



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

Turid Apelland ¹, Kristel Janssens,² Jan Pål Loennechen,^{3,4} Guido Claessen,^{5,6,7} Eivind Sørensen,^{1,8} Amy Mitchell,² Andreas Berg Sellevold,^{3,4} Steve Enger,¹ Sophia Onarheim,¹ Jon Magne Letnes,^{3,4} Hielko Miljoen ^{9,10}, Arnljot Tveit,^{1,11} André La Gerche,^{2,12} Marius Myrstad,^{1,8} on behalf of The NEXAF investigators

To cite: Apelland T, Janssens K, Loennechen JP, *et al*. Effects of training adaptation in endurance athletes with atrial fibrillation: protocol for a multicentre randomised controlled trial. *BMJ Open Sport & Exercise Medicine* 2023;**9**:e001541. doi:10.1136/bmjsem-2023-001541

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjsem-2023-001541>).

Accepted 29 March 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Turid Apelland;
turid.apelland@vestreviken.no

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 adaptation 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 adaptation) or a control group. We define training adaptation 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 \geq 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 \geq 30sec divided by total duration of monitoring. Secondary endpoints include number of AF episodes, adherence to training adaptation, 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).^{1,2} Studies of inactive AF patients have demonstrated that endurance exercise may reduce AF burden even during a short intervention period.³ Paradoxically,

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Endurance athletes have an elevated risk of atrial fibrillation associated with exercise-induced cardiac remodelling.
- ⇒ Despite a lack of evidence to suggest exercise recommendations, endurance athletes suffering atrial fibrillation are often advised to reduce the intensity and amount of exercise.

WHAT THIS STUDY ADDS

- ⇒ This is the first randomised controlled trial that addresses the feasibility and effects of a period of training adaptation in endurance athletes with paroxysmal atrial fibrillation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study has the potential to provide scientific knowledge that could guide development of specific exercise recommendations for endurance athletes with atrial fibrillation.

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 \geq 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 enlargement^{7 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} During exercise, circulatory flow is increased

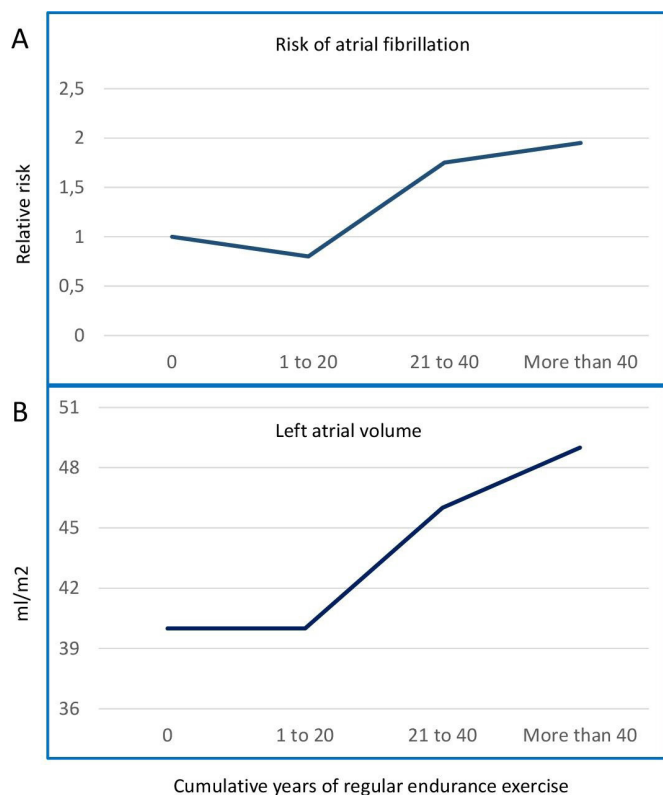


Figure 1 Prolonged exposure to endurance exercise is associated with increased risk of atrial fibrillation (A)⁶ and increased atrial dimensions (B).^{7,8}

up to eight times as compared with rest.¹¹ In response to this haemodynamic stress, long-term endurance exercise is accompanied by structural, functional and electrical cardiac remodelling referred to as the ‘athlete’s heart’.¹² Atrial enlargement is associated with pathological cardiac remodelling and an increased risk of AF in the general population.^{7,13} The extent of atrial remodelling associated with long-term endurance training can be profound.^{7,8} There is a lack of long-term data on cardiac effects of endurance exercise, and the pathophysiological mechanisms behind exercise-associated AF are only partly understood.

