Effects of training adaption in endurance athletes with atrial fibrillation: protocol for a multicentre randomised controlled trial

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ABSTRACT
Endurance athletes have a high prevalence of atrial fibrillation (AF), probably caused by exercise-induced cardiac remodelling. Athletes diagnosed with AF are often advised to reduce the intensity and amount of training but the efficacy of this intervention has not been investigated in endurance athletes with AF. Effects of detraining in endurance athletes with atrial fibrillation is a two-arm international multicentre randomised (1:1) controlled trial on the effects of a period of training adaption on AF burden in endurance athletes with paroxysmal AF. One-hundred-and-twenty endurance athletes diagnosed with paroxysmal AF are randomised to a 16-week period of intervention (training adaption) or a control group. We define training adaption as training with a heart rate (HR) not exceeding 75% of the individual maximum HR (HRmax), and total duration of weekly training not exceeding 80% of the self-reported average before the study. The control group is instructed to uphold training intensity including sessions with HR > 85% of HRmax. AF burden is monitored with insertable cardiac monitors, and training intensity with HR chest- straps and connected sports watches. The primary endpoint, AF burden, will be calculated as the cumulative duration of all AF episodes lasting ≥30 sec divided by total duration of monitoring. Secondary endpoints include number of AF episodes, adherence to training adaption, exercise capacity, AF symptoms and health-related quality of life, echocardiographic signs of cardiac remodelling and risk of cardiac arrhythmias related to upholding training intensity.

Trial registration number NCT04991337.

Study protocol version 4.7 (Date 9 March 2023).

INTRODUCTION
Endurance exercise and atrial fibrillation
Compared with physical inactivity, moderate levels of physical activity reduce the risk of atrial fibrillation (AF).12 Studies of inactive AF patients have demonstrated that endurance exercise may reduce AF burden even during a short intervention period.3 Paradoxically, studies have demonstrated a high prevalence of AF among otherwise healthy male endurance athletes, suggesting vigorous endurance sport practice is a risk factor for the development of AF.4, 5 A dose-response association between AF and cumulative exposure to endurance exercise was demonstrated among more than 3500 Norwegian men aged ≥53 years, where the risk of AF increased with 16% per decade of regular exercise.6 In a subset of these study participants, a similar relationship was demonstrated between prolonged exposure to endurance exercise and cardiac remodelling, such as atrial enlargement7, 8 (figure 1). The high prevalence of AF in endurance athletes has led to the hypothesis that exercise-induced cardiac remodelling is a proarrhythmic condition.9, 10
Prolonged exposure to endurance exercise is associated with increased risk of atrial fibrillation (A)\(^6\) and increased atrial dimensions (B).\(^7\,8\)

Training adaption

Although AF is not a life-threatening condition, high ventricular rates during exercise with AF may cause symptoms, haemodynamic compromise and safety concerns that contribute to a conservative approach among many physicians facing these athletes. The impact of altering endurance exercise load on AF burden in athletes suffering AF remains unexplored. Despite a lack of evidence, endurance athletes with AF have traditionally been advised to reduce both the amount and intensity of exercise, often referred to as detraining.\(^14\) This approach assumes that the exercise stimulus plays a causative role in the development of AF, and that continuation of the same stimulus could lead to further cardiac remodelling and ultimately disease progression. In an animal model, rats experienced increased AF inducibility after 16 weeks of endurance training on treadmill, with AF inducibility returning to baseline levels following 4 weeks of detraining.\(^15\)

While exercise-induced ventricular hypertrophy and dilatation (‘athlete’s heart’) seems to be partially reversible by detraining,\(^16\,18\) data regarding the effects of training adaption on atrial remodelling and exercise-induced AF in humans do not exist.

Present guidelines

While an expert position statement suggests that sports activities can be resumed after diagnostic workup if the episodes of AF are rare,\(^19\) The European Society of Cardiology guidelines on Sports Cardiology and Exercise, and guidelines for the management of AF suggest to counsel athletes that prolonged sport participation may promote AF.\(^20\) Thus, endurance athletes with AF and their physicians are left without specific recommendations regarding the preferred exercise intensity to improve symptoms and reduce the risk of AF recurrence. Studies have shown that many athletes with AF prefer to maintain exercise intensity and competitive activities irrespective of their diagnosis.\(^21\)

Both safety questions and the effects of upholding high exercise volumes on the risk of AF recurrence were highlighted among the major knowledge gaps in the recently published ESC sports cardiology guidelines.\(^19\) Furthermore, neither adherence to training adaption, symptoms nor quality of life (QoL) have been studied in athletes receiving exercise restrictions. Consequently, we designed a randomised controlled trial (RCT) to investigate the effects of training adaption in endurance athletes with paroxysmal AF.

