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# B-Type Natriuretic Peptide and Prognosis in Heart Failure Patients With Preserved and Reduced Ejection Fraction

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**Objectives** This study sought to determine the prognostic value of B-type natriuretic peptide (BNP) in patients with heart failure with preserved ejection fraction (HFPEF), in comparison to data in HF patients with reduced left ventricular (LV) EF (≤40%).

**Background** Management of patients with HFPEF is difficult. BNP is a useful biomarker in patients with reduced LVEF, but data in HFPEF are scarce.

**Methods** In this study, 615 patients with mild to moderate HF (mean age 70 years, LVEF 33%) were followed for 18 months. BNP concentrations were measured at baseline and were related to the primary outcome, that is, a composite of all-cause mortality and HF hospitalization, and to mortality alone. The population was divided in quintiles, according to LVEF, and patients with reduced LVEF were compared with those with HFPEF.

**Results** There were 257 patients (42%) who had a primary endpoint and 171 (28%) who died. BNP levels were significantly higher in patients with reduced LVEF than in those with HFPEF ($p < 0.001$). BNP was a strong predictor of outcome, but LVEF was not. Importantly, if similar levels of BNP were compared across the whole spectrum of LVEF, and for different cutoff levels of LVEF, the associated risk of adverse outcome was similar in HFPEF patients as in those with reduced LVEF.

**Conclusions** BNP levels are lower in patients with HFPEF than in patients with HF with reduced LVEF, but for a given BNP level, the prognosis in patients with HFPEF is as poor as in those with reduced LVEF. (J Am Coll Cardiol 2013; 61:1498–506) © 2013 by the American College of Cardiology Foundation

Heart failure with preserved ejection fraction (HFPEF) is an increasingly large medical and epidemiological problem (1–5). Although older studies reported that HFPEF patients in general had a better prognosis than HF patients with a reduced left ventricular ejection fraction (LVEF) (6), more recent data indicate that mortality in HFPEF patients is in fact similar (3,4). Whereas survival has improved over the last 10 to 20 years in HF patients with reduced LVEF, no change was observed in HFPEF patients.

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A large number of trials have been conducted in HF patients and reduced LVEF patients, examining angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, angiotensin receptor blockers (ARBs), and aldosterone receptor blockers (1,7). These trials reported significant improvements in outcome, leading to strong recommendations for these drugs in current HF guidelines. In contrast, relatively few studies have been conducted in HFPEF. Although a recent meta-analysis showed that medical treatment may improve exercise capacity (8), none of the treatments was convincingly shown to improve outcome, and therefore none of these drugs has received a recommendation for HFPEF in current HF guidelines (1,5,7).

Methodological issues may play a role in the disappointing results from trials in HFPEF: most trials enrolled

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patients based on only a "preserved" LVEF combined with rather "soft" criteria related to symptoms of HF, and a considerable proportion of them may not have had HF (5). Comorbidities are common in HFPEF (9), and symptoms of HF such as dyspnea and fatigue are aspecific and may be secondary to other diseases such as anemia, obesity, and chronic obstructive pulmonary disease (COPD) (10,11). One way to overcome this problem is to employ strict echocardiographic criteria (7,12), but there are many different definitions, and measurement of these parameters is difficult and often not very useful for daily practice (5).

Another approach to define the presence of HF in patients with HFPEF is to use natriuretic peptides: B-type natriuretic peptide (BNP); or N-terminal pro–B-type natriuretic peptide (NT-proBNP). These biomarkers are now used on a large scale (13) and have been proven to be of value in the management of HF patients with reduced LVEF. Recent work has shown that these natriuretic peptides may also be used in HFPEF, both for diagnostic and for prognostic purposes (13–16).

The aim of the present study was therefore to study BNP concentrations in a HF cohort of patients that included a wide range of LVEF. By using BNP to grade the severity of HF, we were able to compare the prognostic value of similar levels of these peptides across the whole range of LVEF; in other words, we were able to examine the prognostic value of specific values of BNP across this range.

