Prognosis and NT-proBNP in heart failure patients with preserved versus reduced ejection fraction

Khibar Salah,1,2 Susan Stienen,1,3 Yigal M Pinto,1 Luc W Eurlings,4 Marco Metra,5 Antoni Bayes-Genís,6 Valerio Verdiiani,7 Jan G P Tijssen,1 Wouter E Kok1

ABSTRACT

Background We assessed the prognostic significance of absolute and percentage change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in patients hospitalised for acute decompensated heart failure with preserved ejection fraction (HFrEF) versus heart failure with reduced ejection fraction (HFpEF).

Methods Patients with left ventricular ejection fraction ≥50% were categorised as HFrEF (n=283), while those with <40% as categorised as HFpEF (n=776). Prognostic values of absolute and percentage change in NT-proBNP levels for 6-months all-cause mortality after discharge were assessed separately in patients with HFrEF and HFpEF by multivariable adjusted Cox regression analysis. Comorbidities were compared between heart failure groups.

Results Discharge NT-proBNP levels predicted outcome similarly in HFrEF and HFpEF: for any 2.7-factor increase in NT-proBNP levels, the HR for mortality was 2.14 for HFrEF (95% CI 1.48 to 3.09) and 1.96 for HFpEF (95% CI 1.60 to 2.40). Mortality prediction was equally possible for NT-proBNP reduction of ≤30% (HR 4.60, 95% CI 1.47 to 14.40 and HR 3.36, 95% CI 1.93 to 5.85 for HFrEF and HFpEF, respectively) and for >30%–60% (HR 3.28, 95% CI 1.07 to 10.12 and HR 1.79, 95% CI 0.99 to 3.26, respectively), compared with mortality in the reference groups of >60% reductions in NT-proBNP levels. Prognostically relevant comorbidities were more often present in patients with HFrEF than patients with HFpEF in low (<3000 pg/mL) but not in high (>3000 pg/mL) NT-proBNP discharge categories.

Conclusions Our study highlights—after demonstrating that NT-proBNP levels confer the same relative risk information in HFrEF as in HFpEF—the possibility that comorbidities contribute relatively more to prognosis in patients with HFrEF with lower NT-proBNP levels than in patients with HFpEF.

INTRODUCTION

While in-hospital mortality is lower in heart failure with preserved ejection fraction (HFrEF) than in heart failure patients with reduced left ventricular ejection fraction (HFpEF),3,4 mortality after discharge has been reported to be similar to that of patients with HFrEF in studies on patients after hospitalisations for acute decompensated heart failure (ADHF).3,4 Recent studies show that in a more stabilised phase, mortality is lower in patients with HFrEF than in patients with HFpEF in populations consisting either of a mix of inpatient and outpatient heart failure patients3,4 or in populations with exclusively outpatients with stable heart failure.5 In the latter situation, there are also lower mortality rates compared with the mortality rate after hospitalisations for heart failure.

The prognostic value of absolute levels of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been well established for patients hospitalised for ADHF with either type of heart failure but also specifically for patients with HFrEF.6 7 10–18 Prognostic information of a single measurement of natriuretic peptide levels has been specifically investigated in the comparison between patients with HFrEF and HFpEF and has been reported to be equal for the two heart failure types either at admission or at discharge.6 7 10 Also, the recently published multicentre study in combined inpatient and outpatient setting with a follow-up of 2 years showed that NT-proBNP levels at clinical stabilisation are strongly and similarly related to survival in heart failure regardless of ejection fraction and that a given level of NT-proBNP portends the same risk of death in HFrEF and HFpEF.8

The suggestion that a single baseline or discharge measurement of BNP or NT-proBNP may be equally useful in risk-stratifying patients with ADHF irrespective of the type of heart failure confronts us with the difficulty of explaining why prognostic is similar between the two groups, first of all because natriuretic peptide plasma levels are almost half in HFrEF compared with HFpEF.6 7 19 Second, absolute levels of NT-proBNP at admission or at discharge are interpreted as single values, but the assumption may then be that the reduction in NT-proBNP during hospitalisation would be equal in both types of heart failure. A third issue is that the risk assessment of hospitalised heart failure patients with the use of natriuretic peptides is done with relative risks, leaving unexplained that lower discharge natriuretic peptides in patients with HFrEF are associated with similar outcomes as in patients with HFpEF who have higher discharge levels. Finally, even if it can be shown that single values of NT-proBNP are predictive of outcome without distinction between HFrEF and HFpEF, the attainability of these levels may become the factor that determines whether HFrEF or HFpEF have a similar prognosis on a population level.

