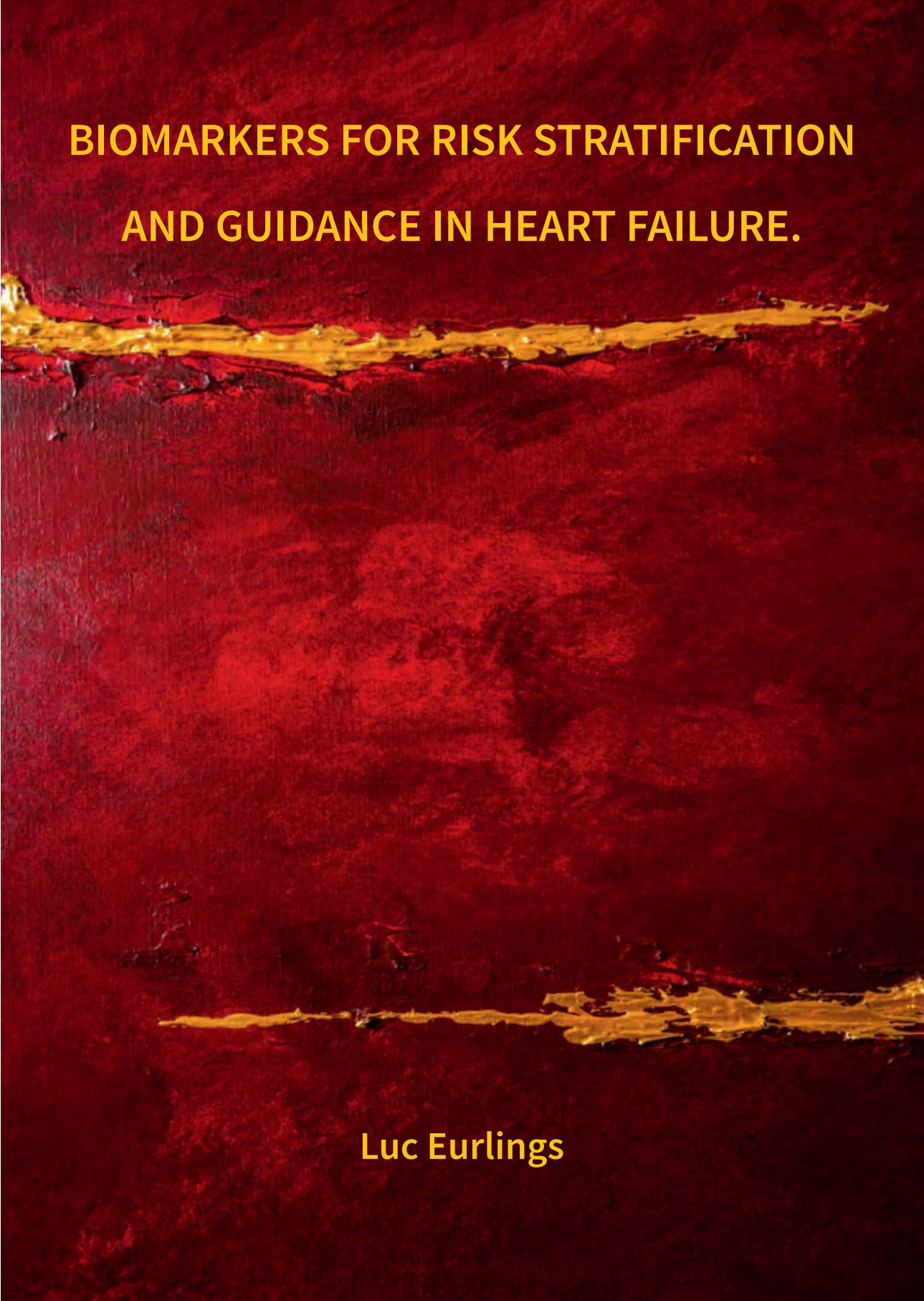
BIOMARKERS FOR RISK STRATIFICATION AND GUIDANCE IN HEART FAILURE.



Luc Eurlings

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BIOMARKERS FOR RISK STRATIFICATION AND GUIDANCE IN HEART FAILURE

PROEFSCHRIFT

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CONTENTS

CHAPTER 1.

Introduction

Heart Failure (HF) is a complex clinical syndrome in which patients have symptoms (e.g. breathlessness, ankle swelling and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles and displaced apex beats) resulting from an abnormality of cardiac structure or function.[1] Although similarity in symptoms exists, the etiologic background of HF is quite diverse, with causes like, but not limited to, coronary artery disease, hypertension, cardiomyopathy and cardiac valve disease.[1]

Approximately 1-2% of the adult population in developed countries has HF, with prevalence rising to more than 10% among persons 70 years or older.[2] The incidence of HF is likely to rise in the near future due to ageing and improved treatment of hypertension as well as valvular and coronary heart disease, allowing patients to survive an early death to later develop HF. It is estimated that in the Netherlands, incidence of HF will rise from 142.000 in 2011 to more than 225.000 patients in 2030.[3] Last decades, treatment of HF has markedly improved by prescription of ACE-inhibitors, AT-2 antagonists, Betablockers, aldosterone receptor antagonists and recently the addition of ivabradine and the neprilysin inhibitor sacubitril to the therapeutic arsenal of HF.[4-9] Furthermore, introduction of the ICD and biventricular pacing devices has clearly improved prognosis.[10,11] Nevertheless, morbidity and mortality of HF remains high, especially after admission because of acute HF. A retrospective cohort trial of more than 2.5 million Americans aged above 65 years demonstrated 30-day, 180-day and one year mortality rate of 11%, 26% and 37% respectively, and a one year readmission rate of 65%.[12] Consequently, HF treatment has high impact on health care cost, with 940 million euro spent on treatment of HF in the Netherlands, which was more than 1% of the national health care budget.[13]

1.1 Dyspnea: one symptom, many causes.

In the majority of patients presenting to the cardiac emergency department (ED) with HF, dyspnea is the main complaint.[14] Dyspnea, or shortness of breath is defined as an uncomfortable abnormal awareness of breathing. The pathophysiologic mechanism of dyspnea is complex and only partially understood[15]. Dyspnea can be caused by a wide variety of diseases like COPD, pneumonia, pulmonary embolism, coronary artery disease and HF, although the cause is often multifactorial.[16] HF has reported to be the most frequent cause of dyspnea at the ED (34%[17]– 58%[18]), and in specialized cardiac emergency departments the incidence of HF among dyspneic patients is expected to be even higher. As dyspnea can be caused by both harmless as well as highly lethal

conditions,[19] and incorrect diagnosis at the ED has been reported to be as high as 20%,[16] accurate risk assessment can help identifying those at highest risk for events, that are in need for admission and further work up.

1.2 Risk assessment in dyspnea.

For many acute settings such as acute coronary syndrome[20] and pulmonary embolism,[21] a risk score for short-term risk assessment has been developed. However for acute or recent onset of dyspnea, a short-term risk score has not yet been established.

Risk stratification for patients with acute dyspnea is a challenging task because of the wide variety of diagnoses involved, all with different pathophysiologic backgrounds. However, the use of biomarkers might be helpful for rapid and accurate risk assessment. Especially a combination of biomarkers reflecting different pathophysiologic backgrounds of diseases causing dyspnea might be beneficial. Both in patients with cardiac and non-cardiac dyspnea, biomarkers reflecting myocardial stretch,[22,23] inflammation,[24] renal failure,[25,26] cardiac myocyte damage[27] and fibrosis[28 29] may have prognostic impact. Developing a risk score based on biomarkers reflecting the aforementioned pathophysiological processes (N-terminal pro-B-type natriuretic peptide [NT-proBNP] for myocardial stretch, [Cys-C] high-sensitivity C-reactive protein [hs-CRP] as a marker for inflammation, cystatin C for renal failure, high-sensitivity cardiac troponin T [hs-c TnT] for cardiac myocyte damage and galectin-3 [Gal-3] for fibrosis, respectively) may lead to accurate risk assessment in a period where risk for events is highest.

1.3 Guided therapy of Heart Failure

As HF-related morbidity and mortality are high, it is of importance not only to detect HF at its earliest stage, but also to identify those HF patients at highest risk for readmission or mortality. Current management of patients with HF is mainly based on clinical signs and symptoms. This approach allows clinicians to respond to worsening HF once it is recognized, but does not allow selection of individuals who are most likely to progress to increased morbidity and mortality.

The B-type natriuretic peptide (BNP) and its cleavage equivalent NT-proBNP have proven to be powerful diagnostic and prognostic markers in both acute and chronic HF.[22,30-33] Natriuretic peptides may therefore be attractive biomarkers to guide management of HF and help select those patients in need of more aggressive therapy.

In 2000, a small pilot study was published suggesting that guiding HF management by aiming for a target NT-proBNP level may improve outcome[34]. In this study, the investigators aimed to achieve NT-proBNP levels of 200 pmol/l (1,700 pg/ml) or lower. Such a low target value is difficult to achieve in many patients with established HF. Several other randomized trials evaluated the clinical value of such low and absolute (NT-pro)BNP target levels in HF.[35-39] These studies failed to show an overall reduction in mortality. However, two of these studies demonstrated a significant improvement by natriuretic peptide-guided therapy in patients aged 75 years or less.[35,36]

The low (NT-pro) BNP target level was achieved only in a minority of patients, ranging from 33% to less then 50%.[36,38] Although the target (NT-pro) BNP level was not achieved in the majority of patients randomized to (NT-pro)BNP-guided therapy, most of these patients received intensified treatment. These studies therefore show that a more generalized intensification of HF therapy might be beneficial in the specific subgroups. However, it was not addressed whether serial assessment of NT-proBNP enables to select patients at risk for increased morbidity and mortality. It is well known that in many HF patients, NT-proBNP levels never normalize, whereas these patients still remain clinically stable over years. This suggests that introducing a patient's individualized target level may allow selection of those HF patients most likely to progress towards events. Such an individual target level could be defined as the lowest level at hospital discharge or at 2 weeks follow-up after admission because of acute HF. However, the prognostic value of such an individualized target value has not yet been assessed. Furthermore, it is unclear whether knowledge of such an individual target level can reduce morbidity and mortality in HF patients.

Guided therapy of heart failure: applicable to all patients?

As mentioned before, the two trials demonstrating a mortality reduction by natriuretic peptide-guided treatment did so only in patients at the age of 75 or less.[35,36] Therefore, it seems that not every patient profits from natriuretic peptide-guided treatment of HF. Question remains if older age itself is a limiting factor, or that age associated comorbidities like renal failure, hypertension and COPD cause natriuretic peptide-guided therapy to fail. Furthermore, etiology of heart failure differs between younger and older patients with HF: in elderly patients, HF with preserved ejection fraction (HFpEF) is more common.[40] HFpEF has a different etiologic background compared with HF with reduced ejection fraction (HFrEF).[41]

As no treatment for HFpEF has proven to affect morbidity and mortality, treatment is limited to the treatment of underlying diseases like hypertension, diabetes and atrial fibrillation.[1]

Since most patients included in the large randomized therapeutic trials which underpin treatment guidelines were not truly elderly, had few comorbidities and had HFrEF, the findings from these trials might be less applicable to the majority of elderly patients seen in clinical practice.[42] Therefore, a clear-cut treatment algorithm of HF is lacking in elderly.

Knowledge of factors associated with successful natriuretic peptide-guided therapy might help selecting those patients that profit the most from natriuretic peptide-guided treatment.

Guided therapy of heart failure: The importance of serial NT-proBNP measurements during and early after admission because of acute heart failure.
Cornerstone of natriuretic peptide-guided therapy of HF is the identification of those patients at highest risk for events. As mentioned before, especially in patients discharged after admission because of acute HF, risk for events is high. Therefore, post-discharge risk stratification is important as it may help to identify those patients in need for intensive outpatient monitoring and (natriuretic peptide-guided) treatment. Natriuretic peptides might be helpful in this regard. In acute HF, both pre-discharge (NT-pro)BNP concentration and decrease in NT-proBNP during hospital admission are related to outcome after hospital discharge.[43,44] Also in chronic HF, not only one single measurement of natriuretic peptides reflects risk, but variation in natriuretic peptides adds to prognostic assessment as well.[45]

However the prognostic value of change in NT-proBNP concentration one month after admission because of acute HF has not yet been evaluated. Furthermore, the incremental prognostic value of serial NT-proBNP measurements during admission and at early after hospital discharge has not yet been assessed. Knowledge of this incremental value might not only lead to a more accurate early outpatient risk assessment; it also gives clinicians a clue how to interpret early outpatient NT-proBNP levels: should we mainly focus on the absolute level, or should we take into account whether levels are decreasing or increasing?

Guided therapy of heart failure: Cardio-renal dilemma

HF and renal dysfunction often coincide,[46,47] and the presence of renal dysfunction in HF is associated with worse outcome.[48] In HF patients, worsening renal function over time has been associated with worse outcome,[49] although reports are conflicting. Worsening renal function can be caused by ominous processes that are related to progression of HF like forward failure, venous congestion and activation of RAAS-system.[50] On the contrary, worsening of renal function can also be caused by factors that are associated with favorable outcome like titration of evidence based HF medication like ACE-inhibitors, AT-2 antagonists and aldosterone receptor blockers.[51-55] Therefore interpretation of change in renal function in HF patients is a challenging task.

Natriuretic peptides have shown to react upon HF treatment; NT-proBNP levels decrease after titration of evidence based HF medication.[56-58] Furthermore, outpatient change in NT-proBNP has been related to outcome.[45]

In the setting of treating HF, clinicians may encounter conflicting prognostic information when evaluating changes in renal function and natriuretic peptides over time if they go in opposite directions. Thus, it is unclear if worsening renal function should get more attention than lowering (NT-pro)BNP levels and vice versa. This may be of particular importance early after hospital discharge when changes in medication are very common and risk for readmission or mortality is highest. Knowledge of both change in renal function and natriuretic peptide concentration may therefore help revealing part of the cardio-renal dilemma.

1.4 Outline of this thesis.

This thesis describes the potential use of biomarkers to manage patients with HF. Particular focus is placed on the role of NT-proBNP, which is the best-studied biomarker in such patients. Several new aspects are addressed to increase the utility and the clinical usefulness of biomarkers that help to not only better classify patients at risk, but also to guide further intervention in this fragile patient group. In order to achieve this aim, it was important to investigate which patients may benefit most and in what way comorbidities are influencing the response to therapy. One of the most important comorbidities in HF patients is renal dysfunction, which often limits the appropriate use of treatment in HF patients. Thus, additional focus is place on the importance of renal dysfunction as compared to severity of HF on the treatment response.

The prognostic value of a multi-marker strategy for the risk-assessment in dyspneic patients presenting to the emergency department using a panel of biomarkers with a wide pathophysiological background is investigated in **chapter 2**.

Chapter 3 describes the main results of the PRIMA study. This multicenter trial assesses the prognostic effect of natriuretic peptide-guided therapy in chronic HF according to an individually set NT-proBNP level. In **chapter 4** insight is given which patients might benefit the most from natriuretic peptide-guided therapy and if comorbidities influence the response to natriuretic peptide-guided therapy. **Chapter 5** investigates the prognostic importance of serial NT-proBNP measurements during and shortly after admission because of acute HF. **Chapter 6** assesses the prognostic value of change in renal function in addition to change in NT-proBNP early after hospital discharge for acute HF.

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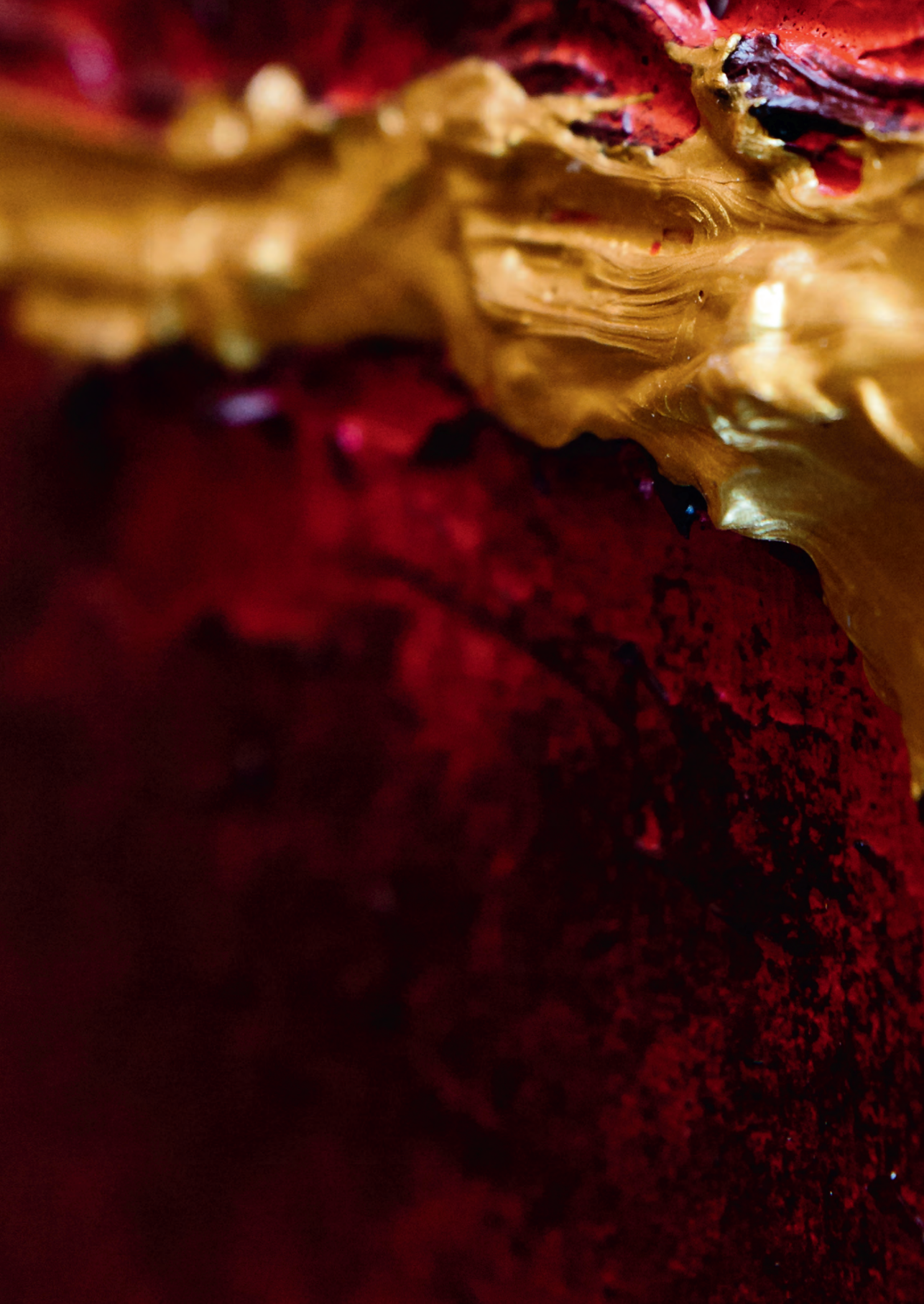

CHAPTER 2

Multimarker strategy for short-term risk assessment in patients with dyspnea in the emergency department

The MARKED (Multi mARKer Emergency Dyspnea)-risk score

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ABSTRACT

Objectives: The study aim was to determine the prognostic value of a multi-marker strategy for risk-assessment in patients presenting to the emergency department (ED) with dyspnea.

Background: Combining biomarkers with different pathophysiological backgrounds may improve risk stratification in dyspneic patients in the ED.

Methods: The study prospectively investigated the prognostic value of the biomarkers N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), Cystatin-C (Cys-C), high-sensitivity C-reactive protein (hs-CRP), and Galectin-3 (Gal-3) for 90-day mortality in 603 patients presenting to the ED with dyspnea as primary complaint.

Results: hs-CRP, hs-cTnT, Cyst-C and NT-proBNP were independent predictors of 90-day mortality. The number of elevated biomarkers was highly associated with outcome (odds ratio=2.94 per biomarker, 95% confidence interval [CI] 2.29-3.78, P<0.001). A multimarker approach had incremental value beyond a single-marker approach. Our multimarker emergency dyspnea-risk score (MARKED-risk score) incorporating age ≥75 years, systolic blood pressure<110 mmHg, history of heart failure, dyspnea New York Heart Association (NYHA) functional class IV, hs-cTnT ≥0.04 µg/L, hs-CRP ≥25 mg/L and Cys-C ≥1.125 mg/L had excellent prognostic performance (area under the curve: 0.85, 95% CI 0.81-0.89), was robust in internal validation analyses and could identify patients with very low (< 3 points), intermediate (≥3, <5 points) and high risk (≥5 points) of 90-day mortality (2%, 14% and 44%, respectively, P<0.001).

Conclusions: A multimarker strategy provided superior risk stratification beyond any single-marker approach. The MARKED-risk score that incorporates hs-cTnT, hs-CRP and Cys-C along with clinical risk factors accurately identifies patients with very low, intermediate and high risk.

INTRODUCTION

Acute onset or progressive increase in dyspnea can indicate both harmless as well as highly lethal conditions[1, 2]. Therefore, accurate risk assessment is important in this patient group. Especially short-term risk stratification can help to triage which patients require particular and immediate attention. Whereas risk scores are widely used in other acute settings such as acute coronary syndrome[3, 4] and acute pulmonary embolism[5], a risk score for short-term risk assessment in acute or recent onset dyspnea is not yet established. A risk score for long-term mortality in acute dyspnea has been developed [6] that takes into account N-terminal pro-B-type natriuretic peptide (NT-proBNP): one of the most studied and clinically implemented biomarkers in acute dyspnea [7]. However, many more biomarkers have emerged over the last years and they are suggested to provide additional or superior prognostic information in patients with dyspnea and acute heart failure [8-13]. Moreover, a single biomarker may not be sufficient to provide adequate risk assessment[14]. Most studies thus far have looked into acute heart failure alone rather than acute or recent-onset dyspnea[10-12, 15] and studies that have assessed the prognostic value of multiple biomarkers in acute dyspnea have compared biomarkers rather than examining the impact of combining them[8, 9]. We hypothesize that prediction of risk in patients with dyspnea at the emergency department (ED) could be improved by combining multiple biomarkers[1, 2]. We studied NT-proBNP, high-sensitivity cardiac troponinT (hs-cTnT), Cystatin-C (Cys-C), high-sensitivity C-reactive protein (hs-CRP), and Galectin-3 (Gal-3) because these are established biomarkers with different pathophysiological backgrounds (i.e. myocyte stretch, myocardial damage, renal function, inflammation and fibrosis, respectively) and investigated the value of a multimarker strategy for risk assessment in dyspnea at the ED.

METHODS

Study population and design

Between June 2007 and October 2009, patients who presented to the cardiology ED of the Maastricht University Medical Center with dyspnea – either at rest or during physical activity - were consecutively enrolled in this prospective study. Patients were eligible if they were ≥18 years old and dyspnea was their main complaint. Patients referred for therapeutic treatment or patients that required immediate therapeutic action (e.g percutaneous coronary intervention or electrical or chemical cardioversion) and patients with dyspnea resulting from chest trauma were excluded. Also, not all physicians in our department participated in the trial and patients that were seen by nonparticipating physicians were not included. All patient characteristics were based on clinical chart review. Left ventricular ejection fraction (LVEF) was obtained from echocardiography when available within a range of 1 year before presentation to 1 month after presentation. Presence of coronary artery disease was defined as having a history of coronary artery bypass grafting, percutaneous coronary intervention, acute myocardial infarction or obstructive coronary artery disease on coronary angiography or CT angiography. Patients were followed for 1 year. Follow-up data was obtained via chart review and, if necessary, from the general practitioner or by enquiry of the municipal register. Primary outcome measure was 90-day all-cause mortality. Secondary outcome measures encompassed 90-day cardiovascular mortality as well as in-hospital, 30 day and 1 year all-cause and cardiovascular mortality. All investigational procedures involved in this study have been approved by the institutional review board (Medical Ethical Committee MUMC) and comply with the Declaration of Helsinki.

Biochemical analysis

Blood samples were obtained on patient arrival at the ED. Measurements of several laboratory parameters, e.g NT-proBNP, conventional cTnT, blood urea nitrogen (BUN), haemoglobin and creatinine were performed immediately after blood collection. Excess of collected serum sample was frozen and aliquots were stored at -80°C until analyzed. Hs-cTnT, hs-CRP, Cys-C and Gal-3 concentrations were measured in 2010 (1 freeze-thaw cycle). Detailed information about the assays and their performance characteristics is provided in appendix 1.[10, 16-20]

Statistical analysis

Data are presented as frequencies, mean±SD or median (interquartile range, IQR). Comparisons between groups were performed using chi-square for categorical data and 1- way analysis of variance or Kruskal-Wallis H test for continuous data, as appropriate. Receiver operating characteristic (ROC) curve analysis was used to assess prognostic accuracy of biomarkers and to determine optimum cut-off points (i.e. maximizing both sensitivity and 1-specificity) of continuous variables for predicting 90-day mortality. Cut off points were rounded off to make them clinically meaningful. Spearman's rank correlations were used to test correlations between biomarkers.

Logistic regression analysis was performed to test the association between biomarkers and 90-day mortality. Multivariable analysis was performed for clustered variables (i.e. for clinical covariates) and laboratory findings separately. We included variables that were univariably associated with 90-day mortality (stepwise with $P<0.1$ as the cut off for entry). Thus, in a first step, a final clinical model and a separate final biomarker panel were established from multivariable analysis. In a second step, the final biomarker panel was added in a stepwise fashion to the final clinical model, which resulted in the final prediction model. We checked for collinearity and interactions among covariates and found none of significance. Model accuracy, calibration and discrimination were evaluated as recently suggested [21] by (i) *c*-statistic, a measure of the area under the curve (AUC), (ii) the Hosmer-Lemeshow statistic, (iii) integrated discrimination improvement (IDI), and (iv) net reclassification index (NRI). Risk categories of <2%, 2-15% and >15% were used for calculation of the NRI [22].

Independent predictive variables in the final prediction model formed the basis for our risk score. When simplifying the score, a loss in AUC of ≥1% was not accepted. The risk score was internally validated by cross-validation (90% of original sample, 10 replications) and by non-parametric bootstrapping (1,000 resamples using random sampling with replacement), as proposed [23].

The PRIDE (ProBNP Investigation of Dyspnea in the ED) mortality score was calculated as proposed [6]. The additional predictive value of the final biomarker panel on top of the PRIDE mortality score [6] was investigated for both 90-day and 1-year mortality in a multivariable logistic regression model and tested by C-statistic, NRI and IDI.

Table 1. Baseline characteristics

	Overall		No marker elevated		1 marker elevated	
	Value	N	Value	N	Value	N
Age, years	75± 12	603	69± 14	148	74± 12	156
Sex, male	334 (55.4%)	603	80 (54.1%)	148	78 (50.0%)	156
Heart Failure	210 (34.8%)	603	39 (26.4%)	148	45 (28.8%)	156
-Ischemic	138 (65.7%)	210	21 (53.8%)	39	35 (77.8%)	45
CAD	280 (46.4%)	603	64 (43.2%)	148	76 (48.7%)	156
Diabetes mellitus	171 (29.2%)	585	31 (21.2%)	146	46 (30.3%)	152
Atrial Fibrillation	187 (31.1%)	601	41 (27.7%)	148	44 (28.2%)	156
COPD	133 (22.2%)	600	29 (19.7%)	147	36 (23.2%)	155
Hypertension	345 (70.4%)	490	79 (67.5%)	117	94 (74.0%)	127
LVEF (%)	45 (28 - 59)	351	50 (35-60)	86	45 (30-60)	91
Dyspnea at rest	230 (38.1%)	603	47 (31.8%)	148	58 (37.2%)	156
Systolic BP, (mmHg)	137± 28.9	573	145± 27.3	141	140±28.5	146
Diastolic BP, (mmHg)	74.7 ±17.4	573	80.5± 17.2	141	75.5±18.0	146
Heart rate (bpm)	91.6± 28.3	600	88.6± 25.6	146	89.6± 27.0	156
QRS-duration	108± 31.3	539	103± 28.2	131	106± 30.1	146
Hemoglobin, (g/dl)	12.7± 2.1	598	13.7± 1.8	145	12.9±2.1	155
Creatinine, (mg/dl)	1.3 (1,0 – 1.7)	603	1.0 (0.9 - 1.1)	148	1.2 (1.0 – 1.4)	156
Blood Urea Nitrogen (mg/dl)	22.4 (17.1 – 35,3)	602	17.1 (13.2 – 21.0)	148	20.4 (17.1 – 28.0)	156
hs-CRP, (mg/L)	13.0 (3.9 - 35.3)	603	3.8 (1.7 - 8.2)	148	9.2 (3.4 - 24.4)	156
hsTNT, (µg/L)	0.031 (0.016 - 0.058)	603	0.014 (0.007 - 0.021)	148	0.023 (0.013 - 0.034)	156
Cystatin-C (µg/L)	1.14 (0.89 - 1.63)	603	0.85 (0.74 - 0.98)	148	1.09 (0.85 - 1.40)	156
NT-proBNP (pg/ml)	3,110 (907 - 8,390)	603	826 (180 - 2,091)	148	1555 (712 - 3,547)	156
Galectin-3, (µg/L)	23 (17 - 32)	603	17 (14 - 20)	148	21 (17 - 27)	156
Diuretics	356 (59.9%)	594	64 (43.8%)	146	90 (58.8%)	153
ACEi/ARB	337 (56.7%)	594	82 (56.2%)	146	93 (60.8%)	153
Beta-blockers	330 (55.6%)	594	79(54.1%)	146	84 (54.9%)	153
Aldosterone antagonists	48 (8.1%)	594	8 (5.5%)	146	12 (7.8%)	153
OAC	222 (37.4%)	594	48 (32.9%)	146	56 (36.6%)	153
Digitalis	77 (13.0%)	594	13 (8.9%)	146	19 (12.4%)	153
Final diagnosis						
ADHF	342 (56.7%)	603	50 (33.8%)	148	74 (47.4%)	156
ACS	46 (7.6%)	603	14 (9.5%)	148	15 (9.6%)	156
IPD	30 (5.0%)	603	9 (6.1%)	148	11 (7.1%)	156
Rhythm/conduction	45 (7.5%)	603	10 (6.8%)	148	12 (7.7%)	156
Other	50 (8.3%)	603	14 (9.5%)	148	19 (12.2%)	156
No pathology	90 (14.9%)	603	51 (34.5%)	148	25 (16.0%)	156

2 markers elevated		3 markers elevated		4 markers elevated		P-value
Value	N	Value	N	Value	N	
78± 9	125	78± 12	119	81± 7	55	<0.001
67 (53.6%)	125	74 (62.2%)	119	35 (63.6%)	55	0.211
45 (36.0%)	125	49 (41.2%)	119	32 (58.2%)	55	<0.001
27 (60.0%)	45	34 (69.4%)	49	21 (65.6%)	32	0.178
49 (39.2%)	125	61 (51.3%)	119	30 (54.5%)	55	0.189
38 (31.4%)	121	39 (34.5%)	113	17 (32.1%)	53	0.159
37 (29.8%)	124	45 (38.1%)	118	20 (36.4%)	55	0.294
25 (20.0%)	125	34 (28.6%)	119	9 (16.7%)	54	0.317
74 (74.7%)	99	65 (64.4%)	101	33 (71.7%)	46	0.410
45 (25-58)	67	35 (25-50)	74	40 (26-48)	33	0.001
42 (33.6%)	125	57 (47.9%)	119	26 (47.3%)	55	0.033
137±28.0	119	134±30.0	117	124±29.3	50	<0.001
73.1± 17.1	119	71.3±15.6	117	68.3± 17.1	50	<0.001
93.7± 31.5	125	93.5± 28.9	119	96.6± 29.2	54	0.925
111± 35.9	107	112± 30.6	109	116± 31.0	46	0.030
12.2±1.9	125	12.1± 2.1	118	11.9± 1.9	55	<0.001
1.3 (1.1 – 1.7)	125	1.7 (1.2 – 2.4)	119	2.0 (1.5 – 2.8)	55	<0.001
25.2 (18.8 – 35,0)	124	33.3 (21.6 – 51.8)	119	45.1 (34.5 – 67.5)	55	<0.001
16.8 (5.4 - 40.9)	125	24.6 (8.3 - 66.4)	119	72.5 (37.7 - 137.0)	55	<0.001
0.036 (0.024 - 0.062)	125	0.063 (0.044 - 0.109)	119	0.096 (0.057 - 0.23)	55	<0.001
1.24 (1.07 - 1.67)	125	1.62 (1.20 - 2.34)	119	1.79 (1.47 - 2.57)	55	<0.001
4,864 (2,127 - 8,352)	125	9,347 (4,924 - 15,907)	119	17,601 (9,805 - 25,085)	55	<0.001
24 (19 - 32)	125	30 (24 - 39)	119	36 (30 - 54)	55	<0.001
78 (63.9%)	122	84 (71.2%)	118	40 (72.7%)	55	<0.001
68 (55.7%)	122	67 (56.8%)	118	27 (49.1%)	55	0.663
64 (52.5%)	122	67 (56.8%)	118	36 (65.5%)	55	0.578
13 (10.7%)	122	8 (6.8%)	118	7 (12.7%)	55	0.367
42 (34.4%)	122	53 (44.9%)	118	23 (41.8%)	55	0.279
12 (9.8%)	122	23 (19.5%)	118	10 (18.2%)	55	0.061
81 (64.8%)	125	94 (79.0%)	119	43 (78.2%)	55	<0.001
11 (8.8%)	125	0 (0%)	119	6 (10.9%)	55	0.014
4 (3.2%)	125	5 (4.2%)	119	1 (1.8%)	55	0.413
9 (7.2%)	125	11 (9.2%)	119	3 (5.5%)	55	0.910
10 (8.0%)	125	6 (5.0%)	119	1 (1.8%)	55	0.089
10 (8.0%)	125	3 (2.5%)	119	1 (1.8%)	55	<0.001

Footnote table 1: Values represent mean ± SD, frequency (%), or median (interquartile range). ACEi = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ADHF = acute decompensated heart failure; ARB = angiotensin II receptor blocker; BP = blood pressure; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease;
hs-CRP = high-sensitivity C-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; OAC = oral anticoagulation; PD = pulmonary diseas.

Kaplan-Meier curve plots were estimated and compared by the log-rank test. For time-dependent analysis, data was censored at the time of last contact. Tests were two-sided with a level of significance of $P<0.05$. Calculations were done using SPSS 16.0 (SPSS inc, Chicago, Illinois, USA) and Sigmaplot 12.0 (Systat Software Inc, Chicago, Illinois, USA).

RESULTS

Baseline characteristics.

Between June 2007 and October 2009, 1,477 patients presented with dyspnea to the ED. One hundred and four patients (7%) were excluded because dyspnea was not their main complaint and 106 (7%) patients were excluded because they required immediate therapeutic action. Of the remaining 1,267 eligible patients, 523 (41%) were admitted during working hours of non participating physicians. In 141 (11%) patients at least one baseline biomarker concentration was missing. Baseline characteristics of the final study population of 603 patients are depicted in table 1. Patients were elderly, with a median age of 75 years, 55% were male, more than one-third had a history of heart failure (HF), and almost one-half had a history of coronary artery disease. A large proportion had cardiovascular risk factors such as hypertension (70%), and diabetes mellitus (29%). Almost 40% had dyspnea at rest at presentation. Final diagnosis at the ED was most commonly acute decompensated heart failure (ADHF, i.e. 57%). A non cardiac diagnosis was made in 28% of the patients and in 15% of patients, no pathology was found.

Eligible patients that were not included (n=664) were younger (72 versus 75 years, P <0.001) compared with included patients, but no difference in gender or final diagnosis was observed. Importantly, patients that were not included due to missing biomarkers (n=141) did not differ regarding age, gender or final diagnosis compared with patients included.

Prediction of outcome

More than half of the patients (n=347, 58%) were admitted to the hospital subsequent to their presentation on the ED. Ninety day follow-up was completed in all patients. After 90 days, 78 patients (13%) had died, 58 (74%) from cardiovascular causes. At a median follow-up of 365 days (IQR 266-365), 145 patients (24%) had died, 100 (69%) from cardiovascular causes.

All biomarkers were highly associated with 90-day mortality (table 2) and had comparable AUCs for the prediction of 90-day mortality, ranging from 0.73 to 0.75 (P>0.5 for all comparisons, table 3). Cut off values determined from ROC-curve analyses were 4,500 pg/ml for NT-proBNP, 0.04 µg/L for hs-cTnT, 1.125 mg/L for Cys-C, 25 mg/L for hs-CRP and 25 µg/L for Gal-3. Biomarkers were significantly correlated, with the strongest correlation being present between Cys-C and Gal-3 (r=0.70, P<0.001) followed by NT-proBNP and hs-cTnT (r=0.55, P<0.001, appendix 2).

In categorical multivariable analysis including all laboratory findings, NT-proBNP, hs-cTnT, hs-CRP and Cys-C remained independently associated with 90-day mortality (table 2) and thus formed the final biomarker panel. The combination of these 4 biomarkers (i.e hs-cTnT, hs-CRP, Cys-C and NT-proBNP) reached a high predictive accuracy with an AUC for 90-day mortality of 0.83 (95% confidence interval [CI]: 0.78-0.87) and the number of biomarkers elevated (i.e. none, 1, 2, 3 or 4) was strongly associated with increased risk of 90-day mortality (odds ratio [OR]: 2.94 per elevated biomarker, 95% CI 2.29-3.78, Wald 71.0, P<0.001) with 90-day mortality rates of 0.7%, 4.5%, 10.4%, 25.2% and 49.1%, respectively (P<0.001). The gradual increase in 90-day mortality rate with increasing number of biomarkers elevated was retained in subgroup analyses of patients with versus without acute decompensated heart failure (ADHF) and renal dysfunction (figure 1.). Each specific combination of either 2 or 3 biomarkers (e.g NT-proBNP + hs-cTnT versus hs-CR + Gal-3) had similar 90-day mortality rates (P>0.1 for all comparisons). The 1-year mortality rate also showed a significant increment with increasing number of biomarkers elevated (6.8%, 11.5%, 23.2%, 45.5%, and 61.8%, P<0.001) which is shown in figure 2A.