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.

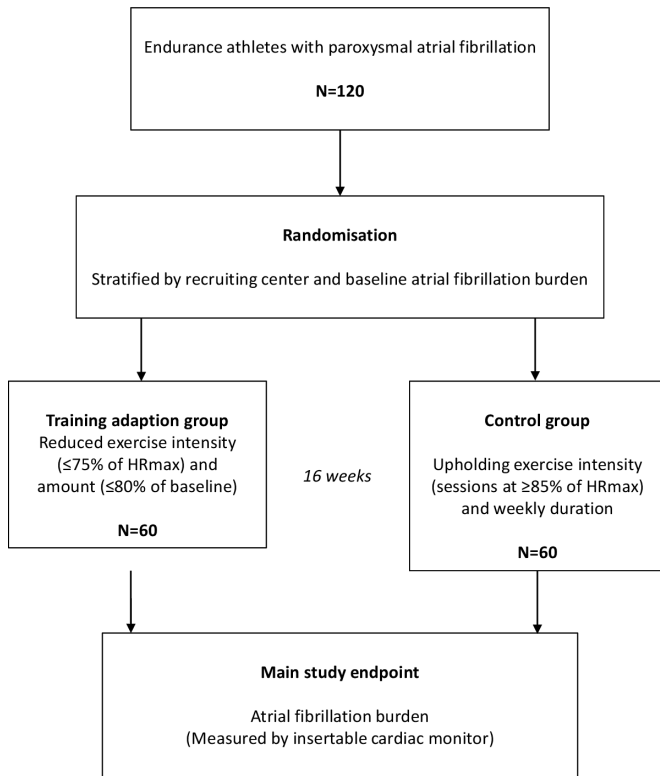


Figure 2 Study design. Overview of the design of the randomised controlled trial NEXAF Detraining. HRmax, maximum heart rate; NEXAF Detraining, Effects of Detraining in Endurance Athletes with Atrial Fibrillation.

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.²⁰ 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

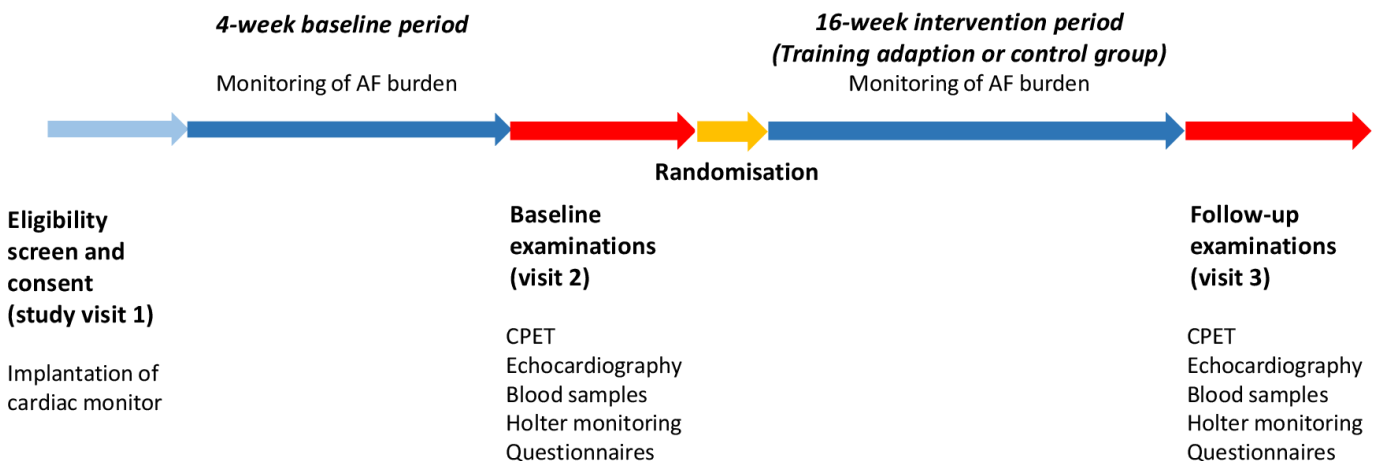


Figure 3 Study visit schedule and study procedures of the randomised controlled trial. AF, atrial fibrillation; CPET, cardiopulmonary exercise testing; NEXAF Detraining, Effects of Detraining in Endurance Athletes with Atrial Fibrillation.