Therefore, we assessed the prognostic contribution of absolute levels of NT-proBNP and percentage change in NT-proBNP levels in patients with HFrEF and HFpEF hospitalised for ADHF. In
addition, we assessed the attainability of several (absolute and relative) discharge NT-proBNP targets in patients with HFpEF and HFrEF. Finally, we assessed the frequencies of prognostically relevant comorbidities in patients with HFpEF and HFrEF for low and high discharge NT-proBNP categories.

METHODS

Source/study populations

The presently studied population consisted of five of seven cohorts from the European collaboration on acute decompensated heart failure database with exact data available on left ventricular ejection fraction. Details on the search strategy, source gathering and explicit information on data collection for these prospective ADHF cohorts have been reported previously. In addition to these five cohorts, data from the Can NT-proBNP guided therapy during hospital admission for acute decompensated heart failure reduce mortality and readmissions? (PRIMA II) trial was used for the analyses. The PRIMA II study was funded by the Dutch Heart Foundation grant 2010B97, and NT-proBNP kits were supplied by Roche Diagnostics. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Statistical analysis

Our primary endpoint for this study was 6-month all-cause mortality; the secondary endpoint was a composite endpoint of 6-month all-cause mortality and 6-month cardiovascular readmission/all-cause mortality. To illustrate the relation between both endpoints (6-month all-cause mortality and 6-month cardiovascular readmission/all-cause mortality) and heart failure types, we plotted the survival curve that is adjusted for clinical variables (age ≥75 years, peripheral oedema at admission, systolic blood pressure (SBP) <115 mm Hg, hyponatraemia (sodium levels <135 mmol/L) and serum urea levels ≥15 mmol/L) and performed the log-rank test. For statistical analysis, we used multivariable Cox regression analysis for both primary and secondary endpoints. Categorisation of absolute discharge NT-proBNP levels was done by making quartiles of NT-proBNP levels at discharge among those patients with HFrEF who died, because this creates an equal distribution of the events among the quartiles. This has the statistical advantage of creating quartiles with equal statistical power to identify predictor variables. For practical purpose, we rounded off the quartile boundaries to convenient cut-offs. It should be noted that for the calculation of the risk estimate and for the construction of the Kaplan Meier (KM) curves, we did use the whole population. The tertiles for NT-proBNP percentage reduction were calculated using the total cohort and were used instead of a previous dichotomous approach, because of the possible interaction with baseline NT-proBNP levels so as to discern more than ‘only’ a 30% reduction in NT-proBNP levels as prognostically relevant.

The focus of our study was to assess a possible difference in the prognostic contribution of NT-proBNP levels in patients with HFrEF versus patients with HFrEF. A separate analysis in HFrEF was not deemed useful, as the main differences were expected between both ends of the spectrum of ejection fractions. For comparison with previous studies, we performed additional analyses using the 2-log and the natural logarithm scale for NT-proBNP levels at discharge for both endpoints (6-month all-cause mortality and 6-month cardiovascular readmission/all-cause mortality). First, univariable Cox proportional hazard regression analysis was performed for both HFrEF and HFrEF using log-transformed NT-proBNP levels at admission and at discharge and a separate analysis using NT-proBNP quartiles at discharge. The univariable model compares the three NT-proBNP categories to the category of NT-proBNP ≤1000, therefore this is the reference category. Thereafter, we excluded the category 1001–3000 pg/mL from the multivariable model in a backward selection fashion, because it did not contain any prognostic information in our univariable model. A multivariable Cox-regression model was then made for both endpoints (6-month all-cause mortality and 6-month cardiovascular readmission/all-cause mortality) with adjustment for aforementioned factors, which previously demonstrated to be prognostically significant. Similarly, HRs for relative NT-proBNP changes in categories were calculated in each of the two populations, with adjustment from the same variables. The proportionality of hazard function after transforming NT-proBNP levels was tested by generating time dependent covariates by creating interactions of the predictors and a function of survival time and including them in the model and further by testing for a non-zero slope in a generalised linear regression of the scaled Schoenfeld residuals on functions of time. Both tests supported the proportional hazards assumption.