METHODS AND ANALYSIS

Study design

Effects of Detraining in Endurance Athletes with Atrial Fibrillation (NEXAF Detraining) is an international multicentre, two-armed, RCT with blinded endpoint evaluation (ClinicalTrials.gov Registry Identifier NCT04991337). The study protocol (V.4.7, 9 March 2023) is in accordance with the SPIRIT 2013 statement regarding standard protocol items for clinical trials (online supplemental table 1),\(^22\) and meets the requirements of the WHO Trial Registration Data Set (online supplemental table 2). Study participants are included at seven participating centres across three countries: Bærum Hospital, Bærum (Norway), St. Olavs Hospital, Trondheim (Norway), The Baker Heart and Diabetes Institute, Melbourne (Australia), The University Hospital of Leuven (Belgium), Antwerp University Hospital (Belgium), AZ Jan Palfijn Gent (Belgium) and Jessa Hospital Hasselt (Belgium). A total of 120 study participants will be randomised to an intervention arm with training adaption or a control arm upholding high intensity exercise for a period of 16 weeks (online supplemental graphical abstract, figure 2). All study participants receive an insertable cardiac monitor (ICM) during the first study visit for continuous monitoring of AF burden.
Subsequently, participants will practice their regular exercise for 4 weeks to allow quantification of baseline AF burden. During the second study visit (week 5) participants will undertake baseline examinations, including echocardiography, cardiopulmonary exercise testing (CPET), questionnaire, blood samples, 24-hour ambulatory ECG and randomisation. All examinations will be repeated during a follow-up study visit after 16 weeks (figure 3).

Objectives and hypothesis
The primary objective of the study is to clarify whether a period of training adaption reduces AF burden in endurance athletes with paroxysmal AF. Secondary objectives are to study the adherence to training adaption, effects of training adaption on AF symptoms and health-related QoL, risk of cardiac arrhythmias related to upholding high-intensity training and to improve the understanding of underlying mechanisms for AF by studying structural and electrical cardiac remodelling. We hypothesise that a period of tailored training will reduce AF burden and improve QoL in endurance athletes with paroxysmal AF.

Endpoints
The primary endpoint is AF burden, as measured by continuous monitoring with ICMs and calculated as the cumulative duration of all AF episodes lasting ≥30 s divided by total duration of monitoring. All AF episodes will be adjudicated by a blinded endpoint committee consisting of two cardiologists, who will adjudicate AF episodes independently and reach consensus in the case of discrepancy. Table 1 shows an overview of study endpoints.

Study population and eligibility criteria
Eligibility criteria include female and male endurance athletes aged ≥18 years, diagnosed with paroxysmal AF. Participants in this study are athletes of elite and recreational levels, who are performing structured, repetitive exercise aiming to improve their physical fitness and are engaged in regular endurance sports such as running and rowing for at least 5 hours/week or cycling and cross-country skiing for at least 8 hours/week on average, or a combination of these sports or other comparable endurance sports characterised by medium or high intensity. As weekly hours of exercise are an arbitrary measure, cut-offs are pragmatic choices and indicative.

We include athletes reporting at least two episodes of AF, of which at least one that has occurred during the past 4 weeks.

4-week baseline period
Monitoring of AF burden

16-week intervention period
(Training adaption or control group)
Monitoring of AF burden

Randomisation

Eligibility screen and consent (study visit 1)
Implantation of cardiac monitor

Baseline examinations (visit 2)
CPET
Echocardiography
Blood samples
Holter monitoring
Questionnaires

Follow-up examinations (visit 3)
CPET
Echocardiography
Blood samples
Holter monitoring
Questionnaires

Figure 2 Study design. Overview of the design of the randomised controlled trial NEXAF Detraining. HRmax, maximum heart rate; NEXAF Detraining, Effects of Detraining in Endurance Athletes with Atrial Fibrillation.

Figure 3 Study visit schedule and study procedures of the randomised controlled trial. AF, atrial fibrillation; CPET, cardiopulmonary exercise testing; NEXAF Detraining, Effects of Detraining in Endurance Athletes with Atrial Fibrillation.
6 months. To minimise the impact of other factors that may have caused AF or may affect AF burden, athletes with arterial hypertension and other cardiovascular risk factors or conditions are excluded from participating in the study. People at high risk of adverse cardiovascular events, including athletes with cardiovascular risk factors, a strong family history of coronary artery disease or sudden death or symptoms during activity, are excluded after a preparticipating screening by questionnaire.20 23 24

Box 1 shows the eligibility criteria for the study. To be included, participants must fulfil all inclusion criteria and have no exclusion criteria.

Informed consent

Eligible participants receive written and oral information about the study and must sign an informed consent form approved by the ethical committee for medical research of the respective study centres.

Atrial fibrillation monitoring

We insert a wireless ICM (Confirm Rx, Abbott, Sylmar, California, USA) subcutaneously near the left paraesternal area over the third or fourth intercostal space at 45° to the sternum in men and 10°–15° in women. At the end of the procedure, we confirm reliable signal quality and R-wave sensing using an external programmer. ICMs are programmed to detect and record arrhythmic events defined as AF episodes lasting ≥30 s, pauses ≥3 s, bradycardia with heart rate (HR) ≤30 beats per minute (bpm) and tachycardia lasting ≥12 beats with a HR ≥180 bpm. In participants with a measured maximum HR (HRmax) >170 bpm, we programme the ICM to detect tachycardia when HR exceeds the recorded HRmax by ≥10 bpm. The device connects via Bluetooth and a smartphone application, and the data are uploaded to a secure server every 24 hours. Summarised reports of data from the ICM are generated every fourth week during the entire study period, reporting total time in AF, number and duration of AF episodes, pauses, bradycardia and tachycardia episodes. The ICM will be removed after the study or kept for up to the battery life expectancy of 2 years, on the participants’ request.