## Methods

**Patients.** All patients in the present study participated in the COACH (Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure) (ISRCNT98675639.) (17,18). COACH was a randomized trial to evaluate the effect of 2 levels of a disease management program (basic support and intensive support) versus care as usual. COACH showed no significant differences between the groups. Patients were randomized before discharge, at the end of a hospitalization for HF, when they were clinically stable. BNP measurements were taken at this time.

Patients had to be ≥18 years of age, had to be in New York Heart Association (NYHA) functional classes II to IV, and had to have evidence of underlying structural heart disease. The primary outcome was a composite of hospitalization for HF or all-cause mortality. A total of 1,023 patients were included in the main study, and follow-up was performed at 1, 3, 6, 12, and 18 months after discharge. Hospitalization for HF was defined as an unplanned overnight stay in a hospital (different dates for admission and discharge) as a result of progression of HF or directly related to HF. All events were adjudicated by an independent endpoint committee. Of the 17 participating centers in COACH, all but 1 agreed to collect additional blood samples. The study followed the principles outlined in the Declaration of Helsinki. Ethical approval, both for the main study and for the present substudy, was obtained from the Medical Ethics Committee of the University Medical Center, Groningen, and the other participating hospitals, and all subjects gave their written informed consent.

**Measurement of BNP.** Plasma BNP concentrations were measured as described in detail elsewhere (19). In short, plasma BNP was measured using a fluorescence immunoassay kit (Triage, Biosite Incorporated, San Diego, California) and the measurable range of BNP assays was 5.0 to 5,000 pg/ml. To convert BNP to picomoles per liter, divide by 3.47.

**Statistical analysis.** Data are given as mean ± SD when normally distributed, as median and interquartile range when distributed not normally or skewed, and as frequencies and percentages for categorical variables. Associations between baseline variables were evaluated by means of 1-way analysis of variance, the Kruskal-Wallis test, and chi-square or Fisher exact tests, when appropriate. LVEF was divided into 5 categories (≤20%, 21% to 30%, 31% to 40%, 41% to 50%, ≥51%) to assess relationships between baseline characteristics and LVEF. The prevalences of BNP are presented in categories for descriptive purposes but in the analyses were used as continuous variables.

To evaluate the association between BNP and the risk of all-cause mortality and hospitalization for worsening HF defined as time to first event, we calculated unadjusted, age- and sex-adjusted, and multivariably adjusted hazard ratios (HRs), and 95% confidence intervals (CIs) using Cox proportional hazards regression models.

In multivariable models, we mutually adjusted relevant predictors of cardiovascular mortality and morbidity. These variables, in the order of strength of association with the risk of all-cause mortality and hospitalization for worsening HF, were: history of cerebrovascular accident (stroke); estimated glomerular filtration rate; previous hospitalization for HF; age; serum sodium, diabetes; NYHA functional class; LVEF; use of diuretics; use of beta-blockers; COPD; (history of) hypertension; body mass index; atrial fibrillation/flutter; use of ACE inhibitors and/or ARB; history of myocardial infarction; underlying heart disease; depressive symptoms; and diastolic and systolic blood pressure. Depressive symptoms were assessed using the Centre for Epidemiological Studies Depression Scale, and a score ≥16 is considered as having depressive symptoms (20).

Initially, we assumed that the effect of BNP was monotonic, which is true for many risk/exposure relationships. The natural starting point, the straight-line model is often

**Abbreviations and Acronyms**

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
BNP = B-type natriuretic peptide
CI = confidence interval
COPD = chronic obstructive pulmonary disease
HFPEF = heart failure with preserved ejection fraction
HR = hazard ratio
LVEF = left ventricular ejection fraction
NT-proBNP = N-terminal pro–B-type natriuretic peptide
NYHA = New York Heart Association

