

The Trial of Intensified Medical Therapy in Elderly patients with Congestive Heart Failure (TIME-CHF)

Citation for published version (APA):

Maeder, M. T. (2018). *The Trial of Intensified Medical Therapy in Elderly patients with Congestive Heart Failure (TIME-CHF): novel insights into hot topics in heart failure*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.20180614mm>

Document status and date:

Published: 01/01/2018

DOI:

[10.26481/dis.20180614mm](https://doi.org/10.26481/dis.20180614mm)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

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Chapter XI

Conclusions and Summary

The Trial of Intensified Medical Treatment in Elderly patients with Congestive Heart Failure (TIME-CHF) is a key study in field of natriuretic peptide-guided therapy for heart failure (HF). In addition, the study design allowed numerous important pre-specified and post-hoc analysis. In the present thesis, three specific aspects were addressed: i) the interaction between HF and renal failure, ii) the prognostic role of heart rate (HR) and its potential implications in different HF populations, and iii) the role of N-terminal-pro-B-type natriuretic peptide (NT-proBNP)-guided management, in particular its long-term effects and its role in patients with HF and preserved left ventricular ejection fraction (LVEF; HFpEF). The key results were as follows:

i) Interaction between HF and renal failure

- Not every rise in serum creatinine is prognostically relevant. Only larger changes, i.e. a rise by more than 44 $\mu\text{mol/l}$, are associated with an adverse outcome (Chapter II).
- Importantly, the clinical context of such changes is relevant. Worsening renal function during loop diuretic therapy is a sign of poor prognosis whereas this is not the case for similar changes occurring during therapy with spironolactone (Chapter III).
- In addition, hyperkalemia was shown to be relatively common in elderly and comorbid heart failure patients, and treatment with spironolactone was a strong predictor of the incidence of hyperkalemia indicating that close surveillance of serum potassium is required in elderly and comorbid patients with heart failure, in particular during treatment with spironolactone (Chapter IV).

ii) Prognostic role of HR and its potential implications in different HF populations

- While in younger patients (≤ 75 years) higher HR was a marker of more advanced disease (lower LVEF, higher NT-proBNP) and a significant predictor of death and HF hospitalisation also after adjustment for baseline characteristics, this was not the case in patients with age >75 years indicating that the prognostic role of HR in HF depends on age (Chapter V).
- In contrast to patients in sinus rhythm, lower HR rather than higher HR was associated with poor outcome in patients with HF and atrial fibrillation (Chapter VI).
- A very simple HR-related parameter, i.e. the change in HR from the supine to the upright position (ΔHR) was found to be an independent predictor of prognosis (Chapter VII).

iii) Role of NT-proBNP-guided management, in particular its long-term effects and its role in patients with HFpEF

- The beneficial prognostic effect of strategy of NT-proBNP-guided management with aggressive up-titration of angiotensin converting enzyme inhibitors, betablockers, and mineralocorticoid receptor antagonists over a period of 12 months in younger patients with HFrEF was maintained after 18 months (Chapter VIII).
- NT-proBNP-guided management had opposite prognostic effects in patients with HFrEF and patients with heart failure and preserved ejection fraction: beneficial effects in HFrEF, and a trend towards worse outcomes in HFpEF patients (Chapter IX).