Intervention

The study participants are randomised 1:1, stratified by recruiting centre and AF burden during the 4-week baseline observation (<4% or ≥4%), to training adaption (intervention) or a control group. The participants are assigned to each group using a predefined permuted block randomisation to avoid imbalanced data. The allocation sequence was prepared by a statistician not directly involved in the study and is unavailable to the study personal and is implemented at each participating centre during the second study visit by use of sealed envelopes.

### Table 1  Primary and secondary endpoints of NEXAF Detraining

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
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<tr>
<td>AF burden</td>
<td>Measured by ICM and calculated as the cumulative duration of all AF episodes lasting ≥30 s divided by total duration of monitoring</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
</tr>
<tr>
<td>AF burden</td>
<td>Number of AF episodes, duration of AF episodes, days with and without AF episodes, relative change in AF burden from the 4-week baseline monitoring period to 4-week periods during the intervention period, HR during AF episodes</td>
</tr>
<tr>
<td>Adherence to training adaption</td>
<td>Total amount of exercise and time during exercise (&gt;80% of exercise sessions spent with HR≥75% of maximum heart rate (HRmax)), measured by HR chest-strap and sports watch and ≤80% of the self-reported average weekly amount of exercise (hours/week) before randomisation.</td>
</tr>
<tr>
<td>Safety of upholding high-intensity exercise</td>
<td>Incidence of ventricular arrhythmias detected by ICM or during examination, adverse events and serious adverse events</td>
</tr>
<tr>
<td>AF treatment</td>
<td>Cardioversions, ablations, hospitalisations</td>
</tr>
<tr>
<td>AF symptoms</td>
<td>mEHRA, self-reported number of symptomatic AF episodes</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>AFEQT questionnaire</td>
</tr>
<tr>
<td>Exercise capacity</td>
<td>Maximum oxygen consumption measured during cardiopulmonary exercise testing</td>
</tr>
<tr>
<td>Cardiac remodelling</td>
<td>Echocardiographic assessment of atrial and ventricular dimensions and function</td>
</tr>
<tr>
<td>Laboratory biomarkers</td>
<td>High-sensitivity cardiac Troponins, NT-pro-BNP, interleukins, C reactive protein</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td>Weight, body mass index, blood pressure, blood lipids</td>
</tr>
<tr>
<td>Incidence of arrhythmias</td>
<td>Number of pauses, episodes of bradycardia and tachycardia and premature atrial and ventricular beats detected by ICM or 24-hour ECG monitoring</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; AFEQT, Atrial Fibrillation Effect on QualiTy-of-life; HR, heart rate; ICM, insertable cardiac monitor; mEHRA, Modified European Heart Rhythm Association Symptom Scale; NEXAF Detraining, Effects of Detraining in Endurance Athletes with Atrial Fibrillation.
The training adaption is individually tailored, based on HRmax and the self-reported average weekly hours of training during the past 6 months. The intervention group is instructed to avoid high-intensity exercise corresponding to a HR >75% of HRmax, and a total duration of exercise (hours/week) corresponding to <80% of the self-reported average weekly amount of exercise (hours/week) for a period of 16 weeks. The control group is instructed to perform at least 3 weekly sessions of high-intensity training, corresponding to a HR of ≥85% HRmax, and otherwise continue endurance exercise as usual, for a period of 16 weeks. For practical reasons, we have chosen to define exercise intensity as a percentage of the individual’s HRmax. We use the highest reliable HRmax value measured in sinus rhythm via ECG monitoring during the CPET or during exercise with a HR chest-strap and a connected sports watch. To avoid caveats related to the use of HRmax in participants using beta-blockers, we use the HRmax derived from CPET performed while the participant has taken their medication.

Based on a pragmatic approach, we have defined training adaption as reducing exercise intensity to ≤75% of HRmax, corresponding to the threshold for moderate intensity suggested in exercise guidelines for the general population. Furthermore, to avoid compensation of the reduced intensity by increased training volume, participants are instructed to reduce their weekly hours of endurance exercise by 20%. Based on previous studies of detraining in animal models and athletes, we considered a period of reduced training intensity of 16 weeks to be sufficient to affect AF burden and at the same time acceptable to the athletes.

**Exercise monitoring**

Participants are instructed to wear a HR monitor strapped around the chest and a sports watch when exercising throughout the entire study period. The HR chest-strap and watch connect using Bluetooth technology. We make use of the study participants’ personal sports watches. Alternatively, study participants receive a HR chest-strap (Garmin HRM-PRO) and sports watch (Garmin Forerunner 745) for the study period. The sports watch connects with Bluetooth technology to a web-based platform (Fitrockr, Digital Rebels, Berlin, Germany or TrainingPeaks, Louisville, Colorado, USA). We register the total amount of exercise and time during exercise sessions at different HR zones, <61%, 61%–70%, 71%–75%, 76%–80%, 81%–84%, 85%–90% and >90% of HRmax, respectively. This exercise monitoring allows assessment of adherence to the study intervention.