As a measure of attainability for a number of preset NT-proBNP levels at discharge and NT-proBNP reduction percentages, the percentage of patients attaining these levels was determined for patients with HFrEF and HFrEF. Finally, the presence of comorbidities of established prognostic relevance was compared between patients with HFrEF and patients with HFrEF in a low (<3000 pg/mL) and high (>3000 pg/mL) category of discharge NT-proBNP levels. The Fisher’s exact test was used to make a comparison. Normally distributed were compared using the Student’s t-test. Other continuous data were compared using the Mann-Whitney U test.

To accommodate for the different cohorts, separate baseline hazard functions were used to adjust for between-study differences. For the multivariable model, we performed multiple imputation pooling algorithms (n=10) to correct for missing values. The imputation method was fully conditional specification with a linear regression for the model for scale variables. Eventually producing output for each ‘complete’ dataset, plus pooled output. We used these pooled results, which are pooled by Rubin’s rules, by taking the average over the parameter estimates from all imputed datasets. All patient, medical history and treatment variables (including outcome variables) were used when creating the multiple imputation data sets.

All probability values were two sided and considered significant if <0.05. Statistical analyses were conducted using SPSS V24.0.0.0.
RESULTS
Demographic characteristics
Patients with HFrEF were significantly older compared with those with HFrEF and HFrEF with significantly more patients aged ≥75 years (table 1). HFrEF was more frequently associated with female sex, hypertension, ischaemic aetiology, higher admission SBP and atrial fibrillation (AF) at admission. Compared with HFrEF and HFrEF, HFpEF patients had significantly lower admission haemoglobin levels and lower admission and discharge NT-proBNP levels. The median NT-proBNP reduction percentage during hospitalisation was equal for HFpEF, HFrEF and HFmrEF. At discharge, significantly less HFpEF patients received ACE-inhibitors or angiotensin II receptor blockers (ARBs) compared with patients with HFrEF and HFmrEF, but diuretics and beta-blockers were prescribed with similar frequency. There was no difference in 6-month all-cause mortality (figure 1A) between patients with HFrEF, HFrEF or HFrEF (14% (n=38) vs 14% (n=23) vs 16% (n=121), respectively, log-rank=0.60). The same pattern was seen for the composite endpoint of 6-month cardiovascular readmission/all-cause mortality (42% vs 40% vs 45%, respectively, log-rank=0.45). The median NT-proBNP percentage reduction stratified for the four NT-proBNP categories at admission for patients with HFrEF and HFrEF showed the higher the admission NT-proBNP, the higher the median percentage reduction (online supplementary materials). Supplementary figures

NT-proBNP and outcome
The lower the admission or discharge NT-proBNP levels, the lower the 6-month all-cause mortality rate (figure 2). For the three NT-proBNP percentage reduction categories, 6-month all-cause mortality decreased with higher percentage NT-proBNP reductions for all three heart failure groups.

Cox regression models
The natural logarithmic scale for NT-proBNP levels at discharge showed that for every 2.7 increase in NT-proBNP level at discharge, the multivariably adjusted HR for 6-month mortality was 2.14 (95% CI 1.48 to 3.09) in patients with HFrEF and 1.96 (95% CI 1.60 to 2.40) in patients with HFrEF. For the composite endpoint of 6-month cardiovascular readmission/all-cause mortality, the HR was 1.27 (95% CI 1.06 to 1.52) in patients with HFrEF and 1.39 (95% CI 1.25 to 1.56) in patients with HFrEF. A log2 transformation scale for NT-proBNP levels at discharge showed an adjusted HR for 6-month mortality of 1.71 (95% CI 1.33 to 2.20) for HFrEF, and 1.60 (95% CI 1.35 to 2.19) for HFrEF for every twofold increase in NT-proBNP levels at discharge and an HR of 1.18 (95% CI 1.04 to 1.34) for HFrEF and 1.26 (95% CI 1.17 to 1.36) for the composite endpoint of 6-month cardiovascular readmission/all-cause mortality.

