## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | CATHETER ABLATION VS. ANTIARRHYTHMIC DRUGS WITH RISK FACTOR MODIFICATION FOR TREATMENT OF ATRIAL FIBRILLATION: A PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL (PRAGUE-25 TRIAL) |
| **AUTHORS** | Osmancik, Pavel; Havránek, Štěpán; Bulková, Veronika; Chovančík, Jan; Roubíček, Tomáš; Heřman, Dalibor; Čarná, Zuzana; Tuka, Vladimír; Matoulek, Martin; Fiala, Martin; Jiravský, Otakar; Stregl-Hruskova, Sylvie; Latiňák, Adam; Kotryová, Jiřina; Jarkovský, Jiří |

## VERSION 1 – REVIEW

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| **REVIEWER** | Uğur Canpolat<br>Türkiye Yüksek İhtisas Training and Research Hospital, Cardiology Clinic |
| **REVIEW RETURNED** | 21-Oct-2021 |

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| **GENERAL COMMENTS** | In this prospective study, the authors will assess the importance of risk factor modification in addition to AAD compared to catheter ablation in AF patients. The design of the study is well organized in general. The importance of risk factor modification will be emphasized after the data would be available. However, the importance of weight loss and alcohol discontinuation in addition to other risk factors control have had a positive impact on disease process in AF. According to very recent guidelines, ABC pathway was suggested for all AF patients in which C denotes to risk factor or comorbid condition control. Thus, it is not ethical not to suggest or intervene for risk factor modification in catheter ablation group compared to risk factor modification control group. |

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| **REVIEWER** | Peter Loewen<br>University of British Columbia Faculty of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences |
| **REVIEW RETURNED** | 12-Jan-2022 |

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| **GENERAL COMMENTS** | This is a protocol of a noninferioirty trial of catheter ablation vs. antiarrhythmic drugs+risk factor modification in objese patient with symptomatic atrial fibrillation. If accepted for publication, it requires moderate copyediting throughout.<br><br>Since the project is funded by the Czech Ministry of Health, it has presumably undgerone some amount peer review, and has been subjected to ethical review at multiple sites. Hence, coupled with the fact that i do not have access to the full funding proposal, my review cannot be construed as a rigorous peer review of the project. My questions and comments for the purpose of publishing this as a coherent manuscript are, nonetheless, below: |

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| | Background<br><br>“Catheter ablation and its limitation” - this heading requires revision as little about limitations of CA are discussed<br><br>“In two well-conceived recent trials comparing CA…” This sentence should disclose the NSR rates in the control (AAD) arms<br><br>Methods<br><br>“Study design and objective” - the first sentence states an objective, but no primary outcome variable. “Efficacy” is not a POV. The paragraph proceeds to disclose secondary outcome variables.<br><br>“Patient and Public Involvement” - what is discussed here is completely anecdotal. Is the trial inception driven by any actual data about AF+obesity rates in the Czech target population?<br><br>“Patient population” - recruitment from where? Much more about the study population is needed. Is this multicenter? In what locations? AF clinic patients? General practice patients? Hospitalized patients?<br><br>What are the recruitment procedures? How will screening and approach work?<br><br>“Symptomatic AF” - documented how? ECG confirmation? By whom? How recently? Are patients with AF of any duration eligible?<br><br>participation in the dietary interventions: are there any exclusions for this? (e.g. can patients with celiac disease participate?)<br><br>Is prior trial/failure of AAD tx an exclusion criterion?<br><br>Randomization: the paragraph implies the trial is multicenter. What actual randomization procedures will be involved? Blocks? site-based? How exactly with the “software account for” the 3 baseline characteristics mentioned? This is meant to be a publication of a study protocol, but much less information about the actual protocol is disclosed in the manuscript than is required. “Randomization will be done outside all partciipating centers” - where will it be done? By whom? How? Phone system? A project specific clinical trial management software system?<br><br>“Risk factor modification and AADs arm” - this section devotes only two lines to the main intervention, which is AADs. When exactly will AAD be started? (See above…. Are these all AAD-naiive patients?) What AADs? How will the be selected? How will they be titrated? Is there an AAD selection and titration protocol? Will this be left to the individual clinicians or standardized?<br><br>Why does this (and subsequent) section refer only to an “RFM arm”? Isnt it the “AAD+RFM arm”?<br><br>Is blinding involved at any stage? Will outcome adjudicators be blinded? If not, why not? Lack of outcome-assessor blinding introduces serious biases given the outcomes involved here.<br><br>Justify the primary analysis being ITT. NI trial best-practices suggest that the per-protocol analysis be primary. Using the ITT analysis as |

