Background—In heart failure with mid-range ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF), feasible surrogate end points are needed for phase II trials. The aim was to assess whether a reduction in N-terminal pro–B-type natriuretic peptide (NT-proBNP) is associated with improved mortality/morbidity in an unselected population of HFmrEF and HFpEF patients.

Methods and Results—In the Swedish Heart Failure Registry, HFmrEF (EF=40%–49%) and HFpEF (EF≥50%) patients reporting at least 2 consecutive outpatient NT-proBNP assessments were prospectively studied. Associations between reduction in NT-proBNP and overall mortality, HF hospitalization, and their composite were assessed by multivariable Cox regressions, with NT-proBNP changes modeled as binary (decrease/increase) or quantitative predictor by restricted cubic splines. In 650 patients, at a median of 7 months between the 2 measurements of NT-proBNP and over a median follow-up of 1.65 years, 361 patients (55%) showed a reduction and 289 patients (45%) an increase in NT-proBNP. Change in NT-proBNP was associated with risk of outcomes. Fifty-seven patients (16%) who decreased their NT-proBNP versus 78 patients (27%) who increased it died from any cause (adjusted hazard ratio=0.53; 95% confidence interval=0.36–0.77), 61 (17%) versus 86 (30%) were hospitalized for HF (hazard ratio=0.41; 95% confidence interval=0.29–0.60), and 96 (27%) versus 125 (43%) reported the composite outcome (hazard ratio=0.46; 95% confidence interval=0.34–0.62). These findings were replicated in HFmrEF and HFpEF separately.

Conclusions—In HFmrEF and HFpEF during routine care, decreases in NT-proBNP were associated with improved mortality and morbidity. Studies to determine whether NT-proBNP changes in response to therapy predict drug efficacy are needed. (Circ Heart Fail. 2016;9:e003105. DOI: 10.1161/CIRCHEARTFAILURE.116.003105.)

Key Words: heart failure with mid-range ejection fraction  □  heart failure with preserved ejection fraction  □  N-terminal pro–B-type natriuretic peptide  □  prognosis  □  registry

Heart failure (HF) is estimated to affect ≈2% of the worldwide population, with an incidence approaching 10 per 1000 persons per year. These numbers are expected to increase with population growth projections, especially of the elderly.1 Half of patients have preserved (HFpEF) or mildly reduced (mid-range: HFmrEF) ejection fraction (EF). Overall prognosis is as poor as in reduced EF (HFrEF),2 whereas HFpEF patients show higher hospitalization rates and die more often of noncardiovascular causes.2

In HFrEF, several trials have demonstrated the efficacy of angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), β-blockers, and mineralocorticoid receptor antagonists. In contrast, HFpEF phase III trials, including in several cases also HFmrEF patients, have not been positive, and phase II trials have been difficult to design partly because there are no established and feasible surrogate end points.3–6

See Clinical Perspective

Evidence supports the use of N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels for the diagnosis of HFrEF, and NT-proBNP levels are associated with ventricular filling pressures, a key pathophysiological component in HFrEF, HFmrEF, and HFpEF. Similarly, several studies have shown an association between high levels of natriuretic peptides and increased mortality and hospitalization rates, confirming NT-proBNP as an important prognostic tool regardless of EF.7,8
NT-proBNP is also being used for eligibility in trials enrolling HFP EF and HFmr EF patients, both to ensure the presence of HF and to enrich the population for HF-related outcomes. However, there are currently no feasible surrogate end points for early-phase HFmr EF and HFP EF trials. Although it would be intuitive, it is unknown whether changes in NT-proBNP correlate with outcomes and, thus, whether changes in NT-proBNP is a potential surrogate end point for phase II HFmr EF and HFP EF trials.

Therefore, the aim of the present study was to investigate whether changes in NT-proBNP levels are associated with the risk of death and HF hospitalization in a large cohort of unselected patients with HFmr EF and HFP EF.

Methods

Study Protocol and Setting

The Swedish Heart Failure Registry (SwedeHF: www.SwedeHF.se) has been previously described. Briefly, it was created in 2000 and spread throughout Sweden in 2003. Inclusion criteria are clinician-judged HF. Approximately 80 variables are recorded at discharge from hospital or after outpatient clinic visit on a web-based case report form and entered into a database managed by the Uppsala Clinical Research Center, Uppsala, Sweden (www.UCR.UU.se). Coverage of all hospital-based Swedish HF patient encounters in 2014 was 53%. This was defined as the number of individuals reported to the Registry divided by the sum of individuals with clinical hospital-based HF encountered in Sweden according to International Statistical Classification of Diseases, Tenth Revision, code for HF plus those reported to the registry. The protocol, case report form, and annual reports are available at www.SwedeHF.se.

The Swedish Board of Health and Welfare (www.socialstyrelsen.se) administers the Population Registry and the Patient Registry. The Population Registry provided date of death. From the Patient Registry, we obtained additional baseline comorbidities and the HF hospitalization outcome, defined according to International Statistical Classification of Diseases, Tenth Revision, codes. International Statistical Classification of Diseases, Tenth Revision, coding in Sweden has been validated. The positive predictive value for most diagnoses is between 85% and 95%; a HF diagnosis was verified in between 86% and 91% of cases. Statistics Sweden (www.scb.se) maintains socioeconomic data on all Swedish citizens and provides additional baseline data. All Swedish citizens have unique personal identification numbers that enable linking of disease-specific health registries and governmental health and statistical registries.

Establishment of the HF registry and this analysis with linking of the above registries were approved by a multisite ethics committee. Individual patient consent was not required, but patients were informed of entry into national registries and allowed to opt out.