Following from categorical multivariable analysis on clinical risk factors, age, gender, HF history, dyspnea New York Heart Association functional class and systolic blood pressure formed the final clinical model (table 2). When correcting the final biomarker panel for the final clinical model, hs-cTnT, hs-CRP and Cys-C remained independent prognostic biomarkers whereas NT-proBNP was dropped (table 2). The final prognostic model therefore consisted of the final clinical model

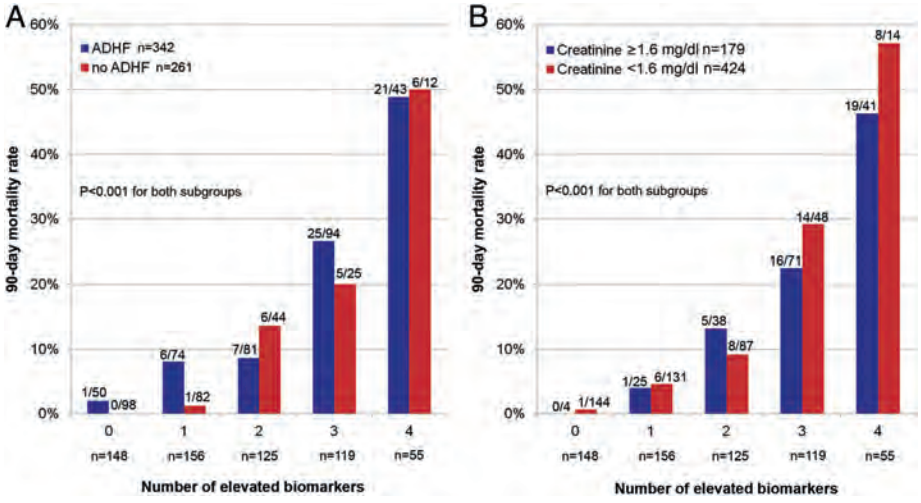
Table 2: Association of clinical characteristics and biomarkers with 90-day mortality

	Univariable Analysis				Multivariable Clustered Analysis (Clinical/Laboratory)				Multivariable Analysis Combining Clinical and Laboratory			
	Wald Test	OR	95% CI	p Value	Wald	OR	95% CI	p Value	Wald	OR	95% CI	p Value
Clinical variables												
Demographics												
Age ≥75 yrs	17.7	3.78	2.03–7.03	<0.001*	17.3	4.01	2.08–7.71	<0.001†	5.3	2.32	1.14–4.75	0.02
Male	5.6	1.84	1.11–3.05	0.02*	4.9	1.86	1.08–3.19	0.03†	1.69	1.48	0.82–2.65	0.19
Medical history												
History of heart failure	19.0	2.98	1.83–4.84	<0.001*	11.5	2.43	1.45–4.07	0.001†	9.8	2.48	1.40–4.37	0.002
Ischemic etiology of heart failure.	15.8	2.75	1.67–4.53	<0.001*	—	—	—	—	—	—	—	—
CAD	6.7	1.90	1.17–3.09	0.009*	—	—	—	—	—	—	—	—
Diabetes mellitus	0.09	0.92	0.54–1.57	0.76	—	—	—	—	—	—	—	—
Atrial fibrillation	4.1	1.66	1.02–2.71	0.04*	—	—	—	—	—	—	—	—
COPD	1.2	1.36	0.79–2.34	0.27	—	—	—	—	—	—	—	—
Hypertension	1.9	0.72	0.44–1.15	0.17	—	—	—	—	—	—	—	—
Signs and symptoms at presentation												
Dyspnea NYHA functional class IV	10.6	2.22	1.37–3.59	0.001*	9.5	2.27	1.35–3.83	0.02†	8.8	2.37	1.34–4.19	0.003
Systolic BP, <110 mm Hg	22.8	3.80	2.20–6.57	<0.001*	20.0	3.92	2.16–7.11	<0.001†	9.4	2.76	1.44–5.27	0.002
Heart rate, ≥100 beats/min	1.8	1.40	0.86–2.29	0.18	—	—	—	—	—	—	—	—
QRS duration ≥100 ms	3.9	1.62	1.01–2.61	0.05*	—	—	—	—	—	—	—	—
Laboratory findings												
Hemoglobin <12 g/dl	14.1	2.52	1.56–4.08	<0.001*	—	—	—	—	—	—	—	—
Creatinine ≥1.4 mg/dl	20.1	3.07	1.88–5.01	<0.001*	—	—	—	—	—	—	—	—
Blood urea nitrogen ≥28 mg/dl	34.2	4.52	2.73–7.50	<0.001*	—	—	—	—	—	—	—	—
NT-proBNP ≥4500 pg/ml	32.2	4.56	2.70–7.71	<0.001*	6.2	2.10	1.17–3.77	0.01‡	—	—	—	—
hs-cTnT ≥0.04 µg/l	41.9	5.95	3.47–10.21	<0.001*	11.9	2.85	1.57–5.17	0.001‡	11.5	2.84	1.55–5.18	0.001
hs-CRP ≥25 mg/l	39.9	5.14	3.10–8.55	<0.001*	24.1	3.88	2.26–6.66	<0.001‡	21.3	3.88	2.18–6.89	<0.001
Cystatin-C ≥1.125 mg/l	30.4	5.71	3.08–10.62	<0.001*	13.7	3.51	1.80–6.82	<0.001‡	7.0	2.58	1.28–5.29	0.008
Galectin-3 ≥25 µg/l	37.8	5.57	3.22–9.62	<0.001*	—	—	—	—	—	—	—	—

*Variables entered into multivariable analysis (cutoff for entry p < 0.1). †Variables that remained significant in multivariable analysis including clinical risk factors (final clinical model). ‡Variables that remained significant in multivariable analysis including laboratory findings and were added stepwise to the final clinical model.
CI =confidence interval; NYHA = New York Heart Association functional class; OR = odds ratio. Other abbreviations as in Table 1.

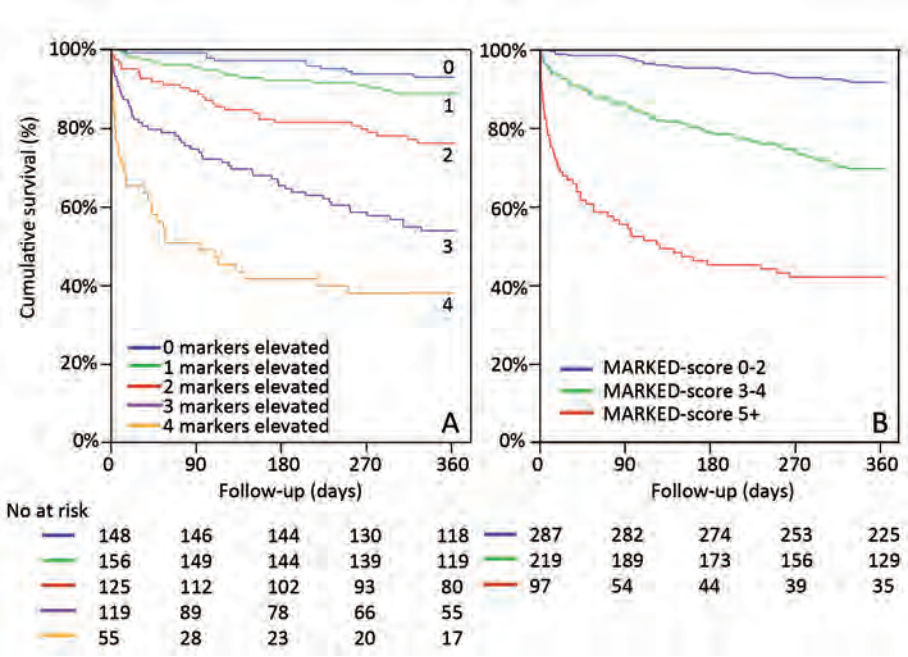
plus hs-cTnT, hs-CRP, and Cys-C and reached a C-statistic of 0.86 (0.82-0.90) with excellent calibration (Hosmer-Lemeshow p=0.78) (table 4) and significantly better model perforance than single-marker models (NRI 13%, p=0.008 and IDI 5%, p<0.001 compared with the model with clinical risk factors and hs-CRP alone, p<0.001). Exclusion of patients with clinical signs of infection did not alter results (data not shown).

Figure 1. 90-day mortality rate by number of elevated biomarkers divided by (A) cause of dyspnea and (B) renal dysfunction.



ADHF=acute decompensated heart failure; Creat=creatinine. Cut-off for low/high creatinine was 1.6 mg/dl. Patient numbers per subgroup: ADHF n= 342, no ADHF n= 261, creat low n= 179, creat high n= 424. P-value for mortality rate by number of biomarkers elevated was <0.001 for all subgroups.

Figure 2: Kaplan-Meier curve for all-cause mortality by (A) number of elevated biomarkers and (B) MARKED-risk score categories.



Multi marker Emergency Dyspnea risk score.

Resulting from the final prognostic model for 90-day mortality, a risk score was established. Simplifying the risk score by giving each factor the same weight (1 point) and by excluding the weakest factor (i.e. gender) did not change performance of the score. Excluding any of the other variables did reduce the AUC by ≥1%. Final variables in the Multi mARKer Emergency Dyspnea-score (MARKED-risk score) therefore consisted of: age ≥75, history of HF, dypnea at rest, systolic blood pressure <110 mmHg, hs-CRP ≥25 mg/L, hs-cTNT ≥0.04 µg/L, and Cys-C ≥1.125 mg/L. The score showed excellent discrimination (AUC 0.85, 95% CI 0.81-0.89) and predicted mortality risk closely resembled observed mortality risk (appendix 3). Internal validation by means of cross-validation (mean AUC 0.85, 95% CI 0.81-0.89) and bootstrapping (AUC 0.85, 95% CI 0.81-0.89) showed that the score's performance was robust. Ninety-day mortality rates gradually increased per MARKED-score point (figure 3).

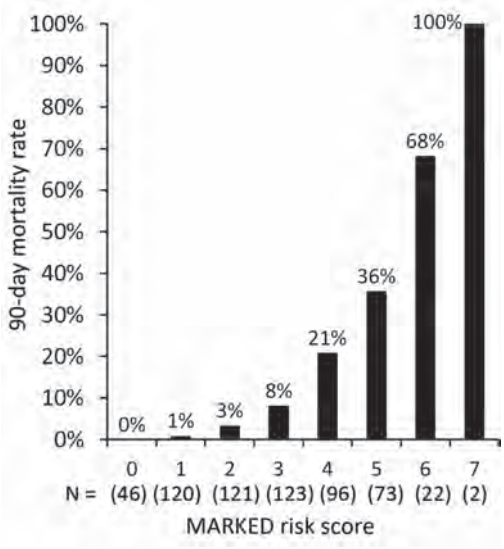
The score was categorized into low (0-2 points), intermediate (3-4 points) and high risk categories (≥5 points). Figure 2B shows the Kaplan-Meier curve for all-

cause mortality by MARKED-risk score category and table 5 depicts secondary endpoint-rates per MARKED-risk score category. The mortality risk of non-admitted versus admitted patients was similar within each risk score category (low: 1% vs 2%, P=0.66, intermediate: 11% vs 15%, P=0.30, high: 39% vs 46%, P=0.64). In addition, 9% of the patients that were discharged from the ED were in the high-risk category and 39% of these patients died within 90 days, underscoring the clinical prognostic uncertainty and the potential importance of the MARKED-risk score in this setting.

Added value of biomarkers on top of PRIDE mortality score

We evaluated the incremental value of the biomarkers Cys-C, hs-cTNT and hs-CRP with the PRIDE mortality score,[6] which includes clinical risk factors and NT-proBNP. For 90-day mortality, the combination of the three biomarkers significantly improved the PRIDE mortality score as depicted by an increase in C-statistic from 0.75 (95% CI 0.69–0.80) to 0.85 (95% CI 0.81 – 0.89, P<0.001), a NRI of 33% (P<0.001) and an IDI of 14% (P<0.001). For 1-year mortality, the C-statistic of the PRIDE mortality score was 0.72 (95% CI 0.68 – 0.77), which improved to 0.79 (95% CI 0.74 – 0.83, P<0.001) by addition of hs-cTnT, hs-CRP and Cys-C.

Figure 3. 90-day mortality rate for MARKED-risk score



N=number of patients per group.

Table 3: Performance of biomarkers for prediction of 90-day mortality

Marker	AUC (95% CI)	P	Cut-off	Sensitivity	Specificity	PPV	NPV
NT-proBNP	0.73 (0.67-0.78)	<0.001	4500 pg/ml	72%	64%	23%	94%
Hs-cTnT	0.74 (0.69-0.80)	<0.001	0.04 µg/L	74%	67%	25%	95%
Hs-CRP	0.73 (0.68-0.79)	<0.001	25 mg/L	67%	72%	26%	94%
Galectin-3	0.75 (0.69-0.81)	<0.001	25 µg/L	76%	64%	24%	95%
Cystatin-C	0.73 (0.68-0.78)	<0.001	1.125 mg/L	83%	53%	21%	96%

AUC=area under curve from receiver operating curve analysis, PPV=positive predictive value; NPV=negative predictive value

Table 4: Performance of predictive models for 90-day mortality

Marker	Wald	OR (95% CI)	Chi-Square model	C-statistic AUC (95% CI)	NRI	IDI	Hos-Lem
Clinical risk factors[a]	-	-	72.3	0.78 (0.73-0.83)	-	-	0.60
+ NT-proBNP	16.1	3.14 (1.80-5.49)	89.4*	0.81 (0.76-0.86)	7%	4%*	0.23
+ HsTnT	25.3	4.33 (2.45-7.67)	100.3*	0.82 (0.78-0.87)#	18%$	6%*	0.50
+ Hs-CRP	29.9	4.69 (2.70-8.16)	104.3*	0.83 (0.78-0.88)$	21%*	7%*	0.57
+ Cystatin-C	13.3	3.44 (1.77-6.67)	87.7*	0.81 (0.77-0.86)#	10%#	2%$	0.29
+ Galectin-3	19.3	3.75 (2.08-6.78)	93.4*	0.82 (0.77-0.87)#	19%$	4%*	0.62
Clinical risk factors + 3 markers[b]	-	-	130.0*	0.86 (0.82-0.90)*	34%*	12%*	0.78

* P<0.001 for comparison with clinical risk model. $ P<0.01 for comparison with clinical risk model. # P<0.05 for comparison with clinical risk model.
a: final clinical model including age ≥75 years, sex, history of heart failure, dyspnea NYHA IV, systolic blood pressure <110. b: final prognostic model including final clinical model plus hs-cTnT, hs-CRP and cystatin-C. OR=odds ratio; AUC=area under curve; NRI = net reclassification index; IDI=integrated discrimination index; Hos-Lem=Hosmer Lemeshow statistic (a P-value close to 1 indicates excellent calibration)

Table 5: Event rates by MARKED-risk score categories

	MARKED score Low: 0-2 (n=287)	MARKED score Intermediate: 3-4 (n=219)	MARKED score high: 5+ (n=97)	P-value
Admission	127 (44%)	146 (67%)	74 (76%)	<0.001
In-hospital mortality	1 (0%)	11 (5%)	18 (19%)	<0.001
30-day mortality	4 (1%)	17 (8%)	32 (33%)	<0.001
30-day CV mortality	2 (1%)	14 (6%)	24 (25%)	<0.001
90-day mortality	5 (2%)	30 (14%)	43 (44%)	<0.001
90-day CV mortality	3 (1%)	22 (10%)	33 (34%)	<0.001
1-year mortality	24 (8%)	65 (30%)	56 (58%)	<0.001
1-year CV mortality	13 (5%)	47 (22%)	40 (41%)	<0.001

CV=cardiovascular

DISCUSSION

We investigated 5 biomarkers (hs-cTnT, hs-CRP, Gal-3, Cys-C and NT-proBNP) with a distinct pathophysiological background for short-term risk stratification in 603 patients with dyspnea presenting to the ED. Hs-cTnT, hs-CRP, Cys-C and NT-proBNP were independent predictors of 90-day all-cause mortality and risk increased substantially as more biomarkers were elevated above cutpoint. Moreover, we present a simple and straightforward score for short-term risk stratification based on biomarkers in combination with clinical risk factors. This MARKED-risk score is able to identify patients with very low, intermediate and excessive high risk for both short- and long-term mortality.

Because the evaluation of dyspneic patients in the ED is difficult and an accurate diagnosis cannot always be acquired promptly, a non-diagnosis-specific risk score is helpful in clinical practice. Especially for decision making in an acute setting, short-term risk assessment is important. Several biomarkers have been found useful for prognostification in the evaluation of dyspneic patients, but single biomarkers may not provide sufficient precision. Therefore, we hypothesized that a multi-marker approach could improve risk stratification in this setting of a heterogeneous patient population. Thus, we examined 5 established biomarkers, (i.e. hs-cTnT, hs-CRP, Cys-C, Gal-3 and NT-poBNP) for risk assessment in ED dyspnea.

Cardiac troponin T is elevated in various chronic[24-26] and acute[27-29] conditions such as heart failure, renal failure, pulmonary embolism and acute dyspnea and is undoubtedly associated with adverse outcome in these settings and even in the general population[30]. CRP, a marker of inflammation, is known to be elevated in both patients with acute[13, 31] and chronic [31, 32] heart failure. CRP elevations in heart failure are related to functional status and prognosis[32, 33]. It was previously already shown that CRP has additive prognostic value to other established biomarkers such as NT-proBNP, haemoglobin and BUN in patients presenting with dyspnea to the ED[34, 35]. Gal-3, a marker that is linked to fibrosis and inflammation, is involved in heart failure, cancer and renal disease and is predictive of all-cause mortality in the general population[36]. Although its diagnostic role in HF is of limited value [12], Gal-3 is a reasonable prognostic marker for short- to intermediate-term outcome in HF[12, 37], but less so for long-term risk prediction[38, 39]. Cystatin C, a marker for renal function which strongly reflects glomerular filtration rate[40], is a strong prognostic biomarker in acute HF independent of NT-proBNP [41] and troponin

T [10], even in patients with normal plasma creatinine[41]. Cystatin C concentrations are not only indicative of renal function, but may also be elevated in response to inflammation and underlying heart disease [42]. Natriuretic peptides (NP's), mainly b-type natriuretic peptide (BNP) and NT-proBNP, are markers that characterize cardiac wall stress and are established biomarkers for diagnosis and prognosis of acute HF[43] and for prognosis of other causes of dyspnea[27, 44-46]. Nonetheless, the prognostic value of NT-proBNP is very limited for short-term risk stratification[9, 14, 15]. Several other biomarkers have shown to be superior for short-term risk stratification in acute HF and ED dyspnea[13, 15].

We found that all investigated biomarkers were predictive of 90-day mortality and had incremental value on top of the clinical risk model (table 3). Gal-3, however, was dropped from the final biomarker panel. This can at least partially be explained by the existence of significant correlations between Gal-3 and other biomarkers[47]. In line with our findings, Gal-3 was not a significant predictor after the inclusion of other predictors in a study of ambulatory heart failure patients [38]. Also, hs-CRP and Cys-C partially cover the pathophysiological background of Gal-3 which may have caused the exclusion of Gal-3. Furthermore, the prognostic value of creatinine and BUN was attenuated in the presence of Cys-C, which was previously also reported[41]. Multi-marker assessment thus revealed 4 markers as independent predictors: hs-CRP, hs-cTnT, Cys-C and NT-proBNP. Importantly, the number of elevated markers was highly predictive for 90-day mortality independent of the specific combination of markers. This indicates that all 4 biomarkers in our study are truly additive to each other and confirms our hypothesis on the independent value of biomarkers from different pathophysiological pathways, which remained true in subgroup analyses of renal function and acute HF diagnosis. When further correcting the final biomarker panel for clinical risk factors, NT-proBNP was excluded from the final prediction model. Previous findings about the inferior predictive value of NT-proBNP for short-term risk prediction as discussed previously support the exclusion of NT-proBNP from our final predictive model, although correlation with other markers probably also plays a role here. The final prediction model and the MARKED-risk score thus included the biomarkers hs-CRP, hs-cTnT and Cys-C in addition to 5 clinical variables.

The MARKED-risk score is the first multimarker score assessing short-term prognosis in ED patients with dyspnea. So far, no experience existed in the combined use of hs-CRP, hs-cTnT and Cys-C with regard to short-term risk stratification in an

unselected population with dyspnea at the ED. One recent study combined BNP, cTnI and hs-CRP in acute heart failure patients and found a gradual increased risk of 31-day mortality with an increasing number of elevated biomarkers (4.3%, 10%, 20.9% and 53.5%, for 0, 1, 2 or 3 elevated biomarkers respectively)[13]. Other reports on combined biomarkers in acute HF or ED dyspnea have focused on long-term rather than short-term risk prediction[8, 11, 35] or have focused mainly on the additive value of one marker on top of NT-proBNP[9, 12]. Moreover, *early* differentiation of risk categories is lacking in most previous studies, whereas our MARKED-risk score provides accurate short-term as well as long-term stratification in distinct risk categories, which is crucial for clinical decision-making. The apparent clinical prognostic uncertainty in our cohort - reflected by the relative high admission rate in the low-risk category and relative high discharge rate in the high-risk category with similar mortality rates between admitted and discharged patients – supports the need for accurate risk stratification. Thus, although our study was not designed to assess any therapeutic consequence, objective stratification using the MARKED-risk score into very low, intermediate and high risk may help the treating physician at the ED to decide on urge of intervention, admission, and timing of re-evaluation. However, a clear-cut treatment advice cannot be given based on our score.

We have chosen to use dichotomized values rather than continuous variables to make the score useful for clinical practice. We acknowledge that using cut-points can result in loss of predictive power, but nonetheless our models and score had excellent prognostic accuracy, discrimination and calibration. Other risk scores that are incorporated in practice guidelines such as CHA_2DS_2–VASc, HAS-BLED, and TIMI[3, 48-50] consist of single cut-point variables as well. Furthermore, the predictive accuracy of our score is at least comparable - if not higher - to those of currently used risk scores in other fields (AUC MARKED 0.85, CHA_2DS_2–VASc, 0.61, HAS-BLED 0.72). Finally, we assessed the value of our multi marker approach on top of the PRIDE-mortality score and found that adding hs-CRP, hs-cTnT and Cys-C to the PRIDE score significantly improved the prognostic accuracy in terms of AUC for both 90-day and 1-year mortality. It should be noted that the PRIDE mortality score was actually developed for 1-year outcome whereas we focus on short-term outcome. Nevertheless, the AUC for 1-year mortality of the PRIDE mortality score in our cohort (0.72, 95% CI 0.68–0.77) was very comparable to the AUC in PRIDE's validation cohort (0.73, 95% CI 0.64-0.82), indicating that our cohort is representative for cohorts with dyspnea at the ED. Moreover, severity

of dyspnea indicated by New York Heart Association functional class in our cohort was comparable to previous cohorts, although the percentage of patients diagnosed with acute HF as well as the 90-day and 1-year mortality rates were somewhat higher in our cohort[6, 51, 52].

Limitations

First our study was performed in a single center ED. In addition, we did not externally validate the MARKED-risk score. However, results were robust in 2 internal validation analyses (cross-validation and bootstrapping) which are known to result in stable and nearly unbiased estimates of performance [23, 53] and our study is comparable to other dyspnea-cohorts as discussed. Second, the number of patients was of moderate size. Taking this together, it will be of interest to validate our findings in a separate, preferably larger cohort. Finally, our study is not able to directly assess the impact of the MARKED-risk score on the management of patients. Therefore, the therapeutic consequence of using the MARKED-risk score in clinical practice for stratifying patients with dyspnea needs prospective evaluation.

Conclusions

We present a simple, straightforward, non-diagnosis-specific multi marker score for short-term risk stratification in patients with dyspnea presenting to the ED, a population with large diagnostic and prognostic uncertainty. This multi-marker approach that incorporates hs-cTnT, hs-CRP and Cys-C along with clinical risk factors (age≥75 years, dyspnea at rest, history of heart failure, and systolic blood pressure <110mmHg) has incremental value beyond a single-marker approach. Moreover, the MARKED risk score is able to accurately identify patients with very low, intermediate and especially those with excessive high risk and may be useful in clinical practice.

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Appendix 1. Assay performance characteristics

Marker	LOD	Interassay CV	Reference value
NT-proBNP[a]	5.1 µg/L*	6.8% at 74.4 µg/L*	99%: males 265 µg/L, females 301 µg/L [16]
Hs-cTnT[b]	0.001 µg/L	3.0% at 0.021 µg/L, 1.4% at 3.03 µg/L	99%: 0.016 µg/L
Hs-CRP[c]	0.175 mg/L**	3.7% at 0.25, 1.0% at 45 mg/L**	95%: 8.4 mg/L [17]
Cystatin-C[d]	0.004 mg/L [20]	2.0% at 0.9 mg/L, 2.2% at 1.8 mg/L [10]	95%: 0.95 mg/L*
Galectin-3[e]	1.13 µg/L [19]	10% at 6 µg/L, 7% at 21 µg/L, 15% at 70 µg/L [19]	95%: 20.3 µg/L [19]

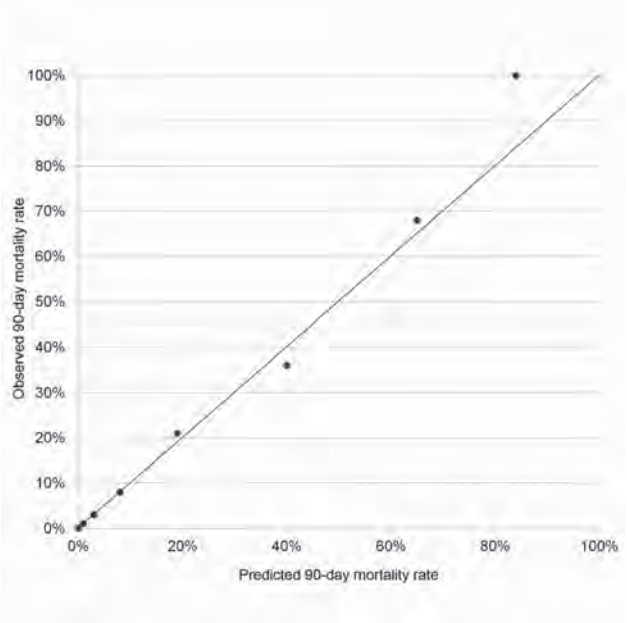
a: measured by the electrochemiluminescence immunoassay using an Elecsys 2010 analyser (Roche Diagnostics GmbH, Mannheim, Germany). b: measured by precommercial highly sensitive fifth generation cTnT assay (hs-cTnT) using an the Elecsys 2010 analyser (Roche Diagnostics GmbH, Mannheim,Germany). c: measured by the CardioPhase hs-CRP assay on the BN ProSpec (Siemens Healthcare Diagnostics Inc. New York, United States) d: measured by the N Latex Cystatin C assay on the BN ProSpec (Siemens Healthcare Diagnostics Inc. New York, United States). e: measured by the Galectin-3 electro-chemiluminescence immunoassay (BG Medicine Inc., Waltham, MA, USA United States) on the iMark™ Microplate Absorbance Reader (Bio-Rad Laboratories, Inc). * provided by manufacturer ** validated in our laboratory. LOD=limit of detection; CV=coefficient of variability.

Appendix 2. Correlations between biomarkers

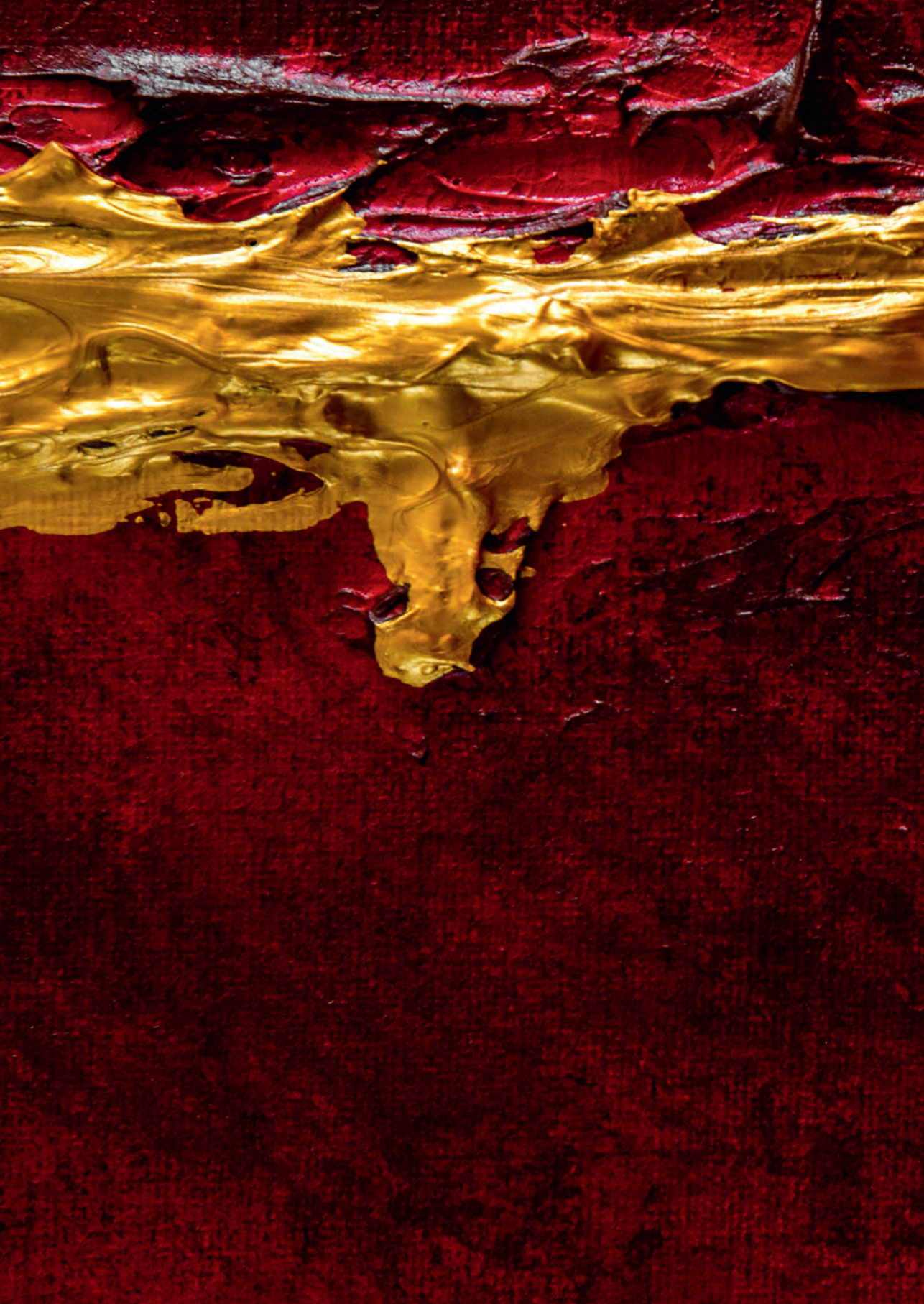
	NT-proBNP	Hs-cTnT	Hs-CRP	Cystatin-C	Galectin-3
NT-proBNP	-	-	-	-	-
Hs-cTnT	0.55*	-	-	-	-
Hs-CRP	0.29*	0.29*	-	-	-
Cystatin-C	0.46*	0.46*	0.19*	-	-
Galectin-3	0.45*	0.45*	0.32*	0.70*	-

* P<0.001

Appendix 3. Predicted versus observed 90-day mortality rate of MARKED-risk score categories.



Each dot resembles the patient group within a marked risk score category, from 0 to 7.



CHAPTER 3

Management of chronic heart failure guided by individual N-Terminal pro–B-type natriuretic peptide targets

Results of the PRIMA study (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?)

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ABSTRACT

Objectives: To assess whether management of heart failure (HF) guided by an individualized N-terminal pro–B-type natriuretic peptide (NT-proBNP) target leads to improved outcome compared with HF management guided by clinical assessment alone.

Background: Natriuretic peptides may be attractive biomarkers to guide management of heart failure (HF) and help select patients in need of more aggressive therapy. The PRIMA study is, to our knowledge, the first large, prospective randomized study to address whether management of HF guided by an individualized target NT-proBNP level improves outcome.

Methods & results: A total of 345 patients hospitalized for decompensated, symptomatic HF with elevated NT-proBNP levels at admission were included. After discharge, patients were randomized to either clinically-guided outpatient management (n=171), or management guided by an individually set NT-proBNP (n=174) defined by the lowest level at discharge or 2 weeks thereafter. The primary end point was defined as number of days alive outside the hospital after index admission.

Results: HF management guided by this individualized NT-proBNP target increased the use of HF medication (p=0.006), and 64% of HF-related events were preceded by an increase in NT-proBNP. Nevertheless, HF management guided by this individualized NT-proBNP target did not significantly improve the primary end point (685 vs. 664 days, p=0.49), nor did it significantly improve any of the secondary end points. In the NT-proBNP-guided group mortality was lower, as 46 patients died (26.5%) versus 57 (33.3%) in the clinically-guided group, but this was not statistically significant (p=0.206).

Conclusions: Serial NT-proBNP measurement and targeting to an individual NT-proBNP value did result in advanced detection of HF-related events and importantly influenced HF-therapy, but failed to provide significant clinical improvement in terms of mortality and morbidity.

INTRODUCTION

Current management of patients with heart failure (HF) is mainly based on clinical signs and symptoms. This approach allows clinicians to respond to worsening HF once it is recognized, but does not allow selection of individuals who are most likely to progress to increased morbidity and mortality and are thus in need of more intensive treatment. Plasma levels of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) are established indicators of decompensated HF[1,2] and predictors of HF morbidity and mortality.[3,4] Natriuretic peptides may therefore be attractive biomarkers to guide management of HF and help select patients in need of more aggressive therapy. Troughton et al.[5] were the first to suggest in a small pilot study that guiding HF management by aiming for a target NT-proBNP level may improve outcome. In this study, the investigators aimed to achieve NT-proBNP levels of 200 pmol/l (1,700 pg/ml) or lower, a goal that is difficult to achieve in many patients with established HF. The clinical value of such stringent (NT-pro)BNP levels has recently been addressed in several other clinical outcome studies.[6-8] These studies failed to show an overall reduction in mortality, but did suggest improved outcome in HF patients under the age of 75 years. Also, the (NT-pro)BNP target value was achieved only in a minority of patients. In the STARS-BNP (Systolic Heart Failure Treatment Supported by BNP) Multicenter study, only 33% reached the BNP target,[6] whereas in TIME-CHF (Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure)[8] and the BATTLESCARRED (NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death) trial,[7] at least 50% of the subjects had not achieved the desired target at the end of the study. At the same time, the TIME-CHF investigators speculated that intensification of therapy might be harmful in the elderly.[8] As the target NT-proBNP level in the aforementioned studies was not achieved in the majority of HF patients randomized to (NT-pro)BNP–guided therapy, most subjects randomized to the (NT-pro)BNP–guided arms received intensified treatment. These studies therefore show that a more generalized intensification of HF therapy may be beneficial in specific subgroups. However, it was not addressed whether serial assessment of NT-proBNP enables to select patients at risk of increased morbidity and mortality. Therefore, the question remains whether it is beneficial to intensify HF therapy only in those patients most likely to progress towards events. It is well known that in many HF patients, NT-proBNP levels never normalize, whereas these patients still remain clinically stable over years. This suggests that

patients with stable NT-proBNP levels (even when clearly elevated) may have an acceptable prognosis. We hypothesized that elevation of outpatient NT-proBNP levels as compared with the patient's individualized target level, allows selection of those HF patients most likely to progress towards events. The individualized target level was defined as the lowest level at discharge or at 2 weeks follow-up after admission because of HF. We further hypothesized that restricting treatment intensification to these selected patients would be beneficial without additional risk of adverse effects. We therefore performed a prospective randomized study to address whether treatment of HF, guided by an individualized target NT-proBNP level, improves outcome in HF patients.

METHODS

Study design and study population

PRIMA is a prospective, randomized, single-blind study executed in 12 Dutch university and large general hospitals. Patients were recruited between June 2004 and September 2007. To be included, patients had to be hospitalized for decompensated, symptomatic HF, fulfilling the European Society of Cardiology (ESC) diagnostic guideline criteria for acute HF.[9] In addition, NT-proBNP levels at admission were required to be at least 1,700 pg/ml, as additional objective evidence of HF.[1] Exclusion criteria were: life-threatening cardiac arrhythmias during the index hospitalization, urgent invasive or surgical intervention performed or planned during the index hospital admission, severe chronic obstructive pulmonary disease with a forced expiratory volume in 1 s (FEV1) of <1 l/s, pulmonary embolism less than 3 months prior to admission, pulmonary hypertension not caused by left ventricular systolic dysfunction, a non-HF-related expected survival of less than 1 year, and patients undergoing hemodialysis or continuous ambulant peritoneal dialysis. A lesser degree of renal dysfunction was not an exclusion criterion. Patients were screened and included during the index admission because of acute HF (Fig. 1). Informed consent was obtained and NT-proBNP levels were measured at hospital discharge. Patients demonstrating a significant decrease in NT-proBNP levels during hospitalization, defined as a decrease of more than 10%, with a drop in NT-proBNP levels of at least 850 pg/ml, were randomized to treatment that was either NT-proBNP-guided or clinically-guided. Patients in whom NT-proBNP levels decreased <10% during admission

were considered not to modulate their NT-proBNP levels enough to allow NT-proBNP-guided treatment. Therefore, these patients were not included.

Regular follow-up visits were scheduled at 2 weeks and 1 month, and then every 3 months until the follow-up period of 2 years was completed. Follow-up visits were performed by dedicated HF cardiologists and nurses. The institutional review board or ethics committee at each site approved the protocol, and all patients provided written informed consent before enrollment. Treatment in the NT-proBNP-guided group was guided by the combination of clinical assessment and NT-proBNP levels. The individual NT-proBNP target value was set at the lowest level at discharge or at 2 weeks follow-up. If at subsequent outpatient visits, NT-proBNP levels were more than 10% with a minimum of 850 pg/ml above this individual target level, NT-proBNP level was considered "off-target," and therapy was intensified according to the ESC HF treatment guidelines.[10] In this treatment group, an electronic case record form indicated at each visit whether NT-proBNP levels were off-target and indicated whether intensification was necessary. Therapy in the clinically-guided treatment group was determined by clinical assessment alone. A therapy advisor, incorporated in the electronic case record form, was designed to give individual treatment advice, depending on several individual variables including the cause of HF (ischemic vs. non-ischemic), left ventricular ejection fraction (LVEF), clinical signs of HF, and creatinine clearance. Also, titration schemes for diuretics, angiotensin-converting enzyme (ACE) inhibitors, betablockers, angiotensin receptor blockers, and aldosterone receptor blockers were provided. In the clinically-guided treatment group, all cardiologists were blinded to the NT-proBNP levels of the patients during follow-up. At every outpatient visit, vital status was assessed. Quality of life (QOL) was assessed at 3-month intervals by the Minnesota Living with Heart Failure Questionnaire.[11]

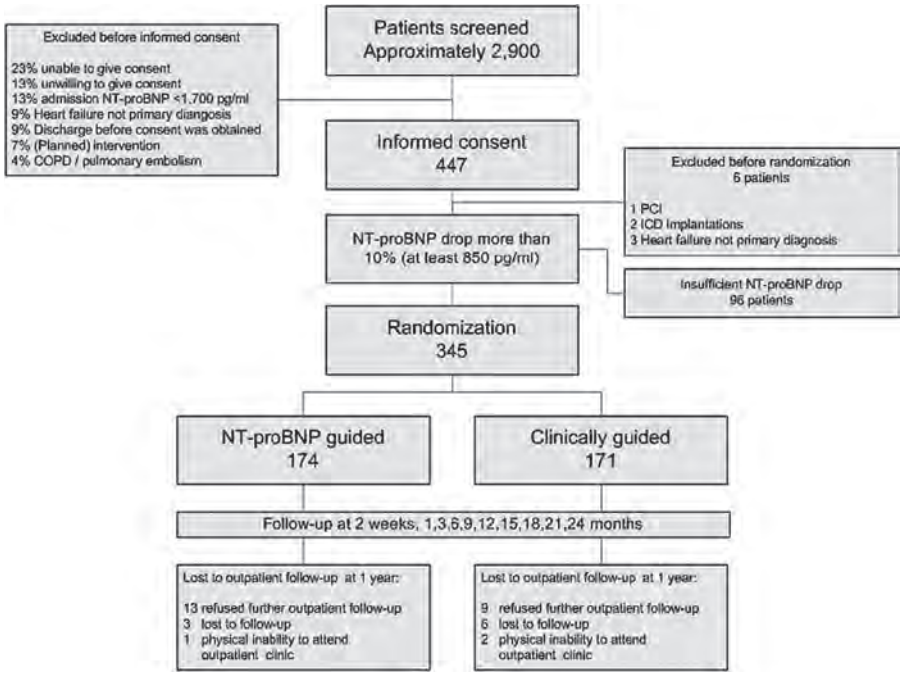
NT-proBNP levels were measured on a Roche Diagnostics Elecsys platform (Roche Diagnostics Ltd., Rotkreuz, Switzerland) at every participating site, except for 1 center where the NT-proBNP levels of patients randomized to the NT-proBNP-guided group were measured within 24 h in a participating university hospital nearby.

