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Lenient rate control versus strict rate control for atrial fibrillation. The Danish Atrial Fibrillation (DanAF) randomised clinical trial

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Abstract

Introduction

Atrial fibrillation is the most common heart arrhythmia with a prevalence of approximately 2% in the western world. Atrial fibrillation is associated with an increased risk of death and morbidity. In most cases, a rate control strategy is recommended over a rhythm control strategy. The optimal heart rate target is controversial despite the results of the RACE II trial.

Methods and analysis

We plan a two-group, superiority randomised clinical trial. 350 outpatients with persistent or permanent atrial fibrillation will be recruited from four hospitals, across three regions in Denmark. Participants will be randomised 1:1 to a lenient medical rate control strategy (80 to 110 beats per minute (bpm) at rest) or a strict medical rate control strategy (< 80 bpm at rest). The recruitment phase is planned to be two years with three years of follow-up.

The primary outcome will be quality of life using the Short Form-36 (SF-36) questionnaire (physical component score). Secondary outcomes will be days alive outside hospital, symptom control using the Atrial Fibrillation Effect on Quality of Life, quality of life using the SF-36 questionnaire (mental component score), and serious adverse events. The primary assessment time point for all outcomes will be one year after randomisation.

Ethics and dissemination Ethics approval was obtained through the ethics committee in Region Zealand. The design and findings will be published in peer reviewed journals as well as be made available on clinicaltrials.gov.

Trial registration: Registered at Clinicaltrials.gov (NCT04542785).

Strength and limitations of this randomised clinical trial

- First trial assessing a lenient versus a strict rate control in patients with persistent atrial fibrillation.
- First superiority trial with quality of life as primary outcome in patients with both permanent atrial fibrillation and persistent atrial fibrillation.
- Pragmatic trial with multiple sites ensuring high external validity.
- Treatment providers are unblinded in a trial that is otherwise expected to have low risk of bias.
- Trial will not have enough power to assess 'hard outcomes' such as mortality and serious adverse events.

INTRODUCTION

Atrial fibrillation is the most common arrhythmia of the heart with a prevalence of approximately 2% in the western world.[1 2] Atrial fibrillation is associated with an increased risk of death and a number of morbidities.[3-9] The risks of both cerebral stroke and heart failure are increased nearly fivefold in patients with atrial fibrillation, and about 20% of all strokes may be due to atrial fibrillation.[3-8] Atrial fibrillation also has a significant impact on healthcare costs and accounts for approximately 1% of the National Health Service budget in the United Kingdom and approximately 26 billion dollars of annual expenses in the United States.[10 11]

Two different overall intervention strategies may be used for atrial fibrillation – a rhythm control strategy or a rate control strategy.[12]

We have previously shown in a systematic review with meta-analysis and Trial Sequential Analysis that rhythm control strategies compared with rate control strategies seem to significantly increase the risk of a serious adverse event in patients with atrial fibrillation. Based on current evidence as well as guidelines, it seems that most patients with atrial fibrillation should be treated with a rate control strategy unless there are specific reasons justifying a rhythm control strategy.[13 14]

The guideline recommended resting heart rate target for rate control has recently changed from below 80 beats per minute (bpm) to below 110 bpm.[13] This change was a result of the RACE II trial which randomised 614 participants to a lenient rate control strategy (< 110 bpm at rest) versus a strict rate control strategy (< 80 bpm at rest).[15] The participants were outpatients with permanent atrial fibrillation. The RACE II trial showed that a lenient rate control strategy was non-inferior compared with a strict rate control strategy on the risk of a composite outcome of mortality, stroke, cardiac arrest, arrhythmic events, systematic

emboli, or major bleeding. Furthermore, the hazard ratio of 0.84 (90% CI 0.58 to 1.21) indicated that the lenient rate control group might have a decreased risk of the composite outcome. The RACE II trial also showed no difference on quality life between the two groups, but this analysis has questionable validity.[16]

A theoretical concern when using a lenient control strategy is that patients may develop heart failure if the heart rate is too fast.[17-19] The RACE II trial found that the lenient strategy was also non-inferior for heart failure patients although it must be noted that the majority of the included participants had preserved ejection fraction at baseline. [20]

A literature search identified only the RACE II trial assessing the effect of a lenient rate control strategy versus a strict rate control strategy in atrial fibrillation. We searched the Cochrane Central Register of Controlled Trials and MEDLINE on September 26 2019, and searched clinicaltrials.gov. We found no systematic reviews or meta-analyses on the topic.

Trial rationale

Currently, lenient rate control is the guideline recommended initial rate control strategy.[13] However, this recommendation is primarily based on the RACE II trial which had two major limitations. First, the validity of the RACE II trial results when assessing symptoms and quality of life were questionable mainly because of substantial problems with missing data. For quality of life and symptom severity, only 437/614 (71%) participants had data available at maximum follow-up.[16] Furthermore, the authors did not use multiple imputation or other valid methods to handle the missing data.[21] Second, the RACE II trial only showed a lenient rate control strategy was non-inferior, but is a lenient rate control strategy superior to a strict rate control strategy? The RACE II trial was not adequately powered to confirm or reject minimal important differences between the two strategies. Conducting a superiority

randomised clinical trial and afterwards performing a systematic review with meta-analysis will give us the possibility of confirming or rejecting that there is a difference in effect between the two strategies, at least on quality of life.

Health-related quality of life as an outcome

There are many definitions of health-related quality of life.[22 23] In general, quality of life questionnaires can be designed in two ways.[22] Generic questionnaires assess multiple domains applicable to a variety of health domains.[22] They more readily permit comparison across different disease and seem to have unquestionable patient relevance.[22 24] Generic quality of life scales are often criticised for being less sensitive to change than disease specific quality of life scales, but when outcome results show no difference it is most often unknown whether the lack of difference is caused by non-sensitive outcome scales or if the results demonstrate that there is no 'true' difference between the compared interventions when assessing 'generic' quality of life.[22 24] The opposite holds true for disease specific questions, which in general are thought to be more responsive to change in the clinical condition than generic disease questionnaires but may be less patient relevant. The disease-specific questionnaires tend to focus more narrowly on the disease. Any increase in quality of life as a result of a treatment for a specific disease may be off-set by unforeseen negative consequences of the treatment which the questionnaire by design will not capture.

We will supplement the assessment using SF-36 with a disease-specific questionnaire. Currently, there seems to be no optimal questionnaire.[24 25] The Atrial Fibrillation Effect on Quality of Life (AFEQT) is a validated, disease specific questionnaire, which aims to capture the objective and subjective burden of disease.[26] It contains 20-items that aim to assess four domains: symptoms, activities, treatment concern and treatment satisfaction. It also

includes a summary score that summarises the first three domains. It assesses the burden of the atrial fibrillation symptoms.[26 27]

When assessing quality of life, it is important to focus on assessing a minimally important difference, which typically can be done using an anchor-based method or a distribution method, or a mix of the two.[28 29] To interpret the clinical significance of future trial results, we will carefully define minimal important differences for all primary and secondary outcomes (see 'Power estimations').[30]

METHODS AND ANALYSIS

Trial design

The design will be a randomised, two-group, superiority trial of lenient rate control versus strict rate control in patients with persistent atrial fibrillation. Treatment providers responsible for the rate control treatment will not be blinded, but other parties including the patients are sought to be blinded.

The present protocol follows the recommendation in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline including all items from the World Health Organization Trial Registration Data Set (supplementary file 1 and 2).

350 outpatients will be recruited from 4 university hospitals in Denmark: Holbaek University Hospital, Hvidovre University Hospital, Region Zealand University Hospital – Roskilde and Odense University Hospital.

Trial conduct

This trial will be conducted according to good clinical research practice (GCP) and the latest Declaration of Helsinki.[31 32]

Objectives

Our primary objective will be to compare a lenient rate control strategy (80 to 110 bpm at rest) with a strict rate control strategy (< 80 bpm at rest).

Randomisation

Participants will be randomised 1:1 to a lenient or a strict medical rate control strategy. The trial will use centralised randomisation at OPEN. Prior to the trial, a computer will generate randomisation sequences with varying block sizes that are unknown to the investigators. An internet-based randomisation system will be set up conducting randomisation stratified according to site, and age (below 70 years or 70 years or above). The randomising investigator will get access to the internet site through a personal pin code. The randomising investigator will not be an outcome assessor.

Blinding

The treatment provider prescribing the rate control medication will not be blinded, as the treatment requires knowledge of the group the participant is randomised to. All other treatment providers, outcome assessors, data managers, statisticians and participants, will be sought blinded (the participants will neither be informed of their rate control target nor their allocated intervention group). Blinded data will be sent to OPEN for blinded data management. Statistical analyses will be performed with the two intervention groups coded as 'A' and 'B' by two independent blinded statisticians. Two blinded conclusions will be drawn by the steering group: one assuming 'A' is the experimental group and 'B' is the control group

— and one assuming the opposite. Based on these two blinded conclusions, two abstracts will be written (will be published as a supplement to the main publication). When the blinding is broken, the 'correct' abstract will be chosen and the conclusions in this abstract will not be revised.

As all medical procedures are available to any treatment provider, we cannot foresee any reason for unblinding participants. If, however, any medical personnel deems it necessary to unblind a participant, the participant will be unblinded.

Selection of participants

Inclusion criteria

1. Atrial fibrillation (ECG-confirmed and diagnosed by the treatment provider) persistent (defined as atrial fibrillation for more than 7 days) and permanent atrial fibrillation (only rate control is considered going forward).
2. Informed consent.
3. Adult (18 years or older).

Exclusion criteria

1. No informed consent.
2. Initial heart rate under 80 bpm at rest (assessed via an electrocardiogram (ECG) before randomisation).
3. Less than 3 weeks of anticoagulation with New Oral Anticoagulants (NOAC) or 4 weeks with efficient warfarin.

4. Participants dependent on a high ventricular rate to maintain a sufficient cardiac output. Such participants could be participants with heart failure, participants with a haemodynamically significant valve dysfunction, or severely dehydrated participants. Such a decision will be made before randomisation by the treatment provider.
5. Participants who are haemodynamic unstable and therefore require immediate conversion.

Participant withdrawal

Participants can withdraw his or her consent at any time point for any reason but will be invited to still participate in the follow-up assessments.

Interventions

Lenient rate control

The heart rate will be assessed on a 12-lead resting ECG measured over 1 minute after 5 minutes of rest. The treatment provider will target a resting heart rate between 80 and 110 beats per minute when treating participants with rate control medications (see below) assigned to the lenient rate control group, i.e. treatment providers are encouraged not to attempt to lower the heart rate if already below 110 unless symptoms or other reasons necessitates this. If the heart rate is below 90, the treatment provider is encouraged to reduce rate limiting treatment. If the patient remains symptomatic due to atrial fibrillation after achieving this definition of heart rate control, Holter monitoring or exercise tests may be deemed necessary by the treatment provider. These evaluations may be followed by

adjustment of rate control drugs, rhythm control (electrical cardioversion, arrhythmia surgery, rhythm control medications) or atrioventricular node ablation.

Strict rate control

Strict rate control achieved by using rate control medication (see below) will be defined as a mean resting heart rate < 80 bpm on a 12-lead resting ECG measured over 1 minute after 5 minutes of rest. Exercise test to determine activity heart rates or Holter monitoring will only be performed if the treatment provider believes this is indicated. These evaluations may also be followed by adjustment of rate control medications, electrical cardioversion, arrhythmia surgery, or atrioventricular node ablation (treatment provider's choice).

Rate control medications

Treatment will be provided according to current guidelines and as such the algorithm for treatment will be differentiated based on the status of left ventricular ejection fraction.[14] For participants with reduced left ventricular ejection fraction, beta-blockers (metoprolol and bisoprolol) will be the primary therapy. Secondary therapies may include digoxin or amiodarone. For participants with preserved left ventricular ejection fraction, the primary therapy will be beta-blockers (metoprolol and bisoprolol) or non-dihydropyridine calcium-channel blockers (verapamil) with secondary therapy consisting of digoxin or amiodaron. Pacing therapies, alone or with atrioventricular node ablation, are utilised as indicated in the view of the treatment provider.

Below we briefly summarise the pharmacological treatment in DanAF.

Table 1: Suggested daily doses for rate control agents.

Metoprolol	50 to 200 mg/d p.o.
Bisoprolol	2.5 to 10 mg/d p.o.
Digoxin	62.5 to 250 µg/d p.o. maintenance dose according to weight, age, and renal function, loading is usually required for 3 to 7 days
Verapamil	120 to 240 mg/d p.o., no loading dose required

Concomitant medication

Besides rate control, the treatment provider will be free to prescribe any other standard medical co-intervention such as the need for anticoagulation (based on the CHA_2DS_2-VASc score and co-morbidity[14]), hypertension management, heart failure management or lipid lowering drugs as long as the prescriptions adhere to guidelines.[14] This also includes recommendations regarding modifiable risk factors that may have adverse effects on atrial fibrillation management (excess alcohol, smoking, sleep apnoea)[14 33] A brief description of what is considered standard management of co-morbidities and risk factors are given in supplementary file 3. All other interventions are allowed, if they are administered evenly in all intervention arms.

Follow-up and outcome events

All participants will be seen the treatment provider a minimum of 2 times with 1 months interval. Further visits are possible with two-week intervals until adequate titration of rate control therapy is as required or for other reasons such as participants having inadequate

symptom control, management of comorbidities, etc. Treatment providers may plan a visit sooner or later if clinically indicated. This trial is a pragmatic trial, attempting at best to replicate real life clinical conditions. As such, no additional strategies will be employed to improve adherence.

After the initial adequate titration of rate control therapy, participants are to follow the normal referral system in the Danish Health care system. A hotline will be established where treatment providers may call and ask for the participants rate control target. If treatment providers themselves do not contact the trial treatment provider, participants are encouraged to contact the trial treatment provider. If possible, a treatment provider involved in the trial will be the managing treatment provider of the referral, if the referral is to a participating department.

Primary outcome

- Quality of life using the SF-36 questionnaire (physical component score).[34]

Secondary outcomes

- Days alive outside hospital
- Symptoms due to atrial fibrillation using the Atrial Fibrillation Effect on Quality of Life (AFEQT).[26]
- Quality of life using the SF-36 questionnaire (mental component score).[34]
- Serious adverse events. We will define a serious adverse event as any untoward medical occurrence that resulted in death, was life-threatening, required

hospitalisation or prolongation of existing hospitalisation, and resulted in persistent or significant disability or jeopardised the patient.[35]

Exploratory outcomes

- All-cause mortality.
- Composite of all-cause mortality, stroke, myocardial infarction and cardiac arrest.
- Cardiac mortality.
- Stroke.
- Hospitalisation for worsening of heart failure.
- Number of hospital admissions.
- Six-minute walking distance.
- Physical activity measured using a trial accelerometer or similar
- Presence of sleep apnoea
- Heart rate
- Confidence in receiving the right treatment
- Healthcare costs.
- Various biomarkers (N-terminal pro-brain natriuretic peptide (nt-proBNP), high sensitivity C reactive protein (hsCRP), high sensitivity troponin I (hsTnI), growth differentiation factor-15 (GDF-15), interleukin 6 (IL6), cystatin-C, YKL40, soluble urokinase plasminogen activator receptor (suPAR) and fibulin-1).
- Switch to rhythm control strategy (such as rhythm control medication, DC-conversion, pulmonary vein isolation or arrhythmia surgery)
- Implantation of a pacemaker or cardioverter–defibrillator with or without AV node ablation.

- The questionnaire WorkQ

Echocardiographic outcomes

- Size of left atrium (LAVi).
- Size of left ventricle.
- Cardiac index (cardiac output / body surface area).
- Left ventricular ejection fraction.
- Tricuspid annular plane systolic excursion (TAPSE).[36]
- Midwall fractional shortening.
- Global longitudinal strain.
- Circumferential end-systolic stress.
- Diastolic dysfunction estimated by the relationship between LV filling and RR interval for the individual patient.
- Pulmonary pressure.

Adverse events

Participants will be asked during visits to the clinic if they had experienced any undesirable medical event.

SUSAR will be reported to the ethics committee within 7 days of investigators being aware of the event. Once a year, a report of all serious adverse events and serious adverse reaction will be submitted to the ethics committee.

Assessment time point

The primary assessment time point for all outcomes will be one year after randomisation.

Procedures for Screening

All participants being followed at Holbaek University Hospital, Hvidovre University Hospital, Region Zealand University Hospital – Roskilde and Odense University Hospital will receive an invitation to participate in the trial upon a routine visit in the clinic or hospitalisation for atrial fibrillation (or related conditions). Possible participants will be identified by trial staff employed at the site.

Procedures for informed consent

Participants will receive written information either immediately after being identified as a possible candidate or during the private, information session where verbal information is given. The information session will take place in an undisturbed environment. The information will be given by the project coordinator on site or medical personnel with equivalent prerequisites for conveying the project. Potential participants will be informed that they can bring a third party if they wish so. The participants will be given up to three weeks to consider participation depending on when they choose to schedule the information session. There will be a minimum of 48 hours from the information session to the obtaining of informed consent.

Data collection

Data will be attempted to be collected from all participants regardless of protocol adherence. Data will be collected after six months as well as after one, two, and three years. **Table 1** summarises the data collection in the trial.

Table 1

Schedule	**Visit 0** Base-line	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 6**	**Visit 7**
Investigations	0 mo	1 mo ± 2 w	2 mo ± 2 w	6 mo ± 2 w	12 mo ± 2 w	24 mo ± 2 w	36 mo ± 2 w
Medical history	**X**				**X**	**X**	**X**
Clinical events (hospital, tests etc.)		**X**	**X**		**X**	**X**	**X**
CHA_2DS_2VASc score	**X**				**X**	**X**	**X**
EHRA SC	**X**	**X**	**X**		**X**	**X**	**X**
SF-36, AFEQT	**X**				**X**	**X**	**X**
Physical examination	**X**				**X**	**X**	**X**
Vital signs (BP, HR)	**X**	**X**	**X**		**X**	**X**	**X**
Concom. Rx, AF Medication	**X**	**X**	**X**		**X**	**X**	**X**
Informed Consent, Inclusion/Exclusion criteria	**X**						
Randomization	**X**						
Clinical Lab. tests (as indicated)	**X**	**X**	**X**		**X**	**X**	
Study Lab. Tests	**X**			**X**	**X**	**X**	**X**

12-lead ECG	X	X	X		X	X	X
Holter monitoring as clinically indicated	X	X	X		X	X	X
Echocardiography	X				X	X	X
Six-minute walking test	X				X	X	X
Accelerometer	X				X	X	X

Abbreviations: mo= months. BP=Blood Pressure. EHRA SC=EHRA symptom classification. HR=Heart rate. Lab. tests=Laboratory tests, SF-36=Short form-36. AFEQT = The Atrial Fibrillation Effect on Quality of Life

Echocardiography will be performed by one of two assessors at each centre. A detailed plan for the echocardiographies will be developed. The echocardiographies will be sent to a core echocardiographic reading centre at Holbaek Hospital to be assessed by one of two assessors that will be blinded.

Biobank

We will further collect blood samples for a research biobank and measure: Nt-proBNP, hsCRP, hsTni, GDF-15, IL6, Cystatin-C, YKL40, suPAR and fibulin-1. In addition to the above blood samples, we will collect the following three types of blood samples: 5 ml serum, 5 ml plasma and 5 ml citrat plasma to be stored for future research. Participants will be given separate information on this blood collection as well as be required to give a separate informed consent (supplementary file 4).

Data management

All data will be sent encrypted to OPEN for management. All data on paper will be securely stored and a copy will be sent to a computerised database.

The computerised database will be continuously checked for missing values and errors at one month intervals. Before a trial site begins recruitment, an internal monitoring of the following procedures will be checked: validation of inclusion and exclusion criteria, informed consent procedure, randomisation procedure, assessment of outcomes, and data entry into Redcap.

Statistical plan and data analyses

Sample size - Quality of life using the SF-36 questionnaire (physical component score)

Using a minimal important difference of 3 points on the physical component score, a standard deviation of 10, power of 80% and a significance level of 5%, a total of 350 participants will be needed.[16 37 38] Based on this sample size, we have estimated the power of all remaining outcomes (see supplementary file 5).

Recruitment plans

We will involve key medical personnel at the different departments as well as hold sessions at the different departments informing of the trial.

Statistical analyses

A detailed statistical analysis plan will be published before or shortly after randomisation begins. In short, our primary conclusions will be based on the results of our single primary outcome. Hence, we will consider a P value of 0.05 as our threshold for statistical significance.[30] We will assess whether the thresholds for statistical and clinical significance are crossed according to the five-step procedure proposed by Jakobsen et al.[30] The two interventions will be compared regarding the primary, secondary, and exploratory outcomes. The analyses of the outcomes will be based on the 'intention to treat' principle, i.e. all randomised participants will be included in the analysis regardless of how much treatment they have received. We will secondarily analyse all outcomes according to the actual heart rate achieved (per protocol analysis) defined as the average heart rate on ECG after 5 minutes of rest. If outcomes are not present due to retraction of informed consent or dropout, the pattern of the missing data will be investigated. Missing data will be handled according to the recommendations proposed by Jakobsen et al.[21]

Analysis methods

Continuous outcomes will be analysed using linear regression, count data (days alive outside hospital) will be analysed using the van Elteren's test, and dichotomous outcomes will be analysed using logistic regression.[39] All outcomes will be analysed according to final value. Our primary analysis will be adjusted for the stratification variables used in the randomisation (site and age). When van Elteren's test is used, the primary analysis will only be adjusted for 'site'. The statistical analyses will be described in detail in a separate paper published before the analysis of the trial results begins.

Subgroup analyses

We will in the two planned statistical analysis plans (see 'Statistical analysis') in detail describe each planned subgroup analysis.