**Blood samples**

Fasting blood samples for analyses of biomarkers for cardiovascular risk factors are collected at rest at baseline and follow-up. Serum and plasma are stored at −80°C for subsequent batch analyses of biomarkers relevant for AF. In addition, we collect blood samples before and at maximal effort during CPET to assess the acute response to exercise (High-sensitive Troponins, NT-proBNP).

**Questionnaires**

At baseline and follow-up, the participants are asked to fill out the Atrial Fibrillation Effect on QualiTy-of-life questionnaire (AFEQT), assessing severity and frequency of AF symptoms, daily activity, treatment concerns and satisfaction. We score the AF symptom severity from none (1) to disabling (4) using the Modified European Heart Rhythm Association Symptom Scale. At baseline, we also obtain patients’ characteristics, self-reported history of endurance exercise and frequency, duration and triggers of AF episodes. At follow-up, participants are requested to fill out a questionnaire concerning AF treatment during the study and their experience with the ICM and the study intervention.

**Transthoracic echocardiography**

Transthoracic echocardiography is performed in sinus rhythm with a study-specific protocol in line with current recommendations. For assessment of cardiac structure and function, we perform resting two-dimensional (2D) and three-dimensional (3D) transthoracic echocardiography using the Vivid E95 ultrasound system (GE Healthcare, Horten, Norway). Images are obtained using a 1.5-4MHz probe. Images are obtained using a 1.5-4MHz probe.
Cardiopulmonary exercise testing (CPET)
We perform CPET using a study-specific protocol. A standard 12-lead ECG is recorded at rest and throughout the test. Peak oxygen consumption (VO2peak) is measured in sinus rhythm using one of three predefined continuous ramp bicycle protocols, based on the patient’s estimated physical capacity. All protocols start with 2 min rest on the bicycle, followed by a 3 min steady state warm-up at 40 or 50 W before gradually increasing resistance at a rate of 20-30 W/min until exhaustion, corresponding to 17–20 on the Borg 6–20 scale. In the recovery phase, the participant will stop cycling completely and rest for at least 6 min, until normalisation of blood pressure. VO2peak is defined as the maximal value obtained from a 30 s rolling average of the six consecutive highest VO2 values recorded from the 5 s averaged data.

24-hour ECG monitoring
We use ambulatory 24-hour ECG monitoring at baseline and follow-up to assess arrhythmias that are not properly registered by the ICM and that may be induced by the maximal effort during CPET.

Adverse events
Any unfavourable and unintended sign, symptom or illness that develops or worsens during the trial period will be reported as adverse events (AE). A serious adverse event (SAE) is defined as death, any life-threatening event or any inpatient hospitalisation. In the analyses, AE will be summarised per treatment group by event type, intensity, seriousness and relationship. The timing of SAE will be categorised as occurring during exercise, within the first hour postexercise, or 1–24-hour postexercise. The activity at the time of the event will be further characterised as occurring during training or competition, at rest or during sleep. All SAE will be reported to the Study Safety Monitoring Committee (SMC) that will independently evaluate the safety of the study. Formal interim analyses of AE summarised per treatment group will be reported to study SMC after 25% and 50% of the participants have completed the study.

Blinding
This is an open label study and participants are not blinded to group allocation. Researchers and staff are unblinded during all procedures. AF burden will be adjudicated by a blinded endpoint committee.

Data management
Data sources are stored at each participating centre according to local procedures. Data entry is performed by local study personal using a web-based electronic case report form (Ledidi Core, Oslo, Norway). After study completion, before database lock and unblinding, all data from 10% of the participants will be checked by a monitor not involved in the study for consistency with source data. Due to the non-commercial nature of the study, the type of intervention and relatively small study size, we considered a data monitoring committee and formal interim analyses not to be required. The final dataset will be accessed by a statistician blinded to group allocation, and researchers will be blinded when performing statistical analyses.

Statistical considerations
We consider a mean difference in the burden of AF of 0.5% between the detraining group and the control group to be clinically meaningful. A 0.5% difference with a SD in each group of 1% was used to calculate a minimum sample size of 64 participants per group using an independent samples t-test and β=0.2 (power 80%) at α=0.05. However, the primary analysis will be a linear mixed model for repeated measurements and a sample size estimation based on t-test provides thereby a conservative estimate. We also performed a power calculation based on a study of Malmo et al for the outcome difference between the groups in change of AF from baseline to follow-up. In that study AF burden measured with ICMs was reduced by 41% (−3.3% (SD 7.2) from a baseline value of 8.1% (SD 11.2) after a 12-week exercise intervention, compared with+4.2% in the control group). Based on t-tests of means, to detect a difference in change in AF burden of 7.5% between the groups with β=0.2 (power 80%) and α=0.05, a minimum of 28 participants per group is required. Because the baseline AF burden is likely to be lower in the current study than in the study by Malmo, we suggested 60 participants per group. Since we cannot rule out a possible worse outcome in the intervention group, we plan to use a two-sided hypothesis test.

All randomised participants will be included in the main analysis of primary and secondary endpoints. Since adherence to detraining is a secondary outcome measure, major comparisons between randomised groups will be performed by the ‘intention-to-treat’ principle, meaning that patients will be analysed according to the planned intervention. However, some analyses may also be performed using ‘per-protocol’ or ‘as-treated’ data. We define adherence to the detraining intervention as ≥80% of total volume of endurance exercise during the study period performed at an intensity corresponding to a HR of ≤75% of HRmax, based on the exercise monitoring with chest-straps and sports watches.