The Registry includes patients without any limitation regarding EF. EF is categorized as <50%, 50% to 39%, 40% to 49%, and 50% to 50%. In the current study, outpatients with EF ≥40% with at least 2 consecutive NT-proBNP levels assessment were selected. EF 40% to 49% is not considered normal or preserved, but there is currently no evidence-based therapy in this group, and future trials should address this mid-EF range and strictly preserved EF (EF ≥50%). Nevertheless, we performed separate analyses in HFmr EF (EF 40% to 49%) and HFP EF (EF ≥50%) groups. When a patient reported more than one NT-proBNP measurement at the follow-up, the value considered was the one obtained at the closest visit to 6 months of follow-up from the first registration. Because shorter term follow-up is most relevant for phase II trials, we also performed a subgroup analysis in patients with the second NT-proBNP value at ≤6 months. The index date was defined as the outpatient clinic visit for HF, occurring between 2000 and December 30, 2012, at which the second NT-proBNP measurement was performed. The outcomes HF hospitalization and all-cause mortality were defined as between the index date and end of follow-up, December 31, 2012, for which an HF diagnosis was required as the primary diagnosis for hospitalization. A composite outcome of HF hospitalization and mortality was also considered.

Statistical Analysis

Change in NT-proBNP levels was expressed as the percent variation between the 2 peptide measurements (%ΔNT-proBNP=[final NT-proBNP−baseline NT-proBNP]/baseline NT-proBNP×100).

Baseline Characteristics

Baseline characteristics at the time of the first NT-proBNP measurement of patients, who subsequently showed an increase versus those who reported a reduction in NT-proBNP levels, were compared by t test or χ2 test to test continuous and categorical variables, respectively. Missing baseline characteristics were reported as percent missing in the baseline characteristics (Table 1) and managed by multiple imputation (n=10) in multivariable models.

Association Between Changes in NT-proBNP and Outcomes

We modeled changes in NT-proBNP as a quantitative predictor of event rates either assuming a linear or curvilinear dose–response relationship. In particular, we used restricted cubic splines to flexibly model potential nonlinearity.

The relationship between changes in NT-proBNP and outcomes was also assessed using NT-proBNP changes as a dichotomous variable (increase versus decrease in NT-proBNP levels, as categorized in Table 1). For the 2 groups (increase versus decrease in NT-proBNP) and for each of the outcome, the raw number of events was reported. To estimate the size of the association between NT-proBNP decreases (versus increases) on end points, proportional hazard ratios (HR) with 95% confidence intervals (CI) were calculated with Kaplan–Meier analyses and then adjusted with Cox proportional hazard models.

We also performed Cox regressions with NT-proBNP categories obtained by dividing the cohort of patients into 4 groups based on the median values of NT-proBNP levels at the baseline and at the follow-up visit: low levels at the baseline and low at the follow-up evaluation (stable low levels of NT-proBNP), low at the baseline and high at the follow-up evaluation (increase in NT-proBNP levels), high at the baseline and low at the follow-up evaluation (decrease in NT-proBNP levels), and high at the baseline and high at the follow-up evaluation (stable high levels of NT-proBNP; reference group). All the Cox regression models reported in the current analyses were adjusted for the variables that correlated with at least one outcome at the univariate analysis with a P value ≤0.05.

Associations Between Baseline Variables and Subsequent Decrease in NT-proBNP

Multivariable logistic regression, using decreases in NT-proBNP as dependent variable and all the variables correlating with decreases in NT-proBNP at the univariate analysis as covariates, with a P value ≤0.05, was run to detect the predictors of decrease in NT-proBNP levels.

Results

Patients

Between May 11, 2000, and December 30, 2012, 55,821 registrations were recorded from 34,188 unique patients. Of these, 650 were outpatients with HFmr EF (40% to 49%; n=363) and HFP EF (left ventricular EF ≥50%; n=287) and reported at least 2 outpatient NT-proBNP measurements.

