Introduction
Chapter 1

GENERAL INTRODUCTION AND AIMS OF THIS THESIS

Heart Failure
Heart failure (HF) has emerged as a major public health problem in developed world. In Europe, 1-2% of the adult population is affected, although it is primarily a disease of the elderly; 6-10% of people aged over 65 years have the disorder. In affluent societies, where average life expectancy is increasing, levels of HF are also expecting to increase. More effective treatment of hypertension and myocardial infarction, as well as advances in HF management may contribute to an increase in the prevalence of HF.

Heart failure is a deadly and highly disabling condition. Community-based surveys show that 30-40% of patients die within one year, and up to 70% die within 5 years. Mortality is even higher in patients with advanced HF (New York Heart Association (NYHA) III and IV), exceeding that of most cancers. HF is the most common cause of hospital admission in people aged over 65 years. Therefore the disease has an enormous burden on health services and cost to society. HF is clinically characterized by a constellation of signs and symptoms that significantly affect quality of life (QoL). Indeed, QoL is affected more by HF than by other chronic conditions.

The syndrome of HF may arise in the presence of either a depressed or a normal/preserved left ventricular ejection fraction (LVEF). Recent studies have shown that as many as half of patients with HF have preserved LVEF, and advancing age, hypertension and female gender are correlates of this syndrome. HF with depressed LVEF is characterized by changes in many neurohormonal mechanisms, but notably activation of the sympathetic and renin-angiotensin systems. Unlike HF with depressed LVEF, the pathophysiological basis of HF with preserved LVEF is not well understood. Many of these patients probably have diastolic dysfunction, though this assumption is disputed. However, HF with preserved LVEF confers a considerable burden on patients, with the risk of disability, hospital admission and mortality comparable to that of HF with depressed LVEF.

Evidence-based treatment in heart failure
The goals of heart failure treatment are to improve survival and QoL of patients. Based on a large number of Randomised Controlled Trials (RCTs), there are now many efficient therapies for HF with depressed LVEF. Current pharmacological treatment is focused on inhibition of neurohormonal systems, which cause progressive worsening of HF syndrome over time. Angiotensin-converting-enzyme-inhibitors (ACEI) and
Beta blockers are the mainstay of current treatment; several meta-analysis of RCTs have shown that reduce hospital admissions, and increase survival.\(^{23,24}\)

Beta blocker therapy, once contraindicated for HF treatment, has now an increasing role in the management of HF with depressed LVEF. In addition to sympathetic inhibition, beta blockers may also benefit via reduction in heart rate and blood pressure, as well as reduction in arrhythmias.\(^{25}\) Current European guidelines on optimal HF treatment\(^{22}\) recommend to start therapy with an ACEI (unless post myocardial infarction), and to add a beta blocker on top of ACEI. However, last evidence suggests that initiation of therapy with a beta blocker may be as safe and efficacious.\(^{26}\)

Despite established benefits on survival, it is uncertain to what extent beta blockers influence QoL of patients with HF. QoL refers to physical, psychological and social domains of health, as distinct areas influenced by person’s beliefs and perceptions.\(^{27}\) Several RCTs included QoL as an end point evaluation.\(^{28}\) The majority show no significant effect of beta blockers on QoL when compared to placebo group, but most studies report a trend towards better QoL in the beta blocker arm. However, to date, no meta-analysis has yet quantified the impact of beta-blocker therapy on QoL in HF patients receiving optimal standard therapy.

While for HF patients with depressed LVEF there are now many efficient therapies, there is no accurate evidence-based treatment for HF with preserved LVEF. So far, only CHARM-Preserved (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) and DIG (The Digitalis Investigation Group) trials have shown that candesartan reduces cardiovascular (CV) hospitalizations, and digoxin reduces HF hospitalizations, but none of the drugs significantly affects CV death.\(^{29,30}\)

Treatment with beta blockers may be beneficial in HF with preserved LVEF.\(^{31}\) However, no RCT exploring the effect of beta-blockers in HF with preserved LVEF has yet been completed. The SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) was the only trial that showed a beneficial effect of the beta blocker nebivolol in elderly patients (age > 70 years) with HF, 35% of whom had preserved LVEF.\(^{32}\) However, the study was not designed to assess the separate effects of nebivolol in patients with preserved LVEF.

**Observational studies of drug effectiveness in heart failure**

At present, the RCT design is the gold standard for evidence on drug efficacy.\(^{33}\) However, due to ethical and scientific reasons, RCTs have strict patient inclusion criteria, which in turn limit the extrapolation of their findings to daily practice populations (external validation).\(^{34}\) In HF, most RCTs excluded elderly, patients with severe comorbidities,
and those with preserved LVEF. Therefore, only a minority (13%) of patients treated in clinical practice would fulfill the entry criteria of at least one landmark trial. Further, most trials were not designed as dose-related studies. Thus, clinicians question whether patients in clinical practice need to reach the target dose to achieve benefit. The dissimilarity between clinical practice and trial setting was mentioned as a possible explanation for the low use of evidence-based therapies.