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

Endpoints	Description
<i>Primary endpoint</i>	
AF burden	Measured by ICM and calculated as the cumulative duration of all AF episodes lasting ≥ 30 s divided by total duration of monitoring
<i>Secondary endpoints</i>	
AF burden	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
Adherence to training adaption	Total amount of exercise and time during exercise ($>80\%$ of exercise sessions spent with $HR \leq 75\%$ of maximum heart rate (HR _{max})), measured by HR chest-strap and sports watch and $\leq 80\%$ of the self-reported average weekly amount of exercise (hours/week) before randomisation.
Safety of upholding high-intensity exercise	Incidence of ventricular arrhythmias detected by ICM or during examination, adverse events and serious adverse events
AF treatment	Cardioversions, ablations, hospitalisations
AF symptoms	mEHRA, self-reported number of symptomatic AF episodes
Health-related quality of life	AFEQT questionnaire
Exercise capacity	Maximum oxygen consumption measured during cardiopulmonary exercise testing
Cardiac remodelling	Echocardiographic assessment of atrial and ventricular dimensions and function
Laboratory biomarkers	High-sensitivity cardiac Troponins, NT-pro-BNP, interleukins, C reactive protein
Cardiovascular risk factors	Weight, body mass index, blood pressure, blood lipids
Incidence of arrhythmias	Number of pauses, episodes of bradycardia and tachycardia and premature atrial and ventricular beats detected by ICM or 24-hour ECG monitoring
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.	

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 parasternal 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 (HR_{max}) > 170 bpm, we programme the ICM to detect tachycardia when HR exceeds the recorded HR_{max} 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 $\geq 4\%$), 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.

Box 1 Eligibility criteria for Effects of Detraining in Endurance Athletes with Atrial Fibrillation

Inclusion criteria

1. Signed informed consent.
2. Age ≥ 18 years.
3. Diagnosed with paroxysmal atrial fibrillation (verified by ECG).
4. Athletes reporting >5 (running, rowing) or >8 (cycling, cross-country skiing) weekly hours, respectively, of endurance sport practice,
5. At least two anamnestic (self-reported) episodes of atrial fibrillation, of which one during the last 6 months.
6. Use a smartphone and agree to connect their sports watch with a web-based platform for monitoring of exercise.

Exclusion criteria

1. Permanent atrial fibrillation.
2. Cardiac conditions (including valvular heart disease of moderate or greater severity, symptomatic ischaemic heart disease).
3. Suspicion of undiagnosed ischaemic heart disease.
4. Left ventricular ejection fraction $<45\%$.
5. Arterial hypertension ($>140/90$ mm Hg).
6. Diabetes mellitus.
7. Hyperthyroidism.
8. Smoking during the last 5 years.
9. Alcohol intake >20 alcohol units/week.
10. Use of illegal or performance enhancing drugs.
11. Body mass index >30 kg/m².
12. Injuries preventing physical exercise.
13. Pregnancy.
14. Participation in conflicting intervention research studies.
15. Planned atrial fibrillation ablation within the next 6 months.
16. The individual refuses to have an insertable cardiac monitor, blood samples taken or be part of the detraining group.

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 $\geq 85\%$ 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 $\leq 75\%$ of HRmax, corresponding to the threshold for moderate intensity suggested in exercise guidelines for the general

population.²⁵ 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.^{15–17}

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.²⁶ We score the AF symptom severity from none (1) to disabling (4) using the Modified European Heart Rhythm Association Symptom Scale.²⁷ 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.^{28–29} 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 1.5–4 MHz



matrix-array transducer (GE 4Vc-D Matrix 4D cardiac probe, GE healthcare, Horten, Norway). 2D-greyscale, colour Doppler and tissue Doppler imaging data will be obtained, in addition to 3D of the left atrium. A physician blinded to the participant's clinical and study information will analyse the acquired images offline (Echo Pac, V.204, GE Vingmed Ultrasound, Horten, Norway). We assess systolic and diastolic volumes of both atria and the left ventricle, and right ventricular size. Comprehensive two-dimensional speckle tracking analyses will be performed of all four chambers, combined with established Doppler parameters to obtain information about systolic and diastolic function.