Baseline Characteristics

Baseline characteristics are reported in Table 1. In Table I in the Data Supplement, the cohort of HFP EF/HFmr EF outpatients with 2 NT-proBNP measurements considered in the current study has been compared with the overall HFP EF/HFmr EF outpatient cohort of the SwedeHF for baseline characteristics. Mean age was 73±12 years, 40% were women, the median
### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>NT-proBNP Decreased 361 Patients (55%)</th>
<th>NT-proBNP Increased 289 Patients (45%)</th>
<th>P</th>
<th>Missing Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>213 (59)</td>
<td>175 (61)</td>
<td>0.748</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>148 (41)</td>
<td>114 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y*</td>
<td>72 (12)</td>
<td>74 (10)</td>
<td>0.052</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient physician</td>
<td>66 (18)</td>
<td>66 (23)</td>
<td>0.170</td>
<td></td>
</tr>
<tr>
<td>Outpatient nurse-based HF clinic</td>
<td>295 (82)</td>
<td>223 (77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Speciality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td>114 (39)</td>
<td>98 (43)</td>
<td>0.370</td>
<td></td>
</tr>
<tr>
<td>Internal medicine or geriatrics</td>
<td>178 (61)</td>
<td>130 (57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up referral speciality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care or other care</td>
<td>84 (24)</td>
<td>86 (31)</td>
<td>0.058</td>
<td></td>
</tr>
<tr>
<td>Cardiology or internal medicine</td>
<td>269 (76)</td>
<td>195 (69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up referral to outpatient HF nurse clinic</td>
<td>256 (72)</td>
<td>186 (66)</td>
<td>0.118</td>
<td>16 (2%)</td>
</tr>
<tr>
<td>Follow-up median (IQR), y</td>
<td>1.81 (0.74–2.93)</td>
<td>1.38 (0.65–2.56)</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of HF, mo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>190 (53)</td>
<td>119 (41)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>≥6</td>
<td>170 (47)</td>
<td>169 (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NYHA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>47 (14)</td>
<td>31 (12)</td>
<td>0.255</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>169 (51)</td>
<td>116 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>117 (35)</td>
<td>109 (42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>1 (0)</td>
<td>2 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EF, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>137 (38)</td>
<td>133 (46)</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>224 (62)</td>
<td>156 (54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood pressure, mean (SD), mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>131 (21)</td>
<td>130 (20)</td>
<td>0.271</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74 (11)</td>
<td>74 (11)</td>
<td>0.370</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mean (SD), mmHg*</td>
<td>93 (13)</td>
<td>93 (12)</td>
<td>0.984</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Heart rate, mean (SD), beats per min</td>
<td>71 (15)</td>
<td>72 (14)</td>
<td>0.312</td>
<td>10 (1)</td>
</tr>
<tr>
<td><strong>Laboratory values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance, mean (SD), mL/min†</td>
<td>71 (31)</td>
<td>69 (32)</td>
<td>0.303</td>
<td>61 (9%)</td>
</tr>
<tr>
<td>Hemoglobin, mean (SD), g/L*</td>
<td>135 (16)</td>
<td>134 (16)</td>
<td>0.738</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NT-proBNP, median (IQR), pg/mL*</td>
<td>1837 (964–4069)</td>
<td>1372 (630–2627)</td>
<td>&lt;0.001</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Concomitant medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor*</td>
<td>228 (63)</td>
<td>179 (62)</td>
<td>0.807</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Angiotensin II receptor blocker*</td>
<td>122 (34)</td>
<td>78 (27)</td>
<td>0.072</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>112 (31)</td>
<td>73 (25)</td>
<td>0.096</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

(Continued)
time between first and second NT-proBNP measurement was 7 months (interquartile range: 4–13 months; Figure I in the Data Supplement), and the median follow-up was 1.65 years (interquartile range 0.70–2.82 years). Patients who showed a decrease compared with those who reported an increase in NT-proBNP levels had a shorter duration of HF, higher levels of baseline NT-proBNP, more history of myocardial infarction, and less atrial fibrillation. Additionally, trends toward younger age and more frequent specialist care were observed in patients who had decrease in NT-proBNP. HFmrEF versus HFpEF was more common in those with a decrease in NT-proBNP (62% versus 38%) than in those with an increase (54% versus 46%).

### Changes in NT-proBNP and Outcomes

We found strong evidence of nonlinearity ($P<0.001$) between NT-proBNP changes and event rates (Figure 1). The rate of change in risk of clinical outcomes depended on the actual values of change in NT-proBNP. A strong inverse association for those with a decrease in NT-proBNP and positive association for those with an increase NT-proBNP were reported (Table 2; Figure 1).

Of 650 patients (1052.23 patient-years), 361 (55%; 653.41 patient-years) showed a decrease in NT-proBNP levels versus 289 (45%) who reported an increase (Figure 3). After adjustments, the HR for all-cause death was 0.53 (95% CI, 0.36–0.77) for patients reporting a decrease versus those showing an increase in NT-proBNP (Table 3). Sixty-one HF hospitalizations (17%; 93 per 1000 patient-years) were reported in patients who decreased NT-proBNP levels versus 86 (30%; 216 per 1000 patient-years) in those who showed an increase in peptides levels (Figure 3). After adjustment, the HR for HF hospitalization was 0.41 (95% CI, 0.29–0.60) for patients reporting a decrease versus those showing an increase in NT-proBNP levels at the follow-up (Table 3).

When the analysis was limited to those patients with time between NT-proBNP evaluations $\leq 6$ months ($n=269$), the HR for all-cause death was 0.53 (95% CI, 0.36–0.77) for patients reporting a decrease versus those showing an increase in NT-proBNP (Table 3). Sixty-one HF hospitalizations (17%; 93 per 1000 patient-years) were reported in patients who decreased NT-proBNP levels versus 86 (30%; 216 per 1000 patient-years) in those who showed an increase in peptides levels (Figure 3). After adjustment, the HR for HF hospitalization was 0.41 (95% CI, 0.29–0.60) for patients reporting a decrease versus those showing an increase in NT-proBNP levels at the follow-up (Table 3). The composite outcome occurred in 96 patients (27%; 147 per 1000 patient-years) reporting a decrease versus those showing an increase in NT-proBNP levels at the follow-up (Table 3). The composite outcome occurred in 96 patients (27%; 147 per 1000 patient-years) reporting a decrease in NT-proBNP levels versus 125 (43%; 313 per 1000 patient-years) of those showing an increase in peptides levels (Figure 3). After adjustments, the HR for the composite outcome was 0.46 (95% CI, 0.34–0.62) for patients who showed a decreased NT-proBNP levels versus those who reported an increase in peptides levels at the follow-up (Table 3).