After adjustment for relevant clinical variables (table 2A), similar significant HRs were found for HFrEF as well as HFrEF.
Heart failure and cardiomyopathies

Figure 1  Relationship between 6-month all-cause mortality and the three types of heart failure adjusted for age ≥75 years, peripheral edema at admission, systolic blood pressure (SBP) <115 mm Hg, hyponatraemia (sodium levels <135 mmol/L) and serum urea levels ≥15 mmol/L. HFmrEF, heart failure with mid range ejection fraction; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Figure 2  Relationship between 6-month all-cause mortality and the four categories of admission and discharge NT-proBNP levels as well as for the categories of percentage reduction during hospitalisation according to the types of HF. HF, heart failure; HFmrEF, heart failure with midrange ejection fraction; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction NT-proBNP, N-terminal pro-B-type natriuretic peptide.

for the highest quartile of absolute NT-proBNP values at discharge (HR 5.68, 95% CI 2.24 to 14.36 and HR 4.79, 95% CI 2.76 to 8.33, respectively). Table 2B shows that for HFrEF and HFrEF, both reduction percentage levels of 30%–60% (HR 3.28, 95% CI 1.07 to 10.12 and HR 1.79, CI 0.99 to 3.26, respectively) as well as ≤30% (HR 4.60, 95% CI 1.47 to 14.40 and HR 3.36, 95% CI 1.93 to 5.83, respectively) are predictors of mortality compared with a reference of >60%. The same pattern was seen for both the discharge NT-proBNP levels as well as percentage reduction levels and the composite endpoint of 6-month cardiovascular readmission/all-cause mortality, although with lower HRs.

Attainability of NT-proBNP levels

For the lowest absolute NT-proBNP target of <1000 pg/mL, 23% of patients with HFpEF attained the target (table 3) versus 14% of patients with HFrEF (p=0.002). Also, for the absolute level of <3000 pg/mL, patients with HFpEF more often attained this target compared with patients with HFrEF (65% vs 43%, respectively, p<0.001). No differences for attaining relative reduction levels were found between HFrEF and HFrEF. No significant differences were found between HFpEF and HFrEF in attainability of absolute or relative levels when stratified for admission NT-proBNP categories (online supplementary materials).

NT-proBNP and comorbidities

Table 4 shows that comorbidities and prognostic factors are evenly distributed among the higher NT-proBNP discharge category in patients with HFpEF and HFrEF (61% and 60% of patients, respectively) but are unevenly distributed within the lower discharge NT-proBNP category in patients with HFpEF compared with in patients with HFrEF (37% of patients versus 24% of patients, respectively, p=0.011). There were no differences in survival between patients with HFpEF and HFrEF as compared in a low (≤3000 pg/mL) or in a high (>3000 pg/mL) NT-proBNP discharge category in KM analysis (online supplementary materials).

DISCUSSION

It was previously reported that a doubling of natriuretic peptides at discharge carries a HR of 1.4 for (18 months) mortality, similarly for patients with HFpEF as for patients with HFrEF.7 In our study, for every twofold increase in discharge NT-proBNP, the multivariably adjusted HR for 6-month mortality was 1.71 in patients with HFpEF and 1.60 in patients with HFrEF, which
also did not differ significantly from each other between HFP EF and HFr EF. Also, for categories, both for HFP EF as well as HFr EF, only the two highest quartiles of absolute NT-proBNP levels at discharge were predictive for mortality after adjustment for covariates, with similar HRs for patients with HFP EF as for patients with HFr EF. Our study also shows similar adjusted prognostic relative risks in patients with HFP EF and HFr EF for the relative changes in NT-proBNP levels during hospitalisation. In this respect, we confirm previous studies that have reported on equal prognostic significance of either admission6 levels or discharge levels of natriuretic peptides in patients with HFP EF and HFr EF hospitalised for ADHF.7 10

For the prognostic ability of relative changes in NT-proBNP during admissions for heart failure, we also confirm results of a small study demonstrating that changes of <30% in NT-proBNP levels during admissions are as predictive of outcome in patients with HFP EF as in a mixed population of patients with HFP EF and HFr EF.11 12 18 It is also in line with another report in a mixed population of patients with HFP EF and HFr EF with ADHF that described that a <50% reduction in NT-proBNP at discharge was a predictor for 6-month mortality without any significant effect from adjustment by ejection fraction.25 In our analysis of three categories of percentage change in NT-proBNP levels, the adjusted multivariable analysis demonstrated a significant and similar contribution to prognosis in patients with HFP EF and HFr EF for a 30%–60% reduction in NT-proBNP as well as for a ≤30% reduction in NT-proBNP. The results endorse our risk stratification model of a mixed population of patients with ADHF, in which both absolute levels at discharge and NT-proBNP reduction percentage are independent predictors of postdischarge mortality,16 and also that both measures may be useful as discharge thresholds in patients hospitalised for ADHF.23

