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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 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 vs 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 2 years with 3 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 1 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 number NCT04542785.

Strengths and limitations of this study

- 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 on 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 UK and approximately $26 dollars of annual expenses in the USA.[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 100–110 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 vs 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 HR 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 EF at baseline.[21]

We searched the Cochrane Central Register of Controlled Trials, MEDLINE and ClinicalTrials.gov on 26 September 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 that the questionnaire by design will not capture.

We will therefore supplement the general assessment using Short Form-36 (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 of the Danish Atrial Fibrillation (DanAF) trial 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 treatment providers (i.e. those

managing co-morbidities) will be attempted blinded as well as participants.

Three hundred and fifty outpatients will be recruited from four 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 guideline including all items from the WHO Trial Registration Data Set (online supplemental files 1 and 2).

Trial conduct

This trial will be conducted according to good clinical research practice 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 and 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 vs permanent) and left ventricular ejection fraction (LVEF) (ejection fraction (EF) ≥40% and EF <40%). The randomising investigator will get access to the internet site through a personal password. 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. Participants withatrial 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 towards whether rhythm control is more appropriate must be considered, especially given the results of the Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST) .[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 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 haemodynamically 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 min after 5 min 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 and 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 further) 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 min after 5 min 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 LVEF, beta-blockers (metoprolol and bisoprolol) will be the primary therapy. Secondary therapies may include digoxin or amiodarone. For participants with preserved LVEF, 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.

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

Concomitant medication

Besides rate control, the treatment provider will be free to prescribe any other standard medical cointervention such as the need for anticoagulation (based on the CHA_2DS_2-VASc score and comorbidity,[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 and sleep apnoea).[14 35] A brief description of what is considered standard management of comorbidities and risk factors are given in online supplemental file 3. All other interventions are allowed if they are administered evenly in all intervention arms.

Table 1 Suggested daily doses for rate control agents

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

Follow-up and outcome events

All participants will attend a minimum of two follow-up visits within 2 months after randomisation. Further visits are possible with 2-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 and so on. 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 healthcare 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 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 (Left atrial volume index)).
- 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 left ventricular filling and the interval between two successive R waves on ECG (R-R 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 1 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 on 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 3 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.

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 (online supplemental 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 1-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, an SD of 10, power of 80% and a significance level of 5% and 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 online supplemental 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.

Table 2 - Study schedule

Schedule	Visit 0 baseline	Visit 1	Visit 2	Visit 3	Visits 4, 5 and 6
Investigations	0 months	1 month±2 week	2 months±2 weeks	6 months±2 weeks	12 months/24 months/36 months ±2 weeks
Medical history	x	×			×
Clinical events (hospital, tests and so on)		×	×		×
CHA_2DS_2VASc score	×				×
EHRA SC	×	×	×		×
SF-36 and AFEQT	×				×
Physical examination	×				×
Vital signs (BP and HR)	×	×	×		×
Treatment adjustment (both for atrial fibrillation and any comorbidities)	×	×	×		×
Informed consent, inclusion/ exclusion criteria	×				
Randomisation	×				
Clinical laboratory tests (as indicated)	×	×	×		×
Study laboratory tests	×			×	×
12-lead ECG	×	×	×		×
Holter monitoring. ()=as clinically indicated	(×)	(×)	×		×
Echocardiography	×				×
Six-minute walking test	×				×

AFEQT, the atrial fibrillation effect on quality of life; BP, blood pressure; CHA_2DS_2VASc score, Score for determining the risk of stroke. Points are given for congestive heart failure (1), hypertension (1), age 75 or above (2), diabetes (1) previous stroke (2), vascular disease (1), age 65-75 (1) and female sex (1); EHRA SC, European heart rhythm association symptom classification; HR, heart rate; SF-36, Short Form-36.

Statistical analyses

A detailed statistical analysis plan will be published around 1 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, that is, 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 min 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 SD with 95% CIs. Count outcomes will be presented as medians and IQRs. 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 vs 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% CIs. 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 with patients without heart failure (including subtypes).
- Men compared with women.
- Different durations of atrial fibrillation at randomisation.
  - Less than 1 year.
  - 1–2 years.
  - More than 2 years.
- Patients with age above compared with below 75 years.
- Patients according to the European Heart Rhythm Association 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 online supplemental 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

Patients 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 with receiving standard care outside the trial. It is therefore ethical for patients to be part of the trial. The potential benefit for future patients is 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 serious adverse events including Suspected unexpected serious adverse reactions within a week as well as a yearly report of serious adverse events. 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 (online supplemental 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 on 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. We will also communicate results 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 3 years after trial results have been collected. Data sharing will be made available on request after approval from ethics committee.

Authorship will be granted according to the recommendations from the International Committee of Medical Journal Editors.[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 remaining 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 further).[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 generalisable 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 V.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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