Author's response to reviews

Title: The prognostic importance of a history of hypertension in patients with symptomatic heart failure is substantially worsened by a short mitral inflow deceleration time

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Version: 3 Date: 31 March 2012

Author's response to reviews: see over
Dear Editor Dr. Peter Bramlage,

We are very grateful for the opportunity to resubmit the manuscript entitled “The prognostic importance of a history of hypertension in patients with symptomatic heart failure is substantially worsened by a short mitral inflow deceleration time”, MS: 1527748502627959. We are thankful to the reviewers, which have helped us in improving the paper. Below, we have systematically answered to all the reviewers’ comments and we hope you will find these satisfying.

All authors have seen and approved the present version of the manuscript. On behalf of the authors,

Best regards

Charlotte Andersson, MD.
Reviewer: Paul Steendijk
Reviewer's report:

1) Only about 30% of the pts had transmitral flow measurements done. This may have introduced a bias towards including patients suspected of inflow abnormalities. Please comment.

It cannot be excluded that this was the case. However, we have previously investigated the characteristics of patients with and without transmitral flow profiles available and we did not find any significant differences. Nevertheless, regrettfully this information was not available in the manuscript and therefore we have now inserted a paragraph about this under the limitation section:

Revised manuscript, discussion: Furthermore, measurements of transmitral flow were not mandatory for the ECHOS trial and only a subgroup of 880 patients had measurements available. These patients resembled the other patients, but it cannot fully be excluded that this subgroup differed in unmeasured characteristics from the rest of the ECHOS screening population.

2) Hypertension (history) was defined as current or previous antihypertensive treatment. This is a somewhat suboptimal because patients with controlled HTN will be included, but pts with untreated HTN are not.

We agree, but regrettfully we did not have measurements of actual blood pressure values available – and we currently emphasize this as a limitation. Nevertheless, these are patients in contact with the hospital system, which would increase the likelihood of being diagnosed and treated for hypertension.

3) The manuscript title mentions 'diastolic function' but the study merely determined mitral inflow deceleration time, which obviously is not the same. I think this is somewhat misleading. To some extend the same holds for the term 'systolic function' in the title since this is based on EF only (which in this populations may have its limitations as a marker of systolic function).

In recent years tissue Doppler variables have begun to play an increasingly important role in the evaluation of cardiac function and although debatable, we still believe that it is not wrong to say that deceleration time is a measure of diastolic function.

We do understand the reviewers point and have now changed the title to:
The prognostic importance of a history of hypertension in patients with symptomatic heart failure is substantially worsened by diastolic dysfunction characterized by short mitral inflow deceleration time.

4) In line with the previous comment, I feel the limitations of deceleration time as an index of diastolic function (or even of restrictive filling) deserves some more attention. You mention that increased RV pressure may lead to short deceleration time. However pseudonormalization is case of delayed relaxation and/or high filling pressure is not discussed.

We did not have complete data on tissue Doppler variables of the apical four chamber view on all patients with data available on deceleration time (and >30% of these patients had atrial fibrillation, making the classification impossible). Therefore we were unable to investigate the prognostic importance of a pseudonormalization and have intentionally chosen to keep this discussion short. We have now added a sentence about this under limitations section:

Revised manuscript, discussion, limitation section:

Unfortunately, we did not have measurements from tissue Doppler or other modern echocardiographic modalities available for analyses (they do however not as yet allow analyses of long-term outcomes).

5) The study uses all-cause mortality as a primary end-point. However, the study group is likely to have a high prevalence of comorbidities. Please discuss.

Patients with heart failure often suffer from comorbid conditions, but from others’ work we know that they most often die from cardiovascular causes (cardiac failure or arrhythmias). We have now inserted the following:

Revised manuscript, discussion, limitation section:

Finally, we did not have causes of deaths available for the present analyses, but from others’ work we know that the majority of patients with heart failure (NYHA II-IV) die from pump failure or arrhythmias.[1]


Reviewer: Claudia Zemmrich
Reviewer's report:
1. **Common statement:**

Although it is already well known, that prognosis of heart failure patients correlates better with mitral flow velocity variables and filling patterns than with LV EF the present paper nicely shows this again. But the title doesn’t reflect this key result of the present study as the goal of the study was obviously to investigate a different question: prognostic importance of diastolic or/and systolic parameters in hypertensive vs. not hypertensive HF patients. It is not consistently clear throughout title, abstract, introduction and results section of the study, if the main investigated factor is RF or hypertension, as the number of patients with RF (425) is nearly double as high as the number of hypertensive patients (257) – those even reflecting a heterogeneous group of patients with significant differences in baseline characteristics.