### EF Subgroups

Results were confirmed in subgroups by HFpEF and HFmrEF. In fact, in the subgroup of HFpEF patients, decreases in

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**Table 1.** Continued

<table>
<thead>
<tr>
<th>Variables</th>
<th>NT-proBNP Decreased 361 Patients (55%)</th>
<th>NT-proBNP Increased 289 Patients (45%)</th>
<th>$P$</th>
<th>Missing Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>48 (13)</td>
<td>44 (15)</td>
<td>0.499</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diuretic*</td>
<td>274 (76)</td>
<td>225 (78)</td>
<td>0.574</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Nitrate*</td>
<td>46 (13)</td>
<td>39 (13)</td>
<td>0.815</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Platelet inhibitor</td>
<td>158 (44)</td>
<td>114 (39)</td>
<td>0.263</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>159 (44)</td>
<td>145 (50)</td>
<td>0.133</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Statin</td>
<td>183 (51)</td>
<td>137 (47)</td>
<td>0.430</td>
<td>0 (0)</td>
</tr>
<tr>
<td>β-Blocker*</td>
<td>311 (86)</td>
<td>239 (83)</td>
<td>0.227</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

**History and comorbidity**

| Hypertension                      | 229 (63)                               | 165 (57)                               | 0.107 | 0 (0)          |
| Diabetes mellitus*                | 70 (19)                                | 68 (23)                                | 0.211 | 0 (0)          |
| Myocardial infarction             | 124 (34)                               | 77 (26)                                | 0.040 | 0 (0)          |
| Peripheral artery disease         | 29 (8)                                 | 16 (6)                                 | 0.276 | 0 (0)          |
| Atrial fibrillation/flutter*      | 187 (51)                               | 178 (62)                               | 0.014 | 0 (0)          |
| Stroke or transient ischemic attack including intracranial bleed | 57 (16) | 53 (18) | 0.401 | 0 (0)          |
| Aortic stenosis*                  | 27 (8)                                 | 26 (9)                                 | 0.564 | 0 (0)          |
| Lung disease*                     | 85 (24)                                | 86 (30)                                | 0.088 | 0 (0)          |

EF indicates ejection fraction; HF, heart failure; IQR, interquartile range; NT-proBNP, N-terminal pro–B-type natriuretic peptide; and NYHA, New York Heart Association.

*Variables significantly associated with the risk of overall mortality or of HF hospitalization or of the composite outcome and were included in the Cox regression model together with percent changes in NT-proBNP levels.

†Creatinine clearance was calculated by Cockcroft–Gault formula.
NT-proBNP were significantly associated with lower mortality (HR, 0.43; 95% CI, 0.25–0.75), HF hospitalization (HR, 0.46; 95% CI, 0.26–0.83), and composite outcome (HR, 0.49; 95% CI, 0.31–0.77) rates (Table 3). Similarly, in the subgroup of HFmrEF patients, rates of overall mortality (HR, 0.53; 95% CI, 0.30–0.92), HF hospitalization (HR, 0.36; 95% CI, 0.22–0.59), and composite outcome (HR, 0.39; 95% CI, 0.26–0.59) were significantly lower in patients showing a reduction of NT-proBNP levels (Table 3).

Combinations of NT-proBNP at First and Second Occasions

Importantly, when taking both NT-proBNP values into account, patients reporting a decrease of NT-proBNP had an improved prognosis as compared with those with stable high peptide levels. Additionally, no difference in risk of all the outcomes was reported between patients reporting a reduction of NT-proBNP and those with stable low levels of peptides, and between patients showing an increase in NT-proBNP and those with stable high levels of peptides (Table II and Figure II in the Data Supplement). In multivariable analyses, as compared with patients who showed stable high NT-proBNP levels (ie, above median at time 1 and at time 2), those with stable low NT-proBNP levels reported HR of 0.47 (95% CI, 0.27–0.79) for overall mortality, HR of 0.38 (95% CI, 0.23–0.63) for HF hospitalization, and HR of 0.44 (95% CI, 0.29–0.65) for the composite outcome; those showing a reduction in NT-proBNP from high to low levels reported HR of 0.45 (95% CI, 0.22–0.94) for overall mortality, HR of 0.38 (95% CI, 0.19–0.76) for HF hospitalization, and HR of 0.39 (95% CI, 0.22–0.68) for the composite outcome; those reporting an increase of NT-proBNP from low to high levels had HR of 1.49 (95% CI, 0.87–2.57) for overall mortality, HR of 0.97 (95% CI, 0.56–1.68) for HF hospitalization, and HR of 1.11 (95% CI, 0.71–1.73) for the composite outcome (Table I and Figure II in the Data Supplement).

Predictors of NT-proBNP Decrease

Of all the variables tested, the decrease of NT-proBNP levels was independently predicted by shorter HF duration (odds ratio [OR]: 1.63; 95% CI, 1.15–2.31; P=0.006), use of ARBs (OR, 1.66; 95% CI, 1.14–2.40; P=0.007) and mineralocorticoid receptor antagonists (OR, 1.59; 95% CI, 1.10–2.31; P=0.014), absence of atrial fibrillation (OR, 0.65; 95% CI, 0.46–0.92; P=0.016), and above median NT-proBNP baseline values (OR, 2.03; 95% CI, 1.42–2.89; P<0.001). There was a strong trend toward a statistically significant association between therapy with ACE-Is or ARBs and decrease of NT-proBNP levels (OR, 1.74; 95% CI, 0.99–3.07; P=0.055).

Discussion

In HFmrEF and HFpEF patients enrolled in the SwedeHF, a large prospective registry of unselected patients with HF, larger reductions of NT-proBNP over a median of 7 months were associated with lower mortality and HF hospitalization rates. In particular, a reduction versus an increase in NT-proBNP levels was associated with a reduced risk of all-cause death by 47%, of HF hospitalization by 59% and of their composite by 54%. This observation was consistent in both patients with HFpEF (EF

Table 2.