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| | primary in a NI trial greatly inflates the probability of rejecting the null hypothesis (i.e. that there IS a different between the interventions) and mistakenly concluding non-inferiority (i.e. a type1 error). There are many guidelines about this, and the authors should justify their approach and reference the guidance they are following.<br><br>Justify using a one-sided alpha for the sample size calculation. In NI trials it is assumed the experimental intervention could be better or worse than control, hence a 2-sided test is more appropriate.<br><br>Are patients who have symptomatic AF recurrence eligible to receive CA or AAD, as appropriate? Are their outcomes censored when they cross over? Are all participants followed for 12mos regardless of having a primary outcome event? |

**VERSION 1 – AUTHOR RESPONSE**

*Reviewer: 1*

*Dr. Uğur Canpolat, Türkiye Yüksek İhtisas Training and Research Hospital*

*Comments to the Author:*

*In this prospective study, the authors will assess the importance of risk factor modification in addition to AAD compared to catheter ablation in AF patients. The design of the study is well organized in general. The importance of risk factor modification will be emphasized after the data would be available. However, the importance of weight loss and alcohol discontinuation in addition to other risk factors control have had a positive impact on disease process in AF. According to very recent guidelines, ABC pathway was suggested for all AF patients in which C denotes to risk factor or comorbid condition control. Thus, it is not ethical not to suggest or intervene for risk factor modification in catheter ablation group compared to risk factor modification control group.*

Response: Thank you for the comment. Indeed, obesity and other metabolic risk factors play an important role in AF; as such, the ABC pathway (with C = risk factor control) is recommended in the treatment of AF patients. This relates to the central question of our study, whether “weak” non-interventional techniques (i.e., RFM and AADs) produce similar effects as interventional techniques and whether patients with AF can avoid CA with aggressive weight loss and AADs only.

Our study will not specifically inform and instruct patients in the CA arm about the importance of obesity and risk factor modification in AF. However, during enrollment, all patients will be fully informed about the impact of obesity, alcohol consumption, hypertension, etc., on AF treatment. All patients will be instructed and encouraged to lose weight, decrease alcohol consumption, and increase physical activity.

Patients randomized to the RFM+AAD arm will be enrolled in a specially dedicated team and program including spiroergometry physical activity under the supervision of a physical trainer with exercise

intensity regulated using fitness band monitors and a special mobile-phone OBESIF application. Such intensive AF teams and programs are not available for AF patients, and ESC guidelines do not describe how risk factors should be modified. Moreover, looking at the newest protocols for AF catheter ablation (e.g., high-power short duration or pulsed-field ablation), the importance of risk factor modification is wholly ignored.

We believe that patients with BMIs greater than 40 have to undergo a special program for weight reduction and modification of other risk factors (including surgery in some cases). Therefore, patients with a BMI > 40 are excluded from our study and are enrolled in other programs for AF treatment.

In the revision, we added to the Methods section that all patients would be fully informed about the danger of obesity and other risk factors and the importance of positive lifestyle interventions. All patients will be strongly encouraged to lose weight, reduce alcohol consumption, increase physical activity, etc. (Methods, paragraph Patient population; Treatment, catheter ablation arm).

*Reviewer: 2*

*Dr. Peter Loewen, University of British Columbia Faculty of Pharmaceutical Sciences*
*Comments to the Author:*

*This is a protocol of a noninferioirty trial of catheter ablation vs. antiarrhythmic drugs+risk factor modification in objese patient with symptomatic atrial fibrillation. If accepted for publication, it requires moderate copyediting throughout.*

*Since the project is funded by the Czech Ministry of Health, it has presumably undgerone some amount peer review, and has been subjected to ethical review at multiple sites. Hence, coupled with the fact that i do not have access to the full funding proposal, my review cannot be construed as a rigorous peer review of the project. My questions and comments for the purpose of publishing this as a coherent manuscript are, nonetheless, below:*

*Background*

*"Catheter ablation and its limitation" - this heading requires revision as little about limitations of CA are discussed*

Response: The title was changed to “The efficacy of catheter ablation in previous clinical studies.”

*"In two well-conceived recent trials comparing CA…" This sentence should disclose the NSR rates in the control (AAD) arms*

Response: Thank you for the comments. We added information on efficacy in the AAD arms in the revised text.

*Methods*

*"Study design and objective" - the first sentence states an objective, but no primary outcome variable. "Efficacy" is not a POV. The paragraph proceeds to disclose secondary outcome variables.*

Response: We changed the sentence; instead of efficacy, the endpoint “Sinus rhythm maintenance” is now used. The endpoint definitions are described in detail in the paragraph “Study outcomes.”

*"Patient and Public Involvement" - what is discussed here is completely anecdotal. Is the trial inception driven by any actual data about AF+obesity rates in the Czech target population?*

Response: The expected number and rates of AF patients with BMIs > 30 is based on (1) the population of patients included in the largest and most recent RCT (CABANA, EAST), (2) in the Czech registry of patients undergoing catheter ablation, and (3) in the registry of patients who underwent CA in the last five years at our Cardiac center. The median BMI in all three patient sets was 30.