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.²³ Peak oxygen consumption (VO_{2peak}) 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.³⁰ In the recovery phase, the participant will stop cycling completely and rest for at least 6 min, until normalisation of blood pressure. VO_{2peak} is defined as the maximal value obtained from a 30 s rolling average of the six consecutive highest VO_2 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.³¹ 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 $\beta=0.2$ (power 80%) at $\alpha=0.05$. 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.*,³ 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 $\beta=0.2$ (power 80%) and $\alpha=0.05$, 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 $\geq 80\%$ of total volume of endurance exercise during the study period performed at an intensity corresponding to a HR of $\leq 75\%$ 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

Research Ethics, the Alfred Hospital Human Research Ethics committee, Melbourne, Australia and the Ethics Committee Research UZ/KU Leuven, Belgium. The first study participant was included at Bærum Hospital on 5 January 2022. As of 10 March 2023, 23 participants have been included at three study centres, 9 of which have completed the study. Recruitment is expected to be completed within 2 years, and the results will be communicated through publications.

CLINICAL IMPLICATIONS

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.

Author affiliations

¹Department of Medical Research, Bærum Hospital Vestre Viken Trust, Gjøttum, Norway

²Baker Heart and Diabetes Institute, Sports Cardiology Laboratory, Melbourne, Victoria, Australia

³Clinic of Cardiology, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway

⁴Department of Circulation and Medical Imaging, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

⁵UHasselt, Faculty of Medicine and Life Sciences, BIOMED-REVAL-Rehabilitation Research Centre, Hasselt University, Diepenbeek, Belgium

⁶Hartcentrum Hasselt, Jessa Hospital Hasselt, Belgium

⁷Department of Cardiovascular Diseases, KU Leuven, Leuven, Belgium

⁸Department of Internal Medicine, Bærum Hospital Vestre Viken Trust, Gjøttum, Norway

⁹Department of Cardiology, Antwerp University Hospital, Antwerp, Belgium

¹⁰Department of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

¹¹Institute of Clinical Medicine, University of Oslo, Oslo, Norway

¹²Department of Medicine, St Vincent's Hospital, University of Melbourne, Fitzroy, Victoria, Australia

Acknowledgements We thank Kristine Seland Folkenborg and Vigdis Bache-Semb, Bærum Hospital, for their contribution to the practical organising of the study, Trond-Inge Weatherup, Vestre Viken Hospital Trust, for his contribution with the data management, Are Hugo Pripp, University of Oslo, for assistance with power calculations and statistical considerations, Hilde Larhammer, Bærum Hospital, Asher Knudson and Tor Håkon Grønli, Abbott Norway, for assisting with ICM implantations and programming and Marte Meyer Walle-Hansen, Bærum Hospital, for her help with the figures. This work was executed within the framework of the research consortium the Norwegian Exercise and Atrial Fibrillation Initiative (NEXAF) (online supplemental file 3).

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.

Funding This study is funded by The Norwegian Health Association and Vestre Viken Hospital Trust, Norway.

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/ S65930. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Turid Apelland <http://orcid.org/0000-0001-9638-7681>

Hielko Miljoen <http://orcid.org/0000-0001-6568-451X>

REFERENCES

- Garnvik LE, Malmö V, Janszky I, *et al*. Physical activity, cardiorespiratory fitness, and cardiovascular outcomes in individuals with atrial fibrillation: the HUNT study. *Eur Heart J* 2020;41:1467–75.
- Morseth B, Graff-Iversen S, Jacobsen BK, *et al*. Physical activity, resting heart rate, and atrial fibrillation: the Tromsø study. *Eur Heart J* 2016;37:2307–13.
- Malmö V, Nes BM, Amundsen BH, *et al*. Aerobic interval training reduces the burden of atrial fibrillation in the short term: a randomized trial. *Circulation* 2016;133:466–73.
- Elliott AD, Linz D, Verdicchio CV, *et al*. Exercise and atrial fibrillation: prevention or causation? *Heart Lung Circ* 2018;27:1078–85.
- Flannery MD, Kalman JM, Sanders P, *et al*. State of the art review: atrial fibrillation in athletes. *Heart Lung Circ* 2017;26:983–9.
- Myrstad M, Nystad W, Graff-Iversen S, *et al*. Effect of years of endurance exercise on risk of atrial fibrillation and atrial flutter. *Am J Cardiol* 2014;114:1229–33.