<table>
<thead>
<tr>
<th>%ΔNT-proBNP</th>
<th>All-Cause Death</th>
<th>HF Hospitalization</th>
<th>Composite Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>−100%</td>
<td>0.48 (0.17–1.38)</td>
<td>0.34 (0.12–0.96)</td>
<td>0.38 (0.16–0.89)</td>
</tr>
<tr>
<td>−80%</td>
<td>0.50 (0.25–1.02)</td>
<td>0.40 (0.19–0.82)</td>
<td>0.45 (0.26–0.81)</td>
</tr>
<tr>
<td>−60%</td>
<td>0.53 (0.29–0.97)</td>
<td>0.48 (0.27–0.85)</td>
<td>0.55 (0.34–0.87)</td>
</tr>
<tr>
<td>−40%</td>
<td>0.62 (0.35–1.08)</td>
<td>0.60 (0.36–1.00)</td>
<td>0.66 (0.44–1.00)</td>
</tr>
<tr>
<td>−20%</td>
<td>0.79 (0.61–1.02)</td>
<td>0.78 (0.62–0.98)</td>
<td>0.81 (0.68–0.98)</td>
</tr>
<tr>
<td>0</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>20%</td>
<td>1.15 (1.03–1.28)</td>
<td>1.22 (1.10–1.36)</td>
<td>1.21 (1.11–1.32)</td>
</tr>
<tr>
<td>40%</td>
<td>1.27 (1.00–1.62)</td>
<td>1.44 (1.13–1.84)</td>
<td>1.44 (1.18–1.75)</td>
</tr>
<tr>
<td>60%</td>
<td>1.38 (0.98–1.94)</td>
<td>1.63 (1.15–2.30)</td>
<td>1.64 (1.24–2.16)</td>
</tr>
<tr>
<td>80%</td>
<td>1.46 (0.96–2.21)</td>
<td>1.78 (1.17–2.70)</td>
<td>1.79 (1.28–2.52)</td>
</tr>
<tr>
<td>100%</td>
<td>1.53 (0.96–2.46)</td>
<td>1.90 (1.18–3.05)</td>
<td>1.93 (1.31–2.83)</td>
</tr>
</tbody>
</table>

Data were fitted with restricted cubic splines Cox regression models. CI indicates confidence interval; HF, heart failure; HR, hazard ratio; and NT-proBNP, N-terminal pro–B-type natriuretic peptide.
Sa varese et al

NT-proBNP Changes in HFpEF and HFmrEF

≥50%) and in those with HFmrEF (EF 40%–49%). Furthermore, the importance of achieving a reduction of NT-proBNP over time was illustrated by those with high values at time 1 and low values at time 2, who had an improved prognosis as compared with patients with stable high NT-proBNP levels.

Need for Surrogate End Points

Currently, no specific treatment for HFmrEF and HFpEF has been established, and the management is limited to symptomatic relief with diuretics and treatment of comorbidities because ACE-Is, ARBs, digoxin, β-blockers, and mineralocorticoid receptor antagonists have not convincingly been demonstrated to improve outcomes in phase III clinical trials. The lack of benefit of these drugs could be explained by heterogeneous phenotypes of HFpEF and HFmrEF and by the absence of phase II data, leading to difficulty defining eligibility criteria and end points. Thus, improved early-phase HFpEF and HFmrEF trial design for potential existing and novel interventions may improve the likelihood of successful phase III trials and would be facilitated by feasible and meaningful surrogate end points. Diastolic dysfunction, increased left ventricular mass and mass/volume ratio, left atrial size, diastolic wall stress, exercise capacity, peakVO₂, and natriuretic peptide levels evaluation have been considered as potential structural and functional targets and surrogate end points in phase II trials in HFpEF/HFmrEF because these have been demonstrated to independently predict outcomes. To our knowledge, reductions in left atrial volume have been demonstrated to translate into improved morbidity or mortality, as suggested by a post hoc analysis from TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist). However, this was the case in both the spironolactone and placebo groups. Furthermore, in the Americas subgroup, where spironolactone was purportedly effective, it did not reduce left atrial volume. Therefore, although reductions in NT-proBNP in our study and left atrial volume in TOPCAT were associated with improved outcomes, this is not the same as a treatment effect and does not adequately support such changes being used as surrogate trial end points. Conversely, phase II studies assessing the efficacy and safety of long-term mineralocorticoid receptor antagonist use in HFpEF demonstrated improved left ventricular

![Baseline and Final NT-proBNP values](image1)

Figure 2. Baseline, final, and %ΔN-terminal pro–B-type natriuretic peptide (NT-proBNP) levels in patients reporting a decrease or an increase in NT-proBNP levels.

![% Changes in NT-proBNP levels](image2)

Figure 3. Kaplan–Meier curves fitted for all-cause death, heart failure (HF) hospitalization, and the composite outcome using decreases vs increases in N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels.
diastolic function, but the following phase III trial, TOPCAT, showed no effect in the overall trial on the primary outcome (composite of death from cardiovascular causes, aborted cardiac arrest, or HF hospitalization), although this analysis may have been confounded by regional differences in patients and treatment effect. It is, therefore, no surprise that other interventional phase II trials showing beneficial effects on some of these putative surrogate end points have not been followed by positive phase III trials. Thus, there is still an urgent need to develop new valid surrogate end points for well-designed phase II HFpEF and HFmrEF trials.