In short, we will in each publication compare:

- Patients with heart failure versus patients without heart failure. Subgroup of heart failure patients:
    - Systolic left ventricular failure with remodelling to a normal stroke volume index
    - Systolic left ventricular failure without remodelling to a normal SI at rest
    - Diastolic failure of the left ventricle due to significantly compromised post systolic relaxation of the myocardium
- Men versus women
- Different durations of atrial fibrillation
    - Less than one year
    - 1-2 years
    - More than 2 years
- Patients with ischaemic heart disease versus patients without
- Patients with a CHA_2DS_2-VASc score above 1 versus those with a CHA_2DS_2-VASc score 1 or below.
- Patients with hypertension versus patients without
- Patients with diabetes versus patients without
- Patients with age above or below 75 years
- Patients according to the European Heart Rhythm Association (EHRA) symptoms score

Data monitoring

A data monitoring committee (DMC) independent from the sponsor and the investigators will be created. The DMC will be free of conflicts of interest. The DMC will be responsible for conducting an interim analysis after 50% of participants have been included. The DMC will make recommendations to the steering committee that will ultimately decide if the trial should stop or continue (further details in supplementary file 6).

Auditing

The trial can be audited by the Regional ethics committee, which is independent from the investigators and sponsor.

Patient and public involvement

Patient were invited to work shop after the initial draft was accepted by all participating departments. They were asked to give inputs to the chosen outcomes, the written material, the relevance of the objective of the trial and any other aspects they found relevant. Patients are anticipated to work as ambassadors after the trial results are available. We will again perform a workshop to involve patients in the best strategy for dissemination.

ETHICS AND DISSEMINATION

The management of patients is in accordance with standard care and as such, patients are in no greater risk compared to receiving standard care outside the trial. It is therefore completely ethical for patients to be part of the trial. The potential benefits for further patients are that we may uncover a superior heart target to be the goal of future management of patients with atrial fibrillation.

The trial protocol has been approved by the regional ethics committee and any changes to the approved protocol will be submitted and approved before commencing the trial.

Site investigators or personnel with equivalent skills will obtain informed consent from possible participants (Supplementary file 7). Additional consent will be obtained in order to store blood samples for future research.

Before enrolment of participants, screening will be done by personnel employed at the study site using the local electronic journal system. Any information collected on potential and enrolled participants will be entered directly into Redcap, using a secure connection.

The project and its data have been registered at the Region Zealand, who is the data controller. Study investigators will have access to the full data set. OPEN, who is in charge of storing the data, will also have access to the full data set. Ethics review will also have access to data upon request. Anonymised data will be made available in a clinical trial repository.

Participants, who suffer harm during the trial, are insured by the Danish Patient Compensation Association.

Trial results will be sought published in a peer-reviewed journal. In addition, results will be communicated directly to relevant patient advocacy groups, relevant medical associations, and attempted presented at relevant congresses. Aggregate data analysis will be published in a clinical trial register no later than three years after trial results have been collected.

Authorship will be granted according to the recommendations from the International Committee of Medical Journal Editors (ICMJE).[40]

Discussion

Our trial has several strengths. It is a pragmatic trial assessing the benefits and harms of a lenient versus a strict rate control strategy in patients with both persistent and permanent atrial fibrillation. The number of inclusion and exclusion criteria is low and hence, the external validity will be high. Participants will be recruited from more than one site, which will further increase the external validity. We have performed a sample size estimation based on previous evidence with realistic intervention effects, we will adjust the thresholds for statistical significance if the sample size is not reached, and we have limited the number of outcome comparisons taking into account problems with multiplicity. Furthermore, we consider risks of bias from the allocation sequence generation, allocation concealment, blinding of outcome assessors and participants, selective outcome reporting, for-profit bias and missing outcome data. Hence, our trial will be conducted with a low risk of random errors ('play of chance') and with as low risk of systematic errors ('bias') as the trial design allows (see below).[30 41]

Our trial also has limitations. The treatment providers responsible for the rate control intervention will not be blinded, which may bias our results. Another limitation is that we do not have sufficient power to assess 'hard outcomes' such as mortality and serious adverse events. This will be explored in a future meta-analysis with individual patient data with the RACE II trial. The consequence may ultimately be that a superiority trial in terms of 'hard endpoints' is needed. Yet another limitation is that participants presumably will receive different medications and procedures in the compared groups. If we show a difference (or lack of a difference) between the groups, it will be difficult to interpret what part of the treatment algorithm for reaching a certain rate target caused this difference.

We expect the results of this trial will guide rate control treatment in patients with both persistent and permanent atrial fibrillation.

Protocol version and amendments

This is version 2.0 (January 2020). Any changes to the original protocol will be submitted to the regional ethics committee. After approval, changes will be conveyed to all investigators, participants, and trial registries.

The findings will be published in a peer reviewed journal as well as be made available on clinicaltrials.gov.

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Author contributors

JF, JCJ, AB, UD, UG, MHO, UDP, and IR participated integrally in the study design. CG provided vital advice on trial conduct. EEN and FS provided designed the echocardiography

plan. MHO designed the plan for analysis of biomarkers. JF, JCJ, and AB drafted the initial manuscript. All other authors provided critical revision and approved the final manuscript.

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Role of sponsors and funders

The trial was investigator initiated. Holbaek Hospital is the sponsor and the region of Zealand is the data controller. The study sponsors and funders had no influence on design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The Danish Heart Foundation requires to be notified by email when a publication is accepted.

Roles and responsibilities of additional parties are described in supplementary file 8.

Competing interests statement

JF (PI), IR, WBN, EEN, FSH, ODP, UG, CG, JCJ report no competing interests.

MHO reports grants from Novo Nordic Foundation outside the submitted work.

AB reports personal fees from Bayer, grants from Biotronik, personal fees from Boehringer Ingelheim, personal fees from Bristol-Myers Squibb, personal fees from MSD, grants from Theravance, outside the submitted work.

UD reports a research grant from Bayer, personal fees from Pfizer, member of advisory board for Boehringer Ingelheim, member of advisory board for Merck, outside the submitted work.

Patient consent for publication

Not required

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary file 2
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-7
	6b	Explanation for choice of comparators	4-7
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16-18

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19 + supplementary file 5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18-19
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20-21
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21 + supplementary file 6
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21 + supplementary file 6
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	22
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	22

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	22
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22-23
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22-23
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	23
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
	31b	Authorship eligibility guidelines and any intended use of professional writers	23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplementary file 7
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	supplementary file 4

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Data category	Trial information
1. Primary registry and trial identifying number	Clinicaltrials.gov (NCT04542785)
2. Date of Registration in Primary Registry	Anticipated October 2020
3. Secondary Identifying Numbers	Region Zealand Ethics committee ID: SJ-797 Internal ID number Region Zealand: REG-078-2019
4. Source(s) of Monetary or Material Support	Holbaek University Hospital Odense University Hospital Hvidovre University Hospital Region Zealand University Hospital - Roskilde Region of Southern Denmark and Region Zealand joint research fund 2018 The Danish Heart foundation grant number 19-R134-A8959-22123 The University of Southern Denmark A.P. Moeller Foundation
5. Primary Sponsor	Holbaek Hospital Smedelundsgade 60, 4300 Holbaek Hospital Denmark
6. Secondary Sponsor(s)	
7. Contact for Public Queries	JF
8. Contact for Scientific Queries	JF
9. Public Title	Lenient rate control versus strict rate control for atrial fibrillation. The Danish Atrial Fibrillation (DanAF) randomised clinical trial
10. Scientific Title	Lenient rate control versus strict rate control for atrial fibrillation. The Danish Atrial Fibrillation (DanAF) randomised clinical trial
11. Countries of Recruitment	Denmark
12. Health Condition(s) or Problem(s) Studied	Atrial Fibrillation
13. Intervention(s)	Lenient rate control versus strict rate control
14. Key Inclusion and Exclusion Criteria	Inclusion criteria: 1. Atrial fibrillation (ECG-confirmed and diagnosed by the treating physician) persistent (defined as atrial fibrillation for more than 7 days) and permanent atrial fibrillation (only rate control is considered going forward); 2.Informed consent; 3.Adult (18 years or older). Exclusion criteria: 1. No informed consent; 2.Initial heart rate under 80 bpm at rest (assessed via an electrocardiogram (ECG) before randomisation); 3. Less than 3 weeks of anticoagulation with NOAC or 4 weeks with efficient warfarin; 4. Participants dependent on a high ventricular rate to maintain a sufficient cardiac output. Such participants could be participants with heart failure, participants with a hemodynamically significant valve dysfunction, or severely dehydrated

	participants. Such a decision will be made before randomisation by the treating physician; 5. Participants who are hemodynamic unstable and therefore require immediate conversion.
15. Study Type	1. Interventional study 2. Method of allocation: Randomised Masking: Participant and outcome assessors blinded Assignment: parallel Primary purpose: Comparing two strategies
16. Date of First Enrollment	Anticipated end of august 2020.
17. Sample Size	350 planned, 0 enrolled.
18. Recruitment Status	Pending
19. Primary Outcome(s)	Short Form-36 (SF-36) questionnaire (physical component score).
20. Key Secondary Outcomes	Secondary outcomes will be days alive outside hospital, symptom control using the Atrial Fibrillation Effect on Quality of Life, quality of life using the SF-36 questionnaire (mental component score), and serious adverse events.
21. Ethics Review	Approved on 30.10.2019 by The Ethics committee in Region Zealand. Alléen 15, 4180 Soroe. Telephone number: 57 87 52 83
22. Completion Date	Anticipated completion date October 2025
23. Summary Results	Not yet available
24. IPD Sharing Statement	Plan to Share IPD: Yes

Supplementary file 3 - Management of co-morbidities

Management of heart failure and hypertension

Management of heart failure will follow the recommendations of the European Society of Cardiology. Briefly, the table below summarizes the recommendations for medical therapy. Ultimately, any management is at the discretion of the treatment providers and participants.

	LVEF <40	LVEF ≥ 40
Step 1: All participants	ACEi (Ramipril 10 mg) or ARB (Losartan 150 mg x 1)	
Step 2: If still symptomatic	Spiron 50 mg x 1	
Step 3: If still symptomatic	ARNI 97/103 x 2 instead of ACEi/ARB	
Signs of congestion	Bendroflumethiazid 2.5 -10 mg/day or Furosemide 20-40 mg/day	Bendroflumethiazid 2.5 -10 mg or Furosemide 20-40 mg
Additional treatment if HomeBP > 130/80	Bendroflumethiazid 2.5 -10 mg or amlodipine 5-10 mg x 1 (or spiron 25-50 mg if not on step 2)	ACEi (Ramipril 10 mg) or ARB (Losartan 150 mg x 1) or Bendroflumethiazid 2.5 -10 mg or amlodipine 5-10 mg x 1 (Possibly spiron 25-50mg)

Sleep apnea

Participants will be systematically screen for signs of sleep apnea. If signs and symptoms of sleep apnea are discovered, participants will be referred to treatment if appropriate.

Obesity

Weight loss will be encouraged if BMI > 25. General advice will be provided and involvement of participants in local municipal programs will be discussed.

Smoking

Participants will be asked about their smoking habits as part of the initial work-up. Participants will be informed of the detrimental effects of smoking on health. Current smokers will be encouraged to quit and will be informed of available support programs through the municipals.

Alcohol

Participants will be asked about their alcohol habits as part of the initial work-up. Participants will be informed of current evidence regarding alcohol in atrial fibrillation and will be encouraged to abstain from alcohol or alternatively reduce their alcohol intake. Special emphasis will be put on participants who drink above 10 standard drinks/week.[1 2]

Physical activity

Participants will be asked about their physical activity and physical function. Based on an individual assessment, some participants may be offered exercised based cardiac rehabilitation, but it will not be systematically prescribed.[3] This will typically be participants who are limited in their daily activities or who have had a recent significant decline in their physical function. Participants with ischemic heart disease, heart failure or recent operation for valve disease will in general be referred to exercise-based cardiac rehabilitation.

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Supplementary file 4 - biobank

We will further collect blood samples for a research biobank and measure: Nt-proBNP, hsCRP, hsTni, GDF-15, IL6, Cystatin-C, YKL40, suPAR and Fibulin-1. Due to the manner of which these analysis have to be analysed and the variations in the measurement depending on blood sample kit is used, blood samples will be collected at the first visit, after 6 months, and at follow-up after 1 year and analysed together. Follow up after two and three years will be analysed together. These analyses will require 10 mL of blood per collection. The blood samples are expected to be analysed either at a laboratory in Sweden or a laboratory in Denmark, but may end up being analysed in another EU country. The storage of data will abide by the Danish General Data Protection Regulation and the Danish Data Protection Act in Denmark.

Any spare blood that is collected will be stored in a biobank in Denmark for future unspecified research purposes. The storage of data will still abide by the Danish General Data Protection Regulation and the Danish Data Protection Act in Denmark.

In addition to the above blood samples, we will collect three different types of blood samples: 7 ml. serum, 7 ml plasma and 7 ml citrat plasma to be stored for future research. This will total approximately 31 mL of blood. The blood samples are expected to be analysed either at a laboratory in Sweden or a laboratory in Denmark, but may end up being analysed in another EU country. Participants will be given separate information on this blood collection as well as be required to give a separate informed consent.

The storage of data will abide by the Danish General Data Protection Regulation and the Danish Data Protection Act in Denmark.

Supplementary file 5 – Power estimations of secondary outcomes

The below power calculations are based on a sample size of 350 participants as specified in the main document.

Days alive outside hospital

Using a minimal important difference of 3 days, a standard deviation of 9, a risk of type I error of 5%, and accounting for the fact that the data is expected not to be normal distributed, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 82.1%.[1]

The Atrial Fibrillation Effect on Quality-of-Life (AFEQT)

In previous trials the observed difference between groups was normally distributed with a standard deviation of 21.[2 3] Using a minimal important difference of 7, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 87.5%. The Type I error probability associated with this test of this null hypothesis is 5%.

Quality of life using the SF-36 questionnaire (mental component score)

In previous trials the observed difference between groups was normally distributed with a standard deviation 10.[4-6] Using a minimal important difference of 4, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 96%. The Type I error probability associated with this test of this null hypothesis is 5%.

Serious adverse events

We anticipate a failure rate among control of 20%. If we anticipate a relative risk reduction of 60%, we will be able to reject the null hypothesis with probability (power) of 90.2%. The Type I error probability associated with this test of this null hypothesis is 5%.

POWER ESTIMATIONS OF EXPLORATORY OUTCOMES

All-cause mortality

Prior data indicate that the mortality rate among controls is about 5%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.7%. The Type I error probability associated with this test of this null hypothesis is 5%.

Composite of all-cause mortality, stroke, myocardial infarction and cardiac arrest

Prior data indicate that this outcome occurs in controls in about 8%.[7 8] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.9%. The Type I error probability associated with this test of this null hypothesis is 5%.

Cardiac mortality

Prior data indicate that the failure rate among controls is 3.9%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.4%. The Type I error probability associated with this test of this null hypothesis is 5%.

Stroke

Prior data indicate that cardiac mortality among controls is 3.9%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.4%. The Type I error probability associated with this test of this null hypothesis is 5%.

Hospitalisation for worsening of heart failure

Prior data indicate that heart failure among controls is 27.4%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 9.0%. The Type I error probability associated with this test of this null hypothesis is 5%.

Number of hospital admissions

Prior data indicate that number of participant who are hospitalised is 27.4%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 9%. The Type I error probability associated with this test of this null hypothesis is 5%.

Six-minute walking distance

In previous trials the observed difference between groups was normally distributed with a standard deviation 75.[9-11] Using a minimal important difference of 40, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 99.9%. The Type I error probability associated with this test of this null hypothesis is 5%.

Physical activity using trial accelerometer

Prior data indicates that the standard deviation among groups was 65 minutes pr. Day when measuring sedentary behaviour. Assuming a difference in groups of 20 minutes/day, we will be able to reject the null hypothesis with a probability of 81.9%. The type 1 error probability associated with this test of this null hypothesis is 5%.[12 13]

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Supplementary file 6. Short description of the independent Data Monitoring and Safety Committee (DMSC)

The DMSC will be responsible for securing the safety of the trial participants. The DMSC may also provide recommendations regarding other aspects of the trial at their leisure. The DMSC will give its recommendations to the steering committee (SC).

The exact composition of the DMSC will be specified later but is expected to consist of two clinicians and one person with adequate statistical knowledge to conduct the interim analysis. The members of the DMSC will be free of conflicts of interest.

The DMSC will conduct an interim analysis after 50% of participants have been included and data secured for the six months follow-up. Based on this, the DMSC will recommend whether to continue the trial with/without alterations, or stop the trial early. The SC will make the ultimate decision. The DMSC will not be scheduled to meet in person. However, if by consensus the DMSC deems this necessary, a physical meeting can be arranged. Otherwise the DMSC will be in contact by email and phone as they deem necessary. The interim analysis will be conducted by independent statistician (to be decided). The data will be presented blinded to the DMSC but the DMSC can request unblinding.

Supplementary file 7 – informed consent form

(S4)

Informed consent to participate in a health-related research project

Research project title: Lenient rate control versus strict rate control for atrial fibrillation. The Danish Atrial Fibrillation (DanAF) randomised clinical trial

Statement from trial participant:

I have received both written and verbal information and have received enough information regarding purpose, methods, harms and benefits to give informed consent.

I know that it is voluntary to participate and that I always have the right to withdraw my consent without losing my right to treatment now or in the future.

I give my consent to participate in the research project and that my biological material may be collected with the intention of storing it in a research biobank. I have received a copy of this consent form along with written information regarding the project for my personal use.

Participant name: _____

Date: _____ Signature: _____

If during the research project significant information regarding your health, you will be informed. If you would like not to be informed of any new information regarding your health that comes to our attention during the trial, we ask that you mark here: _____ (mark with an x)

Do you wish to be informed of the results of the trial and possible consequences for you?:

Yes _____ (mark with an x) No _____ (mark with an x)

Statement from the person providing information to the participant:

I declare that the participant has received written and verbal information about the trial.

To my knowledge there has been given enough information to make a decision to participate in the trial.

Printed name of the person, who has given the information:

Date: _____ Signature: _____

Regional ethics commitee project identification:

69694

Supplementary file 8 - Roles and responsibilities

Principal investigator (Joshua Feinberg)

Design and conduct of DanAF

Preparation of protocol and revisions

Design of Redcap database

Organising steering committee meetings

Publication of study reports

In charge of supervising start-up of sites

Budget administration and contractual issues with individual centres

Organisation of central serum sample collection

Randomisation

Site investigators

Joshua Feinberg (Holbaek University Hospital), Axel Brandes (Odense University Hospital), Ulrik Dixen (Hvidovre University Hospital) and Ole Dyg Pedersen (Region of Zealand University Hospital - Roskilde)

Responsible for the proper conduct at respective sites.

In charge of reporting SUSAR to PI in a timely manner as well as reporting serious adverse events for annual review.

Steering committee (SC)

All authors of the protocol will be invited to be part of the steering committee.

Agreement of final protocol

Reviewing progress of study and if necessary agreeing changes to the protocol.

In charge of reviewing proper conduct of the trial according to GCP, Helsinki-declaration and ethics review demands.

Providing advice to lead investigators and personnel.

Assistance with international review

Data manager

Maintenance of trial IT system and data entry (OPEN).

Data verification (OPEN in collaboration with PI)

Outcome adjudication committee

Responsible for adjudicating serious adverse events

BMJ Open

Lenient rate control versus strict rate control for atrial fibrillation. A protocol for the Danish Atrial Fibrillation (DanAF) randomised clinical trial

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Primary Subject Heading:	Cardiovascular medicine
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Keywords:	Cardiology < INTERNAL MEDICINE, Adult cardiology < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY

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Lenient rate control versus strict rate control for atrial fibrillation. A protocol for the Danish Atrial Fibrillation (DanAF) randomised clinical trial

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Abstract

Introduction

Atrial fibrillation is the most common heart arrhythmia with a prevalence of approximately 2% in the western world. Atrial fibrillation is associated with an increased risk of death and morbidity. In many cases, a rate control strategy is recommended. The optimal heart rate target is disputed despite the results of the Comparison between Lenient versus Strict Rate Control **II** (RACE II) trial.

Our primary objective will be to compare a lenient rate control strategy (<110 beats per minute (bpm) at rest) with a strict rate control strategy (<80 bpm at rest).

Methods and analysis

We plan a two-group, superiority randomised clinical trial. 350 outpatients with persistent or permanent atrial fibrillation will be recruited from four hospitals, across three regions in Denmark. Participants will be randomised 1:1 to a lenient medical rate control strategy (<110 bpm at rest) or a strict medical rate control strategy (< 80 bpm at rest). The recruitment phase is planned to be two years with three years of follow-up. Recruitment is expected to start in January 2021.

The primary outcome will be quality of life using the Short Form-36 (SF-36) questionnaire (physical component score). Secondary outcomes will be days alive outside hospital, symptom control using the Atrial Fibrillation Effect on Quality of Life, quality of life using the SF-36 questionnaire (mental component score), and serious adverse events. The primary assessment time point for all outcomes will be one year after randomisation.

Ethics and dissemination Ethics approval was obtained through the ethics committee in Region Zealand. The design and findings will be published in peer reviewed journals as well as be made available on clinicaltrials.gov.

Trial registration: The trial has been registered at clinicaltrials.gov (NCT04542785).

Strength and limitations of this randomised clinical trial

- First trial assessing a lenient versus a strict rate control in patients with persistent atrial fibrillation.
- First superiority trial with quality of life as primary outcome in patients with both permanent atrial fibrillation and persistent atrial fibrillation.
- Pragmatic trial with multiple sites ensuring high external validity.

- Treatment providers are not blinded in a trial that is otherwise expected to have low risk of bias regarding blinding of other domains.
- Trial will not have enough power to assess 'hard outcomes' such as mortality and serious adverse events.