### Table 2A Cox regression for absolute NT-proBNP levels at discharge and 6-month all-cause mortality

<table>
<thead>
<tr>
<th>NT-proBNP levels at discharge, pg/mL</th>
<th>HFP EF (EF ≥50%)</th>
<th>HFr EF (EF &lt;40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable model</td>
<td>Multivariable model*</td>
</tr>
<tr>
<td>NT-proBNP ≥1000</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NT-proBNP 1001–3000</td>
<td>6.59 (0.87 to 49.83)</td>
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<tr>
<td>NT-proBNP 3001–9000</td>
<td>7.73 (0.97 to 61.33)</td>
<td>1.38 (0.58 to 3.27)</td>
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<tr>
<td>NT-proBNP &gt;9000</td>
<td>29.50 (3.74 to 232.87)</td>
<td>5.68 (2.24 to 14.36)</td>
</tr>
</tbody>
</table>

### Cox regression for absolute NT-proBNP levels at discharge and the composite endpoint of 6-month cardiovascular readmission/all-cause mortality

<table>
<thead>
<tr>
<th>NT-proBNP levels at discharge, pg/mL</th>
<th>HFP EF (EF ≥50%)</th>
<th>HFr EF (EF &lt;40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable model</td>
<td>Multivariable model*</td>
</tr>
<tr>
<td>NT-proBNP ≥1000</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NT-proBNP 1001–3000</td>
<td>1.62 (0.93 to 2.85)</td>
<td>1</td>
</tr>
<tr>
<td>NT-proBNP 3001–9000</td>
<td>2.04 (1.13 to 3.69)</td>
<td>1.29 (0.82 to 2.02)</td>
</tr>
<tr>
<td>NT-proBNP &gt;9000</td>
<td>3.13 (1.58 to 6.17)</td>
<td>1.81 (0.98 to 3.33)</td>
</tr>
</tbody>
</table>

*Adjusted for age ≥75 years, peripheral oedema, systolic blood pressure ≤115 mm Hg, hyponatraemia (sodium level <135 mmol/L), serum urea ≥15 mmol/L. EF, ejection fraction; HFP EF, heart failure with preserved ejection fraction; HFr EF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

### Table 2B Cox regression for NT-proBNP percentage reduction during hospitalisation and 6-month all-cause mortality

<table>
<thead>
<tr>
<th>NT-proBNP percentage reduction during hospitalisation</th>
<th>HFP EF (EF ≥50%)</th>
<th>HFr EF (EF &lt;40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable model</td>
<td>Multivariable model*</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30%–60%</td>
<td>3.35 (1.11 to 10.11)</td>
<td>3.28 (1.07 to 10.12)</td>
</tr>
<tr>
<td>≤30%</td>
<td>5.01 (1.62 to 15.55)</td>
<td>4.60 (1.47 to 14.40)</td>
</tr>
</tbody>
</table>

### Cox regression for NT-proBNP percentage reduction during hospitalisation and the composite endpoint of 6-month cardiovascular readmission/all-cause mortality

<table>
<thead>
<tr>
<th>NT-proBNP percentage reduction during hospitalisation</th>
<th>HFP EF (EF ≥50%)</th>
<th>HFr EF (EF &lt;40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable model</td>
<td>Multivariable model*</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30%–60%</td>
<td>1.51 (0.91 to 2.49)</td>
<td>1.41 (0.83 to 2.38)</td>
</tr>
<tr>
<td>≤30%</td>
<td>1.63 (1.03 to 2.60)</td>
<td>1.69 (1.06 to 2.71)</td>
</tr>
</tbody>
</table>

*Adjusted for age ≥75 years, peripheral oedema, systolic blood pressure ≤115 mm Hg, hyponatraemia (sodium level <135 mmol/L), serum urea ≥15 mmol/L. EF, ejection fraction; HFP EF, heart failure with preserved ejection fraction; HFr EF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
levels are almost half in patients with HFpEF, the HR of 1.6–1.7 that we found for doubling NT-proBNP levels would lead to an expected reduced mortality in HFpEF with almost a factor 0.60, that is, from our reported 16% mortality in HFpEF patients to an expected 10% in patients with HFpEF. This was obviously not the case in our study, with 16% vs 14% mortality in patients with HFpEF versus patients with HFpEF after 6 months. Still, in outpatient populations and in mixed populations of outpatients and patients discharged from hospital, HFpEF patients have lower mortality rates than patients with HFpEF, which would be more in accordance with the lower NT-proBNP levels in patients with HFpEF (MAGGIC and Lam et al).

