# Reducing Atrial Pacing Rate to Reduce Atrial Fibrillation in Patients With Sick Sinus Syndrome.

ID: M-2013-225-13

Protocol date 08.08.2018 and statistical analysis plan dated 02.03.2023.

# Table of contents

# List of investigators

Prof. Jens Cosedis Nielsen, Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

Dr. Mads Brix Kronborg, Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.

Dr. Maria Hee Jung Park Frausing, Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.

Dr. Jerzy Malczynski, Department of Cardiology, Goedstrup Hospital, Herning, Denmark.

Prof. Sam Riahi, Department of Cardiology, Aalborg University Hospital, Denmark.

Dr. Katja Fiedler Holm, Department of Cardiology, Aalborg University Hospital, Denmark.

Dr. Jens Haarbo, Department of Cardiology, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark.

Dr. Charlotte Ellen Larroudé, Department of Cardiology, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark.

Dr. Andi Eie Albertsen, Department of Cardiology, Viborg Hospital, Viborg, Denmark.

Dr. Lene Svendstrup, Department of Cardiology, Aabenraa Hospital, Aabenraa, Denmark.

Dr. Ulrik Hinze, Department of Cardiology, Esbjerg Hospital, Esbjerg, Denmark.

Dr. Ole Dyg Pedersen, Department of Cardiology, Roskilde Hospital, Roskilde, Denmark.

Dr. Ulla Davidsen, Department of Cardiology, Bispebjerg Hospital, Copenhagen, Denmark.

Dr. Thomas Fischer, Vejle Hospital, Vejle, Denmark.

Dr. Jens Brock Johansen, Department of Cardiology, Odense University Hospital, Odense, Denmark.

Dr. Jens Kristensen, Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.

Dr. Christian Gerdes, Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.

# DANPACE II

## Minimised atrial pacing in patients with sick sinus syndrome: a multicentre, randomised controlled study

**Principal investigators**

Jens Cosedis Nielsen, M.D. Ph.D. DMSc

Mads Brix Kronborg, M.D. Ph.D. DMSc

Department of Cardiology

Aarhus University Hospital

Palle Juul-Jensens Boulevard 99

8200 Aarhus N

Denmark

**Study Coordinating Centre**

Department of Cardiology

Aarhus University Hospital

Palle Juul-Jensens Boulevard 99

8200 Aarhus N

Denmark

# Table of Contents

# Protocol

Version 06.06.2018 (final)

## 1. Background

Atrial fibrillation (AF) is common in patients with pacemakers and is associated with an increased risk of thromboembolism (1). Recently, we have shown that treatment with dual chamber pacing (DDD) reduces AF when compared to treatment with a single-lead atrial pacemaker (AAIR) (2), and today, DDD pacing is preferred for patients who require treatment for SSS. Typically, the pacemaker is set at a lower rate of 60 bpm and programmed to increase the heart rate during physical activity (rate-response (RR) function on). Using this setting, AF is observed in 50% of the patients with SSS within the first two years after pacemaker implantation (3). Studies have indicated that the incidence of AF increases with higher proportions of atrial pacing (4). It is not known whether an increased amount of atrial pacing *causes* AF, or simply indicates that patients who require more atrial pacing also have an increased risk of developing AF. Atrial pacing causes an abnormal electrical activation of the atria, which often leads to prolonged atrioventricular (AV) conduction resulting in more frequent ventricular pacing; all factors that have been shown capable of increasing the incidence of AF (5-11). Recent studies have confirmed that atrial overdrive pacing (intended atrial pacing at a higher rate than the intrinsic heart rhythm) does not reduce the incidence of AF and this is not recommendable (12). No other studies have investigated whether a lower pacing rate - and thus a lower proportion of atrial pacing - reduces the incidence of AF. The present randomised trial aims to test the hypothesis that reducing the atrial pacing rate to 40 bpm with the rate-response function off, reduces the incidence of AF when compared to conventional pacemaker programming at a rate of 60 bpm and activated rate-response function in patients with SSS.

## 2. Hypothesis

Reducing the pacing rate to 40 bpm with the RR function off (DDD-40) significantly reduces the incidence of AF when compared to conventional pacemaker programming at a lower rate of 60 bpm and an activated RR function (DDDR-60) in patients with SSS.