Definition of study end points

The primary end point of the PRIMA (Can PRo-brain-natriuretic peptide-guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study was defined as the difference in total number of days alive and outside the hospital between the NT-proBNP-guided and the clinically-guided group. This

primary end point replaced the initial end point of reduction in number of events, as the end point of number of days alive outside the hospital included hospital admission as mortality. The primary end point was changed before any patient had been included, in the start-up phase of the study. Major secondary end points encompassed total and cardiovascular mortality, total and cardiovascular hospitalization, and the combined end points of total and cardiovascular morbidity and mortality. Furthermore, renal function, left ventricular systolic function, and age subgroups were analyzed. Additionally, analysis of the use of evidence-based HF medication was performed. Evidence-based HF medication target dose was defined as the recommended maintenance dose approved for the treatment of HF in Europe.[10] Finally, it was predefined to analyze the prognostic impact of NT-proBNP levels above the individually set target level at outpatient visits.

Figure 1. Flowchart and trial outline



Overview of patients screened, reasons for exclusion, total number of patients randomized and 1 year follow-up. COPD=chronic obstructive pulmonary disease; ICD= implantable cardioverter-defibrillator; FU=follow-up; HF=heart failure; NT-proBNP=N-terminal pro–B-type natriuretic peptide; PCI=percutaneous coronary intervention; PE=pulmonary embolism.

Table 1. Baseline characteristics.

Characteristics	NT-proBNP Guided (n=174)	Clinically Guided (n=171)	P-value
Baseline			
Age, yrs	71.6 ±2.0	72.8 ±11.7	NS
Female	79 (45.4)	69 (40.3)	NS
Hypertension	83 (47.7)	84 (49.1)	NS
Diabetes mellitus	44 (25.3)	47 (27.5)	NS
Transient ischemic attack	8 (4.6)	25 (14.6)	0.002
Stroke	17 (9.8)	18 (10.5)	NS
COPD	29 (16.7)	30 (17.5)	NS
Atrial fibrillation			NS
-Chronic	29 (16.7)	29 (17.0)	
-Paroxysmal	28 (16.1)	26 (15.2)	
Coronary artery disease	97 (55.7)	109 (63.7)	NS
Myocardial infarction	65 (37.4)	74 (43.3)	NS
PCI	20 (11.5)	24 (14.0)	NS
CABG	32 (18.4)	29 (17.0)	NS
Valve replacement	11 (6.3)	9 (5.3)	NS
Pacemaker	11 (6.3)	21 (12.3)	NS
ICD	13 (7.5)	10 (5.8)	NS
History of HF			NS
-Ischemic	40 (23.0)	33 (19.3)	
-Non-ischemic	26 (14.9)	26 (15.2)	
cause unknown	1 (0.6)	0	NS
Discharge			
NYHA functional class			
I	20 (11.5)	17 (9.9)	NS
II	113 (64.9)	121 (70.8)	
III	41 (23.6)	33 (19.3)	
LVEF, %	34.9 ±13.7	36.7 ±14.8	NS
Mitral regurgitation grade ≥II	84 ±48.3	63 ±36.8	NS
Systolic BP, mmHg	116.8 ±18.5	119.4 ±22.4	NS
Diastolic BP, mmHg	68.7 ±11.3	69.2 ±11.6	NS
HR, beats/min	72.1 ±11.4	74.5 ±16.1	NS
Sodium, mmol/l	139.5 ±3.2	139.1 ±3.8	NS
Potassium, mmol/l	4.27 ±0.46	4.27 ±0.46	NS
Urea, U/l	11.5 (8.2–16.2)	11.9 (9.0–16.0)	NS
Creatinine, U/l	121 (97.8–157.3)	126 (104.0–166.3)	NS
Hemoglobin, mmol/l	8.5 ±1.2	8.4 ±1.3	NS
NT-proBNP, pg/ml			NS
Admission	8,034 (4,210–13,831)	8,168 (4,288–14,051)	
Discharge	2,961 (1,383–5,144)	2,936 (1,291–5,525)	NS
Target	2,491 (1,109–4,435)		

Data is presented as mean±standard deviation, median(interquartile range) or frequency(%). COPD=chronic obstructive pulmonary disease; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; ICD=internal cardioverter defibrillator; HF=heart failure; LVEF= left ventricular ejection fraction; BP=blood pressure; HR=heart rate; NT-proBNP=N-terminal pro-B-type natriuretic peptide.

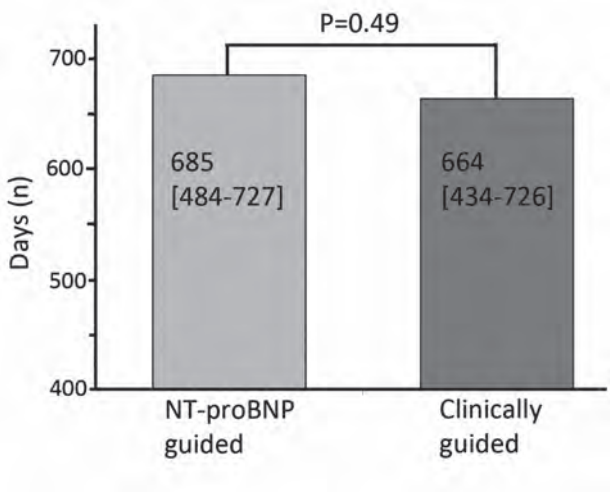
All events were adjudicated by a blinded event committee, consisting of medical specialists in cardiology, nephrology, vascular medicine, pulmonology, and neurology. Serious adverse events included admissions to the emergency room, hospital admissions, and death. Treatment in the NT-proBNP group was considered to be protocol adherent when 1 of the following actions was undertaken upon an elevated outpatient NT-proBNP level: starting or intensifying HF medication according to the ESC guidelines, all therapeutic and diagnostic actions searching for underlying causes of HF such as hypertension, ischemic heart disease, valvular heart disease, anemia, and cardiac arrhythmias; hospital admission (for decompensated HF); or registering for heart transplantation.

Statistical analysis

Based on previous studies and observations, it was estimated that, with an event rate of 20%, 480 patients would be needed to reach a relative risk reduction in number of events of 50% in the NT-proBNP-guided group compared with the clinically-guided group at an α level of 0.05 and a power level of 0.80. Although the primary end point changed during the start-up phase of the study, power analysis remained the same. One year after the first patient being included, a pre-specified interim analysis was performed, with a difference in events ($p<0.01$) as criterion to preliminary stop according to lan-DeMets alpha spending rule. The interim analysis demonstrated a pooled event rate of 65%. Thereupon the power analysis was re-evaluated. It was calculated that 364 patients were needed to demonstrate a minimum reduction in pooled events of 30%.

Results are presented as frequencies, mean (SD), or median (interquartile range [IQR]), where appropriate. Between group comparisons were performed using the *t* test, Mann-Whitney U test, or chi-square test where appropriate. Event rates for all-cause mortality were estimated by the Kaplan-Meier method. Hazard ratios were calculated using Cox regression analysis. Time-dependent Cox regression analysis was performed to analyze the prognostic impact of elevated NT-proBNP levels above target value at the outpatient clinic. All calculations were performed with the use of the SPSS statistical package version 15.0 (SPSS Inc., Chicago, Illinois).

Figure 2. Primary endpoint: number of days outside the hospital.



RESULTS

Baseline characteristics

In total, 345 patients were randomized: 174 patients to the NT-proBNP-guided treatment group and 171 patients to the clinically-guided group. Baseline characteristics are shown in Table 1, which did not reveal significant differences between the 2 study groups except for the number of transient ischemic attacks (4.6% in the NT-proBNP-guided vs. 14.6% in the clinically-guided group, p=0.002). Patients were elderly with a mean age of 72 years, more than 40% were female, and a large proportion had cardiovascular risk factors such as hypertension and diabetes mellitus. History of HF was present in 37% of subjects, and almost a quarter had a LVEF above 45%. After the index admission, most patients were in New York Heart Association functional class II at discharge. The median NT-proBNP target value in the NT-proBNP-guided treatment group was 2,491 pg/ml.

End points

The median follow-up was 702 days (IQR: 488 to 730 days). In 34 patients (17 in both randomization groups, see Fig. 1), outpatient follow-up visits after 1-year follow-up were not completed.

Management guided by an individualized NT-proBNP target did not significantly improve the primary end point, the number of days alive outside the hospital: median number of days alive outside the hospital was 685 versus 664 days, p=0.49 (Fig. 2). In the NT-proBNP-guided group, mortality was lower, as 46 patients died (26.5%), versus 57 (33.3%) in the clinically-guided group (Fig. 3), but this was not statistically significant. The number of scheduled visits did not differ between the NT-proBNP-guided and the clinically- guided group (mean 7.1±3.1 vs. 6.9±3.0, p=0.424). However, there was a trend towards an increase in unscheduled visits in the NT-proBNP-guided group (mean 1.4±1.9 vs. 1.1±1.7, p=0.063). The total number of cardiovascular and HF-related admissions between the NT-proBNP-guided and the clinically-guided groups were not different (mean 1.11±2.20 vs. 1.05±1.47, p=0.552, and 0.70±1.89 vs. 0.60±1.25, p=0.989). In addition, none of the other prespecified end points was statistically significantly different between the groups (Table 2).

In the subset of patients with left ventricular systolic dysfunction (ejection fraction below 45%), total mortality tended to be lower in the NT-proBNP-guided group, which however did not reach statistical significance (mortality: 25% in NT-proBNP-guided vs. 33% in usual care, p=0.164). In contrast, in patients with preserved left ventricular systolic function, mortality was identical in both groups (31%).

Furthermore, in patients under 75 years of age, a trend was seen towards improved outcome in the NT-proBNP-guided treatment arm (number of days alive outside hospital as percentage of total follow-up: 87.4% vs. 82.8%, p=0.114). Therapy guided by NT-proBNP levels also tended to be favorable in patients with lower discharge creatinine levels, but again these differences did not reach statistical significance (number of days alive outside hospital as percentage of total follow-up: 92.7% vs. 87.9%, p=0.076).

Table 2. Secondary outcome measures in the overall study population and in subgroups.

		Days alive outside hosp*			Mortality		CV mortality		Days admitted hosp†	
	Group	**N**	**Median (IQR)**	**P-value**	**N (%)**	**P log rank**	**N (%)**	**P log rank**	**Median (IQR)**	**P-value**
Overall	NT-proBNP-guided	174	99.0(74.4–100.0)	0.174	46(26)	0.206	34(20)	0.705	0.68(0.00–4.56)	0.490
	Clinically-guided	171	98.5(64.4–99.9)		57(33)		36(21)		0.93(0.14–4.62)	
LVEF ≤45%	NT-proBNP-guided	112	99.2(82.2–100.0)	0.140	28(25)	0.164	20(18)	0.439	0.48(0.00–4.42)	0.334
	Clinically-guided	117	98.6(57.3–99.9)		39(33)		25(21)		0.93(0.07–0.51)	
LVEF >45%	NT-proBNP-guided	42	97.3(42.8–99.7)	0.946	13(31)	0.861	12(29)	0.421	1.67(0.16–8.52)	0.760
	Clinically-guided	42	98.0(82.3–99.6)		13(31)		9(21)		1.04(0.30–4.73)	
NT-proBNP >2,950 pg/ml	NT-proBNP-guided	87	97.5(43.8–99.7)	0.325	31(36)	0.139	21(24)	0.504	2.19(0.17–8.47)	0.897
	Clinically-guided	85	92.9(33.6–99.5)		41(48)		24(28)		1.23(0.16–7.91)	
NT-proBNP ≤2,950 pg/ml	NT-proBNP-guided	87	99.7(96.8–100.0)	0.248	15(17)	0.845	13(15)	0.853	0.24(0.00–2.05)	0.196
	Clinically-guided	86	99.2(95.4–99.9)		16(19)		12(14)		0.55(0.00–3.16)	
Age ≤74 yrs	NT-proBNP-guided	92	99.5(95.4–100.0)	0.114	17(18)	0.225	13(14)	0.653	0.37(0.00–2.71)	0.138
	Clinically-guided	81	98.7(88.6–99.9)		21(26)		13(16)		0.93(0.14–3.83)	
Age >74 yrs	NT-proBNP-guided	82	97.9(42.2–99.9)	0.908	29(35)	0.745	21(26)	0.874	1.23(0.10–7.83)	0.587
	Clinically-guided	90	96.6(50.6–99.8)		36(40)		23(26)		0.88(0.10–4.96)	
Discharge creatinine ≤123 U/l	NT-proBNP-guided	85	99.7(97.8–100.0)	0.076	11(13)	0.198	7(8)	0.157	0.27(0.00–1.39)	0.116
	Clinically-guided	80	99.4(96.4–100.0)		16(20)		12(15)		0.55(0.00–2.71)	
Discharge creatinine >123U/l	NT-proBNP-guided	81	95.4(37.0–99.6)	0.742	32(40)	0.656	24(30)	0.561	2.33(0.16–9.82)	0.804
	Clinically-guided	82	93.0(33.8–99.3)		37(45)		21(26)		1.85(0.17–8.41)	

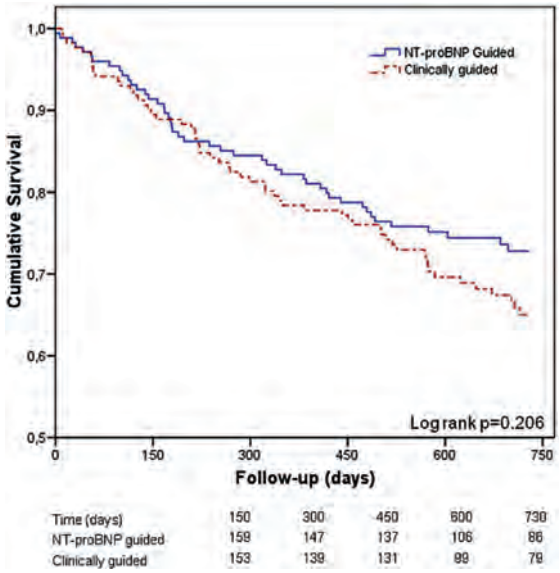
*The number of days alive outside the hospital as a percentage of total days of follow-up. †days admitted to the hospital as a percentage of total days alive. Hosp=hospitalization; IQR=interquartile range. Other abbreviations as in table 1.

Table 3. Response to elevated NT-proBNP levels in the NT-proBNP-guided group during follow-up.

Type of intervention	N (%)
Drug intervention*	**202(75.1)**
Diuretics	109(40.5)
ACE-I's	17(6.3)
Beta-blockers	30(11.2)
Digoxin	9(3.3)
Aldosterone antagonists	11(4.1)
ARBs	11(4.1)
Nitrates	10(3.7)
Alpha-blocker	1(0.4)
Anti-arrhythmic	1(0.4)
Hydralazine	1(0.4)
Decrease calcium-channel blocker	2(0.7)
Diagnostics	**28(10.4)**
Echocardiogram	8(3.0)
Ischemia†	6(2.2)
Holter monitoring	7(2.6)
Consultation‡	5(1.9)
Chest X-ray	2(0.7)
Other interventions	**34(12.6)**
Admission HF	18(6.7)
ED visit	1(0.4)
Pacemaker implantation	1(0.4)
ICD implantation	2(0.7)
Admission other	2(0.7)
Rehabilitation for HF	1(0.4)
Analysis/treatment anemia	3(1.1)
Life style advice	2(0.7)
Electro cardioversion	4(1.5)
No intervention	**56(20.8)**
No treatment options	5(1.9)
On dialysis	2(0.7)
Severe hypotension	1(0.4)
No valid reason	46(17.1)
No NT-proBNP at disposal	1(0.4)
Intervention refused by patient	1(0.4)
Total number visits with elevated NT-proBNP	**269 (100)**

*Except for calcium-channel blockers, drug intervention indicates start, increase or switch in medication. †MIBI stress test, coronary angiography, or exercise test. ‡Specialized cardiologist/internal medicine/other. ACE-I=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; NT-proBNP=N-terminal pro–B-type natriuretic peptide.

Figure 3. Overall survival by treatment group.



NT-proBNP levels and use of medication.

After 1-year follow-up, 80% of patients were at or below their individual target level. In 23% of all outpatient visits, NT-proBNP levels were above the individualized target level. In 79% of all outpatient visits with an off-target NT-proBNP level, protocol adherent action was undertaken (Table 3). Evidence-based medication for HF was extensively used in both groups (Table 4). Renin-angiotensin inhibition was used significantly more frequently after 1 year in the NT-proBNP-guided group. Management guided by an individualized NT-proBNP target also led to an overall increased use of HF medication (Table 5). An increased NT-proBNP value most often prompted physicians to intensify diuretic therapy (Table 3). The lack of significant beneficial outcomes suggests that intensifying diuretic therapy may not be adequate to prevent events. We therefore compared the effects of intensifying evidence-based HF medication (i.e., increase renin-angiotensin system blockade, beta-blockade, and spironolactone) to the effect of intensifying diuretics in response to an increased NT-proBNP level. However, no differences were found between the 2 types of treatment in their ability to get more patients on or below target level at the next outpatient follow-up (40% vs. 33%, p= 0.369). Moreover, in general, intensifying HF medication (evidence-based HF medication or diuretics) compared with no pharmacological HF intervention was not associated with a

significantly higher number of patients who reached their NT-proBNP target (47% vs. 36%, p=0.117).

During follow-up, NT-proBNP levels and levels of urea and creatinine did not significantly differ between both treatment groups, although there was a trend for increased creatinine in the NT-proBNP-guided group (Table 6). Also, no difference was seen in QOL between the NT-proBNP-guided and the clinically-guided groups: median QOL at discharge: 47 (IQR: 34 to 62) versus 48 (IQR: 36 to 60), p=0.95, at 6-month follow-up: 23 (IQR: 10 to 39) versus 25 (IQR: 11 to 42), p=0.64, and at 12-month follow-up: 20 (IQR: 6 to 36) versus 23 (IQR: 10 to 38), p=0.6. The individualized NT-proBNP target value appeared to be of prognostic importance. Most HF-related events (64%) were preceded by off-target NT-proBNP levels at previous outpatient follow-up. Outpatient elevation of NT-proBNP levels above this individualized target value indicated an increased risk for major end points such as total mortality (hazard ratio [HR]: 1.84, p=0.007), cardiovascular mortality (HR: 2.53, p<0.001), and HF-related mortality (HR: 3.69, p<0.001) (Table 7).

Table 4. Use of evidence based HF medication at index admission and during follow-up by treatment group.

	Admission		Discharge		6-Month		12-Month	
	NBNP	Clinical	NBNP	Clinical	NBNP	Clinical	NBNP	Clinical
Loop diuretics	104(60)	111(65)	169(97)	162(95)	131(93)	128(93)	119(91)	110(92)
ACE-I	71(41)	75(44)	112(64)	111(65)	90(64)	82(59)	84(66)*	66(55)*
dose	60(45)	51(38)	60(45)	57(61)	71(91)	64(59)	76(95)	69(55)
ARB	28(16)	31(18)	31(18)	34(20)	30(21)	29(21)	35(28)	35(29)
dose	82(63)	93(63)	98(91)	92(64)	71(65)	85(88)	66(62)	88(87)
β-blockers	96(55)	97(57)	139(80)	126(74)	120(85)	110(80)	111(87)*	95(79)*
dose	45(28)	51(34)	47(49)	49(56)	47(32)	58(43)	53(36)	58(39)
MRA	28(16)	36(21)	92(53)	95(56)	62(44)	69(50)	59(47)	62(52)
dose	98(35)	125(81)	99(45)	109(48)	86(31)	93(44)	92(41)	97(41)
ACE-I/ARB	94(54)	101(59)	138(79)	134(78)	115(82)	107(78)	111(87)†	93(78)†
≥50% target dose	60(35)	68(40)	104(60)	90(53)	84(60)*	67(49)*	79(62)	66(55)
ACE-I/ARB +β-blocker	69(40)	67(39)	117(67)*	98(57)*	99(70)	88(64)	98(77)†	76(63)†
≥50% target dose	21(12)	26(15)	37(21)	30(18)	39(28)	33(24)	38(30)	33(28)

Data is presented as frequency (%) or as mean(standard deviation). For ACE inhibitors, ARBs, beta-blockers and MRAs the dosage is expressed as percentage of target dose. *p<0.1; †p<0.05. ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; MRA=mineralocorticoid receptor antagonist; NBNP=NT-proBNP-guided; Clinical=clinically-guided; HF=heart failure.

Table 5. Number of increases in HF medication during follow-up.

	NT-proBNP-Guided (n=174)	Clinically-Guided (n=171)	P-value
Diuretics	168	120	0.02
Beta-blockers	105	95	0.35
ACE-I	77	55	0.1
ARB	41	22	0.39
MRA	19	15	0.86
Digoxin	14	19	0.63
Total	424	326	0.006

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; MRA=mineralocorticoid receptor antagonist.

Table 6. Changes in NT-proBNP, urea and creatinine levels during follow-up

	6-Month			12-Month		
Parameter	NT-proBNP-guided	Clinically-Guided	P-value	NT-proBNP-guided	Clinically-Guided	P-value
NT-proBNP, pg/ml	-254 (-1,415 to 530)	-287 (-1,186 to 688)	0.60	-432 (1,392 to 297)	-572 (-1,329 to 434)	0.99
Urea, mmol/l	-0.5 (-3.8 to 2.6)	-0.8 (-3.3 to 1.2)	0.41	0.0 (-3.8 to 2.2)	-1.0 (-4.1 to 1.7)	0.16
Creatinine, µmol/l	7.00 (-12.0 to 32.0)	2.0 (-15 to 19)	0.06	8.0 (-10.3 to 31.8)	3.0 (-14.0 to 22.0)	0.07

Values are expressed as median (interquartile range). NT-proBNP=N-terminal pro–B-type natriuretic peptide.

Table 7. Time-dependent HR if the outpatient NT-proBNP level is above the individually set target value

Outcome	N (%)	HR	95% CI	P-value
Total mortality	103(29.9)	1.84	1.18–2.85	0.007
CV mortality	70(20.3)	2.53	1.52–4.21	<0.001
HF mortality	45(13.0)	3.69	2.02–6.72	<0.001
First CV admission	193(55.9)	2.70	1.96–3.73	<0.001
First HF admission	115(33.3)	4.17	2.84–6.13	<0.001

CI=confidence interval; CV=cardiovascular; HF=heart failure; HR=hazard ratio; NT-proBNP=N-terminal pro–B-type natriuretic peptide.

DISCUSSION

The PRIMA study is a prospective randomized study to address whether HF therapy, guided by an individualized NT-proBNP level, improves outcome in HF patients. The PRIMA study randomized 345 patients to HF therapy guided by an individually set NT-proBNP target level in addition to clinical signs, or by clinical signs only. It addressed the benefit of selective intensification of therapy only when NT-proBNP increases beyond the individually defined "optimal" NT-proBNP level. Assessing the optimum natriuretic peptide target level is most challenging.[12] As such, the PRIMA study complements the recent studies on the benefits of a more general intensification of therapy by aiming for absolute NT-proBNP targets.[7, 8] PRIMA showed that selective intensification by an individualized NT-proBNP target did not significantly improve any of the pre-specified primary or secondary outcome measures. Although treatment guided by an individualized NT-proBNP target slightly improved the number of days alive outside the hospital, and improved overall mortality, these changes were not statistically significant. Individualized NT-proBNP-guided therapy resulted in significantly intensified pharmacological HF therapy reflected by an increased use of diuretics and ACE inhibitors or angiotensin II receptor antagonists in the NT-proBNP-guided group. We hypothesized that individualized NT-proBNP-guided treatment would improve outcome.

Our first assumption was that stability of NT-proBNP would portend an improved prognosis, even when the stable NT-proBNP level is well above normal. This first assumption was confirmed in this study. Patients who maintained their individual NT-proBNP target level indeed had a highly significantly better outcome. Most events occur in patients with an unstable NT-proBNP. Indeed, increases of NT-proBNP level above each individual optimum was a strong predictor of HF-related events with hazard ratios up tot 4.17, $p < 0.001$.

Our second assumption was that treatment of HF guided by an individualized target NT-proBNP level could avert HF events. Despite the ability to detect 64% of the imminent events, and despite the subsequent intensification of HF medication, events were not significantly averted. This suggests that although NT-proBNP measurement can help detect worsening HF, current standard-of-care HF therapy is unable to avert subsequent events. NT-proBNP levels react upon ventricular wall stretch.[13] Therefore, deterioration of HF is needed before levels rise. Elevated marker levels before an increase in cardiac pressures takes

place might help us identify patients at risk for events; in such an early phase, medical intervention can still avert worse outcome. NT-proBNP appears to be a "passenger-seat" marker: you can see which direction your car is heading, but you are not in control of the steering wheel. In order to reduce morbidity and mortality, a "driver-seat" marker is urgently needed. A number of reasons may account for this lack of significant improvement. First, not enough events during follow-up may have been detected, as 36% of events were undetected by measurement of NT-proBNP at 3-month intervals. Second, intensification of treatment against a background of high use of evidence-based HF therapy may not suffice to avert an imminent event. Third, current "gold-standard" HF therapy may altogether be inadequate in preventing HF-related events in patients with deterioration of HF.

Subgroups analyzed.

The effects of NT-proBNP guidance seemed mitigated in patients with preserved systolic function, although differences did not reach statistical significance. The lack of well-established medical or other intervention measures for patients with preserved ejection fraction HF may limit the success of interventions prompted by off-target NT-proBNP in this group. The effects of NT-proBNP guidance seemed more favorable in younger patients (age under 75 years) and those with better renal function, although these differences also did not reach statistical significance. Both younger patients and patients with preserved renal function have less comorbidity and are expected to better tolerate intensification of therapy. It is these type of patients that have been included in most landmark trials that yielded the evidence for HF therapy. Elderly patients with severe renal dysfunction and patients with preserved left ventricular systolic function HF form the majority of HF patients, but they are underrepresented in landmark trials.[14] Therefore, speculatively, it seems that the intensified use of evidence-based HF therapy is mainly effective in the subgroups where this evidence was obtained. Previous studies have demonstrated that NT-proBNP levels fall in response to optimizing HF therapy.[15-17] In PRIMA, intensifying HF therapy in patients with rising NT-proBNP levels failed to lower these levels. The lack of benefit seen in our study is in line with the overall lack of benefit seen with studies of NT-proBNP-guided therapy by an absolute NT-proBNP target.[7, 8] PRIMA shows that treatment of HF guided by an individualized NT-proBNP target against a background of optimal HF therapy does not have additional beneficial effects.

Study limitations

As opposed to what could be expected from large HF surveys,[18] only a minority of patients included in our study had a history of HF. NT-proBNP levels might decrease more in response to HF treatment in patients with de novo HF compared with patients with a history of HF and background therapy before admission. Because we excluded patients if NT-proBNP levels decreased <10%, with a minimum of 850 pg/ml, more patients with a history of HF and prolonged exposure to therapy might be excluded than patients with de novo HF. Power analysis was based on the initial primary end point of reduction in events.

Sample size was calculated to demonstrate a minimum reduction in pooled events of 30%. A post hoc power analysis indicated that a difference of 4% in percentage of time (approximately 28 days) alive outside the hospital could have been detected. One may surmise that choosing an individual (often elevated) NT-proBNP target is not accurate enough, and that more stringent targets should be aimed for in all subjects. However, the prognostic impact we observed of NT-proBNP levels above the individual target, even when the target is clearly elevated, argues against this notion.

Furthermore, the most common reaction to an elevated NT-proBNP level was to increase dosage of diuretics. We have not been able to demonstrate the ability of any subtype of intervention (evidence-based medication, diuretics, or non-pharmacologic) to be more effective in lowering off-target NT-proBNP levels. The use of our electronic therapy advisor might have led to more intensified treatment in the clinically-guided group than would occur in daily practice where such advices are not generated. Previous studies have demonstrated that discharge NT-proBNP levels, decrease in NT-proBNP levels during admission because of HF, and outpatient NT-proBNP levels in patients with stable, chronic HF were of prognostic importance.[4, 19, 20] The possible additive value of a combination of static and dynamic NT-proBNP levels for determining individual prognosis still remains to be assessed.

Conclusions

This is the first study to our knowledge that evaluated whether HF therapy guided by an individualized NT-proBNP target level improves outcome. PRIMA shows that unstable NT-proBNP levels indeed indicate imminent events, but that intensification of currently used medication in patients on optimal HF therapy does not prevent further deterioration.

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EDITORIAL

Biomarker-Guided Treatment of Heart Failure

Still Waiting for a Definitive Answer

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Whether clinicians need a biomarker to guide heart failure therapy is a question that has generated considerable debate in the last decade.[1,2] The concept of tailoring heart failure treatment to achieve a target level of B-type natriuretic peptide (BNP) and thereby reduce cardiovascular event rates was first tested in the late 1990s.[3,4] Since then, a series of studies using a variety of study designs have addressed this strategy in small and moderate-sized cohorts.[5-8]

The rationale for attempting to improve the treatment of heart failure is undisputed: heart failure prevalence is increasing, and associated mortality and hospitalization rates remain high even with modern therapies and multidisciplinary care.[9,10] There is currently no reliable objective guide to optimal pharmacotherapy of heart failure that can be easily applied to individual patients in the ambulant chronic heart failure setting. Additionally, despite clear treatment guidelines, target doses for medications that have been shown in controlled trials to improve clinical outcomes are frequently not achieved in the real world. This undertreatment is not explained simply by differences in patient populations.[10-12] The reasons for suboptimal treatment are many, but of particular importance is the fact that clinical assessment is insensitive and frequently does not identify hemodynamic decompensation or allow accurate assessment of filling pressures, making it an inexact guide to diuretic dosing.[13] Treatment options for systolic heart failure have become complex, and a range of medications and devices with proven efficacy now need to be considered, often in combination.[10] In contrast, the optimal choice of treatment and dosing in heart failure with preserved ejection fraction remains uncertain.[14] There is also inherent and understandable hesitancy when it comes to up-titration of treatment in apparently stable patients, especially when there are concerns about hypotension, azotemia, or other adverse medication effects.

The B-type natriuretic peptides (BNP and N-terminal pro–B-type natriuretic peptide [NT-proBNP]) stand out as biomarkers with the potential to guide therapy. Commercial assays for both peptides are readily available and analytical variation is minimal, particularly for NT-proBNP.[15] Plasma levels of both peptides reflect cardiac function and filling pressures and are powerful predictors of mortality and clinical outcome.[16] Irrespective of innate within-patient variation, serial peptide measurements provide incremental prognostic value in both the in- and out-patient setting, with a fall in peptide levels being associated with better outcomes.[17,18] Additionally, plasma levels of both peptides fall during treatment with proven therapies and mirror beneficial changes in left ventricular structure and function.[19,20]

The hypothesis that BNP levels could be used to guide therapy is appealing as it offers the possibility of individualizing therapy according to an objective measure of function and risk. With this strategy, patients with high BNP/ NT-proBNP levels—who are at higher risk for adverse events—are targeted to receive higher doses of medications that are proven to increase survival. Conversely, patients with low or normal peptide levels are spared higher doses that may be associated with adverse medication effects. To date, 5 published studies have tested this strategy, with slightly different study designs, but all with 1 central characteristic that an absolute peptide level was targeted in the treatment group assigned to BNP- or NT-proBNP-guided care.[4-8] In the largest of these studies—TIME-CHF (Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure)— a higher NT-proBNP level was used as a target for subjects over 75 years of age (800 pg/ml) compared with those ages 60 to 74 years (400 pg/ml).[7] Findings from these 5 studies have varied, with some documenting significant clinical benefit from biomarker-guided management, at least in younger patients,[4-7] but 2 larger studies reporting no overall improvement in clinical outcomes or quality of life.[5,7]

Critics of the concept of biomarker-guided treatment of heart failure question the need for a biomarker to prompt up-titration of proven therapy, stating that all patients should automatically be titrated to tolerated maximal dose.[2] They also note that common peptide targets were frequently not achieved in earlier biomarker-guided studies and suggest that individualized targets may be more achievable. In the face of confounders of BNP/NT-proBNP levels, such as renal dysfunction, myocardial ischemia, and atrial fibrillation, some critics of biomarker-guided treatment question whether a true feedback loop can be achieved and whether peptide levels can be consistently lowered by intensifying therapy. Others have expressed caution in using the biomarker approach in view of intrapatient variability of natriuretic peptide levels.[21]

In a novel study published in this issue of the Journal, Eurlings et al.[22] address 1 criticism of earlier studies by testing an individualized NT-proBNP level as a target. The PRIMA (Can PRo-brain-natriuretic peptide-guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study recruited 345 patients who had been hospitalized with decompensated symptomatic heart failure. Eligibility required an NT-proBNP level >1,700 pg/ml (a higher level than other biomarker-guided studies), and subjects also had to demonstrate a fall in NT-

proBNP of >10% and at least 850 pg/ml during hospitalization (not a requirement of earlier studies). For the 174 subjects randomized to the NT-proBNP-guided group, an individualized target NT-proBNP level was identified based on the lowest NT-proBNP level obtained at discharge or within 2 weeks after discharge. For these subjects, up-titration of treatment was triggered if their NT-proBNP level at scheduled 3-monthly visits was >10% and at least 850 pg/ml above their individual baseline level. For the 171 subjects in the comparator clinically-guided group, treatment was up-titrated on the basis of standard clinical assessment. After a median follow-up of 702 days, no difference was found in the primary end point of days alive and out of hospital, despite the fact that there was greater up-titration of treatment in the NT-proBNP-guided group— especially in the use of inhibitors of the renin-angiotensin system and in diuretic dosing—and despite the fact that 80% of subjects achieved NT-proBNP levels below their individualized target level at 1-year follow-up. The investigators did observe fewer deaths in the NT-proBNP-guided group, particularly in patients younger than age 75 years and in subjects with a left ventricular ejection fraction below 45%, although none of these comparisons achieved statistical significance. Neither was there any statistically significant difference between groups in hospitalization rates, quality of life scores, or estimated glomerular filtration rates.

The PRIMA study is the largest to study an individualized NT-proBNP target, and the investigators should be congratulated for addressing this question and undertaking such a comprehensive study of this strategy. Why did the PRIMA study not show a significant benefit from treatment guided by an individualized NT-proBNP target? The first possibility is that there is indeed no significant benefit to be gained by the approach taken in this study. Perhaps more likely is the possibility that aspects of the PRIMA study design may have served to obscure benefits of biomarker guidance.

First, the study highlights 1 potential limitation of treatment based on an individualized NT-proBNP target. If the target is derived from a BNP or NT-proBNP level that is set too high and therefore is not a reasonable estimate of the nadir, this will reduce the occasions when up-titration of therapy is prompted. In the PRIMA study, the NT-proBNP target level was based on the lowest plasma level for an individual either at baseline or 2 weeks after hospital discharge. The timing of this assessment may partly explain the relatively high median target level of 2,491 pg/ml. It is likely that levels measured at this time would not represent the

true nadir for most patients. Findings from observational studies and the control arm of earlier biomarker-guided treatment trials indicate that in the absence of clinical deterioration, BNP or NT-proBNP levels continue to fall for months after discharge.[5,7,23] The PRIMA investigators report that 80% of subjects achieved levels lower than their individual target NT-proBNP levels by 1 year and that NT-proBNP levels were only above target on 23% of occasions during follow-up. Therefore, on the remaining 77% visits where NT-proBNP levels were at or below target, up-titration of therapy would not have been triggered, despite the fact that NT-proBNP levels may have been at levels generally associated with increased risk of adverse events. By comparison, previous studies showing benefits from biomarker-guided therapy used comparatively stringent absolute levels of NT-proBNP or BNP, and although target NT-proBNP levels were achieved in only 40% to 70% of subjects, up-titration of therapy was triggered on more occasions than in the current study.[5-7]

Second, the definition of an "off-target" NT-proBNP may have further reduced the occasions when up-titration of therapy for patients in the NT-proBNP group was triggered. The PRIMA study design mandated that to trigger an increase in treatment, NT-proBNP levels at follow-up had to be higher than target level by at least 10% and by a minimum of 850 pg/ml. For one-half of the cohort with NT-proBNP levels at or below the median of 2,491 pg/ml, a rise of 850 pg/ml, required to trigger increasing treatment, actually represents an increase of 30% or more. A patient in PRIMA with a median NT-proBNP level at baseline would have therefore required an NT-proBNP level of 3,350 pg/ml at follow-up to trigger treatment titration, a level that is nearly 3X higher than required in the biomarker-guided arm of BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial and between 4X and 8X higher than agestratified targets in TIME-CHF.[5,7] As a result, for many patients, this feature of the PRIMA study design may have further limited the opportunity to apply the treatment strategy, possibly diluting its effect. Whether target levels should take account of variability in peptide measurements on serial testing is debatable. In our view, this is unnecessary, especially for NT-proBNP, where analytical variability is very low. Although innate within-patient variability in peptide levels has been recognized in apparently stable patients, the causes are poorly understood. Many contributing factors such as myocardial ischemia or subclinical arrhythmia are clinically relevant and could contribute to adverse outcomes. Regardless,

it is clear that even small changes in NT-proBNP levels during serial testing are predictive of outcome.[23] In this context, application of an absolute BNP or NT-proBNP level seems appropriate. How best to determine the target level? Data from earlier biomarker-guided studies and observational studies may be helpful in this regard. An approach similar to that used in the TIME-CHF study may have greatest merit— choosing levels associated with increased risk and using simple stratification based on age.[1,7]

Third, like earlier biomarker-guided studies, PRIMA suffered from inadequate power to test the effect of biomarker-guided treatment on some hard clinical outcomes. The initial power calculation optimistically estimated a 50% reduction in cardiovascular events by NT-proBNP-guided treatment. The primary end point was changed prior to the initiation of recruitment to "days alive and out of hospital"—arguably a less robust end point for heart failure trials that may be skewed by the potentially large number of subjects who do not suffer a hospitalization.[24] Mortality and hospitalization are more robust and unbiased outcome measures that were routinely used as primary end points in other biomarker-guided studies. It is interesting to note that in PRIMA, there was a nonsignificant 21% lowering of mortality rates in the NT-proBNP-guided arm. However, PRIMA was not powered to test mortality, and the modified target sample size further reduced the ability to detect clinically significant reductions in this end point. For the observed mortality rate and effect size described in PRIMA, a study of about 2,000 patients would have been needed to provide adequate power. The trend to lower mortality in PRIMA mirrors the trends seen in trials such as TIME-CHF and BATTLESCARRED, where there were reductions in mortality, particularly in younger patients. In an attempt to address the issue of inadequate power from individual studies, 2 recently published literature-based meta-analyses combining recent biomarker-guided studies, including PRIMA, suggest that treatment guided by BNP or NT-proBNP may in fact be associated with up to a 30% mortality reduction compared with usual clinical care.[25,26] These meta-analyses, however, cannot be seen as definitive since they were based only on the available summary data extracted from reports.

