Author's response to reviews

Title: Comparison of the rhythm control treatment strategy versus the rate control strategy in patients with permanent or long-standing persistent atrial fibrillation and heart failure treated with cardiac resynchronization therapy - rationale and design of a pilot study of the randomized controlled Cardiac Resynchronization in Atrial Fibrillation Trial (Pilot-CRAfT).

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Author's response to reviews: see over
Dear Doctor Nascimento,

At first, I would like to thank you for the time you spent to prepare profound revision of the manuscript and all of the remarks.

Please, find below the comments to your revision.

1. Following Your suggestion about adverse effects of amiodarone, I have added a separate paragraph about this issue in the “Discussion” section.
2. We believe that BiVp% is a clinical outcome that would reflect the best the clinical efficacy of both treatment arms – the “rate control” arm as well. It is not obvious whether all the patients from this treatment arm will have an AV node ablation procedure offered. AVNA is an option due to discretion of consulting team. As a routine and following the guidelines, we offer it to the patients in whom an advanced pharmacological approach to slow the conduction is not sufficient.
   It seems that accuracy of BiVp% was proved sufficiently in the cited works of Gasparini et al. and Hayes et al and approved by the ESC guidelines. Moreover, it is a factor that may be monitored in “real-life” CRT patients on regular control visits.
   Taking into consideration all mentioned issues, we would leave the BiVp% as a primary end-point for the considered number of patients. Nevertheless, we are aware and we share your doubts about its indirect character as a clinical outcome measurement. That is why we propose several other, more-direct measurements as a secondary end-points such as 6MWT, CPX and ECHO examination. They would also serve as a control measurement of the efficacy of the primary outcome.
3. As far as we are concerned, the half of the population of PABA-CHF study had permanent or long-term persistent AF and the beneficial effect of the “rhythm control strategy” was more profound in this group [1] (Two separate paragraphs citing the PABA-CHF trial in the “Background” and “Discussion” sections have been added).
4. I have changed the chi2 for chi-square in the “Statistical methods” section.
5. The possibility of PVI procedure would surely make the “rhythm control group” less consistent. That is why we would consider this procedure to the patients which respond to EEC, not sooner than after the 2nd recurrence of AF. I have added this statement in the section concerning the methodology of the rhythm control strategy. One of our main goals while constructing this trial was to treat the population in a way that reflects the best “real-life” population so we reluctantly resigned from a PVI option, as a not “obvious and easy” approach.

I hope that enclosed comments clarify our point of view and our assumptions sufficiently.

Respectfully yours,

Jan Ciszewski

References:

Warsaw, 6 August 2014,

Dear Doctor Proietti,

In the name of all of co-authors I would like to thank you for the time dedicated to improve the paper and your warm welcome of our manuscript and all of the suggestions.

In response, please find below my comments upon the issues you emphasized.

1. Following your suggestions, I have added the missing studies concerning AFib CRT patients with the inclusion of three meta-analyses and the PABA-CHF study which was cited by you. They can be found in the “Background” and “Discussion” sections. My original idea was to concentrate on the RCT studies and so the meta-analyses which contain the observational studies were omitted.

2. The term “AF substrate ablation” was to mean pulmonary vein isolation. I have clarified that in the revised manuscript version, which I am uploading now.

3. Being aware of the influence of the time in SR on the BiVp% we want to measure a mean BiVp% through the whole follow-up period. That is what I meant by writing “an overall BiVp% during the one-year study period” in the “End points” section. I have further clarified it and I hope you will find it clear now.

   The change of the BiVp% from the baseline is measured by us as well. I have added it as the 1st point in the “Secondary end-points” table.

4. Following your suggestions I have written additional statements about the influence on both the HF and CRT on AF in the “Discussion section”. As the study is currently ongoing and its strength as a pilot study is limited, it would be difficult to add in an initially approved study additional measurements regarding the influence on biohumoral markers. The issue is surely worth evaluating while constructing the larger study.

5. I have read your study about the influence of HF on cognitive function with a lot of interest. It is worth examining without any doubt. We are aware of the limitations and subjective nature of the QoL assessment. That is why we treat this end-point as a control measurement of the efficacy of rhythm control strategy rather than a positive measurement of CRT function. I hypothesize that a need of additional hospitalizations and additional arrangements resulting from cardioversions may negatively influence QoL in some of the patients. Our choice of Minnessota Living with Heart Failure Questionnaire was driven by the fact that most CRT trials used this QoL assessment so our results would be easier to compare with other studies.

6. Inter-atrial septum pacing can be considered in some patients with CRT and IAD but we usually meet patients with already implanted atrial lead - usually in RA appendage due to site routine. Post-cardioversion ECG analysis to evaluate A-P delay and P-wave duration is obviously worth considering in rhythm control group.

I am looking forward to reading your opinion about the revised manuscript and enclosed corrections and explanations.

Respectfully yours,

Jan Ciszewski