INTRODUCTION

Atrial fibrillation is the most common arrhythmia of the heart with a prevalence of approximately 2% in the western world.[1 2] Atrial fibrillation is associated with an increased risk of death and a number of morbidities.[3-9] The risks of both cerebral stroke and heart failure are increased nearly fivefold in patients with atrial fibrillation, and about 20% of all strokes may be due to atrial fibrillation.[3-8] Atrial fibrillation also has a significant impact on healthcare costs and accounts for approximately 1% of the National Health Service budget in the United Kingdom and approximately 26 billion dollars of annual expenses in the United States.[10 11]

Two different overall intervention strategies may be used for atrial fibrillation – a rhythm control strategy or a rate control strategy.[12-14]

We have previously shown in a systematic review with meta-analysis and Trial Sequential Analysis that rhythm control strategies compared with rate control strategies seem to significantly increase the risk of a serious adverse event in patients with atrial fibrillation.[13 14] Based on current evidence as well as guidelines, it seems that most patients with atrial fibrillation should be treated with a rate control strategy unless there are specific reasons justifying a rhythm control strategy.[13 14]

The guideline recommended resting heart rate target for rate control has recently changed from below 80 beats per minute (bpm) to below 100 to 110 bpm at rest depending on the

guideline.[12 14 15] This change was a result of the Comparison between Lenient versus Strict Rate Control II (RACE II) trial which randomised 614 participants to a lenient rate control strategy (< 110 bpm at rest) versus a strict rate control strategy (< 80 bpm at rest).[16] The participants were outpatients with permanent atrial fibrillation. The RACE II trial showed that a lenient rate control strategy was non-inferior compared with a strict rate control strategy on the risk of a composite outcome of mortality, stroke, cardiac arrest, arrhythmic events, systematic emboli, or major bleeding. Furthermore, the hazard ratio of 0.84 (90% CI 0.58 to 1.21) indicated that the lenient rate control group might have a decreased risk of the composite outcome. The RACE II trial also showed no difference on quality life between the two groups, but this analysis has questionable validity.[17]

A theoretical concern when using a lenient control strategy is that patients may develop heart failure if the heart rate is too fast.[18-20] The RACE II trial found that the lenient strategy was also non-inferior for heart failure patients although the majority of the participants had preserved ejection fraction at baseline. [21]

A literature search identified only the RACE II trial assessing the effect of a lenient rate control strategy versus a strict rate control strategy in atrial fibrillation. We searched the Cochrane Central Register of Controlled Trials and MEDLINE on September 26 2019, and searched clinicaltrials.gov. We found no systematic reviews or meta-analyses on the topic.

Trial rationale

Currently, lenient rate control is the guideline recommended initial rate control strategy.[14] However, this recommendation is primarily based on the RACE II trial which had two major limitations. First, the validity of the RACE II trial results when assessing symptoms and quality of life were questionable mainly because of substantial problems with missing data.

Regarding quality of life and symptom severity, only 437/614 (71%) participants had data available at maximum follow-up.[17] Furthermore, the authors did not use multiple imputation or other valid methods to handle the missing data.[22] Second, the RACE II trial only showed a lenient rate control strategy was non-inferior, but is a lenient rate control strategy superior to a strict rate control strategy? The RACE II trial was not adequately powered to confirm or reject minimal important differences between the two strategies. Conducting a superiority randomised clinical trial and afterwards performing a systematic review with meta-analysis will give us the possibility of confirming or rejecting that there is a difference in effect between the two strategies, at least on quality of life.

Health-related quality of life as an outcome

There are many definitions of health-related quality of life.[23 24] In general, quality of life questionnaires can be designed in two ways.[23] Generic questionnaires assess multiple domains applicable to a variety of health domains.[23] They more readily permit comparison across different disease and seem to have unquestionable patient relevance.[23 25] Generic quality of life scales are often criticised for being less sensitive to change than disease specific quality of life scales, but when outcome results show no difference it is most often unknown whether the lack of difference is caused by non-sensitive outcome scales or if the results demonstrate that there is no 'true' difference between the compared interventions when assessing 'generic' quality of life.[23 25] The opposite holds true for disease specific questions, which in general are thought to be more responsive to change in the clinical condition than generic disease questionnaires but may be less patient relevant. The disease-specific questionnaires tend to focus more narrowly on the disease. Any increase in quality

of life as a result of a treatment for a specific disease may be off-set by unforeseen negative consequences of the treatment which the questionnaire by design will not capture.

We will supplement the general assessment using SF-36 with a disease-specific questionnaire. Currently, there seems to be no optimal questionnaire.[25 26] The Atrial Fibrillation Effect on Quality of Life (AFEQT) is a validated, disease specific questionnaire, which aims to capture the objective and subjective burden of disease.[27] It contains 20-items that aim to assess four domains: symptoms, activities, treatment concern and treatment satisfaction. It also includes a summary score that summarises the first three domains. It assesses the burden of the atrial fibrillation symptoms.[27 28]

When assessing quality of life, it is important to focus on a minimally important difference, which typically can be done using an anchor-based method or a distribution–based method, or a mix of the two.[29 30] To interpret the clinical significance of future trial results, we will carefully define minimal important differences for all primary and secondary outcomes (see 'Statistical plan and data analyses').[31]

Objectives

Our primary objective will be to compare a lenient rate control strategy (< 110 bpm at rest) with a strict rate control strategy (< 80 bpm at rest).

METHODS AND ANALYSIS

Trial design

The design will be a randomised, two-group, superiority trial of lenient rate control versus strict rate control in patients with persistent or permanent atrial fibrillation at inclusion who

accept rate control as the main strategy. Treatment providers responsible for the rate control treatment will not be blinded. Any other involved personnel will be attempted blinded as well as participants.

Three hundred and fifty outpatients will be recruited from 4 university hospitals in Denmark: Holbaek University Hospital, Hvidovre University Hospital, Region Zealand University Hospital – Roskilde and Odense University Hospital.

The present protocol follows the recommendation in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline including all items from the World Health Organization Trial Registration Data Set (supplementary file 1 and 2).

Trial conduct

This trial will be conducted according to good clinical research practice (GCP) and the latest Declaration of Helsinki.[32 33]

Randomisation

Participants will be randomised 1:1 to a lenient or a strict medical rate control strategy. The trial will use centralised randomisation at OPEN. Prior to the trial, a computer will generate randomisation sequences with varying block sizes between 6-10 that are unknown to the investigators. An internet-based randomisation system will be set up conducting randomisation stratified according to site, type of atrial fibrillation at inclusion (persistent versus permanent) and LVEF (EF ≥ 40% and EF < 40%). The randomising investigator will get access to the internet site through a personal pin code. The randomising investigator will not be an outcome assessor.

Blinding

The investigator prescribing the rate control medication (treatment provider) will not be blinded, as the treatment requires knowledge of the group the participant is randomised to. All other treatment providers, outcome assessors, data managers, statisticians and participants will be sought blinded (the participants will neither be informed of their rate control target nor their allocated intervention group). Blinded data will be sent to OPEN for blinded data management. Statistical analyses will be performed with the two intervention groups coded as 'A' and 'B' by two independent blinded statisticians. Two blinded conclusions will be drawn by the steering group: one assuming 'A' is the experimental group and 'B' is the control group — and one assuming the opposite. Based on these two blinded conclusions, two abstracts will be written (will be published as a supplement to the main publication). When the blinding is broken, the 'correct' abstract will be chosen and the conclusions in this abstract will not be revised.

As all medical procedures are available to any treatment provider, we cannot foresee any reason for unblinding participants. If, however, any medical personnel deems it necessary to unblind a participant, the participant will be unblinded.

Selection of participants

Inclusion criteria

1. Atrial fibrillation (ECG-confirmed and diagnosed by the treatment provider) who at inclusion have either persistent (defined as atrial fibrillation for more than 7 days) or permanent atrial fibrillation (only rate control is considered going forward).

2. Rate control must be accepted as being the primary management strategy going forward. Consideration toward whether rhythm control is more appropriate must be considered, especially given the results of the EAST trial.[34]
3. Informed consent.
4. Adult (18 years or older).

Exclusion criteria

1. No informed consent.
2. Initial heart rate under 80 bpm at rest (assessed via an electrocardiogram (ECG) before randomisation).
3. Less than 3 weeks of anticoagulation with New Oral Anticoagulants (NOAC) or 4 weeks with efficient warfarin.
4. Participants dependent on a high ventricular rate to maintain a sufficient cardiac output. This will be based on an individual assessment of the possible participant. Such participants could be participants with heart failure, participants with a haemodynamically significant valve dysfunction, or severely dehydrated participants. Other factors such as echocardiographic assessments, stability of the disease, and similar will be factored in when judging if a participant is dependent on a high ventricular rate. Such a decision will be made before randomisation by the treatment provider.
5. Participants who are haemodynamic unstable and therefore require immediate electrical cardioversion.

Participant withdrawal

Participants can withdraw his or her consent at any time point for any reason but will be invited to still participate in the follow-up assessments.

Interventions

Lenient rate control

The heart rate will be assessed on a 12-lead resting ECG measured over 1 minute after 5 minutes of rest. The treatment provider will target the highest tolerable resting heart rate < 110 bpm. Treatment providers are encouraged not to attempt to lower the heart rate if already below 110 unless symptoms or other reasons necessitates this. If the heart rate is below 90, the treatment provider is encouraged to reduce rate limiting treatment. If the patient remains symptomatic due to atrial fibrillation after achieving this definition of heart rate control, Holter monitoring or exercise tests may be deemed necessary by the treatment provider.

These evaluations may be followed by adjustment of rate control drugs, rhythm control (electrical cardioversion, arrhythmia surgery, rhythm control medications), or atrioventricular node ablation. In case of the need for rhythm control or atrioventricular node ablation, the allocated heart rate target is no longer relevant in management.

Strict rate control

Strict rate control achieved by using rate control medication (see below) will be defined as a mean resting heart rate < 80 bpm with a general recommendation of targeting 70 bpm on a 12-lead resting ECG measured over 1 minute after 5 minutes of rest. Exercise test to determine activity heart rates or Holter monitoring will only be performed if the treatment

provider believes this is indicated. These evaluations may also be followed by adjustment of rate control medications, electrical cardioversion, arrhythmia surgery, or atrioventricular node ablation (treatment provider's choice).

Rate control medications

Treatment will be provided according to current guidelines and as such the algorithm for treatment will be differentiated based on the status of left ventricular ejection fraction.[14] For participants with reduced left ventricular ejection fraction, beta-blockers (metoprolol and bisoprolol) will be the primary therapy. Secondary therapies may include digoxin or amiodarone. For participants with preserved left ventricular ejection fraction, the primary therapy will be beta-blockers (metoprolol and bisoprolol) or non-dihydropyridine calcium-channel blockers (verapamil) with secondary therapy consisting of digoxin or amiodarone.

Below we briefly summarise the pharmacological treatment in the DanAF trial (table 1).

Table 1: Suggested daily doses for rate control agents.

Metoprolol	50 to 200 mg
Bisoprolol	2.5 to 10 mg
Digoxin	62.5 to 250 µg maintenance dose according to weight, age, and renal function, loading is usually required for 3 to 7 days
Verapamil	120 to 240 mg - no loading dose required

Concomitant medication

Besides rate control, the treatment provider will be free to prescribe any other standard medical co-intervention such as the need for anticoagulation (based on the CHA_2DS_2-VASc score and co-morbidity[14]), hypertension management, heart failure management, or lipid lowering drugs as long as the prescriptions adhere to guidelines.[14] This also includes recommendations regarding modifiable risk factors that may have adverse effects on atrial fibrillation management (excess alcohol, smoking, sleep apnoea).[14 35] A brief description of what is considered standard management of co-morbidities and risk factors are given in supplementary file 3. All other interventions are allowed, if they are administered evenly in all intervention arms.

Follow-up and outcome events

All participants will attend a minimum of two follow-up visits within two months after randomisation. Further visits are possible with two-week intervals until adequate titration of rate control therapy is as required or for other reasons such as participants having inadequate symptom control, management of comorbidities, etc. Treatment providers may plan a visit sooner or later if clinically indicated. To assess if the ECG guided heart rate target is representative of the heart rate under normal conditions, we will perform 24 hour Holter monitoring at the end of the titration phase and after 1 year of follow-up for documentation purposes.

After the initial adequate titration of rate control, participants are to follow the normal referral system in the Danish Health care system. A hotline will be established where treatment providers may call and ask for the participant's rate control target. If treatment providers themselves do not contact the trial treatment provider, participants are encouraged to contact the trial treatment provider. If possible, a treatment provider

involved in the trial will be the managing treatment provider of the referral, if the referral is to a participating department.

Primary outcome

- Quality of life using the SF-36 questionnaire (physical component score), continuous outcome.[36]

Secondary outcomes

- Days alive outside hospital, count outcome.
- Symptoms due to atrial fibrillation using the Atrial Fibrillation Effect on Quality of Life (AFEQT), continuous outcome.[27]
- Quality of life using the SF-36 questionnaire (mental component score), continuous outcome.[36]
- Serious adverse events, dichotomous outcome. We will define a serious adverse event as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, and resulted in persistent or significant disability or jeopardised the patient.[33]

Exploratory outcomes

- All-cause mortality, dichotomous outcome.
- Composite of all-cause mortality, stroke, myocardial infarction and cardiac arrest, dichotomous outcome.
- Cardiac mortality, dichotomous outcome.
- Stroke, dichotomous outcome.

- Hospitalisation for worsening of heart failure dichotomous outcome.
- Number of hospital admissions, count outcome.
- Six-minute walking distance, continuous outcome.
- Healthcare costs.
- Various biomarkers (N-terminal pro-brain natriuretic peptide (nt-proBNP), high sensitivity C reactive protein (hsCRP), high sensitivity troponin I (hsTnI), growth differentiation factor-15 (GDF-15), interleukin 6 (IL6), cystatin-C, YKL40, soluble urokinase plasminogen activator receptor (suPAR) and fibulin-1).
- Switch to rhythm control strategy (such as rhythm control medication, DC-conversion, pulmonary vein isolation or arrhythmia surgery), dichotomous outcome.
- Implantation of a pacemaker or cardioverter–defibrillator with or without AV node ablation, dichotomous outcome

Echocardiographic outcomes

- Size of left atrium (LAVi).
- Size of left ventricle.
- Cardiac index (cardiac output / body surface area).
- Left ventricular ejection fraction.
- Tricuspid annular plane systolic excursion (TAPSE).[37]
- Midwall fractional shortening.
- Global longitudinal strain.
- Circumferential end-systolic stress.

- Diastolic dysfunction estimated by the relationship between LV filling and RR interval for the individual patient.
- Pulmonary pressure.

All secondary, exploratory, and echocardiographic outcomes will only be hypothesis-generating.

Adverse events

Participants will be asked during visits to the clinic if they had experienced any undesirable medical events.

Suspected unexpected serious adverse reactions (SUSAR) will be reported to the ethics committee within 7 days of investigators being aware of the event. Once a year, a report of all serious adverse events and serious adverse reaction will be submitted to the ethics committee.

Assessment time point

The primary assessment time point for all outcomes will be one year after randomisation.

Procedures for Screening

Potential participants according to inclusion and exclusion criteria at Holbaek University Hospital, Hvidovre University Hospital, Region Zealand University Hospital – Roskilde and Odense University Hospital will receive an invitation to participate in the trial upon a routine

visit in the clinic or hospitalisation for atrial fibrillation. Possible participants will be identified by trial staff employed at the site.

Procedures for informed consent

Participants will receive printed material containing details of each study visit, the design and rational of the trial, participant rights (such as the right to withdraw), possible adverse reactions of medication, and more. The printed material will be given either immediately after being identified as a possible candidate or during a private, information session where verbal information is given and the participants can ask any questions they may have. The information session will take place in an undisturbed environment. The information will be given by the project coordinator on site or medical personnel with equivalent prerequisites for conveying the project. Potential participants will be informed that they can bring a third party if they wish so. The participants will be given up to three weeks to consider participation depending on when they choose to schedule the information session. There will be a minimum of 48 hours from the information session to the obtaining of informed consent.

Data collection

Data will be attempted to be collected from all participants regardless of protocol adherence. Study plan and data will be as shown in **Table 2**.

Table 2

Schedule	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4,**

	Base-line				**5, 6**
Investigations	0 mo	1 mo ± 2 w	2 mo ± 2 w	6 mo ± 2 w	12 mo/ 24 mo/ 36 mo/ ± 2 w
Medical history	**X**				**X**
Clinical events (hospital, tests etc.)		**X**	**X**		**X**
CHA_2DS_2VASc score	**X**				**X**
EHRA SC	**X**	**X**	**X**		**X**
SF-36, AFEQT	**X**				**X**
Physical examination	**X**				**X**
Vital signs (BP, HR)	**X**	**X**	**X**		**X**
Concom. Rx, AF Medication	**X**	**X**	**X**		**X**
Informed Consent, Inclusion/Exclusion criteria	**X**				
Randomization	**X**				
Clinical lab. tests (as indicated)	**X**	**X**	**X**		**X**
Study lab. tests	**X**			**X**	**X**
12-lead ECG	**X**	**X**	**X**		**X**
Holter monitoring. () = as clinically indicated	**(X)**	**(X)**	**X**		**X**

Echocardiography	**X**				**X**
Six-minute walking test	**X**				**X**

Abbreviations: mo= months. BP=Blood Pressure. EHRA SC=EHRA symptom classification. HR=Heart rate. Lab. tests=Laboratory tests, SF-36=Short form-36. AFEQT = The Atrial Fibrillation Effect on Quality of Life

Echocardiography will be performed according to current international guidelines.[38] A detailed plan for the echocardiographic examination and recordings has been developed. The echocardiograms will be sent to a core echocardiographic reading centre at Holbaek Hospital to be assessed by one of two assessors that will be blinded.

Biobank

We will collect blood samples for a research biobank and measure: Nt-proBNP, hsCRP, hsTni, GDF-15, IL6, Cystatin-C, YKL40, suPAR and fibulin-1. In addition to the above blood samples, we will collect the following three types of blood samples: 5 ml serum, 5 ml plasma, and 5 ml citrat plasma to be stored for future research. Participants will be given separate information on this blood collection as well as be required to give a separate informed consent (supplementary file 4).

Data management

All data will be sent encrypted to OPEN for management. All data on paper will be securely stored and a copy will be sent to a computerised database.

The computerised database will be continuously checked for missing values and errors at one month intervals. Before a trial site begins recruitment, an internal monitoring of the following procedures will be checked: validation of inclusion and exclusion criteria, informed consent procedure, randomisation procedure and data entry into Redcap.

Statistical plan and data analyses

Sample size - Quality of life using the SF-36 questionnaire (physical component score)

Using a minimal important difference of 3 points on the physical component score, a standard deviation of 10, power of 80%, and a significance level of 5%, a total of 350 participants will be needed.[17 39 40] Based on this sample size, we have estimated the power of all remaining outcomes (see supplementary file 5).

Recruitment plans

We will involve key medical personnel at the different departments as well as hold sessions at the different departments informing of the trial.

Statistical analyses

A detailed statistical analysis plan will be published around one month after the trial has been launched. In short, our primary conclusions will be based on the results of our single primary outcome. Hence, we will consider a P value of 0.05 as our threshold for statistical significance.[31] The results of secondary outcomes, exploratory outcomes, subgroup analyses,

and possible per protocol analyses will be hypothesis generating only. We will assess whether the thresholds for statistical and clinical significance are crossed according to the five-step procedure proposed by Jakobsen et al.[31] The analyses of the outcomes will be based on the 'intention to treat' principle, i.e. all randomised participants will be included in the analysis regardless of how much treatment they have received. In case of more than 5% not receiving the allocated heart rate target, we will secondarily analyse all outcomes according to the actual heart rate achieved (per protocol analysis) defined as the average heart rate on ECG after 5 minutes of rest. If outcomes are not present due to retraction of informed consent or dropout, the pattern of the missing data will be investigated. Missing data will be handled according to the recommendations proposed by Jakobsen et al.[22]

Analysis methods

Continuous outcomes will be presented as means and standard deviations with 95% confidence intervals. Count outcomes will be presented as medians and interquartile ranges. We will analyse continuous outcomes using mixed effects linear regression with 'site' as a random intercept using an exchangeable covariance matrix and type of atrial fibrillation at inclusion (persistent versus permanent) and LVEF (EF ≥ 40% and EF < 40%) as a fixed effect.[41] We will analyse count data using the van Elteren's test stratifying for 'site'.[42] Dichotomous outcomes will be presented as proportions of participants in each group with the event, as well as risk ratios with 95% confidence intervals. Dichotomous outcomes will be analysed using mixed effects generalised linear models using a log link function with 'site' as a random intercept using an exchangeable covariance matrix, and type of atrial fibrillation will be included as a fixed effect. .[42] All outcomes will be analysed according to final value.

Subgroup analyses

All subgroup analyses will be regarded as hypothesis generating only and we will not base any conclusions on these. We will in the planned statistical analysis plan (see 'Statistical analysis') in detail describe each planned subgroup analysis.

In short, we will in each publication compare:

- Patients with heart failure compared to patients without heart failure (including subtypes).
- Men compared to women
- Different durations of atrial fibrillation
    - Less than one year
    - 1-2 years
    - More than 2 years
- Patients with age above compared to below 75 years
- Patients according to the European Heart Rhythm Association (EHRA) symptoms score

Data monitoring

A data safety monitoring committee (DSMC) independent from the sponsor and the investigators will be created. The DSMC will be free of conflicts of interest. The DSMC will be responsible for conducting an interim analysis after 50% of participants have been included and monitor if the trial still holds scientific merit. The DSMC will decide when / if a new interim analysis should be performed. The DSMC will make recommendations to the

steering committee whether the trial should stop or continue (further details in supplementary file 6)."

Auditing

The trial can be audited by the Regional ethics committee, which is independent from the investigators and sponsor.

Patient and public involvement

Patient were invited to work shop after the initial draft was accepted by all participating departments. They were asked to give inputs to the chosen outcomes, the written material, the relevance of the objective of the trial and any other aspects they found relevant. Patients are anticipated to work as ambassadors after the trial results are available. We will again perform a workshop to involve patients in the best strategy for dissemination.

ETHICS AND DISSEMINATION

The management of patients is in accordance with standard care and as such, patients are in no greater risk compared to receiving standard care outside the trial. It is therefore completely ethical for patients to be part of the trial. The potential benefits for further patients are that we may uncover a superior heart target to be the goal of future management of patients with atrial fibrillation.

The trial protocol has been approved by the regional ethics committee which is a branch of the Danish ethics committee, the regulatory body approving research in Denmark. As such, the committees are independent from the trial. The committee reviewed the full protocol, the written material for the participants, the consent form and the administered

questionnaires before giving approval. The ethics committee has the option of conducting an audit of the trial if it wishes to do so. The committee must be provided with a notification of any SAE including SUSARs within a week as well as a yearly report of SAE. Any changes to the approved protocol will be submitted and approved before continuing the trial.

Site investigators or personnel with equivalent skills will obtain informed consent from possible participants (Supplementary file 7). Additional consent will be obtained in order to store blood samples for future research.