We understand the reviewer's arguments, and we changed the paragraph accordingly. The essential question to be answered by our study is whether non-invasive techniques (RFM+AAD) could produce similar effects as invasive strategies.

*"Patient population" - recruitment from where? Much more about the study population is needed. Is this multicenter? In what locations? AF clinic patients? General practice patients? Hospitalized patients?*

Response: We extended this paragraph and added additional information. The study is multicentric; this information was mentioned in the "Methods and analysis” and the "Study design and objective "paragraph. The number of participating centers and locations was added: the study will involve five centers in the Czech Republic, and outpatients will be enrolled from these centers.

*What are the recruitment procedures? How will screening and approach work?*

Response: The information was added in the "Patient population" paragraph.

*"Symptomatic AF" - documented how? ECG confirmation? By whom? How recently? Are patients with AF of any duration eligible?*

Response: Thank you for the information; we added more information about AF documentation. AF has to be documented using a standard 12-lead ECG or Holter recording. AF patients with AF of any duration are eligible – as it is noted in the inclusion criteria, patients with long-standing persistent AF can be included. However, treatment efficacy in such patients will be thoroughly discussed during

enrollment (similar to when such patients are enrolled to CA), and only symptomatic patients will be enrolled.

*Participation in the dietary interventions: are there any exclusions for this? (e.g. can patients with celiac disease participate?)*

Response: Participation in special dietary interventions (vegetarians, diets for Crohn's disease, etc.) is not an exclusion criterion; we have a very experienced dietary team that will be able to design special diets for our unique patient cohorts. Only insulin-dependent patients will be excluded, as mentioned in the Inclusion/Exclusion paragraph.

*Is prior trial/failure of AAD tx an exclusion criterion?*

Response: No, it is not; both AAD-naïve, as well as patients with a history of AAD treatment can enroll. We added this information to the document's revised version (“Patient population” paragraph).

*Randomization: the paragraph implies the trial is multicenter. What actual randomization procedures will be involved? Blocks? site-based? How exactly with the "software account for" the 3 baseline characteristics mentioned? This is meant to be a publication of a study protocol, but much less information about the actual protocol is disclosed in the manuscript than is required. "Randomization will be done outside all partciipating centers" - where will it be done? By whom? How? Phone system? A project specific clinical trial management software system?*

Response: Thank you for the comment. We added more information on the randomization process to the revised document.

*"Risk factor modification and AADs arm" - this section devotes only two lines to the main intervention, which is AADs. When exactly will AAD be started? (See above…. Are these all AAD-naiive patients?) What AADs? How will the be selected? How will they be titrated? Is there an AAD selection and titration protocol? Will this be left to the individual clinicians or standardized?*

Response: Thank you for the comment; we added more information on AADs. AAD-naive patients, as well as patients with a history of AAD treatment, can be enrolled; this is noted in the "Patient population" paragraph. The exact AADs that are currently allowed are explicitly named in the revised manuscript; AAD selection will be left to the treating physician, as will the AAD titration process. The titration must be done during the blanking period.

*Why does this (and subsequent) section refer only to an "RFM arm"? Isnt it the "AAD+RFM arm"?*

Response: We agree; we changed the name of the RFM arm; it is now called the RFM+AAD arm.

*Is blinding involved at any stage? Will outcome adjudicators be blinded? If not, why not? Lack of outcome-assessor blinding introduces serious biases given the outcomes involved here.*

Response: Blinding is not required for patients and study physicians. However, we understand the importance of blinding during RCT; it is impossible to conduct a study such as ours fully blinded. However, the ECG outcome assessments will be blinded, and the evaluation of the Holter recordings will be done by an organization outside the clinical study; the CEC will also be blinded relative to the randomization of particular patients. We added this information to the "Randomization" paragraph, which is now titled "Randomization and blinding."

*Justify the primary analysis being ITT. NI trial best-practices suggest that the per-protocol analysis be primary. Using the ITT analysis as primary in a NI trial greatly inflates the probability of rejecting the null hypothesis (i.e. that there IS a different between the interventions) and mistakenly concluding non-inferiority (i.e. a type1 error). There are many guidelines about this, and the authors should justify their approach and reference the guidance they are following.*

Response: We agree entirely. In the original manuscript, we noted falsely that the primary analysis would be undertaken using the intention-to-treat and the per-protocol population; however, this was not possible because it used two different analyses for one primary endpoint calculation. We changed and corrected it in the revised manuscript; the primary analysis will be done in the per-protocol population and secondarily using the ITT principle. The paragraph was changed to reflect this.