The PRIMA study is an important addition to the series of biomarker-guided heart failure studies and provides valuable new insights. How should we therefore interpret PRIMA and other recent studies of biomarker-guided care? First, an

overview of trials—including recent metaanalyses—suggests that BNP- or NTproBNP-guided therapy may reduce mortality, especially in younger patients. Thus, it may have a role as an adjunct to standard of care, especially in younger patients, particularly those with systolic dysfunction. Second, the PRIMA study highlights the potential limitations of using an individualized target NT-proBNP level. Use of a single target level of BNP or NT-proBNP, perhaps adjusted for clinical covariates such as age,[7,27] appears to offer the best opportunity for the biomarker-guided strategy to alter management. As is the case for their use as diagnostic markers, changes in serial BNP and NT-proBNP levels should be interpreted within the entire clinical context, including reference to other tests, such as those for renal function.

Finally, further data are needed from more robust, adequately powered trials with hard clinical outcomes and from a meta-analysis utilizing individual patient data (rather than summary grouped data) before guidelines can confidently endorse a biomarker-guided strategy. Recent studies, including biomarker-guided studies, have highlighted the lack of efficacy of medical therapy in heart failure with preserved systolic function and more particularly in elderly patients.[5,7,28] Whether the biomarker-guided strategy is applicable to elderly patients and those with heart failure and preserved left ventricular ejection fraction remains unclear and needs further evaluation.

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LETTER TO THE EDITOR

Reports of Heart Failure Trials and the Dissociation With the Prevailing Clinical Practice

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The report[1] and editorial[2] in a recent issue of the Journal on N-terminal pro–B-type natriuretic peptide (NT-proBNP) in the management of patients with heart failure (HF) led to the conclusion that B-type natriuretic peptide has not fulfilled original expectations, although NT-proBNP provided advanced detection of events and enhanced medication use. The editorial pointed out that although NT-proBNP did not improve events, this could partially reflect the need for a larger study, adoption of individualized NT-proBNP targets, timing of the sampling for the nadir of NT-proBNP, and threshold percentage rise in NT-proBNP for up-titrating therapy. They also recommended consideration of the patients' age, other factors influencing BNP, systolic dysfunction, and use of individual patient data in meta-analyses.

Trials of HF should include, along with the parameters under study, a minimum of information currently used in the management of patients. The cornerstone of the assessment of a patient with HF is the history and physical examination (pulmonary rales, elevated mean jugular venous pressure, and peripheral edema [PERED]), although these conditions are insensitive and do not correlate with hemodynamics.[3] PERED is often undetected until the patient has accumulated approximately 10 l of fluid.[4] Body weight (BW) is used in all clinical encounters with patients with HF, and it should be a study variable in HF trials. Did the researchers have BW measurements of their patients? If so, what was the correlation between the BW and NT-proBNP percentage perturbations? The quoted "negative" study[3] included a "positive" correlation (r = 0.82) of proportional pulse pressure (systolic blood pressure [SBP] diastolic blood pressure [DBP]/SBP) with cardiac index. The mean SBP and DBP in Table 1 (1) were not statistically significant, although individual patient values are needed to calculate proportional pulse pressure.

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REPLY

We would like to thank Dr. Madias for his valuable comments on our study[1] assessing the effect of N-terminal pro–B-type natriuretic peptide (NT-proBNP)-guided therapy in the management of chronic heart failure (HF). As rightfully indicated, quantification of fluid retention by physical examination is troublesome, and the correlation between symptoms and severity of cardiac dysfunction is poor. Trials such as the PRIMA (Can PRo-brain-natriuretic peptide-guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study[1] have been performed in order to assess the additive value of serial BNP or NT-proBNP measurements at the outpatient management of HF patients.

Dr. Madias asks for data on body weight (BW). This was not initially reported as we felt that with outpatient visits occurring at an interval of up to 3 months, the value of reporting outpatient BWs with such wide intervals would be quite limited.

However, we did collect data on BW at index admission, at discharge, and at every outpatient visit during the follow-up period of our study. During the index hospitalization because of acute HF, BW decreased with a median value of 4.48 kg (interquartile range: 1.8 to 6.2 kg). The change in BW during index admission correlated weakly, yet significantly, with changes in NT-proBNP levels ($r = 0.144$, $p = 0.016$). At the outpatient clinic, there was no statistically significant correlation between changes in BW and NT-proBNP levels.

In addition, Dr. Madias expresses an interest in possible correlations between the proportional pulse pressure (PPP) and NT-proBNP. We failed to find any correlation between PPP and NT-proBNP (correlation between PPP and NT-proBNP at admission: $r = 0.019$, $p = 0.723$; at discharge: $r = 0.035$, $p = 0.532$; and at 2-week follow-up: $r = 0.023$, $p = 0.689$).

We also did not find a correlation in the subgroups of patients with left ventricular systolic dysfunction HF or those with preserved left ventricular systolic function HF.

In conclusion, Dr. Madias rightfully points out the value of physical examination in the management of outpatient HF with special emphasis on BW. In the PRIMA study, changes in BW during the index admission correlated weakly, yet statistically significantly, with NT-proBNP.[1] No correlation was found between outpatient NT-proBNP values and either BW or PPP, which for the latter may be explained by the fact that PPP seems to reflect cardiac output, a parameter correlating poorly with BNP.[2]

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CHAPTER 4

Which heart failure patients profit from natriuretic peptide-guided therapy? A meta-analysis from individual patient data of randomized trials

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ABSTRACT

Aims

Previous analyses suggest that heart failure (HF) therapy guided by (N-terminal pro-)brain natriuretic peptide (NT-proBNP) might be dependent on left ventricular ejection fraction, age and comorbidities, but the reasons remain unclear.

Methods and results

To determine interactions between (NT-pro)BNP-guided therapy and HF with reduced [ejection fraction (EF) ≤45%; HF with reduced EF (HFrEF), *n* = 1731] vs. preserved EF [EF > 45%; HF with preserved EF (HFpEF), *n* = 301] and comorbidities (hypertension, renal failure, chronic obstructive pulmonary disease, diabetes, cerebrovascular insult, peripheral vascular disease) on outcome, individual patient data (*n* = 2137) from eight NT-proBNP guidance trials were analysed using Cox-regression with multiplicative interaction terms. Endpoints were mortality and admission because of HF. Whereas in HFrEF patients (NT-pro)BNP-guided compared with symptom-guided therapy resulted in lower mortality [hazard ratio (HR) = 0.78, 95% confidence interval (CI) 0.62 - 0.97, *P* = 0.03] and fewer HF admissions (HR = 0.80, 95% CI 0.67 - 0.97, *P* = 0.02), no such effect was seen in HFpEF (mortality: HR = 1.22, 95% CI 0.76 - 1.96, *P* = 0.41; HF admissions HR = 1.01, 95% CI 0.67 - 1.53, *P* = 0.97; interactions *P* < 0.02). Age (74 ± 11 years) interacted with treatment strategy allocation independently of EF regarding mortality (*P* = 0.02), but not HF admission (*P* = 0.54). The interaction of age and mortality was explained by the interaction of treatment strategy allocation with comorbidities. In HFpEF, renal failure provided strongest interaction (*P* < 0.01; increased risk of (NT-pro) BNP-guided therapy if renal failure present), whereas in HFrEF patients, the presence of at least two of the following comorbidities provided strongest interaction (*P* < 0.01; (NT-pro)BNP-guided therapy beneficial only if none or one of chronic obstructive pulmonary disease, diabetes, cardiovascular insult, or peripheral vascular disease present). (NT-pro) BNP-guided therapy was harmful in HFpEF patients without hypertension (*P* = 0.02).

Conclusion

The benefits of therapy guided by (NT-pro) BNP were present in HFrEF only. Comorbidities seem to influence the response to (NT-pro) BNP-guided therapy and may explain the lower efficacy of this approach in elderly patients.

INTRODUCTION

A recent individual patient data meta-analysis showed that (*N*-terminal pro-) brain natriuretic peptide (NT-proBNP)-guided therapy improves outcome in heart failure (HF), at least in those aged 75 years or younger;[1] in line with other aggregate data meta-analyses of (NT-pro)BNP-guided therapy in HF.[2,3] Thus, treatment effects of (NT-pro)BNP-guided therapy may be dependent on age.[1] One possible explanation of the apparent dependency of the efficacy of natriuretic peptide (NP)-guided treatment upon age is that comorbidities, which are more common with increasing age, may limit HF therapy titration and/or reduce the benefits of treatment. This question has, however, not yet been appropriately addressed.

In HF, data on the elderly, those patients with significant comorbidities and those with HFpEF are scant. Therefore, these questions may not only shed further light on the efficacy of biomarker-guided therapy in HF, but also on potential differences in treatment response dependent upon age and comorbidities. As most patients included in the large randomized therapeutic trials that underpin clinical practice guidelines[4] had HF with reduced left-ventricular ejection fraction (HFrEF), were not truly elderly and had few comorbidities, the findings from these trials might be less applicable to the majority of patients seen in daily practice; thus, perceived shortcomings of biomarker-guided HF care may reflect limitations of therapeutic efficacy in patients with co-morbidity.

Moreover, no treatment interaction with left ventricular ejection fraction (LVEF) was seen in previous analysis, but less than 10% of the trial participants had preserved LVEF (HFpEF) >45%, precluding any firm conclusions in this patient group. As no randomized therapeutic trials in HFpEF have shown convincing benefit from medical therapy,[5-7] it is uncertain whether (NT-pro)BNP-guidance is equally effective in HFpEF and HFrEF, i.e. LVEF ≤45%.

Therefore, we investigated (i) potential interactions between comorbidities and (ii) age with treatment response, as well as (iii) potential differences in treatment response between HFrEF and HFpEF in patients included in randomized trials of (NT-pro)BNP-guided therapy in HF.

METHODS

Criteria for inclusion of studies and patient data

For this analysis, we used the collaborative database formed for the recently published individual patient data meta-analysis on the effect of (NT-pro)BNP-guided treatment of chronic HF.[1]

As the current meta-analysis focuses on effects of (NT-pro)BNP-guided therapy on outcome in subgroups we have included only those studies that provided individual patient data[8 - 15] and excluded aggregated data presented in the primary meta-analysis. In addition, data from STARBRITE[16] were not included as we did not have access to perform additional analyses on this dataset. Conversely, we added the recently published results from the HFpEF subgroup in TIME-CHF to increase the number of HFpEF patients included,[17] which increased the percentage of HFpEF from 8% to 15% of the total cohort. In 5% of cases LVEF was not known. These patients were excluded from endpoint analyses. The HF patients with no known LVEF did not differ significantly with respect to their baseline characteristics from those included except that chronic obstructive pulmonary disease (COPD) was more common in those without LVEF measured in BATTLESCARRED[12] (43% vs. 18%, P = 0.004) and in PRIMA[9] (34% vs. 15%, P = 0.01) and age was greater in BATTLESCARRED (77.3 ± 6.6 years vs. 73.6 ± 9.4 years, P = 0.04; other data not shown). The inclusion and exclusion criteria of each individual trial have been published previously. [8 - 15,17]

Data extraction

Individual patient data from eligible studies were entered into the meta-analysis database. The data included patient age, sex, comorbidities, baseline BNP or NT-proBNP level (pg/mL), baseline creatinine (μmol/L), baseline LVEF (%), treatment assignment (NP-guided or clinically-guided) and randomization date. The presence or absence of comorbidities was based on the medical history listed in the medical records of individual patients in all trials. No specific additional testing was done for the diagnosis of comorbidities. Outcome data encompassed all-cause mortality, date of all-cause death or last follow-up, and first HF hospitalization along with the date of hospitalization. Only events occurring during the application of the treatment strategy were included in the analysis.

We used the same cut-off to distinguish HFrEF from HFpEF (i.e. LVEF of 45%), as in the previous analysis, which was based on the cut-off used in the majority of the trials.[1] Using cut-offs of 40% or 50% did not change results significantly and are therefore not presented.

Statistical analysis

Data are presented as frequencies, mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate. Comparisons of baseline characteristics between the different studies and between HFpEF and HFrEF were performed using χ^2-test for categorical data and one-way ANOVA or Kruskal - Wallis *H*-test for continuous data, as appropriate.

The pre-specified primary endpoint was all-cause mortality. Secondary endpoints encompassed time to first HF admission and the combined endpoint of HF hospitalization or death. We analysed time-to-event for assessing outcome by using unadjusted Cox proportional hazards regression models. Effect of treatment strategy allocation on outcome in HFpEF and HFrEF patients was visualized by Kaplan - Meier analysis. After analysis of potential differences in the treatment effect between HFrEF and HFpEF in all patients, further analyses were performed for HFpEF and HFrEF separately. Heterogeneity between studies was tested by treatment × study interaction effect across studies. Cox proportional hazard regression models were used to test the influence of comorbidities on treatment response in both HFpEF and HFrEF. Furthermore, interaction between treatment strategy allocation and comorbidities on outcome was assessed by incorporating comorbidities × treatment as terms in the Cox regression model. All analyses were performed using IBM SPSS Statistics version 21.0 apart from aggregated hazard ratios (HR), which were calculated using Review Manager 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

The baseline characteristics of the patients participating in the eight trials included in this analysis are depicted in *Table 1*. The patients were on average elderly, one-third were female and comorbidities were frequent.

There were significant differences in patients' characteristics between the studies ($P < 0.05$ for all), as shown in detail in *Table 1*. In addition, not all studies

collected all the information used for this analysis (*Table 1*). In three trials, patients with HFrEF only were included,[10,11,15] whereas five also included patients with relatively preserved LVEF (HFpEF, i.e. LVEF >45%).[8,9,12,13,17] One study included only five such patients, none of which experienced an event.[13] Therefore, HFpEF patients of this study (i.e. Signal-HF) were not included in the endpoint analysis, leaving four studies, which included a total of 296 HFpEF patients.[8,9,12,17]

Heart failure with preserved ejection fraction vs. heart failure with reduced ejection fraction

Patients with HFpEF were significantly older, more often female, with slightly higher body mass index (BMI) and lower NT-proBNP concentrations than patients with HFrEF *(Table 2)*. Hypertension, renal disease and peripheral vascular disease (PVD) were more prevalent in HFpEF than in HFrEF. HFpEF was more often treated with loop diuretics, but less frequently with β -blockers. There was no difference between HFpEF and HFrEF in terms of mortality (HR = 1.15, 95% CI 0.89 - 1.50, P = 0.28 for HFpEF vs. HFrEF) or HF admission (HR = 1.20, 95% CI 0.95 - 1.51, P = 0.12), but the combined endpoint of HF hospitalization or death was more common in HFpEF patients (HR = 1.24, 95% CI 1.02 - 1.51, P = 0.03; 1 and 2-year event rate in HFpEF vs. HFrEF 36% and 50% vs. 30% and 44%, respectively). This increased hazard in HFpEF was not independent of age (bivariate Cox regression: HR = 1.14, P = 0.18 after adjustment for age).

Figure 1 depicts the effects of (NT-pro)BNP-guided therapy on mortality based on the individual data of patients showing a significant beneficial effect in HFrEF (HR = 0.78, 95% CI 0.62 - 0.97), but not in HFpEF patients (HR = 1.22, 95% CI 0.76 - 1.96; interaction *P* = 0.016). Data from individual studies are depicted in *Figure 2*, showing no significant heterogeneity between studies according to LVEF subgroup.

Time to first HF admission was significantly prolonged by (NT-pro)BNP-guided therapy in the HFrEF group (HR = 0.80, 95% CI 0.67 - 0.97, *P* = 0.02), but not in the HFpEF group (HR = 1.01, 95% CI 0.67 - 1.53, P = 0.97; interaction *P* = 0.007) with no significant heterogeneity between studies. The combined endpoint of HF admission or death was also reduced in HFrEF patients by the use of (NT-pro) BNP-guided therapy (HR = 0.78, 95% CI 0.66 - 0.92, *P* = 0.004), but not in the HFpEF group (HR = 1.08, 95% CI 0.76 - 1.53, *P* = 0.66; interaction *P* = 0.001). There was no significant heterogeneity between studies.

Table 1 Baseline characteristics from participating studies

	Overall (n = 2137)	BATTLESCARRED (n = 242)[12]	Troughton et al. (n = 69)[15]	PRIMA (n = 345)[9]	PROTECT (n = 151)[10]	Signal-HF (n = 252)[13]	TIME-CHF (n = 622)[14,17]	UPSTEP (n = 268)[11]	Berger et al. (n = 188)[8]
Age (years)	73.5 ± 10.6	74.0 ± 9.2	70.0 ± 9.9	72.2 ± 11.9	63.3 ± 14.0	77.8 ± 7.6	76.9 ± 7.6	70.8 ± 9.8	71.1 ± 11.8
Age ≥75 years	1123 (53%)	138 (57%)	24 (35%)	167 (48%)	38 (25%)	183 (73%)	380 (61%)	105 (39%)	88 (47%)
Male gender	1406 (66%)	157 (65%)	53 (77%)	199 (58%)	127 (*n* = 84%)	180 (71%)	369 (59%)	196 (73%)	125 (66%)
BMI (kg/m2) (*n* = 1591)	26.5 ± 4.8	26.8 ± 4.9	27.4 ± 4.8 (*n* = 67)	26.5 ± 5.0 (*n* = 238)	na	na	25.6 ± 4.4	27.3 ± 4.8	27.1 ± 5.2
Hypertension (*n* = 2129)	1251 (59%)	117 (48%)	45 (66% of 68)	167 (49% of 338)	79 (52%)	139 (55%)	462 (74%)	116 (43%)	126 (67%)
Renal failure (*n* = 1985)	524 (26%)	63 (26%)	16 (23%)	47 (14% of 344)	na	6 (2%)	355 (57%)	7 (3%)	30 (16%)
CVI/TIA (*n* = 1986	325 (16%)	52 (21%)	19 (28%)	66 (19%)	na	30 (12%)	98 (16%)	39 (15%)	21 (11%)
Diabetes	668 (31%)	52 (21%)	16 (23%)	91 (26%)	63 (42%)	53 (21%)	222 (36%)	85 (32%)	86 (46%)
COPD	364 (17%)	52 (21%)	23 (33%)	59 (17%)	31 (21%)	28 (11%)	124 (20%)	17 (6%)	30 (16%)
PVD (*n* = 1798)	249 (14%)	30 (12%)	12 (17%)	65 (19%)	na	0 (0%)	124 (20%)	18 (15%)	na
Cancer (*n* = 1554)	186 (12%)	na	5 (7%)	47 (14% of 343)	na	24 (10%)	86 (14%)	24 (9%)	na
NYHA ≥ III	1163 (54%)	56 (23%)	14 (20%)	74 (21%)	83 (55%)	96 (38%)	473 (76%)	184 (69%)	183 (93%)
LVEF ≤45%*	1731 (85%)	134 (63%)	69 (100%)	229 (73%)	151 (100%)	204 (98%)	499 (80%)	268 (100%)	177 (94%)
LVEF >45%*	301 (15%)	78 (37%)	0	84 (27%)	0	5 (2%)	123 (20%)	0	11 (6%)
LVEF unknown	105 (5%)	30 (12%)	0	32 (9%)	0	43 (17%)	0	0	0
LVEF (%) (*n* = 1672)	32 [25 - 40]	40 [28 - 53] (*n* = 212)	27 [21 - 34]	34 [25 - 48] (*n* = 313)	26 [20 - 34]	34 (25 - 38] (*n* = 209)	32 [25 - 42]	na	30 [22 - 35] (*n* = 96)
Creatinine (µmol/L) (*n* = 2125)	109 [88.2 - 140]	110 [90 - 130]	90 [80 - 110]	121 [101 - 158]	124 [97 - 150]	95 [76 - 117] (*n* = 242)	108 [87 - 140]	100 [83 - 126] (*n* = 264)	115 [89 - 149]
NT-proBNP or BNP (pg/mL)	2645 [1434 - 5088] (excl UPSTEP)	2001 [1236 - 2974]	1467 [1077 - 2807]	2950 [1319 - 5445]	2118 [1122 - 3831]	2363 [1373 - 4040]	3836 [1916 - 6905]	609 [356 - 947]†	2280 [1256 - 5193]

Table 1 Continued

	Overall (n = 2137)	BATTLESCARRED (n = 242)[12]	Troughton et al. (n = 69)[15]	PRIMA (n = 345)[9]	PROTECT (n = 151)[10]	Signal-HF (n = 252)[13]	TIME-CHF (n = 622)[14,17]	UPSTEP (n = 268)[11]	Berger et al. (n = 188)[8]
ACE-inhibitor (*n* = 1976)	1460 (74%)	202 (83%)	69 (100%)	255 (74%)	na	130 (54%) (*n* = 242)	479 (77%)	196 (73%)	129 (69%)
ARB (*n* = 1976)	401 (20%)	47 (19%)	0 (0%)	63 (18%)	na	55 (23%) (*n* = 242)	102 (16%)	95 (35%)	39 (21%)
β -Blocker (*n* = 1976)	1443 (73%)	131 (54%)	5 (7%)	284 (82%)	na	146 (60%) (*n* = 242)	476 (77%)	252 (94%)	149 (79%)
Spironolactone (*n* = 1976)	716 (36%)	27 (11%)	0 (0%)	186 (54%)	na	36 (15%) (*n* = 242)	234 (38%)	151 (56%)	82 (44%)
Loop diuretic (*n* = 1976)	1706 (86%)	232 (96%)	69 (100%)	333 (97%)	na	112 (46%) (*n* = 242)	574 (92%)	232 (87%)	154 (82%)
(NT-pro)BNP-guided therapy	1072 (50%)	121 (50%)	33 (48%)	174 (50%)	75 (50%)	127 (50%)	310 (50%)	140 (52%)	92 (49%)

Numbers are n (%) unless otherwise indicated.

* Percentage of those with known left ventricular ejection fraction (LVEF).

† BNP levels.

BMI, body mass index; CVI, cerebrovascular insult; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; NYHA, New York heart association classification; ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; (NT-pro)BNP, (N-terminal pro-)brain natriuretic peptide; na, not available.

Influence of comorbidities on (*N*-terminal pro-)brain natriuretic peptide-guided therapy

Comorbidities influenced response to (NT-pro)BNP-guided therapy with respect to mortality in both HFrEF and HFpEF (*Figure 3*). In HFrEF, the response to (NT-pro)BNP-guided therapy was primarily seen in patients without COPD, diabetes, cardiovascular insult (CVI)/transient ischaemic attack (TIA) or PVD. Although any single co-morbidity interaction with treatment efficacy did not reach statistical significance, when comorbidities were considered in combination, this interaction was significant. Thus, compared with symptom-guided therapy, (NT-pro)BNP-guided therapy reduced mortality (HR = 0.61, 95% CI 0.42 - 0.88, P = 0.008) in patients with no history of CVA/TIA, diabetes or COPD. Such benefit was absent in those with any one of these comorbidities (HR = 0.94, 95% CI 0.71 - 1.24, P = 0.65). When also considering PVD, patients with none or only one of these four comorbidities (i.e. COPD, diabetes, CVI/TIA, PVD) had a mortality benefit of 33% (HR = 0.67, 95% CI 0.51 - 0.89, P = 0.005), whereas those with two or more of them did not benefit (HR = 0.99, 95% CI 0.62 - 1.59, P = 0.97). Interestingly, a history of renal failure had no influence on treatment response (*Figure 3*). When using baseline estimated glomerular filtration rate (eGFR) to define renal failure (i.e. ≤60 mL/min.1.73m^2 using simplified Modification of Diet in Renal Disease equation),[18] treatment response was not influenced by either eGFR >60 (n = 776: HR = 0.78, 95% CI 0.51 - 1.20, P = 0.25) or eGFR ≤60 (n = 944: HR = 0.81, 95% CI 0.63 - 1.06, P = 0.12; interaction p > 0.2).

In HFpEF, comorbidities also influenced treatment response, but the pattern differed from that in HFrEF. Patients without hypertension allocated to (NT-pro)BNP-guided therapy had worse outcome than those allocated to clinically-guided therapy, whereas in those with hypertension no such harm was seen (interaction P = 0.02). Conversely, HFpEF patients with a history of renal failure fared worse on (NT-pro)BNP-guided therapy. This was also the case when using eGFR to define renal failure (eGFR >60 n = 98: HR = 0.71, 95% CI 0.27 - 1.86; eGFR ≤60 n = 203: HR = 1.47, 95% CI 0.85 - 2.55; interaction P = 0.05). In contrast to HFrEF, other comorbidities or combinations thereof did not influence treatment response (*Figure 3*).

Table 2 Baseline characteristics comparing patients with preserved vs. reduced left ventricular ejection fraction (LVEF)

	HFpEF (*n* = 296)	HFrEF (*n* = 1731)	*P*	Age <75 years (*n* = 977)	Age ≥75 years (*n* = 1050)	*P*
Age (years)	77.2 ± 9.3	72.6 ± 10.7	<0.001	64.7 ± 8.7	81.2 ± 4.0	-
Age ≥75 years	200 (68%)	850 (49%)	<0.001	0 (0%)	1050 (100%)	-
Male gender	121 (41%)	1215 (70%)	<0.001	713 (73%)	623 (59%)	<0.001
BMI (kg/m2) (*n* = 1546)	27.2 ± 5.2 (*n* = 257)	26.3 ± 4.6 (*n* = 1289)	0.01	27.6 ± 5.0 (n = 747)	25.3 ± 4.2 (*n* = 799)	<0.001
Hypertension (*n* = 2019)	216 (73%) of 295	982 (57%) of 1724	<0.001	517 (53%)	681 (65%) of 1042	<0.001
Renal failure (*n* = 1875)	117 (40%)	395 (25%) of 1579	<0.001	182 (21%) of 863	330 (33%) of 1012	<0.001
CVI/TIA (*n* = 1876)	58 (20%)	253 (16%) of 1580	0.13	120 (14%) of 864	191 (19%) of 1012	0.004
Diabetes	89 (30%)	549 (32%)	0.57	331 (34%)	307 (29%)	0.03
COPD	44 (15%)	289 (17%)	0.43	170 (17%)	163 (16%)	0.26
PVD (*n* = 1688)	60 (21%) of 285	174 (12%) of 1403	<0.001	95 (12%) of 764	139 (15%) of 924	0.12
Cancer (*n* = 1474)	32 (15%) of 207	143 (11%) of 1267	0.09	57 (9%) of 667	118 (15%) of 807	<0.001
CVI/TIA, COPD or diabetes (*n* = 1876)	152 (51%)	798 (51%)	0.79	439 (51%) of 864	551 (50%) of 1012	0.89
CVI/TIA, COPD, diabetes or PVD (*n* = 1688)	163 (57%)	745 (53%)	0.21	401 (52%) of 764	507 (55%) of 924	0.33
NYHA ≥ III	149 (50%)	980 (57%)	0.04	504 (52%)	625 (60%)	<0.001
LVEF (%) (*n* = 1667)	55 [50 - 60] (*n* = 289)	30 [23 - 35] (*n* = 1378)	-	30 [22 - 37] (*n* = 771)	35 [25 - 45] (*n* = 896)	<0.001
HFrEF	0 (0%)	1731 (100%)	-	881 (90%)	850 (81%)	<0.001
Creatinine (µmol/L) (*n* = 2016)	111 [87 - 142]	108 [88 - 140] (*n* = 1720)	0.35	103 [85 - 132] (*n* = 972)	114 [90 - 146] (*n* = 1044)	<0.001
NT-proBNP (pg/mL) (*n* = 1758)*	2061 [1350 - 3933]	2811 [1467 - 5481] (*n* = 1462)*	<0.001	2077 [1110 - 4026] (*n* = 813)*	3256 [1818 - 6323] (*n* = 945)*	<0.001
ACE-inhibitor (*n* = 1866)	207 (70%)	1179 (75%) of 1570	0.06	660 (76%) of 863	726 (72%) of 1003	0.04
ARB (*n* = 1866)	55 (19%)	332 (21%) of 1570	0.32	191 (22%) of 863	196 (20%) of 1003	0.17
β -Blocker (*n* = 1866)	195 (66%)	1184 (75%) of 1570	0.001	662 (77%) of 863	717 (71%) of 1003	0.01
Spironolactone (*n* = 1866)	81 (27%)	407 (26%) of 1570	0.61	265 (31%) of 863	223 (22%) of 1003	<0.001
Loop diuretic (*n* = 1866)	274 (93%)	1349 (86%) of 1570	0.002	757 (88%) of 863	866 (86%) of 1003	0.38
(NT-pro)BNP-guided therapy	144 (49%)	862 (50%)	0.75	493 (50%)	513 (49%)	0.47

Numbers are n (%) unless otherwise indicated.

* Excluding patients from UPSTEP trial.

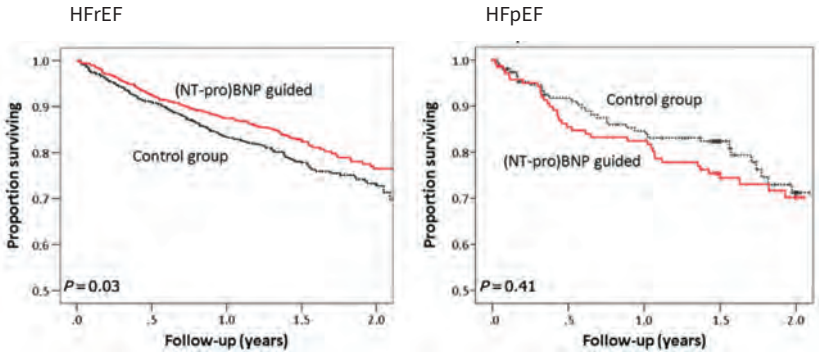
HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; BMI, body mass index; CVI, cerebrovascular insult; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; NYHA, New York Heart Association classification; ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; (NT-pro)BNP, (N-terminal pro-)brain natriuretic peptide.

The influence of comorbidities on the response to (NT-pro)BNP-guided therapy with respect to HF admissions was considerably less than for mortality. For this end-point, no statistically significant interaction between comorbidities and the efficacy of (NT-pro)BNP-guided treatment was found in either HFrEF or HFpEF. The hazard ratios for HF admission on (NT-pro)BNP-guided therapy compared with clinically-guided management according to comorbidities are given in the Supplementary tables, *Table S1; Table S2* gives an overview of the number of patients included in each subgroup and the number of events.

Influence of age on (*N*-terminal pro-)brain natriuretic peptide-guided therapy

The previously described interaction between age and treatment strategy allocation on mortality was confirmed in the current analysis. Thus in HFrEF patients, the beneficial effect was mainly seen in patients aged <75 years (HR = 0.68, 95% CI 0.48 - 0.96, P = 0.03; n = 881), but not in those aged ≥75 years (HR = 0.87, 95% CI 0.65 - 1.16, P = 0.35; n = 850; interaction P = 0.22). In HFpEF patients aged <75 years, NT-proBNP-guided therapy resulted in a HR of 0.76 (95% CI 0.29 - 1.96, P = 0.56; n = 96), whereas in those aged ≥75 years the HR was 1.56 (95% CI 0.90 - 2.70, P = 0.11; n = 200; interaction P = 0.02). The interaction between age and treatment efficacy disappeared when interactions between comorbidities and treatment strategy allocation were considered (*Table 3*), whereas the interactions between comorbidities and treatment efficacy were not influenced by age. Thus in patients with HFpEF, the effect of age on treatment response was no longer apparent when additional interactions with renal failure or the combination of CVI, diabetes mellitus, and COPD were considered. In patients with HFrEF, the presence of one of the following four comorbidities explained the potential influence of age: CVI/TIA, diabetes, COPD, or PVD. In both HFpEF and HFrEF, the benefit of (NT-pro)BNP-guided therapy was greater in patients with hypertension, independently of the interaction with age.

Age had little impact upon the effect of (NT-pro)BNP-guided therapy upon HF admissions in either patient group (both interactions P > 0.30).



BNP-guided	787	708	558	355	136	147	115	109	75	40
# events		58	94	121	135		20	24	33	37
Control	793	699	525	377	139	154	128	117	87	34
# events		71	124	154	167		12	22	25	32

Interaction P = 0.016

Figure 1 Kaplan - Meier curves of survival comparing patients allocated to (N-terminal pro-)brain natriuretic peptide (NT-proBNP)-guided treatment or control group with reduced left ventricular ejection fraction (HFrEF)) and preserved left ventricular ejection fraction (HFpEF).

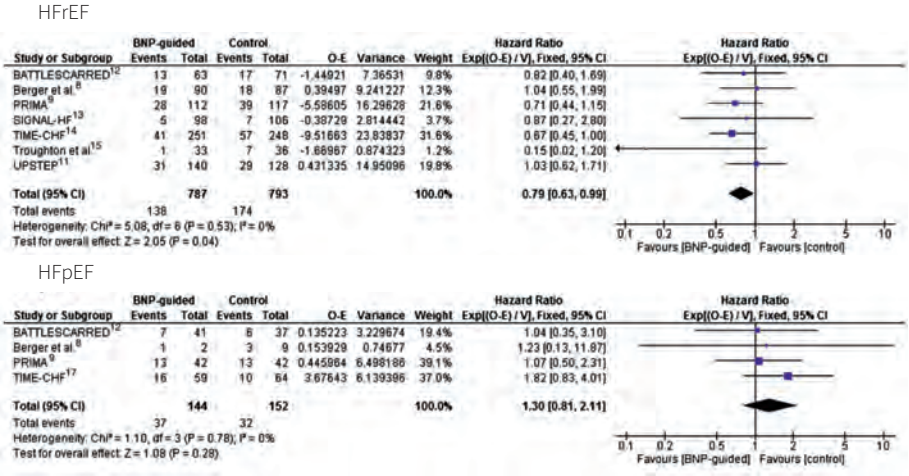


Figure 2 Forest plot of the primary endpoint, overall mortality, showing unadjusted individual and mean hazard ratios with 95% confidence intervals for seven studies providing individual patient data of patients with heart failure with reduced ejection fraction (HFrEF) and four studies also including patients with heart failure with preserved ejection fraction (HFpEF). BNP-guided, (*N*-terminal pro-)brain natriuretic peptide (NT-proBNP)-guided treatment.

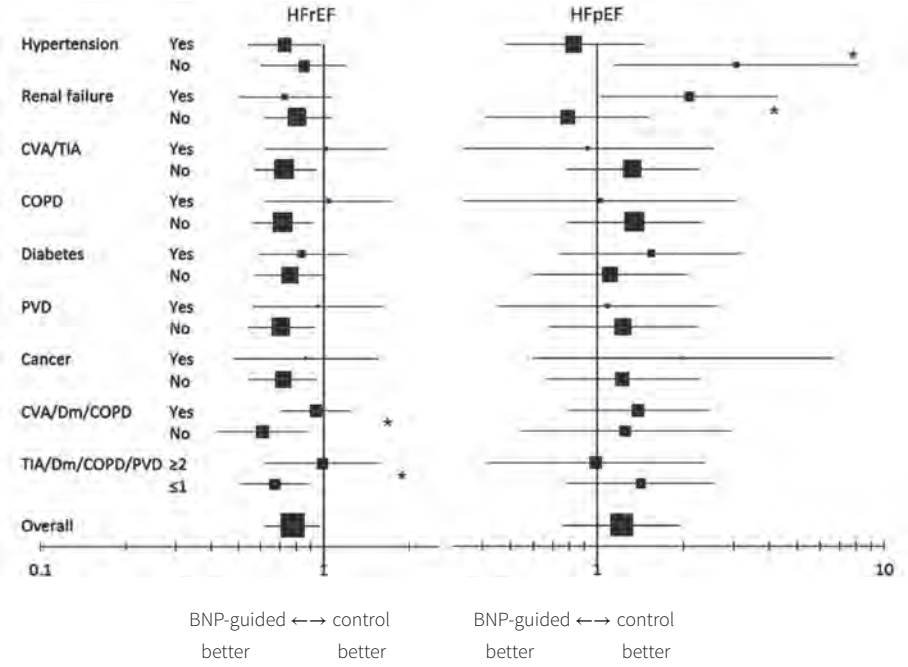


Figure 3 Univariable hazard ratios (HR) on mortality with 95% confidence intervals of (N-terminal pro-) brain natriuretic peptide (NT-proBNP)-guided therapy compared with control group depending on presence (yes) or absence (no) of various comorbidities in patients with heart failure with reduced ejection fraction (HFrEF) (left) and heart failure with preserved ejection fraction (HFpEF) (right). 'Overall' refers to all patients irrespective of the presence or absence of comorbidities. HR <1.0 indicates beneficial effects of (NT-pro)BNP-guided therapy.

Table 3 Level of significance for interaction terms with treatment strategy allocation group regarding mortality

	HFpEF	HFrEF
Age ≥75 years	0.08*	0.05*
Hypertension	0.005†	0.05†
Age ≥75 years	0.22	0.51
Renal failure	0.01*	0.11
Age ≥75 years	0.19	0.61
CVI/Dm/COPD	0.03*	0.06 *
Age ≥ 75 years	0.03*	0.52
CVI/Dm/COPD/PVD ≥2	0.61	0.01*

Significant interactions indicate different response to treatment with as compared to without presence of indicated criterion in bivariate interaction Cox-regression model.
* Less positive effect of (NT-pro)BNP-guided therapy in patients with this criterion.
† More positive effect of (NT-pro)BNP-guided therapy in patients with this criterion.
HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; CVI, cerebrovascular insult (also includes transient ischaemic attack); Dm, diabetes mellitus; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.

DISCUSSION

There is considerable uncertainty as to which patients will benefit from (NT-pro) BNP-guided therapy for HF. The present analysis based on individual patient data from eight randomized trials provides important insights, showing that positive effects were seen almost exclusively in patients with reduced LVEF. Importantly, comorbidities strongly influenced the response to guided therapy and explained the lower efficacy of this approach in elderly patients. These findings better define the group of patients possibly benefiting from guided therapy and suggests lack of uniformity of response to evidence-based treatments among HF patients.

Influence of comorbidities on biomarker-guided therapy

In addition to the interactions with age and LVEF outlined above, the efficacy of (NT-pro)BNP-guided therapy was significantly influenced by comorbidities. In fact, the suggested effect of age on (NT-pro)BNP-guided therapy efficacy can be explained entirely by the presence of comorbidities. This was true with respect to mortality but less to the combined endpoint and not to HF hospitalizations (data not shown), in line with the finding that the effect of age was only seen with respect to mortality, but not HF hospitalizations.[1] Thus, HF hospitalization might be reduced by more intense HF-specific treatment irrespective of the presence or absence of comorbidities.

Our results call into question the belief that (NT-pro)BNP-guided HFrEF care is limited simply by age. We hypothesize that comorbidities rather than age *per se* globally affect HF care. Thus, it might be that comorbidities influence the treatment response to HF medication. It is well known that comorbidities negatively influence prognosis in HF patients. Moreover, there are numerous studies showing the potential risk of drug-drug interactions leading to adverse effects with the increasing number of comorbidities and, as a consequence, increasing number of prescribed drugs.[19] However, it is less clear if this may result in fewer beneficial effects of HF-specific medication. Unfortunately, full understanding of how multiple comorbidities in'real world' patients affect effectiveness of proven therapies for HF is lacking. Based on the large randomized treatment trials in HF, trends were seen towards less positive effects of active treatment in patients with comorbidities (e.g. SENIORS, EMPHASIS-HF),[20,21] but a systematic evaluation of such potential interaction is, to the best of our knowledge, still lacking. Therefore, the potential reason(s) for lower effectiveness of more intensified therapy in HF patients with comorbidities must remain speculative.