### Table 3. Cox Regression Model Fitted for All-Cause Death, HF Hospitalization, and the Composite Outcome According the Decreases or Increases in NT-proBNP Levels From the Baseline to the Follow-Up Evaluation in the Overall Cohort and in Patients With Left Ventricular Ejection Fraction ≥50% or =40%–49% Separately

<table>
<thead>
<tr>
<th></th>
<th>All-Cause Death</th>
<th>HF Hospitalization</th>
<th>Composite Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) No. *1000 Patient-Years</td>
<td>HR (95% CI) P Value</td>
<td>No. (%) No. *1000 Patient-Years</td>
</tr>
<tr>
<td>Overall cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔNT-proBNP &lt;0</td>
<td>57 (16%) 87</td>
<td>0.53 (0.36–0.77) 0.001</td>
<td>61 (17%) 93</td>
</tr>
<tr>
<td>%ΔNT-proBNP ≥0</td>
<td>78 (27%) 196</td>
<td>1.00 (ref)</td>
<td>86 (30%) 216</td>
</tr>
<tr>
<td>HFpEF (EF ≥50%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔNT-proBNP &lt;0</td>
<td>25 (18%) 109</td>
<td>0.43 (0.25–0.75) 0.003</td>
<td>22 (16%) 96</td>
</tr>
<tr>
<td>%ΔNT-proBNP ≥0</td>
<td>43 (32%) 192</td>
<td>1.00 (ref)</td>
<td>37 (63%) 166</td>
</tr>
<tr>
<td>HFmrEF (EF 40%–49%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔNT-proBNP &lt;0</td>
<td>32 (14%) 90</td>
<td>0.53 (0.30–0.92) 0.024</td>
<td>39 (17%) 109</td>
</tr>
<tr>
<td>%ΔNT-proBNP ≥0</td>
<td>35 (22%) 141</td>
<td>1.00 (ref)</td>
<td>49 (31%) 198</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; and NT-proBNP, N-terminal pro–B-type natriuretic peptide.

### Single Measurements of NT-proBNP
Several studies assessed the prognostic value of plasma concentrations of BNP and NT-proBNP in patients with HFpEF and HFmrEF. In I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study), baseline NT-proBNP >339 pg/mL was independently associated with increased rates of all-cause mortality, of the composite of all-cause mortality and cardiovascular hospitalization, and of the composite of death for HF and sudden death and HF hospitalization. Similarly, in PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure), a progressive increase in morbidity and mortality was observed with increasing quartiles of NT-proBNP, and in CHARM-Preserved (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity), NT-proBNP >600 pg/mL was the sole predictor of the primary outcome, the composite of cardiovascular mortality, HF hospitalization, myocardial infarction, or stroke. Certainly, we confirmed that lower NT-proBNP is favorable, with dramatically better prognosis with NT-proBNP levels versus 55% who reported an increase in peptides levels.

### Changes in NT-proBNP
Although the impact of single evaluations of NT-proBNP on prognosis in patients with EF ≥40 has been well studied, the role of changes in NT-proBNP levels over time has been studied only in HFpEF and in one single previous report in patients with HFpEF or HFmrEF. The latter was a post hoc analysis of I-PRESERVE, enrolling 2612 patients with EF ≥45%, where a decrease and increase in NT-proBNP levels <1000 pg/mL from baseline to 6-month follow-up was associated with a 27% reduction and 2-fold increase in rates of cardiovascular death or HF hospitalization, respectively, whereas beyond a 1000 pg/mL rise or fall, there was only little change in risk. However, these findings coming from a randomized clinical trial, which by their nature are highly selective and while internally valid, may not be representative of the heterogeneity, comorbidity, and resulting competing events of HF patients in the community and thus have limited external validity and generalizability. At the moment, only one successful phase II randomized clinical trial in HFpEF (PARAMOUNT [Prospective Comparison of ARNI With ARB on Management of Heart Failure with Preserved Ejection Fraction]) used changes in NT-proBNP as end point to assess the efficacy of LCZ696 in patients with EF ≥45%, however, it remains to be verified whether this positive result will be translated into reduced hard end points in the ongoing phase III trial (PARAGON-HF [Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity on Mortality in Heart Failure Patients With Preserved Ejection Fraction]).

### Predictors of Reduction in NT-proBNP
In our cohort of 650 unselected patients with HFpEF or HFmrEF, 45% of the subjects showed a decrease in NT-proBNP levels versus 55% who reported an increase in peptides levels.
A decrease in NT-proBNP was predicted by several baseline characteristics. Use of ACE-Is and ARBs has not been shown to improve outcomes in randomized trials, but large observational studies, including one from SwedeHF, suggest that they may be associated with improved outcomes. In the present study, the use of ACE-Is or ARBs was also independently associated with reductions in NT-proBNP, suggesting but not proving, that if an intervention reduces NT-proBNP, it also improves outcomes, a fundamental characteristic of an appropriate surrogate endpoint. We also observed that sinus rhythm but not atrial fibrillation was related to a decrease of NT-proBNP. Because atrial fibrillation is associated with enlarged left atrial volume and more elevated levels of NT-proBNP, it is conceivable that a decrease of natriuretic peptide levels is more difficult to achieve in patients with HFpEF/HFmrEF and concomitant atrial fibrillation.

**Study Limitations**

Our observational study is subject to selection bias and confounding. Additionally, in this real-world setting, there was some missing data, which was handled by multiple imputation. SwedeHF, together with population-wide registries, provided a large amount of baseline variables known to influence outcomes that were adjusted for in multivariable analyses. However, we cannot exclude that the adjustments at the multivariable analysis were not sufficient to rule out the effects of potential confounders on our analysis. In our analysis, we considered cause-specific hospitalization but not cause-specific death, and this is another limitation.