*Justify using a one-sided alpha for the sample size calculation. In NI trials it is assumed the experimental intervention could be better or worse than control, hence a 2-sided test is more appropriate.*

Response: We understand and agree. Our initial plan was to test non-inferiority first and then superiority, assuming it failed the non-inferiority test. In the revised manuscript, we changed it to the 2-sided alpha.

*Are patients who have symptomatic AF recurrence eligible to receive CA or AAD, as appropriate? Are their outcomes censored when they cross over? Are all participants followed for 12mos regardless of having a primary outcome event?*

Response: Of course, as in any RCT, cross-over can happen and cannot be prohibited for ethical reasons (it would be difficult to prohibit cross-over in severely symptomatic patients). Cross-over can happen in both directions (from CA to RFM+AAD or vice versa). All investigators were encouraged to use cross-overs only in the event of treatment failure (i.e., AF/AT recurrences) as opposed to patient preference. In the event of a cross-over, the patient's outcomes will be censored, as done in other RCT studies. However, since the only primary outcome is arrhythmia recurrence, and cross-overs happen only in cases of arrhythmia recurrences, the cross-over would only affect secondary outcomes.

## VERSION 2 – REVIEW

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| **REVIEWER** | Uğur Canpolat<br>Türkiye Yüksek İhtisas Training and Research Hospital, Cardiology Clinic |
| **REVIEW RETURNED** | 05-Mar-2022 |

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| **GENERAL COMMENTS** | The authors replied all my previous comments in a reasonable fashion. I have no further comments. |

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| **REVIEWER** | Peter Loewen<br>University of British Columbia Faculty of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences |
| **REVIEW RETURNED** | 28-Mar-2022 |

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| **GENERAL COMMENTS** | This is a protocol of an open-label noninferioirty trial of catheter ablation vs. antiarrhythmic drugs+risk factor modification in objese patients with symptomatic atrial fibrillation. If accepted for publication, it requires light copyediting throughout.<br><br>I was a reviewer of a previous version and the responses to reviewes are to my original comments. I am satisfied with the modifications to the manuscript made on the basis of those. The manuscript has been significantly strengthened and meets the SPIRIT reporting requirements for protocols. Notably, this trial is already underway, reportedly with all the required ethical and adminstrative approvals.<br><br>Further suggestions:<br><br>"ETHICS AND DISSEMINATION”<br><br>•<br>it is not accurate to say that "there are no specific ethical considerations” because no new drugs or devices are involved. Importantly, the protocol outlines how patients randomized to one arm or the other will be able to receive appropriate “rescue” treatment if they require it. (e.g. ablation for patients in the AAD arm if their sumptoms become intolerable; AADs in the CA ablation arm for pateints with recurrent symptomatic AF). Suggest addressing these issues in this section.<br><br>•<br>the topic of “dissemination” is not mentioned in this section. |

## VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Dr. Uğur Canpolat, Türkiye Yüksek İhtisas Training and Research Hospital
Comments to the Author:
The authors replied all my previous comments in a reasonable fashion. I have no further comments.

We thank for the previous commnets.

Reviewer: 2
Dr. Peter Loewen, University of British Columbia Faculty of Pharmaceutical Sciences
Comments to the Author:
This is a protocol of an open-label noninferioirty trial of catheter ablation vs. antiarrhythmic drugs+risk factor modification in objese patients with symptomatic atrial fibrillation. If accepted for publication, it requires light copyediting throughout.

I was a reviewer of a previous version and the responses to reviewes are to my original comments. I am satisfied with the modifications to the manuscript made on the basis of those. The manuscript has been significantly strengthened and meets the SPIRIT reporting requirements for protocols. Notably, this trial is already underway, reportedly with all the required ethical and adminstrative approvals.

Further suggestions:

"ETHICS AND DISSEMINATION"

It is not accurate to say that "there are no specific ethical considerations" because no new drugs or devices are involved. Importantly, the protocol outlines how patients randomized to one arm or the other will be able to receive appropriate "rescue" treatment if they require it. (e.g. ablation for patients in the AAD arm if their sumptoms become intolerable; AADs in the CA ablation arm for pateints with recurrent symptomatic AF). Suggest addressing these issues in this section.

As we noted in the Study protocol (paragraph „Statistical analysis plan", page 17), a cross-over to the other treatment strategy is allowed if there is re-occurrence of atrial fibrillation Treatment failure). However, the cross-over wil be done on the voluntary basis, and will respect the current clinical recommendaton for AF treatment. Therefore, comparing our study with studies tested new drugs/devices, there are really no *significant* specific ethical consideration, patients will be treated according with the current recommendations. Based on the wish of the reviewer, we changed the text of this paragraph.

The topic of "dissemination" is not mentioned in this section.

Dissemination was added in this paragraph.