## 3. Aim

To investigate, in a randomised design, whether reducing the pacing rate to 40 bpm with the rate-response function off reduces the incidence of AF compared to conventional pacemaker programming at a lower pacing rate of 60 bpm and activated rate-response function in patients with SSS.

## 4. Study design

A Danish, multicentre, randomised study with participation of all Danish pacemaker-implanting centres. Expected inclusion during a period of 2-2½ years, and two years of follow-up.

## 5. Inclusion criteria

- Sick sinus syndrome with or without AV block and an indication for first-time implantation of a DDD pacemaker: symptomatic sinus pauses (>2 seconds) or bradycardia with or without paroxysmal AF
- Age ≥18 years
- Patient informed consent

## 6. Exclusion criteria

- Permanent or persisting (>7 days) AF prior to implantation
- Persistent symptomatic sinus bradycardia and/or chronotropic incompetence where DDD-pacing at a frequency of >40 bpm is indicated (verified with long term ECG monitoring)
- Life expectancy <1 year
- Participation in another interventional research study
- Indication for implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT)
- Pregnancy

## 7. Study course

Patients fulfilling the inclusion criteria will be asked to participate in the study either before the operation or within the first two days after the operation. Randomisation into the two study arms will be internet-based. Randomisation will be stratified for paroxysmal AF and sex documented before pacemaker implantation (bradycardia-tachycardia syndrome). The pacemaker will be programmed into the assigned pacing mode shortly after the implantation, or after randomisation if randomised after implantation. The case report form (CRF) will be internet-based. Patients will be followed-up in the outpatient clinic after 3 months, 12 months, and 24 months. Pacemakers from the following companies may be implanted, as these include home monitoring: Biotronik, Boston Scientific, Medtronic, and St. Jude Medical.

## 8. Baseline data

- Age
- Sex
- Arrhythmia (SSS with pauses >2 sec without AF/bradycardia-tachycardia syndrome (paroxysmal AF and sinus pauses/bradycardia)/SSS without pauses or AF)
- Symptoms (syncope/presyncope or dizzy spells/palpitations)
- Height and weight
- QRS duration

- Medical treatment, anticoagulation treatment (warfarin, dabigatran, or the like, and ASA)
- Previous PCI or CABG
- Previous acute myocardial infarction
- Claudication (peripheral atherosclerosis)
- Medical treatment (beta-blocker, Angiotensin-converting enzyme inhibitors (ACE-I)/Angiotensin receptor blockers (ARB), diuretics, calcium channel blocker, amiodarone, sotalol, digoxin, class Ic antiarrhythmics)
- Creatinine, $Na^+$, and $K^+$
- Previous TCI or stroke
- PR interval
- Diabetes mellitus
- NYHA functional class
- Significant heart valve disease or previous heart valve operation
- Hypertension (medically treated)
- Chronic obstructive lung disease (medically treated)
- Heart dimensions measured by echocardiography<3 months prior to implantation (LVEF, LVEDV, LVESV, and LA volume by Simpson's biplane method, and m-mode echocardiography with LA diameter, incl. LVEDD and LVESD)
- Recording of RV electrode position (apical/other) and RA electrode position (auricle/other) during the implantation

A 12-lead ECG of the intrinsic heart rhythm must be recorded prior to the pacemaker implantation and sent to the study secretariat. The ECG will be scanned into the CRF.

## 9. Follow-up data

All patients will be connected to remote monitoring, which will be followed centrally by a dedicated technician/nurse located at the coordinating centre. If desired, the implantation centres may review data from their patients via remote monitoring. All endpoints via remote monitoring will be validated.

The following data will be collected via remote monitoring:

- Pacemaker settings and values
- Time to first episodes of AF >6 min, >6 hours, and >24 hours, respectively
- Number of AF episodes >6 min, >6 hours, and >24 hours
- Percentage of time in mode switch
- Percentages of atrial- and ventricular pacing

The following data will be collected at pacemaker follow-up after 3 months, 12 months, and 24 months, and at any additional visits and entered to the CRF:

- Has the patient crossed from one study arm to another (date and cause)

- Hospitalisation(s) for AF since last visit (date)
- Direct current (DC) cardioversion or cardioversion using antiarrhythmics (date and type)
- Did the patient developed persistent AF (>7 days) (date)
- Did the patient have a stroke/TCI (date)
- Did the patient have other thromboembolic events (type and date)
- Pacemaker complications since last visit (type and date)

