NT-proBNP as a risk stratification tool for the management of acute decompensated heart failure

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Chapter 1

Introduction and outline of the thesis

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INTRODUCTION AND OUTLINE OF THE THESIS

The ancient Greeks and Romans were not alone in describing signs and symptoms of heart failure and discussing cardiovascular pathology.¹ The medieval scholar Abu-Ali Hussein ibn Abdullah ibn Sina, to the West known as Avicenna, born in 980 AD in Khorasan, a historical region lying in northeast of Persia, including part of Central Asia and Afghanistan, was the most famous physician, philosopher, mathematician and astronomer of his time.¹² He was an absolute authority on heart disease and the Latin translation of his writings entitled ‘The book on drugs for cardiac diseases’ (Kitab al-Adviyt-al-Qalbiye) was widely used in the west in the 14th century.¹² However, it was not until 1900s when the German physiologist O. Frank and the British physiologist E.H. Starling provided separately from each other the fundamentals for understanding the pathophysiology of heart failure.³⁴ Although E.H. Starling’s conclusions seemed in contradiction to the 19th century view that a weakened heart was caused by dilatation,¹ he made a significant shift by describing that an increase in venous inflow produces a greater diastolic volume allowing more forcible contraction, without a decrease in output.¹³

Despite significant advances of our understanding of heart failure in the 1960s by the introduction of cardiac catheterization and cardiac surgery, the pathophysiology of heart failure was still not completely understood.¹⁵ In the 1980s and 1990s therapies like nitrates and alfa-blockers tackled the mechanisms that involved increased afterload and increased filling pressure as causes of development of congestion or worsening of heart failure.⁷⁸ At the same time, it became apparent that in the early phase of heart failure the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) are activated in response to low cardiac output in order to increase cardiac contractility, increase sodium and fluid retention and enhance peripheral vasoconstriction resulting in more adequate organ perfusion.⁹⁻¹¹ However in heart failure cardiac output is reduced chronically, which results in chronic activation of this neuroendocrine response leading to functional and structural damaging of the heart.¹⁹⁻¹¹² The consequence of these discoveries was a new way of treating heart failure by introducing therapies aimed at blocking these neuroendocrine pathways like beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor II blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), drugs consisting of nepriysin inhibitor and an ARB, and also drugs that selectively reduce heart rate like ivabradine in addition to beta-blockers.¹³⁻²¹ Adding an implantable cardioverter defibrillator and resynchronization pacing therapy to the treatment strategy further improved prognosis in heart failure.²²⁻²³

However, despite these remarkable progression in treatment options, the burden of heart failure remains high with a prevalence of 1–2% of the adult population in
developed countries, rising to ≥10% among elderly (>70 years of age)\textsuperscript{13,24,25} with high morbidity and mortality rates among patient with chronic heart failure with mortality rates of 10-26\% within 6-months, up to 37\% within one year and with a 5-year mortality rate of approximately 50\%, which is worse than many cancers.\textsuperscript{21,26,27} More worrisome figures of up to 50-65\% of readmission or mortality within 6 months or one year has been reported for patients hospitalized for acute decompensated heart failure (ADHF),\textsuperscript{27-30} which is defined as a new onset of severe heart failure or the acute worsening of chronic heart failure requiring hospitalization. Precipitating events include coronary ischemia, arrhythmias, infection, anemia, therapy incompliance and progression of heart failure itself.\textsuperscript{9,25} One could argue that this is the price we pay for the success of reperfusion (either with thrombolysis or angioplasty) in the treatment of acute myocardial infarction and an aging population.\textsuperscript{1,9} Others have suggested that the recognition of heart failure in the presence of preserved ejection fraction (HFpEF) has contributed to the increased diagnosis of heart failure.\textsuperscript{1} Whatever the reason for these figures, it is clear that with a continued aging of the population heart failure remains a major health problem and we should find ways for the management of these patients.

It was already known in the 1990s that in patients with severely reduced left ventricular function lowering of pulmonary artery wedge pressure (transmitted from the left atrial pressure and left end-diastolic ventricular pressure) was an important predictor of survival.\textsuperscript{31} However, the ESCAPE study was not successful to improve prognosis in patients hospitalized for ADHF with systolic HF, after guiding these patients towards lower filling pressures (pulmonary wedge pressure ≤15 mmHg, right atrial pressure ≤ 8 mmHg) before discharge, compared to patients treated with usual care.\textsuperscript{32} The investigators did however show that filling pressure can be reduced successfully and subsequently they confirmed that pulmonary wedge pressure (and right atrial pressure) was a strong predictor of prognosis.\textsuperscript{32,33} After the observation that changes in B-type natriuretic peptide (BNP) correlated with changes in filling pressures, the idea was born to follow heart failure patients during admissions and to survey their natriuretic peptide levels in the outpatient clinic as a measure of severity of heart failure, which was primarily correlated with filling pressures, and also as a measure of success after initiating heart failure therapies.\textsuperscript{34}

The first biomarker to be identified as indicator of cardiac wall stretch in patients with heart failure was atrial natriuretic peptide (ANP).\textsuperscript{9,35,36} However, because of its instability\textsuperscript{9,36} it was replaced by Brain or B-Type natriuretic peptide (BNP) and its precursor N-terminal pro–brain natriuretic peptide (NT-proBNP), which are indicators of ventricular wall stretch.\textsuperscript{36-38} To date these two natriuretic peptides, BNP and NT-proBNP, are the best markers for diagnosis and prognosis in patients hospitalized for ADHF\textsuperscript{13,38-42} Although both are well established makers in ADHF\textsuperscript{43}, studies have shown that NT-proBNP was slightly superior to BNP for predicting death or rehospital-
ization for chronic heart failure and the longer half-life of NT-pro-BNP may make it a more accurate predictor of prognosis. Underlying the application of NT-proBNP as useful biomarker for prognosis is that it is particularly useful as representing cardiac status, i.e. being a cardiac specific marker.

