Author's response to reviews

Title: Rationale, design and baseline results of the Treatment Optimisation in Primary care of Heart failure in the Utrecht region (TOPHU) study: a cluster randomised controlled trial

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Author's response to reviews: see over
Dr. Elaine Zhang
Editor BMC Family Practice

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Dear Mrs Zhang,

Thank you very considering our manuscript “Rationale, design and baseline results of the Treatment Optimisation in Primary care of Heart failure in the Utrecht region (TOPHU) study: a cluster randomised controlled trial” (MS: 1089637341161824) for publication. The comments of the reviewers helped us to improve the manuscript. We could answer all their questions, and please find below our detailed response to the comments. As requested, we removed the baseline results in our revised manuscript.

We hope you find our revised article suitable for publication in BMC Family Practice.

On behalf of all authors

Yours Sincerely,

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Response to referees “Rationale, design and baseline results of the Treatment Optimisation in Primary care of Heart failure in the Utrecht region (TOPHU) study: a cluster randomised controlled trial” (MS: 108963734116 1824)

Comments to reviewer 1

- The design of the present study is clear. However, several points need to be described more precisely, especially regarding the statistical point of view. For sample size estimation an intra-class correlation coefficient should be considered in order to avoid lack of statistical power. For statistical analyses, the use of random-effects models seems most appropriate because common statistical tests do not consider ‘correlated’ data.

  • *We did indeed not adequately mentioned how we controlled for intra-class correlation. We used an intra-cluster correlation coefficient of 0.05 in our power calculation.*¹ In the statistical analyses we will apply a multilevel approach to correct for the fact that we randomized at the level of the GP practice and not at the patient level. We changed the text in the revised text accordingly.

- Page 4: it is not clear what is the period of 1 year: the screening period?

  • *All follow-up data mentioned in the manuscript are calculated from the start of the study onwards, that is, the date on which GPs of the intervention group received their training in the management of heart failure.*

    In the revised manuscript we better clarify this point.

- Two hours of training seems short considering 2 years of follow-up. Some new ‘formations’ during the follow-up period may be considered.
• Indeed, a half-day training in the management of heart failure is short considering the complexity of the disease. Importantly, however, participating GPs in both groups could at any time consult the Dutch GP guidelines on heart failure. Moreover, the GPs in the intervention group received a flow chart that could help them with initiating and uptitrating drugs (Appendix). We agree with the reviewer that nevertheless repetition of the training of the intervention group could have been considered, although, such repetitive training is not often done in research. In the Discussion paragraph of the revised manuscript we will discuss this point.

- The criteria of the ESC guidelines for heart failure diagnosis may be presented in a dedicated table.
  • We agree this is helpful and added such a table in the revised manuscript.

- It is not clear if hr-QoL, drugs, CV outcomes will be evaluated at each time point or just at 6 months for drugs, 12 months for hr-QoL and 24 months for CV outcomes. All these outcomes, in my opinion, must be obtained at each time point.
  • We agree with the reviewer this seems optimal. But so many measurements is very time consuming and costly. Moreover, frequent practice visits and contacts with patients does affect especially the GPs and patients in the care as usual arm with the risk that such care drifts away from ‘real’ care as usual. We therefore chose to only measure these three outcomes once during follow up. In the revised article we clarify this point.
- Use of Ivabradine will not be evaluated? It is recommended in the ESC 2012 guidelines on heart failure.

- **Ivabradine is recommended in the ESC guidelines 2012 on heart failure in selected patients with level of evidence IIA, which means ‘should be considered’. It should be considered in patients with HFrEF and sinus rhythm who remain symptomatic after optimal treatment with ACE-inhibitors, beta-blockers, and MRAs. Moreover, the heart rate should be above 77 beats/minute. We suspect that not many patients will be eligible, and consultation of a cardiologist should be considered. Nevertheless, we will evaluate if patients will receive this drug during follow up. At baseline, none of the patients was prescribed Ivabradine.**

  *In the revised text we added a sentence about the use of Ivabradine in the section describing the training.*

- A detailed description of the up-titration chart is required.

- **We agree with the reviewer this would be informative and we are pleased to add such a leaflet as an appendix in the revised manuscript.**

- A detailed description of the 2 hours training is required.

- **We provided more details about the training in the revised manuscript. The interactive training deals mainly with disease management, especially drug treatment. We also explain the GPs of the intervention group the difference between HFrEF and HFpEF regarding both aetiology and management. HFpEF**
patients should receive diuretics when fluid overloaded and receive adequate blood pressure treatment. The medical treatment of HFrEF is more complicated. Diuretics are needed in case of fluid overload. In any patient with HFrEF, ACE-inhibitors (or ARB in case of not tolerating ACE-inhibitors), β-blockers and an MRA should be prescribed, and when tolerated uptitrated to the optimal dose as recommended by guidelines. Ivabradine should be considered in patients with HFrEF and sinus rhythm with a frequency above 77 beats/minute who remain symptomatic after optimal treatment with ACE-inhibitors, beta-blockers, and MRAs. Moreover, the heart rate should be above 77 beats/minute. Most common interactions and adverse effects of HF drugs will be explained. General aspects such as adherence and polypharmacy are discussed.