We plan to publish a detailed statistical analysis plan separately before randomisation of the last study participant.

TRIAL STATUS
The study has been approved by the ethical committees of the Norwegian Regional Committees for Medical and Health
Cardiac arrhythmias in athletes represent a major challenge for sports cardiologists. Ventricular arrhythmias and sudden cardiac death in young athletes have been the main focus of research and discussions in this field. AF is a less severe but much more prevalent condition, especially in middle-aged and older male athletes. While several studies and meta-analyses have related the risk of AF to endurance sport practice, the mechanisms underlying this association have been less studied. With the aim to design an intervention that is sufficient to have an effect, but also acceptable to athletes and feasible in real-life, the training intervention in the current study represent a pragmatic compromise with regards to intensity and amount of exercise and duration of the intervention period. Female athletes have been under-represented in previous studies and the association between endurance exercise and AF is less clear in female compared with male athletes. With the aim to increase the knowledge regarding exercise-induced cardiac remodelling and arrhythmias among female athletes, both female and male athletes are included.32

CONCLUSION
Endurance athletes with AF and their physicians are left without specific recommendations regarding the preferred exercise intensity to improve symptoms and reduce the risk of AF recurrence. This RCT addresses the feasibility and effects of training adaptation in endurance athletes with paroxysmal AF and has the potential to guide development of exercise recommendations for athletes with AF.

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Contributors
All authors have contributed to the design of the study. TA and MM drafted the manuscript. All authors read and contributed to the manuscript, gave approval and agreed to be accountable for all aspects of the work.

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Disclaimer
The funders did not have any role in the study design and will not have any role in the collection, management, analysis and interpretation of data or in the writing of the report or decision to submit the report for publication.

Competing interests
None declared.

Patient and public involvement
Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication
Not applicable.

Ethics approval
This study involves human participants and was approved by Ethics approval Ethics committee reference number Norway: REK sør-øst A/212748, Australia: HREC/76210/Alfred-2021 Project No. 470/21, Belgium: Ethics Committee Research UZ/KU Leuven/ 65930. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review
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Data availability statement
No data are available.

Supplemental material
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9 Heibuchel H. The athlete’s heart is a proarhythmic heart, and what that means for clinical decision making. *European Heart Journal* 2018;20:1401–11.
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

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<th>Item No</th>
<th>Description</th>
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<td>5c</td>
<td>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</td>
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<td><strong>Introduction</strong></td>
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<td>Background and rationale</td>
<td>6a</td>
<td>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</td>
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<tr>
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<td>6b</td>
<td>Explanation for choice of comparators</td>
</tr>
<tr>
<td>Objectives</td>
<td>7</td>
<td>Specific objectives or hypotheses</td>
</tr>
<tr>
<td>Trial design</td>
<td>8</td>
<td>Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)</td>
</tr>
</tbody>
</table>
### 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 |
| 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) |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered |
| 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) |
| 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) |
| 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial |
| 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 |
| 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) |
| 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 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size |

### 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 |
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

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how

17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial

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

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

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

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

20b Methods for any additional analyses (eg, subgroup and adjusted analyses)

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)

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
### 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

**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

### Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

### Ethics and dissemination

#### Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

24 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)

#### Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

26a Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

#### 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

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

#### Financial and other competing interests for principal investigators for the overall trial and each study site

28 Financial and other competing interests for principal investigators for the overall trial and each study site

#### Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

#### Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

#### 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

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

31b Authorship eligibility guidelines and any intended use of professional writers

31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
### Appendices

<table>
<thead>
<tr>
<th>Informed consent materials</th>
<th>32</th>
<th>Model consent form and other related documentation given to participants and authorised surrogates</th>
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<tbody>
<tr>
<td>Biological specimens</td>
<td>33</td>
<td>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</td>
</tr>
</tbody>
</table>

*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.*
### Supplementary table 2. World Health Organization Trial Registration Data Set (Version 1.3.1)

<table>
<thead>
<tr>
<th>Item Nr.</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1.       | Primary Registry and Trial Identifying Number  
ClinicalTrials.gov Identifier NCT04991337 |
| 2.       | Date of Registration in Primary Registry  
5 August 2021 |
| 3.       | Secondary Identifying Numbers  
Vestre Viken Hospital Trust Data Protection Officer reference 21/05277-1 |
| 4.       | Source(s) of Monetary or Material Support  
The study is funded by The Norwegian Health Association and Vestre Viken Hospital Trust, Norway. |
| 5.       | Primary Sponsor  
Bærum sykehus, Vestre Viken Hospital Trust |
| 6.       | Secondary Sponsor(s)  
N/A |
| 7.       | Contact for Public Queries  
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Australia:  
André La Gerche, MD, PhD |