*In response to the previous reviewer, we have changed the title, so that the aim of the present paper should stand more clearly.*

**New title:**

The prognostic importance of a history of hypertension in patients with symptomatic heart failure is substantially worsened by a short mitral inflow deceleration time

We agree with the reviewer that data from the present trial nicely highlight the strong prognostic importance of a restrictive mitral flow velocity in heart failure patients, but the aim of the present manuscript was to investigate whether patients with hypertension had a differential prognostic importance of a short mitral deceleration time, compared to patients without a history of hypertension (this is not well-investigated previously).

2. **Detailed comments:**

a. **Abstract:**

Methods section: misleading number of patients investigated for the present study: not 3078 patients have been studied for the topic, but 122 RF hypertensive patients against 303 restrictive but not hypertensive patients or 257 hypertensive vs. 621 not hypertensive pts 880 patients with mitral inflow measurements available, in results section 878 patients complete data available, please clarify incomplete or complete number of data.

*For investigation of the prognostic importance of hypertension according to LVEF, all patients were included.*

2 patients had not data on hypertension status. *This is now clarified under results section in manuscript.*

**Results section, revised manuscript:**
In total 3078 patients were screened. Of these 878 patients had complete measurements of the mitral inflow, LVEF and hypertension status. (880 patients had measurements of mitral inflow, but two of these lacked data on hypertension status). Baseline characteristics for overall population and for patients with and without hypertension are shown in Table 1, and for patients with and without hypertension stratified by mitral filling pattern in Table 2.

b. Results section of abstract: isn’t is the way round, that hypertension influenced the outcome associated with RF as RF is the real prognosis relevant factor, not hypertension

This depends on what one would like to emphasize; we primary wanted to investigate the prognostic importance of a history of hypertension in patients with and without a restrictive filling and therefore preferred this way of presenting data in abstract. As the reviewer will see below (paragraph 2 e), we have now put the reverse relationship into a clearer perspective (including a separate graph) – as suggested.

c. Results:
Mean age 73±11, if median of all groups 75 years or higher?? Possible?? The hypertensive and not hypertensive patient do significantly differ in terms of patient characteristics (diabetes, BMI, LVEF, pharmacological treatment). We need adjusted Kaplan-Meier curves to interpret the remaining mortality differences, when these factors are eliminated (are there any left after adjustment at all?)

The age distributions (means and medians, respectively) were not “typographic errors”, but indicate that the distribution of age was slightly skewed.

With respect to the Kaplan-Meier curves, we are not comfortable with adjusted KM analyses, because they look very artificial and are somehow difficult to interpret. Indeed, adjusted KM is a mathematical construction that makes results look nicer than they actually may be. Curves never cross, as there is a constant difference between groups, thus we prefer to present KM curves without adjustment, and Cox analysis as adjusted results.

d. Discussion: an important limitation (no data on actual blood pressure values) is redundantly mentioned and discussed twice, here and again in limitation section.

We believe that this was very important to emphasize and therefore chose to mention it twice. We have now added “as previously mentioned” during the limitations section:

Revised manuscript, discussion part, limitations: Some important limitations should be noted. As previously mentioned, data on exact blood pressure values were not available for the present study and the diagnosis of hypertension relied on patient history and anti-hypertensive treatment. LVEF was

e. Figure 3 Should include HR of RF and non RF patients with and without hypertension
We have now included these data as a Figure 3a and renamed Figure 3 to Figure 3b. Furthermore, we have made new layouts for all figures, which are nicer and in a higher solution than the old ones.

Results section: Figure 2 a+b presents Kaplan-Meier curves for patients with and without a restrictive filling pattern stratified by hypertension status. As previously shown,[7] having a restrictive filling pattern was associated with an increased risk of mortality, overall HR of 1.58 (1.32-1.89), significantly higher in patients with hypertension (HR 2.50 [1.78-3.51]) than in patients without hypertension (HR 1.33 [1.08-1.64]), p for difference <0.0001, but importantly this relative risk was substantially higher among patients with hypertension than among patients without hypertension (Figure 3a). Further, the transmitral filling pattern was shown to substantially influence the outcomes associated with hypertension; p for interaction <0.001; Figure 3b. A history of hypertension was associated with 25% decrease in relative risk of mortality (HR 0.75 [0.57-0.99]) among those with a non-restrictive filling pattern and a 41% increase in relative risk of mortality (HR 1.41 [1.08-1.84]) among those with a restrictive filling pattern. As Figure 3b also illustrates, the hazard ratios associated with hypertension in relation to the mitral filling pattern were not dependent on LVEF. In subgroup analysis of patients with available measurements on left ventricle posterior wall diameter (n=753), no interaction was found between hypertension and left ventricle posterior wall (p=0.4).
Figure 3a:

- RF overall
- RF in patients without HT
- RF in patients with HT

Hazard ratio

p < 0.001
All-cause mortality, hypertension

Survival (proportion)

Time (years)

- RF
- no RF

p < 0.001
All-cause mortality, no hypertension

Survival (proportion)

Time (years)

no RF

p=0.27

RF