Before enrolment of participants, screening will be done by personnel employed at the study site using the local electronic journal system. Any information collected on potential and enrolled participants will be entered directly into Redcap, using a secure connection.

The project and its data have been registered at the Region Zealand, who is the data controller. Study investigators will have access to the full data set. OPEN, who is in charge of storing the data, will also have access to the full data set. Ethics review will also have access to data upon request.

Participants, who suffer harm during the trial, are insured by the the Danish Patient Compensation Association.

Trial results will be sought published in a peer-reviewed journal. In addition, results will be communicated directly to relevant patient advocacy groups, relevant medical associations, and attempted presented at relevant congresses. Aggregate data analysis will be published in a clinical trial register no later than three years after trial results have been collected. Data sharing will be made available upon request after approval from ethics committee.

Authorship will be granted according to the recommendations from the International Committee of Medical Journal Editors (ICMJE).[43]

Discussion

Our trial has several strengths. It is a pragmatic trial assessing the benefits and harms of a lenient versus a strict rate control strategy in patients with both persistent and permanent atrial fibrillation. The number of inclusion and exclusion criteria is low and hence, the external validity will be high. Participants will be recruited from more than one site, which will further increase the external validity. We have performed a sample size estimation based on previous evidence with realistic intervention effects, we will adjust the thresholds for statistical significance if the sample size is not reached, and we have chosen only one outcome we will base conclusion on and the rest will be considered hypothesis generating only thereby taking into account problems with multiplicity. Furthermore, we consider risks of bias from the allocation sequence generation, allocation concealment, blinding of outcome assessors and participants, selective outcome reporting, for-profit bias and missing outcome data. Hence, our trial will be conducted with a low risk of random errors ('play of chance') and with as low risk of systematic errors ('bias') as the trial design allows (see below).[31 44] In Denmark, a complete follow-up of all participants for death and hospitalisations is secured by an unique number given to all born in Denmark, Central Person Register.

Our trial also has limitations. The treatment providers responsible for the rate control intervention will not be blinded, which may bias our results. We will use 12-lead ECG to guide rate control therapy. Holter monitoring and measurement of the heart rate during exercise will only be used at the discretion of the investigator if deemed necessary. And

such, there may be fluctuations in the heart rate we do not detect. Another limitation is that we do not have sufficient power to assess 'hard outcomes' such as mortality and serious adverse events. This will be explored in a future meta-analysis with individual patient data with the RACE II trial. The consequence may ultimately be that a superiority trial in terms of 'hard outcomes' is needed. Our results will only be generalizable to a population where rate control is considered appropriate as the main strategy going forward. The results of the EAST trial is expected to delay the initiation of rate control for many patients and hence, our results will need to be interpreted in light of this. Yet another limitation is that participants presumably will receive different medications and procedures in the compared groups. If we show a difference (or lack of a difference) between the groups, it will be difficult to interpret what part of the treatment algorithm for reaching a certain rate target caused this difference.

We expect the results of this trial will play a part of future recommendations for rate control treatment in patients with both persistent and permanent atrial fibrillation.

Protocol version and amendments

This abbreviated version of the full protocol, is based on version 2.0 (January 2020). Any changes to the original protocol will be submitted to the regional ethics committee. After approval, changes will be conveyed to all investigators, participants, and trial registries.

The findings will be published in a peer reviewed journal as well as be made available on clinicaltrials.gov.

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Contributors

JBF, JCJ, AB, UD, UG, WBN, MHO, ODP, and IR participated integrally in the study design. CG provided vital advice on trial conduct. EEN and FS designed the echocardiography plan. MHO designed the plan for analysis of biomarkers. JBF, JCJ, and AB drafted the initial manuscript. All other authors provided critical revision and approved the final manuscript.

Finance

The trial was initiated by clinicians at the participating hospitals. The research salary for research nurses is partly funded by the Region of Southern Denmark and Region Zealand joint research fund 2018 for year 1. The salary of the lead author for years 2 and 3 are provided by the Danish Heart foundation grant number 19-R134-A8959-22123. The salary for year 1 is granted by the University of Southern Denmark. The participating departments

support the trial by dedicating work hours of the other investigators, supportive staff, logistical support and administrative support.

Role of sponsors and funders

The trial is investigator initiated. Holbaek Hospital is the sponsor and the region of Zealand is the data controller. The study sponsors and funders had no influence on design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The Danish Heart Foundation requires to be notified by email when a publication is accepted.

Roles and responsibilities of additional parties are described in supplementary file 8.

Competing interests statement

JBF (PI), IR, WBN, EEN, FSH, ODP, UG, CG, JCJ report no competing interests.

MHO reports grants from Novo Nordic Foundation outside the submitted work.

AB reports personal fees from Bayer, grants from Biotronik, personal fees from Boehringer Ingelheim, personal fees from Bristol-Myers Squibb, personal fees from MSD, grants from Theravance, outside the submitted work.

UD reports a research grant from Bayer, personal fees from Pfizer, member of advisory board for Boehringer Ingelheim, member of advisory board for Merck, outside the submitted work.

Patient consent for publication

Not required

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary file 2
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-7
	6b	Explanation for choice of comparators	4-7
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16-18

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19 + supplementary file 5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18-19
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20-21
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21 + supplementary file 6
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21 + supplementary file 6
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	22
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	22

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	22
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22-23
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22-23
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	23
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
	31b	Authorship eligibility guidelines and any intended use of professional writers	23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplementary file 7
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	supplementary file 4

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Data category	Trial information
1. Primary registry and trial identifying number	Clinicaltrials.gov (NCT04542785)
2. Date of Registration in Primary Registry	September 2020
3. Secondary Identifying Numbers	Region Zealand Ethics committee ID: SJ-797 Internal ID number Region Zealand: REG-078-2019
4. Source(s) of Monetary or Material Support	Holbaek University Hospital Odense University Hospital Hvidovre University Hospital Region Zealand University Hospital - Roskilde Region of Southern Denmark and Region Zealand joint research fund 2018 The Danish Heart foundation grant number 19-R134-A8959-22123 The University of Southern Denmark A.P. Moeller Foundation
5. Primary Sponsor	Holbaek Hospital Smedelundsgade 60, 4300 Holbaek Hospital Denmark
6. Secondary Sponsor(s)	
7. Contact for Public Queries	JBF
8. Contact for Scientific Queries	JBF
9. Public Title	Lenient rate control versus strict rate control for atrial fibrillation. The Danish Atrial Fibrillation (DanAF) randomised clinical trial
10. Scientific Title	Lenient rate control versus strict rate control for atrial fibrillation. The Danish Atrial Fibrillation (DanAF) randomised clinical trial
11. Countries of Recruitment	Denmark
12. Health Condition(s) or Problem(s) Studied	Atrial Fibrillation
13. Intervention(s)	Lenient rate control versus strict rate control
14. Key Inclusion and Exclusion Criteria	Inclusion criteria: 1. Atrial fibrillation (ECG-confirmed and diagnosed by the treating physician) persistent (defined as atrial fibrillation for more than 7 days) and permanent atrial fibrillation (only rate control is considered going forward); 2. Rate control must be accepted as being the primary management strategy going forward. 3.Informed consent; 4.Adult (18 years or older). Exclusion criteria: 1. No informed consent; 2.Initial heart rate under 80 bpm at rest (assessed via an electrocardiogram (ECG) before randomisation); 3. Less than 3 weeks of anticoagulation with NOAC or 4 weeks with efficient warfarin; 4. Participants dependent on a high ventricular rate to maintain a sufficient cardiac output. This will be based on an individual assessment of the possible

	participant. 5. Participants who are hemodynamic unstable and therefore require immediate conversion.
15. Study Type	1. Interventional study 2. Method of allocation: Randomised Masking: Participant and outcome assessors blinded Assignment: parallel Primary purpose: Comparing two strategies
16. Date of First Enrollment	Anticipated end of January 2021.
17. Sample Size	350 planned, 0 enrolled.
18. Recruitment Status	Pending
19. Primary Outcome(s)	Short Form-36 (SF-36) questionnaire (physical component score).
20. Key Secondary Outcomes	Secondary outcomes will be days alive outside hospital, symptom control using the Atrial Fibrillation Effect on Quality of Life, quality of life using the SF-36 questionnaire (mental component score), and serious adverse events.
21. Ethics Review	Approved on 30.10.2019 by The Ethics committee in Region Zealand. Alléen 15, 4180 Soroe. Telephone number: 57 87 52 83
22. Completion Date	Anticipated completion date January 2026
23. Summary Results	Not yet available
24. IPD Sharing Statement	Plan to Share IPD: Yes

Supplementary file 3 - Management of co-morbidities

Management of heart failure and hypertension

Management of heart failure will follow the recommendations of the European Society of Cardiology. Briefly, the table below summarizes the recommendations for medical therapy. Ultimately, any management is at the discretion of the treatment providers and participants.

	LVEF <40	LVEF ≥ 40
Step 1: All participants	ACEi (Ramipril 10 mg) or ARB (Losartan 150 mg x 1)	
Step 2: If still symptomatic	Spiron 50 mg x 1	
Step 3: If still symptomatic	ARNI 97/103 x 2 instead of ACEi/ARB	
Signs of congestion	Bendroflumethiazid 2.5 -10 mg/day or Furosemide 20-40 mg/day	Bendroflumethiazid 2.5 -10 mg or Furosemide 20-40 mg
Additional treatment if HomeBP > 130/80	Bendroflumethiazid 2.5 -10 mg or amlodipine 5-10 mg x 1 (or spiron 25-50 mg if not on step 2)	ACEi (Ramipril 10 mg) or ARB (Losartan 150 mg x 1) or Bendroflumethiazid 2.5 -10 mg or amlodipine 5-10 mg x 1 (Possibly spiron 25-50mg)

Sleep apnea

Participants will be systematically screen for signs of sleep apnea. If signs and symptoms of sleep apnea are discovered, participants will be referred to treatment if appropriate.

Obesity

Weight loss will be encouraged if BMI > 25. General advice will be provided and involvement of participants in local municipal programs will be discussed.

Smoking

Participants will be asked about their smoking habits as part of the initial work-up. Participants will be informed of the detrimental effects of smoking on health. Current smokers will be encouraged to quit and will be informed of available support programs through the municipals.

Alcohol

Participants will be asked about their alcohol habits as part of the initial work-up. Participants will be informed of current evidence regarding alcohol in atrial fibrillation and will be encouraged to abstain from alcohol or alternatively reduce their alcohol intake. Special emphasis will be put on participants who drink above 10 standard drinks/week.[1 2]

Physical activity

Participants will be asked about their physical activity and physical function. Based on an individual assessment, some participants may be offered exercised based cardiac rehabilitation, but it will not be systematically prescribed.[3] This will typically be participants who are limited in their daily activities or who have had a recent significant decline in their physical function. Participants with ischemic heart disease, heart failure or recent operation for valve disease will in general be referred to exercise-based cardiac rehabilitation.

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3. Risom SS, Zwisler AD, Johansen PP, et al. Exercise-based cardiac rehabilitation for adults with atrial fibrillation. *Cochrane Database Syst Rev* 2017;2:Cd011197. doi: 10.1002/14651858.CD011197.pub2 [published Online First: 2017/02/10]

Supplementary file 4 - biobank

We will further collect blood samples for a research biobank and measure: Nt-proBNP, hsCRP, hsTni, GDF-15, IL6, Cystatin-C, YKL40, suPAR and Fibulin-1. Due to the manner of which these analysis have to be analysed and the variations in the measurement depending on blood sample kit is used, blood samples will be collected at the first visit, after 6 months, and at follow-up after 1 year and analysed together. Follow up after two and three years will be analysed together. These analyses will require 10 mL of blood per collection. The blood samples are expected to be analysed either at a laboratory in Sweden or a laboratory in Denmark, but may end up being analysed in another EU country. The storage of data will abide by the Danish General Data Protection Regulation and the Danish Data Protection Act in Denmark.

Any spare blood that is collected will be stored in a biobank in Denmark for future unspecified research purposes. The storage of data will still abide by the Danish General Data Protection Regulation and the Danish Data Protection Act in Denmark.

In addition to the above blood samples, we will collect three different types of blood samples: 7 ml. serum, 7 ml plasma and 7 ml citrat plasma to be stored for future research. This will total approximately 31 mL of blood. The blood samples are expected to be analysed either at a laboratory in Sweden or a laboratory in Denmark, but may end up being analysed in another EU country. Participants will be given separate information on this blood collection as well as be required to give a separate informed consent.

The storage of data will abide by the Danish General Data Protection Regulation and the Danish Data Protection Act in Denmark.

Supplementary file 5 – Power estimations of secondary outcomes

The below power calculations are based on a sample size of 350 participants as specified in the main document.

Days alive outside hospital

Using a minimal important difference of 3 days, a standard deviation of 9, a risk of type I error of 5%, and accounting for the fact that the data is expected not to be normal distributed, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 82.1%.[1]

The Atrial Fibrillation Effect on Quality-of-Life (AFEQT)

In previous trials the observed difference between groups was normally distributed with a standard deviation of 21.[2 3] Using a minimal important difference of 7, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 87.5%. The Type I error probability associated with this test of this null hypothesis is 5%.

Quality of life using the SF-36 questionnaire (mental component score)

In previous trials the observed difference between groups was normally distributed with a standard deviation 10.[4-6] Using a minimal important difference of 4, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 96%. The Type I error probability associated with this test of this null hypothesis is 5%.

Serious adverse events

We anticipate a failure rate among control of 20%. If we anticipate a relative risk reduction of 60%, we will be able to reject the null hypothesis with probability (power) of 90.2%. The Type I error probability associated with this test of this null hypothesis is 5%.

POWER ESTIMATIONS OF EXPLORATORY OUTCOMES

All-cause mortality

Prior data indicate that the mortality rate among controls is about 5%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.7%. The Type I error probability associated with this test of this null hypothesis is 5%.

Composite of all-cause mortality, stroke, myocardial infarction and cardiac arrest

Prior data indicate that this outcome occurs in controls in about 8%.[7 8] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.9%. The Type I error probability associated with this test of this null hypothesis is 5%.

Cardiac mortality

Prior data indicate that the failure rate among controls is 3.9%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.4%. The Type I error probability associated with this test of this null hypothesis is 5%.

Stroke

Prior data indicate that cardiac mortality among controls is 3.9%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.4%. The Type I error probability associated with this test of this null hypothesis is 5%.

Hospitalisation for worsening of heart failure

Prior data indicate that heart failure among controls is 27.4%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 9.0%. The Type I error probability associated with this test of this null hypothesis is 5%.

Number of hospital admissions

Prior data indicate that number of participant who are hospitalised is 27.4%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 9%. The Type I error probability associated with this test of this null hypothesis is 5%.

Six-minute walking distance

In previous trials the observed difference between groups was normally distributed with a standard deviation 75.[9-11] Using a minimal important difference of 40, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 99.9%. The Type I error probability associated with this test of this null hypothesis is 5%.

Physical activity using trial accelerometer

Prior data indicates that the standard deviation among groups was 65 minutes pr. Day when measuring sedentary behaviour. Assuming a difference in groups of 20 minutes/day, we will be able to reject the null hypothesis with a probability of 81.9%. The type 1 error probability associated with this test of this null hypothesis is 5%.[12 13]

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Supplementary file 6. Short description of the independent Data Safety and Monitoring Committee (DSMC)

Introduction

This Charter defines the primary responsibilities for the independent Data safety and monitoring Committee (DSMC) of the randomised clinical trial DanAF. This includes the relationships with other aspects of the trial.

Primary responsibility of the DSMC

The DSMC will ensure the safety of trial participants. This will be achieved by the following tasks:

- Performing planned analyses of outcomes related to the safety of participants from the two rate control strategies during the trial.
- Continuously monitoring if the trial still holds scientific merit

Members of the DSMC

The exact composition of the DSMC will be specified later but is expected to consist of two clinicians and one person with adequate statistical knowledge to conduct the interim analysis. One member will be chosen as the committee chair.

Recommendations are recommended to be anonymous. However, in case of members not coming to an agreement, members will vote. The points of discussion will be part of the discussion of the DSMC report to the Steering Committee (SC). The members of the DSMC will be free of conflicts of interest. Assessment if members are free of conflict of interest will be decided by the SC.

Meetings

This is the initial DSMC charter. The final charter will be determined and signed as the last part of the first meeting of the DSMC (see below).

1. Meeting

The first meeting will be a finalization of the DSMC role during the trial. The following will be agreed on and finalized.

- How DSMC can request additional (unblinded) data
- How meetings will be held (virtually, physical meeting, phone)
- How many meetings are necessary.
- Decision on whether a test run is necessary.
- Finally, the charter will be finalised and signed.

2. meeting

The second meeting will take place as part of an interim analysis after 50% of the participants (n=175) have been recruited.

The DSMC will be allowed to conduct additional interim analyses independently of the SC. The following meeting may take place virtually, in person or by phone.

Communication

Different formats will be used in order to secure proper communication is established. The formats include open and closed reports as well as open and closed sessions.

Closed Sessions

These sessions will involve only DSMC members. Discussions will be based on a closed report that will be based on blinded data provided by the data manager. A single member will be in charge of preparing the report but may receive input from the other two members before finalizing the closed report.

If the DSMC deems it necessary, they may ask for unblinding of the data from the steering committee.

Data for review will be the composite outcome all-cause mortality, stroke, myocardial infarction and cardiac arrest mortality (and its individual components), serious adverse events including any serious adverse reactions.

Recommendations to the steering committee (open report)

The DSMC will report its recommendations to the SC based on safety considerations. If the DSMC recommends anything other than continuing the trial, there will be held a virtual meeting between the DSMC and the SC. The DSMC will here present the reasoning behind its recommendations.

The SC ultimately makes the decisions regarding all aspects of the trial.

Data

The DSMC will be provided with data on the following variables

1. Randomisation code (this will not reveal the allocated heart rate target)
2. The composite outcome of all-cause mortality, stroke, myocardial infarction and cardiac arrest and the individual components:
    a. All-cause mortality
    b. Stroke
    c. Myocardial infarction
    d. Cardiac arrest
3. Serious adverse events including subcategories of individual events
4. Numbers of participants lost to follow up

The DSMC will not be provided with data on site or any identifier the data is considered anonymized.

Analyses

The DSMC is recommended to use Lan-DeMets sequential monitoring boundaries.

Meta data

The DSMC will be provided with a detailed codebook that explains all the coding in the data set.

Supplementary file 7 – informed consent form

(S4)

Informed consent to participate in a health-related research project

Research project title: Lenient rate control versus strict rate control for atrial fibrillation. The Danish Atrial Fibrillation (DanAF) randomised clinical trial

Statement from trial participant:

I have received both written and verbal information and have received enough information regarding purpose, methods, harms and benefits to give informed consent.

I know that it is voluntary to participate and that I always have the right to withdraw my consent without losing my right to treatment now or in the future.

I give my consent to participate in the research project and that my biological material may be collected with the intention of storing it in a research biobank. I have received a copy of this consent form along with written information regarding the project for my personal use.

Participant name: _____

Date: _____ Signature: _____

If during the research project significant information regarding your health, you will be informed. If you would like not to be informed of any new information regarding your health that comes to our attention during the trial, we ask that you mark here: _____ (mark with an x)

Do you wish to be informed of the results of the trial and possible consequences for you?:

Yes _____ (mark with an x) No _____ (mark with an x)

Statement from the person providing information to the participant:

I declare that the participant has received written and verbal information about the trial.

To my knowledge there has been given enough information to make a decision to participate in the trial.

Printed name of the person, who has given the information:

Date: _____ Signature: _____

Regional ethics commitee project identification:

69694

Supplementary file 8 - Roles and responsibilities

Daily management team (including the Principal investigator (PI))

Conduct of DanAF

Preparation of protocol and revisions

Design of Redcap database

Organising steering committee meetings

Conceive manuscripts of results for review by the steering committee

In charge of supervising start-up of sites

Budget administration and contractual issues with individual centres

Organisation of central serum sample collection

Design of randomisation

Securing that the GDPR is complied with (by interaction with the Regional data controller)

Site investigators

Joshua Buron Feinberg (Holbaek University Hospital), Axel Brandes (Odense University Hospital), Ulrik Dixen (Hvidovre University Hospital) and Ole Dyg Pedersen (Region of Zealand University Hospital - Roskilde)

Responsible for the proper conduct at respective sites.

In charge of reporting Serious adverse events (SAE) including Suspected unexpected serious adverse reactions (SUSAR) to PI in a timely manner as well as reporting serious adverse events for annual review by the regional ethics committee.

Steering committee (SC)

All authors of the protocol will be invited to be part of the steering committee.

Agreement of final protocolReviewing progress of study and if necessary agreeing changes to the protocol.

In charge of reviewing proper conduct of the trial according to GCP, Helsinki-declaration and ethics review demands.

Providing advice to lead investigators and personnel.

Review of analyses provided by the blinded statistician

Review of manuscript prepared by daily management team

Assistance with international review

Data manager

Maintenance of trial IT system and data entry (OPEN).

Data verification (OPEN in collaboration with PI)

Providing data to the DSMC

Providing data to the blinded statistician

Outcome adjudication committee

Responsible for adjudicating serious adverse events.

Data safety monitoring committee

Responsible for the safety of trial participants and the continuous scientific merit for the trial. Will report findings to the SC.