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**Phone number:** +61 481 300 929 |
| 8. **Contact for Scientific Queries**  
Primary investigator  
Marius Myrstad, MD, PhD  
Address: Department of Internal Medicine, and Department of Medical Research, Bærum Hospital Vestre Viken Hospital Trust, Sogneprest Munthe Kaas vei 100, N-1346 Gjettum, Norway  
**E-mail address:** Marius.Myrstad@vestreviken.no  
**Phone number:** +47-92255945 |
| 9. **Public Title**  
Effects of Detraining in Endurance Athletes with Atrial Fibrillation (The NEXAF Detraining study). An international multicentre randomized controlled trial |
| 10. **Scientific Title**  
Effects of Detraining in Endurance Athletes with Atrial Fibrillation (The NEXAF Detraining study). An international multicentre randomized controlled trial |
| 11. **Countries of Recruitment**  
Australia, Belgium, Norway |
| 12. **Health conditions studied**  
Atrial fibrillation |
| 13. **Intervention (s)**  
Detraining (tailored training adaption) group:  
Will be instructed to avoid high-intensity exercise corresponding to a heart rate >75% of maximum heart rate (HR), and a total duration of exercise (hours/week) corresponding to >80% of the self-reported average weekly amount of exercise (hours/week) during the past six months, for a period of 16 week.  
Control group:  
Will be instructed to perform at least three weekly sessions of high intensity exercise, corresponding to a HR ≥85% of maximum heart rate, and otherwise continue endurance exercise as usual. |
| 14. **Key Inclusion and Exclusion Criteria**  
Inclusion Criteria:  
Signed informed consent  
Age ≥ 18 years  
Diagnosed with paroxysmal atrial fibrillation (verified by electrocardiogram)  
Report ≥5 (running, rowing) or ≥8 (cycling, cross-country skiing), weekly hours, respectively, of endurance sport |
At least two anamnestic (self-reported) episodes of atrial fibrillation, of which one during the last six months
Use a smartphone and agree to connect their sportswatch with a web-based platform for monitoring of exercise

Exclusion Criteria:
Permanent atrial fibrillation
Cardiac conditions (including valvular heart disease of moderate or greater severity, symptomatic ischemic heart disease)
Left ventricular ejection fraction <45%
Hypertension (>140/90)
Diabetes mellitus
Hyperthyroidism
Smoking during the last 5 years
Alcohol intake >20 alcohol units/week
Use of illegal or performance enhancing drugs
Body mass index >30kg/m2
Injuries preventing physical exercise
Pregnancy
Participation in conflicting intervention research studies
Planned atrial fibrillation ablation within the next six months
The individual refuses to have an insertable cardiac monitor, blood samples taken or be part of the detraining group