In HFrEF patients forming the majority of the study population, comorbidities including diabetes, PVD, CVI/TIA and COPD influenced the effects of NT-proBNP-guided therapy upon mortality. Diabetes mellitus and COPD are frequent comorbidities in HF.[22] They are of independent prognostic importance[23] and might, therefore, influence prognosis such that NT-proBNP-guided therapy has less effect. Interestingly, no interaction was seen with renal failure, which is in line with the recent finding that intensifying HFrEF therapy may reduce the negative effects of worsening renal failure on prognosis.[24] This might be related to the fact that renal dysfunction is often an expression of poor cardiac function in patients with HFrEF, whereas this is not so much the case in HFpEF.

In addition to a better understanding of the effects of (NT-pro) BNP-guided therapy in HF, our results shed new light on HF treatment in general. Only a minority of real-life HF patients fulfil the enrolment criteria of landmark HF trials[25] because patients with comorbidities have often been excluded. In contrast, most of the (NT-pro)BNP-guided HF trials did not have similarly restrictive inclusion criteria, resulting in recruitment of more 'real world' patients. Our results on comorbidities might explain why in daily practice, recommended therapies are often not used in adequate doses. It might be speculated that in elderly multi-morbid patients, use of biomarkers may help to identify patients in whom avoiding up-titration or down-titration may be superior to the current approach. The effect of HF medication in patients with combined comorbidities and the feasibility and wisdom of titrating to currently recommended target doses in such patients remains to be assessed in future trials.

Heart failure with preserved vs. reduced left ventricular ejection fraction

Compared with patients with HFrEF, patients with HFpEF have substantially different demographics.[26-28] Previous data suggest lower event rates among those with HFpEF compared with HFrEF even after correction for other significant predictors.[7,26] However, in our cohort, patients with HFpEF and HFrEF had comparable mortality rates and the combined endpoint of hospitalization because of HF or death was more often reached in HFpEF patients. This difference might be partly explained by the fact that the studies which included HFpEF (TIME-CHF, PRIMA, BATTLESCARRED and Vienna) included patients (recently) hospitalized for acutely decompensated HF.[8,9,12,17] As survival differences between HFrEF and HFpEF diminish with increasing age,[26] inclusion of the generally more aged HFpEF group of TIME-CHF[17] could also have contributed to this finding. Finally, guided

therapy positively influenced mortality and combined endpoint rates in HFrEF only, where treatments that reduce mortality are available, in contrast to HFpEF.

The lack of benefit from (NT-pro)BNP-guided therapy in HFpEF was not detected in our previous meta-analysis, probably owing to the very limited power by the small number of HFpEF cases included.[1] TIME-CHF contributes substantially to this lack of benefit in HFpEF and it might be argued that this is entirely caused by TIME-CHF. When excluding the TIME-CHF data the interaction between the treatment response on mortality and the two groups based on LVEF was no longer statistically significant (data not shown). However, the treatment effects were homogeneous between studies in both the HFpEF and the HFrEF group. In addition to the notion that HFrEF and HFpEF may be two distinct diseases,[17] several other concepts may be relevant to these findings. Although a large cohort study found some positive results of renin-angiotensin system blockade in patients with LVEF of 40% or higher,[29] such treatments failed to improve outcome in HFpEF in large prospective randomized therapeutic trials.[5-7] Therefore, it is not surprising that delivering currently available HF therapies in an alternative manner does not affect outcome. Notably, HFpEF patients without hypertension and those with renal failure incurred worse outcomes when treated with guided therapy, whereas those with hypertension and/or without renal failure showed neutral results. In contrast, medical and device treatment has markedly improved prognosis in HFrEF over recent decades.[4] Our findings support current treatment recommendations for HFpEF, which are restricted to treatment of comorbidities and symptoms[4] and the role of natriuretic peptides in HFpEF appears limited, at least at present, to diagnosis and prognosis.[30,31]

Limitations

Our study has important limitations. We were able to include only those studies on NT-proBNP-guided therapy that provided individual patient data, which might introduce a bias. Although based on individual patient data, our analyses could not address potentially important aspects of management because such information was not collected equally in the trials. In particular, we do not know if effects of comorbidities on (NT-pro)BNP-guided therapy were mainly driven by less uptitration in such patients compared with those with little or no comorbidities. Uptitration was less in elderly patients irrespective of treatment if reported specifically (BATTLESCARRED, TIME-CHF),12,14 but it was still significantly more in the NT-proBNP-guided group than in the control group in TIME-CHF.14

Moreover, results on HF hospitalizations were not influenced by comorbidities, arguing against lack of therapy intensification as main reason for this finding. In addition, diagnosis of comorbidities was not based on specific testing, but rather on medical records. However, this is common practice and represents clinical care in patients with HF. Moreover, we do not have sufficient data in the majority of the studies to calculate an established co-morbidity index (e.g. Charlson index), although we included the most common comorbidities in HF patients. In addition, this is a post-hoc analysis best regarded as hypothesis-generating. Finally, the number of patients was not sufficiently large to address all subgroup analyses with sufficient power. This is particularly true for HFpEF patients, in which the number of events was small. In addition, we used multiple testing and statistical tests for interactions are not powerful. This prevented us from doing in-depth analysis which factors may explain the different response between HFrEF and HFpEF. Finally, we do not have sufficient data to test if uptitration differed between these two groups. However, in the study including most HFpEF patients, uptitration of medication did not differ between the two groups, but reduction in NT-proBNP levels was less in HFpEF patients.17 Thus, interpretation of our findings must be done with caution, particularly in patients with HFpEF.

Conclusion

Our individual patient data meta-analysis indicates that NT-proBNP-guided therapy may be helpful in HFrEF but not in HFpEF. Our results support the notion that HFrEF and HFpEF are two distinct entities. Moreover, the effects of intensifying HF treatment seem to be strongly influenced by comorbidities and not by age per se, but further prospective studies are required to test these hypotheses.

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Conflict of interest:

H-P.B.LR. received unrestricted grant support and honoraria from Roche Diagnostics. L.E. received consultancy fees from Roche Diagnostics. M.R. received honoraria, travel grants, and research grants from Roche Diagnostics and Alere. J.J. received grant support from Siemens, Brahms, and Singulex. consultancy fees from Roche Diagnostics, Sphingotec, Critical Diagnostics. U.D. received consultancy fees from Vifor Pharma, Alere, and Novartis, honoraria from Roche Diagnostics and unrestricted grant support from Astra Zeneca. H.G. received honoraria or consultancy fees from Roche Diagnostics, Critical Diagnostics, and Luitpold Pharmaceuticals. C.O'C. received institutional grant support from Roche Diagnostics. R.T. received grant support and honoraria from Roche Diagnostics and St Jude Medical. The remaining authors report no conflicts of interest.

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SUPPLEMENTARY TABLES

Suppl Table 1 Hazard ratio (HR) of HF admission comparing (NT-pro)BNP-guided therapy with symptom-guided therapy with presence and absence of co-morbidities.

		HFpEF			HFrEF		
		HR	95%-CI	p	HR	95%-CI	p
Hypertension	No	1.19	0.53-2.65	0.68	0.82	0.62-1.10	0.18
	Yes	0.96	0.59-1.57	0.88	0.78	0.61-1.00	0.05
Renal failure	No	0.86	0.49-1.50	0.60	0.83	0.66-1.05	0.12
	Yes	1.31	0.70-2.46	0.40	0.78	0.56-1.10	0.15
CVI	No	1.10	0.69-1.76	0.69	0.78	0.63-0.97	0.03
	Yes	0.67	0.26-1.68	0.39	0.97	0.63-1.49	0.90
Diabetes	No	1.23	0.75-2.03	0.41	0.86	0.67-1.09	0.22
	Yes	0.63	0.28-1.42	0.27	0.77	0.57-1.03	0.08
COPD	No	0.99	0.62-1.57	0.97	0.80	0.65-0.99	0.04
	Yes	1.30	0.49-3.47	0.60	0.77	0.50-1.17	0.22
PVD	No	0.92	0.57-1.48	0.73	0.81	0.65-1.01	0.06
	Yes	2.10	0.67-6.53	0.20	1.15	0.66-1.98	0.63
CVI/Dm/ COPD	No	1.37	0.74-2.54	0.32	0.80	0.59-1.09	0.16
	Yes	0.78	0.43-1.41	0.41	0.85	0.66-1.09	0.19
CVI/Dm/ COPD/PVD	No	1.15	0.71-1.88	0.57	0.83	0.65-1.05	0.12
	Yes	0.74	0.30-1.79	0.50	0.85	0.56-1.30	0.45

Abbreviations: CVI = cerebro-vascular insult (also includes transient ischemic attack), Dm = diabetes mellitus, COPD = chronic obstructive pulmonary disease, PVD = peripheral vascular disease.

Suppl Table 2 Number of patients and number of events in the different subgroups, related to the presence and absence of co-morbidities.

		HFpEF			HFrEF		
		# of patients whole group	# of deaths	# of HF admissions	# of patients whole group	# of deaths	# of HF admissions
Hyper-tension	No	79	18	24	742	129	185
	Yes	216	50	65	982	181	254
Renal failure	No	179	36	50	1184	204	282
	Yes	117	33	39	395	108	135
CVI	No	238	43	70	1327	249	333
	Yes	58	15	19	253	63	84
Diabetes	No	207	60	63	1182	195	262
	Yes	89	29	26	549	117	180
COPD	No	252	55	72	1442	252	356
	Yes	44	14	17	289	60	86
PVD	No	225	44	68	1229	219	304
	Yes	60	21	16	174	56	54
CVI/Dm/ COPD	No	144	22	42	782	120	161
	Yes	152	47	47	798	192	256
CVI/Dm/ COPD/PVD	No	122	16	34	658	97	132
	Yes	163	49	50	745	178	226

CHAPTER 5

Risk Stratification With the Use of Serial N-Terminal Pro-B-Type Natriuretic Peptide Measurements During Admission and Early After Discharge in Heart Failure Patients: Post Hoc Analysis of the PRIMA Study

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ABSTRACT

Objective

The aim of this work was to assess the prognostic value of absolute N-terminal-pro-B-type natriuretic peptide (NT-proBNP) concentration in combination with changes during admission because of acute heart failure (AHF) and early after hospital discharge.

Background

In AHF, readmission and mortality rates are high. Identifying those at highest risk for events early after hospital discharge might help to select patients in need of intensive outpatient monitoring.

Methods and results:

We evaluated the prognostic value of NT-proBNP concentration on admission, at discharge, 1 month after hospital discharge and change over time in 309 patients included in the PRIMA (Can PRo-brain-natriuretic peptide-guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study. Primary outcome measures were mortality and the combined end point of heart failure (HF) readmission or mortality. In a multivariate Cox regression analysis, change in NT-proBNP concentration during admission, change from discharge to 1 month after discharge, and the absolute NT-proBNP concentration at 1 month after discharge were of independent prognostic value for both end points (hazard ratios for HF readmission or mortality: 1.71, 95% confidence interval [CI] 1.13-2.60, Wald 6.4 [P = .011] versus 2.71, 95% CI 1.76-4.17, Wald 20.5 [P < .001] versus 1.81, 95% CI 1.13-2.89, Wald 6.1 [P = .014], respectively.

Conclusions

Knowledge of change in NT-proBNP concentration during admission because of AHF in combination with change early after discharge and the absolute NT-proBNP concentration at 1 month after discharge allows accurate risk stratification.

INTRODUCTION

Acute heart failure (HF) is not only associated with a high in-hospital mortality rate,[1] but short- and long-term prognosis after hospital discharge also remains poor, with high mortality and readmission rates.[2,3] Therefore, post-discharge risk stratification is important because it may help to identify those patients in need of intensive outpatient monitoring and treatment. Unfortunately, even for trained clinicians it can be quite challenging to accurately stratify risk in those who have recently been admitted because of acute HF. During the last decade, B-type natriuretic peptide (BNP) and its cleavage equivalent N-terminal pro-BNP (NT-proBNP) have proved to be powerful prognostic markers in both acute and chronic HF. In acute HF, both pre-discharge (NT-pro)BNP concentration and decrease in NT-proBNP during hospital admission are related to outcome after hospital discharge.[4,5] Also in chronic HF, not only does a single measurement of natriuretic peptides reflect risk, but variation in natriuretic peptides also adds to prognostic assessment.[6]

However, the prognostic value of change in NT-proBNP concentration 1 month after admission because of acute HF has not yet been evaluated. Furthermore, the incremental value of serial NT-proBNP measurements during admission and early after hospital discharge has not yet been assessed. Therefore, we sought to identify which NT-proBNP parameters during admission and early after discharge (ie, absolute NT-proBNP concentration at admission, discharge, 1 month after hospital discharge, change in NT-proBNP during admission [''inpatient change''], and change in NT-proBNP concentration between discharge and 1 month after discharge [''early outpatient change'']) were of independent prognostic importance. Finally, because biologic variation of NT-proBNP in HF has been reported to be high in chronic HF,[7] one might conclude that only large early outpatient changes in NT-proBNP have prognostic impact. Therefore, we also assessed the prognostic impact of relatively small early outpatient changes in NT-proBNP (ie, changes up to 30%).

METHODS

Study Design and Study Population

This was a post hoc analysis of patients included in the PRIMA (Can PRo-brain-natriuretic peptide-guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study, a prospective randomized multicenter study assessing the effect of management of chronic HF guided by individual NT-proBNP targets.[8] Inclusion criteria have been published previously.[8] In short, patients were included during hospital admission for acute HF. NT-proBNP concentration at admission was required to be ≥1,700 pg/mL, and included patients also needed to demonstrate a decrease in NT-proBNP concentration of at least 10% with a minimum of 850 pg/mL during admission. At discharge, patients were randomized to outpatient treatment that was either clinically-guided where NT-proBNP was measured but not revealed to the physician, or to outpatient treatment where NT-proBNP levels were provided to guide therapy. The follow-up period was up to 2 years. For the present analysis, patients with outpatient NT-proBNP concentration available 1 month after hospital discharge were included. As a result, patients not attending the outpatient clinic 1 month after discharge (because of death, readmission, or any other reason) were not included. All events occurring before the outpatient visit 1 month after hospital discharge were censored.

Definition of Study End Points

Primary outcome measures were mortality and the combined end point of HF readmission or mortality within the follow-up period after the outpatient visit 1 month after discharge. Secondary end points encompassed the primary end points reached at 90, 180, and 365 days of follow-up.

Statistical Analysis

Data are presented as frequencies, mean ±SD, or median (interquartile range [IQR]). Comparisons between groups were performed with the use of Fischer exact test for categoric data and 1-way analysis of variance or Kruskal-Wallis H test for continuous data, as appropriate. Glomerular filtration rate was estimated (eGFR) with the use of the Modified Diet in Renal Disease equation.[9]

Univariate Cox proportional hazard regression analysis was performed to assess clinical covariates associated with mortality. Spearman rank correlations where used to test correlations among the various NT-proBNP parameters.

Multivariate Cox proportional hazard regression analysis was performed with the use of all covariates associated with outcome, except renal function and NT-proBNP concentration, to assess the clinical model. Variables were added in a stepwise fashion with $P < .05$ and $P < .1$ as the cutoffs for entry or retention, respectively. After assessment of the clinical model, renal function (eGFR < 30 mL/min, eGFR 30-60 mL/min, or eGFR >60 mL/min) was added to form the reference model. To assess the independent prognostic value of NT-proBNP concentration on admission, at discharge, inpatient change, early outpatient change, and NT-proBNP concentration at 1 month after hospital discharge, these parameters were added to the reference model in a stepwise fashion to form the final NT-proBNP model.

Model accuracy and discrimination were evaluated for both mortality and the combined end point of HF readmission or mortality within 1 year of follow-up by (i) c-statistic, a measure of the area under the receiver operating characteristic curve (AUC) and (ii) integrated discrimination improvement (IDI). Calculations were done with the use of IBM SPSS Statistics 21.0 (IBM, Armonk, New York) and Medcalc 13.3.3.0 (Medcalc Software, Ostend, Belgium).

Composite NT-proBNP Score

Independent predictive NT-proBNP parameters were used to form the composite NT-proBNP score. This was done by giving each independent prognostic NT-proBNP parameter 1 point. To assess the prognostic impact of the composite NT-proBNP score, 90-, 180, and 365-day mortality and the combined end point of HF readmission or mortality were calculated for every composite NT-proBNP score category. Furthermore, Kaplan-Meier survival curves were assessed and compared with the use of the log-rank test.

Finally the value of relatively small early outpatient changes in NT-proBNP (ie, decrease vs increase in NT-proBNP concentration of <30%) was assessed in a multivariate manner.

RESULTS

Patient Characteristics

In 309 out of 345 patients included in the PRIMA study, NT-proBNP levels at admission, discharge, and 1 month after hospital discharge were available. Patient

characteristics at baseline and 1 month after hospital discharge are presented in Table 1. Patients were overall elderly and predominantly male, more than one-half had coronary artery disease, and about one-half had an ischemic etiology of HF. At admission because of acute HF, median NT-proBNP concentration was clearly elevated, and during admission the median decrease in NT-proBNP concentration was >60%. One month after hospital discharge, median NT-proBNP concentration was 2,538 pg/mL.

Table 1. Baseline Characteristics of the Overall Population and According to Composite NT-proBNP Score Group

Patient Characteristic	Overall (n = 309)	Group 1: 0 Points (n = 62)	Group 2: 1 Point (n = 94)	Group 3: 2 Points (n = 83)	Group 4: 3 Points (n = 70)	P Value (Overall)
Baseline						
Age, y	72.0 (12.0)	68.4 (12.2)	70.0 (11.0)	75.1 (12.6)	74.4 (11.2)	.001
Female	132 (42.7)	30 (48.4)	39 (41.5)	35 (42.2)	28 (40.0)	.782
BMI, kg/m2	25 (4.8)	24.8 (4.7)	25.6 (4.6)	24.1 (4.7)	25.6 (5.2)	.213
Hypertension	153 (49.5)	31 (50.0)	50 (53.2)	33 (39.8)	39 (55.7)	.191
Diabetes mellitus	86 (27.8)	15 (24.2)	22 (23.4)	20 (24.1)	29 (41.4)	.040
Stroke or TIA	55 (17.8)	12 (19.4)	18 (19.1)	14 (16.9)	11 (15.7)	.924
Peripheral artery disease	58 (18.8)	9 (14.5)	20 (21.3)	18 (21.7)	11 (15.7)	.571
COPD	53 (17.2)	9 (14.5)	18 (19.1)	14 (16.9)	12 (17.1)	.905
Atrial fibrillation	97 (31.4)	14 (22.6)	29 (30.9)	26 (31.3)	28 (40.0)	.200
Coronary artery disease	182 (58.9)	28 (45.2)	49 (52.1)	58 (69.9)	47 (67.1)	.005
Myocardial infarction	124 (40.1)	11 (17.7)	33 (35.1)	43 (51.8)	37 (52.9)	<.001
PCI	36 (11.7)	3 (4.8)	13 (13.8)	8 (9.6)	12 (17.1)	.130
CABG	54 (17.5)	8 (12.9)	13 (13.8)	16 (19.3)	17 (24.3)	.241
Valve replacement	20 (6.5)	1 (1.6)	2 (2.1)	5 (6.0)	12 (17.1)	<.001
Pacemaker	28 (9.1)	2 (3.2)	6 (6.4)	9 (10.8)	11 (15.7)	.057
ICD	20 (6.5)	1 (1.6)	4 (4.3)	5 (6.0)	10 (14.3)	.014
Mitral regurgitation ≥II	135 (48.2)	26 (44.1)	42 (48.3)	41 (56.2)	26 (42.6)	.391
Previous episode of HF	108 (35.0)	10 (16.1)	25 (26.6)	31 (37.3)	42 (60.0)	<.001
Ischemic cause of HF	141 (45.8)	17 (27.4)	43 (45.7)	45 (54.2)	36 (52.2)	.007

Table 1. continued

Patient Characteristic	Overall (n = 309)	Group 1: 0 Points (n = 62)	Group 2: 1 Point (n = 94)	Group 3: 2 Points (n = 83)	Group 4: 3 Points (n = 70)	P Value (Overall)
NT-proBNP at admission, pg/mL	7,897 (4,345-14,030)	7,561 (4,120-12,340)	5,101 (3,234-10,491)	12,280 (6,542-17,597)	8,618 (4,915-15,729)	<.001
Discharge						
NYHA functional class ≥III	67 (21.7)	9 (14.5)	25 (26.6)	17 (20.5)	16 (22.9)	.342
Mean arterial pressure, mm Hg	85.5 (12.9)	88.5 (11.5)	88.4 (13.5)	82.6 (11.0)	82.3 (14.2)	.001
Heart rate, beats/min	76.8 (15.6)	77.3 (18.2)	77.4 (15.7)	76.0 (14.8)	76.6 (14.3)	.938
QRS duration, ms	112 (94-140)	102 (89-125)	103 (92-128)	116 (100-138)	131 (98-170)	.002
LVEF, %	35.9 (14.3)	37.7 (14.0)	36.7 (14.3)	33.6 (13.7)	35.8 (15.4)	.381
Hemoglobin, mmol/L	8.5 (1.2)	8.8 (1.4)	8.8 (1.1)	8.3 (1.2)	8.0 (1.1)	.003
Sodium, mmol/L	139.2 (3.5)	139.8 (3.7)	139.6 (3.5)	138.7 (3.0)	138.9 (4.0)	.154
Potassium, mmol/L	4.3 (0.5)	4.2 (0.4)	4.3 (0.5)	4.3 (0.4)	4.3 (0.5)	.685
Urea, mmol/L	11.7 (8.4-15.9)	9.9 (7.4-12.7)	10.7 (8.2-14.6)	12.6 (8.2-17.2)	14.3 (10.6-19.0)	<.001
Creatinine, µmol/L	119 (100-158)	103 (88-124)	114 (98-149)	131 (105-168)	149 (111-209)	<.001
eGFR, mL/min	48.1 (33.2-63.9)	60.1 (45.6-69.5)	50.4 (39.3-65.0)	42.9 (31.1-59.5)	39.6 (24.7-54.6)	<.001
NT-proBNP, pg/mL	2,936 (1,344-5,505)	1,531 (854-2,544)	1,608 (892-3,847)	4,398 (2,512-6,712)	5,112 (2,873-8,429)	<.001
NT-proBNP decrease during index hospitalization, %	61.8 (43.2-76.6)	79.4 (69.6-83.9)	66.8 (51.5-79.0)	57.4(37.6-71.7)	41.5 (29.7-51.2)	<.001
Medication at discharge						
Diuretics	299 (96.8)	60 (96.8)	90 (95.7)	81 (97.6)	68 (97.1)	.945
ACE inhibitors	222 (71.8)	51 (82.3)	68 (72.3)	56 (67.5)	47 (67.1)	.182
ARB	60 (19.4)	6 (9.7)	18 (19.1)	20 (24.1)	16 (22.9)	.140
Beta-blockers	237 (76.7)	46 (74.2)	76 (80.9)	64 (77.1)	51 (72.9)	.631
Aldosterone antagonists	164 (53.1)	33 (53.2)	44 (46.8)	46 (55.4)	41 (58.6)	.477
Digoxin	87 (28.2)	14 (22.6)	33 (35.1)	23 (27.7)	17 (24.3)	.289
Outpatient visit at 1 month						
Mean arterial pressure, mm Hg	84.7 (13.6)	89.3 (12.1)	86.4 (13.0)	82.0 (14.7)	81.4 (13.1)	.001
Urea, mmol/L	11.0 (8.3-16.7)	8.6 (6.6-11.0)	10.3 (7.2-13.8)	12.5 (8.8-18.0)	14.9 (10.7-22.7)	<.001
Creatinine, µmol/L	130 (100-167)	102 (87-140)	119 (101-148)	133 (105-180)	160 (127-205)	<.001
Early outpatient change NT-proBNP, %	3.5(-34.2 to 46.3)	-42.0 (-20.8 to -63.9)	-7.2 (-44.2 to 42.6)	8.0 (-15.8 to 54.3)	45.2 (25.1-89.9)	<.001
NT-proBNP, pg/mL	2,538 (1,272-5,434)	663 (387-1,360)	1,598 (1,051-2,159)	4,661 (3,052-6,958)	7,614 (4,949-12,928)	<.001

NT-proBNP, N-terminal pro-B-type natriuretic peptide; BMI, body mass index; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICD, implantable cardiac defibrillator; HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; ACE,

angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
Values are expressed as n (%), mean (SD), or median (interquartile range).

Prediction of Outcome

Median time from hospital discharge to the outpatient visit 1 month after discharge was 30 days (IQR 27-36 days), with a median follow-up duration of 675 days (IQR 472-700 days) after this visit.

Within the follow-up period, 83 patients died (26.9%) and 131 patients reached the combined end point of HF readmission or mortality (42.4%). Both mortality and the combined end point at 90, 180, and 365 days in the overall population are presented in Table 2. In univariate Cox regression analyses, all NT-proBNP parameters except NT-proBNP concentration at admission were highly associated with mortality (Table 3).

Comparison With Patients Not Included in This Analysis

In 309 of 345 patients, NT-proBNP concentration 1 month after hospital discharge was available. Of the patients not included for the present analysis, 5 died within 30 days after hospital discharge and 6 had reached the combined end point of HF-related readmission or mortality. After exclusion of these patients, there was a trend toward increased mortality in patients with no NT-proBNP concentration available 1 month after hospital discharge compared to those with NT-proBNP concentration available (HR 1.75, 95% CI 0.96-3.21; P=.070). However, no difference was seen in combined end point (HR 1.14, 95% CI 0.66-1.97; P= .65).

Correlation Among NT-proBNP Parameters

Correlations among NT-proBNP parameters are depicted in Supplemental Table 1. No correlation existed between inpatient change in NT-proBNP concentration and early outpatient change (r=-0.01; P= .815). Modest correlations existed between NT-proBNP concentration 1 month after hospital discharge and both inpatient and early outpatient change in NT-proBNP concentration, with strongest correlation being present between inpatient change and NT-proBNP concentration at 1 month follow-up (r= 0.56; P < .001). However, we found strong correlations between the absolute NT-proBNP concentration at admission, discharge, and 1 month after hospital discharge, with strongest correlation between NT-proBNP at admission and at discharge (r = 0.79; P < .0001).

Multivariate Analysis

Based on the multivariate analysis on clinical risk factors, previous episode of HF, ischemic etiology of HF, age, and mean arterial pressure (MAP) were included in the clinical model. In addition, renal function at 1 month after discharge (eGFR <30 mL/min, 30-60 mL/min, or >60 mL/min) was added to form the reference model. Adding eGFR as a continuous instead of a categoric variable did not change the predictive performance of the reference model.

When adding the NT-proBNP parameters to this reference model, inpatient change in NT-proBNP concentration (decrease below vs above the median), early outpatient change in NT-proBNP (increase vs decrease), and NT-proBNP concentration at 1 month after discharge (above vs below the median) remained independent prognostic markers, whereas the absolute NT-proBNP concentration at discharge dropped out of the model (Table 3).

The final NT-proBNP prognostic model therefore consisted of the reference model plus inpatient change in NT-proBNP concentration, early outpatient change in NT-proBNP, and the absolute NT-proBNP concentration 1 month after discharge.

Model accuracy and discrimination of the NT-proBNP prognostic model for 1-year mortality and 1-year HF readmission or mortality are presented in Table 4. Model accuracy and discrimination for HF readmission and mortality reached a c-statistic of 0.85 (95% CI 0.81-0.90), with excellent calibration (Hosmer-Lemeshow: P= .77), and had significantly better model performance than models with 1 NT-proBNP parameter (IDI ranging from 6% to 13% [P < .001], improvement in c-statistic ranging from 0.03 to 0.07 [P < .05]; Table 4). For mortality, the same trend was seen (Table 4).

Table 2. Mortality and Combined End Point of HF Readmission or Mortality of the Overall Population and According to the composite NT-proBNP Score

Outcome	Total Group (n = 309)	Group 1: 0 Points (n= 62)	Group 2: 1 Point (n= 94)	Group 3: 2 Points (n= 83)	Group 4: 3 Points (n= 70)	P Value
Mortality, n (%)						
90 days	16 (5.2)	0 (0)	2 (2.1)	4 (4.8)	10 (14.3)	.001
180 days	32 (10.4)	0 (0)	5 (5.3)	10 (12.0)	17 (24.3)	<.001
365 days	55 (17.8)	0 (0)	9 (9.6)	17 (20.5)	29 (41.4)	<.001
HF-related readmission or mortality, n (%)						
90 days	50 (16.2)	1 (1.6)	8 (8.5)	14 (16.9)	27 (38.6)	<.001
180 days	77 (24.9)	2 (3.2)	14 (14.9)	21 (25.3)	40 (57.1)	<.001
365 days	103 (33.3)	2 (3.2)	21 (22.3)	27 (32.5)	53 (75.7)	<.001

Abbreviations as in Table 1.

Table 3. Univariate and Adjusted Multivariate Hazard Ratios for Predictors of Mortality and for the Composite End Point of HF Readmission or Mortality

	Univariate Analysis				Adjusted Multivariate Analysis*			
	HR	95% CI	Wald	*P* Value	HR	95% CI	Wald	*P* Value
Mortality								
NT-proBNP at admission above versus below the median	1.33	0.86-2.05	1.7	.197				
Inpatient decrease NT-proBNP below vs above the median	3.07	1.90-4.98	20.9	<.001	1.72	1.01-2.91	4.0	.045
NT-proBNP at discharge above vs below the median	2.52	1.58-4.00	15.2	<.001				
Early outpatient increase vs decrease in NT-proBNP	4.94	2.90-8.43	34.4	<.001	1.88	1.12-3.16	5.6	.018
NT-proBNP at 1 month above vs below the median	2.61	1.62-4.19	15.6	<.001	2.09	1.10-3.97	5.1	.024
HF readmission or mortality								
NT-proBNP at admission above versus below the median	1.23	0.87-1.73	1.4	.242				
Inpatient decrease NT-proBNP below vs above the median	2.34	1.64-3.36	21.6	<.001	1.71	1.13-2.60	6.4	.011
NT-proBNP at discharge above vs below the median	1.71	1.21-2.43	9.2	.002				
Early outpatient increase vs decrease in NT-proBNP	3.31	2.25-4.86	37.1	<.001	2.71	1.76-4.17	20.5	<.001
NT-proBNP at 1 month above vs below the median	3.41	2.34-4.98	40.3	<.001	1.81	1.13-2.89	6.1	.014

HR, hazard ratio; CI, confidence interval; other abbreviations as in Table 1. Hazard ratios calculated within the total follow-up period.

*Adjusted for clinical parameters.

Table 4. Performance of Predictive Models for 1-Year Mortality and the Combined End Point of HF Readmission or Mortality

Model	χ2 Model	c-Statistic: AUC (95% CI)	IDI	Hos-Lem*
Mortality				
Clinical risk factors†	45.0	0.77 (0.71-0.84)		.833
+ Inpatient change in NT-proBNP	50.3§	0.79 (0.72-0.85)	2%‡	.924
+ Early outpatient change in NT-proBNP	53.7‖	0.80 (0.74-0.86)‡	3%§	.472
+ NT-proBNP at 1 month follow-up	57.0‖	0.80 (0.74-0.87)‡	4%#	.806
Clinical risk factorsy + inpatient change in NT-proBNP	50.3	0.79 (0.72-0.85)		.924
+ Early outpatient change NT-proBNP + NT-proBNP at 1 month	64.1#	0.82 (0.77-0.88)§	5%#	.461
Clinical risk factors‡ + early outpatient change in NT-proBNP	53.7	0.80 (0.74-0.86)		.472
+ Inpatient change in NT-proBNP + NT-proBNP at 1 month	64.1‖	0.82 (0.77-0.88)	4%‖	.461
Clinical risk factors† + NT-proBNP at 1 month	57.0	0.80 (0.74-0.87)		.806
+ Inpatient change in NT-proBNP + early outpatient change in NT-proBNP	64.1§	0.82 (0.77-0.88)	2%‡	.461
HF-related readmission or mortality				
Clinical risk factors†	60.7	0.76 (0.70-0.82)		.225
+ Inpatient change in NT-proBNP	72.2#	0.78 (0.73-0.84)	3%‖	.475
+ Early outpatient change in NT-proBNP	96.9#	0.82 (0.77-0.87)‖	10%#	.523
+ NT-proBNP at 1 month follow-up	83.4#	0.81 (0.76-0.86)§	7%#	.365
Clinical risk factors† + inpatient change in NT-proBNP	72.2	0.78 (0.73-0.84)		.475
+ Early outpatient change in NT-proBNP + NT-proBNP at 1 month	117.1#	0.85 (0.81-0.90)#	13%#	.773
Clinical risk factors† + early outpatient change NT-proBNP	96.9	0.82 (0.77-0.87)		.523
+ Inpatient change in NT-proBNP + NT-proBNP at 1 month	117.1#	0.85 (0.81-0.90)§	6%#	.773
Clinical risk factors† + NT-proBNP at 1 month	83.4	0.81 (0.76-0.86)		.365
+ Inpatient change in NT-proBNP + early outpatient change in NT-proBNP	117.1#	0.85 (0.81-0.90)‖	9%#	.773

AUC, area under the receiver operating characteristic curve; IDI, integrated discrimination index, Hos-Lem, Hosmer-Lemeshow; other abbreviations as in Tables 1 and 3.

*For the Hosmer-Lemeshow statistic, a *P* value close to 1 indicates excellent calibration.

†Reference model including previous episode of HF, ischemic etiology of HF, age, mean arterial pressure, and eGFR.

‡<0.1.

§<0.05.

‖<0.01.

#<0.001.

Composite NT-proBNP Score

By combining the independent prognostic NT-proBNP parameters (ie, inpatient decrease in NT-proBNP concentration below vs above the median, early outpatient increase vs decrease in NT-proBNP, and NT-proBNP concentration at 1 month after discharge above vs below the median), a composite NT-proBNP score was formed by giving 1 point for each parameter that was elevated. This resulted in patients being divided into 4 groups: from 0 parameters elevated (group 1) to 3 parameters elevated (group 4). Baseline characteristics of all groups are depicted in Table 1. With increasing NT-proBNP parameters elevated, patients were older, more often had a previous episode of heart failure, and more often had ischemic cause of HF. Increasing composite NT-proBNP score was also associated with lower blood pressure and more impaired renal function. Interestingly left ventricular ejection fraction did not differ among the 4 groups.

The composite NT-proBNP score strongly predicted events: both short- and long-term prognosis differed significantly among the 4 groups regarding mortality and the combined end point HF-related readmission or mortality (Table 2; Fig. 1). All patients without NT-proBNP parameters elevated (group 1; n= 62) survived 1 year follow-up, whereas 41% of patients with all 3 NT-proBNP parameters elevated (group 4; n= 70) died within 1 year of follow-up.

Prognostic Impact of Small Outpatient Changes in NT-proBNP Concentration

Small changes in NT-proBNP concentration are associated with outcome. In multivariate analysis including the reference model, inpatient change in NT-proBNP, and NT-proBNP concentration at 1 month after discharge, early outpatient increase in NT-proBNP concentration <30% was associated with worse outcome compared with early outpatient decrease in NT-proBNP <30% (HR for mortality 2.05, 95% CI 1.02-4.13, Wald 4.1 [P=.04], HR for the combined end point 2.59, 95% CI 1.45-4.64, Wald 10.2 [P= .001]). Interestingly, there was no significant difference in mortality or the combined end point between patients with an early outpatient decrease of <30% vs >30% (HR for the combined end point 1.04, 95% CI 0.50-2.18, Wald 0.01; P= .914). Likewise, an increase in NT-proBNP concentration of <30% yielded a clinically similar hazard for events compared with an increase >30% (HR for the combined end point 0.96, 95% CI 0.62-1.47, Wald 0.04; P= .837).

Prognostic Value of NT-proBNP Parameters in Both Treatment Arms of the PRIMA Study

Because in one-half of the patients included in the PRIMA study the treating physician was not blinded to the outpatient NT-proBNP concentration, knowledge of NT-proBNP might have influenced the decision whether to admit a patient or not. However, in multivariate analysis correcting for the reference model and randomization group, inpatient change in NT-proBNP, early outpatient change in NT-proBNP, and NT-proBNP concentration 1 month after hospital discharge remained independent prognostic factors (Supplemental Table 2). Moreover, in both treatment arms all 3 NT-proBNP parameters were of prognostic importance (Supplemental Figs. 1 and 2).

DISCUSSION

In this study, we evaluated the prognostic value of serial NT-proBNP measurements during and early after an admission for acute HF. We demonstrated that the a) inpatient change in NT-proBNP concentration, b) early outpatient change, and c) absolute NT-proBNP concentration at 1 month after discharge were each independent prognosticators and together enabled accurate short- and long-term outpatient risk assessment. Importantly, even small changes in the early outpatient phase (ie, <30% change in NT-proBNP) had prognostic meaning.

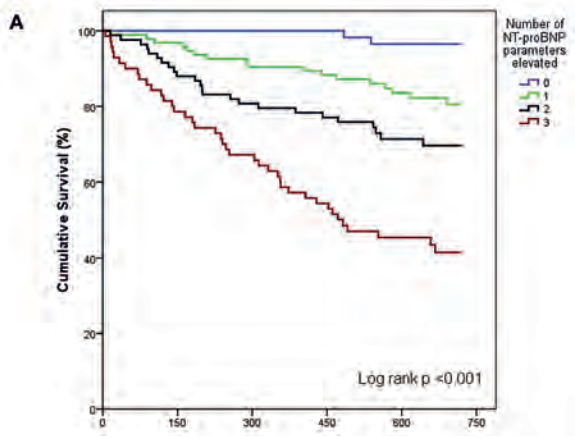
Inpatient NT-proBNP Measurements

Although the natriuretic peptide concentration at admission for acute HF predicts inpatient mortality,[10] its prognostic effect after discharge seems to be small. This is in sharp contrast to NT-proBNP concentration at discharge and changes in NT-proBNP during admission, which both seem to be better predictors of outcome. For example, Bettencourt et al[4] demonstrated that a NT-proBNP level >6,779 pg/mL at hospital admission predicted a nonsignificant trend toward hazard of readmission or death, but the NT-proBNP concentration at discharge of 4,137 pg/mL was a much stronger predictor of hazard (log rank P for cumulative hospitalization-free survival: <.001). They furthermore found that inpatient decrease in NT-proBNP values of ≥30% was related to favorable outcome. In addition, Kubler et al[11] demonstrated that the optimal cutoff value for inpatient decrease in NT-proBNP was 65%. A decrease in NT-proBNP concentration in

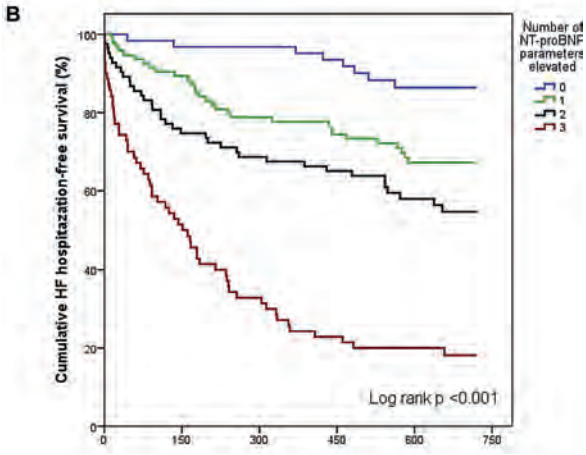
acutely decompensated HF is related to hemodynamic improvement[12] and is thereby a marker of success of HF treatment during admission. It is therefore not surprising that the extent of decrease in NT-proBNP during admission reflects outpatient outcome after discharge. Our findings go beyond these conclusions, showing that inpatient changes in NT-proBNP are of prognostic importance independently from early outpatient changes as well as independently from NT-proBNP levels measured at 1 month after hospital discharge.