adequate, but other models must be investigated for possible improvements in fit. We looked for nonlinearity by fitting a first-order polynomial to the data (21). The best power transformation $x^p$ was found, with the power p chosen from the candidates −2, −1, −0.5, 0, 0.5, 1, 2, and 3, where $x^0$ denotes log x. The set includes the straight-line (i.e., no transformation) p = 1, and the reciprocal, the square root and square transformations. The best fitting power was p = 0 (logarithmic transformation). BNP showed a log-linear functional shape with the response variables and was transformed to a 2-log scale. This means that risk estimates should be interpreted as the relative risk if values of BNP were doubled (e.g., from 10 to 20 pg/ml). In the multivariable models, we additionally examined whether LVEF modified the effect of BNP on all-cause mortality and hospitalization for worsening HF by including an interaction term. In a sensitivity analysis, we also analyzed the robustness of the predictive value of BNP in relation to LVEF by dichotomizing LVEF in 40%, 45%, and 50% groups. The risk estimates of the adjusted analyses were graphically presented for increasing LVEF with different levels of BNP. For reference, BNP concentrations of 250 and 750 pg/ml were chosen (based on values in the 2008 HF guidelines [22]) conditionally on a LVEF of 40%. The risk estimate curves were constructed using the medians of these 3 BNP groups (0 to 250 pg/ml, 251 to 750 pg/ml, and >750 pg/ml).

The assumption of proportionality of hazards was checked by means of Schoenfeld residuals, using procedure "stphtest" in STATA (StataCorp, College Station, Texas), which is based on the methods described by Grambsch and Therneau (23). No severe deviations from parallelism were evident. The assumption of linearity was checked graphically by studying the smoothed marginal residuals from the null model plotted against the covariate variables. The linearity assumptions were satisfied.

Statistical analyses were performed using SPSS (version 16.0, SPSS Inc., Chicago, Illinois) and STATA (version 11.0). A 2-sided p value <0.05 was considered to be significant.

## Results

**Study population.** There were 615 HF patients in whom LVEF and BNP measurements at baseline were available (Table 1). Baseline characteristics of this population of 615 patients were generally comparable to those of the complete COACH cohort (n = 1,023), although there are a few small differences (Online Table 1). First, patients in the entire COACH population overall had a slightly better functional class than in the present population: 51% versus 48% NYHA class II; and 49% versus 52% NYHA class III/IV, respectively, p = 0.017. Second, hemoglobin levels were slightly lower (12.6 vs. 12.8 g/dl, p = 0.031).

BNP baseline measurements were available, respectively, in 132 patients with LVEF ≤20%, in 199 patients with LVEF 21% to 30%, in 129 patients with LVEF 31% to 40%, in 81 patients with LVEF 41% to 50%, and in 74 patients with LVEF >50%. Of the 615 LVEF measurements in the current study, 523 (85%) were measured by echocardiography; 88 (14%) were measured by radionuclide imaging; and 4 (1%) were measured during angiography. There were 180 patients in the group BNP 0 to 250 pg/ml, 238 patients in the group of BNP 251 to 750 pg/ml, and 197 patients in the group BNP >750 pg/ml. Median BNP values in these 3 groups were 135 pg/ml, 450 pg/ml, and 1,260 pg/ml, respectively.

**Association between LVEF, clinical characteristics, and BNP.** Patients with higher LVEF were older, more often female, and they had a higher systolic blood pressure (Table 1). Body mass index was also higher, and hemoglobin levels were lower in patients with higher LVEF. The prevalence of obesity, (history of) hypertension, and anemia all increased in patients with higher LVEF (all p < 0.05), whereas a trend for more COPD was observed (p = 0.05). The frequency of depression, diabetes, and (history of) stroke did not differ between the groups.

Use of HF medication was different for ACE inhibitors and beta-blockers, and these drugs were less often used in those with higher LVEF. Median levels of both BNP decreased as LVEF increased (both p < 0.001 for trend).

Distribution of the levels of natriuretic peptides in the 5 LVEF groups is shown in Figure 1. In the higher LVEF groups, there were a higher proportion of patients with low BNP, whereas in the lower LVEF groups most patients were in the highest BNP group.

**Association between BNP and outcome.** During the 18-month study, the primary endpoint (all-cause mortality and HF hospitalization) occurred in 257 patients (42%), and 171 of the 615 (28%) patients died. Follow-up was 100% complete, and no patients were lost.