<table>
<thead>
<tr>
<th>15. Study type</th>
<th>Randomized controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. Date of First Enrollment</td>
<td>5 Januar 2022</td>
</tr>
<tr>
<td>17. Sample size</td>
<td>120</td>
</tr>
<tr>
<td>18. Recruitment status</td>
<td>Recruiting: participants are currently being recruited and enrolled</td>
</tr>
<tr>
<td>19. Primary Outcome(s)</td>
<td>Outcome Name: Atrial fibrillation burden Metric/method of measurement: Atrial fibrillation burden (time with atrial fibrillation) as measured by continuous monitoring with insertable cardiac monitor and calculated as the cumulative duration of all atrial fibrillation episodes lasting ≥30sec divided by total duration of monitoring and reported as percentages. Timepoint: Measured during the last 4 weeks (week 13-16) of the 16-week intervention period</td>
</tr>
<tr>
<td>20. Key Secondary Outcomes</td>
<td>Outcome Name: Atrial fibrillation burden</td>
</tr>
<tr>
<td>Metric/method of measurement</td>
<td>Outcome Name</td>
</tr>
<tr>
<td>------------------------------</td>
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</tr>
<tr>
<td>Atrial fibrillation burden (time with atrial fibrillation) as measured by continuous monitoring with insertable cardiac monitor and calculated as the cumulative duration of all atrial fibrillation episodes lasting ≥30sec divided by total duration of monitoring and reported as percentages.</td>
<td>Atrial fibrillation burden</td>
</tr>
<tr>
<td>Timepoint: Measured during the first 4 weeks (week 1-4) of the 16-week intervention period</td>
<td>Timepoint: Measured during week 5-8 of the 16-week intervention period</td>
</tr>
<tr>
<td>Outcome Name: Cumulative atrial fibrillation burden</td>
<td>Outcome Name: Atrial fibrillation episode duration</td>
</tr>
<tr>
<td>Metric/method of measurement: Atrial fibrillation burden (time with atrial fibrillation) as measured by continuous monitoring with insertable cardiac monitor and calculated as the cumulative duration of all atrial fibrillation episodes lasting ≥30sec divided by total duration of monitoring and reported as percentages.</td>
<td>Metric/method of measurement: Mean duration of atrial fibrillation episodes lasting ≥30sec</td>
</tr>
<tr>
<td>Timepoint: Measured during the entire 16-week intervention period</td>
<td>Timepoint: Measured during the 16-week intervention period</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome Name</th>
<th>Metric/method of measurement</th>
<th>Timepoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation episodes</td>
<td>Number of atrial fibrillation episodes lasting ≥30 sec, as measured by insertable cardiac monitor</td>
<td>Measured during week 5-8 of the 16-week intervention period</td>
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<tr>
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<tr>
<td>Atrial fibrillation episodes</td>
<td>Number of atrial fibrillation episodes lasting ≥30 sec, as measured by insertable cardiac monitor</td>
<td>Measured during week 9-12 of the 16-week intervention period</td>
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<tr>
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<tr>
<td>Atrial fibrillation episodes</td>
<td>Number of atrial fibrillation episodes lasting ≥30 sec, as measured by insertable cardiac monitor</td>
<td>Measured during week 13-16 of the 16-week intervention period</td>
</tr>
<tr>
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<tr>
<td>Cumulative atrial fibrillation episodes</td>
<td>Number of atrial fibrillation episodes lasting ≥30 sec, as measured by insertable cardiac monitor</td>
<td>Measured during the 16-week intervention period</td>
</tr>
<tr>
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<tr>
<td>Days with atrial fibrillation</td>
<td>Days with at least one episode of atrial fibrillation lasting ≥30 sec</td>
<td>Measured during the 16-week intervention period</td>
</tr>
<tr>
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<tr>
<td>Days without atrial fibrillation</td>
<td>Days without at least one episode of atrial fibrillation lasting ≥30 sec</td>
<td>Measured during the 16-week intervention period</td>
</tr>
<tr>
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<tr>
<td>Relative change in atrial fibrillation burden</td>
<td>Relative change in atrial fibrillation burden as measured by continuous monitoring with insertable cardiac monitor and calculated as the cumulative duration of all atrial fibrillation episodes lasting ≥30 sec divided by total duration of monitoring</td>
<td>Measured during the 4-week baseline period prior to randomization and during the last 4 weeks of the 16-week intervention period</td>
</tr>
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<tr>
<td>Relative change in atrial fibrillation burden</td>
<td>Relative change in atrial fibrillation burden as measured by continuous monitoring with insertable cardiac monitor and calculated as the cumulative duration of all atrial fibrillation episodes lasting ≥30 sec divided by total duration of monitoring</td>
<td>Measured during the 4-week baseline period prior to randomization and during the first 4 weeks of the 16-week intervention period</td>
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<tr>
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<tr>
<td>Relative change in atrial fibrillation burden</td>
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<tr>
<td>Outcome Name</td>
<td>Metric/method of measurement</td>
<td>Timepoint</td>
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<tr>
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</tr>
<tr>
<td>adherence to prescribed exercise</td>
<td>adherence to prescribed exercise (&gt;80% of exercise with ≥85% and ≤75% of maximum heart rate, respectively) registered with sports watches</td>
<td>16 weeks</td>
</tr>
<tr>
<td>exercise capacity</td>
<td>peak oxygen uptake (VO2peak) measured during cardiopulmonary exercise testing</td>
<td>Measured at the baseline study visit and at the final study visit after the 16-week intervention period</td>
</tr>
<tr>
<td>atrial volumes</td>
<td>right and left atrial volumes measured with echocardiography</td>
<td>Measured at the baseline study visit and at the final study visit after the 16-week intervention period</td>
</tr>
<tr>
<td>ventricular volumes</td>
<td>right and left ventricular volumes measured with echocardiography</td>
<td>Measured at the baseline study visit and at the final study visit after the 16-week intervention period</td>
</tr>
<tr>
<td>atrial function</td>
<td>right and left atrial function measured with strain during echocardiography</td>
<td>Measured at the baseline study visit and at the final study visit after the 16-week intervention period</td>
</tr>
<tr>
<td>ventricular function</td>
<td>right and left ventricular function measured with strain during echocardiography</td>
<td>Measured at the baseline study visit and at the final study visit after the 16-week intervention period</td>
</tr>
<tr>
<td>ventricular systolic function</td>
<td>right and left ventricular ejection fraction measured with strain during echocardiography</td>
<td>Measured at the baseline study visit and at the final study visit after the 16-week intervention period</td>
</tr>
<tr>
<td>Outcome Name</td>
<td>Metric/method of measurement</td>
<td>Timepoint</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Atrial fibrillation symptoms</td>
<td>Self-reported number of symptomatic atrial fibrillation episodes by questionnaire</td>
<td>Measured at the baseline study visit and at the final study visit after the 16-week intervention period</td>
</tr>
<tr>
<td>Atrial Fibrillation Effect on Quality-of-life</td>
<td>Measured with the Atrial Fibrillation Effect on Quality-of-life questionnaire (AFEQT). Minimum score 0, maximum score 100, higher values indicate better quality of life</td>
<td>Measured at the baseline study visit and at the final study visit after the 16-week intervention period</td>
</tr>
<tr>
<td>Atrial fibrillation hospitalizations</td>
<td>Number of unplanned hospitalizations due to atrial fibrillation cardioversion or ablation</td>
<td>Throughout study completion, an average of 22 weeks</td>
</tr>
<tr>
<td>Modified European Heart Rhythm Association Symptom Scale (mEHRA) symptom classification</td>
<td>Modified European Heart Rhythm Association Symptom Scale (mEHRA) questionnaire. The scale ranges from minimum 1 to maximum 4, a higher score indicates a worse symptom burden</td>
<td>Measured at the baseline study visit and at the final study visit after the 16-week intervention period</td>
</tr>
<tr>
<td>Number of ventricular arrhythmias</td>
<td>Ventricular arrhythmias lasting ≥12 ventricular complexes as measured by continuous monitoring with insertable cardiac monitor</td>
<td>Throughout study completion, an average of 22 weeks</td>
</tr>
<tr>
<td>Number of adverse events</td>
<td>Any unfavorable and unintended sign, symptom or illness that develops or worsens during the trial period will be reported as adverse events (AE). A serious adverse event (SAE) is defined as death, any life-threatening event or any inpatient hospitalization</td>
<td>Throughout study completion, an average of 22 weeks</td>
</tr>
<tr>
<td>Cardiovascular risk factors measured by blood pressure</td>
<td>Measure of blood pressure (mmHg)</td>
<td>Measured at baseline and after the 16-week intervention period</td>
</tr>
<tr>
<td>Cardiovascular risk factors measured by blood lipids</td>
<td>Blood lipids (mmol/L)</td>
<td>Measured at baseline and after the 16-week intervention period</td>
</tr>
</tbody>
</table>
Outcome Name: Cardiovascular risk factors measured by body weight
Metric/method of measurement: Weight (kg)
Timepoint: Measured at baseline and after the 16-week intervention period