In contrast to inpatient change in NT-proBNP, NT-proBNP concentration at discharge failed to retain prognostic impact in multivariate analysis.

The presence of strong correlations between the absolute NT-proBNP concentrations will certainly have influenced the selection process in multivariate analysis that led to the uptake of NT-proBNP concentration at 1 month after hospital discharge over NT-proBNP at hospital discharge (Supplemental Table 1). However, the fact that NT-proBNP concentration 1 month after hospital discharge remained the strongest prognostic NT-proBNP value is not surprising, because it is the most recent measurement. This is also shown by univariate analysis: NT-proBNP concentration 1 month after hospital discharge yielded the highest Wald score for mortality (15.6 vs 15.2 for NT-proBNP at discharge).



No. at risk	Follow-up (days)				
	62	62	62	62	54
	94	91	85	81	67
	83	73	67	62	43
	70	55	47	47	38



No. at risk	Follow-up (days)				
	62	60	60	57	44
	94	84	74	68	54
	83	62	57	53	36
	70	36	23	16	13

Fig. 1. Kaplan-Meier curve for (A) mortality and (B) the combined end point of HF hospitalization-free survival according to the composite N-terminal pro-B-type natriuretic peptide (NT-proBNP) score.

Outpatient NT-proBNP Measurements and Prognosis

The prognostic value of changes in NT-proBNP at the outpatient clinic compared with only a single measurement seems to depend on the outpatient setting. One study reported that absolute NT-proBNP concentration at 3 months after acute HF admission had more predictive power in multivariate analysis than percentage change within 3 months (chi-square value of log NT-proBNP after 3 months 41.5, compared with 7.5 for NT-proBNP percentage change).[13]

Also in chronic stable HF, the prognostic power of absolute NT-proBNP concentration appears to be superior to relative changes in NT-proBNP. A subanalysis of the Val-HeFT trial, for example, demonstrated a higher prognostic discrimination of a single determination of NT-proBNP compared with relative changes after 4-month follow-up (AUC 0.70 vs 0.60, respectively).[6]

Changes in NT-proBNP concentration seem to have higher prognostic impact in outpatient destabilized HF; Bayes-Genis et al, for example, reported a 21% reduction in events for every 10% decrease in NT-proBNP within 2 weeks.[14] In contrast, the absolute NT-proBNP concentration at 2 weeks lost its predictive power in multivariate analysis.

We show that 1 month after hospital discharge, change in NT-proBNP has prognostic power similar to the absolute NT-proBNP concentration measured at 1 month for prediction of mortality (Table 3). For prediction of the combined end point of HF readmission or mortality, early outpatient change in NT-proBNP is clearly superior to the absolute concentration at 1 month (Wald 20.5 vs 6.1, respectively; Table 3). Thus it seems that in patients at highest risk for events (outpatient destabilized HF and early after admission because of acute HF), a change in NT-proBNP concentration between 2 measurements at relatively short interval is an important predictor for events, and clinical stability cannot be assumed by only 1 NT-proBNP measurement.

Prognostic Importance of Small Changes in NT-proBNP Concentration 1 Month After Hospital Discharge

Changes in natriuretic peptide concentrations may reflect changes in cardiac wall stress and cardiac performance, but may also depend on the biologic variability of these biomarkers. For NT-proBNP, biologic variability has been assessed in chronic HF patients at different time intervals (within-day, week-to-week, 1 to 3 months, and year-to year[7,15-19]). Short term biologic variability in terms of reference change values (RCVs) differed widely among studies published, varying from 23%[19] to 98%,[7] suggesting that changes in NT-proBNP concentration even up to 100% may be safely accepted. Our finding that small changes in NT-proBNP concentration (ie, <30%) early after hospital discharge are of prognostic importance challenges these interpretations of so-called “biologic variability” of NT-proBNP. The high RCVs found in the previously mentioned studies are controversial because they appear to be related to the skewed distribution of measured NT-proBNP values and improve after normalizing transformation of the data.[16] Also, median NT-proBNP concentrations in studies assessing biologic variability of NT-proBNP were relatively low (579-1,323 pg/mL)[15,16] and biologic variability has been shown to decrease with elevating NT-proBNP concentration.[15] Furthermore patient numbers were limited in these studies (20-78 patients).[18,19] Most importantly, these studies assumed that their patients were in a stable condition based on clinical characteristics and on their stability in the past, but did not take into account the long-term survival after measurement of NT-proBNP concentration. Moreover, it was assumed that clinical stability can easily be assessed without in-depth diagnostic testing, which is most likely not the case. Therefore, objective evidence of clinical stability was lacking and subclinical changes in NT-proBNP

concentration might have actually been an early - subclinical - sign of worsening HF. Indeed, in line with this reasoning, the only study assessing short term biologic variability of NT-proBNP with a follow-up period of 6 months showed the lowest RVC, 23%.[19]

Composite NT-proBNP Score and Implications for Clinical Practice

A composite NT-proBNP score that combines inpatient change in NT-proBNP with early outpatient change and the absolute NT-proBNP concentration 1 month after hospital discharge identified HF patients at very low (1.6%), intermediate (8.5%-16.9%), and high (38.6%) risk for early readmission or mortality. The prognostic impact remained after one year follow-up. The composite NT-proBNP score has been designed to illustrate the incremental information from the different NT-proBNP measurements. Because the cutpoints for the NT-proBNP parameters were defined by the distribution within the PRIMA study, application of these cutpoints cannot be used in clinical practice until validation analysis has been performed. Furthermore, whether knowledge of the individual risk for events would lead to reduction in morbidity and mortality remains to be assessed by future trials and cannot be answered by the present study. However, it seems plausible that patients at highest risk for events might benefit most from intensified outpatient follow-up in combination with increased prescription of evidence-based HF medication, such as angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists.

Recent trials assessing the effect of natriuretic peptide-guided therapy in HF that randomized patients into 3 treatment arms (ie, regular outpatient care vs intensified outpatient care with or without knowledge of natriuretic peptide concentration) have shown that intensified outpatient care leads to a decrease in HF related readmissions and mortality compared to usual care.[20,21] The BATTLESCARRED (NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death) trial, eg, demonstrated 1-year mortality being lower in the intensified outpatient treatment group (9.1%) compared with usual care (18.9%; P= .03).[21] Furthermore, in all 4 studies demonstrating a positive effect of natriuretic peptide-guided therapy,[20,22-24] a marked increase in evidence-based HF medication was seen in the natriuretic peptide-guided arm compared with the usual care arm. Thus, intensified treatment in combination with increase in evidence-based HF medication appears to lead to better outcome. In 2 of these 4 trials, patients allocated to the NT-proBNP-guided therapy arm had fewer

prescription of loop diuretics compared with usual care management.[20,22] In the PRIMA study, which failed to demonstrate a significant reduction in end points by NT-proBNP-guided therapy, outpatient elevated NT-proBNP levels led most frequently to an increase in diuretic dosage (>40%).[8]

Given the association between loop diuretics and worsening of renal function, neurohumoral activation, and adverse outcome in HF,[25] the use of diuretics is recommended to be limited to achieve and maintain an euvolemic state with the lowest achievable dose.[26]

Combining individual risk assessment with the previously mentioned findings from the recent natriuretic peptide-guided therapy studies might lead to an early outpatient individual treatment approach that should be confirmed in future trials. It is assumed that if individual risk for events is low (ie, low composite NT-proBNP score) and a patient is clinically euvolemic, then diuretic dosage should be lowered and outpatient follow-up might be directed to the primary care. If individual risk is high (ie, high composite NT-proBNP score) and the patient is clinically euvolemic, then outpatient follow-up should be intensified at a dedicated outpatient HF clinic with extra attention being paid to compliance and intensified prescription of evidence-based HF medication. If clinical signs of overt or worsening HF occur, diuretic dosage should be increased first, followed by intensification of evidencebased HF medication. However, as already said, large randomized trials are needed to further clarify this issue.

Study Limitations

There are some limitations to the present study. It should be emphasized that the composite NT-proBNP score was calculated to visualize the incremental value of serial NT-proBNP measurements during and early after admission because of acute HF. It was not the intention to develop a risk score that can be used in clinical practice. The NT-proBNP cutpoints were defined from patients included in the PRIMA study. To be included in the PRIMA study, NT-proBNP concentration during admission needed to decrease ≥10% with a minimum of 850 pg/mL. Therefore, we cannot extrapolate our results to patients with a smaller decrease, or an increase in NT-proBNP concentration, during admission. Also, as this study is a post hoc analysis, results remain to be validated by another, preferably larger, prospective study.

CONCLUSION

For adequate individual risk assessment early after hospital discharge, knowledge of serial NT-proBNP values is important. Early changes in NT-proBNP concentration after admission because of HF, the extent of decrease in NT-proBNP concentration during admission and the absolute NT-proBNP concentration 1 month after hospital discharge are independent prognostic parameters. They may help to further individualize risk of readmission because of HF or mortality. Even relative small early outpatient changes in NT-proBNP are associated with outcome, suggesting that biologic variability is small and that changes in these levels do reflect underlying pathophysiologic processes. Knowledge of individual risk might lead to an individualized treatment approach, and the effect of such an approach should be assessed in future randomized trials.

Disclosures
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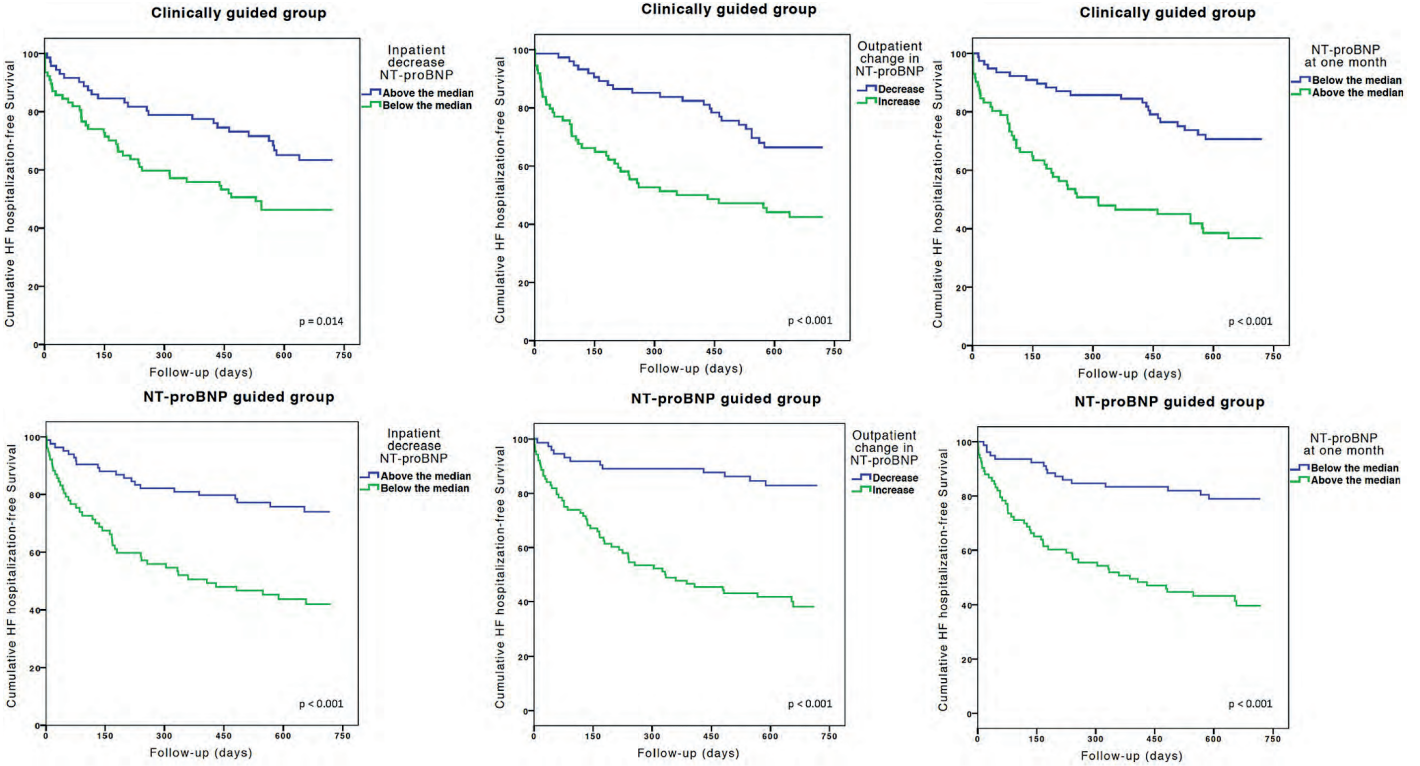
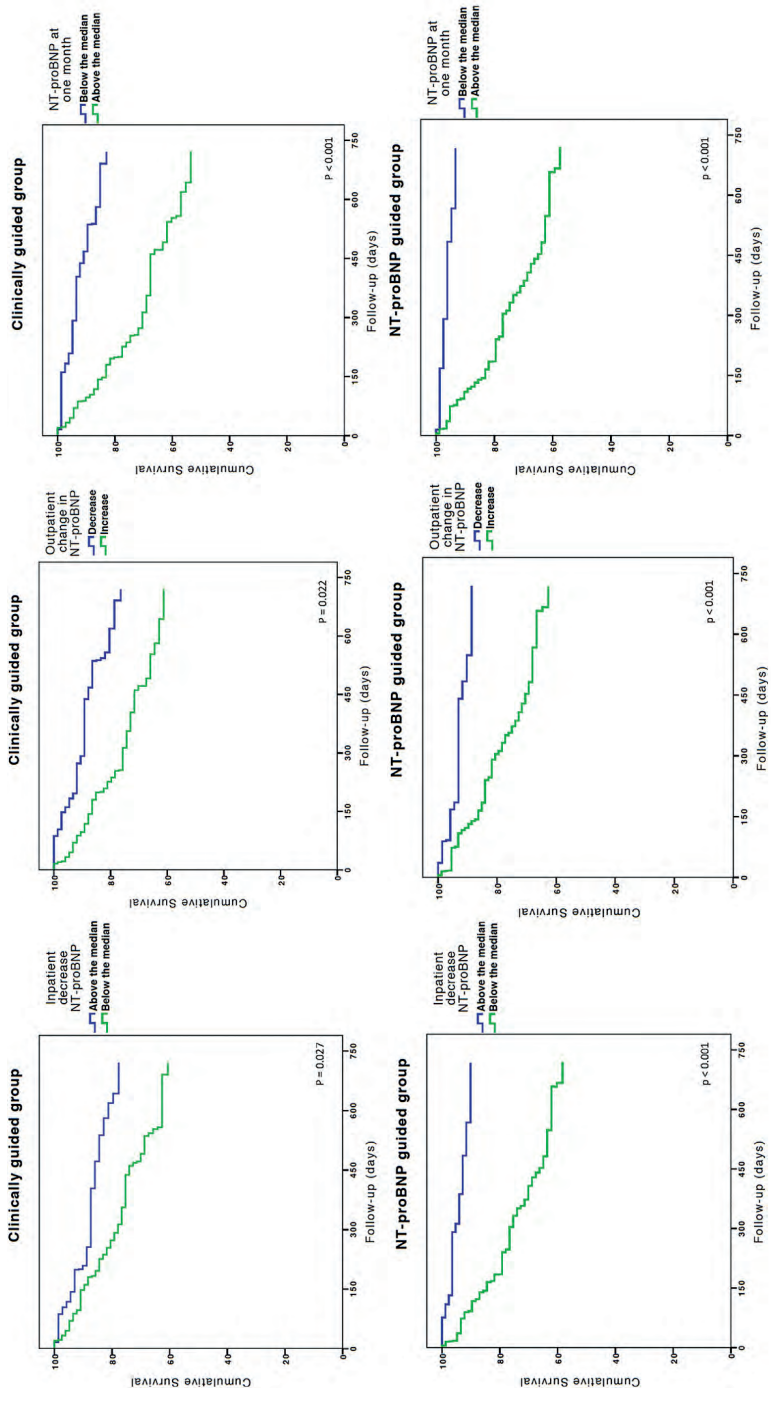
Supplemental Tables and Figures.



Supplemental figure 1. Kaplan-Meier curves for HF hospitalization-free survival in clinically-guided (top) and NT-proBNP-guided patients (bottom) by NT-proBNP decrease during admission (left), outpatient change in NT-proBNP (center) and NT-proBNP one month after hospital discharge (right).



Supplementa figure 2. Kaplan Meier curves demonstrating survival in clinically-guided (top) and NT-proBNP-guided patients (bottom) by NT-proBNP decrease during admission (left), outpatient change in NT-proBNP (center) and NT-proBNP one month after hospital discharge (right).

Supplemental table 1. Correlation between NT-proBNP parameters.

	Admission	Inpatient change	Discharge	Outpatient change	One month
Admission	-	0.06	0.79**	-0.19*	0.56**
Inpatient change	0.06	-	0.62**	-0.13	0.56**
Discharge	0.79**	0.62**	-	-0.15*	0.76**
Outpatient change	-.19*	-0.01	-0.15*	-	0.45**
One month	0.56**	0.56**	0.76**	0.45**	-

* p < 0.01, ** P<0.001

Supplemental table 2. Multivariate analysis including group allocation (clinically-guided versus NT-proBNP-guided)

	Adjusted multivariate analysis*			
	HR	95% CI	Wald	p
Mortality				
Inpatient decrease NT-proBNP below vs above the median	1.69	1.00-2.87	3.8	0.052
Early outpatient increase versus decrease in NT-proBNP	1.85	1.10-3.12	5.3	0.021
NT-proBNP at 1 month above versus below the median	2.15	1.13-4.11	5.4	0.020
Group alllocation: clinically-guided versus NT-proBNP-guided	1.20	0.77-1.88	0.7	0.415
HF readmission / mortality				
Inpatient decrease NT-proBNP below vs above the median	1.71	1.13 - 2.58	6.3	0.012
Early outpatient increase versus decrease in NT-proBNP	2.69	1.74 – 4.14	20.1	<0.001
NT-proBNP at 1 month above versus below the median	1.86	1.16 – 2.99	6.5	0.011
Group allocation: clinically-guided versus NT-proBNP-guided	1.20	0.83-1.72	0.93	0.336

* Adjusted for clinical parameters.

CHAPTER 6

Change in NT-proBNP has more prognostic power than change in eGFR after admission because of acute heart failure.

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ABSTRACT

Objectives

To assess the prognostic value of change in renal function as estimated by changes in eGFR in addition to change in NT-proBNP early after hospital discharge for acute heart failure.

Background

Renal dysfunction (RD) and heart failure (HF) often coincide and are independently correlated with prognosis. Likewise, change in renal function and the natriuretic peptide NT-proBNP have been associated with risk for morbidity and mortality. However, the prognostic importance of change in renal function in relation to change in NT-proBNP has not been investigated.

Methods

We evaluated the prognostic value of change in renal function as estimated by changes in eGFR in addition to change in NT-proBNP in patients recently admitted because of acute HF between hospital discharge and 1 month after hospital discharge in 271 patients included in the PRIMA study. Primary endpoint was HF readmission or mortality within one year of follow-up.

Results

In a multivariate Cox regression analysis, decrease versus increase in eGFR yielded no prognostic impact (Hazard ratio [HR] = 1.27, 95% CI 0.83-1.94, P=0.28). A decrease in eGFR more than 20% also wasn't related to the combined endpoint (HR for decrease >20% versus change between 20% 1.34, 95% CI 0.80-2.24, P=0.262). This in contrast to change in NT-proBNP (HR for increase versus decrease in NT-proBNP 4.04, 95% CI 2.35-6.97, P<0.001), and NT-proBNP concentration at discharge (HR = 2.11 per log NT-proBNP, 95%-CI 1.21-3.70, P=0.009).

Conclusion

The prognostic impact of change in renal function early after hospital discharge because of acute HF is subordinate to change in NT-proBNP.

INTRODUCTION

Presence of renal dysfunction (RD) is common in patients with heart failure (HF). More than 50% of patients with HF have at least mild RD defined as eGFR <60 ml/min.[1] RD in the setting of HF is attributed to biochemical, hormonal, and hemodynamic factors, in association with pharmacological interventions.[2] Although the pathophysiologic background for RD in HF patients is complex and only partially understood,[3] presence of concomitant renal and cardiac dysfunction is associated with worse outcome.[4,5]

In both acute and chronic HF, changes in renal function may occur over time. Reports about the prognostic impact of these changes are conflicting,[3,6] but most studies and a recently published meta analysis do demonstrate that worsening renal function (WRF) negatively impacts outcome.[7]

During the last decade, the B-type natriuretic peptide (BNP) and its cleavage equivalent N-terminal pro-B-type natriuretic peptide (NT-proBNP) have proven to be powerful prognostic markers in both acute and chronic HF. In acute HF, both pre-discharge (NT-pro)BNP concentration and decrease in NT-proBNP during hospital admission were related to outcome after hospital discharge.[8,9] We recently demonstrated that after acute HF admission, change in NT-proBNP concentration one month after hospital discharge was an independent predictor of mortality, together with change in NT-proBNP during admission and the absolute NT-proBNP concentration one month after hospital discharge.[10] Also in chronic, stable HF, apart from one single measurement, variation in natriuretic peptides adds to prognostic assessment as well.[11]

In the setting of treating HF, clinicians may encounter conflicting prognostic information when evaluating changes in renal function and natriuretic peptides over time if they go in opposite directions. Thus, it is unclear if WRF should get more attention than lowering (NT-pro)BNP levels and vice versa. This may be of particular importance early after hospital discharge when changes in medication are very common and risk for readmission or mortality is highest. We therefore assessed the added prognostic value of changes in renal function next to changes in NT-proBNP early after hospital discharge.

METHODS

Study design and population

This is a post-hoc analysis of patients included in the PRIMA study, a prospective randomized multicenter study assessing the effect of management of chronic heart failure guided by individual NT-proBNP targets.[12] Inclusion- and exclusion criteria have been published previously.[12] In short, patients were included during hospital admission for acute HF. NT-proBNP concentration on admission was required to be at least 1,700 pg/ml and patients included also needed to demonstrate a minimum decrease in NT-proBNP concentration of 10% with a minimum of 850 pg/ml during admission. At discharge, patients were randomized to outpatient treatment that was either clinically-guided where NT-proBNP was measured but not revealed to the physician, or to outpatient treatment that was clinically-guided but where additionally NT-proBNP levels were provided to guide therapy. The follow-up period was up to 2 years.

For this sub analysis, we included patients with creatinine and NT-proBNP measurements available at discharge and the follow-up visit 1 month after hospital discharge. Patients were divided into four groups based on change in estimated glomerular filtration rate (eGFR) and NT-proBNP concentration during the first month post-discharge:

Group 1. Decrease in NT-proBNP in combination with an increase in eGFR
Group 2. Decrease in NT-proBNP in combination with a decrease in eGFR
Group 3. Increase in NT-proBNP in combination with an increase in eGFR
Group 4. Increase in NT-proBNP in combination with a decrease in eGFR

Definition of study endpoints

Primary outcome measure was the combined endpoint of HF readmission or mortality within one year follow-up. Secondary endpoints encompassed one year mortality, and all endpoints at 90 and 180 days of follow-up.

Statistical analysis

Data are presented as frequencies, mean ±SD or median (interquartile range, IQR). Comparisons between groups were performed using Fischer´s exact test for categorical data and one-way ANOVA or Kruskal-Wallis H test for continuous data, as appropriate. If baseline characteristics differed significantly among the 4 groups

(overall P<0.05), all groups were individually compared with each other in order to assess which groups caused this difference. Glomerular filtration rate (GFR) was estimated by using the Modified Diet in Renal Disease equation (MDRD).[13] Kaplan Meijer survival curves were assessed and compared using the log-rank test and Cox proportional-hazard regression analysis. Univariate Cox proportional-hazard regression analyses was performed in order to assess clinical covariates associated with the combined endpoint. We checked for interaction between all covariates and found interaction between urea baseline and a previous history of myocardial infarction. In multivariate analyses we corrected for this interaction. Multivariate Cox proportional hazard regression analysis was performed using all covariates associated with outcome to assess the clinical model. Variables were added in a stepwise fashion with $p < 0.05$ and $P < 0.1$ as the cut-off for entry or retention, respectively. After assessment of the clinical model, NT-proBNP, eGFR, Urea, change in renal function (decrease versus increase in eGFR) and change in NT-proBNP (increase versus decrease) were added to form the cardiorenal model. Finally, the prognostic impact of severe worsening of renal function defined as a decrease in eGFR >20% and improvement of renal function (IRF) defined as an increase in eGFR >20% compared with a change in eGFR within 20% was analyzed in a multivariate manner.

Calculations were done using SPSS 21.0 (IBM corp, Armonk, New York, USA).

RESULTS

In 271 out of 345 patients included in the PRIMA study, NT-proBNP and creatinine levels at discharge and at the outpatient visit one month after hospital discharge were available. Patient characteristics at hospital discharge and one month after hospital discharge are depicted in table 1. Overall, patients were elderly, predominantly male, more than half of patients had a history of coronary heart disease, and most patients had been admitted because of de novo acute HF. Patients were divided into 4 groups based on increase versus decrease in NT-proBNP and eGFR. Overall group differences were seen in incidence of coronary artery disease, myocardial infarction, PCI or CABG, ICD, previous episode of HF and renal function at hospital discharge (table 1).

Table 1. Baseline characteristics of the overall population and divided by change in NT-proBNP and eGFR.

Patient characteristics	Overall		Decrease NT-proBNP				Increase NT-proBNP				
			Increase eGFR		Decrease eGFR		Increase eGFR		Decrease eGFR		
	(n=271)	n	(n= 55)	n	(n=70)	n	(n=69)	n	(n=77)	n	P overall
Baseline											
Age, yrs	72.4 (12.1)	271	71.2 (13.3)	55	71.8 (11.7)	70	72.1 (10.3)	69	74.2 (13.2)	77	0.473
Female	115 (42.4)	271	30 (54.5)	55	24 (34.3)	70	28 (40.6)	69	33 (42.9)	77	0.152
BMI	24.8 (4.6)	212	24.1 (5.2)	42	24.8 (4.4)	56	25.3 (4.3)	52	24.9 (4.7)	62	0.649
Hypertension	137 (50.6)	271	25 (45.5)	55	32 (45.7)	70	41 (59.4)	69	39 (50.6)	77	0.336
Diabetes Mellitus	74 (27.3)	271	10 (18.2)	55	18 (25.7)	70	25 (36.2)	69	21 (27.3)	77	0.160
Hypercholesterolemia	66 (24.4)	271	10 (18.2)	55	15 (21.4)	70	20 (29.0)	69	21 (27.3)	77	0.464
Stroke or TIA	46 (17.0)	271	10 (18.2)	55	11 (15.7)	70	10 (14.5)	69	15 (19.5)	77	0.854
Peripheral Artery Disease	44 (16.2)	271	9 (16.4)	55	11 (15.7)	70	11 (15.9)	69	13 (16.9)	77	1.000
COPD	45 (16.6)	271	8 (14.5)	55	12 (17.1)	70	12 (17.4)	69	13 (16.9)	77	0.975
Atrial fibrillation	90 (33.2)	271	16 (29.1)	55	19 (27.1)	70	24 (34.8)	69	31 (40.3)	77	0.342
Coronary artery disease	157 (57.9)	271	27 (49.1)	55	35 (50.0)	70	46 (66.7)	69	49 (63.6)	77	0.081
Myocardial infarction	109 (40.2)	271	15 (27.3)	55	22 (31.4)	70	36 (52.2)**‡	69	36 (46.8)†	77	0.009
PCI	30 (11.1)	271	3 (5.5)	55	4 (5.7)	70	8 (11.6)	69	15 (19.5)†§	77	0.023
CABG	45 (16.6)	271	5 (9.1)	55	10 (14.3)	70	14 (20.3)	69	16 (20.8)	77	0.248
PCI or CABG	64 (23.6)	271	8 (14.5)	55	12 (17.1)	70	19 (27.5)	69	25 (32.5)†§	77	0.045
Pacemaker	27 (10.0)	271	6 (10.9)	55	4 (5.7)	70	5 (7.2)	69	12 (15.6)	77	0.188
ICD	20 (7.4)	271	1 (1.8)	55	2 (2.9)	70	9 (13.0) **‡	69	8 (10.4)	77	0.028
Pacemaker or ICD	42 (15.5)	271	7 (12.7)	55	5 (7.1)	70	13 (18.8)	69	17 (22.1)	77	0.065
Mitral regurgitation ≥ II	122 (49.8)	245	21 (42.9)	49	36 (55.4)	65	30 (49.2)	61	35 (50.0)	70	0.630
Previous episode of HF	99 (36.5)	271	17 (30.9)	55	18 (25.7)	70	33 (47.8)‡	69	31 (40.3)	77	0.036
Ischemic cause of HF	116 (43.0)	270	19 (34.5)	55	26 (37.1)	70	34 (50.0)	68	37 (48.1)	77	0.194
Discharge											
NYHA functional class ≥ III	57 (21.0)	271	11 (20.0)	55	8 (11.4)	70	17 (24.6)	69	21 (27.3)	77	0.100
Mean Arterial Pressure, mmHg	85.0 (12.8)	257	88.1 (12.7)	52	85.8 (11.9)	68	82.7 (12.3)	62	84.0 (13.6)	75	0.118
Heart rate, beats/minute	77.2 (15.8)	256	79.3 (18.1)	51	76.0 (15.5)	67	78.2 (15.0)	63	76.0 (15.4)	75	0.591
QRS duration, msec	110 (94-138)	223	110 (93-127)	45	104 (91-129)	57	110 (94-150)	59	117 (96-147)	62	0.229
LVEF	35.8 (14.7)	210	39.0 (15.5)	40	34.4 (13.0)	57	35.4 (15.3)	55	35.3 (15.3)	58	0.490
Hemoglobin, mmol/l	8.4 (1.2)	186	8.6 (1.3)	39	8.3 (1.2)	45	8.6 (1.3)	49	8.3 (1.1)	53	0.354
Sodium, mmol/l	139.0 (3.5)	271	138.9 (3.6)	55	139.6 (3.5)	70	138.4 (3.3)	69	138.9 (3.4)	77	0.256

Potassium, mmol/l	4.3 (0.5)	271	4.3 (0.5)	55	4.2 (0.4)	70	4.3 (0.5)	69	4.4 (0.4)§	77	0.150
Urea, mmol/l	11.7 (8.5-16.2)	265	10.8 (7.4-15.8)	53	10.5 (7.9-12.9)	69	13.9 (9.4-16.6)** ‡	66	12.8 (9.3-17.0)§†	77	0.001
Creatinine, µmol/l	121 (100-162)	271	108 (97-150)	55	106 (88-148)	70	136 (109-191)**‡	69	137 (108-165)§	77	<0.001
eGFR, ml/min	47.0 (32.6-64.0)	271	51.9 (32.0-67.4)	55	59.2 (41.3-68.3)	70	44.7 (29.0-53.0)‡	69	42.5 (31.1-56.4)§	77	<0.001
NT-proBNP, pg/ml	2948 (1404-5525)	271	2322 (1288-5517)	55	3441 (1733-5342)	70	2241 (903-5379)	69	3115 (1646-6064)	77	0.115
Medication at discharge											
Diuretics	263 (97.0)	271	55 (100)	55	67 (95.7)	70	66 (95.7)	69	75 (97.4)	77	0.497
ACE-inhibitors	191 (70.5)	271	38 (69.1)	55	54 (77.1)	70	43 (62.3)	69	56 (72.7)	77	0.273
ARB	57 (21.0)	271	9 (16.4)	55	9 (12.9)	70	21 (30.4)	69	18 (23.4)	77	0.059
ACE-inhibitors or ARB	235 (86.7)	271	46 (83.6)	55	62 (88.6)	70	62 (89.9)	69	65 (84.4)	77	0.673
Beta blockers	209 (77.1)	271	40 (72.7)	55	55 (78.6)	70	56 (81.2)	69	58 (75.3)	77	0.691
Aldosterone antagonists	149 (55.0)	271	27 (49.1)	55	43 (61.4)	70	35 (50.7)	69	44 (57.1)	77	0.463
Digoxin	79 (29.2)	271	19 (34.5)	55	17 (24.3)	70	17 (24.6)	69	26 (33.8)	77	0.388
Outpatient visit 1 month											
Mean Arterial Pressure, mmHg	84.0 (13.6)	268	87.3 (13.9)	55	82.7 (11.6)*	70	85.8 (14.8)	69	80.9(13.5)†‖	74	0.031
Heart rate, beats/minute	76.5 (17.9)	264	74.7 (18.1)	55	74.0 (16.1)	67	78.2 (17.4)	67	78.5 (19.6)	75	0.330
Sodium, mmol/l	138.4 (3.6)	270	138.9 (2.9)	55	137.9 (3.6)	70	138.9 (4.1)	68	138.2 (3.5)	77	0.224
Potassium, mmol/l	4.4 (0.5)	270	4.2 (0.4)	55	4.6 (0.5)*	70	4.3 (0.6)‡	69	4.5 (0.5)†‖	76	<0.001
Urea, mmol/l	10.9 (8.3-16.9)	267	8.9 (6.6-12.1)	52	11.1 (8.4-17.4)*	70	10.3 (8.0-13.6)	68	14.5 (10.4-23.1)†§‖	77	<0.001
Creatinine, µmol/l	130 (100-167)	271	102 (87-137)	55	130 (102-161)*	70	119 (96-143)	69	153 (126-209)†§‖	77	<0.001
eGFR, ml/min	46.1 (31.3-60.1)	271	56.7 (38.0-73.7)	55	46.4 (33.5-60.6)*	70	50.9 (36.5-64.0)	69	33.5 (27.1-47.1)†§ ‖	77	<0.001
Change eGFR, %	-3.0 (-16.5-12.0)	271	10.9 (4.9-20.8)	55	-14.6 (-24.9 - -6.7)*	70	17.3 (4.6-30.5)‡	69	-16.5 (-25.0- -8.1)†‖	77	<0.001
NT-proBNP, pg/ml	2718 (1271-6051)	271	1477 (672-3245)	55	1649 (850-3235)	70	3516 (1631-7703)** ‡	69	4975 (2650 - 9254)†§‖	77	<0.001
Change NT-proBNP, %	4.2 (-28.8 - 47.8)	271	-30.4 (-62.5 - -15.0)	55	-40.2 (-55.1- -16.0)	70	43.3 (20.1-104.7)** ‡	69	45.9 (14.7-79.0)†§	77	<0.001

* P<0.05 between group 1 and 2
** P<0.05 between group 1 and 3
† P<0.05 between group 1 and 4
‡ P<0.05 between group 2 and 3
§ P<0.05 between group 2 and 4
‖ P<0.05 between group 3 and 4

Values are expressed as n (%), mean (SD), or median (interquartile range)

BMI= body mass index; TIA = Transient ischemic attack ; COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; ICD = implantable cardiac defibrillator; HF = heart failure; NYHA = New York Heart Association ; LVEF = left ventricular ejection fraction; eGFR = estimated glomerular filtration rate; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

These differences in patient baseline characteristics and renal function at hospital discharge seemed to be mainly caused by change in NT-proBNP. For example, in patients with an increase in eGFR, those with an increase in NT-proBNP had higher incidence of myocardial infarction compared to those with a decrease in NT-proBNP (52% versus 27%, see table 1). Interestingly, NT-proBNP concentration at hospital discharge did not differ between all groups.

Prediction of outcome

Median time from hospital discharge to the outpatient visit one month after discharge was 30 days (IQR 26 – 36 days). All surviving patients included for this analysis had a follow-up duration of 365 days after the outpatient visit one month after hospital discharge.

At 90-days follow-up, 47 patients (17.3%) had reached the combined endpoint of HF readmission or mortality and 14 patients (5.2%) had died. After one year, 95 patients (35.1%) had reached the combined endpoint and 51 patients (18.8%) had died.

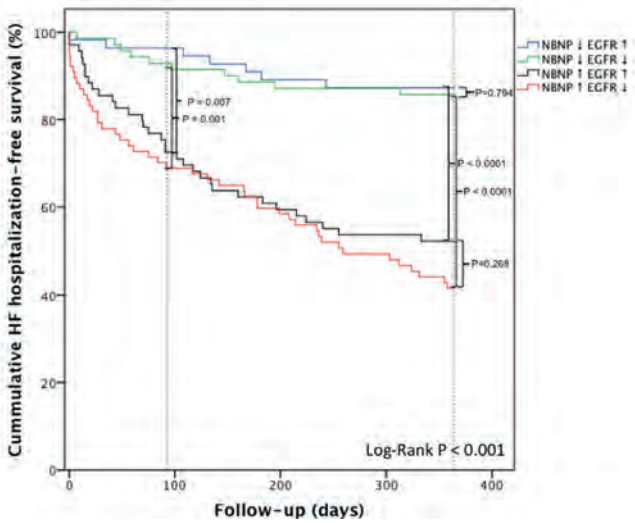
Outcome per group based on increase versus decrease in NT-proBNP and eGFR is depicted in table 2 and figures 1a and b. Patients with a decrease in NT-proBNP had reasonable short- and long-term prognosis with no change in outcome between those having a decrease versus increase in eGFR. In patients with an increase in NT-proBNP outcome was worse compared to those with a decrease in NT-proBNP, but again no significant difference was seen between patients with a decrease versus increase in eGFR.

Table 2. Outcome divided by change in NT-proBNP and eGFR.

Outcome	NBNP ↓ eGFR ↑	NBNP↓ eGFR ↓	NBNP ↑ eGFR ↑	NBNP ↑ eGFR ↓	P overall
n	55	70	69	77	
HF related admission / mortality, n (%)					
- 90 days	2 (3.6)	5 (7.1)	17 (24.6)	23 (29.9)	<0.0001
- 180 days	5 (9.1)	8 (11.4)	26 (37.7)	31 (40.3)	<0.0001
- 365 days	7 (12.7)	10 (14.3)	33 (47.8)	45 (58.4)	<0.0001
Mortality, n (%)					
- 90 days	1 (1.8)	1 (1.4)	6 (8.7)	6 (7.8)	0.101
- 180 days	2 (3.6)	4 (5.7)	10 (14.5)	12 (15.6)	0.048
- 365 days	5 (9.1)	6 (8.6)	16 (23.2)	24 (31.2)	0.001

HF = heart failure

A



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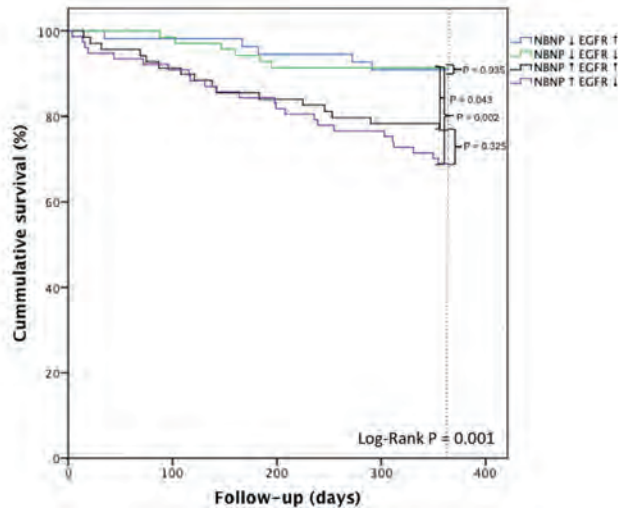

Figure 1. Kaplan-Meier curve for the combined endpoint HF readmission or mortality (a) and mortality (b) by change in eGFR and NT-proBNP.