Our data are not from a trial, and the reductions in NT-proBNP reflect real-life standard of care rather than any specific intervention. Therefore, we cannot show that a reduction in NT-proBNP that might occur in a trial also would translate into improved outcomes. We also acknowledge that, given the >55,821 registrations and >34,186 unique patients, the sample size of 650 is small. NT-proBNP was not widely available and used in the early 2000s. Furthermore, NT-proBNP is indicated in Sweden for diagnosis of and prognosis in HF but currently not for serial follow-up or guiding therapy. Therefore, longer surviving patients may have had longer time to get a repeat measurement (survival bias), but on the contrary, deteriorating patients may also have had a greater indication for a repeat measurement (bias by indication). Although we cannot rule out such biases, this should affect survival in opposite directions, and the overall survival at 1 year (14.3%) was similar to other reports from outpatients in HFpEF/HFmrEF from SwedeHF. Additionally, the mentioned limitations did not allow us to perform the analyses calculating the change in peptide levels at different time points (ie, 3, 6, 9, and 12 months).

Finally, patients were included in SwedeHF based on clinician-judged HF. Thus, we cannot rule out that few patients with preserved left ventricular EF may not have HF.

**Conclusions**

The current study provides evidence of a strong relationship between reduction in NT-proBNP levels and subsequent lower risk of all-cause death, HF hospitalization, and their composites. These findings suggest that changes in NT-proBNP have potential as a surrogate endpoint for future phase II HFpEF and HFmrEF clinical trials, but studies to verify whether NT-proBNP changes predict drug efficacy are still required.

**Sources of Funding**

This study was supported by The County Council of Stockholm, The Swedish Heart and Lung Foundation, and The Swedish Research Council.

**Disclosures**

None.

**References**


Natriuretic peptides are diagnostic and prognostic in heart failure with preserved ejection fraction (EF) and reduced EF. The importance of changes over time is less clear. In heart failure with reduced EF, reductions in N-terminal pro-B-type natriuretic peptide during standard therapy have been shown to correlate with improved prognosis. In I-PRESERVE (Irbesartan in Patients with Heart Failure and Reduced EF), reductions in N-terminal pro-B-type natriuretic peptide were associated with subsequent lower risk of mortality and heart failure hospitalization. These findings were confirmed separately in patients with truly preserved EF (≥50%) and also in the mid-range EF 40% to 49%. These results support the use of changes in N-terminal pro-B-type natriuretic peptide in assessing prognosis (prognostic marker). We did not study changes in natriuretic peptides in response to any particular intervention. Therefore, our findings suggest but do not prove that changes in natriuretic peptides may be useful as surrogate end points in early-stage interventional trials, although such a use would require an understanding of drug effects on natriuretic peptide levels.

**CLINICAL PERSPECTIVE**

Natriuretic peptides are diagnostic and prognostic in heart failure with preserved ejection fraction (EF) and reduced EF. The importance of changes over time is less clear. In heart failure with reduced EF, reductions in N-terminal pro-B-type natriuretic peptide during standard therapy have been shown to correlate with improved prognosis. In I-PRESERVE (Irbesartan in Patients with Heart Failure and Reduced EF), reductions in N-terminal pro-B-type natriuretic peptide were associated with subsequent lower risk of mortality and heart failure hospitalization. These findings were confirmed separately in patients with truly preserved EF (≥50%) and also in the mid-range EF 40% to 49%. These results support the use of changes in N-terminal pro-B-type natriuretic peptide in assessing prognosis (prognostic marker). We did not study changes in natriuretic peptides in response to any particular intervention. Therefore, our findings suggest but do not prove that changes in natriuretic peptides may be useful as surrogate end points in early-stage interventional trials, although such a use would require an understanding of drug effects on natriuretic peptide levels.
Reductions in N-Terminal Pro-Brain Natriuretic Peptide Levels Are Associated With Lower Mortality and Heart Failure Hospitalization Rates in Patients With Heart Failure With Mid-Range and Preserved Ejection Fraction

Gianluigi Savarese, Camilla Hage, Nicola Orsini, Ulf Dahlström, Pasquale Perrone-Filardi, Giuseppe M.C. Rosano and Lars H. Lund

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SUPPLEMENTAL MATERIAL

REDUCTIONS IN N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE LEVELS ARE ASSOCIATED WITH LOWER MORTALITY AND HEART FAILURE HOSPITALIZATION RATES IN PATIENTS WITH HEART FAILURE WITH MID-RANGE AND PRESERVED EJECTION FRACTION

Gianluigi Savarese, MD¹, Camilla Hage, PhD¹, Nicola Orsini, PhD², Ulf Dahlström, MD, PhD³, Pasquale Perrone-Filardi, MD, PhD⁴, Giuseppe MC Rosano, MD, PhD⁵, and Lars H Lund, MD, PhD¹