LVEF was not associated with the primary composite endpoint and there were no significant differences between the 5 LVEF groups (Fig. 2). The highest incidence of the primary endpoint was 51% in patients with LVEF 41% to 50%, and the lowest incidence was 33% in patients with LVEF 31% to 40%. LVEF was also not associated with all-cause mortality alone and varied from 22% in patients with LVEF 31% to 40% to 33% in those with LVEF 41% to 50%.

BNP was a strong predictor for outcome (Fig. 2), both in the whole population, as well as in the 2 subgroups of patients with LVEF ≤40% and in those with LVEF >40%. Figure 3 shows the Kaplan-Meier survival curves for the composite primary endpoint for BNP, for all patients (Fig. 3A), for patients with LVEF ≤40% (Fig. 3B), and for patients with LVEF >40% (Fig. 3C). The association between BNP was also examined for all-cause mortality alone in the 3 LVEF groups (Figs. 4A to 4C). BNP remained an independent prognostic predictor after adjustment for LVEF (expressed continuously or dichotomized using different LVEF cutoff values) and in the mutually adjusted analyses. Doubling of BNP was associated with a statistically significant 1.3-fold risk

**Table 1 Baseline Characteristics of the Study Population**

| | All Patients (N = 615) | LVEF ≤20% (n = 132) | LVEF 21%–30% (n = 199) | LVEF 31%–40% (n = 129) | LVEF 41%–50% (n = 81) | LVEF >50% (n = 74) | p Value for Trend |
|---|---|---|---|---|---|---|---|
| Age, yrs | 70 ± 12 | 67 ± 12 | 70 ± 12 | 71 ± 11 | 75 ± 10 | 73 ± 11 | <0.001 |
| Female | 38 | 32 | 37 | 35 | 41 | 55 | 0.002 |
| NYHA functional class | | | | | | | 0.029 |
| II | 48 | 44 | 47 | 43 | 53 | 60 | |
| III/IV | 52 | 56 | 53 | 57 | 47 | 40 | |
| LVEF, mean | 33 | 16 | 27 | 36 | 47 | 59 | |
| Heart rate, beats/min | 74 ± 14 | 76 ± 14 | 75 ± 12 | 77 ± 16 | 71 ± 11 | 72 ± 13 | 0.031 |
| Systolic BP, mm Hg | 118 ± 21 | 111 ± 19 | 115 ± 19 | 122 ± 22 | 124 ± 22 | 124 ± 22 | <0.001 |
| Diastolic BP, mm Hg | 69 ± 12 | 68 ± 11 | 68 ± 12 | 71 ± 15 | 69 ± 14 | 68 ± 11 | 0.719 |
| BMI, kg/m$^2$ | 27 ± 5 | 25 ± 5 | 26 ± 5 | 27 ± 6 | 26 ± 5 | 28 ± 6 | 0.001 |
| Hemoglobin, g/l | 12.8 ± 1.9 | 13.4 ± 1.8 | 12.9 ± 1.9 | 12.7 ± 2.1 | 12.5 ± 1.9 | 12.1 ± 2.0 | <0.001 |
| Sodium, mEq/l | 139 ± 4 | 139 ± 4 | 138 ± 4 | 139 ± 5 | 139 ± 4 | 138 ± 4 | 0.503 |
| eGFR, ml/min/1.73 m$^2$ | 56 ± 22 | 58 ± 19 | 55 ± 23 | 57 ± 24 | 51 ± 19 | 54 ± 20 | 0.044 |
| Natriuretic peptides | | | | | | | |
| BNP, pg/ml | 463 (212–918) | 534 (275–1130) | 502 (243–1120) | 447 (215–798) | 424 (179–828) | 256 (112–598) | <0.001 |
| Medical history | | | | | | | |
| Previous HF-hospitalization | 34 | 23 | 33 | 40 | 35 | 41 | 0.010 |
| Primary cause of HF | | | | | | | |
| Ischemic | 42 | 38 | 42 | 44 | 49 | 34 | 0.828 |
| Nonischemic | 58 | 62 | 58 | 56 | 51 | 66 | |
| Comorbidities | | | | | | | |
| Atrial fibrillation/flutter* | 36 | 31 | 31 | 39 | 48 | 41 | 0.010 |
| Obesity† | 22 | 14 | 21 | 23 | 26 | 33 | 0.002 |
| Diabetes | 27 | 20 | 34 | 23 | 25 | 30 | 0.599 |
| Hypertension | 42 | 31 | 40 | 45 | 52 | 49 | 0.001 |
| Stroke | 10 | 11 | 10 | 8 | 16 | 8 | 0.920 |
| COPD | 26 | 21 | 28 | 25 | 22 | 39 | 0.050 |
| Anemia | 38 | 26 | 35 | 40 | 42 | 49 | 0.007 |
| Depressive symptoms‡ | 39 | 42 | 34 | 39 | 48 | 39 | 0.296 |
| Medication | | | | | | | |
| ACE-I | 74 | 78 | 79 | 76 | 59 | 64 | <0.001 |
| ARB | 12 | 13 | 11 | 7 | 16 | 14 | 0.693 |
| ACE-I and/or ARB | 84 | 89 | 88 | 83 | 74 | 74 | <0.001 |
| Beta-blocker | 66 | 79 | 68 | 61 | 58 | 50 | <0.001 |
| Diuretic | 97 | 97 | 98 | 95 | 95 | 97 | 0.606 |
| Digoxin | 32 | 33 | 31 | 33 | 35 | 34 | 0.652 |