Univariate predictors of outcome.

Also in univariate analysis, decrease versus increase in eGFR was no risk factor (HR for for the combined endpoint of HF readmission or mortality eGFR 1.19, 95% CI 0.79-1.78, P=0.410, see table 3.).

In contrast, change in NT-proBNP was an important predictor for outcome (HR for increase in NT-proBNP concentration versus decrease 5.17, 95% CI 3.06-8.75, P <0.001).

Although change in renal function had no prognostic impact, baseline eGFR was clearly related to outcome (HR for the combined endpoint per mL/min/1.73m^2 0.97, 95% CI 0.96-0.98, P <0.001). Likewise, urea and NT-proBNP concentration at hospital discharge were related to the combined endpoint.

Impact of severe worsening and outspoken improvement in renal function

In total 53 patients (19.6%) experienced severe worsening in renal function (WRF), defined as a decrease in eGFR > 20%. Forty-three patients (15.9%) experienced an outspoken improvement in renal function (increase in eGFR >20%) and in 175 patients (64.6%) change in eGFR was less than 20%. After 1 year follow-up 21 patients (39.6%) with severe WRF reached the combined endpoint, versus 18 patients (41.9%) with an increase >20%, versus 56 patients (32%) with change in eGFR less than 20% (figure 2a). This difference was not statistically significant (log-rank p=0.276).

Mortality was the same among the 3 eGFR-groups (figure 2b). Interestingly, change in NT-proBNP concentration between hospital discharge and 1 month follow-up visit was significantly different between patients with a decrease >20%, patients with a change less than 20%, and patients with an increase in eGFR >20% (median change + 9.8% (IQR -40.0% – 69.1%) versus 0.0% (IQR -30.4%-35.0%), versus 32.7 % (-20.0%-94.4%) respectively, p=0.028.

When dividing patients in groups based on 20% change in eGFR and increase versus decrease in NT-proBNP, prognosis was mainly dependent on change in NT-proBNP (supplemental figure 1a and b.).

Multivariate analysis

Multivariate analysis of baseline characteristics identified a previous episode of heart failure and myocardial infarction as independent risk factors for the combined endpoint (table 3.). After addition of eGFR, Urea, NT-proBNP and change in both eGFR and NT-proBNP the definite cardiorenal model was formed. In this model, change in eGFR had no prognostic power, whether change in NT-proBNP remained an important independent prognostic factor as depicted in table 3.

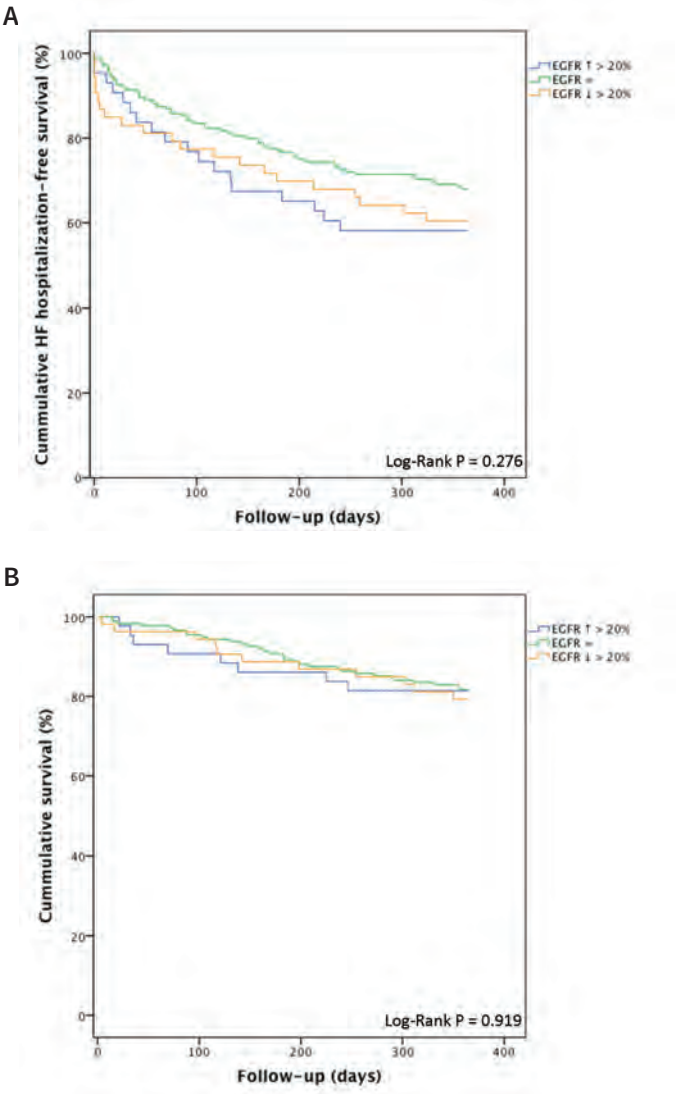

Figure 2. Kaplan-Meier curve for the combined endpoint HF readmission or mortality (a) and mortality (b) by 20 % change in eGFR.

Change in eGFR was defined as 1) an increase in eGFR more than 20% (eGFR ↑ > 20%), 2) a change in eGFR less than 20% (eGFR =) and a decrease in eGFR more than 20% (eGFR ↓ > 20%).

In multivariate analysis a decrease or increase in eGFR more than 20% was not associated with risk for events compared with patients with a change in eGFR between 20% (HR for the combined endpoint 1.34, 95% CI 0.80–2.24, P=0.262 and HR 0.77, 95% CI 0.43–1.37, P=0.379 respectively).

Table 3. Univariable and adjusted multivariable hazard ratios for predictors of the combined endpoint HF free survival.

	Univariate analysis				Adjusted multivariate analysis			
	HR	95% CI	Wald	P	HR	95% CI	Wald	P
HF readmission / mortality								
Previous episode of heart failure	2.91	1.94 - 4.38	26.5	<0.001	2.0	1.29 - 3.09	9.7	0.002
Myocardial infarction	1.90	1.27 - 2.85	9.8	0.002	2.51	0.95 - 6.62	3.5	0.062
Urea at hospital discharge (per mmol/L)	1.06	1.04 - 1.09	30.4	<0.001	1.12	1.02 - 1.23	5.1	0.024
eGFR at discharge (per mL/min/1.73m^2)	0.97	0.96 - 0.98	32.6	<0.001	0.99	0.97 - 1.00	2.7	0.103
LogNT-proBNP at hospital discharge (per Log)	3.18	1.92 - 5.26	20.1	<0.001	2.11	1.21 - 3.70	6.8	0.009
Increase versus decrease in NT-proBNP	5.17	3.06 - 8.75	37.6	<0.001	4.04	2.35 - 6.97	25.3	<0.001
Decrease versus increase in eGFR	1.19	0.79 - 1.78	0.68	0.410	1.27	0.83 - 1.94	1.2	0.276
Urea at discharge * Myoardial infarction					0.95	0.90 - 1.00	4.1	0.043

Hazard ratios calculated within the 1-year follow-up period.

DISCUSSION

In our study, early changes in NT-proBNP after hospital discharge due to acute HF had significant prognostic impact whereas changes in renal function did not. This finding might lead to the assumption that treatment of heart failure should be focused on improvement in cardiac function in such patients even if renal function slightly deteriorates.

Although not entirely uniform,[3,14] most studies showed increased risk of worsening renal function (WRF) in heart failure patients. In a recently performed meta-analysis, presence of worsening renal function in both acute and chronic HF was associated with increased risk for mortality (OR 1.81, 95% CI 1.55-2.12, p<0.001).[7] It has been postulated that any detectable decrease in renal function in patients hospitalized for HF has prognostic impact.[15] Still, this is not confirmed for patients early after admission because of HF by our study, which is in line with a recent analysis showing no prognostic impact of mild WRF defined as an increase in creatinine of 0.2 up to 0.5 mg/dl, in a comparable outpatient setting.[16] The prognostic impact of improvement of renal function (IRF) is less well known and mainly investigated in acute HF, where it has been associated with worse

outcome.[17,18] In contrast in chronic HF, improvement in renal function defined as a decrease in creatinine of >0.3 mg/dl predicted lower mortality (HR 0.8, 95% CI 0.6-1.0).[19] As can be seen in figures 2a and b, we found no significant impact on outcome of increase in eGFR of >20%.

Worsening renal function in HF patients can be caused by ominous processes like forward failure, venous congestion, neurohumoral activation, and release of vasoactive substances resulting in low renal perfusion.[20] On the contrary, WRF can also be caused by factors that are associated with favorable outcome like titration of evidence based HF medication like ACE-inhibitors, AT-2 antagonist and aldosterone receptor blockers.[21-25] WRF can also reflect intravascular volume depletion caused by diuretic treatment of HF.[26] As a consequence, it is very likely that the prognostic implication of WRF may depend on the underlying cause, and can be quite different. The assumption that there are multiple triggers for WRF with different pathophysiologic and prognostic backgrounds is strengthened by the inability to predict patients at risk for WRF. Although WRF is related to various factors like baseline renal function, hypertension, diabetes, diuretic use, age, anemia, vascular disease, signs of congestion and many more,[7] attempts to create a predictive model for WRF have failed.[27] In our study, patients with a decrease or increase in eGFR more than 20% showed a wide variety of change in NT-proBNP ((IQR-40.0%-69.1%) and (-20.0%-94.4%)) respectively. This finding strengthens the assumption that both worsening and improvement in eGFR can be caused by a wide variety of pathophysiological processes, with different prognostic impact.

The ambivalent prognostic power of WRF is further illustrated by Testani et al.[26] WRF, defined as a decrease in eGFR more than 20%, was related to worse prognosis, but was also associated with haemoconcentration, a factor clearly associated with lower 180-day mortality (HR 0.31, p=0.01). Metra et al showed that WRF in acute HF patients was not related to one year mortality or urgent heart transplant in patients that appeared euvolemic at discharge by physical examination.[14] In patients with persistent signs of congestion, WRF was well related to worse outcome, but the increased risk appeared to be primarily driven by the presence of congestion. These findings are in line with our results, where changes in the probably most important biomarker of cardiac function, i.e. (NT-pro)BNP, had clearly superior prognostic impact as compared to WRF.

Changes in NT-proBNP have been reported to correlate with changes in clinical status, possibly giving insight in the success of HF treatment.[28] Moreover, both in

acute HF, early after admission because of acute HF, and chronic HF, changes in NT-proBNP were related to outcome.[8,10,11]

In line with the prognostic impact of changes in (NT-pro)BNP concentration, natriuretic peptide-guided therapy may result in significantly improved outcome. A recently published meta-analysis based on individual trial data[29] demonstrated a reduction in mortality by natriuretic peptide-guided therapy (HR 0.62, 95% CI 0.45-0.86, P=0.004). Still, the individual studies failed to come up with a clear-cut treatment algorithm when treating patients according to natriuretic peptide levels. Interestingly, in all individual studies demonstrating a positive effect of natriuretic peptide-guided therapy,[30-33] a significant increase in evidence based HF medication was seen in the natriuretic peptide-guided arm compared to the usual care arm. In two other studies also significantly increasing evidence based HF medication, but without improving the primary endpoint, a significant improvement by natriuretic peptide-guided therapy even in mortality was seen in patients aged 75 years or less.[34,35] Furthermore, in 2 of these 6 trials, patients allocated to the NT-proBNP-guided therapy arm had fewer prescription of loop diuretics compared to usual care management.[30,31]

Knowledge of change in NT-proBNP may help identifying the cause and particularly the impact of change in renal function and may therefore have therapeutic implications. Thus, WRF in combination with a decrease in NT-proBNP might reflect intravascular volume depletion or WRF caused by HF medication like ACE-inhibitors. If not severe, it may be acceptable.[16] Diuretic therapy may be reduced and limited to achieve and maintain an euvolemia with the lowest achievable dose, given the association between loop diuretics and worsening of renal function, neurohumoral activation and adverse outcome in HF.[36] Importantly, evidence based HF medication should not be reduced, but after stabilizing renal function further intensified. An improvement in renal function in combination with a decrease in NT-proBNP might be caused by increased renal perfusion after adequate HF therapy, supporting further intensifying of evidence based HF medication if not yet at maximum in combination with decrease in diuretic therapy. WRF in combination with an increase in NT-proBNP might reflect progression of HF, often with venous congestion, but possible alternative causes for increasing (NT-pro)BNP levels such as significant infection or an additional primarily renal problem must be considered.[37] Underlying cause of deterioration needs to be determinedly sought and appropriately treated; this obviously includes treatment of congestion if present. An improvement in renal function

in combination with an increase in NT-proBNP might be caused by dilution caused by fluid accumulation in worsening HF with the need of intensifying HF medication. Given the positive results of those natriuretic peptide-guided trials intensifying evidence based HF medication, this should focus on increasing diuretic therapy only in those patients with clinically evident congestion. Although these hypotheses and recommendations are plausible and supported not only by our results but also by the studies discussed above,[14,26,29] they should be confirmed and tested prospectively by future clinical research.

Limitations

There are some limitations to our study. The data used for this analysis was derived from a multicenter trial assessing the effect of NT-proBNP-guided therapy in chronic heart failure. Therefore, in half of the study-population, NT-proBNP concentration was known to the treating physician at the outpatient clinic, and in all of the patients included for this subanalysis, renal function at discharge and at 1 month follow-up visit was available. Knowledge of NT-proBNP and renal function may have influenced therapeutic decisions. However, in multivariate analysis correcting for randomization group, results regarding the effects of changes in NT-proBNP and eGFR were not significantly altered. In order to be included into the PRIMA study NT-proBNP concentration during admission needed to decrease at least 10% with a minimum of 850 pg/ml. Therefore, we cannot exclude that results in patients with a smaller decrease or an increase in NT-proBNP concentration during hospital admission could have been different. Furthermore, as the current study is a post-hoc analysis the hypothesis derived from our data needs to be tested in a prospective, preferably larger study.

Conclusion

In HF patients early after hospital discharge, change in NT-proBNP may give insight in the potential cause of worsening renal function because it specifically addresses the cardiac part of the cardiorenal syndrome. Our data suggest that this cardiac part is significantly more important than the renal part and may help to better target therapy in this patient group prone to cardiovascular events. However, future studies on the correlation of specific treatment strategies in different cardiorenal groups is needed to propose an individual treatment algorithm based on the combination of changes in natriuretic peptides and renal function.

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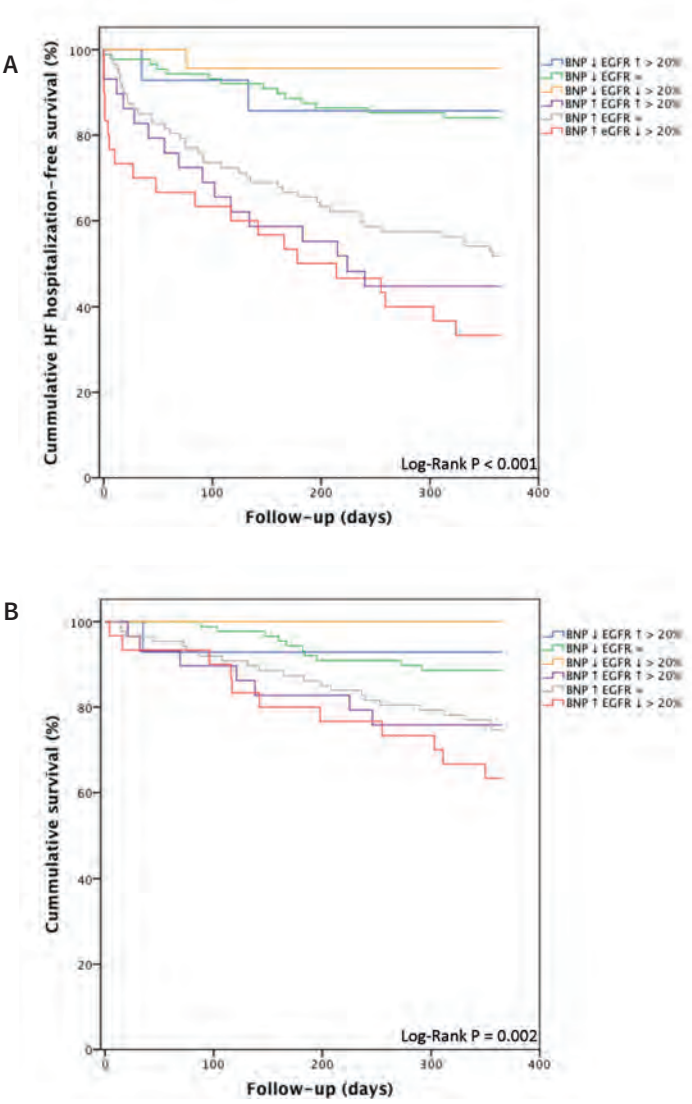

Supplemental figure 1. Kaplan-Meier curve for the combined endpoint HF readmission or mortality (a) and mortality (b) by 20% change in eGFR and change in NT-proBNP concentration.

Change in eGFR was defined as 1) an increase in eGFR more than 20% (eGFR ↑ > 20%), 2) a change in eGFR less than 20% (eGFR =) and a decrease in eGFR more than 20% (eGFR ↓ > 20%).

CHAPTER 7

General Discussion

Heart failure (HF) is a complex syndrome characterized by high morbidity, mortality and disease associated health care costs.[1,2] In order to adequately treat HF it is important not only to diagnose HF at is earliest stage, but also to detect worsening heart failure once cardiac status deteriorates. Dyspnea is the main complaint in HF, however dyspnea can be caused by a wide variety of diseases where some are harmless while others are deadly. Last decades, several biomarkers have been proposed for risk stratification and treatment guidance in heart failure with natriuretic peptides being the most investigated.

This thesis aims to (i) assess the additive value of multiple biomarkers for risk assessment in patients presenting to the emergency department with dyspnea as main complaint and (ii) assess the value of natriuretic peptides in the treatment of chronic heart failure.

7.1 RISK ASSESSMENT IN EMERGENCY DEPARTMENT DYSPNEA: MARKED-RISK SCORE IN PERSPECTIVE

In **chapter 2** we investigated 5 biomarkers (N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), high-sensitivity C-reactive protein (hs-CRP), galectin-3 (Gal-3) and cystatin-C (Cys-C)) with a distinct pathophysiological background for short-term risk stratification in 603 patients with dyspnea presenting to the emergency department (ED). Combining these biomarkers with other clinical risk factors we found that hs-CRP, hs-cTnT and Cys-C were of independent prognostic importance. These independent risk factors led to development of the multi marker emergency dyspnea-risk score (MARKED-risk score) incorporating risk factors age ≥75 years, systolic blood pressure < 110 mmHg, history of heart failure, dyspnea NYHA fc IV, hs-cTnT ≥ 0.04 µg/l, hs-CRP ≥ 25 mg/l and Cys-C ≥ 1.125 mg/l. This score predicted 90-day mortality excellently with an area under the curve (AUC) of 0.85 (95% confidence interval (CI) 0.81 to 0.89) and identified patients at low (2%), intermediate (14%) and high (44%) risk of 90-day mortality. The predictive accuracy of our model is much higher compared those of currently used risk scores in other fields like CHA_2DS_2-Vasc[3] (AUC 0.61) or HAS-BLED[4] (AUC 0.72).

In the majority of patients presenting to the cardiac emergency department (ED) with HF, dyspnea is the main complaint[5]. Dyspnea can be caused by a wide variety of diseases although HF has reported to be the most frequent cause of

dyspnea at the ED, ranging from 34% to 58% of dyspneic patients[6,7]. Many risk scores have been developed for diseases that might cause dyspnea like heart failure,[8] acute coronary syndromes,[9] atrial fibrillation[3], pulmonary embolism,[10] exacerbation of COPD[11] and pneumonia.[12] Proposed risk scores for emergency department dyspnea were developed for long-term risk stratification,[13,14] however, a general risk score for short-term prognosis in dyspneic patients was still lacking. Because the evaluation of dyspneic patients in the ED is difficult[15] and dyspnea can be caused by both harmless as well as highly lethal conditions, [16] an accurate non-diagnosis-specific short-term mortality risk score is expected to be helpful in clinical practice. This notion is strengthened by our finding that there was a relatively high admission rate in the low-risk category (44%) and high discharge rate in the high-risk category (24%) with similar mortality rates between admitted and discharged patients. Thus, knowledge of individual risk might help the treating physician at the ED to decide on urge of intervention, admission and timing of re-evaluation. However, in contrast to the widely implemented CHA_2DS_2-Vasc and HAS-BLED risk scores, the MARKED-Risk score is currently not used in general practice. Main reason is the lack of therapeutic consequences: if knowledge of individual risk leads to improvement of prognosis still remains to be assessed in future trials.

Biomarkers in HF and dyspnea

In 2008, Braunwald[17] classified circulating biomarkers related to HF into seven categories based on their pathophysiological effects in the disease and hypothesized that multiple biomarkers in combination would provide a valuable means for risk stratification (figure 1). Biomarkers used in our multi marker study encompassed five of these seven categories: Myocardial stretch (NT-proBNP), myocyte injury (hs-cTnT), Matrix remodeling / fibrosis (Gal-3), inflammation (hs-CRP / Gal-3) and renal dysfunction (Cys-C). Recently many potential biomarkers for HF have been investigated for risk stratification in acute HF. The natriuretic peptide NT-proBNP characterizes cardiac wall stress and is an established biomarker for diagnosis and prognosis of acute HF.[18] However the prognostic value of NT-proBNP is limited for short-term risk stratification in acute heart failure (AHF) compared with other biomarkers.[19,20]

Galectin-3, a marker that is linked to fibrosis and inflammation is involved in heart failure, cancer and renal disease and is predictive for all-cause mortality in the general population.[21] Although its diagnostic role in HF is of limited value[20],

Gal-3 is a reasonable prognostic marker for short- and long-term outcome in acute HF.[20,22]

Hs-cTnT, released from the heart due to myocyte injury, is associated with all cause mortality in acute[23] and chronic[24] heart failure, even in patients with normal conventional TnT levels. hs-CRP, a marker for inflammation, has demonstrated prognostic power in both acute[25,26] and chronic[27] heart failure, independent of clinical risk factors and other biomarkers among which (NT-pro)BNP. Cystatin C, a marker for renal function that strongly reflects glomerular filtration rate[28] is a strong prognostic marker for mortality, in AHF independent of NT-proBNP[29] and TnT[30], even in patients with normal plasma creatinine[29].

Thus, all markers that were analyzed in our multi marker study have proven prognostic power in heart failure. Although all investigated biomarkers had incremental value on top of the clinical risk model (table 3, chapter2), Gal-3 was dropped from the final biomarker panel and NT-proBNP was excluded from the final prediction model including other clinical parameters. This drop-out might partially be explained by the existence of significant correlations between both Gal-3 and NT-proBNP and other biomarkers[31]. The previously reported findings about the inferior predictive value of NT-proBNP for short-term risk prediction compared to other biomarkers in acute HF might also play an important role in the exclusion of NT-proBNP in the final model. Moreover, as our study included patients with dyspnea and more then 40% of patients had other diagnoses than acute HF, knowledge of prognostic power of these biomarkers in other dyspnea causing diseases is important. Although Gal-3 has recently been related to long term cardiovascular mortality in coronary artery disease[32] and levels are increased in acute coronary syndrome (ACS) patients compared to patients with stable coronary artery disease[33], prognostic effect of Gal-3 in ACS patients still remains to be assessed. Gal-3 is also known to be elevated in atrial fibrillation and pneumonia, in contrast to COPD, however no data exists on prognostic effect of Gal-3 in pneumonia, COPD or pulmonary embolism. In contrast, CRP, [34-36] troponin[37-40] and cystatin C[41-43] have been correlated to prognosis or disease severity in a wide variety of diseases causing dyspnea.

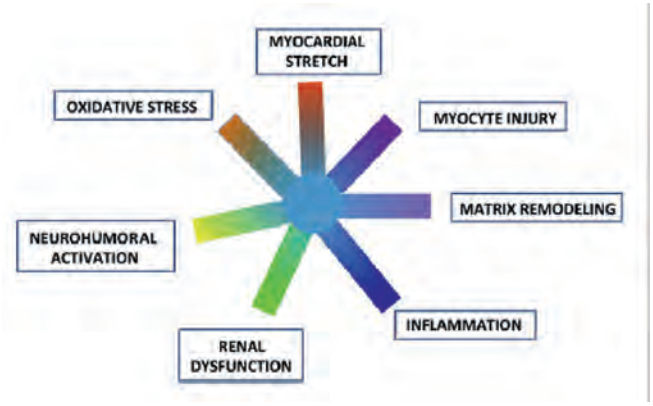

Figure 1. Seven major classes of biomarkers contributing to the biomarker profile in HF. Adapted from[103] with permission from dr. E. Braunwald.

7.2 GUIDED THERAPY OF HEART FAILURE: THE PRIMA STUDY IN PERSPECTIVE.

The PRIMA study, a multicenter randomized investigator initiated study, addressed whether therapy of chronic heart failure guided by an individualized NT-proBNP target improves outcome (**chapter 3** of this thesis). 345 Patients where randomized to heart failure therapy guided by an individually set NT-proBNP target level in addition to clinical signs, or by clinical signs alone. The individually set NT-proBNP target level was defined as the lowest NT-proBNP concentration at hospital discharge or 2 weeks follow-up. PRIMA demonstrated that selective intensification by an individualized NT-proBNP target did not significantly improve any of the pre-specified primary or secondary outcome measures. Although treatment guided by an individualized NT-proBNP target slightly improved the number of days alive outside the hospital and overall mortality, these changes were not statistically significant. Interestingly, a trend was seen towards improved outcome by NT-proBNP-guided therapy in patients with age < 75 years, HF with reduced left ventricular ejection fraction (HFrEF) and patient with preserved renal function (table 2 Chapter 3).

Until today many studies assessing the effect of natriuretic peptide (NP)-guided therapy have been published.[44-56] Inclusion criteria, population size, treatment target, treatment response, and outcome measures were quite diverse among the studies (table 1). None of these studies demonstrated mortality reduction in the overall population, although two studies demonstrated a significant

improvement in survival by natriuretic peptide-guided therapy in patients aged 75 years or less.[47,49] Literature-based meta-analysis using aggregate data have suggested that natriuretic peptide-guided treatment may be associated with a 20-30% reduction in all-cause mortality.[57-60] Recently a meta-analysis based on individual patient data of 2000 patients included in the major natriuretic peptide-guided therapy studies demonstrated a reduction in all cause mortality of 38% by natriuretic peptide-guided treatment of HF ((HR 0.62 (0.45-0.86); P = 0.004).[61] This survival benefit was only seen in patients younger than 75 years (HR 0.62 (0.45-0.84); P=0.009, see figure 2.

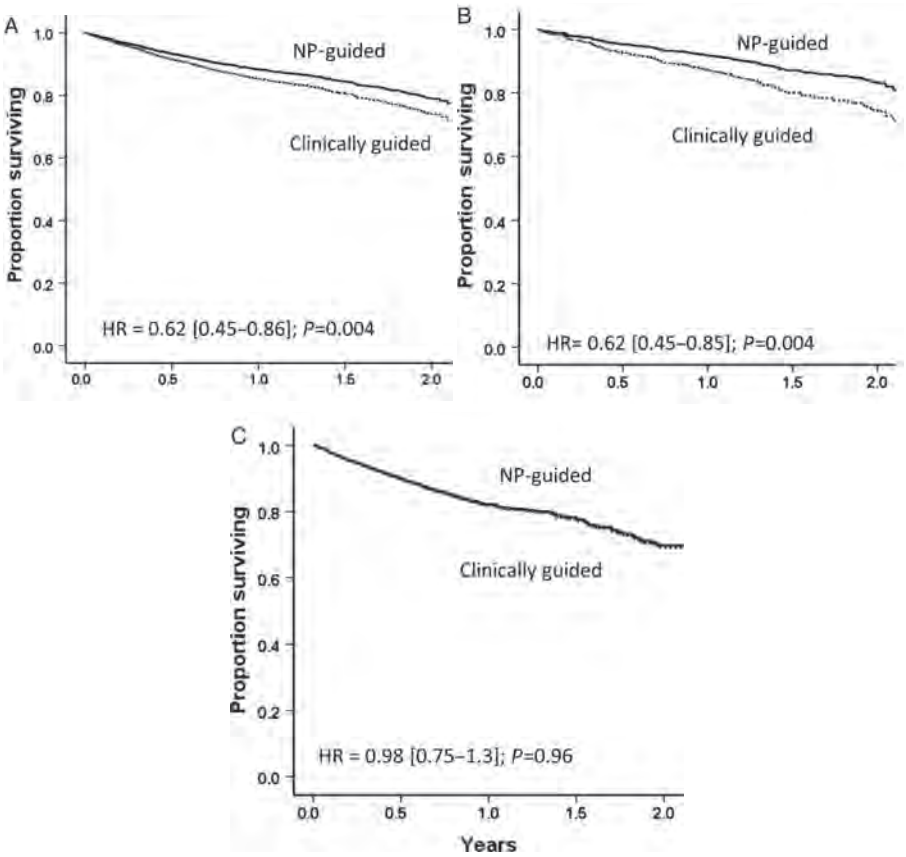

Figure 2. Kaplan-Meier survival curves for overall mortality in (A) total group, (B), below age 75 years (n=982) and (C) 75 years or above (n=1018). Figure adapted from an individual patient meta-analysis[61]

Table 1

	Troughton 2000[44]	STARS-BNP 2007[46]	TIME-CHF 2009[49]	Battle-scarred 2009[47]	Berger 2010[48]	SIGNAL-HF 2010[52]	PRIMA 2010[51]	STARBRITE 2011[55]	UPSTEP 2011[54]	PROTECT 2011[53]	Northstar 2013[56]
N	69	220	499	364	278	252	345	130	279	151	407
Blinding	Double	Unknown	Single	Double	No	Single	Single	No	No	No	No
Marker	NT-proBNP	BNP	NT-proBNP	NT-proBNP	NT-proBNP	NT-proBNP	NT-proBNP	BNP	BNP	NT-proBNP	NT-proBNP
Single/ multicenter	Single	Multi (17)	Multi (15)	Single	Multi (8)	Multi (45)	Multi (12)	Multi (3)	Multi (19)	Single	Multi (18)
Incl after hospital adm	Partially	No	< 1 yr	Yes	Yes	No	Yes	Yes	Partially	Partially	No
Exclusion renal dysfunction	Kreat > 200 µmol/l	Kreat > 250 µmol/l	Kreat > 220 µmol/l	Kreat > 250 µmol/l	No	Kreat > 265 µmol/l	Dialysis	Kreat > 309 µmol/l	Kreat > 250 µmol/l	Kreat > 221 µmol/l	Kreat > 200 µmol/l
(NT-pro)BNP aim, pg/ml	1695	100	400/800*	1271	2200	50% ↓	(post) discharge	2x discharge	150/300*	1000	< 30% increase
(NT-pro)BNP BL, pg/ml†	1839-2127	352	3998-4657	2012 - 1996 -2012	2216 - 2469 - 2359	2661-2429	2961 - 2936	453-440	631 - 596	2344 - 1946	1955
Control aim	HF score	UC	NYHA ≤ fc II	IC/UC	IC/UC	UC	UC	CS	UC	UC	UC
Age	70	66	76	76	71	78	72	59	71	63	73
Female	23%	42%	34%	36%	35%	29%	43%	31%	27%	15%	25%
LVEF, % (incl;BL)	<40; 27	<45; 30	≤45; 30	No; 39	<40 or CT-ratio > 0.5; 29	<50; 32	No; 36	≤35; 20	<40; 57% <30	≤40; 27	≤45; 30
Isch. HF	74%	52%	58%	72%	64%	?	60%	41%	?	56%	43%
ACE/ARB↑†	Yes	Yes	Yes	No‡	Yes§	No	Yes	Yes	No	Yes	No
β-block↑†	No	Yes	Yes	No‡	Yes	No	No	Yes	No	Yes	No
MRA↑†	Yes	?	Yes	No‡	No	No	No	No	No	Yes	No
Diuretics↑†	Yes	?	No	No‡	(Decrease)‖	No	Yes	No	No	Decrease	No
FU, months	9.5	15	18	24	≥12; 18	9	≥15, 24	>3	≥ 12	≥6; 10	≥6;30

1° EP	CV mort, CV hosp , outpatient HF	HF mort, HF hosp	All-cause mort, all-cause hosp	All-cause mort	All-cause mort, HF hosp.	Days alive without CV hosp	Days alive outside hospital	Days alive outside hospital	CEP mort, hosp, worsening HF	CV events	CEP mort, CV hosp
1° Effect	Pos	Pos	Neg	Neg	Pos	Neg	Neg	Neg	Neg	Pos	Neg
Effect mortality	1 vs 7, p=0.06	7 vs 11, p=n.s.	Trend pos, p=0.06	Neg (BM vs IC)	Neg (BM vs IC)	Neg	Neg	Neg	Neg	Neg	Neg
(NT-pro)BNP ↓	↓ BNP in BNP group	↓ BNP in BNP group	↓ BNP in both groups	↓ BNP in BM and IC	↓ BNP in BM and IC, not in UC	Modest ↓ BNP both groups ~10%	↓ BNP in both groups	No difference in final BNP levels	-	↓ BNP in BNP group	Modest ↓ BNP both groups
Target reached (%)	-	33% at 3 months	<50% at 6 months	<50% at 24 months	-	19%	80% at 1 year	68%	-	44%	-
Inter. Age	-	-	Yes	Yes	No	-	N.S.	-	No	No	No
Inter. LVEF	-	-	Yes	-	-	-	-	-	-	-	-
Other	Betablocker used in only 7% of pts.	Already on optimized HF treatment at randomisation.	Survival benefit in patients < 75 years	Survival benefit in patients < 75 years	Higher mortality UC vs IC/BM	Study performed in primary care setting	Excluded pt without initial ↓NT-proBNP	Pilot study	Responders (↓BNP > 30%) had lower mortality	More visits in BNP group	Already on optimized HF treatment at randomisation.

NT-proBNP = n-terminal pro B-type natriuretic peptide; BNP = brain natriuretic peptide; incl = inclusion; adm = admission; UC = usual care; IC = intensified care; CS = congestion score; LVEF = left ventricular ejection fraction; CT-ratio = Cor/thorax ratio; isch. = ischemic; HF = heart failure; ACE = aniotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; β-block = beta blocker; MRA = mineralocorticoid receptor antagonist; FU = follow-up; 1° = primary ; EP = endpoint; CV = cardiovascular; mort = mortality; hosp = hospitalization; CEP = composite endpoint; BM = (NT-pro)BNP-guided; BNP group = (NT-pro)BNP-guided; inter. = interaction

* Different cutoffs for younger and more elderly-subjects

† (NT-pro)BNP-guided group versus clinically-guided group.

‡ NT-proBNP-guided versus IC.

§ More patients treated with triple therapy in NT-proBNP-guided group versus IC group.

‖ NT-proBNP-guided group compared to usual care

7.3 GUIDED THERAPY OF HEART FAILURE: APPLICABLE TO ALL PATIENTS?

One possible explanation of the apparent dependency of the efficacy of NP-guided treatment upon age is that comorbidities, which are more common with increasing age, may limit HF therapy titration and / or reduce benefits of treatment. Another interesting finding of the previously mentioned meta-analysis was that, as only 10% of the trial participants had heart failure with preserved left ventricular ejection fraction (HFpEF), the effect of natriuretic peptide-guided therapy in this patient group still remained to be assessed. These findings have led to debate whether there are potential differences in treatment response between HFrEF and HFpEF, as well as potential interactions between comorbidities and age with treatment response in patients included in randomized trials of (NT-pro) BNP-guided therapy in HF.

In **chapter 4** of this thesis, we address these questions in a meta-analysis consisting of the previously mentioned cohort[61] with the addition of the HFpEF subgroup in TIME-CHF[62]. We found that (i) positive effects of natriuretic peptide-guided therapy were indeed only seen in patients with reduced EF and (ii) comorbidities strongly influenced the response to guided therapy and explained the lower efficacy of this approach in elderly patients. In patients with reduced EF, natriuretic peptide-guided therapy only led to mortality reduction in patients with none or only one of the following comorbidities: CVA/TIA, diabetes, COPD or peripheral vascular disease.

Natriuretic peptide-guided therapy in HFpEF

In HPEF patients, no positive effect of natriuretic peptide-guided therapy was seen. Strikingly: in patients with preserved ejection fraction without hypertension and in patients with renal dysfunction, natriuretic peptide-guided therapy even increased mortality.

Compared to HFrEF, patients with HFpEF have substantially different demographics.[63] In addition to the notion that HFrEF and HFpEF may be two distinct diseases,[62] several other concepts may be relevant to the finding that natriuretic peptide-guided therapy is ineffective in HFpEF. Until today, no prospective large randomized therapeutic trial has demonstrated positive results of HF therapies.[64-66] In contrast, medical and device treatment has markedly improved prognosis in HFrEF over the last decades.[67] It is therefore not surprising

that increasing HF therapy upon an elevated (NT-pro) BNP level does not lead to improved outcome in HFpEF patients. Our findings support current treatment recommendations for HFpEF which are restricted to treatment of comorbidities and symptoms.[67]

Natriuretic peptide-guided therapy in HFrEF

Our results call into question the belief that (NT-pro)BNP-guided HFrEF care is limited simply by age. We hypothesize that comorbidities influence the treatment response to HF medication. It is well known that comorbidities negatively influence prognosis in HF patients.[68] Moreover, there are numerous studies showing the potential risk of drug-drug interactions leading to adverse effects with the increasing number of comorbidities and as a consequence increasing number of prescribed drugs.[69] However it is less clear if this may result in less beneficial effects of HF specific medication. On the other hand, there is a direct correlation between the number of medications, number of daily doses and dosage adjustments, and the rate of nonadherence to pharmacological therapies.[70] A poor compliance to therapy has been linked to a poorer outcome and higher risk of HF decompensation, hospitalization and death.[71] In fact, full understanding of how multiple comorbidities in "real world" HF patients affect effectiveness of proven therapies for HF is lacking. In addition to a better understanding of the effects of (NT-pro)BNP-guided therapy in HF, our results shed new light on HF treatment in general. Only a minority of the real-life HF patients fulfill the enrolment criteria of landmark HF trials[72] because patients with comorbidities have often been excluded. In contrast, most of the (NT-pro) BNP-guided HF trials did not have similarly restrictive inclusion criteria, resulting in recruitment of more "real world" patients. Our results on comorbidities might partially explain why in daily practice, recommended therapies are often not used in adequate doses. Further studies on the effect of HF medication in patients with combined comorbidities and the feasibility and wisdom of titrating to currently recommended target doses in such patients are utterly needed.

7.4 NATRIURETIC PEPTIDE-GUIDED THERAPY IN DAILY PRACTICE.

Enough evidence?