At 12 months follow-up the following supplementary evaluation will be done:

- QOL questionnaire (SF-36), the questionnaire will be mailed to the patient from the study secretariat after approximately 10 months. The patient will be asked to complete the questionnaire, and either bring it at 12 months follow-up, or return it directly to the study secretariat.
- 6-minute walk test (6-MWT)

In cases where patients develop symptoms raising suspicion of chronotropic incompetence, and the responsible physician finds an indication for changing the pacemaker programming from DDD-40 to DDDR-60, the following procedure must be complied with before crossing over: a 24-hour Holter monitoring must be completed (including the patient recording of symptoms) and an exercise test. Subsequently, the pacemaker programming can be changed to DDDR-60. The patient must undergo clinical re-evaluation after one month. If there is a clinical effect of the changed programming the pacemaker should be left in DDDR mode at 60 bpm. If symptoms have not improved, the pacemaker must be reprogrammed to the allocated modus (DDD-40), and the cause of symptoms be determined by other means. This is to minimise unnecessary crossovers.

If pacemaker complications are detected via remote monitoring, the implanting centre will be informed by the study secretariat. In case of AF lasting >24 hours, the implanting centre will be informed via the study secretariat for the purpose of possible DC cardioversion and/or initiation of anticoagulation treatment.

# 10. Pacemaker programming

## 11. Intervention group

DDD, lower pacing rate 40 bpm, RR function off, mode-switch active with shift to DVIR/DDIR/VVIR 60 bpm, atrio-ventricular interval (AVI) paced 150 ms and sensed 130 ms with prolongation of AVI by AVI-hysteresis promoting intrinsic conduction to a max AVI of 230 ms, and rate adaptive AVI.

## 12. Control group

DDDR, lower pacing rate 60 bpm, RR activated (low-moderate), mode-switch active with shift to DVIR/DDIR/VVIR 60 bpm, AVI paced 150 ms, and sensed 130 ms with prolongation of AVI by AVI-hysteresis promoting intrinsic conduction to a maximum AVI of 230 ms, and rate adaptive AVI.

No AF suppression algorithms are used. Change to AAI(R) pacing mode is not allowed. The maximum AVI of 230 ms must not be exceeded.

# 13. Endpoints

## 14. Primary endpoint

Time to first episode of AF >6 minutes detected by the pacemaker.

## 15. Secondary endpoints

- Time to first episode of AF>6 hours detected by the pacemaker
- Time to first episode of AF>24 hours detected by the pacemaker
- Number of AF episodes
- Percentage of time in AF
- Time to persistent AF
- Hospitalisation due to AF
- Time to DC cardioversion or medical conversion for AF
- Time to crossover (reprogramming of the pacing rate)
- Time to stroke, TCI, or thromboembolic event
- Time to death
- QOL
- 6MWT

## 16. Adjudication of endpoints

Primary endpoint: first episode of AF>6 min is adjudicated documented by electrocardiogram. This will be carried out by an independent group of electrophysiologists or competent pacemaker doctors and will be blinded with regard to randomisation arm.

Secondary endpoints: stroke, TCI, thromboembolic events, and first episode of AF >6 hours and 24 hours will be adjudicated by an independent group of electrophysiologists or competent pacemaker doctors and will be blinded with regard to randomisation. Data from patient files will be collected via the study secretariat.

# 17. Statistics

## 18. Sample size estimate

Estimation of the study population size: in the control group detection of AF after two years of follow-up is assumed in 50% of the patients as seen in the DANPACE study. With $\alpha$=0.05, 1- $\beta$=0.80, and a two-sided test, 262 patients are needed in each group to detect a reduction of an absolute 12.5% (=relative 25 %) to AF in 37.5% of the patients in the intervention group. Therefore, we are planning inclusion of a total of 540 patients randomised equally into the two groups. Patients will be stratified according to prior AF or atrial flutter.

