Treatment of heart failure and patient outcomes in real life
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Summary
SUMMARY

Heart failure (HF) has emerged as a major public health problem in developed world. It is primarily a disease of the elderly; in Europe, 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. HF is a major disorder, associated with impaired quality of life (QoL) and poor prognosis.

The syndrome of HF may arise in the presence of either a depressed or a normal/preserved cardiac systolic function, as measured by left ventricular ejection fraction (LVEF). Recent studies have shown that as many as half of patients with HF have preserved LVEF, and this entity is more common in the elderly, women and patients with hypertension.

Based on a large number of randomized controlled trials (RCTs), beta blockers and angiotensin-converting-enzyme-inhibitors (ACEI) have become the mainstay of current treatment in HF; several meta-analysis of RCTs have shown that increase survival, and reduce hospital admissions. However, RCTs have strict patient inclusion criteria, which in turn limit the extrapolation of their findings to daily practice populations. In HF, most RCTs excluded elderly, patients with severe comorbidities, and those with preserved left ventricular ejection fraction (LVEF).

The observational study design has emerged as a research tool to complement information provided by RCTs. Observational studies allow the assessment of the drug benefit in real life health-care setting. 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 RCT. Also, they may generate hypotheses that can later be tested in RCTs.

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 Chapter 2, we performed a meta-analysis of RCTs to quantify the impact of beta blocker therapy on QoL in patients with HF receiving optimal standard medication. At present, there are conflicting hypotheses regarding the impact of beta blocker therapy on QoL. Primarily, an improvement in QoL is expected, due to beneficial effects on cardiac function and hospitalisations. On the other hand, QoL might be adversely affected due to the side effects of beta blocker medication, especially during the initiation of therapy. A total of nine RCTs involving 1954 patients were included into analysis. QoL was assessed through a disease specific instrument, the Minnesota Living with Heart Failure questionnaire (MLHF) or the Quality of Life with Heart Failure questionnaire (QLHF). We found that beta blocker therapy, on top of standard medication, does not affect QoL (neither improvement nor impairment). However, there is a trend towards better QoL in HF patients additionally treated with beta blockers.

In Chapter 3, we explored whether evidence-based drug therapy is associated with better QoL in daily practice HF patients. QoL was assessed with the RAND 36-item health survey questionnaire. Medication was classified as either evidence-based treatment or under-treatment, according to the 2001 European guidelines on HF treatment. Only 57% of the patients were prescribed evidence-based treatment regimens, while 43% received treatment patterns including less than recommended drugs. Under-treatment was more frequent as severity of disease increased, ranging from 33% in NYHA I to almost 70% in NYHA III and IV. However, we found that conventional step-up medication approach in HF is not associated with better QoL. Similar to our meta-analysis of RCTs, this study shows that current HF medication may improve survival but does not seem beneficial in relation to QoL.

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. Studies that assessed QoL with a disease specific questionnaire were included. We found that at present there is a paradox in HF treatment. Life prolonging therapies, such as Angiotensin-converting-enzyme-inhibitors (ACEI), and Angiotensin receptor blockers (ARB) improve modestly or only delay the progressive worsening of QoL in HF. Treatment with beta blockers does not affect QoL in any way. However, this neutral effect of beta blockers may also be due to some methodological limitations, such as the small number of patients included in beta blocker trials or the short duration of follow-up. Disease specific questionnaires may also have some limitations, e.g. are not sensitive enough to detect small changes in QoL. On the other hand, therapies that significantly improve QoL in HF (e.g. inotropic agents) do not seem beneficial in relation to survival. We conclude that assessment of QoL in HF remains an open field,
in which new therapies but also clarification of methodology are required. In the mean
time, the use of life prolonging therapies appears as a safe measure to modestly improve
or maintain QoL.

In **Chapter 5**, we aimed to assess the contribution of observational studies to
actual knowledge regarding drug effectiveness in patients with HF. For this purpose,
we reviewed observational studies of drug effectiveness published between 1990-2005.
A total of 23 observational studies were included. We found that observational studies
in HF validate the effectiveness of ACEI and beta blockers in patient populations
underrepresented or excluded from RCTs, such as elderly patients with a broad range
of EF, elderly with depressed EF, and patients with renal insufficiency. Low-dose ACEI
and beta blocker may have beneficial effects. Target doses of ACEI seem superior to low-
doses, but there is no clear dose-response relationship. Effectiveness of ACEI and beta
blockers in HF with preserved LVEF is not clear from actual published studies, although
last evidence suggest a potential benefit of ACEI. We conclude that observational studies
of drug effectiveness provide necessary additional information for clinical practice.

In **Chapter 6**, we assessed first, whether prescription of a $\beta$-blocker at discharge is
associated with better survival in a daily practice cohort of patients with HF, and second,
whether this association is modified by the age of the patient. Patients with advanced
HF (NYHA III and IV) were included into the study, irrespective of LVEF (45% had
EF>40%). In total, 625 patients were included, and the cohort was followed-up for an
average of 22 months. We found that prescription of a beta blocker was associated with a
significant mortality reduction (45% relative risk reduction). The relative risk reduction
was similar with prescription of low- or high doses of beta blockers. However, the
beneficial effects of beta blockers appeared to be higher in younger patients, particularly
in those younger than 80 years.

In **Chapter 7** we assessed specifically the association between beta blocker
prescription at discharge and survival in a daily practice cohort of patients with HF and
preserved LVEF. We prospectively studied a cohort of 443 patients with advanced HF
and preserved LVEF (LVEF≥40). Mean duration of follow-up was 25 months. We found
that prescription of a beta blocker was associated with a significant mortality reduction
(43% relative risk reduction). The relative risk reduction appeared to be dose related,
with high-dose rather than low-dose therapy being associated with a lower risk of death.
This evidence on the beneficial effects of beta blocker use needs to be further confirmed
in prospective, randomised clinical trials.

In **Chapter 8** we performed a post-hoc analysis in the SENIORS (Study of
the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors
with Heart Failure) trial to assess tolerability and dose-related effects of the beta blocker nebivolol in elderly patients with HF. We analysed the data by classifying the patients assigned to nebivolol into four groups, according to the dose achieved at the end of titration phase: 0 mg, low dose (1.25 or 2.5 mg), medium dose (5 mg), and target dose (10 mg). Overall, 67% patients tolerated the target dose, and only 7% were unable to tolerate any dose. After adjustment, all cause mortality or cardiovascular (CV) hospitalisation was significantly reduced in the target dose nebivolol group compared to placebo (25% relative risk reduction). The medium dose nebivolol group had rather a similar benefit as high dose (27% relative risk reduction), although of borderline statistical significance, while the low dose group achieved a non-significant benefit. Patients unable to tolerate any dose of nebivolol had a two-fold higher risk of death or CV hospitalisation. We concluded that the beta blocker nebivolol is well tolerated in elderly HF population. Higher doses (i.e. medium to target) appear superior to low doses. Patients who cannot tolerate any dose have the worst outcome.

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