- 7 Sørensen E, Myrstad M, Solberg MG, *et al.* Left atrial function in male veteran endurance athletes with paroxysmal atrial fibrillation. *Eur Heart J Cardiovasc Imaging* 2021;23:137–46.
- 8 Sørensen E, Myrstad M, Solberg MG, *et al.* Right heart structure and function in lifelong recreational endurance athletes with and without paroxysmal atrial fibrillation. *J Am Soc Echocardiogr* 2022;35:1259–68.
- 9 Heidbuchel H. The athlete's heart is a proarrhythmic heart, and what that means for clinical decision making. *Europace* 2018;20:1401–11.
- 10 La Gerche A, Wasfy MM, Brosnan MJ, *et al.* The athlete's heart—challenges and controversies: JACC focus seminar 4/4. *J Am Coll Cardiol* 2022;80:1346–62.
- 11 La Gerche A, Claessen G, Van de Bruaene A, *et al.* Cardiac MRI: a new gold standard for ventricular volume quantification during high-intensity exercise. *Circ Cardiovasc Imaging* 2013;6:329–38.
- 12 Prior DL, La Gerche A. The athlete's heart. *Heart* 2012;98:947–55.
- 13 Olsen FJ, Møgelvang R, Jensen GB, *et al.* Relationship between left atrial functional measures and incident atrial fibrillation in the general population: the copenhagen city heart study. *JACC Cardiovasc Imaging* 2019;12:981–9.
- 14 Heidbüchel H, Panhuyzen-Goedkoop N, Corrado D, *et al.* Recommendations for participation in leisure-time physical activity and competitive sports in patients with arrhythmias and potentially arrhythmogenic conditions Part I: supraventricular arrhythmias and pacemakers. *Eur J Cardiovasc Prev Rehabil* 2006;13:475–84.
- 15 Guasch E, Benito B, Qi X, *et al.* Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model. *J Am Coll Cardiol* 2013;62:68–77.
- 16 Pedlar CR, Brown MG, Shave RE, *et al.* Cardiovascular response to prescribed detraining among recreational athletes. *J Appl Physiol (1985)* 2018;124:813–20.
- 17 Petek BJ, Groezinger EY, Pedlar CR, *et al.* Cardiac effects of detraining in athletes: a narrative review. *Ann Phys Rehabil Med* 2022;65:101581.
- 18 D'Ascenzi F, Pelliccia A, Natali BM, *et al.* Training-Induced dynamic changes in left atrial reservoir, conduit, and active volumes in professional soccer players. *Eur J Appl Physiol* 2015;115:1715–23.
- 19 Heidbuchel H, Adami PE, Antz M, *et al.* Recommendations for participation in leisure-time physical activity and competitive sports in patients with arrhythmias and potentially arrhythmogenic conditions: Part 1: supraventricular arrhythmias. A position statement of the section of sports cardiology and exercise from the European association of preventive cardiology (EAPC) and the European heart rhythm association (ehra), both associations of the European Society of cardiology. *Eur J Prev Cardiol* 2021;28:1539–51.
- 20 Pelliccia A, Sharma S, Gati S, *et al.* 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021;42:17–96.
- 21 Myrstad M, Aaronæs M, Graff-Iversen S, *et al.* Physical activity, symptoms, medication and subjective health among veteran endurance athletes with atrial fibrillation. *Clin Res Cardiol* 2016;105:154–61.
- 22 Chan A-W, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
- 23 Balady GJ, Chaitman B, Driscoll D, *et al.* Recommendations for cardiovascular screening, staffing, and emergency policies at health/fitness facilities. *Circulation* 1998;97:2283–93.
- 24 Borjesson M, Urhausen A, Kouidi E, *et al.* Cardiovascular evaluation of middle-aged/ senior individuals engaged in leisure-time sport activities: position stand from the sections of exercise physiology and sports cardiology of the european association of cardiovascular prevention and rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2011;18:446–58.
- 25 Vanhees L, De Sutter J, Gelada S, *et al.* Importance of characteristics and modalities of physical activity and exercise in defining the benefits to cardiovascular health within the general population: recommendations from the EACPR (part I). *Eur J Prev Cardiol* 2012;19:670–86.
- 26 Spertus J, Dorian P, Bubien R, *et al.* Development and validation of the atrial fibrillation effect on quality-of-life (AFEQT) questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;4:15–25.
- 27 Wynn GJ, Todd DM, Webber M, *et al.* The European heart rhythm association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace* 2014;16:965–72.
- 28 Lang RM, Badano LP, Mor-Avi V, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233–70.
- 29 Nagueh SF, Smiseth OA, Appleton CP, *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the american society of echocardiography and the european association of cardiovascular imaging. *J Am Soc Echocardiogr* 2016;29:277–314.
- 30 Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 1970;2:92–8.
- 31 Solberg EE, Borjesson M, Sharma S, *et al.* Sudden cardiac arrest in sports—need for uniform registration: a position paper from the sport cardiology section of the European association for cardiovascular prevention and rehabilitation. *Eur J Prev Cardiol* 2016;23:657–67.
- 32 Myrstad M, Sørensen E, Janssens K, *et al.* Exercise-induced cardiac remodeling and atrial fibrillation in female endurance athletes. *J Am Soc Echocardiogr* 2023;36:344–5.