Blinded statistician

Prepare analysis for the steering committee to review

Regional data controller (independent from trial)

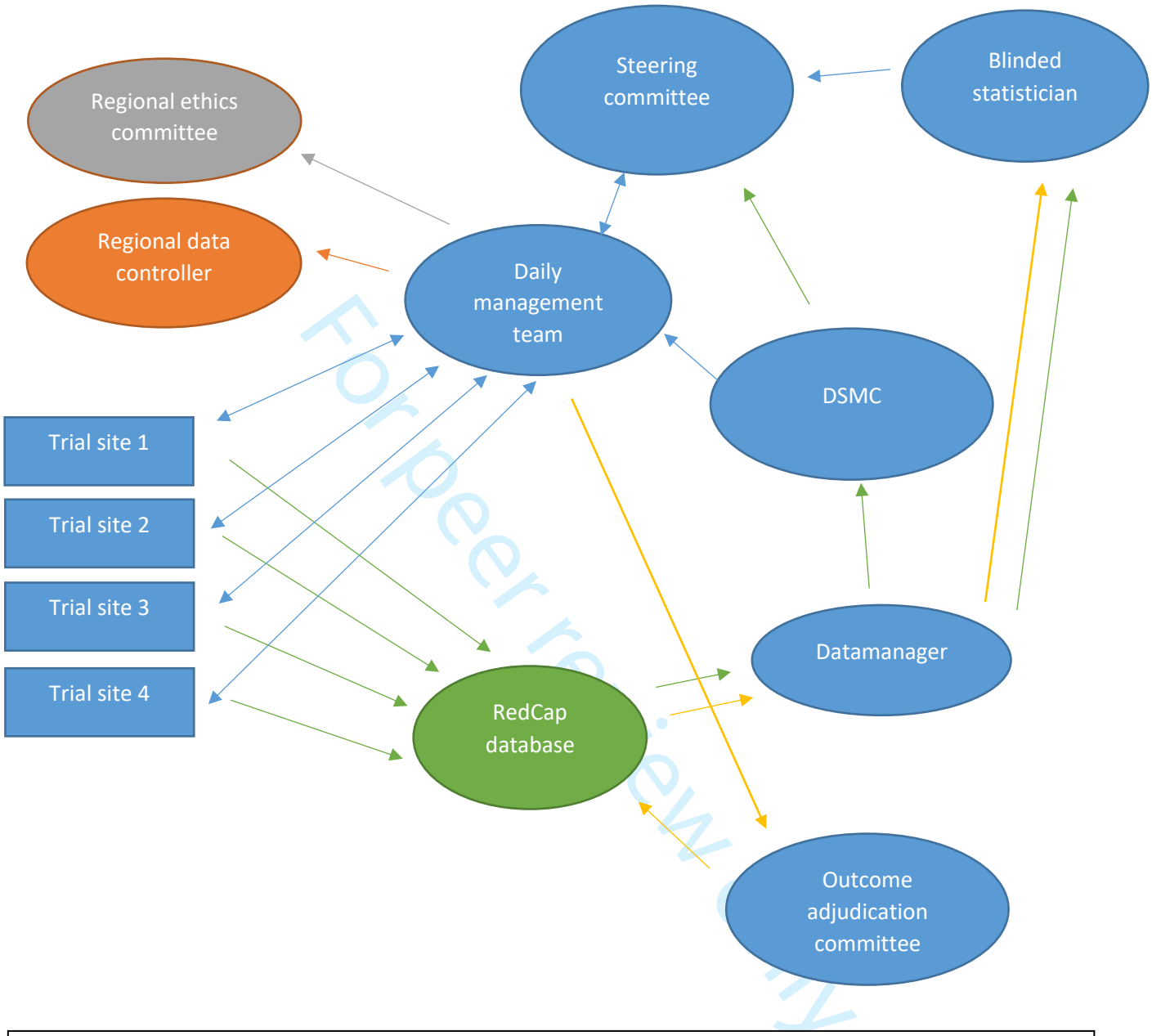
Data controller for the study hence must keep record of the type of data kept, data processor agreements and any other requirements needed to comply with GDPR

Regional ethics committee (independent from trial)

Approve the trial by review of protocol, written participant material, informed consent forms, etc.

Monitor trial through reports of SAE and SUSAR reported to them by the daily management team as well as the yearly report submitted by the PI.

Figure outlying the organisation



Grey arrow: Serious adverse events including SUSAR. Orange arrow: Information necessary to follow GDPR. Green arrow: Data. Yellow arrow: data for adjudication/adjudicated data.

Blue bubbles: Part of the trial organization. Green bubble: database. Orange/grey bubble: External regulatory body.

BMJ Open

Lenient rate control versus strict rate control for atrial fibrillation. A protocol for the Danish Atrial Fibrillation (DanAF) randomised clinical trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044744.R2
Article Type:	Protocol
Date Submitted by the Author:	18-Feb-2021
Complete List of Authors:	Feinberg, Joshua; Holbaek Hospital, Department of Internal Medicine – Cardiology Section; University of Southern Denmark Faculty of Health Sciences, Department of Regional Health Research Olsen, Michael; University of Southern Denmark Faculty of Health Sciences, Department of Regional Health Research; Holbaek Hospital, Department of Internal Medicine – Cardiology Section Brandes, Axel; Odense University Hospital, Department of Cardiology Raymond, llan; Holbaek Hospital, Department of Internal Medicine – Cardiology Section Bjorn, Walter; Holbaek Hospital, Department of Internal Medicine – Cardiology Section Nielsen, Emil; Holbaek Hospital, Department of Internal Medicine – Cardiology Section; Capital Region of Denmark, Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital and The Cochrane Hepato-Biliary Group Stensgaard-Hansen, Frank; Holbaek Hospital, Department of Internal Medicine – Cardiology Section Dixen, Ulrik; Hvidovre University Hospital, Department of cardiology Pedersen, Ole; Zealand University Hospital Roskilde, Department of cardiology Gang, Uffe; Zealand University Hospital Roskilde, Department of cardiology Gluud, Christian; Capital Region of Denmark, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital and The Cochrane Hepato-Biliary Group; University of Southern Denmark Faculty of Health Sciences, Department of Regional Health Research Jakobsen, Janus; Capital Region of Denmark, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital and The Cochrane Hepato-Biliary Group; University of Southern Denmark Faculty of Health Sciences, Department of Regional Health Research
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Cardiology < INTERNAL MEDICINE, Adult cardiology < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY

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Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scored as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

Lenient rate control versus strict rate control for atrial fibrillation. A protocol for the Danish Atrial Fibrillation (DanAF) randomised clinical trial

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Abstract

Introduction Atrial fibrillation is the most common heart arrhythmia with a prevalence of approximately 2% in the western world. Atrial fibrillation is associated with an increased risk of death and morbidity. In many patients, a rate control strategy is recommended. The optimal heart rate target is disputed despite the results of the the RAte Control Efficacy in permanent atrial fibrillation: a comparison between lenient versus strict rate control II (RACE II)trial.

Our primary objective will be to investigate the effect of lenient rate control strategy (< 110 beats per minute (bpm) at rest) compared with strict rate control strategy (< 80 bpm at rest) on quality of life in patients with persistent or permanent atrial fibrillation.

Methods and analysis We plan a two-group, superiority randomised clinical trial. 350 outpatients with persistent or permanent atrial fibrillation will be recruited from four hospitals, across three regions in Denmark. Participants will be randomised 1:1 to a lenient medical rate control strategy (< 110 bpm at rest) or a strict medical rate control strategy (< 80 bpm at rest). The recruitment phase is planned to be two years with three years of follow-up. Recruitment is expected to start in January 2021.

The primary outcome will be quality of life using the Short Form-36 (SF-36) questionnaire (physical component score). Secondary outcomes will be days alive outside hospital, symptom control using the Atrial Fibrillation Effect on Quality of Life, quality of life using the

SF-36 questionnaire (mental component score), and serious adverse events. The primary assessment time point for all outcomes will be one year after randomisation.

Ethics and dissemination Ethics approval was obtained through the ethics committee in Region Zealand. The design and findings will be published in peer reviewed journals as well as be made available on clinicaltrials.gov.

Trial registration: The trial has been registered at clinicaltrials.gov (NCT04542785).

Strength and limitations of this randomised clinical trial

- First trial assessing lenient versus strict rate control in patients who upon inclusion are considered as having persistent atrial fibrillation. Hence, this trial is expected to provide data on patients who upon inclusion have a relatively short duration of atrial fibrillation.
- First superiority trial with quality of life as primary outcome in patients with both permanent atrial fibrillation and persistent atrial fibrillation upon inclusion.
- Pragmatic trial with multiple sites ensuring high external validity.
- Treatment providers are not blinded in a trial that is otherwise expected to have low risk of bias regarding blinding of other domains.
- Trial will not have enough power to assess 'hard outcomes' such as mortality and serious adverse events.

INTRODUCTION

Atrial fibrillation is the most common arrhythmia of the heart with a prevalence of approximately 2% in the western world.[1 2] Atrial fibrillation is associated with an increased risk of death and a number of morbidities.[3-9] The risks of both cerebral stroke and heart failure are increased nearly fivefold in patients with atrial fibrillation, and about 20% of all strokes may be due to atrial fibrillation.[3-8] Atrial fibrillation also has a significant impact on healthcare costs and accounts for approximately 1% of the National Health Service budget in the United Kingdom and approximately 26 billion dollars of annual expenses in the United States.[10 11]

Two different overall intervention strategies may be used for atrial fibrillation – a rhythm control strategy or a rate control strategy.[12-14]

We have previously shown in a systematic review with meta-analysis and Trial Sequential Analysis that rhythm control strategies compared with rate control strategies seem to significantly increase the risk of serious adverse events in patients with atrial fibrillation.[13 14] Based on current evidence as well as guidelines, it seems that most patients with atrial fibrillation should be treated with a rate control strategy unless there are specific reasons justifying a rhythm control strategy.[13 14]

The resting heart rate target for rate control has recently changed from below 80 beats per minute (bpm) to below 100 to 110 bpm at rest depending on the guideline.[12 14 15] This change was a result of the the RAte Control Efficacy in permanent atrial fibrillation: a

comparison between lenient versus strict rate control II (RACE II) trial which randomised 614 participants to a lenient rate control strategy (< 110 bpm at rest) versus a strict rate control strategy (< 80 bpm at rest).[16] The participants were outpatients with permanent atrial fibrillation. The RACE II trial showed that the lenient rate control strategy was non-inferior compared with the strict rate control strategy on the risk of a composite outcome of mortality, stroke, cardiac arrest, arrhythmic events, systematic emboli, or major bleeding. Furthermore, the hazard ratio of 0.84 (90% CI 0.58 to 1.21) suggested that the lenient rate control group might decrease the risk of the composite outcome. The RACE II trial also showed no difference of the two strategies on quality life, but this analysis has questionable validity.[17]

A theoretical concern when using a lenient control strategy is that patients may develop heart failure if the heart rate is too fast.[18-20] The RACE II trial found that the lenient strategy was also non-inferior for heart failure patients but the majority of the participants had preserved ejection fraction at baseline.[21]

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, clinicaltrials.gov on September 26, 2019. Our literature search identified only the RACE II trial assessing the effect of lenient rate control versus strict rate control in atrial fibrillation. We found no systematic reviews or meta-analyses on the topic.

Trial rationale

Currently, lenient rate control is the guideline recommended initial rate control strategy.[14] However, this recommendation is primarily based on the RACE II trial which had two major limitations. First, the validity of the RACE II trial results when assessing symptoms and quality of life were questionable mainly because of substantial problems with missing data. Regarding quality of life and symptom severity, only 437/614 (71%) participants had data available at maximum follow-up.[17] Furthermore, the authors did not use multiple imputation or other valid methods to handle the missing data.[22] Second, the RACE II trial only showed a lenient rate control strategy was non-inferior, but could not answer if a lenient rate control strategy is superior to a strict rate control strategy. The RACE II trial was not adequately powered to confirm or reject minimal important differences between the two strategies. Conducting a superiority randomised clinical trial and afterwards performing a systematic review with meta-analysis will give us the possibility of confirming or rejecting that there is a difference in effect between the two strategies, at least on quality of life.

Health-related quality of life as an outcome

There are many definitions of health-related quality of life.[23 24] In general, quality of life questionnaires can be designed in two ways.[23] Generic questionnaires assess multiple domains applicable to a variety of health domains.[23] They more readily permit comparison across different disease and seem to have unquestionable patient relevance.[23 25] Generic quality of life scales are often criticised for being less sensitive to change than disease specific quality of life scales, but when outcome results show no difference it is most often unknown whether the lack of difference is caused by non-sensitive outcome scales or if the results demonstrate that there is no 'true' difference between the compared interventions

when assessing 'generic' quality of life.[23 25] The opposite holds true for disease specific questions, which in general are thought to be more responsive to change in the clinical condition than generic disease questionnaires but may be less patient relevant. The disease-specific questionnaires tend to focus more narrowly on the disease. Any increase in quality of life as a result of a treatment for a specific disease may be off set by unforeseen negative consequences of the treatment which the questionnaire by design will not capture.

We will therefore supplement the general assessment using SF-36 with a disease-specific questionnaire. Currently, there seems to be no optimal questionnaire.[25 26] The Atrial Fibrillation Effect on Quality of Life (AFEQT) is a validated, disease specific questionnaire, which aims to capture the objective and subjective burden of disease.[27] It contains 20-items that aim to assess four domains: symptoms, activities, treatment concern and treatment satisfaction. It also includes a summary score that summarises the first three domains. It assesses the burden of the atrial fibrillation symptoms.[27 28]

When assessing quality of life, it is important to focus on a minimally important difference, which typically can be done using an anchor-based method or a distribution-based method, or a mix of the two.[29 30] To interpret the clinical significance of future trial results, we will carefully define minimal important differences for all primary and secondary outcomes (see 'Statistical plan and data analyses').[31]

Objectives

Our primary objective will be to investigate the effect of a lenient rate control strategy (< 110 bpm at rest) compared with a strict rate control strategy (< 80 bpm at rest) on quality of life in patients with persistent or permanent atrial fibrillation.

METHODS AND ANALYSIS

Trial design

The design will be a randomised, two-group, superiority trial of lenient rate control versus strict rate control in patients with persistent or permanent atrial fibrillation at inclusion who accept rate control as the main strategy. Treatment providers responsible for the rate control treatment will not be blinded. Any other involved personnel will be attempted blinded as well as participants.

Three hundred and fifty outpatients will be recruited from 4 university hospitals in Denmark: Holbaek University Hospital, Hvidovre University Hospital, Region Zealand University Hospital – Roskilde and Odense University Hospital.

The present protocol follows the recommendation in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline including all items from the World Health Organization Trial Registration Data Set (supplementary file 1 and 2).

Trial conduct

This trial will be conducted according to good clinical research practice (GCP) and the latest Declaration of Helsinki.[32 33]

Randomisation

Participants will be randomised 1:1 to a lenient or a strict medical rate control strategy. The trial will use centralised randomisation at OPEN. Prior to the trial, a computer will generate randomisation sequences with varying block sizes between 6-10 that are unknown to the investigators. An internet-based randomisation system will be set up conducting randomisation stratified according to site, type of atrial fibrillation at inclusion (persistent versus permanent) and LVEF (EF ≥ 40% and EF < 40%). The randomising investigator will get access to the internet site through a personal pin code. The randomising investigator will not be an outcome assessor.

Blinding

The investigator prescribing the rate control medication (treatment provider) will not be blinded, as the treatment requires knowledge of the group the participant is randomised to. All other treatment providers, outcome assessors, data managers, statisticians and participants will be sought blinded (the participants will neither be informed of their rate control target nor their allocated intervention group). Blinded data will be sent to OPEN for blinded data management. Statistical analyses will be performed with the two intervention groups coded as 'A' and 'B' by two independent blinded statisticians. Two blinded conclusions will be drawn by the steering group: one assuming 'A' is the experimental group and 'B' is the

control group — and one assuming the opposite. Based on these two blinded conclusions, two abstracts will be written (will be published as a supplement to the main publication). When the blinding is broken, the 'correct' abstract will be chosen and the conclusions in this abstract will not be revised.

As all medical procedures are available to any treatment provider, we cannot foresee any reason for unblinding participants. If, however, any medical personnel deem it necessary to unblind a participant, the participant will be unblinded.

Selection of participants

Inclusion criteria

1. Atrial fibrillation (electrocardiogram (ECG)-confirmed and diagnosed by the treatment provider) who at inclusion have either persistent (defined as atrial fibrillation for more than 7 days) or permanent atrial fibrillation (only rate control is considered going forward).
2. Rate control must be accepted as being the primary management strategy going forward. Consideration toward whether rhythm control is more appropriate must be considered, especially given the results of the EAST trial.[34]
3. Informed consent.
4. Adult (18 years or older).

Exclusion criteria

1. No informed consent.
2. Initial heart rate under 80 bpm at rest (assessed via ECG before randomisation).
3. Less than 3 weeks of anticoagulation with new oral anticoagulants (NOAC) or 4 weeks with efficient warfarin.
4. Participants dependent on a high ventricular rate to maintain a sufficient cardiac output. This will be based on an individual assessment of the possible participant. Such participants could be participants with heart failure, participants with a haemodynamically significant valve dysfunction, or severely dehydrated participants. Other factors such as echocardiographic assessments, stability of the disease, and similar will be factored in when judging if a participant is dependent on a high ventricular rate. Such a decision will be made before randomisation by the treatment provider.
5. Participants who are haemodynamic unstable and therefore require immediate electrical cardioversion.

Participant withdrawal

Participants can withdraw his or her consent at any time point for any reason but will be invited to still participate in the follow-up assessments.

Interventions

Lenient rate control

The heart rate will be assessed on a 12-lead resting ECG measured over 1 minute after 5 minutes of rest. The treatment provider will target the highest tolerable resting heart rate < 110 bpm. Treatment providers are encouraged not to attempt to lower the heart rate if already below 110 unless symptoms or other reasons necessitates this. If the heart rate is below 90, the treatment provider is encouraged to reduce rate limiting treatment. If the patient remains symptomatic due to atrial fibrillation after achieving this definition of heart rate control, Holter monitoring or exercise tests may be deemed necessary by the treatment provider.

These evaluations may be followed by adjustment of rate control drugs, rhythm control (electrical cardioversion, arrhythmia surgery, rhythm control medications), or atrioventricular node ablation. In case of the need for rhythm control or atrioventricular node ablation, the allocated heart rate target is no longer relevant in management.

Strict rate control

Strict rate control achieved by using rate control medication (see below) will be defined as a mean resting heart rate < 80 bpm with a general recommendation of targeting 70 bpm on a 12-lead resting ECG measured over 1 minute after 5 minutes of rest. Exercise test to determine activity heart rates or Holter monitoring will only be performed if the treatment provider believes this is indicated. These evaluations may also be followed by adjustment of rate control medications, electrical cardioversion, arrhythmia surgery, or atrioventricular node ablation (treatment provider's choice).

Rate control medications

Treatment will be provided according to current guidelines and as such the algorithm for treatment will be differentiated based on the status of left ventricular ejection fraction.[14] For participants with reduced left ventricular ejection fraction, beta-blockers (metoprolol and bisoprolol) will be the primary therapy. Secondary therapies may include digoxin or amiodarone. For participants with preserved left ventricular ejection fraction, the primary therapy will be beta-blockers (metoprolol and bisoprolol) or non-dihydropyridine calcium-channel blockers (verapamil) with secondary therapy consisting of digoxin or amiodarone.

Below we briefly summarise the pharmacological treatment in the DanAF trial (table 1).

Table 1: Suggested daily doses for rate control agents.

Metoprolol	50 to 200 mg
Bisoprolol	2.5 to 10 mg
Digoxin	62.5 to 250 µg maintenance dose according to weight, age, and renal function, loading is usually required for 3 to 7 days
Verapamil	120 to 240 mg - no loading dose required

Concomitant medication

Besides rate control, the treatment provider will be free to prescribe any other standard medical co-intervention such as the need for anticoagulation (based on the CHA_2DS_2-VASc

score and co-morbidity[14]), hypertension management, heart failure management, or lipid lowering drugs as long as the prescriptions adhere to guidelines.[14] This also includes recommendations regarding modifiable risk factors that may have adverse effects on atrial fibrillation management (excess alcohol, smoking, sleep apnoea).[14 35] A brief description of what is considered standard management of co-morbidities and risk factors are given in supplementary file 3. All other interventions are allowed if they are administered evenly in all intervention arms.

Follow-up and outcome events

All participants will attend a minimum of two follow-up visits within two months after randomisation. Further visits are possible with two-week intervals until adequate titration of rate control therapy is as required or for other reasons such as participants having inadequate symptom control, management of comorbidities, etc. Treatment providers may plan a visit sooner or later if clinically indicated. To assess if the ECG guided heart rate target is representative of the heart rate under normal conditions, we will perform 24 hour Holter monitoring at the end of the titration phase and after 1 year of follow-up for documentation purposes.

After the initial adequate titration of rate control, participants are to follow the normal referral system in the Danish Health care system. A hotline will be established where treatment providers may call and ask for the participant's rate control target. If treatment providers themselves do not contact the trial treatment provider, participants are

encouraged to contact the trial treatment provider. If possible, a treatment provider involved in the trial will be the managing treatment provider of the referral, if the referral is to a participating department.

Primary outcome

- Quality of life using the SF-36 questionnaire (physical component score), continuous outcome.[36]

Secondary outcomes

- Days alive outside hospital, count outcome.
- Symptoms due to atrial fibrillation using the Atrial Fibrillation Effect on Quality of Life (AFEQT), continuous outcome.[27]
- Quality of life using the SF-36 questionnaire (mental component score), continuous outcome.[36]
- Serious adverse events, dichotomous outcome. We will define a serious adverse event as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, and resulted in persistent or significant disability or jeopardised the patient.[33]

Exploratory outcomes

- All-cause mortality, dichotomous outcome.

- Composite of all-cause mortality, stroke, myocardial infarction and cardiac arrest, dichotomous outcome.
- Cardiac mortality, dichotomous outcome.
- Stroke, dichotomous outcome.
- Hospitalisation for worsening of heart failure dichotomous outcome.
- Number of hospital admissions, count outcome.
- Six-minute walking distance, continuous outcome.
- Healthcare costs.
- Various biomarkers (N-terminal pro-brain natriuretic peptide (nt-proBNP), high sensitivity C reactive protein (hsCRP), high sensitivity troponin I (hsTnI), growth differentiation factor-15 (GDF-15), interleukin 6 (IL6), cystatin-C, YKL40, soluble urokinase plasminogen activator receptor (suPAR) and fibulin-1).
- Switch to rhythm control strategy (such as rhythm control medication, DC-conversion, pulmonary vein isolation or arrhythmia surgery), dichotomous outcome.
- Implantation of a pacemaker or cardioverter–defibrillator with or without AV node ablation, dichotomous outcome

Echocardiographic outcomes

- Size of left atrium (LAVi).
- Size of left ventricle.
- Cardiac index (cardiac output / body surface area).
- Left ventricular ejection fraction.
- Tricuspid annular plane systolic excursion (TAPSE).[37]

- Midwall fractional shortening.
- Global longitudinal strain.
- Circumferential end-systolic stress.
- Diastolic dysfunction estimated by the relationship between LV filling and RR interval for the individual patient.
- Pulmonary pressure.