## 19. Analysis

The incidence of the primary endpoint will be presented with Kaplan-Meier plots, and the statistical comparison between treatment groups will be estimated using log-rank tests and Cox regression

analysis with calculation of hazard ratios. The following subgroup analyses are planned: effect of the intervention in patients with and without AF prior to pacemaker implantation, effect of the intervention in patients with a baseline PR interval of longer or shorter duration than the median value. The incidence of the secondary endpoints will be presented by Kaplan-Meier plots and compared using log-rank tests, or will be reported as absolute values and percentages, mean value with standard deviation, or median with quartiles, and compared using t-tests provided normally distributed data, or corresponding non-parametric test or $\chi 2$-test. Multivariate analysis of predictors of the primary endpoint will be done using Cox regression analysis. Besides randomisation we are planning to include in the analysis the following baseline parameters: bradycardia-tachycardia syndrome, age, sex, PR-interval, LA size, LVEF. The predictive value of $CHADS_2$-VASC-score for the primary endpoint will be evaluated.

# 20. Side effects, risks, and disadvantages

The implantation implies no additional side effects, risks, complications, or disadvantages compared to standard pacemaker implantation. Potential side effects to the intervention (reduction in pacing rate to 40 bpm) are dizziness, fatigue, and reduced functional capacity. In the event of such symptoms, verified by Holter monitoring and an exercise test to result from a lack of increase in heart rate, the pacemaker may easily be reprogrammed to the conventional setting at 60 bpm. Compared to standard pacemaker follow-up the disadvantages are as follows: slightly prolonged follow-up visits (around 10 minutes longer), and at 12 months follow-up completion of a quality-of-life questionnaire and a 6-MWT.

# 21. Ethical considerations

The guidelines of the Helsinki Declaration will be followed. Study approval has been obtained from the local ethics committee and The Danish Data Protection Agency. The patients are included after written informed consent. Our study may potentially show that reducing the pacing rate causes less AF, thereby probably reducing stroke risk in these patients with SSS. All patients will be treated with a pacemaker, as indicated. Potential side effects to the intervention (reduction in pacing rate to 40 bpm) are dizziness, fatigue, and reduced functional capacity. In the event of such symptoms, the pacemaker may easily be reprogrammed to the conventional setting at 60 bpm. The intervention is not considered to imply a risk of serious adverse effects. The patients (in both randomisation arms) may potentially profit from their participation in the study, as AF is detected earlier via remote monitoring, thus facilitating prompt and appropriate treatment hereof. Reducing atrial pacing by programming a lower rate may prolong pacemaker battery longevity and thereby imply the benefit of postponed pacemaker changes.

# 22. Study organisation

## 23. Coordinating centre

Department of Cardiology, Aarhus University Hospital, Skejby, 8200 Aarhus N, Denmark

## 24. Steering committee

Aarhus University Hospital, Department of Cardiology, chairman of the steering committee and coordinating investigator Jens Cosedis Nielsen, Professor, MD DMSc

Aarhus University Hospital, Department of Cardiology, secretary for the steering committee and co-investigator Mads Brix Kronborg, MD PhD

Odense University Hospital, Department of Cardiology, investigator Jens Brock Johansen, MD PhD

Regionshospitalet Herning, Medical Department, investigator Jerzy Malczynski, MD

Sygehus Sønderjylland, Aabenraa, Medical Department, investigator Lene Svendstrup, MD PhD

Sydvestjysk Sygehus, Esbjerg, Department of Cardiology, investigator Ulrik Hintze, MD PhD

Gentofte Hospital, Department of Cardiology, investigator Jens Haarbo, MD DMSc

Bispebjerg Hospital, Department of Cardiology, investigator Ulla Davidsen, MD PhD

Hillerød Hospital, Department of Cardiology, investigator Michael Dilou Jacobsen, MD

Aalborg Sygehus, Department of Cardiology, investigator Sam Riahi, MD PhD

Regionshospitalet Viborg, Medical Department, investigator Per Dahl Christensen, MD

Roskilde Sygehus, Department of Cardiology, investigator Thomas Melchior, MD PhD

Sygehus Lillebælt, Vejle, Department of Cardiology, investigator Ulrik Hedegaard Eriksen, MD PhD

Rigshospitalet, Heart Centre, investigator Jesper Hastrup Svendsen, Professor, MD DMSc

## 25. Economy

The study has been initiated by doctors from the pacemaker implanting centres in Denmark. The study organisation will apply private and public foundations for financial support to cover the study expenses. The Danish Heart Foundation has granted DKK 512.000, Arvid Nilssons Foundation DKK 200.000, The Danish Council for Independent Research DKK 1.800.000, The Danish Pacemaker and ICD Register DKK 600.000, and Karen Elise Jensen's Fund DKK 500.000. The principal investigator is a member of The Danish Heart Foundation and part of their biomedical research committee. The principal investigator has no relation to Arvid Nilssons Foundation, Karen Elise Jensen's Foundation or The Danish Council for Independent Research. Remote monitoring is not general practise in patients with pacemakers. Therefore, we have applied the pacemaker companies for coverage of the expenses for remote monitoring during the study period. The patients receive no compensation for their participation in the study.