The general hypothesis of this thesis is that NT-proBNP can be used as a risk stratification tool in the management of patients hospitalized for ADHF. Previous studies have shown that absolute levels of NT-proBNP at discharge as well as the percentage reduction of NT-proBNP during hospitalization, from admission to discharge predict prognosis. Prognostication is important, because it allows clinicians to triage patients during and after hospitalization and a reliable risk stratification model before discharge from the hospital may be used to select patients at high risk to further intensify therapies or follow-up.

**Part I** of this thesis describes the importance of NT-proBNP as a risk stratification tool for patients hospitalized for ADHF. In chapter 2 we built a large European database and developed a novel, simple discharge risk-score, using absolute NT-proBNP values at discharge and the percentage reduction during hospitalization, to provide a tool that potentially could be applied in the clinical setting before discharge. In order to reliably use a risk-score in clinical practice it should not only predict outcome well in a derivation cohort, but also in one or more independent cohorts. Therefore, we validated the risk-score in in an external cohort with ADHF. However, because of some limitations of this external cohort, we set out in chapter 3 to calibrate and revalidate the risk-score score in another cohort of patients hospitalized for ADHF.

**Part II** focusses on comparing other important risk factors with NT-proBNP in patients hospitalized for ADHF. An important paradox of heart failure is that therapies aimed at blocking the aforementioned neuroendocrine pathways like ACE-inhibitors and ARB’s for HF also impair renal function, the impairment of which is associated with poorer outcome in heart failure patients. We discuss this issue of the balance between the improvement of cardiac status and the impairment of renal function during admissions for ADHF in chapter 4, by analyzing dynamic changes in renal function and investigating the extent to which NT-proBNP (as a cardiac parameter) in combination with parameters of renal function predicted outcome. Another problem with treating patients with ADHF with diuretics is that it activates the renin-angiotensin-aldosterone system and therefore enhances circulating aldosterone levels and promotes renal retention of salt and water in an effort to restore normal perfusion pressure. During hospitalizations for heart failure serum potassium levels may be either decreased (by loop diuretics and thiazide diuretics) or increased (beta blockers of ACE-inhibitors, ARB’s of MRA’s). Because little is known about the prognostic value of these serum potassium changes during hospitalization, we addressed this issue.
in chapter 5, by evaluating the relationship between serum potassium changes during hospitalization and 6 months mortality in patients after hospitalization for ADHF.

Part III deals with a relatively unknown area of NT-proBNP use in heart failure, as it concerns patients with heart failure and preserved ejection fraction (HFpEF), comprising approximately one third of the patients hospitalized for ADHF.\textsuperscript{58–60} Three studies have reported that prognostic information of absolute natriuretic peptide levels are equal for HFpEF as well as for heart failure with reduced ejection fraction (HFrEF),\textsuperscript{61–63} and that mortality is the same in both HF groups, despite the fact that natriuretic peptide plasma levels are almost twice lower in patients with HFpEF than in patients with HFrEF.\textsuperscript{61,62,64} In chapter 6, we therefore assessed whether the prognostic contribution of absolute levels of NT-proBNP as well as the contribution of a percentage change in NT-proBNP levels, in patients hospitalized for ADHF, was the same in the two HF groups of HFpEF and HFrEF separately. In addition, to better understand the problem why lower NT-proBNP levels in patients with HFpEF do not translate into lower mortality than that in patients with HFrEF, we assessed the attainability of several (absolute and relative) NT-proBNP targets and the frequency of prognostically relevant comorbidities in HFpEF patients and HFrEF patients for low and high discharge NT-proBNP categories.

Part IV focuses on the use of NT-proBNP as a guiding tool for patients hospitalized for ADHF. The ESC heart failure guideline of 2016 recommends that natriuretic peptide could help in the planning of the discharge of patients hospitalized for ADHF, but it does not recommend to guide therapy based on the changes of natriuretic peptide levels.\textsuperscript{13} Guiding therapy in patients with chronic heart failure with regularly monitoring of natriuretic peptide levels did not show an overall beneficial prognostic effect.\textsuperscript{65–72} In two major studies it was shown that natriuretic peptide guiding therapy was only beneficial for patient aged less than 75 years.\textsuperscript{66,67} Until recently, guiding therapy in patients hospitalized for ADHF was not studied. Hence, we initiated an international, multicenter, randomized controlled trial to study NT-proBNP guided treatment compared to conventional care in patients hospitalized for ADHF. The design of the study is described in chapter 7 and the results in chapter 8. Finally, chapter 9 summarizes the major novel findings reported in this thesis and concludes with final remarks and future perspectives.
REFERENCES