All secondary, exploratory, and echocardiographic outcomes will only be hypothesis-generating.

Adverse events

Participants will be asked during visits to the clinic if they had experienced any undesirable medical events.

Suspected unexpected serious adverse reactions (SUSAR) will be reported to the ethics committee within 7 days of investigators being aware of the event. Once a year, a report of all serious adverse events and serious adverse reaction will be submitted to the ethics committee.

Assessment time point

The primary assessment time point for all outcomes will be one year after randomisation.

Procedures for screening

Potential participants according to inclusion and exclusion criteria at Holbaek University Hospital, Hvidovre University Hospital, Region Zealand University Hospital – Roskilde and Odense University Hospital will receive an invitation to participate in the trial upon a routine visit in the clinic or hospitalisation for atrial fibrillation. Possible participants will be identified by trial staff employed at the site.

Procedures for informed consent

Participants will receive printed material containing details of each study visit, the design and rational of the trial, participant rights (such as the right to withdraw), possible adverse reactions of medication, and more. The printed material will be given either immediately after being identified as a possible candidate or during a private, information session where verbal information is given and the participants can ask any questions they may have. The information session will take place in an undisturbed environment. The information will be given by the project coordinator on site or medical personnel with equivalent prerequisites for conveying the project. Potential participants will be informed that they can bring a third party if they wish so. The participants will be given up to three weeks to consider participation depending on when they choose to schedule the information session. There will be a minimum of 48 hours from the information session to the obtaining of informed consent.

Data collection

Data will be attempted to be collected from all participants regardless of protocol adherence.

Study plan and data will be as shown in **Table 2**.

Table 2

Schedule	**Visit 0** Base-line	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4, 5, 6**
Investigations	0 mo	1 mo ± 2 w	2 mo ± 2 w	6 mo ± 2 w	12 mo/ 24 mo/ 36 mo/ ± 2 w
Medical history	**X**				**X**
Clinical events (hospital, tests etc.)		**X**	**X**		**X**
CHA_2DS_2VASc score	**X**				**X**
EHRA SC	**X**	**X**	**X**		**X**
SF-36, AFEQT	**X**				**X**
Physical examination	**X**				**X**
Vital signs (BP, HR)	**X**	**X**	**X**		**X**
Concom. Rx, AF Medication	**X**	**X**	**X**		**X**
Informed Consent, Inclusion/Exclusion criteria	**X**				

Randomization	**X**				
Clinical lab. tests (as indicated)	**X**	**X**	**X**		**X**
Study lab. tests	**X**			**X**	**X**
12-lead ECG	**X**	**X**	**X**		**X**
Holter monitoring. () = as clinically indicated	**(X)**	**(X)**	**X**		**X**
Echocardiography	**X**				**X**
Six-minute walking test	**X**				**X**

Abbreviations: mo=months. BP=Blood pressure. EHRA SC= European Heart Rhythm Association symptom classification. HR=Heart rate. Lab. tests=Laboratory tests. SF-36=Short form-36. AFEQT= The Atrial Fibrillation Effect on Quality of Life. ECG=electrocardiogram.

Echocardiography will be performed according to current international guidelines.[38] A detailed plan for the echocardiographic examination and recordings has been developed. The echocardiograms will be sent to a core echocardiographic reading centre at Holbaek Hospital to be assessed by one of two assessors that will be blinded.

Biobank

We will collect blood samples for a research biobank and measure: Nt-proBNP, hsCRP, hsTni, GDF-15, IL6, Cystatin-C, YKL40, suPAR and fibulin-1. In addition to the above blood samples, we will collect the following three types of blood samples: 5 ml serum, 5 ml plasma, and 5 ml citrat plasma to be stored for future research. Participants will be given separate information

on this blood collection as well as be required to give a separate informed consent (supplementary file 4).

Data management

All data will be sent encrypted to OPEN for management. All data on paper will be securely stored and a copy will be sent to a computerised database.

The computerised database will be continuously checked for missing values and errors at one month intervals. Before a trial site begins recruitment, an internal monitoring of the following procedures will be checked: validation of inclusion and exclusion criteria, informed consent procedure, randomisation procedure and data entry into Redcap.

Statistical plan and data analyses

Sample size - Quality of life using the SF-36 questionnaire (physical component score)

Using a minimal important difference of 3 points on the physical component score, a standard deviation of 10, power of 80%, and a significance level of 5%, a total of 350 participants will be needed.[17 39 40] Based on this sample size, we have estimated the power of all remaining outcomes (see supplementary file 5).

Recruitment plans

We will involve key medical personnel at the different departments as well as hold sessions at the different departments informing of the trial.

Statistical analyses

A detailed statistical analysis plan will be published around one month after the trial has been launched. In short, our primary conclusions will be based on the results of our single primary outcome. Hence, we will consider a P value of 0.05 as our threshold for statistical significance.[31] The results of secondary outcomes, exploratory outcomes, subgroup analyses, and possible per protocol analyses will be hypothesis generating only. We will assess whether the thresholds for statistical and clinical significance are crossed according to the five-step procedure proposed by Jakobsen et al.[31] The analyses of the outcomes will be based on the 'intention to treat' principle, i.e. all randomised participants will be included in the analysis regardless of how much treatment they have received. In case of more than 5% not receiving the allocated heart rate target, we will secondarily analyse all outcomes according to the actual heart rate achieved (per protocol analysis) defined as the average heart rate on ECG after 5 minutes of rest. Participants who receive a rhythm control strategy (assessed by the treating physician) at our primary assessment time point will be excluded from this analysis. If outcomes are not present due to retraction of informed consent or dropout, the pattern of the missing data will be investigated. Missing data will be handled according to the recommendations proposed by Jakobsen et al.[22] In short, we will conduct a worst-best and best-worst case scenario, testing the potential impact of missing data.[22] If the pattern of missing data allows it, we will also conduct multiple imputations.[22]

Analysis methods

Continuous outcomes will be presented as means and standard deviations with 95% confidence intervals. Count outcomes will be presented as medians and interquartile ranges. We will analyse continuous outcomes using mixed effects linear regression with 'site' as a random intercept using an exchangeable covariance matrix and type of atrial fibrillation at inclusion (persistent versus permanent) and LVEF (EF ≥ 40% and EF < 40%) as a fixed effect.[41] We will analyse count data using the van Elteren's test stratifying for 'site'.[42] Dichotomous outcomes will be presented as proportions of participants in each group with the event, as well as risk ratios with 95% confidence intervals. Dichotomous outcomes will be analysed using mixed effects generalised linear models using a log link function with 'site' as a random intercept using an exchangeable covariance matrix, and type of atrial fibrillation will be included as a fixed effect.[42] All outcomes will be analysed according to final value.

Subgroup analyses

All subgroup analyses will be regarded as hypothesis generating only and we will not base any conclusions on these. We will in the planned statistical analysis plan (see 'Statistical analysis') in detail describe each planned subgroup analysis.

In short, we will in each publication compare:

- Patients with heart failure compared to patients without heart failure (including subtypes).
- Men compared to women

- Different durations of atrial fibrillation at randomisation
    - Less than one year
    - 1 to 2 years
    - More than 2 years
- Patients with age above compared to below 75 years
- Patients according to the European Heart Rhythm Association (EHRA) symptoms score

Data monitoring

A data safety monitoring committee (DSMC) independent from the sponsor and the investigators will be created. The DSMC will be free of conflicts of interest. The DSMC will be responsible for conducting an interim analysis after 50% of participants have been included and monitor if the trial still holds scientific merit. The DSMC will decide when / if a new interim analysis should be performed. The DSMC will make recommendations to the steering committee whether the trial should stop or continue (further details in supplementary file 6).

Auditing

The trial can be audited by the regional ethics committee, which is independent from the investigators and sponsor.

Patient and public involvement

Patient were invited to a workshop after the initial draft was accepted by all participating departments. They were asked to give inputs to the chosen outcomes, the written material, the relevance of the objective of the trial and any other aspects they found relevant. Patients are anticipated to work as ambassadors after the trial results are available. We will therefore perform a second workshop to involve patients in the best strategy for dissemination.

ETHICS AND DISSEMINATION

The management of patients is in accordance with standard care and as such, patients are at no greater risk compared to receiving standard care outside the trial. It is therefore ethical for patients to be part of the trial. The potential benefits for further patients are that we may uncover a superior heart target to be the goal of future management of patients with atrial fibrillation.

The trial protocol has been approved by the regional ethics committee which is a branch of the Danish ethics committee, the regulatory body approving research in Denmark. As such, the committees are independent from the trial. The committee reviewed the full protocol, the written material for the participants, the consent form and the administered questionnaires before giving approval. The ethics committee has the option of conducting an audit of the trial if it wishes to do so. The committee must be provided with a notification of any SAE including SUSARs within a week as well as a yearly report of SAE. Any changes to the approved protocol will be submitted and approved before continuing the trial.

Site investigators or personnel with equivalent skills will obtain informed consent from possible participants (Supplementary file 7). Additional consent will be obtained in order to store blood samples for future research.

Before enrolment of participants, screening will be done by personnel employed at the study site using the local electronic journal system. Any information collected on potential and enrolled participants will be entered directly into REDcap, using a secure connection.

The project and its data have been registered at the Region Zealand, who is the data controller. Study investigators will have access to the full data set. OPEN, who is in charge of storing the data, will also have access to the full data set. Ethics review will also have access to data upon request.

Participants, who suffer harm during the trial, are insured by the the Danish Patient Compensation Association.

Trial results will be sought published in a peer-reviewed journal. In addition, results will be communicated directly to relevant patient advocacy groups, relevant medical associations, and attempted presented at relevant congresses. Aggregate data analysis will be published in a clinical trial register no later than three years after trial results have been collected. Data sharing will be made available upon request after approval from ethics committee.

Authorship will be granted according to the recommendations from the International Committee of Medical Journal Editors (ICMJE).[43]

Discussion

Our trial has several strengths. It is a pragmatic trial assessing the benefits and harms of a lenient versus a strict rate control strategy on quality of life in patients with persistent or permanent atrial fibrillation. The number of inclusion and exclusion criteria is low and hence, the external validity will be high. Participants will be recruited from more than one site, which will further increase the external validity. We have performed a sample size estimation based on previous evidence with realistic intervention effects, we will adjust the thresholds for statistical significance if the sample size is not reached, and we have chosen only one outcome we will base conclusion on. The remaing outcomes will be considered hypothesis generating only thereby taking into account problems with multiplicity. Furthermore, we have taken measures to reduce the risks of bias from the allocation sequence generation, allocation concealment, blinding of outcome assessors and participants, selective outcome reporting, for-profit bias and missing outcome data. Hence, our trial will be conducted with a low risk of random errors ('play of chance') and with as low risk of systematic errors ('bias') as the trial design allows (see below).[31 44] In Denmark, a complete follow-up of all participants for death and hospitalisations is secured by an unique number given to all born in Denmark, Central Person Register.

Our trial also has limitations. The treatment providers responsible for the rate control intervention will not be blinded, which may bias our results. We will use 12-lead ECG to guide rate control therapy. Holter monitoring and measurement of the heart rate during exercise will only be used at the discretion of the investigator if deemed necessary. As such, there may be fluctuations in the heart rate we do not detect. Another limitation is that we do not have sufficient power to assess 'hard outcomes' such as mortality and serious adverse events. This will be explored in a future meta-analysis with individual patient data from the RACE II trial and other trials. The consequence may ultimately be that a superiority trial in terms of 'hard outcomes' is needed. Our results will only be generalizable to a population where rate control is considered appropriate as the main strategy going forward. The results of the EAST trial is expected to delay the initiation of rate control for many patients and hence, our results will need to be interpreted in light of this. Yet another limitation is that participants presumably will receive different medications and procedures in the compared groups. If we show a difference (or lack of a difference) between the groups, it will be difficult to interpret what part of the treatment algorithm for reaching a certain rate target caused this difference.

We expect the results of this trial will play a part of future recommendations for rate control treatment in patients with both persistent and permanent atrial fibrillation.

Protocol version and amendments

This abbreviated version of the full protocol is based on version 2.0 of the protocol (January 2020). Any changes to the original protocol will be submitted to the regional ethics committee. After approval, changes will be conveyed to all investigators, participants, and trial registries.

The findings will be published in a peer reviewed journal as well as be made available on clinicaltrials.gov.

Acknowledgements

The authors would like to thank the patient advisory committee at Holbaek Hospital. We would also like to thank Lise Pedersen and Bo Christensen from the department of clinical biochemistry as well as Palle Lyngsie Pedersen from the Region of Zealand biobank for their help in planning the logistics surrounding the biobank.

Contributors

JBF, JCJ, AB, UD, UG, WBN, MHO, ODP, and IR participated integrally in the study design. CG provided vital advice on trial conduct. EEN and FS designed the echocardiography plan. MHO designed the plan for analysis of biomarkers. JBF, JCJ, and AB drafted the initial manuscript. All other authors provided critical revision and approved the final manuscript.

Finance

The trial was initiated by clinicians at the participating hospitals. The research salary for research nurses is partly funded by the Region of Southern Denmark and Region Zealand joint research fund 2018 for year 1. The salary of the lead author for years 2 and 3 are provided by the Danish Heart foundation grant number 19-R134-A8959-22123. The salary for year 1 is granted by the University of Southern Denmark. The participating departments support the trial by dedicating work hours of the other investigators, supportive staff, logistical support and administrative support.

Role of sponsors and funders

The trial is investigator initiated. Holbaek Hospital is the sponsor and the Region Zealand is the data controller. The study sponsors and funders had no influence on design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The Danish Heart Foundation requires to be notified by email when a publication is accepted.

Roles and responsibilities of additional parties are described in supplementary file 8.

Competing interests statement

JBF (PI), IR, WBN, EEN, FSH, ODP, UG, CG, and JCJ report no competing interests.

MHO reports grants from Novo Nordic Foundation outside the submitted work.

AB reports personal fees from Bayer, grants from Biotronik, personal fees from Boehringer

Ingelheim, personal fees from Bristol-Myers Squibb, personal fees from MSD, grants from Theravance, outside the submitted work.

UD reports a research grant from Bayer, personal fees from Pfizer, member of advisory board for Boehringer Ingelheim, member of advisory board for Merck, outside the submitted work.

Patient consent for publication

Not required

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary file 2
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-7
	6b	Explanation for choice of comparators	4-7
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16-18

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19 + supplementary file 5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18-19
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20-21
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21 + supplementary file 6
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21 + supplementary file 6
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	22
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	22

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	22
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22-23
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22-23
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	23
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
	31b	Authorship eligibility guidelines and any intended use of professional writers	23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplementary file 7
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	supplementary file 4

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Data category	Trial information
1. Primary registry and trial identifying number	Clinicaltrials.gov (NCT04542785)
2. Date of Registration in Primary Registry	September 2020
3. Secondary Identifying Numbers	Region Zealand Ethics committee ID: SJ-797 Internal ID number Region Zealand: REG-078-2019
4. Source(s) of Monetary or Material Support	Holbaek University Hospital Odense University Hospital Hvidovre University Hospital Region Zealand University Hospital - Roskilde Region of Southern Denmark and Region Zealand joint research fund 2018 The Danish Heart foundation grant number 19-R134-A8959-22123 The University of Southern Denmark A.P. Moeller Foundation
5. Primary Sponsor	Holbaek Hospital Smedelundsgade 60, 4300 Holbaek Hospital Denmark
6. Secondary Sponsor(s)	
7. Contact for Public Queries	JBF
8. Contact for Scientific Queries	JBF
9. Public Title	Lenient rate control versus strict rate control for atrial fibrillation. The Danish Atrial Fibrillation (DanAF) randomised clinical trial
10. Scientific Title	Lenient rate control versus strict rate control for atrial fibrillation. The Danish Atrial Fibrillation (DanAF) randomised clinical trial
11. Countries of Recruitment	Denmark
12. Health Condition(s) or Problem(s) Studied	Atrial Fibrillation
13. Intervention(s)	Lenient rate control versus strict rate control
14. Key Inclusion and Exclusion Criteria	Inclusion criteria: 1. Atrial fibrillation (ECG-confirmed and diagnosed by the treating physician) persistent (defined as atrial fibrillation for more than 7 days) and permanent atrial fibrillation (only rate control is considered going forward); 2. Rate control must be accepted as being the primary management strategy going forward. 3.Informed consent; 4.Adult (18 years or older). Exclusion criteria: 1. No informed consent; 2.Initial heart rate under 80 bpm at rest (assessed via an electrocardiogram (ECG) before randomisation); 3. Less than 3 weeks of anticoagulation with NOAC or 4 weeks with efficient warfarin; 4. Participants dependent on a high ventricular rate to maintain a sufficient cardiac output. This will be based on an individual assessment of the possible

	participant. 5. Participants who are hemodynamic unstable and therefore require immediate conversion.
15. Study Type	1. Interventional study 2. Method of allocation: Randomised Masking: Participant and outcome assessors blinded Assignment: parallel Primary purpose: Comparing two strategies
16. Date of First Enrollment	Anticipated end of January 2021.
17. Sample Size	350 planned, 0 enrolled.
18. Recruitment Status	Pending
19. Primary Outcome(s)	Short Form-36 (SF-36) questionnaire (physical component score).
20. Key Secondary Outcomes	Secondary outcomes will be days alive outside hospital, symptom control using the Atrial Fibrillation Effect on Quality of Life, quality of life using the SF-36 questionnaire (mental component score), and serious adverse events.
21. Ethics Review	Approved on 30.10.2019 by The Ethics committee in Region Zealand. Alléen 15, 4180 Soroe. Telephone number: 57 87 52 83
22. Completion Date	Anticipated completion date January 2026
23. Summary Results	Not yet available
24. IPD Sharing Statement	Plan to Share IPD: Yes

Supplementary file 3 - Management of co-morbidities

Management of heart failure and hypertension

Management of heart failure will follow the recommendations of the European Society of Cardiology. Briefly, the table below summarizes the recommendations for medical therapy. Ultimately, any management is at the discretion of the treatment providers and participants.

	LVEF <40	LVEF ≥ 40
Step 1: All participants	ACEi (Ramipril 10 mg) or ARB (Losartan 150 mg x 1)	
Step 2: If still symptomatic	Spiron 50 mg x 1	
Step 3: If still symptomatic	ARNI 97/103 x 2 instead of ACEi/ARB	
Signs of congestion	Bendroflumethiazid 2.5 -10 mg/day or Furosemide 20-40 mg/day	Bendroflumethiazid 2.5 -10 mg or Furosemide 20-40 mg
Additional treatment if HomeBP > 130/80	Bendroflumethiazid 2.5 -10 mg or amlodipine 5-10 mg x 1 (or spiron 25-50 mg if not on step 2)	ACEi (Ramipril 10 mg) or ARB (Losartan 150 mg x 1) or Bendroflumethiazid 2.5 -10 mg or amlodipine 5-10 mg x 1 (Possibly spiron 25-50mg)

Sleep apnea

Participants will be systematically screen for signs of sleep apnea. If signs and symptoms of sleep apnea are discovered, participants will be referred to treatment if appropriate.

Obesity

Weight loss will be encouraged if BMI > 25. General advice will be provided and involvement of participants in local municipal programs will be discussed.

Smoking

Participants will be asked about their smoking habits as part of the initial work-up. Participants will be informed of the detrimental effects of smoking on health. Current smokers will be encouraged to quit and will be informed of available support programs through the municipals.

Alcohol

Participants will be asked about their alcohol habits as part of the initial work-up. Participants will be informed of current evidence regarding alcohol in atrial fibrillation and will be encouraged to abstain from alcohol or alternatively reduce their alcohol intake. Special emphasis will be put on participants who drink above 10 standard drinks/week.[1 2]

Physical activity

Participants will be asked about their physical activity and physical function. Based on an individual assessment, some participants may be offered exercised based cardiac rehabilitation, but it will not be systematically prescribed.[3] This will typically be participants who are limited in their daily activities or who have had a recent significant decline in their physical function. Participants with ischemic heart disease, heart failure or recent operation for valve disease will in general be referred to exercise-based cardiac rehabilitation.

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Supplementary file 4 - biobank

We will further collect blood samples for a research biobank and measure: Nt-proBNP, hsCRP, hsTni, GDF-15, IL6, Cystatin-C, YKL40, suPAR and Fibulin-1. Due to the manner of which these analysis have to be analysed and the variations in the measurement depending on blood sample kit is used, blood samples will be collected at the first visit, after 6 months, and at follow-up after 1 year and analysed together. Follow up after two and three years will be analysed together. These analyses will require 10 mL of blood per collection. The blood samples are expected to be analysed either at a laboratory in Sweden or a laboratory in Denmark, but may end up being analysed in another EU country. The storage of data will abide by the Danish General Data Protection Regulation and the Danish Data Protection Act in Denmark.

Any spare blood that is collected will be stored in a biobank in Denmark for future unspecified research purposes. The storage of data will still abide by the Danish General Data Protection Regulation and the Danish Data Protection Act in Denmark.

In addition to the above blood samples, we will collect three different types of blood samples: 7 ml. serum, 7 ml plasma and 7 ml citrat plasma to be stored for future research. This will total approximately 31 mL of blood. The blood samples are expected to be analysed either at a laboratory in Sweden or a laboratory in Denmark, but may end up being analysed in another EU country. Participants will be given separate information on this blood collection as well as be required to give a separate informed consent.

The storage of data will abide by the Danish General Data Protection Regulation and the Danish Data Protection Act in Denmark.

Supplementary file 5 – Power estimations of secondary outcomes

The below power calculations are based on a sample size of 350 participants as specified in the main document.

Days alive outside hospital

Using a minimal important difference of 3 days, a standard deviation of 9, a risk of type I error of 5%, and accounting for the fact that the data is expected not to be normal distributed, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 82.1%.[1]

The Atrial Fibrillation Effect on Quality-of-Life (AFEQT)

In previous trials the observed difference between groups was normally distributed with a standard deviation of 21.[2 3] Using a minimal important difference of 7, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 87.5%. The Type I error probability associated with this test of this null hypothesis is 5%.

Quality of life using the SF-36 questionnaire (mental component score)

In previous trials the observed difference between groups was normally distributed with a standard deviation 10.[4-6] Using a minimal important difference of 4, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 96%. The Type I error probability associated with this test of this null hypothesis is 5%.

