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

16 September, 2015

Dear Mrs Zhang,

Thank you for accepting, in principle, for publication 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).

The comments of the reviewers helped us further to improve our manuscript. We were able to answer their questions, and please find below our detailed response to the comments.

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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Minor formatting revisions suggested by the editorial board:

- (1) Title page: please include emails of all the authors
- (2) Please include a List of Abbreviations after the Discussion Section
- (3) Please include a section of Figure Titles and Legends at the end of the main manuscript (main .doc word file), and upload the figure images separately (without the titles and legends).

We adjusted our manuscript accordingly.

Reviewer 1:

- You have to change the title of the manuscript since HF diagnosis is one of the objective of your study and is not currently in your title.

We disagree on this point with the reviewer. Our aim was a cluster randomized trial of patients with heart failure in primary care. For this goal, we had to confirm or refute the GP’s diagnosis of heart failure to be sure to only include those with ‘true’ heart failure. We used an expert panel to achieve this goal. Thus, setting the diagnosis was not the main objective of our study, but could be considered as an inclusion criterium. We therefore did not change the title of our manuscript.

- Since you have a very short training (2 hours) it is mandatory to have a longer evaluation of HF drugs prescription and not only for 6 months. Thus, we can imagine that the up-titration and optimization of HF drugs may be less important after 6 months.
We agree with the reviewer that our training was short, as was our follow up period. For logistic reasons and to remain realistic regarding the possibility of future implementation in clinical practice, we decided to give a concise training. Regarding follow up, we consider 3 to 6 months long enough to (further) uptitrate patients already on HF drugs because the GP considered them already to have heart failure. Our main end points were evaluated one and two years after the start of the study, in our opinion a reasonable period of time for drugs to show beneficial effects, and in line with follow up periods of major landmark trials in heart failure.

- A short training is a choice and I understand it suites well to the Netherlands scheme. However, absence of additional training may probably induce a negative or neutral effect.

We agree that reminders and repetition of the training would be an option. Again, however, such an intervention would reduce implementation in clinical practice. In the Discussion paragraph, we explained why we choose for a single training; it is feasible and it helps to implement such a training and uptitration scheme in everyday clinical practice. See page 12, line 5.

- Add Ivabradine in the up-titration scheme.

We answered this request of the reviewer already in our first rebuttal. We want to refer to our previous answer and the changes we made in our first revised manuscript.

In short; The ESC guidelines 2012 recommend (class IIA) prescription of ivabradine if patients remain symptomatic with ACE-inhibitors/ARBs, beta-blockers, and MRA’s, and in >80% cases also diuretics. This, however, in the subgroup with sinus rhythm and a heart rate >77 bpm,
and the highest possible dose of beta-blockers. This subgroup is very small, and as we already mentioned in our first revised document, we would like to recommend that in such cases the GPs consult the cardiologist on initiating ivabradine.

- Delete the numbers of included patients in the Figure 1

We assume that the reviewers want these numbers to be deleted because they suggest the study has already started. This is indeed the case, and it is rather common to publish the design article after the start of a study. Moreover, it is common to present such numbers, if available, also in BMC Family Practice. Moreover, we consider these numbers helpful for the readers.

We therefore kept the numbers in, in Figure 1 of our revised manuscript. If, however, the editor thinks it should be deleted, we will be happy to do so.
Reviewer 2:

“This article has received two critical peer assessment in the first round. The authors are commended for their robust rebuttal and replies with changes to comments made from both reviewers. The final criticism is based on the structure of this methods paper. In this is to ensure a good introduction to understand the need for the study, a robust method to ensure study is reproducible; results (not needed) and discussion to present the thinking behind the methods. It appears the authors have largely addressed these issues.”

- The final criticism is the discussion. “Perhaps it could be strengthened to cover more domains even the ones in the cover letter.”

We thank the reviewer for considering our first rebuttal as appropriate. We assume that the reviewer wants us to include in the Discussion the following three topics:

1. Arguments why hr-QoL, drug prescriptions, and cardiovascular outcomes and mortality were not evaluated each time point of the study.
2. Arguments why also patients with HFpEF will be evaluated, and not selectively those with HFrEF.
3. An explanation why not 100% of patients underwent echocardiography.

We changed our Discussion paragraph section as follows:

1. ‘A possible limitation is that we measure outcomes only once; drug prescriptions after 6 months, hr-QoL after 12 months, and CV morbidity and mortality after 24 months. More frequent measurements of outcomes would result in ‘disturbing’ GPs, and multiple times filling out questionnaires by participants. It would easily result in ‘drifting away’ from ‘real’ care as usual of those in that arm of the study’. See page 12, line 10-15.
2. ‘We evaluated both HFrEF and HFpEF patients, although, for HFpEF ‘clear’ evidence-based
treatment is lacking. Nevertheless, HFpEF is part of the heart failure spectrum, and has
nearly as poor a prognosis as HFrEF. Moreover, these patients suffer of symptoms, notably
fluid retention causing shortness of breath and peripheral oedema. These symptoms can
adequately managed with diuretics. Physicians should realize that symptom relieve is of
utmost importance in these patients by titrating the dose of diuretics as optimally as
possible. Adjustments of diuretic dose to filling status is really the ‘art’ of medicine. Even
more can be done in patients with HFpEF; blood pressure and comorbidities should be
adequately managed according to the ESC guidelines 2012.’ See page 12 line 21-page 13
line 7.

3. ‘not all patients will undergo echocardiography in this practice-based study. The
advantage of a practice study is the inclusion of ‘real’ patients and the assessment of drugs
in ‘real’ practice. The downside is missings on some variables. In real live practice not
everybody labeled with heart failure underwent echocardiography. Nevertheless, for our
cluster randomized trial we will selectively include those with definite HF, that is, symptoms
of HF and functional/ structural abnormalities with echocardiography, evaluated by an
expert panel of two cardiologists and a GP.’ See page 12, line 15-21.