Although multiple meta-analyses demonstrate natriuretic peptide-guided therapy, at least in HFrEF patients without many comorbidities, leads to improved outcome,[57-61] current European guidelines still do not support such an approach.[67] The American guidelines recommend use natriuretic peptide-guided therapy for titration of evidence based HF medication in clinically euvolemic patients, although they claim that usefulness to reduce hospitalization or mortality in patients with HF is not well established.[73] Question remains why the guidelines have been reluctant to recommend usage of natriuretic peptides to guide therapy. As BNP and NT-proBNP are used as routine measurements in the diagnosis of heart failure, these peptides are widely assessable, and results are available within one hour after measurement. However, before a natriuretic peptide-guided treatment algorithm can be introduced in daily practice, the effectiveness of such approach should be confirmed in at least one, sufficiently powered, randomized controlled trial. A large multicenter trial on natriuretic peptide-guided therapy with an estimated inclusion rate of 1,100 patients is currently on its way (GUIDE-IT).[74] Primary results are to be expected in 2018. Furthermore, the treatment strategy has to be proven cost-effective. Unfortunately, there are only few published reports on the cost-effectiveness of using natriuretic peptides to guide therapy.[75-77] The largest cost-effectiveness study conducted among patients included in the TIME-CHF trial demonstrated that NT-proBNP-guided therapy has a high probability of being cost-effective, saving almost $3,000 per patient.[77] However, the net cost reduction was mainly caused by a reduction in residence cost and it is not clear whether this effect is solely contributable to NT-proBNP-guided therapy. The previously mentioned GUIDE-IT trial will contain a cost-effectiveness analysis; results of this trial need to be awaited before any firm conclusions about cost-effectiveness can be drawn.

What natriuretic peptide target value should be implemented?

Furthermore it should become more clear what natriuretic peptide target value should be implemented. As mentioned before, no uniform treatment target was used in the previously published trials. However, the majority of studies performed used a fixed (NT-pro) BNP target value (table 1). Moreover, all studies demonstrating any positive effect of natriuretic peptide-guided therapy

used fixed (NT-pro)BNP target values as treatment goal.[44,46-49,53,54] NT-proBNP concentration above 1,000 pg/ml is associated with increased risk in HF.[78,79] Therefore, one could argue that solely implementing a fixed (NT-pro)BNP target should be the most efficient way to treat outpatient HF. However, the fixed and stringent target values used in these studies were achieved only in a minority of patients, (table 1). This leads to the question whether treating HF patients upon such fixed target value selects those patients at highest risk for events and at highest need for intensified treatment, or that the target value is merely a wake-up call for the treating physician to consider intensifying treatment in more then half of the patients. In the PRIMA study we demonstrated that an individualized NT-proBNP target yielded important prognostic impact (see table 7, chapter 3). Interestingly, in PRIMA, 80% of patients were on their individualized target after one year of follow-up. In **chapter 5** we evaluated the prognostic effect of change in NT-proBNP during and early after admission because of acute HF. We found that even modest changes in NT-proBNP one month after hospital discharge (ie change less then 30%) were of prognostic importance, independent of the NT-proBNP level at one-month follow-up and change during admission. Also in outpatient destabilized HF, change in NT-proBNP has been associated with prognosis: Bayes-Genis et al, for example, reported a 21% reduction in events for every 10% decrease in NT-proBNP within 2 weeks.[80] Thus it seems that both early after hospital discharge and in outpatient destabilized HF, not only the absolute concentration is of importance, but also whether or not NT-proBNP concentration is decreasing. Kazanegra et al. have demonstrated that decreasing NT-proBNP levels reflect improvement of cardiac status[81]. Therefore we hypothesize that the most efficient natriuretic peptide target level might be a combination of a fixed and relative target: the primary aim could be to decrease the NT-proBNP concentration < 1,000 pg/ml. However, if subsequent NT-proBNP levels decrease with more than 10%, it might be considered as on target, even though this level is above this fixed target.

Such strategy would possibly lead to a more selective and individualized risk stratification then implementing a stringent, fixed NT-proBNP level as target alone.

Response to off-target natriuretic peptide levels.

Although some natriuretic peptide-guided therapy studies provided a treatment algorithm, final decision how to react to natriuretic peptide levels that were too

high was mostly left at the discretion of the treating physician. As treatment of HF is complex and multifactorial, it is impossible to provide fixed HF treatment algorithms. However, it seems plausible that patients at highest risk for events (i.e. with increased or increasing natriuretic peptide levels) might benefit the most from intensified outpatient follow-up in combination with increased prescription of evidence-based HF medication, such as ACE-inhibitors, beta-blockers, and aldosterone antagonists. Recent trials assessing the effect of natriuretic peptide-guided therapy in HF that randomized patients into 3 treatment arms (ie, regular outpatient care vs intensified outpatient care with or without knowledge of natriuretic peptide concentration) have shown that intensified outpatient care leads to a decrease in HF related readmissions and mortality compared to usual care.[47,48] The BATTLESCARRED trial for example demonstrated 1-year mortality being lower in the intensified outpatient treatment group (9,1%) compared with usual care (18.9%, P=0.03).[47] Furthermore, in all 4 studies demonstrating a reduction in primary endpoint by natriuretic peptide-guided therapy[44,46,48,53] a marked increase in evidence based HF medication was seen in the natriuretic peptide-guided therapy arm compared with the usual care arm. Thus, intensified treatment in combination with increase in evidence-based HF medication appears to lead to better outcome. In 2 of these 4 trials, patients allocated to the NT-proBNP-guided therapy arm had fewer prescription of loop diuretics compared with usual care management.[48,53] In the PRIMA study, which failed to demonstrate a significant reduction in endpoints by NT-proBNP-guided therapy, outpatient elevated NT-proBNP levels led most frequently to an increase in diuretic dosage (>40%).[51]

Given the association between loop diuretics and worsening of renal function, neurohumoral activation, and adverse outcome in HF,[82] the use of diuretics is recommended to be limited to achieve and maintain an euvolemic state with the lowest achievable dose.

Therefore it can be hypothesized that patients at lowest risk (i.e. stable or decreasing NT-proBNP levels below 1,000 pg/ml) do not need intensified outpatient follow-up in dedicated HF clinics. In contrast, patients at highest risk for events (increasing NT-proBNP levels, or levels above 1,000 pg/ml) indeed should receive intensified outpatient follow-up. If NT-proBNP levels increase, or are stable above 1,000 pg/ml it should be aimed to increase evidence based HF medication if the patient is clinically euvolaemic. However, if a patient is clinically decompensated diuretics should be increased first. If NT-proBNP levels are above

1,000 pg/ml but decreasing, diuretic dosage could be reduced and evidence based HF medication should be uptitrated to recommended dosages. Such decision-making algorithm should be investigated in future trials.

Clinical challenges of NT-proBNP-guided therapy: cardiorenal interaction.
When treating HF, clinicians may encounter conflicting prognostic information by evaluating changes in renal function and natriuretic peptides over time. In other words: how should outpatient change in renal function in relation to change in natriuretic peptides be interpreted? In chapter 5 we already demonstrated that both the absolute outpatient NT-proBNP level, as change in NT-proBNP early after hospital discharge after admission because of acute HF have independent prognostic impact. Although not entirely uniform,[83,84] most studies showed increased risk of worsening renal function (WRF) in heart failure patients. In a recently performed meta-analysis, presence of worsening renal function in both acute and chronic HF was associated with increased risk for mortality (OR 1.81, 95% CI 1.55-2.12, P<0.001)[85]. The prognostic impact of improvement of renal function (IRF) is less well known and mainly investigated in acute HF, where it has been associated with worse outcome.[86,87] In contrast in chronic HF, improvement in renal function defined as a decrease in creatinine of >0.3 mg/dl predicted lower mortality (HR 0.8, 95% CI 0.6-1.0).[88] In **chapter 6** we investigated the prognostic impact of change in renal function in addition to change in NT-proBNP early after hospital discharge after admission because of acute heart failure. We found that early changes in NT-proBNP after hospital discharge due to acute HF had significant prognostic impact whereas changes in renal function did not. This finding might lead to the assumption that i) treatment of heart failure should be focused on improvement in cardiac function in such patients even if renal function slightly deteriorates and ii) there are multiple triggers for changes in renal function with different pathophysiologic and prognostic backgrounds. Worsening renal function in HF patients can be caused by ominous processes like forward failure, venous congestion, neurohumoral activation, and release of vasoactive substances resulting in low renal perfusion.[89] On the contrary, WRF can also be caused by factors that are associated with favorable outcome like titration of evidence based HF medication like ACE-inhibitors, AT-2 antagonist and aldosterone receptor blockers.[90-94] WRF can also reflect intravascular volume depletion caused by diuretic treatment of HF.[95] On the other hand; improvement in renal function might reflect an increase in renal perfusion as a result of

adequate treatment of heart failure. On the contrary, improvement in renal function defined as a decrease in serum creatinine concentration might reflect expansion of the intravascular volume caused by progressive heart failure[96]. NT-proBNP might be helpful in identifying the cause of change in renal function; Worsening renal function in combination with a decrease in NT-proBNP might be caused by titration of evidence based HF medication or intravascular volume depletion. Worsening renal function combined with an increase in NT-proBNP can be caused by decreased renal perfusion as a result of worsening heart failure. Improvement in renal function in combination with a decrease in NT-proBNP might result from improved renal perfusion caused by successful treatment of heart failure. “Improvement in renal function” reflected by a decrease in plasma creatinine concentration combined with an increase in NT-proBNP is likely to be cased by expansion of the intravascular volume caused by progressive heart failure. The aforementioned assumptions are based on few studies and should be confirmed in large randomized trials.

7.5 FUTURE PERSPECTIVE OF BIOMARKERS IN HF: A BRIDGE TOWARDS PERSONALIZED MEDICINE?

The potential role of biomarkers in Heart Failure has been widely investigated (see figure 3). Last decade numerous biomarkers have been proposed, and validated, for risk assessment in heart failure. As mentioned before, natriuretic peptides have been the most investigated. In contradiction to the tremendous amount of research that has been done, apart from natriuretic peptides, biomarkers are still hardly used for risk assessment and treatment guidance of HF patients. In fact, even natriuretic peptide-guided therapy is still not advocated by the ESC guidelines due to previously discussed caveats in evidence. The most important reason for the reluctant use of biomarkers in current clinical practice is inability of these markers to reduce morbidity and mortality. Knowledge of individual risk in HF is mostly important if it can lead to reduction in morbidity and mortality. Thus far, only natriuretic peptides have such a proven effect, although only demonstrated in meta-analyses.[57-61]

Current treatment of HF with reduced left ventricular ejection fraction is based on one-size-fits-all approach with initiation of renin-angiotensin system blockers, beta-blockers and aldosterone antagonists and uptitration towards

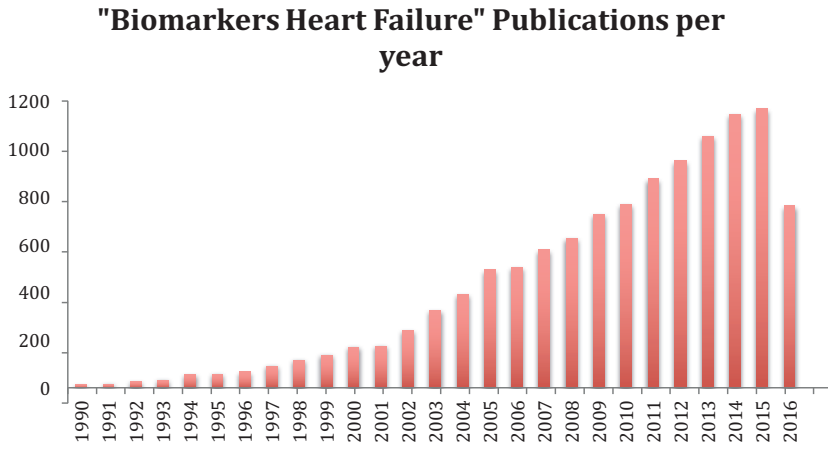

Figure 3. Number of publications per year for Biomarkers in Heart Failure.
Source: www.pubmed.gov. Keywords: "Biomarkers Heart Failure".

fixed recommended dosages being the cornerstone of treatment.[67,73] However, it can be argued if such a generalized treatment of HF is the best way to treat individual HF patients. As stated earlier in this discussion, real-life HF population differs from the landmark trials on which guidelines have been based, including mostly younger patients with no or little comorbidities. It is generally known that in real life, especially in the elderly, evidence based dosages of HF medication is only achieved in a minority of patients, partly due to (i) multiple comorbidities, (ii) side effects of HF medication, (iii) negative effects of polypharmacy among which increased risk of toxicity, drug interactions and poor compliance.[97]

Additionally, several studies have suggested that tolerability and possibly also effects of HF medication might vary significantly between patients. Studies assessing the effect of genetic polymorphism have demonstrated differences in effect of beta-blockers, ACE-inhibitors and diuretics, however there is still no evidence that tailoring therapy according to polymorphisms for beta-blockers and ACE-inhibitors is effective.[98]

Furthermore, as etiology of HF is quite diverse, it might be argued that specific etiological background should lead to specific HF therapy.

These findings have led to increased interest in personalized medicine for HF, defined as identifying patients most likely to benefit and those most likely to experience adverse reactions in response to specific drugs, and tailoring therapy based on this knowledge. Implementing such personalized therapy strategy in heart failure might lead to (i) more effective therapy by only prescribing drugs that

alter outcome, (ii) less side effects resulting in increased quality of life as needless therapy can be avoided, and (iii) a more cost effective treatment.

Using a broad panel of biomarkers, with different pathophysiologic backgrounds, might be helpful in identifying specific subgroups of HF patients, each with a different treatment approach. For example: elevated ST2 has been associated with increased effect of beta-blocker treatment[99]. Also, interaction seems to exist between the level of galectin-3 and the effects of statin therapy.[100] However, although it has been suggested that patients with heart failure and raised levels of galectin-3 might benefit more from aldosterone antagonist therapy than patients with lower levels recent analysis failed to demonstrate such specific benefit.[101,102]

In order to assess a multi marker panel for individualized HF therapy, it is important first to evaluate possible interaction between different biomarkers and specific HF therapy in retrospective analyses. Thereafter prospective trials should be designed to validate the hypothesis gained from the retrospective trials.

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Samenvatting

Hartfalen is een complex syndroom dat ontstaat als het hart faalt in zijn functie om voldoende bloed door het lichaam te pompen. Deze tekortkoming in pompfunctie kan ontstaan door een verminderde knijpkracht van het hart (Hartfalen met een gereduceerde ejectiefractie, HFrEF), of door een verminderde ontspanning van de hartspier (hartfalen met een behouden ejectiefractie, HFpEF). De oorzaken van hartfalen zijn zeer divers. Het ziektebeeld komt relatief vaak voor, met name bij ouderen. De prognose van hartfalen is slecht, ondanks de ontwikkeling van medicatie, nieuwe technieken om hartkleppen te repareren of vervangen en speciale pacemakers die de pompfunctie van het hart in sommige gevallen kunnen herstellen. Het ziektebeeld gaat daarnaast gepaard met een grote ziektelast door klachten als kortademigheid, vermoeidheid, vochtophoping in de benen en herhaalde opnamen in het ziekenhuis. De verwachting is dat met de vergrijzing van de bevolking steeds meer mensen last zullen krijgen van hartfalen. Om deze patiënten op een adequate manier te kunnen behandelen is het niet alleen belangrijk om het ziektebeeld zo snel mogelijk op te sporen, maar moet enige achteruitgang van de klinische status van de individuele patiënt zo vroeg mogelijk worden gedetecteerd zodat de behandeling kan worden aangepast.

De laatste decennia is veel aandacht ontstaan voor biomarkers - biologische markers, meestal eiwitten - die we in het bloed kunnen meten en die een bepaald onderliggend mechanisme van het hartfalen weergeven. De biomarkers BNP en NT-proBNP, eiwitten die door de hartspier worden uitgescheiden als de rek op de hartspier toeneemt, zijn hierbij het meest onderzocht. Dit proefschrift beschrijft de toegevoegde waarde van biomarkers, met name NT-proBNP, als leidraad bij de risico stratificatie en behandeling van patiënten met hartfalen.

In het eerste gedeelte van dit proefschrift is onderzocht welke combinatie van biomarkers het beste in staat is om het risico in te schatten op overlijden bij patiënten die zich met kortademigheidsklachten op de eerste harthulp presenteren. De biomarkers high-sensitivity troponine T (hsTNT), high-sensitivity C-reactive protein (hsCRP) en cystatin-C bleken de belangrijkste voorspellers. De combinatie van deze biomarkers helpt patiënten te selecteren met het hoogste en laagste risico op overlijden, hetgeen de behandeling kan beïnvloeden. Of de wetenschap van het individuele risico van de patiënt met kortademigheidsklachten ook daadwerkelijk kan leiden tot een verlaging van het risico op sterfte dient nog te worden onderzocht.

In het tweede deel van dit proefschrift is de toegevoegde waarde van poliklinische NT-proBNP-geleide behandeling van patiënten na opname in verband met hartfalen onderzocht in de PRIMA-studie. Basisgedachte bij deze studie was dat als de NT-proBNP-concentratie op de polikliniek boven de individuele targetwaarde (= laagste waarde bij ontslag of de eerste poliklinische controle na ontslag) steeg, de therapie van hartfalen moest worden geïntensiveerd. Deze studie, die in 12 Nederlandse ziekenhuizen is uitgevoerd, toonde geen significant voordeel van NT-proBNP-bepalingen bij ieder poliklinisch bezoek. Wel bleek een poliklinische stijging van de concentratie NT-proBNP van belangrijke prognostische waarde: indien de NT-proBNP-concentratie boven de individuele targetwaarde steeg was sprake van een verhoogd risico op opname in verband met hartfalen of sterfte. De laatste jaren zijn diverse onderzoeken naar de meerwaarde van BNP en NT-proBNP bij de behandeling van hartfalen onderzocht, met verschillende uitkomsten. Een uitgevoerde meta-analyse, waarbij het effect van (NT-pro)-BNP-geleide behandeling van hartfalen bij alle patiënten uit 9 studies is onderzocht, toonde een lagere mortaliteit bij patiënten die (NT-pro)-BNP-geleid werden behandeld. Dit voordeel werd alleen gezien bij jongere patiënten (<75 jaar). Een belangrijk probleem bij de interpretatie van deze gegevens is dat de studies die voor de meta-analyse zijn gebruikt verschillende behandelstrategieën hebben toegepast. Zo heeft onze studie het effect van een individuele NT-proBNP-targetwaarde onderzocht terwijl andere studies een universele, voor iedere patiënt gelijk zijnde lage targetwaarde als behandeldoelstelling hebben bestudeerd. Vooraleer (NT-pro)-BNP-geleide behandeling in de praktijk kan worden ingevoerd dient een voldoende grote studie te worden uitgevoerd met een helder behandelprotocol.

In het derde deel van het proefschrift is onderzocht welke patiënten wel en welke niet lijken te profiteren van (NT-pro)-BNP-geleide behandeling van hartfalen. In een meta-analyse van 8 verschillende studies is aangetoond dat (NT-pro)-BNP-geleide behandeling alleen effectief lijkt in patiënten met hartfalen door een verminderde knijpkracht van het hart (HFrEF). Het eerdergenoemde verschil in effectiviteit van behandeling tussen patiënten jonger en ouder dan 75 jaar bij patiënten met HFrEF bleek volledig toe te schrijven aan de aanwezigheid van bijkomende ziekten (comorbiditeiten). Hartfalen gaat vaak gepaard met comorbiditeiten als COPD en diabetes mellitus. Bij patiënten met HFrEF en minimaal twee bijkomende ziekten (COPD, diabetes mellitus, perifeer vaatlijden of een TIA dan wel

herseninfarct) bleek (NT-pro)-BNP-geleide behandeling niet te leiden tot minder sterfte. Bij patiënten met hartfalen en een behouden linker kamer ejectiefractie (HFpEF) bleek dat (NT-pro)-BNP-geleide behandeling zelfs schadelijk was bij patiënten die nierfunctiestoornissen hadden en bij patiënten die niet bekend waren met hoge bloeddruk. Deze resultaten onderstrepen de aanbevelingen die gedaan worden in de richtlijnen met betrekking tot de behandeling van patiënten met HFpEF: aanbevolen wordt enkel bijkomende ziektebeelden te behandelen zoals hoge bloeddruk. Een specifieke behandelstrategie voor het hartfalen bij HFpEF patiënten is helaas nog niet effectief gebleken. Bij patiënten met HFrEF zijn wel specifieke medicamenteuze behandelstrategieën bewezen. De huidige richtlijnen baseren zich hierbij op studies waarbij patiënten met veel bijkomende ziekten niet zijn onderzocht. Onze studie laat zien dat deze groep patiënten mogelijk minder goed reageren op medicamenteuze behandeling van hartfalen. Hoe patiënten met hartfalen en veel bijkomende aandoeningen moeten worden behandeld zal in toekomstige studies moeten worden onderzocht.

Het vierde deel van het proefschrift onderzoekt de voorspellende waarde van verschillende NT-proBNP-bepalingen bij patiënten tijdens en vlak na een opname in verband met hartfalen. In deze analyse is aangetoond dat de mate van daling van NT-proBNP gedurende opname, de verandering tussen ontslag en policontrole na één maand en de absolute NT-proBNP-concentratie na één maand onafhankelijke voorspellers zijn voor sterfte en heropname voor hartfalen. Op basis van deze NT-proBNP-waarden konden patiënten worden ingedeeld in zeer laag risico, gemiddeld risico en zeer hoog risico op overlijden of heropname. Kennis over het individuele risico van patiënten met hartfalen die net zijn ontslagen kan inzicht geven in welke patiënten zeer strikt moeten worden gevolgd, zowel op de polikliniek als via thuismonitoring door E-health toepassingen, en bij welke patiënten een minder strikte opvolging veilig is. Uiteraard dienen onze resultaten te worden geverifieerd in een groter onderzoek en dient na eventuele bevestiging van de resultaten een gerandomiseerd onderzoek plaats te vinden naar de veiligheid van dergelijke individuele behandelstrategieën.

In het laatste deel van dit proefschrift is de aanvullende prognostische waarde van poliklinische verandering in nierfunctie ten opzichte van veranderingen in de NT-proBNP-concentratie vlak na opname in verband met hartfalen onderzocht.

Bij behandeling van patiënten met hartfalen zien we vaak veranderingen in zowel nierfunctie als NT-proBNP-concentratie. Hoe de verandering van nierfunctie moet worden geïnterpreteerd in relatie tot verandering in NT-proBNP is onbekend. Dit kan ertoe leiden dat bij verslechtering van nierfunctie hartfalen medicatie wordt verminderd. Omgekeerd kan een ogenschijnlijke verbetering van nierfunctie bij een stijgend NT-proBNP de indruk wekken dat een patiënt stabiel is. In onze studie bleek enkel verandering in de NT-proBNP-concentratie tussen ontslag en de policontrole één maand na ontslag van prognostische waarde. Verandering in nierfunctie bleek geen effect te hebben op sterfte of heropname in verband met hartfalen. De nierfunctie wordt geschat door het creatinine in het bloed te meten. Creatinine is een afbraakproduct van creatininefosfaat in het spierweefsel en wordt door het lichaam met een vrij constante snelheid geproduceerd. Het wordt door de nieren uitgescheiden. Als het creatinine stijgt, kan dat het gevolg zijn van verslechtering van de nierfunctie. Bij patiënten met hartfalen is de oorzaak van verslechtering van nierfunctie heel divers. Zo kan de nierfunctie verslechteren doordat stuwing van de nieren plaatsvindt veroorzaakt door verergering van hartfalen. De nierfunctie kan echter ook verslechteren door lichte uitdroging bij gebruik van plasmedicatie, of door gebruik van medicatie als ACE-remmers of aldosteron antagonisten. Deze medicatie heeft een positief effect op de overleving van patiënten met HFrEF. Het is aannemelijk dat de eerste reden van verslechtering van nierfunctie een slechtere prognose heeft dan de tweede. Een verbetering van nierfunctie kan optreden als de pompfunctie van het hart verbetert waardoor de nieren beter worden doorbloed. De nierfunctie kan ogenschijnlijk verbeteren doordat bij vocht vasthouden het creatinine wordt verdund. In het laatste geval is de nierfunctie dus niet echt verbeterd, maar lijkt een verbetering plaats te vinden door verdunning van het creatinine. Een proces dat duidt op verergering van hartfalen met hoog risico op heropname of overlijden. De verschillende mechanismen voor (ogenschijnlijke) verbetering dan wel verslechtering van nierfunctie maakt dat uit verandering in nierfunctie vlak na ontslag geen uniforme conclusie kan worden getrokken. Dat verandering in de NT-proBNP-concentratie wel van prognostische waarde is ligt in de lijn der verwachting: als door progressie van hartfalen meer druk op de hartspier wordt uitgeoefend zal meer NT-proBNP in de bloedbaan worden uitgescheiden. Vermindert de druk op het hart dan zal de NT-proBNP-concentratie dalen. Bij de behandeling van hartfalen zal voor risico inschatting dus met name gekeken moeten worden naar hoe het NT-proBNP op de behandeling reageert. Een (geringe) verslechtering van de nierfunctie

lijkt vaak acceptabel, zolang het NT-proBNP maar daalt. Andersom: als de NT-proBNP-concentratie stijgt, maar de nierfunctie lijkt te verbeteren bestaat een verhoogde kans op heropname of sterfte. Deze patiënten profiteren mogelijk van agressieve behandeling van hartfalen en frequente poliklinische controle. Bovenstaande bevindingen en hypothesen zullen moeten worden geverifieerd middels vervolgonderzoek.

Valorisatie

MAATSCHAPPELIJKE EN ECONOMISCHE RELEVANTIE.

Hartfalen is een syndroom dat gepaard gaat met hoge ziektelast door onder andere kortademigheid, vochtophoping in de benen en een hoog risico op opname voor behandeling. Daarnaast is ook sprake van een hoge kans op overlijden: de 5-jaars overleving na het stellen van de diagnose is minder dan 50%. Het geschatte voorkomen is 1 tot 2% van de totale bevolking, waarbij 88 procent van de patiënten met hartfalen ouder is dan 65 jaar. Het ziektebeeld gaat gepaard met hoge kosten: 1% van de totale kosten van de gezondheidszorg wordt besteed aan de diagnostiek en zorg rond hartfalen. Van dit budget wordt 60% besteed aan ziekenhuiskosten. Denk daarbij aan kosten voor frequente polibezoeken en opnames.

Het is de verwachting dat tot 2025 het voorkomen van hartfalen met 50% zal toenemen. Belangrijkste reden hiervoor is de vergrijzing. Daarentegen zullen door de vergrijzing de inkomsten dalen waardoor minder budget voor de gezondheidszorg beschikbaar zal zijn. Kortom, de huidige arbeidsintensieve zorg van hartfalen is in de toekomst onbetaalbaar. We moeten dus op zoek gaan naar mogelijkheden om de kwaliteit van hartfalen zorg te verbeteren, of op zijn minst op peil te houden, met minder kosten per patiënt.

Zowel in de acute als de chronische fase van hartfalen kunnen biomarkers -meetbaar in bloed- behulpzaam zijn bij het maken van een individuele risico-inschatting op opname of overlijden.

In het eerste deel van dit proefschrift hebben we aangetoond dat met behulp van een aantal biomarkers de kans op overlijden op korte termijn goed kan worden ingeschat bij patiënten die zich met kortademigheidsklachten presenteren op de eerste harthulp (EHH). Deze biomarkers kunnen uit bloed worden bepaald en zijn reeds algemeen beschikbaar. Een dergelijke risico-inschatting kan ertoe leiden dat patiënten met een laag risico om op korte termijn te overlijden niet nodeloos opgenomen hoeven te worden. Van de andere kant: bij patiënten met een hoog risico op overlijden dient snel de juiste diagnose te worden gesteld om adequate behandeling te kunnen bieden. In deze categorie kan een opname aansluitend op het EHH-bezoek mogelijk een latere en langdurige heropname of overlijden voorkomen. Door deze strategie toe te passen kan de ziektelast worden beperkt en kunnen mogelijk kosten worden bespaard.

In het tweede deel van het proefschrift ligt de focus met name op de poliklinische behandeling van hartfalen na een recente opname. Met behulp van de biomarker NT-proBNP kunnen patiënten met een hoog risico worden onderscheiden van patiënten met een laag risico op heropname of overlijden. Hierdoor is het mogelijk de zorg te intensiveren bij de groep patiënten die er mogelijk het meest van profiteert, namelijk de groep patiënten met hoog risico op events. Bij patiënten met een laag risico op events kan de intensiteit van geboden poliklinische zorg mogelijk worden verminderd, zonder dat het risico op heropname of overlijden wordt beïnvloed. Bij deze laatste groep patiënten is wellicht een belangrijke rol weggelegd voor de 1,5 lijns- of keten-zorg hartfalen: een zorgprogramma waarbij patiënten met hartfalen worden gevolgd door de huisarts en de praktijkondersteuner, met de mogelijkheid tot laagdrempelig overleg met de tweede lijn. Tevens hebben we aangetoond welke groep patiënten voordeel heeft van (NT-pro)BNP geleide behandeling van hartfalen, namelijk de patiënt met hartfalen door een verminderde knijpkracht van het hart (HFrEF) die weinig bijkomende ziekten heeft (comorbiditeiten). Deze bevinding draagt ook bij aan het efficiënter maken van de zorg door de relatief dure (NT-pro) BNP bepalingen in ieder geval bij deze categorie patiënten op reguliere basis uit te voeren. Door dergelijke efficiëntie toe te passen zal de kwaliteit van zorg mogelijk verbeteren terwijl de kosten kunnen worden gereguleerd.

Doelgroepen

De doelgroepen die met name zullen profiteren van de bevindingen van dit proefschrift zijn in eerste instantie patiënten met de diagnose hartfalen, cardiologen en hartfalen verpleegkundigen. Maar ook huisartsen en praktijkondersteuners, die in de toekomst steeds meer patiënten met hartfalen gaan opvolgen, zullen door meer kennis te vergaren omtrent het gebruik van biomarkers bij hartfalen hun patiënten op een effectievere manier kunnen behandelen.

Onze onderzoeksresultaten zijn ook belangrijk voor de medische industrie. De verwachting is dat met de toename van kennis omtrent de meerwaarde van biomarkers bij hartfalen meer biomarker bepalingen zullen plaatsvinden. Met name fabrikanten van analyseapparatuur voor NT-proBNP en de overige onderzochte biomarkers zullen dus mogelijk voordeel hebben van onze bevindingen. Tot slot zullen ook de overheid en zorgverzekeraars onze bevindingen kunnen gebruiken aangezien onze bevindingen de basis leggen voor individuele risico inschatting en een individueel, op de specifieke patiënt gericht zorgaanbod met bijbehorende zorgzwaarte. Hierdoor kan de kwaliteit van zorg verbeteren en kunnen de kosten per patiënt worden gereduceerd.

Activiteiten/producten

De bevindingen van dit proefschrift zullen bijdragen aan het opstellen van individuele behandelstrategieën bij patiënten met hartfalen. Deze behandelstrategieën kunnen worden opgenomen in zorgpaden. Zorgpaden die door de zorglijnen heen kunnen worden opgesteld in zogenaamde ketenzorg programma's. In deze ketenzorgprogramma's werken cardiologen, hartfalen verpleegkundigen, huisartsen en praktijkondersteuners samen om de zorg rondom patiënten met hartfalen zo optimaal mogelijk in te richten. Dit onder het motto: zorg dicht bij huis waar het kan (laag-risicopatiënten worden opgevolgd door de huisarts en praktijkondersteuner) en in de tweede lijn waar het moet (hoog-risicopatiënten).

Innovatie

De bevindingen van dit proefschrift staan niet op zichzelf; de laatste jaren is veel onderzoek verricht naar de meerwaarde van biomarkers bij hartfalen. Deze onderzoeken hebben met name een prognostisch karakter; ze helpen een adequate risico inschatting te kunnen maken op events bij de individuele patiënt met hartfalen. In hoeverre wetenschap van dit individuele risico leidt tot verbetering van zorg (zowel in kwaliteit als efficiëntie) moet nog worden onderzocht. Onze resultaten kunnen bijdragen aan het opstellen van dergelijk vervolgonderzoek.

Planning en realisatie

Dit proefschrift beantwoordt belangrijke vragen omtrent de rol die biomarkers, met name NT-proBNP, spelen bij de behandeling van hartfalen. Alvorens deze biomarkers een belangrijke rol bij de behandeling van hartfalen kunnen innemen zal zeker vervolgonderzoek nodig zijn. Met name dient de vraag te worden beantwoord of kennis van het individuele risico van de patiënt met hartfalen ook daadwerkelijk leidt tot een meer efficiënte verdeling van zorg en een reductie van het risico op opname of overlijden. Deze onderzoeken zullen een duidelijke behandelstrategie moeten hebben, dienen prospectief te worden uitgevoerd en dienen zich te baseren op de reeds voorhanden zijnde literatuur, waar dit proefschrift een belangrijke bijdrage aan heeft geleverd. Het tijdspad voor dergelijke prospectieve onderzoeken is al gauw enkele jaren. Hopelijk is binnen 5 jaar bekend wat daadwerkelijk de rol van biomarkers bij de individuele behandeling van hartfalen gaat zijn.

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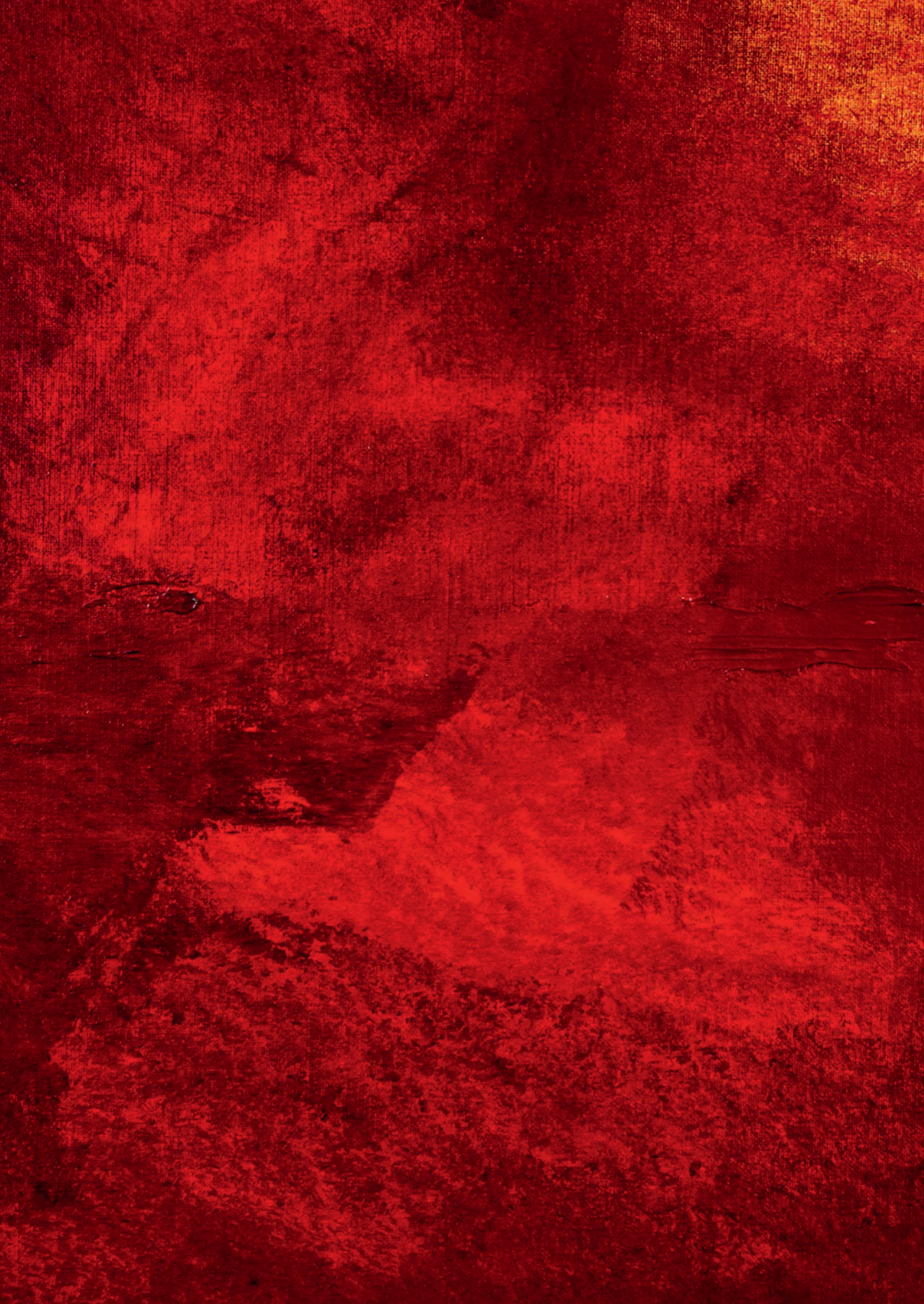

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Members of the assessment committee: Prof. dr. S.R.B. Heymans, Prof. dr. C.E. Mueller, Dr. C. Knackstedt, Prof. dr. B.L.M. Schroen, and Prof dr. A.A. Voors. Thank you for your carefull evaluation of my thesis.

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Curriculum Vitae

Luc Eurlings was born on the 2nd of September 1977 in Valkenburg, the Netherlands. After completing secondary school at Sint-Maartenscollege in Maastricht in 1996, he started his medical training at Maastricht University. After obtaining his medical degree in 2002 he started working as physician at the cardiology department at VieCuri MC in Venlo in 2003, followed by 6 months in 2004 at the cardiology department at Maastricht University Medical Center. In 2005, he became a PhD-fellow under supervision of Prof. dr. Y.M. Pinto and dr. D.J. van Kraaij focusing on the the clinical impact of NT-proBNP-guided therapy of chronic heart failure. He was allowed to present his work on several occasions at large international congresses, among which presentation of the results of the PRIMA study in 2009 as late-breaking clinical trial at the ACC congress in Orlando.

His cardiology training started in 2008 at Maastricht University Medical Center, guided by prof. dr. H.J.G.M. Crijns and dr. E.C. Cheriex. In 2009 he continued his training as resident internal medicine at the Orbis Medical Center in Sittard under supervision of dr. B.J. Looij. After 3 months continuing his PhD project in Maastricht, he worked in 2012 for one year as resident cardiology at VieCuri Medical Center in Venlo under supervision of dr. J.G. Meeder. In 2013 and 2014 he completed his cardiology training in Maastricht University Medical Center. From 2015 he works as a cardiologist at VieCuri Medical Center in Venlo.

In de voorbereidingen op het maken van dit kunstwerk heb ik een inventariserend gesprek met Luc gehad, waarin naar voren kwam dat de stof NT-proBNP een rode draad vormt door vrijwel alle geschreven publicaties. Zo kan de basiskleur van dit kunstwerk rood al gekoppeld worden aan bloed, bloedrood, bloedonderzoek.

In het promotieonderzoek wordt vooral gekeken naar de mogelijkheid om de hoeveelheid NT-proBNP als indicator te gebruiken voor de kans te bepalen op leven of overlijden bij hartfalen. Vandaar dat in het kunstwerk eveneens goud, als zijnde leven en donkerrood, bijna zwart, als zijnde de dood, terug te vinden zijn. Rood/donkerpaars is ook de kleur van rouw en bezinning. Maar het deel met deze kleur in het werk is minimaal. De hoofdkleuren zijn karmijn, bordeauxrood en goud. De warme kleur rood die tevens een verwijzing is naar rode wijn. Luc als wijnliefhebber, levensgenieter. En af en toe een glaasje wijn is, dacht ik als leek, ook goed voor het hart.

In het doek zelf zijn gouden strepen te zien, die de lijnen van het onderzoek weergeven. Daarnaast is de kleur goud een weergave van de gouden rand om het hele onderzoek. De overwinning; het behalen van de doctorstitel. Luc, gefeliciteerd met dit bijzonder wetenschappelijk onderzoek!

Dank dat je mij deze kans gegeven hebt een passend kunstwerk te maken.

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