG), a MRI scan of the brain will be made at baseline and an extensive NPO examination will be conducted. At the end of the study, all patients will be asked whether they want to take a shortened NPO. The aim of this research is to see whether atrial fibrillation leads to reduced blood flow to the brain and to problems with memory and other psychological symptoms.

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

• Age > 18 years;
• Total history <10 years of paroxysmal, self-terminating AF;
• At least one documented episode of AF and 2 symptomatic episodes or two documented episodes, documented as:
o AF on ECG, Holter-recording, loop recorder, event recorder or MyDiagnostic; or
o Subclinical AF (SCAF) detected in a Medtronic pacemaker (atrial read > 190 bpm lasting > 6 minutes).
• Able and willing to sign informed consent for the registry;
• Able and willing to undergo implantation of ILR (in patients without a CIED);
• CHA2DS2-VASc score <=5
• No other indication for oral anticoagulation (e.g. mechanical valve prosthesis)

Exclusion criteria

• Non-self-terminating, persistent AF;
• Only AF due to a trigger (i.e. postoperative, due to infection);
• Congenital heart disease;
• Refusing to temporarily stop (N)OAC for coagulation phenotyping (in patients already on (N)OAC before inclusion in this study), with the exception for patients with a history of ischemic stroke/ transient ischemic attack;
• Prior pulmonary vein isolation (PVI) or on waiting list for PVI or expected to be placed on waiting list within one year;
• Expected to start with, or currently using amiodarone;
• Pregnancy;
• ICD, CRT or pacemaker that is not a Medtronic pacemaker;

• Life expectancy of less than 2.5 years.;
• Ventricular pacing >50% In patients with a Medtronic pacemaker.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	28-06-2017
Enrollment:	750
Type:	Actual

Medical products/devices used

Generic name:	Implantable loop recorder (ILR)
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	15-03-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-05-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-09-2017

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
Other	Clinicaltrials.gov NCT02726698
CCMO	NL53561.042.16