One of the possible answers to this paradox is that although natriuretic peptides levels are equal indicators of relative risk in patients with HFpEF and HFrEF, it is only a matter of chance finding that the outcomes of patients with HFpEF and HFrEF are alike, because other predictors of death (and possibly mode of death) and also other drivers of high NT-proBNP may be present in uneven distribution in patients with HFpEF and HFrEF, who also differ in many other baseline characteristics.

It was previously suggested that to understand prognosis in patients with HFpEF, absolute NT-proBNP levels in the lower, most frequent, categories are less contributing to prognosis in HFpEF than other prognostic variables such as kidney function or age. Also in our study, compared with patients with HFpEF, patients with HFpEF have significantly more comorbidities with significantly older patients, more frequently with hypertension, more AF at admission and lower mean levels of haemoglobin at admission, all of which were previously reported to be of prognostic significance in HFpEF but also in patients with HFrEF. Our report extends these findings, in that the presence of comorbidities probably precedes rising NT-proBNP levels more in patients with HFpEF than in patients with HFrEF, so that HFpEF patients already seem to have more comorbidities at lower NT-proBNP levels than patients with HFrEF. With higher NT-proBNP levels, the comorbidities and prognostic factors increase but are then as frequently present in HFpEF as in patients with HFrEF. To further investigate the problem of risk prediction with natriuretic peptides in the face of comorbidities, outcome differentiation and/or increasing the number of contributing comorbidities in the prognostic models both seem worthwhile.

### Attainability of NT-proBNP levels in HFpEF and HFrEF

That patients with HFpEF more often have lower NT-proBNP and BNP levels than patients with HFrEF, at similar levels of end-diastolic left ventricular pressure, is explained by the correlation of natriuretic peptide levels with diastolic wall stress, which is lower for smaller left ventricular volumes and thicker left ventricular walls, which are both hallmarks for patients with HFrEF. The similar improvements in percentage reductions in NT-proBNP in HFpEF and HFrEF may be somewhat unexpected, since there are less prognostically beneficial therapies for HFpEF than for HFrEF. At discharge, there were no significant differences in the prescription of beta-blockers or diuretics between HFpEF and HFrEF patients, while ACE inhibitors/ARBs were less often prescribed in HFpEF. We know that ARBs do not affect NT-proBNP levels in patients with HFpEF, and another explanation must be found why NT-proBNP reductions were as large in patients with HFpEF as in patients with HFrEF. The significantly higher SBP is notable among patient with HFpEF, which may have given the clinicians more opportunity to increase the dosage of diuretics during hospitalisation in HFpEF patients.

A strategy that uses absolute NT-proBNP values as risk thresholds and uses relative reductions in NT-proBNP as targets may benefit from the finding that both patient groups will be able to reach realistic but still prognostically important reductions in NT-proBNP. As for outcome, cardiovascular outcomes may be predicted by natriuretic peptides in HFpEF and HFrEF, but this study and other studies demonstrate that for patients with HFpEF with low NT-proBNP levels outcome improvements

### Table 3: Attainability of absolute and relative NT-proBNP targets for types of heart failure

<table>
<thead>
<tr>
<th>Types of heart failure</th>
<th>HFpEF (EF ≥50%)</th>
<th>HFrEF (40%–49%)</th>
<th>HFrEF (EF &lt;40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute NT-proBNP targets at discharge, pg/mL</td>
<td>&lt;1000, n (%)</td>
<td>62 (23)</td>
<td>25 (16)</td>
</tr>
<tr>
<td></td>
<td>&lt;3000, n (%)</td>
<td>175 (65)</td>
<td>84 (52)</td>
</tr>
<tr>
<td>NT-proBNP reduction during hospitalisation, %</td>
<td>&gt;30, n (%)</td>
<td>187 (70)</td>
<td>97 (62)</td>
</tr>
<tr>
<td></td>
<td>&gt;60, n (%)</td>
<td>86 (32)</td>
<td>55 (35)</td>
</tr>
</tbody>
</table>