Outcome Name: Cardiovascular risk factors measured by body mass index (BMI)
Metric/method of measurement: BMI (weight and height will be combined to report BMI in kg/m²)
Timepoint: Measured at baseline and after the 16-week intervention period

Outcome Name: Cardiovascular risk factors measured by smoking
Metric/method of measurement: Self-reported smoking (pack years)
Timepoint: Measured at baseline and after the 16-week intervention period

Outcome Name: Cardiovascular risk factors measured by alcohol use
Metric/method of measurement: Self-reported alcohol use (units)
Timepoint: Measured at baseline and after the 16-week intervention period

Outcome Name: Cardiovascular biomarkers - inflammation markers
Metric/method of measurement: Markers for inflammation markers; interleukines and hrCRP (mg/L)
Timepoint: Measured at baseline and after the 16-week intervention period

Outcome Name: Cardiovascular biomarkers - markers for myocardial damage
Metric/method of measurement: Markers for myocardial damage, measured by troponin T (ng/L) and NT-ProBNP (ng/L)
Timepoint: Measured at baseline and after the 16-week intervention period

Outcome Name: Immediate effects on arrhythmia burden of high-intensity exercise
Metric/method of measurement: Arrhythmias measured with 24-hour electrocardiogram after peak cardiopulmonary exercise testing
Timepoint: 24 hours after peak exercise testing

Outcome Name: Immediate effects on biomarkers of exercise
Metric/method of measurement: Blood sampling at peak exercise for analyses of cardiac Troponins, NT-pro-BNP, interleukins, C-reactive protein
Timepoint: At peak exercise during cardiopulmonary exercise testing

21. Ethics Review

Approved 29 April 2021 by The Regional Committee for Health Research Ethics, Oslo, Norway (REK sør-øst A/212748)

Approved 1 September 2020 by The Alfred Hospital Ethics Committee, Melbourne, Australia (HREC/76210/Alfred-2021)

Approved 13 October 2022 by The Ethics Committee Research KU/UZ Leuven, Leuven, Belgium (S65930)
<table>
<thead>
<tr>
<th></th>
<th>Completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Summary Results</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>IPD sharing statement</td>
</tr>
<tr>
<td></td>
<td>Data sharing between the participating institutions is regulated by Study agreements between The Sponsor and each participating center.</td>
</tr>
</tbody>
</table>
The Norwegian Exercise and Atrial Fibrillation Initiative

This work was executed within the framework of the research consortium the Norwegian Exercise and Atrial Fibrillation Initiative (NEXAF), which is a national research initiative aiming to increase knowledge about exercise in individuals with atrial fibrillation. NEXAF consists of several studies that will examine the impact of exercise on various endpoints for different groups of atrial fibrillation patients.

The NEXAF consortium

Bente Morseth1,2, Marius Myrstad1,4, Bjarne Martens Nes5, Jan Pål Loennechen5,6, Maja-Lisa Løchen7, Arnljot Tveit4,8, Turid Apelland4, Kristine Folkenborg4, Kristoffer Robin Johansen1,2, Kristin Espolin Johnson4, Jon Magne Letnes3,6, Vegard Malmo5,6, Andreas Berg Sellevold5,6, Eivind Sørensen3,4, Rune Byrkjeland1,4, Steve Enger4, Hilde Larhammer1,4, Sophia Onarheim5, Vigdis Bache-Semb8.

Affiliations

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2 Centre for Research and Education, University Hospital of North Norway, Tromsø, Norway
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5 Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, NTNU, Trondheim, Norway
6 Department of Cardiology, St.Olavs Hospital, Trondheim, Norway
7 Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway
8 Faculty of Medicine, Institute for Clinical Medicine, University of Oslo, Oslo, Norway
Effects of Training Adaption in Endurance Athletes with Atrial Fibrillation

**BASELINE**
Atrial fibrillation monitoring with insertable cardiac monitor during the entire study period

**RANDOMISATION**
16 week intervention period

**INTERVENTION**
- Training Adaption
- Control
  - Reduced exercise intensity (HR ≤ 75% of HRmax)
  - High exercise intensity (HR ≥ 85% of HRmax)

**PRIMARY ENDPOINT**
Atrial fibrillation burden