PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Exercise Training in the Treatment of Paroxysmal Atrial Fibrillation: Study Protocol of the Cologne ExAfib Trial
AUTHORS	Zacher, Jonas; Dillschnitter, Katrin; Freitag, Nils; Kreutz, Thorsten; Bjarnason, Birna; Bloch, Wilhelm; Predel, Hans-Georg; Schumann, Moritz

VERSION 1 – REVIEW

REVIEWER	Bente Morseth UiT The Arctic University of Norway
REVIEW RETURNED	30-May-2020

GENERAL COMMENTS	This protocol addresses a randomised and controlled exercise intervention study in the treatment of paroxysmal AF. The manuscript is structured, well written, and addresses all important elements of an RCT protocol in a clear and detailed approach. Updated and relevant references are cited. There is clearly a lack of intervention studies on exercise in the treatment of AF, and the need for this study, as well as the novelty, is evident. The discussion is clear and balanced, addressing relevant topics. I only have som minor comments and suggestions for the authors. It would be helpful if the authors could indicate when this study will/did take place. Sometimes the authors use "will be performed" and other places "was performed" is used. Page 4, line 2: Perhaps a reference could be attached to the 2% prevalence statement. Page 7, line 20: "be used do design phase II..:" - typing error. Page 8: Sample size calculations should preferably be calculated for all outcomes, although I appreciate that the expected clinically meaningful differences may be difficult to know. Page 9, line 18-19: How will one-lead ECG be measured and when? Page 10, line 17-25 Measurements: The time of each measurement could have been better specified, for example in the figure. What is measured at T0, T1, T2? Page 12, line 3: Some more information on the Holter ECG would be helpful: When is Holter applied (before or after the tests at T0?) Also at T2 but not T1? I assume the Holter is 12-lead?

	Figure: Perhaps the figure also could indicate which measures will be done at T0, T1, T2

REVIEWER	Professor Gorm B. Jensen MD, DMSc Copenhagen City Heart Study Frederiksberg Hospital Nordre Fasanvej 57 2000 Frederiksberg C Denmark
REVIEW RETURNED	10-Jun-2020

GENERAL COMMENTS	The background for the study is clinically relevant. The main problem is the patient selection. Patients with a diagnosis of Paroxysmal atrial fibrillation (PAF) may have a short bouts of self-limiting AF every other year, or may have multiple attacks leading to frequent hospitalisation. Patient recruitment should be limited to subjects with a clear and well-defined morbidity profile. The main problems in these patients are the number, duration and severity of attacks. The outcome assessment should take this into account and should focus on these clinical problems. Can training reduce the number and severity of attacks? Assessment wit 24-hour Holter is useless in the majority of such patients. They shoud have continuous monitoring by R-test or implanted reveal. Other outcomes such as QAL and exercise capacity are relevant but of lesser importance.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

1.This protocol addresses a randomised and controlled exercise intervention study in the treatment of paroxysmal AF. The manuscript is structured, well written, and addresses all important elements of an RCT protocol in a clear and detailed approach. Updated and relevant references are cited. There is clearly a lack of intervention studies on exercise in the treatment of AF, and the need for this study, as well as the novelty, is evident. The discussion is clear and balanced, addressing relevant topics. I only have som minor comments and suggestions for the authors.

Thank you for the thorough review of our manuscript. We are happy to hear that you share our view on the urgent need of interventional studies for patients with AF. Please find below our point-by-point responses to your comments.

It would be helpful if the authors could indicate when this study will/did take place. Sometimes the authors use "will be performed" and other places "was performed" is used.

Thank you for this important comment. We have added this information and revised the corresponding parts of the paper.

Page 4, line 2: Perhaps a reference could be attached to the 2% prevalence statement.

A reference has been added.

Page 7, line 20: "be used do design phase II..:" - typing error.

This has been modified.

Page 8: Sample size calculations should preferably be calculated for all outcomes, although I appreciate that the expected clinically meaningful differences may be difficult to know.

We agree with your comment that a sample size calculation for all outcomes may be desirable. However, as you also noticed the expected effects are unknown at this stage. This is why we decided to include a pilot phase, based on which we will be able to refine sample sizes for clinical endpoints during the latter part of the study.

Page 9, line 18-19: How will one-lead ECG be measured and when?

Thank you for this comment. We have clarified this in the text.

Page 10, line 17-25 Measurements: The time of each measurement could have been better specified, for example in the figure. What is measured at T0, T1, T2?

This is an important point. We have now added another Table which better describes the time points and corresponding measures.

Page 12, line 3: Some more information on the Holter ECG would be helpful: When is Holter applied (before or after the tests at T0?) Also at T2 but not T1? I assume the Holter is 12-lead?

Thank you, we have added more information on the Holter ECG in the text.

Figure: Perhaps the figure also could indicate which measures will be done at T0, T1, T2

Thank you, we have added this information to Table 2.

Reviewer #2

The background for the study is clinically relevant. The main problem is the patient selection. Patients with a diagnosis of Paroxysmal atrial fibrillation (PAF) may have a short bouts of self-limiting AF every other year, or may have multiple attacks leading to frequent hospitalisation. Patient recruitment should be limited to subjects with a clear and well-defined morbidity profile.
The main problems in these patients are the number, duration and severity of attacks.
The outcome assessment should take this into account and should focus on these clinical problems.
Can training reduce the number and severity of attacks? Assessment wit 24-hour Holter is useless in the majority of such patients. They shoud have continuous monitoring by R-test or implanted reveal.
Other outcomes such as QAL and exercise capacity are relevant but of lesser importance.

We fully agree with the reviewers comment: Patients with paroxysmal AF are a heterogenous group with largely varying frequency, length and intensity of AF-episodes. We also agree that trials are needed to assess the effects of different training interventions on the clinical characteristics of the disease.
However, based on the available literature and the associated paucity of high quality data regarding safety and feasibility of different training interventions, we have decided to commence our study with a pilot phase addressing this issue. Furthermore, we aim to gain insights into mechanistic processes of PAF, i.e. by atrial strain analysis. We believe that these findings are beneficial, even if they do not primarily target the clinical outcome. We view this a solid base to conduct follow-up trials to address the clinically relevant end-point of AF-burden.

As such, the objective measure of the AF burden is considered a secondary outcome of the present study. Consequently, we have decided to include only symptomatic patients with NYHA II or higher during AF-Episodes, to at least be able to document potential subjective changes in AF-burden and -intensity, and to be able to document AF-episodes when the patient presents due to symptoms. We have now reacted to your comment by specifying further to include only patients with subjective AF-Episodes at least every 4 weeks. Further, we are already preparing follow-up trials focusing on the clinically relevant outcome by a) initiating a cooperation with other centers to recruit AF-patients eligible for loop-recorder implantation and b) seeking cooperation with companies designing wearables that allow for continuous rhythm monitoring.

VERSION 2 – REVIEW

REVIEWER	Bente Morseth UiT The Arctic University of Norway, Norway
REVIEW RETURNED	22-Jul-2020

GENERAL COMMENTS	The authors have addressed all my concerns and the manuscript now appears ready for publication.