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

### Table 4: Distribution of risk factors according to NT-proBNP levels at discharge and heart failure groups

<table>
<thead>
<tr>
<th>Age ≥75years, n (%)</th>
<th>HFrEF</th>
<th>HFpEF</th>
<th>P value</th>
<th>HFrEF</th>
<th>HFpEF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic aetiology, n (%)</td>
<td>97 (63)</td>
<td>147 (51)</td>
<td>0.027</td>
<td>43 (54)</td>
<td>174 (44)</td>
<td>0.108</td>
</tr>
<tr>
<td>Peripheral oedema at admission, n (%)</td>
<td>100 (63)</td>
<td>162 (54)</td>
<td>0.060</td>
<td>66 (73)</td>
<td>255 (65)</td>
<td>0.218</td>
</tr>
<tr>
<td>SBP ≤115 mm Hg at admission, n (%)</td>
<td>27 (16)</td>
<td>84 (26)</td>
<td>0.007</td>
<td>24 (26)</td>
<td>188 (45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation at admission, n (%)</td>
<td>85 (51)</td>
<td>110 (37)</td>
<td>0.005</td>
<td>50 (57)</td>
<td>162 (42)</td>
<td>0.017</td>
</tr>
<tr>
<td>Anaemia at admission, n (%)</td>
<td>77 (46)</td>
<td>129 (41)</td>
<td>0.290</td>
<td>59 (63)</td>
<td>241 (60)</td>
<td>0.640</td>
</tr>
<tr>
<td>Hypotension (&lt;90 mmHg) at admission, n (%)</td>
<td>19 (14)</td>
<td>34 (11)</td>
<td>0.435</td>
<td>18 (21)</td>
<td>94 (23)</td>
<td>0.778</td>
</tr>
<tr>
<td>Serum urea &gt;5.5 mmol/L at admission, n (%)</td>
<td>14 (11)</td>
<td>31 (11)</td>
<td>1.000</td>
<td>32 (41)</td>
<td>145 (39)</td>
<td>0.899</td>
</tr>
</tbody>
</table>

HFrEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.
should probably also be sought in therapies targeting non-cardiovascular outcomes. Alternatively, when natriuretic peptides levels are to be used as surrogate endpoints, these endpoints should be better defined as cardiovascular endpoints.

LIMITATIONS
Variation in NT-proBNP assays used should be considered. Nevertheless, this range in markers reflects the day-to-day clinical practice. The relatively small sample size of patients with HFpEF in the cohort compared with that of HFrEF patients should be considered, with possible impact on the statistical significance of the used NT-proBNP categories. We did correct for the bias from data missing at random by using multiple imputation pooling algorithms. The endpoint of all-cause mortality is limiting, as cardiac markers should be best used for cardiac outcomes. It is clear that CV mortality explains 63%–87% of mortality after cardiac markers should be best used for cardiac outcomes. It is considered, with possible impact on the statistical significance of the cohort compared with that of HFrEF patients should be considered. Nevertheless, this range in markers reflects the day-to-day clinical practice. Variation in NT-proBNP assays used should be considered.

CONCLUSIONS
Our study suggests that there is no difference between patients with HFpEF and HFrEF in relative risk prediction of 6-month mortality by absolute discharge NT-proBNP levels or by percentage NT-proBNP changes. To explain the similar long-term mortality in HFpEF as in HFrEF, despite lower NT-proBNP discharge levels in HFrEF, we raise the possibility that the larger burden of prognostic relevant comorbidities in patients with HFpEF with low NT-proBNP levels unfavourably affects their prognosis.

Correction notice This article has been corrected since it first published online. The open access licence type has been amended.

Contributors KS, WEK and YMP had the idea for the project, designed the collaborative analysis and undertook searches of published work. KS and SS collected the individual patient data and prepared for analysis. Statistical analysis and elaboration of figures was done by KS, WEK and JGPT. KS wrote the paper with important contribution from WEK, SS and YMP and input from MM, LWE, AB-G, JGPT, MM and VV provided valuable comments on the report. All principal investigators shared individual patient data and had an opportunity to contribute to the interpretation of results and to the drafting of the report. All authors reviewed and revised the manuscript and approved the final version.

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Competing interests YMP is a recipient of payments for lectures including service on speakers’ bureaus and research grants from Roche Diagnostics. YMP has an unrelated biomarker patent and stocks in a university spinoff company. WEK received a grant (2010B97) from the Dutch Heart Foundation for the PRIMA II study and has participated in advisory board meetings of Roche Diagnostics and Novartis. MM is a member of the board in Corthera and Novartis and receives payment for lectures including service on speakers’ bureaus from Servier and Stroder.

Patient consent for publication Not required.

Ethics approval All studies were approved by the ethical committees in their respective centres.

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