Values are mean ± SD, %, or median (interquartile range). *Atrial fibrillation/flutter on baseline echocardiogram. †Obesity defined as BMI ≥30 kg/m$^2$. ‡Assessed by the Centre for Epidemiological Studies Depression Scale in which of >16 was used to define depressive symptoms (17).

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

of the composite of all-cause mortality and HF hospitalization ($p < 0.001$) (Table 2), and a 1.4-fold increased risk of all-cause mortality alone ($p < 0.001$) (Table 2). Introducing LVEF continuously or dichotomized using different cutoff values hardly changed the point estimates and confidence intervals of the hazard rates of BNP.

When we determined risk estimates of LVEF on outcome across the whole spectrum of LVEF for several specific BNP (Fig. 5), there were no statistically significant changes in the prognostic value of BNP with increasing LVEF, neither for the primary composite endpoint of all-cause mortality and HF hospitalization (Fig. 5A) nor for all-cause mortality alone (Fig. 5B). For the composite primary endpoint, the hazard ratio for specific BNP values slightly increased with higher LVEF, but this was not statistically significant (HR: 1.00 [95% CI: 1.00 to 1.02], $p = 0.178$), whereas for mortality alone it remained the same (HR: 1.00 [95% CI: 0.99 to 1.02], $p = 0.512$). Subsequent interaction analyses did not show any statistically significant interaction between LVEF and BNP. The additional sensitivity analyses showed similar results. Similar findings were also observed when the dataset was limited to patients without atrial fibrillation or flutter.

## Discussion

Patients with HFPEF overall have lower levels of BNP than do HF patients with reduced LVEF, but for a given BNP level, the associated risk of all-cause mortality and HF

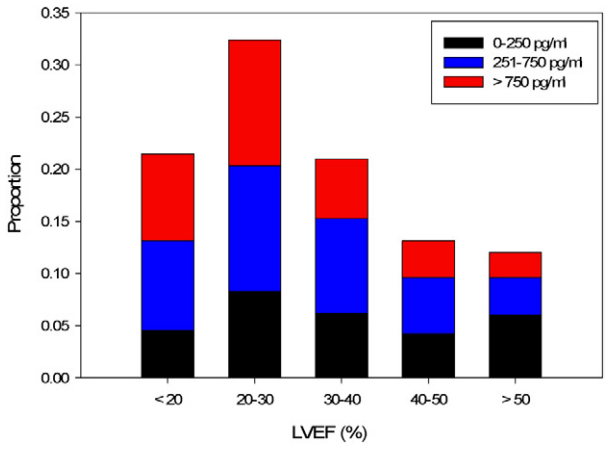


**Figure 1** **Distribution of Patients in the 5 LVEF Groups for BNP**

The following divisions were made: low: 0 to 250 pg/ml; middle: 251 to 750 pg/ml; and high: >750 pg/ml. The proportion is depicted in **stacked bars**. BNP = B-type natriuretic peptide; LVEF = left ventricular ejection fraction.