Serious adverse events

We anticipate a failure rate among control of 20%. If we anticipate a relative risk reduction of 60%, we will be able to reject the null hypothesis with probability (power) of 90.2%. The Type I error probability associated with this test of this null hypothesis is 5%.

POWER ESTIMATIONS OF EXPLORATORY OUTCOMES

All-cause mortality

Prior data indicate that the mortality rate among controls is about 5%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.7%. The Type I error probability associated with this test of this null hypothesis is 5%.

Composite of all-cause mortality, stroke, myocardial infarction and cardiac arrest

Prior data indicate that this outcome occurs in controls in about 8%.[7 8] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.9%. The Type I error probability associated with this test of this null hypothesis is 5%.

Cardiac mortality

Prior data indicate that the failure rate among controls is 3.9%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.4%. The Type I error probability associated with this test of this null hypothesis is 5%.

Stroke

Prior data indicate that cardiac mortality among controls is 3.9%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 5.4%. The Type I error probability associated with this test of this null hypothesis is 5%.

Hospitalisation for worsening of heart failure

Prior data indicate that heart failure among controls is 27.4%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 9.0%. The Type I error probability associated with this test of this null hypothesis is 5%.

Number of hospital admissions

Prior data indicate that number of participant who are hospitalised is 27.4%.[7] If we anticipate a relative risk reduction of 10%, we will be able to reject the null hypothesis with probability (power) of 9%. The Type I error probability associated with this test of this null hypothesis is 5%.

Six-minute walking distance

In previous trials the observed difference between groups was normally distributed with a standard deviation 75.[9-11] Using a minimal important difference of 40, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 99.9%. The Type I error probability associated with this test of this null hypothesis is 5%.

Physical activity using trial accelerometer

Prior data indicates that the standard deviation among groups was 65 minutes pr. Day when measuring sedentary behaviour. Assuming a difference in groups of 20 minutes/day, we will be able to reject the null hypothesis with a probability of 81.9%. The type 1 error probability associated with this test of this null hypothesis is 5%.[12 13]

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Supplementary file 6. Short description of the independent Data Safety and Monitoring Committee (DSMC)

Introduction

This Charter defines the primary responsibilities for the independent Data safety and monitoring Committee (DSMC) of the randomised clinical trial DanAF. This includes the relationships with other aspects of the trial.

Primary responsibility of the DSMC

The DSMC will ensure the safety of trial participants. This will be achieved by the following tasks:

- Performing planned analyses of outcomes related to the safety of participants from the two rate control strategies during the trial.
- Continuously monitoring if the trial still holds scientific merit

Members of the DSMC

The exact composition of the DSMC will be specified later but is expected to consist of two clinicians and one person with adequate statistical knowledge to conduct the interim analysis. One member will be chosen as the committee chair.

Recommendations are recommended to be anonymous. However, in case of members not coming to an agreement, members will vote. The points of discussion will be part of the discussion of the DSMC report to the Steering Committee (SC). The members of the DSMC will be free of conflicts of interest. Assessment if members are free of conflict of interest will be decided by the SC.

Meetings

This is the initial DSMC charter. The final charter will be determined and signed as the last part of the first meeting of the DSMC (see below).

1. Meeting

The first meeting will be a finalization of the DSMC role during the trial. The following will be agreed on and finalized.

- How DSMC can request additional (unblinded) data
- How meetings will be held (virtually, physical meeting, phone)
- How many meetings are necessary.
- Decision on whether a test run is necessary.
- Finally, the charter will be finalised and signed.

2. meeting

The second meeting will take place as part of an interim analysis after 50% of the participants (n=175) have been recruited.

The DSMC will be allowed to conduct additional interim analyses independently of the SC. The following meeting may take place virtually, in person or by phone.

Communication

Different formats will be used in order to secure proper communication is established. The formats include open and closed reports as well as open and closed sessions.

Closed Sessions

These sessions will involve only DSMC members. Discussions will be based on a closed report that will be based on blinded data provided by the data manager. A single member will be in charge of preparing the report but may receive input from the other two members before finalizing the closed report.

If the DSMC deems it necessary, they may ask for unblinding of the data from the steering committee.

Data for review will be the composite outcome all-cause mortality, stroke, myocardial infarction and cardiac arrest mortality (and its individual components), serious adverse events including any serious adverse reactions.

Recommendations to the steering committee (open report)

The DSMC will report its recommendations to the SC based on safety considerations. If the DSMC recommends anything other than continuing the trial, there will be held a virtual meeting between the DSMC and the SC. The DSMC will here present the reasoning behind its recommendations.

The SC ultimately makes the decisions regarding all aspects of the trial.

Data

The DSMC will be provided with data on the following variables

1. Randomisation code (this will not reveal the allocated heart rate target)
2. The composite outcome of all-cause mortality, stroke, myocardial infarction and cardiac arrest and the individual components:
    a. All-cause mortality
    b. Stroke
    c. Myocardial infarction
    d. Cardiac arrest
3. Serious adverse events including subcategories of individual events
4. Numbers of participants lost to follow up

The DSMC will not be provided with data on site or any identifier the data is considered anonymized.

Analyses

The DSMC is recommended to use Lan-DeMets sequential monitoring boundaries.

Meta data

The DSMC will be provided with a detailed codebook that explains all the coding in the data set.

Supplementary file 7 – informed consent form

(S4)

Informed consent to participate in a health-related research project

Research project title: Lenient rate control versus strict rate control for atrial fibrillation. The Danish Atrial Fibrillation (DanAF) randomised clinical trial

Statement from trial participant:

I have received both written and verbal information and have received enough information regarding purpose, methods, harms and benefits to give informed consent.

I know that it is voluntary to participate and that I always have the right to withdraw my consent without losing my right to treatment now or in the future.

I give my consent to participate in the research project and that my biological material may be collected with the intention of storing it in a research biobank. I have received a copy of this consent form along with written information regarding the project for my personal use.

Participant name: _____

Date: _____ Signature: _____

If during the research project significant information regarding your health, you will be informed. If you would like not to be informed of any new information regarding your health that comes to our attention during the trial, we ask that you mark here: _____ (mark with an x)

Do you wish to be informed of the results of the trial and possible consequences for you?:

Yes _____ (mark with an x) No _____ (mark with an x)

Statement from the person providing information to the participant:

I declare that the participant has received written and verbal information about the trial.

To my knowledge there has been given enough information to make a decision to participate in the trial.

Printed name of the person, who has given the information:

Date: _____ Signature: _____

Regional ethics commitee project identification:

69694

Supplementary file 8 - Roles and responsibilities

Daily management team (including the Principal investigator (PI))

Conduct of DanAF

Preparation of protocol and revisions

Design of Redcap database

Organising steering committee meetings

Conceive manuscripts of results for review by the steering committee

In charge of supervising start-up of sites

Budget administration and contractual issues with individual centres

Organisation of central serum sample collection

Design of randomisation

Securing that the GDPR is complied with (by interaction with the Regional data controller)

Site investigators

Joshua Buron Feinberg (Holbaek University Hospital), Axel Brandes (Odense University Hospital), Ulrik Dixen (Hvidovre University Hospital) and Ole Dyg Pedersen (Region of Zealand University Hospital - Roskilde)

Responsible for the proper conduct at respective sites.

In charge of reporting Serious adverse events (SAE) including Suspected unexpected serious adverse reactions (SUSAR) to PI in a timely manner as well as reporting serious adverse events for annual review by the regional ethics committee.

Steering committee (SC)

All authors of the protocol will be invited to be part of the steering committee.

Agreement of final protocolReviewing progress of study and if necessary agreeing changes to the protocol.

In charge of reviewing proper conduct of the trial according to GCP, Helsinki-declaration and ethics review demands.

Providing advice to lead investigators and personnel.

Review of analyses provided by the blinded statistician

Review of manuscript prepared by daily management team

Assistance with international review

Data manager

Maintenance of trial IT system and data entry (OPEN).

Data verification (OPEN in collaboration with PI)

Providing data to the DSMC

Providing data to the blinded statistician

Outcome adjudication committee

Responsible for adjudicating serious adverse events.

Data safety monitoring committee

Responsible for the safety of trial participants and the continuous scientific merit for the trial. Will report findings to the SC.

Blinded statistician

Prepare analysis for the steering committee to review

Regional data controller (independent from trial)

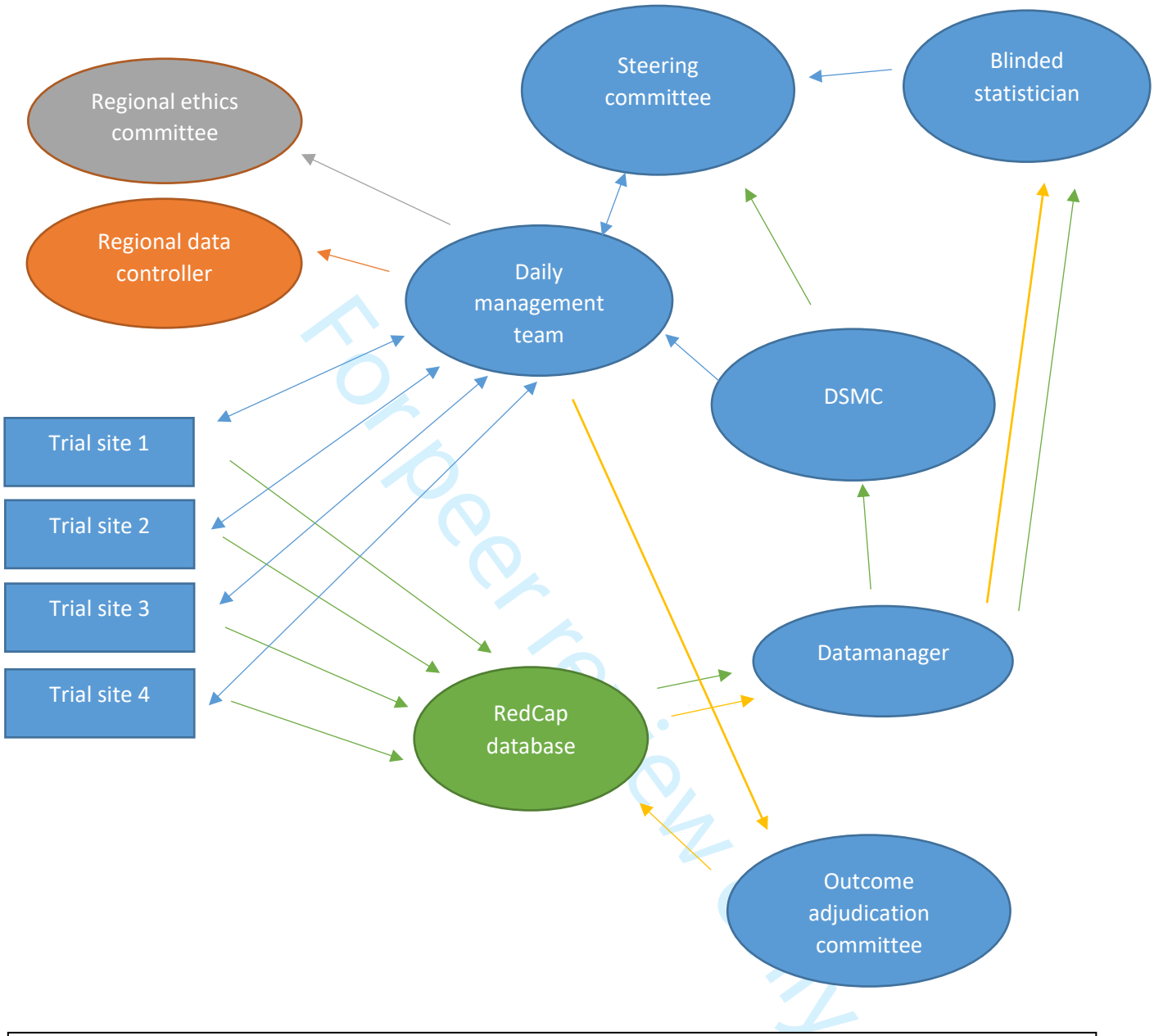
Data controller for the study hence must keep record of the type of data kept, data processor agreements and any other requirements needed to comply with GDPR

Regional ethics committee (independent from trial)

Approve the trial by review of protocol, written participant material, informed consent forms, etc.

Monitor trial through reports of SAE and SUSAR reported to them by the daily management team as well as the yearly report submitted by the PI.

Figure outlying the organisation



Grey arrow: Serious adverse events including SUSAR. Orange arrow: Information necessary to follow GDPR. Green arrow: Data. Yellow arrow: data for adjudication/adjudicated data.

Blue bubbles: Part of the trial organization. Green bubble: database. Orange/grey bubble: External regulatory body.

Lenient rate control versus strict rate control for atrial fibrillation. A protocol for the Danish Atrial Fibrillation (DanAF) randomised clinical trial

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Abstract

Introduction

Atrial fibrillation is the most common heart arrhythmia with a prevalence of approximately 2% in the western world. Atrial fibrillation is associated with an increased risk of death and morbidity. In many patients~~cases~~, a rate control strategy is recommended. The optimal heart rate target is disputed despite the results of the the RAte Control Efficacy in permanent atrial fibrillation: a comparison between lenient versus strict rate control II (RACE II)~~Comparison between lLenient versus sStrict rRate cControl II (RACE II)~~ trial.

Our primary objective will be to investigate~~compare~~ the effect of ~~a~~ lenient rate control strategy (< 110 beats per minute (bpm) at rest) compared with ~~a~~ strict rate control strategy (< 80 bpm at rest) on ~~the~~ quality of life ~~for~~in ~~of~~ patients with persistent or permanent atrial fibrillation.

Methods and analysis

We plan a two-group, superiority randomised clinical trial. 350 outpatients with persistent or permanent atrial fibrillation will be recruited from four hospitals, across three regions in Denmark. Participants will be randomised 1:1 to a lenient medical rate control strategy (< 110 bpm at rest) or a strict medical rate control strategy (< 80 ~~-~~bpm at rest). The recruitment phase is planned to be two years with three years of follow-up. Recruitment is expected to start in January 2021.

The primary outcome will be quality of life using the Short Form-36 (SF-36) questionnaire (physical component score). Secondary outcomes will be days alive outside hospital, symptom control using the Atrial Fibrillation Effect on Quality of Life, quality of life using the SF-36 questionnaire (mental component score), and serious adverse events. The primary assessment time point for all outcomes will be one year after randomisation.

Ethics and dissemination Ethics approval was obtained through the ethics committee in Region Zealand. The design and findings will be published in peer reviewed journals as well as be made available on clinicaltrials.gov.

Trial registration: The trial has been registered at clinicaltrials.gov (NCT04542785).

Strength and limitations of this randomised clinical trial

- First trial assessing ~~a~~ lenient versus ~~a~~ strict rate control in patients who upon inclusion are considered ~~with~~ as having persistent atrial fibrillation. Hence, this trial is expected to provide data on patients who upon inclusion have a relatively short~~er~~ duration of atrial fibrillation.
- First superiority trial with quality of life as primary outcome in patients with both permanent atrial fibrillation and persistent atrial fibrillation upon inclusion.
- Pragmatic trial with multiple sites ensuring high external validity.
- Treatment providers are not blinded in a trial that is otherwise expected to have low risk of bias regarding blinding of other domains.

- Trial will not have enough power to assess 'hard outcomes' such as mortality and serious adverse events.

INTRODUCTION

Atrial fibrillation is the most common arrhythmia of the heart with a prevalence of approximately 2% in the western world.[1 2] Atrial fibrillation is associated with an increased risk of death and a number of morbidities.[3-9] The risks of both cerebral stroke and heart failure are increased nearly fivefold in patients with atrial fibrillation, and about 20% of all strokes may be due to atrial fibrillation.[3-8] Atrial fibrillation also has a significant impact on healthcare costs and accounts for approximately 1% of the National Health Service budget in the United Kingdom and approximately 26 billion dollars of annual expenses in the United States.[10 11]

Two different overall intervention strategies may be used for atrial fibrillation – a rhythm control strategy or a rate control strategy.[12-14]

We have previously shown in a systematic review with meta-analysis and Trial Sequential Analysis that rhythm control strategies compared with rate control strategies seem to significantly increase the risk of ~~a~~ serious adverse events in patients with atrial fibrillation.[13 14] Based on current evidence as well as guidelines, it seems that most patients with atrial fibrillation should be treated with a rate control strategy unless there are specific reasons justifying a rhythm control strategy.[13 14]

The ~~guideline recommended~~ resting heart rate target for rate control has recently changed from below 80 beats per minute (bpm) to below 100 to 110 bpm at rest depending on the guideline.[12 14 15] This change was a result of the the RAte Control Efficacy in permanent atrial fibrillation: a comparison between lenient versus strict rate control II (RACE II)~~Comparison between lLenient versus sStrict rRate cControl II (RACE II)~~ trial which randomised 614 participants to a lenient rate control strategy (< 110 bpm at rest) versus a strict rate control strategy (< 80 bpm at rest).[16] The participants were outpatients with permanent atrial fibrillation. The RACE II trial showed that the~~a~~ lenient rate control strategy was non-inferior compared with the~~a~~ strict rate control strategy on the risk of a composite outcome of mortality, stroke, cardiac arrest, arrhythmic events, systematic emboli, or major bleeding. Furthermore, the hazard ratio of 0.84 (90% CI 0.58 to 1.21) suggested~~indicated~~ that the lenient rate control group might ~~have a~~ decrease~~d~~ the risk of the composite outcome. The RACE II trial also showed no difference of the two strategies on quality life ~~between the two groups~~, but this analysis has questionable validity.[17]

A theoretical concern when using a lenient control strategy is that patients may develop heart failure if the heart rate is too fast.[18-20] The RACE II trial found that the lenient strategy was also non-inferior for heart failure patients but~~although~~ the majority of the participants had preserved ejection fraction at baseline.[21]

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, clinicaltrials.gov on September 26, 2019. Our~~A~~ literature search identified only the RACE II trial assessing the effect of ~~a~~ lenient rate control ~~strategy~~ versus ~~a~~ strict rate control ~~strategy~~ in atrial fibrillation. ~~We searched the Cochrane Central Register of Controlled Trials and MEDLINE on September 26 2019, and searched clinicaltrials.gov.~~ We found no systematic reviews or meta-analyses on the topic.

Trial rationale

Currently, lenient rate control is the guideline recommended initial rate control strategy.[14] However, this recommendation is primarily based on the RACE II trial which had two major limitations. First, the validity of the RACE II trial results when assessing symptoms and quality of life were questionable mainly because of substantial problems with missing data. Regarding quality of life and symptom severity, only 437/614 (71%) participants had data available at maximum follow-up.[17] Furthermore, the authors did not use multiple imputation or other valid methods to handle the missing data.[22] Second, the RACE II trial only showed a lenient rate control strategy was non-inferior, but could not answer if ~~is~~ a lenient rate control strategy is superior to a strict rate control strategy.~~?~~ The RACE II trial was not adequately powered to confirm or reject minimal important differences between the two strategies. Conducting a superiority randomised clinical trial and afterwards performing a systematic review with meta-analysis will give us the possibility of confirming or rejecting that there is a difference in effect between the two strategies, at least on quality of life.

Health-related quality of life as an outcome

There are many definitions of health-related quality of life.[23 24] In general, quality of life questionnaires can be designed in two ways.[23] Generic questionnaires assess multiple domains applicable to a variety of health domains.[23] They more readily permit comparison across different disease and seem to have unquestionable patient relevance.[23 25] Generic quality of life scales are often criticised for being less sensitive to change than disease specific quality of life scales, but when outcome results show no difference it is most often unknown whether the lack of difference is caused by non-sensitive outcome scales or if the results demonstrate that there is no 'true' difference between the compared interventions when assessing 'generic' quality of life.[23 25] The opposite holds true for disease specific questions, which in general are thought to be more responsive to change in the clinical condition than generic disease questionnaires but may be less patient relevant. The disease-specific questionnaires tend to focus more narrowly on the disease. Any increase in quality of life as a result of a treatment for a specific disease may be off-set by unforeseen negative consequences of the treatment which the questionnaire by design will not capture.

We will therefore supplement the general assessment using SF-36 with a disease-specific questionnaire. Currently, there seems to be no optimal questionnaire.[25 26] The Atrial Fibrillation Effect on Quality of Life (AFEQT) is a validated, disease specific questionnaire, which aims to capture the objective and subjective burden of disease.[27] It contains 20-items that aim to assess four domains: symptoms, activities, treatment concern and treatment satisfaction. It also includes a summary score that summarises the first three domains. It assesses the burden of the atrial fibrillation symptoms.[27 28]

When assessing quality of life, it is important to focus on a minimally important difference, which typically can be done using an anchor-based method or a distribution-based method, or a mix of the two.[29 30] To interpret the clinical significance of future trial results, we will carefully define minimal important differences for all primary and secondary outcomes (see 'Statistical plan and data analyses').[31]

Objectives

Our primary objective will be to ~~compare~~investigate the effect of a lenient rate control strategy (< 110 bpm at rest) compared with a strict rate control strategy (< 80 bpm at rest) on ~~the~~ quality of life ~~for~~in~~of~~ patients with persistent or permanent atrial fibrillation.

METHODS AND ANALYSIS

Trial design

The design will be a randomised, two-group, superiority trial of lenient rate control versus strict rate control in patients with persistent or permanent atrial fibrillation at inclusion who accept rate control as the main strategy. Treatment providers responsible for the rate control treatment will not be blinded. Any other involved personnel will be attempted blinded as well as participants.

Three hundred and fifty outpatients will be recruited from 4 university hospitals in Denmark: Holbaek University Hospital, Hvidovre University Hospital, Region Zealand University Hospital – Roskilde and Odense University Hospital.

The present protocol follows the recommendation in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline including all items from the World Health Organization Trial Registration Data Set (supplementary file 1 and 2).

Trial conduct

This trial will be conducted according to good clinical research practice (GCP) and the latest Declaration of Helsinki.[32 33]

Randomisation

Participants will be randomised 1:1 to a lenient or a strict medical rate control strategy. The trial will use centralised randomisation at OPEN. Prior to the trial, a computer will generate randomisation sequences with varying block sizes between 6-10 that are unknown to the investigators. An internet-based randomisation system will be set up conducting randomisation stratified according to site, type of atrial fibrillation at inclusion (persistent versus permanent) and LVEF (EF ≥ 40% and EF < 40%). The randomising investigator will get access to the internet site through a personal pin code. The randomising investigator will not be an outcome assessor.