## 26. Feasibility

With an annual number exceeding 1000 of primary pacemaker implantations in patients with SSS in Denmark the study is considered feasible. The organisation of Danish centres performing pacemaker implantations recently finalized the DANPACE trial [2] which has impacted current international guidelines on cardiac pacing (13). The principal investigator has a long-standing experience in

conducting and coordinating single- and multicentre trials within the field of arrhythmia management (14-16).

## 27. Publication

The study results, positive or negative, will be published in an international journal with the members of the steering committee as co-authors (requires inclusion of at least 25 patients at the centre).

## 28. Summary

Atrial fibrillation (AF) is observed in 50 % of the patients with sick sinus syndrome (SSS) within the first two years after pacemaker implantation. Studies have indicated that the incidence of AF increase with higher proportion of atrial pacing. The purpose of the DANPACE II trial is to test the hypothesis that reducing the amount of atrial pacing by programming a lower rate of 40 bpm with the rate response function off reduces the incidence of AF compared to conventional pacemaker programming with a lower rate of 60 bpm and activated rate response function in patients with SSS. In a multicentre randomized study 540 patients will be randomized equally between the two study arms over two years with a follow-up period of two years. All patients will be followed via remote monitoring. The primary end point is time to first episode of AF>6 min detected by the pacemaker. Secondary endpoints include amount of AF, time to stroke, TCI, or thromboembolic event, time to death, quality of life assessments, and a 6-minute walk test.

## 29. Dansk resume

Syg sinusknude syndrom er årsagen til næsten halvdelen af alle pacemakerimplantationer i Danmark. I løbet af de først 2 år efter implantationen af pacemakeren vil halvdelen af disse patienter få konstateret for-kammerflimren. Dette er forbundet med en øget risiko for blodpropper i hjernen og død. Nogle studier tyder på, at der er en øget forekomst af forkammerflimren hos de patienter, hvor pacemakeren i en stor andel af tiden stimulerer i forkamrene. DANPACE II er et dansk multicenterstudie med forventet 540 deltagere, der vil undersøge, om det at reducere andelen af pacemakerstimulering i forkamrene vil nedsætte risikoen for at få forkammerflimren.

# Protocol amendments

## 30. Change in study population, May 2017

A recent study has shown that the incidence of AF among pacemaker patients without prior AF is as high in patients with AV block as in patients with SSS (1). It is reasonable to presume that the electromechanical effects of atrial pacing on the myocardium are the same in both populations. Hence, we also assume that they will have the same risk of AF and may therefore also potentially benefit from reduced atrial pacing. Moreover, there is no added risk from participating in this study for patients with AV block compared to patients with SSS. Therefore, we changed the inclusion criteria in the original protocol to include patients with SSS with or without AV block to enable inclusion of patients with AV block, an indication for a DDD pacemaker, and episodes of bradycardia (<60 bpm). Likewise, second- or third-degree AV block was removed from the exclusion criteria.

Minor changes:

- The exclusion criterium 'expected survival <2 years' is changed to 'expected survival <1 year'
- Changes to the investigator list. New investigators from Bisbebjerg Hospital, Hillerød Hospital, and Roskilde Hospital joined the study.
- Additional funding received from The Danish Council for Independent Research (DKK 1.800.000), The Danish Pacemaker and ICD Register (DKK 600.000), and Karen Elise Jensen's Fund (DKK 500.000).

## 31. Change in sample size estimation, June 2018

After three years of inclusion, approximately 300 patients have been enrolled. Various efforts have been made to increase the rate of enrolment; however, this appears to be futile. Hence, it is no longer realistic to enrol 900 patients into this study as originally protocolled.