hospitalization is at least as high in patients with HFPEF as it is in those with low LVEF. This finding may have important clinical implications. Indeed, the data suggest that when the prognosis of HF patients is assessed, BNP can and should be used, irrespective of LVEF. In addition,

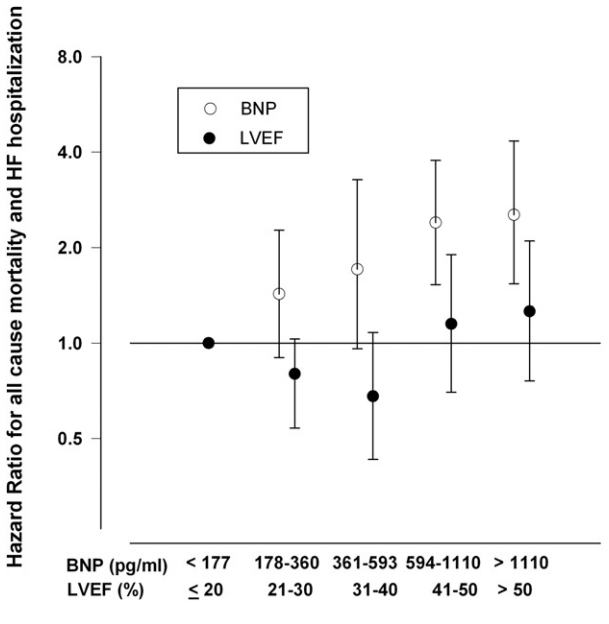


**Figure 2** **Association Between LVEF and BNP, and Risk of the (Composite) Primary Endpoint of All-Cause Death and HF Hospitalization**

For LVEF, the population is grouped in percentages and for BNP in quintiles. Risk on the y axis is shown as hazard ratio ± 95% confidence intervals using the multivariate proportional hazards regression model. HF = heart failure; other abbreviations as in Figure 1.