- How will the primary care practices be chosen and randomized?
  - A random selection of general practices in and around Amersfoort, a city in the Netherlands was eligible, with urban, suburban, and rural sites. The project manager in a blinded fashion undertook the randomisation of the participating GPs. General practitioners working at the same location were allocated to the same group to avoid contamination.

  In the revised manuscript we describe randomisation in more detail.

- I think it will be more interesting and relevant to present the results of HFrEF population since this population is the center of the study. Furthermore, as well explained by the authors, use of drugs in HFpEF is not clearly established.
• The results of patients with HFrEF will be presented separately. We consider presenting the results of those with HFpEF also worthwhile, the more because many physicians tend to be nihilistic in their approach of these patients. Importantly, however, symptoms can be relieved, and blood pressure and comorbidities may be adequately managed.

- I don’t understand why not 100% of patients did have a TTE?

• We wanted to study patients considered to have heart failure by their GP. As we mention in the Introduction, many GPs still not use echocardiography to come to a diagnosis. Therefore, by studying ‘real-life’ patients as we did, a part of the participants did not have had an echocardiogram. Five months before the study, GPs in both groups received a list of patients they had labelled with heart failure and they were stimulated to refer patients for echocardiography. Importantly, in the randomized study we only included patients with definite heart failure, that is, heart failure according to a panel of two cardiologists and an experienced GP based on all available diagnostic results, including echocardiography. Those without echocardiography results were not eligible for the randomized trial. In the revised manuscript we further clarify this.


Comments to reviewer 2

- Abstract: wording a language could be strengthened.
  
  - We improved the English of the abstract in the revised manuscript.

- Introduction: There seem to be a mismatch between the association for GP diagnosis and subsequent titration of medications. I believe the focus here is on education and optimising treatment in primary care. The issue of diagnosis is completely separate, if not the authors will need to clarify how so?
  
  - The focus of our study is indeed on education and optimising HF treatment in primary care. Before considering treatment a diagnosis should be established. Certainty about the diagnosis of heart failure and knowing if it is HFpEF or HFrEF may effect treatment and persistence of physicians in uptitration. In this respect uncertainty about the diagnosis may be an important barrier to optimal treatment. In the revised article we changed the Introduction accordingly.

- The sentence "uncertainty is an important barrier to treatment" does not fit very well in the context of the paragraph.
  
  - We revised the text in the revised version of the manuscript.

- I am not sure why it is important to mention treatment of HFpEF.
  
  HFpEF is part of the ‘HF family’. Heart failure means that patients have symptoms such as shortness of breath and these should be adequately treated
with diuretics if there are signs of fluid overload. There are more diseases in which the focus is on managing symptoms and not improving prognosis.

- The Methods section should have headings.
  - We thank the reviewer and added headings in the revised manuscript.

- I am not sure that the baseline results are vital for this paper. It may be best to just focus on methods.
  - We decided to remove the baseline results from the manuscript, the more because the Editor also wants us to delete it.

- The discussion is inadequate. The authors should discuss the many aspects of the methods. I again point to previous HF trials with published methods. In this case it would be of interest for the authors to discuss
  - why they did not choose for a nurse led model
    - Heart failure management is complex and in the Netherlands primary care practice nurses are not trained in the management of this disease.
  - self care as an alternative
    - Self care is indeed important and always an important element in the care of patients with heart failure. However, self care alone would not be enough and initiating drugs and uptitration should be done by a physician.

In the revised document we added some information on self care.
- What are the cost ramifications for GPs to focus so much on one disease
  - *Does the reviewer want to stress the time spend on optimising treatment? Ain’t it good clinical practice to provide the best care to patients with a five year’s mortality rate of 50%? When the reviewer means a cost-effectiveness study; we do not plan to perform a cost-effectiveness study. We only want to improve evidence-based care that is not yet optimally provided to community-dwelling people with heart failure general practice.*

- Why only one training session
  - *We agree with the reviewer that more trainings could be considered. However, this is difficult to organize and burdensome for the GPs. Importantly, however, participating GPs in both groups could at any time consult the Dutch GP guidelines on heart failure. Moreover, the GPs in the intervention group received a flow chart that could help them with initiating and uptitrating drugs (Appendix). We agree with the reviewer that nevertheless repetition of the training of the intervention group could have been considered, although, such repetitive training is not often done in research.*

- What about technology assisted tools?
  - *An uptitration scheme is an assisting tool. Telemonitoring could also be considered, but was not evaluated.*
In the Discussion paragraph of the revised manuscript we will now discuss the aforementioned points.