The initial plan was to include enough patients to show a reduction in the incidence of AF from 50% to 40% (i.e., an absolute risk reduction of 10% corresponding to a relative risk reduction of 20%). This would require enrolment of nearly 900 patients. Assuming we only need to show a reduction in the incidence of AF from 50% to 37.5% (i.e., an absolute risk reduction of 12.5% corresponding to a relative risk reduction of 25%), this would require enrolment of only 524 patients (evenly distributed between groups). After close consideration by the Steering Committee, it was decided to change the original premise and aim for enrolment of 540 patients instead, to show a relative risk reduction of 25% in the incidence of AF in the intervention group compared to the control group. This remains a clinically relevant risk reduction, and inclusion of 540 patients is achievable. All participating centres have committed to this goal and will contribute until 540 patients have been enrolled. From an ethical perspective, it is desirable to change the study objective at this point rather than to terminate at an arbitrary time, when centres eventually cease to enrol. Finally, study completion is financially secured if terminated at enrolment of 540 patients.

# References


1. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366(2):120-9.
2. Nielsen JC, Thomsen PE, Højberg S, et al. A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. Eur Heart J. 2011;32(6):686-96.
3. Nielsen JC, Thomsen PE, Højberg S, et al. Atrial fibrillation in patients with sick sinus syndrome: the association with PQ-interval and percentage of ventricular pacing. Europace. 2012;14(5):682-9.
4. Elkayam LU, Koehler JL, Sheldon TJ, et al. The influence of atrial and ventricular pacing on the incidence of atrial fibrillation: a meta-analysis. Pacing Clin Electrophysiol. 2011;34(12):1593-9.
5. Strohmer B, Pichler M, Froemmel M, et al. Evaluation of atrial conduction time at various sites of right atrial pacing and influence on atrioventricular delay optimization by surface electrocardiography. Pacing Clin Electrophysiol. 2004;27(4):468-74.
6. Sanagala T, Johnston SL, Groot GD, et al. Left atrial mechanical responses to right ventricular pacing in heart failure patients: implications for atrial fibrillation. J Cardiovasc Electrophysiol. 2011;22(8):866-74.
7. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation. 2003;107(23):2932-7.
8. Schuchert A, Muto C, Maounis T, et al. Lead complications, device infections, and clinical outcomes in the first year after implantation of cardiac resynchronization therapy-defibrillator and cardiac resynchronization therapy-pacemaker. Europace. 2013;15(1):71-6.
9. Papageorgiou P, Monahan K, Boyle NG, et al. Site-dependent intra-atrial conduction delay. Relationship to initiation of atrial fibrillation. Circulation. 1996;94(3):384-9.
10. Wang M, Siu CW, Lee KL, et al. Effects of right low atrial septal vs. right atrial appendage pacing on atrial mechanical function and dyssynchrony in patients with sinus node dysfunction and paroxysmal atrial fibrillation. Europace. 2011;13(9):1268-74.
11. Kronborg MB, Nielsen JC. Pacing in sinus node disease to prevent atrial fibrillation. Expert Rev Cardiovasc Ther. 2012;10(7):851-8.
12. Hohnloser SH, Healey JS, Gold MR, et al. Atrial overdrive pacing to prevent atrial fibrillation: insights from ASSERT. Heart Rhythm. 2012;9(10):1667-73.
13. Gillis AM, Russo AM, Ellenbogen KA, et al. HRS/ACCF expert consensus statement on pacemaker device and mode selection. Developed in partnership between the Heart Rhythm Society (HRS) and the American College of Cardiology Foundation (ACCF) and in collaboration with the Society of Thoracic Surgeons. Heart Rhythm. 2012;9(8):1344-65.
14. Andersen HR, Nielsen JC, Thomsen PE, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet (London, England). 1997;350(9086):1210-6.
15. Nielsen JC, Kristensen L, Andersen HR, et al. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. J Am Coll Cardiol. 2003;42(4):614-23.
16. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med. 2012;367(17):1587-95.

# Statistical analysis plan

Version 03.20.2023

**Sample size calculation**

We anticipate that 50% of patients in the control group will have developed AF (>6 minutes) within two years, as observed in DANPACE. To show a relative reduction of 25% to an absolute incidence of 37.5% with $\alpha$=0.05 and a $\beta$=0.80, 262 patients must be included in each group. The trial thus included a total of 540 patients.

**Randomization**

Randomisation is accomplished via a web-based system. Patients are randomised 1:1 to

- DDD-40, or
- DDDR-60

Stratification is performed according to previous AF or atrial flutter (AFL) and sex. In both treatment arms, mode switch is active with a change to DVIR/DDIR/VVIR 60 beats per minute, atrioventricular (AVI) paced 150 milliseconds (ms) and sensed 130 ms with AVI prolongation in case of AVI hysteresis promoting spontaneous conduction up to a maximum AVI of 230 ms, as well as rate-adaptive AVI.