The observational study design has emerged as a research tool to complement information provided by RCTs. After the successful conclusion of treatment benefit under study conditions, its applicability to daily practice needs to be tested. Observational studies allow the assessment of the drug benefit in real life health-care setting (effectiveness). Further, they may be valuable to assess drug effectiveness in subgroups not studied in RCTs, or to assess the long-term beneficial effects of drugs already proven effective in short-term RCTs. Also, they may generate hypotheses that can later be tested in a RCTs. Though largely inclusive, observational studies are more exposed to biases, that can partly be addressed through rigorous study design or statistical analysis (Table 1).

At present, a number of observational studies have been conducted in HF, but no study has yet summarized their added value on the knowledge of drug effectiveness. Despite considerable contribution, there are still many issues to be explored. While the ultimate goal of guideline treatment is to improve QoL of the patients in daily practice, no observational study had yet explored the effect of evidence-based therapy on QoL in daily care. Second, given the advanced age of patients treated in clinical practice, no study has explored whether the effect of beta-blocker therapy is modified by the age of the patient. Further, no observational study has assessed the effect of beta-blocker therapy in HF with preserved LVEF. Such information is particularly important given the high percentage of patients with this disorder, and the lack of evidence-based recommendations for its management. Last, little is known about the tolerability and dose-related effects of beta-blockers in elderly patients with HF. Such information may have important implications for daily practice.
Table 1. Comparison of observational studies and randomized controlled trials

<table>
<thead>
<tr>
<th>Item</th>
<th>Cohort studies</th>
<th>Randomised controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Populations studied</td>
<td>Diverse populations of patients who are treated in a range of settings</td>
<td>Highly selected populations who are treated at selected sites</td>
</tr>
<tr>
<td>Allocation to the intervention</td>
<td>Based on decisions made by providers or patients</td>
<td>Based on chance (randomization)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Can be defined after the intervention and can include rare events</td>
<td>Primary outcomes are determined before patients are entered into study and are based on predicted benefits and risks</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Prospective or retrospective studies; provide an opportunity for long follow-up</td>
<td>Prospective studies; often have short follow-up because of costs and pressure to produce timely evidence</td>
</tr>
<tr>
<td>Analysis</td>
<td>Sophisticated statistical analysis</td>
<td>Analysis is straightforward</td>
</tr>
<tr>
<td>Threats to validity</td>
<td>Internal validation (risk of confounding)</td>
<td>External validation (exclusions)</td>
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Adapted after Rochon et al.39

**Scope of this thesis**

In this thesis we investigated the impact of pharmacological treatment on patient outcomes in real-life HF setting, with special focus on the effect of beta blocker therapy.

The main aims of the thesis are:

1. To investigate the impact of pharmacological treatment on quality of life in patients with heart failure
2. To assess the impact of pharmacological treatment on survival in patients with heart failure

In the first part of the thesis we investigated the effect of pharmacological treatment on QoL.

To assess the evidence-based background on this health-related outcome, in **Chapter 2** we quantified the effect of beta-blocker therapy on QoL in HF patients receiving optimal standard therapy, through a systematic review and meta-analysis of RCTs.

In **Chapter 3**, we explored whether evidence-based therapy is related with a better quality of life in daily practice patients with HF.
In Chapter 4 we reviewed RCTs that assessed the impact of life prolonging therapies on QoL, and we discussed some methodological limitations of QoL assessment in HF.

In the second part of the thesis we focused on the effect of pharmacological treatment on survival in daily practice patients.

In Chapter 5, we summarized the contribution of observational studies of ACEI and beta blockers to the knowledge of drug effectiveness in HF.

In Chapter 6, we assessed the effect of beta blocker therapy on survival in a daily practice cohort of patients with HF, and we explored whether the effect is modified by the age of the patient.

Because HF with preserved EF represents nearly half of patients with HF, and there is no accurate evidence-based therapy for its management, in Chapter 7 we assessed specifically the effect of beta-blocker therapy in HF with preserved LVEF.

In Chapter 8, we evaluated the tolerability and dose-related effects of nebivolol in elderly patients with heart failure, using data from the SENIORS trial.

Finally, in Chapter 9, the main findings of the studies are presented. Additionally, the implications for clinical practice and future research are discussed.

REFERENCES


19. Petrie MC, Hogg K, Caruana L, McMurray JJ. Poor concordance of commonly used echocardiographic measures of left ventricular diastolic function in patients with suspected heart failure but preserved systolic function: is there a reliable echocardiographic measure of diastolic dysfunction? Heart 2004;90:511-517.


