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# Bridging the gap between clinical trials and clinical practice Sacubitril-valsartan in heart failure as a model

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## Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Hörsal B, Unod T Plan 9 Tandläkarhögskolan, fredagen den 6 november, kl. 09:00. Länk för att delta via Zoom: <https://umu.zoom.us/j/8181748727>, password 556677. Avhandlingen kommer att försvaras på svenska.

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**Abstract**

When novel treatments prove more effective than standard therapies, a swift and effective implementation is needed to reach cost-effectiveness and to benefit eligible patients. Meanwhile, women and elderly are often under-represented in clinical trials, which creates a knowledge gap on how to optimize treatment in clinical practice. The arrival of the angiotensin receptor-neprilysin inhibitor sacubitril-valsartan to patients with chronic heart failure and reduced ejection fraction (HFrEF) offered an opportunity to develop and test a new systematic introduction approach, as well as to investigate eligibility and management of sacubitril-valsartan in clinical practice. The aims of this thesis were to investigate obstacles to implement sacubitril-valsartan in a real-world heart failure population, as well as to develop a systematic and effective method to implement novel treatments in patients with chronic disease.

With an observational cross-sectional study design, patients were retrospectively included if they had a heart failure diagnosis, living within the Umeå University Hospital catchment area, and had at least one visit at the Heart Centre or Department of internal medicine between January 2010 and March 2016. Eligibility to sacubitril-valsartan was based on the enrollment criteria applied in the landmark trial, PARADIGM-HF. We showed that the primary obstacle to implement sacubitril-valsartan was that only a quarter of the real-world HFrEF population was eligible. The most prominent difference was that real-world patients were significantly older compared with the PARADIGM-HF population. Disproportionally many patients, especially women, were ineligible for sacubitril-valsartan due to intolerance of renin-angiotensin system inhibitors in target doses. With multivariable linear regression analyses, we showed that the lower target doses in women were explained by biological sex differences.

Management of heart failure treatment involve many titration steps that risk stressing the resources of both healthcare and patients. We prospectively investigated a direct switch to maximum dose sacubitril-valsartan in patients who tolerated target dose renin-angiotensin system inhibitors (equivalent to enalapril 10 mg twice daily). We showed that the simplified introduction was safe and generally well tolerated during the first year.

The systematic introduction approach is a seven-step procedure: step 1, define a few main criteria; step 2, primary scan patients with the one or two main criteria using computerized medical records/databases/ clinical registries; step 3, identify patients applying the other predefined criteria; step 4, evaluate if any examinations/laboratory test updates are required; step 5, summon identified patients with an information letter; step 6, discuss treatment with the patient and prescribe if appropriate; step 7, follow-up on initiated therapy and evaluate the process. We evaluated the approach with a mixed method, including both a case study of the sacubitril-valsartan implementation and an interview study with qualitative content analysis. The new systematic introduction approach effectively implemented sacubitril-valsartan in clinical practice, by identifying eligible patients with limited resources and time. The patients were overall satisfied with the new approach and their confidence in healthcare was maintained.

In conclusion, we found that the strict inclusion criteria in the PARADIGM-HF trial would exclude a majority of patients with heart failure if they are implemented and that these criteria have an inherent bias versus the old and the frail, which in turn disproportionately affects women. We further found that patients who are on maximum recommended dose of renin-angiotensin system inhibitors can be safely switched to maximum dose sacubitril-valsartan and that our method of systematic introduction was effective in implementing sacubitril-valsartan to a heart failure population. The approach is a promising example of how to reduce the gap between clinical trials and clinical practice in patients with chronic disease.

**Keywords**

Systematic implementation, healthcare quality improvement, chronic disease management, heart failure, sacubitril-valsartan, real-world population, sex differences

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