**Statistical principles**

The primary analysis will be conducted according to the intention-to-treat (ITT) principle (as a superiority analysis) and analysed using a Cox proportional hazard regression model. Kaplan-Meier curves will be used to display differences in AF occurrence over follow-up and compared using a two-sided log-rank test. In addition to analysis of the entire cohort, analyses and Kaplan-Meier curves will be provided for each stratum (+/- previous AF/AFL, PR interval above or below the median, age above or below the median, and in men and women). Predictors for the primary outcome will be assessed using a multivariable Cox proportional hazard regression model. Following baseline covariates will be included in this model: age, sex, bradycardia-tachycardia syndrome, PR interval, LA size, and left ventricular ejection fraction (LVEF) (model 1). The predictive value of individual components of the CHA2DS2-VASC score on the primary outcome will be evaluated (model 2). Heterogeneity of treatment effects across levels of different baseline characteristics will be assessed using an interaction term in the Cox proportional hazards model between the treatment group and relevant covariates.

Patients are followed for two years or until death, or study withdrawal. The appropriateness of the proportional hazard (PH) assumption will be assessed using conventional graphical techniques. All estimates with be presented with 95% confidence intervals (CIs) and both relative and absolute risks will be reported. A two-sided P-value ≤0.05 will be considered to indicate statistical significance. Secondary analyses are exploratory and results from these will be considered hypothesis-generating.

All statistical analyses will be performed in Stata 17.0.

**Outcomes**

*1.1. Primary endpoint*

The primary endpoint is time to first episode of device-detected AF >6 minutes evaluated at two years after randomisation.

*1.1. Secondary endpoints:*

- Time to first device-detected episode of AF>6 hours
- Time to first device-detected episode of AF>24 hours
- Time to persistent AF
- Time to hospitalisation due to AF
- Time to cardioversion of AF
- Time to crossover
- Time to stroke, TCI or thromboembolic event
- Time to death
- Quality of Life (QoL)
- 6MHWT

*1.2. Safety endpoints*

- Time to syncope or near-syncope
- Device complications

*1.3. Explanatory endpoints*

- % time in mode switch
- % A-pace
- % V-pace
- Association between % A-pacing and % time in mode-switch
- Association between % V-pacing and % time in mode switch
- Number of patients undergoing catheter ablation for AF

*1.4. Subgroups*

Subgroup analyses will be performed for:

- Patients with and without prior AF/AFL
- Patients with a baseline PR-interval shorter or longer than the median value for the study population
- Men and women

- Age above or below the median values for the study population

**Missing data**

We expect no missing information on the primary outcome. In case of missing information in outcome variables or covariates, this will be handled using multiple imputation providing we can reasonably assume the mechanism of missingness to be at random. Complete case analyses will be preferred in case missing data is prevalent in <5% of patients, and information about patients with missing data will be provided.

**Multiplicity considerations**

As noted previously, secondary analyses are considered exploratory only, and results from these will be considered hypothesis-generating. Therefore, we will not control for the type 1/familywise error rate. A statement will be provided in the methods section to note that the CIs have not been adjusted for multiplicity.

**Sensitivity analyses**

If outcome information is missing, different imputation methods will be performed (e.g., complete case analysis, worst case analysis, interpolation, last observation carried forward) to demonstrate the sensitivity of the results for assumptions. Competing risks regression and cumulative incidence curves will be generated considering the competing risk of death.

**Planned tables**

- Table 1: Baseline characteristics
- Table 2: Primary and secondary outcomes
- Table 3: Subgroup analyses

**Planned figures**

- CONSORT diagram
- Kaplan-Meier curves
- Scatter plots of association between % pacing and % time in mode switch
- Forest plot (stratified analyses on the primary outcome)
- Kaplan-Meier curve showing time to crossover (including reason for crossover)

**Commentary**

During preparation of the statistical research plan, minor changes were made. Although not originally protocolled, device-related complications as well as the occurrence of syncope or presyncope were added as safety endpoints. Information about device complications and syncope or presyncope were registered during follow-up in the online CRF, but by mistake, this was not included in the protocol as endpoints. Moreover, subgroup analyses according to sex and age above or below the median were included.