Blinding

The investigator prescribing the rate control medication (treatment provider) will not be blinded, as the treatment requires knowledge of the group the participant is randomised to. All other treatment providers, outcome assessors, data managers, statisticians and participants will be sought blinded (the participants will neither be informed of their rate control target nor their allocated intervention group). Blinded data will be sent to OPEN for blinded data management. Statistical analyses will be performed with the two intervention groups coded as 'A' and 'B' by two independent blinded statisticians. Two blinded conclusions will be drawn by the steering group: one assuming 'A' is the experimental group and 'B' is the control group — and one assuming the opposite. Based on these two blinded conclusions, two abstracts will be written (will be published as a supplement to the main publication). When the blinding is broken, the 'correct' abstract will be chosen and the conclusions in this abstract will not be revised.

As all medical procedures are available to any treatment provider, we cannot foresee any reason for unblinding participants. If, however, any medical personnel deem~~s~~ it necessary to unblind a participant, the participant will be unblinded.

Selection of participants

Inclusion criteria

1. Atrial fibrillation (electrocardiogram (ECG)~~ECG~~-confirmed and diagnosed by the treatment provider) who at inclusion have either persistent (defined as atrial fibrillation for more than 7 days) or permanent atrial fibrillation (only rate control is considered going forward).
2. Rate control must be accepted as being the primary management strategy going forward. Consideration toward whether rhythm control is more appropriate must be considered, especially given the results of the EAST trial.[34]
3. Informed consent.
4. Adult (18 years or older).

Exclusion criteria

1. No informed consent.
2. Initial heart rate under 80 bpm at rest (assessed via ~~an electrocardiogram (~~ECG~~)~~ before randomisation).
3. Less than 3 weeks of anticoagulation with n~~N~~ew o~~O~~ral a~~A~~nticoagulants (NOAC) or 4 weeks with efficient warfarin.
4. Participants dependent on a high ventricular rate to maintain a sufficient cardiac output. This will be based on an individual assessment of the possible participant. Such participants could be participants with heart failure, participants with a haemodynamically significant valve dysfunction, or severely dehydrated participants. Other factors such as echocardiographic assessments, stability of the disease, and similar will be factored in when judging if a participant is dependent on a high

ventricular rate. Such a decision will be made before randomisation by the treatment provider.

5. Participants who are haemodynamic unstable and therefore require immediate electrical cardioversion.

Participant withdrawal

Participants can withdraw his or her consent at any time point for any reason but will be invited to still participate in the follow-up assessments.

Interventions

Lenient rate control

The heart rate will be assessed on a 12-lead resting ECG measured over 1 minute after 5 minutes of rest. The treatment provider will target the highest tolerable resting heart rate < 110 bpm. Treatment providers are encouraged not to attempt to lower the heart rate if already below 110 unless symptoms or other reasons necessitates this. If the heart rate is below 90, the treatment provider is encouraged to reduce rate limiting treatment. If the patient remains symptomatic due to atrial fibrillation after achieving this definition of heart rate control, Holter monitoring or exercise tests may be deemed necessary by the treatment provider.

These evaluations may be followed by adjustment of rate control drugs, rhythm control (electrical cardioversion, arrhythmia surgery, rhythm control medications), or atrioventricular node ablation. In case of the need for rhythm control or atrioventricular node ablation, the allocated heart rate target is no longer relevant in management.

Strict rate control

Strict rate control achieved by using rate control medication (see below) will be defined as a mean resting heart rate < 80 bpm with a general recommendation of targeting 70 bpm on a 12-lead resting ECG measured over 1 minute after 5 minutes of rest. Exercise test to determine activity heart rates or Holter monitoring will only be performed if the treatment provider believes this is indicated. These evaluations may also be followed by adjustment of rate control medications, electrical cardioversion, arrhythmia surgery, or atrioventricular node ablation (treatment provider's choice).

Rate control medications

Treatment will be provided according to current guidelines and as such the algorithm for treatment will be differentiated based on the status of left ventricular ejection fraction.[14] For participants with reduced left ventricular ejection fraction, beta-blockers (metoprolol and bisoprolol) will be the primary therapy. Secondary therapies may include digoxin or amiodarone. For participants with preserved left ventricular ejection fraction, the primary therapy will be beta-blockers (metoprolol and bisoprolol) or non-dihydropyridine calcium-channel blockers (verapamil) with secondary therapy consisting of digoxin or amiodarone.

Below we briefly summarise the pharmacological treatment in the DanAF trial (table 1).

Table 1: Suggested daily doses for rate control agents.

Metoprolol	50 to 200 mg
Bisoprolol	2.5 to 10 mg
Digoxin	62.5 to 250 µg maintenance dose according to weight, age, and renal function, loading is usually required for 3 to 7 days
Verapamil	120 to 240 mg - no loading dose required

Concomitant medication

Besides rate control, the treatment provider will be free to prescribe any other standard medical co-intervention such as the need for anticoagulation (based on the CHA_2DS_2-VASc score and co-morbidity[14]), hypertension management, heart failure management, or lipid lowering drugs as long as the prescriptions adhere to guidelines.[14] This also includes recommendations regarding modifiable risk factors that may have adverse effects on atrial fibrillation management (excess alcohol, smoking, sleep apnoea).[14 35] A brief description of what is considered standard management of co-morbidities and risk factors are given in supplementary file 3. All other interventions are allowed if they are administered evenly in all intervention arms.

Follow-up and outcome events

All participants will attend a minimum of two follow-up visits within two months after randomisation. Further visits are possible with two-week intervals until adequate titration of rate control therapy is as required or for other reasons such as participants having inadequate symptom control, management of comorbidities, etc. Treatment providers may plan a visit sooner or later if clinically indicated. To assess if the ECG guided heart rate target is representative of the heart rate under normal conditions, we will perform 24 hour Holter monitoring at the end of the titration phase and after 1 year of follow-up for documentation purposes.

After the initial adequate titration of rate control, participants are to follow the normal referral system in the Danish Health care system. A hotline will be established where treatment providers may call and ask for the participant's rate control target. If treatment providers themselves do not contact the trial treatment provider, participants are encouraged to contact the trial treatment provider. If possible, a treatment provider involved in the trial will be the managing treatment provider of the referral, if the referral is to a participating department.

Primary outcome

- Quality of life using the SF-36 questionnaire (physical component score), continuous outcome.[36]

Secondary outcomes

- Days alive outside hospital, count outcome.
- Symptoms due to atrial fibrillation using the Atrial Fibrillation Effect on Quality of Life (AFEQT), continuous outcome.[27]
- Quality of life using the SF-36 questionnaire (mental component score), continuous outcome.[36]
- Serious adverse events, dichotomous outcome. We will define a serious adverse event as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, and resulted in persistent or significant disability or jeopardised the patient.[33]

Exploratory outcomes

- All-cause mortality, dichotomous outcome.
- Composite of all-cause mortality, stroke, myocardial infarction and cardiac arrest, dichotomous outcome.
- Cardiac mortality, dichotomous outcome.
- Stroke, dichotomous outcome.
- Hospitalisation for worsening of heart failure dichotomous outcome.
- Number of hospital admissions, count outcome.
- Six-minute walking distance, continuous outcome.
- Healthcare costs.
- Various biomarkers (N-terminal pro-brain natriuretic peptide (nt-proBNP), high sensitivity C reactive protein (hsCRP), high sensitivity troponin I (hsTnI), growth

differentiation factor-15 (GDF-15), interleukin 6 (IL6), cystatin-C, YKL40, soluble urokinase plasminogen activator receptor (suPAR) and fibulin-1).

- Switch to rhythm control strategy (such as rhythm control medication, DC-conversion, pulmonary vein isolation or arrhythmia surgery), dichotomous outcome.
- Implantation of a pacemaker or cardioverter–defibrillator with or without AV node ablation, dichotomous outcome

Echocardiographic outcomes

- Size of left atrium (LAVi).
- Size of left ventricle.
- Cardiac index (cardiac output / body surface area).
- Left ventricular ejection fraction.
- Tricuspid annular plane systolic excursion (TAPSE).[37]
- Midwall fractional shortening.
- Global longitudinal strain.
- Circumferential end-systolic stress.
- Diastolic dysfunction estimated by the relationship between LV filling and RR interval for the individual patient.
- Pulmonary pressure.

All secondary, exploratory, and echocardiographic outcomes will only be hypothesis-generating.

Adverse events

Participants will be asked during visits to the clinic if they had experienced any undesirable medical events.

Suspected unexpected serious adverse reactions (SUSAR) will be reported to the ethics committee within 7 days of investigators being aware of the event. Once a year, a report of all serious adverse events and serious adverse reaction will be submitted to the ethics committee.

Assessment time point

The primary assessment time point for all outcomes will be one year after randomisation.

Procedures for ~~s~~Screening

Potential participants according to inclusion and exclusion criteria at Holbaek University Hospital, Hvidovre University Hospital, Region Zealand University Hospital – Roskilde and Odense University Hospital will receive an invitation to participate in the trial upon a routine visit in the clinic or hospitalisation for atrial fibrillation. Possible participants will be identified by trial staff employed at the site.

Procedures for informed consent

Participants will receive printed material containing details of each study visit, the design and rational of the trial, participant rights (such as the right to withdraw), possible adverse reactions of medication, and more. The printed material will be given either immediately after being identified as a possible candidate or during a private, information session where verbal information is given and the participants can ask any questions they may have. The information session will take place in an undisturbed environment. The information will be given by the project coordinator on site or medical personnel with equivalent prerequisites for conveying the project. Potential participants will be informed that they can bring a third party if they wish so. The participants will be given up to three weeks to consider participation depending on when they choose to schedule the information session. There will be a minimum of 48 hours from the information session to the obtaining of informed consent.

Data collection

Data will be attempted to be collected from all participants regardless of protocol adherence. Study plan and data will be as shown in **Table 2**.

Table 2

Schedule	**Visit 0** Base-line	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4, 5, 6**
Investigations	0 mo	1 mo ± 2 w	2 mo ± 2 w	6 mo ± 2 w	12 mo/ 24 mo/ 36 mo/ ± 2 w
Medical history	**X**				**X**
Clinical events (hospital, tests etc.)		**X**	**X**		**X**
CHA_2DS_2VASc score	**X**				**X**
EHRA SC	**X**	**X**	**X**		**X**
SF-36, AFEQT	**X**				**X**
Physical examination	**X**				**X**
Vital signs (BP, HR)	**X**	**X**	**X**		**X**
Concom. Rx, AF Medication	**X**	**X**	**X**		**X**
Informed Consent, Inclusion/Exclusion criteria	**X**				
Randomization	**X**				
Clinical lab. tests (as indicated)	**X**	**X**	**X**		**X**
Study lab. tests	**X**			**X**	**X**
12-lead ECG	**X**	**X**	**X**		**X**

Holter monitoring. () = as clinically indicated	**(X)**	**(X)**	**X**		**X**
Echocardiography	**X**				**X**
Six-minute walking test	**X**				**X**

Abbreviations: mo=-months. BP=Blood pPressure. EHRA SC= European Heart Rhythm Association~~EHRA~~ symptom classification. HR=Heart rate. Lab. tests=Laboratory tests,- SF-36=Short form-36. AFEQT-= The Atrial Fibrillation Effect on Quality of Life. ECG=electrocardiogram.

Echocardiography will be performed according to current international guidelines.[38] A detailed plan for the echocardiographic examination and recordings has been developed. The echocardiograms will be sent to a core echocardiographic reading centre at Holbaek Hospital to be assessed by one of two assessors that will be blinded.

Biobank

We will collect blood samples for a research biobank and measure: Nt-proBNP, hsCRP, hsTni, GDF-15, IL6, Cystatin-C, YKL40, suPAR and fibulin-1. In addition to the above blood samples, we will collect the following three types of blood samples: 5 ml serum, 5 ml plasma, and 5 ml citrat plasma to be stored for future research. Participants will be given separate information on this blood collection as well as be required to give a separate informed consent (supplementary file 4).

Data management

All data will be sent encrypted to OPEN for management. All data on paper will be securely stored and a copy will be sent to a computerised database.

The computerised database will be continuously checked for missing values and errors at one month intervals. Before a trial site begins recruitment, an internal monitoring of the following procedures will be checked: validation of inclusion and exclusion criteria, informed consent procedure, randomisation procedure and data entry into Redcap.

Statistical plan and data analyses

Sample size - Quality of life using the SF-36 questionnaire (physical component score)

Using a minimal important difference of 3 points on the physical component score, a standard deviation of 10, power of 80%, and a significance level of 5%, a total of 350 participants will be needed.[17 39 40] Based on this sample size, we have estimated the power of all remaining outcomes (see supplementary file 5).

Recruitment plans

We will involve key medical personnel at the different departments as well as hold sessions at the different departments informing of the trial.

Statistical analyses

A detailed statistical analysis plan will be published around one month after the trial has been launched. In short, our primary conclusions will be based on the results of our single primary outcome. Hence, we will consider a P value of 0.05 as our threshold for statistical significance.[31] The results of secondary outcomes, exploratory outcomes, subgroup analyses, and possible per protocol analyses will be hypothesis generating only. We will assess whether the thresholds for statistical and clinical significance are crossed according to the five-step procedure proposed by Jakobsen et al.[31] The analyses of the outcomes will be based on the 'intention to treat' principle, i.e. all randomised participants will be included in the analysis regardless of how much treatment they have received. In case of more than 5% not receiving the allocated heart rate target, we will secondarily analyse all outcomes according to the actual heart rate achieved (per protocol analysis) defined as the average heart rate on ECG after 5 minutes of rest. Participants who receive a rhythm control strategy (assessed by the treating physician) at our primary assessment time point will be ~~no longer with atrial fibrillation will be~~ excluded ~~in~~from this analysis. ~~The treating physician will determine this at the corresponding assessment time point.~~ If outcomes are not present due to retraction of informed consent or dropout, the pattern of the missing data will be investigated. Missing data will be handled according to the recommendations proposed by Jakobsen et al.[22] In short, we will conduct a worst-best and best-worst case scenario~~s~~, testing the potential impact of missing data.[22] If the pattern of missing data allows it, we will also conduct multiple imputations.[22]

Analysis methods

Continuous outcomes will be presented as means and standard deviations with 95% confidence intervals. Count outcomes will be presented as medians and interquartile ranges. We will analyse continuous outcomes using mixed effects linear regression with 'site' as a random intercept using an exchangeable covariance matrix and type of atrial fibrillation at inclusion (persistent versus permanent) and LVEF (EF ≥ 40% and EF < 40%) as a fixed effect.[41] We will analyse count data using the van Elteren's test stratifying for 'site'.[42] Dichotomous outcomes will be presented as proportions of participants in each group with the event, as well as risk ratios with 95% confidence intervals. Dichotomous outcomes will be analysed using mixed effects generalised linear models using a log link function with 'site' as a random intercept using an exchangeable covariance matrix, and type of atrial fibrillation will be included as a fixed effect.[42] All outcomes will be analysed according to final value.

Subgroup analyses

All subgroup analyses will be regarded as hypothesis generating only and we will not base any conclusions on these. We will in the planned statistical analysis plan (see 'Statistical analysis') in detail describe each planned subgroup analysis.

In short, we will in each publication compare:

- Patients with heart failure compared to patients without heart failure (including subtypes).
- Men compared to women
- Different durations of atrial fibrillation at randomisation

- Less than one year
- 1 to -2 years
- More than 2 years

- Patients with age above compared to below 75 years
- Patients according to the European Heart Rhythm Association (EHRA) symptoms score

Data monitoring

A data safety monitoring committee (DSMC) independent from the sponsor and the investigators will be created. The DSMC will be free of conflicts of interest. The DSMC will be responsible for conducting an interim analysis after 50% of participants have been included and monitor if the trial still holds scientific merit. The DSMC will decide when / if a new interim analysis should be performed. The DSMC will make recommendations to the steering committee whether the trial should stop or continue (further details in supplementary file 6)."

Auditing

The trial can be audited by the r~~R~~egional ethics committee, which is independent from the investigators and sponsor.

Patient and public involvement

Patient were invited to a work-shop after the initial draft was accepted by all participating departments. They were asked to give inputs to the chosen outcomes, the written material, the relevance of the objective of the trial and any other aspects they found relevant. Patients are anticipated to work as ambassadors after the trial results are available. We will therefore ~~again~~ perform a second workshop to involve patients in the best strategy for dissemination.

ETHICS AND DISSEMINATION

The management of patients is in accordance with standard care and as such, patients are at~~in~~ no greater risk compared to receiving standard care outside the trial. It is therefore ~~completely~~ ethical for patients to be part of the trial. The potential benefits for further patients are that we may uncover a superior heart target to be the goal of future management of patients with atrial fibrillation.

The trial protocol has been approved by the regional ethics committee which is a branch of the Danish ethics committee, the regulatory body approving research in Denmark. As such, the committees are independent from the trial. The committee reviewed the full protocol, the written material for the participants, the consent form and the administered questionnaires before giving approval. The ethics committee has the option of conducting an audit of the trial if it wishes to do so. The committee must be provided with a notification of any SAE including SUSARs within a week as well as a yearly report of SAE. Any changes to the approved protocol will be submitted and approved before continuing the trial.

Site investigators or personnel with equivalent skills will obtain informed consent from possible participants (Supplementary file 7). Additional consent will be obtained in order to store blood samples for future research.

Before enrolment of participants, screening will be done by personnel employed at the study site using the local electronic journal system. Any information collected on potential and enrolled participants will be entered directly into REDedcapcap, using a secure connection.

The project and its data have been registered at the Region Zealand, who is the data controller. Study investigators will have access to the full data set. OPEN, who is in charge of storing the data, will also have access to the full data set. Ethics review will also have access to data upon request.

Participants, who suffer harm during the trial, are insured by the the Danish Patient Compensation Association.

Trial results will be sought published in a peer-reviewed journal. In addition, results will be communicated directly to relevant patient advocacy groups, relevant medical associations, and attempted presented at relevant congresses. Aggregate data analysis will be published in a clinical trial register no later than three years after trial results have been collected. Data sharing will be made available upon request after approval from ethics committee.

Authorship will be granted according to the recommendations from the International Committee of Medical Journal Editors (ICMJE).[43]

Discussion

Our trial has several strengths. It is a pragmatic trial assessing the benefits and harms of a lenient versus a strict rate control strategy on ~~the~~ quality of life ~~for~~in~~of~~ patients with persistent or permanent atrial fibrillation ~~in patients with both persistent and permanent atrial fibrillation~~. The number of inclusion and exclusion criteria is low and hence, the external validity will be high. Participants will be recruited from more than one site, which will further increase the external validity. We have performed a sample size estimation based on previous evidence with realistic intervention effects, we will adjust the thresholds for statistical significance if the sample size is not reached, and we have chosen only one outcome we will base conclusion on. ~~and~~ T~~t~~he remaing outcomes~~st~~ will be considered hypothesis generating only thereby taking into account problems with multiplicity. Furthermore, we have taken measures to reduce the~~consider~~ risks of bias from the allocation sequence generation, allocation concealment, blinding of outcome assessors and participants, selective outcome reporting, for-profit bias and missing outcome data. Hence, our trial will be conducted with a low risk of random errors ('play of chance') and with as low risk of systematic errors ('bias') as the trial design allows (see below).[31 44] In Denmark, a complete follow-up of all participants for death and hospitalisations is secured by an unique number given to all born in Denmark, Central Person Register.

Our trial also has limitations. The treatment providers responsible for the rate control intervention will not be blinded, which may bias our results. We will use 12-lead ECG to guide rate control therapy. Holter monitoring and measurement of the heart rate during exercise will only be used at the discretion of the investigator if deemed necessary. ~~And~~ As such, there may be fluctuations in the heart rate we do not detect. Another limitation is that we do not have sufficient power to assess 'hard outcomes' such as mortality and serious adverse events. This will be explored in a future meta-analysis with individual patient data from~~with~~ the RACE II trial and other trials. The consequence may ultimately be that a superiority trial in terms of 'hard outcomes' is needed. Our results will only be generalizable to a population where rate control is considered appropriate as the main strategy going forward. The results of the EAST trial is expected to delay the initiation of rate control for many patients and hence, our results will need to be interpreted in light of this. Yet another limitation is that participants presumably will receive different medications and procedures in the compared groups. If we show a difference (or lack of a difference) between the groups, it will be difficult to interpret what part of the treatment algorithm for reaching a certain rate target caused this difference.

We expect the results of this trial will play a part of future recommendations for rate control treatment in patients with both persistent and permanent atrial fibrillation.

Protocol version and amendments

This abbreviated version of the full protocol~~,~~ is based on version 2.0 of the protocol (January 2020). Any changes to the original protocol will be submitted to the regional ethics committee. After approval, changes will be conveyed to all investigators, participants, and trial registries.

The findings will be published in a peer reviewed journal as well as be made available on clinicaltrials.gov.

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Contributors

JBF, JCJ, AB, UD, UG, WBN, MHO, ODP, and IR participated integrally in the study design. CG provided vital advice on trial conduct. EEN and FS designed the echocardiography plan. MHO designed the plan for analysis of biomarkers. JBF, JCJ, and AB drafted the initial manuscript. All other authors provided critical revision and approved the final manuscript.

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Role of sponsors and funders

The trial is investigator initiated. Holbaek Hospital is the sponsor and the Rregion ~~of~~ Zealand is the data controller. The study sponsors and funders had no influence on design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The Danish Heart Foundation requires to be notified by email when a publication is accepted.

Roles and responsibilities of additional parties are described in supplementary file 8.

Competing interests statement

JBF (PI), IR, WBN, EEN, FSH, ODP, UG, CG, and JCJ report no competing interests.

MHO reports grants from Novo Nordic Foundation outside the submitted work.

AB reports personal fees from Bayer, grants from Biotronik, personal fees from Boehringer

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UD reports a research grant from Bayer, personal fees from Pfizer, member of advisory board for Boehringer Ingelheim, member of advisory board for Merck, outside the submitted work.

Patient consent for publication

Not required

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