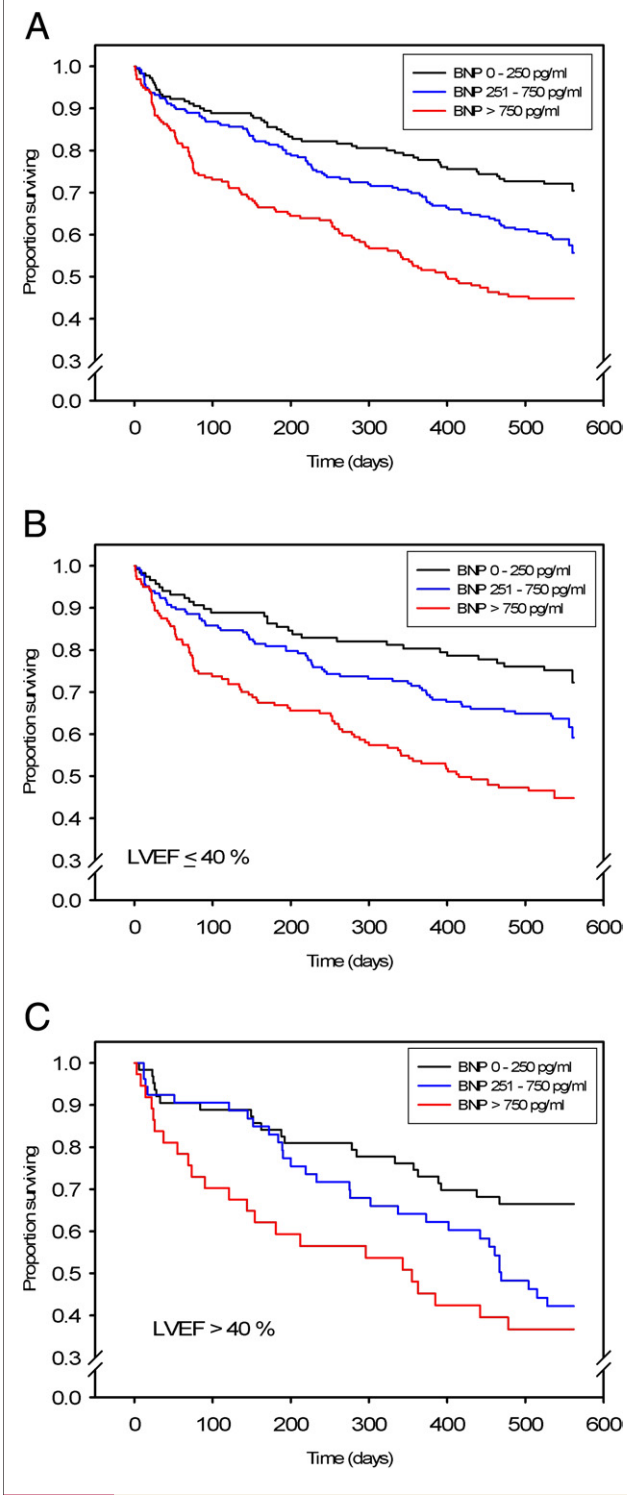


**Figure 3** **BNP and Primary Endpoint (Death and HF Hospitalization) in LVEF ≤40% and >40%**

Kaplan-Meier survival curves of the association between BNP and the primary endpoint (death and HF hospitalizations) in the whole population **(A),** in patients with LVEF ≤40% **(B),** and in patients with LVEF >40% **(C).** Abbreviations as in Figures 1 and 2.