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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

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
-----------------	-----	---

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	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

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*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)

Item Nr.	Description
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 Norway: 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 Gjøttum, Norway E-mail address: Marius.Myrstad@vestreviken.no Phone number: +47-92255945 Belgium: Guido Claessen, MD, PhD Address: Department of Cardiovascular Diseases, UZ Leuven, Herestraat 49, B-3000 Leuven, Belgium E-mail address: guido.claessen@uzleuven.be Phone number: +32 16 34 20 09 Australia: André La Gerche, MD, PhD

	<p>Address: Baker Heart and Diabetes Institute, 75 Commercial Road, Melbourne VIC 3004, Australia E-mail address: Andre.LaGerche@baker.edu.au Phone number: +61 481 300 929</p>
8.	<p>Contact for Scientific Queries</p> <p>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 Gjøttum, Norway E-mail address: Marius.Myrstad@vestreviken.no Phone number: +47-92255945</p>
9.	<p>Public Title</p> <p>Effects of Detraining in Endurance Athletes with Atrial Fibrillation (The NEXAF Detraining study). An international multicentre randomized controlled trial</p>
10.	<p>Scientific Title</p> <p>Effects of Detraining in Endurance Athletes with Atrial Fibrillation (The NEXAF Detraining study). An international multicentre randomized controlled trial</p>
11.	<p>Countries of Recruitment</p> <p>Australia, Belgium, Norway</p>
12.	<p>Health conditions studied</p> <p>Atrial fibrillation</p>
13.	<p>Intervention (s)</p> <p>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.</p> <p>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.</p>
14.	<p>Key Inclusion and Exclusion Criteria</p> <p>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</p>

	<p>At least two anamnestic (self-reported) episodes of atrial fibrillation, of which one during the last six months</p> <p>Use a smartphone and agree to connect their sportswatch with a web-based platform for monitoring of exercise</p> <p>Exclusion Criteria:</p> <p>Permanent atrial fibrillation</p> <p>Cardiac conditions (including valvular heart disease of moderate or greater severity, symptomatic ischemic heart disease)</p> <p>Left ventricular ejection fraction <45%</p> <p>Hypertension (>140/90)</p> <p>Diabetes mellitus</p> <p>Hyperthyroidism</p> <p>Smoking during the last 5 years</p> <p>Alcohol intake >20 alcohol units/week</p> <p>Use of illegal or performance enhancing drugs</p> <p>Body mass index >30kg/m²</p> <p>Injuries preventing physical exercise</p> <p>Pregnancy</p> <p>Participation in conflicting intervention research studies</p> <p>Planned atrial fibrillation ablation within the next six months</p> <p>The individual refuses to have an insertable cardiac monitor, blood samples taken or be part of the detraining group</p>
15.	<p>Study type</p> <p>Randomized controlled trial</p>
16.	<p>Date of First Enrollment</p> <p>5 Januar 2022</p>
17.	<p>Sample size</p> <p>120</p>
18.	<p>Recruitment status</p> <p>Recruiting: participants are currently being recruited and enrolled</p>
19.	<p>19. Primary Outcome(s)</p> <p>Outcome Name: Atrial fibrillation burden</p> <p>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.</p> <p>Timepoint: Measured during the last 4 weeks (week 13-16) of the 16-week intervention period</p>
20.	<p>20. Key Secondary Outcomes</p> <p>Outcome Name: Atrial fibrillation burden</p>