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³Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden
⁴Department of Advanced Biomedical Sciences; Federico II University, Naples, Italy
⁵Cardiovascular and Cell Sciences Research Institute, St George’s University, London, UK; IRCCS San Raffaele Pisana, Rome, Italy
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Overall NT-proBNP cohort 650 pts</th>
<th>HFPEF SwedeHF outpatient cohort 9,555 pts</th>
<th>p</th>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>389 (60)</td>
<td>5,791 (60)</td>
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</tr>
<tr>
<td>Female</td>
<td>262 (40)</td>
<td>3,764 (40)</td>
<td></td>
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<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>73 (12)</td>
<td>72 (12)</td>
<td>0.17</td>
</tr>
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<td><strong>Location</strong></td>
<td></td>
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</tr>
<tr>
<td>Outpatient physician</td>
<td>132 (20)</td>
<td>2,600 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outpatient nurse-based HF clinic</td>
<td>518 (80)</td>
<td>6,955 (73)</td>
<td></td>
</tr>
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<td><strong>Speciality</strong></td>
<td></td>
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<tr>
<td>Cardiology</td>
<td>212 (32)</td>
<td>3,988 (42)</td>
<td>&lt;0.001</td>
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<td>Internal medicine or Geriatrics</td>
<td>308 (48)</td>
<td>3,872 (40)</td>
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<tr>
<td><strong>Follow-up referral speciality</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Primary care or Other care</td>
<td>170 (26)</td>
<td>3,218 (34)</td>
<td>&lt;0.001</td>
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<tr>
<td>Cardiology or Internal medicine</td>
<td>464 (71)</td>
<td>6,048 (63)</td>
<td></td>
</tr>
<tr>
<td>Follow up referral to outpatient HF nurse clinic</td>
<td>442 (68)</td>
<td>3,871 (40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of heart failure, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>310 (47)</td>
<td>4,203 (44)</td>
<td>0.08</td>
</tr>
<tr>
<td>&gt;6</td>
<td>339 (52)</td>
<td>5,327 (56)</td>
<td></td>
</tr>
<tr>
<td><strong>NYHA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>78 (13)</td>
<td>1,337 (14)</td>
<td>0.001</td>
</tr>
<tr>
<td>II</td>
<td>285 (48)</td>
<td>4,139 (43)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>226 (38)</td>
<td>2,495 (26)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>3 (1)</td>
<td>96 (1)</td>
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<tr>
<td><strong>LVEF, %</strong></td>
<td></td>
<td></td>
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<tr>
<td>&gt;50</td>
<td>270 (42)</td>
<td>4,128 (43)</td>
<td>0.41</td>
</tr>
<tr>
<td>40 - 49</td>
<td>380 (58)</td>
<td>5,427 (57)</td>
<td></td>
</tr>
<tr>
<td><strong>Blood pressure, mean (SD), mmHg</strong></td>
<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>130 (20)</td>
<td>130 (21)</td>
<td>0.79</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74 (11)</td>
<td>74 (12)</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Mean arterial blood pressure, mean (SD), mmHg</strong></td>
<td>93 (12)</td>
<td>93 (13)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Heart Rate, mean (SD), beats/min</strong></td>
<td>71 (14)</td>
<td>70 (14)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Laboratory Values</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance, mean (SD), ml/min^</td>
<td>70 (32)</td>
<td>71 (33)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hemoglobin, mean (SD), g/L</td>
<td>134 (16)</td>
<td>134 (16)</td>
<td>0.44</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor</td>
<td>408 (63)</td>
<td>6,084 (64)</td>
<td>0.53</td>
</tr>
<tr>
<td>Angiotensin II receptor blocker</td>
<td>200 (31)</td>
<td>2,484 (26)</td>
<td>0.01</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>185 (28)</td>
<td>2,375 (25)</td>
<td>0.05</td>
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<tr>
<td>Digoxin</td>
<td>92 (14)</td>
<td>1,403 (15)</td>
<td>0.73</td>
</tr>
<tr>
<td>Diuretic</td>
<td>500 (77)</td>
<td>6,699 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nitrate</td>
<td>85 (13)</td>
<td>1,238 (13)</td>
<td>0.96</td>
</tr>
<tr>
<td>Platelet inhibitor</td>
<td>272 (42)</td>
<td>4,317 (45)</td>
<td>0.09</td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>304 (47)</td>
<td>3,939 (41)</td>
<td>0.007</td>
</tr>
<tr>
<td>Statin</td>
<td>320 (49)</td>
<td>4,590 (48)</td>
<td>0.63</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>550 (85)</td>
<td>8,031 (84)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hypertension</td>
<td>394 (61)</td>
<td>4,386 (46)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>138 (21)</td>
<td>2,052 (21)</td>
<td>0.92</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>202 (31)</td>
<td>3,137 (33)</td>
<td>0.32</td>
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<tr>
<td>Peripheral artery disease</td>
<td>45 (7)</td>
<td>777 (8)</td>
<td>0.30</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>367 (56)</td>
<td>4,995 (52)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Supplemental Material Table 1. Baseline characteristics in the cohort of HFpEF/HFmrEF out-patients with two NT-proBNP measurements considered for the current study vs. the overall HFpEF/HFmrEF out-patient population in SwedeHF. NT-proBNP: N-Terminal pro-B-type Natriuretic Peptide; SD: Standard Deviation; NYHA: New York Heart Association; EF: Ejection Fraction. ^Creatinine Clearance was calculated by Cockcroft-Gault Formula.

<table>
<thead>
<tr>
<th>Stroke or transient ischemic attack incl intracranial bleed</th>
<th>110 (17)</th>
<th>1,391 (15)</th>
<th>0.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic stenosis</td>
<td>53 (8)</td>
<td>880 (9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Lung disease</td>
<td>171 (26)</td>
<td>2,196 (23)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Supplemental Material Table 2. Cox Regression Model fitted for All-cause Death, HF Hospitalization and the Composite Outcome according to categorical changes in NT-proBNP. HF: Heart Failure; HR: Hazard Ratio; CI: Confidence Interval.
**Supplemental Material Figure 1.** Difference in time between first and second NT-proBNP levels evaluation
Supplemental Material Figure 2. Kaplan Meier Curves fitted for All-Cause Death, HF Hospitalization and the Composite Outcome using categorical changes of NT-proBNP (low baseline – low final; low baseline – high final; high baseline – low final; high baseline – high final). NT-proBNP: N-Terminal pro-B-type Natriuretic Peptide; HF: Heart Failure.