<p>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 first 4 weeks (week 1-4) of the 16-week intervention period</p> <p>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 week 5-8 of the 16-week intervention period</p> <p>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 week 9-12 of the 16-week intervention period</p> <p>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 week 13-16 of the 16-week intervention period</p> <p>Outcome Name: Cumulative 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 entire 16-week intervention period</p> <p>Outcome Name: Atrial fibrillation episode duration Metric/method of measurement: Mean duration of atrial fibrillation episodes lasting ≥ 30sec Timepoint: Measured during the 16-week intervention period</p> <p>Outcome Name: Atrial fibrillation episodes Metric/method of measurement: Number of atrial fibrillation episodes lasting ≥ 30sec, as measured by insertable cardiac monitor Timepoint: Measured during the first 4 weeks (week 1-4) of the 16-week intervention period</p> <p>Outcome Name: Atrial fibrillation episodes</p>

<p>Metric/method of measurement: Number of atrial fibrillation episodes lasting ≥ 30sec, as measured by insertable cardiac monitor Timepoint: Measured during week 5-8 of the 16-week intervention period</p> <p>Outcome Name: Atrial fibrillation episodes Metric/method of measurement: Number of atrial fibrillation episodes lasting ≥ 30sec, as measured by insertable cardiac monitor Timepoint: Measured during week 9-12 of the 16-week intervention period</p> <p>Outcome Name: Atrial fibrillation episodes Metric/method of measurement: Number of atrial fibrillation episodes lasting ≥ 30sec, as measured by insertable cardiac monitor Timepoint: Measured during week 13-16 of the 16-week intervention period</p> <p>Outcome Name: Cumulative atrial fibrillation episodes Metric/method of measurement: Number of atrial fibrillation episodes lasting ≥ 30sec, as measured by insertable cardiac monitor Timepoint: Measured during the 16-week intervention period</p> <p>Outcome Name: Days with atrial fibrillation Metric/method of measurement: Days with at least one episode of atrial fibrillation lasting ≥ 30sec Timepoint: Measured during the 16-week intervention period</p> <p>Outcome Name: Days without atrial fibrillation Metric/method of measurement: Days without at least one episode of atrial fibrillation lasting ≥ 30sec Timepoint: Measured during the 16-week intervention period</p> <p>Outcome Name: Relative change in atrial fibrillation burden Metric/method of measurement: 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 ≥ 30sec divided by total duration of monitoring Timepoint: Measured during the 4-week baseline period prior to randomization and during the last 4 weeks of the 16-week intervention period</p> <p>Outcome Name: Relative change in atrial fibrillation burden Metric/method of measurement: 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 ≥ 30sec divided by total duration of monitoring Timepoint: Measured during the 4-week baseline period prior to randomization and during the first 4 weeks of the 16-week intervention period</p> <p>Outcome Name: Relative change in atrial fibrillation burden</p>
--

<p>Metric/method of measurement: 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 ≥ 30sec divided by total duration of monitoring Timepoint: Measured during the 4-week baseline period prior to randomization and during the entire 16-week intervention period</p> <p>Outcome Name: Adherence to prescribed exercise Metric/method of measurement: Adherence to prescribed exercise ($>80\%$ of exercise with $\geq 85\%$ and $\leq 75\%$ of maximum heart rate, respectively) registered with sports watches Timepoint: 16 weeks</p> <p>Outcome Name: Exercise capacity Metric/method of measurement: Peak oxygen uptake (VO_{2peak}) measured during cardiopulmonary exercise testing Timepoint: Measured at the baseline study visit and at the final study visit after the 16-week intervention period</p> <p>Outcome Name: Atrial volumes Metric/method of measurement: Right and left atrial volumes measured with echocardiography Timepoint: Measured at the baseline study visit and at the final study visit after the 16-week intervention period</p> <p>Outcome Name: Ventricular volumes Metric/method of measurement: Right and left ventricular volumes measured with echocardiography Timepoint: Measured at the baseline study visit and at the final study visit after the 16-week intervention period</p> <p>Outcome Name: Atrial function Metric/method of measurement: Right and left atrial function measured with strain during echocardiography Timepoint: Measured at the baseline study visit and at the final study visit after the 16-week intervention period</p> <p>Outcome Name: Ventricular function Metric/method of measurement: Right and left ventricular function measured with strain during echocardiography Timepoint: Measured at the baseline study visit and at the final study visit after the 16-week intervention period</p> <p>Outcome Name: Ventricular systolic function Metric/method of measurement: Right and left ventricular ejection fraction measured with strain during echocardiography Timepoint: Measured at the baseline study visit and at the final study visit after the 16-week intervention period</p>

<p>Outcome Name: Atrial fibrillation symptoms Metric/method of measurement: Self-reported number of symptomatic atrial fibrillation episodes by questionnaire Timepoint: Measured at the baseline study visit and at the final study visit after the 16-week intervention period</p> <p>Outcome Name: Atrial Fibrillation Effect on QualiTy-of-life Metric/method of measurement: 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 Timepoint: Measured at the baseline study visit and at the final study visit after the 16-week intervention period</p> <p>Outcome Name: Atrial fibrillation hospitalizations Metric/method of measurement: Number of unplanned hospitalizations due to atrial fibrillation cardioversion or ablation Timepoint: Throughout study completion, an average of 22 weeks</p> <p>Outcome Name: Modified European Heart Rhythm Association Symptom Scale (mEHRA) symptom classification Metric/method of measurement: 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 Timepoint: Measured at the baseline study visit and at the final study visit after the 16-week intervention period</p> <p>Outcome Name: Number of ventricular arrhythmias Metric/method of measurement: Ventricular arrhythmias lasting ≥ 12 ventricular complexes as measured by continuous monitoring with insertable cardiac monitor Timepoint: Throughout study completion, an average of 22 weeks</p> <p>Outcome Name: Number of adverse events Metric/method of measurement: 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 Timepoint: Throughout study completion, an average of 22 weeks</p> <p>Outcome Name: Cardiovascular risk factors measured by blood pressure Metric/method of measurement: Measure of blood pressure (mmHg) Timepoint: Measured at baseline and after the 16-week intervention period</p> <p>Outcome Name: Cardiovascular risk factors measured by blood lipids Metric/method of measurement: Blood lipids (mmol/L) Timepoint: Measured at baseline and after the 16-week intervention period</p>

	<p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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 after peak exercise testing</p> <p>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</p>
21.	<p>Ethics Review</p> <p>Approved 29 April 2021 by The Regional Committee for Health Research Ethics, Oslo, Norway (REK sør-øst A/212748)</p> <p>Approved 1 September 2020 by The Alfred Hospital Ethics Committee, Melbourne, Australia (HREC/76210/Alfred-2021)</p> <p>Approved 13 October 2022 by The Ethics Committee Research KU/UZ Leuven, Leuven, Belgium (S65930)</p>

22.	Completion date N/A
23.	Summary Results N/A
24.	IPD sharing statement Data sharing between the participating institutions is regulated by Study agreements between The Sponsor and each participating center.

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 Morseth^{1,2}, Marius Myrstad^{3,4}, Bjarne Martens Nes⁵, Jan Pål Loennechen^{5,6}, Maja-Lisa Løchen⁷, Arnljot Tveit^{4,8}, Turid Apelland⁴, Kristine Folkenborg⁴, Kristoffer Robin Johansen^{1,2}, Kristin Espolin Johnson⁵, Jon Magne Letnes^{5,6}, Vegard Malmo^{5,6}, Andreas Berg Sellevold^{5,6}, Eivind Sørensen^{3,4}, Rune Byrkjeland^{3,4}, Steve Enger⁴, Hilde Larhammer^{3,4}, Sophia Onarheim⁴, Vigdis Bache-Semb⁴.

Affiliations

¹ School of Sport Sciences, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

² Centre for Research and Education, University Hospital of North Norway, Tromsø, Norway

³ Department of Internal Medicine, Bærum Hospital, Vestre Viken Hospital Trust, N-1346 Gjøttum, Norway

⁴ Department of Medical Research, Bærum Hospital, Vestre Viken Hospital Trust, N-1346 Gjøttum, Norway

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