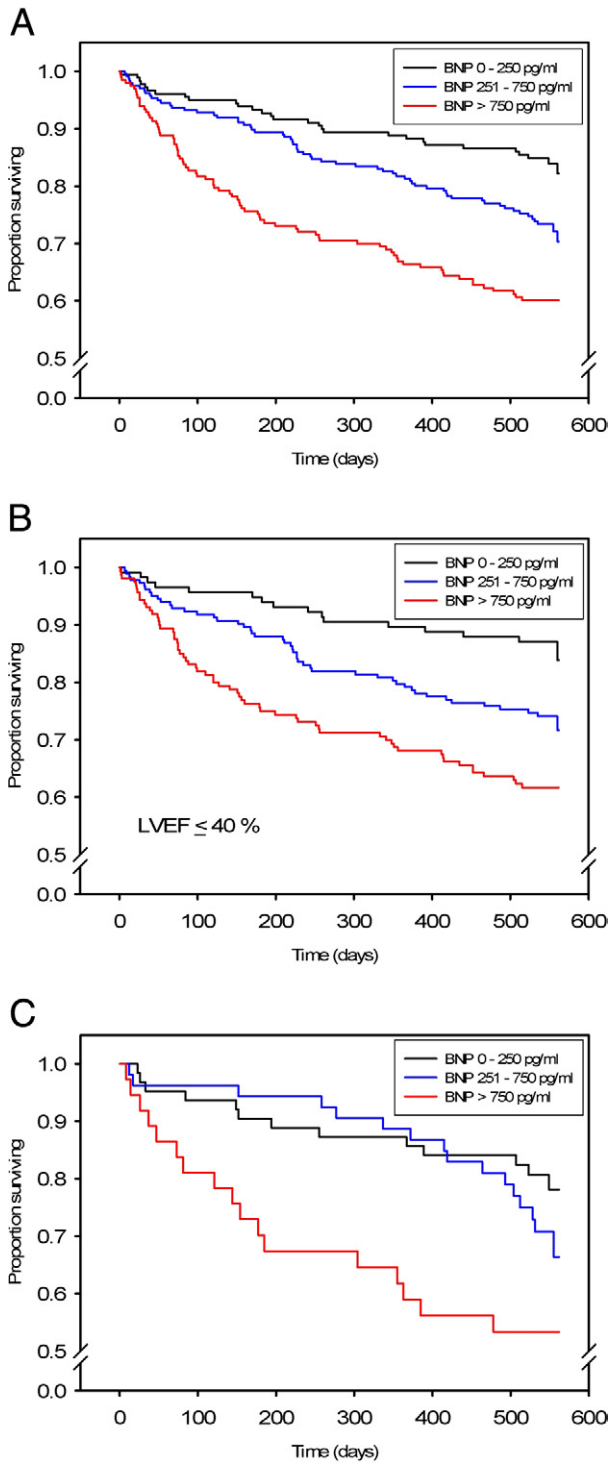


**Figure 4** BNP and All-Cause Mortality in LVEF ≤40% and >40%

Kaplan-Meier survival curves of the association between BNP and the primary endpoint (all-cause mortality) in the whole population **(A),** in patients with LVEF ≤40% **(B),** and in patients with LVEF >40% **(C).** Abbreviations as in Figures 1 and 2.

if populations of patients with HFPEF are examined, for example to investigate the value of a new drug or device, a (minimal) BNP level may be used to ensure a representative HF population, that may benefit from treatment.

In the present study, BNP levels were overall lower in patients with HFPEF than in HF patients with reduced LVEF, a finding that has been reported before, both in acute (24) and chronic HF (25). Patients with HFPEF, however, more often had obesity and anemia, and COPD tended to be more frequent. Interestingly, all these 3 conditions have been reported to mimic HF (10,11), and it can be speculated that in some patients in the higher LVEF groups, who were assumed to have HF, their complaints may have been due to these other conditions. Indeed, in many of such patients, BNP levels will most likely be normal or only moderately elevated.

Despite the fact that BNP levels were overall lower in the present study in patients with HFPEF than in those with reduced LVEF, the associated risk for reaching the primary endpoint was at least similar for a given BNP level. The finding that BNP is the primary driver of outcome, and that adding LVEF has limited value in prognostication, has been reported before in patients with acute HF (26) and in a recent community study (27). The present results are in line with this and suggest that this may also be true in patients with nonacute (or chronic) HF. On an individual patient basis, natriuretic peptides can also be used to predict outcome, when incorporated into a risk model (28). For a long time it has been

**Table 2** HR for Outcome According to Doubling of BNP

| | HR (95% CI) | Z | p Value |
|---|---|---|---|
| All-cause mortality and HF hospitalization | | | |
| BNP unadjusted | 1.29 (1.19–1.41) | 5.96 | <0.001 |
| BNP mutually adjusted with LVEF analyzed as a continuous variable* | 1.24 (1.13–1.38) | 4.26 | <0.001 |
| BNP mutually adjusted with LVEF below and above 40% | 1.25 (1.13–1.38) | 4.33 | <0.001 |
| BNP mutually adjusted with LVEF below and above 45% | 1.24 (1.13–1.37) | 4.31 | <0.001 |
| BNP mutually adjusted with LVEF below and above 50% | 1.25 (1.13–1.38) | 4.28 | <0.001 |
| All-cause mortality | | | |
| BNP unadjusted | 1.41 (1.27–1.58) | 6.19 | <0.001 |
| BNP mutually adjusted with LVEF analyzed as a continuous variable* | 1.36 (1.20–1.54) | 4.69 | <0.001 |
| BNP mutually adjusted with LVEF 40% | 1.36 (1.20–1.55) | 4.75 | <0.001 |
| BNP mutually adjusted with LVEF 45% | 1.35 (1.19–1.54) | 4.66 | <0.001 |
| BNP mutually adjusted with LVEF 50% | 1.36 (1.20–1.55) | 4.72 | <0.001 |

*Adjusted for the following: history of cerebrovascular accident (stroke); estimated glomerular filtration rate; previous hospitalization for HF; diabetes; serum sodium; age; NYHA functional class; sex; use of glycosides; atrial fibrillation/flutter; use of beta-blockers; use of diuretics; COPD; history of hypertension; (history of) use of ACE inhibitors and/or angiotensin receptor blockers; heart rate; underlying heart disease; body mass index; depressive symptoms; history of myocardial infarction; systolic and diastolic blood pressure.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

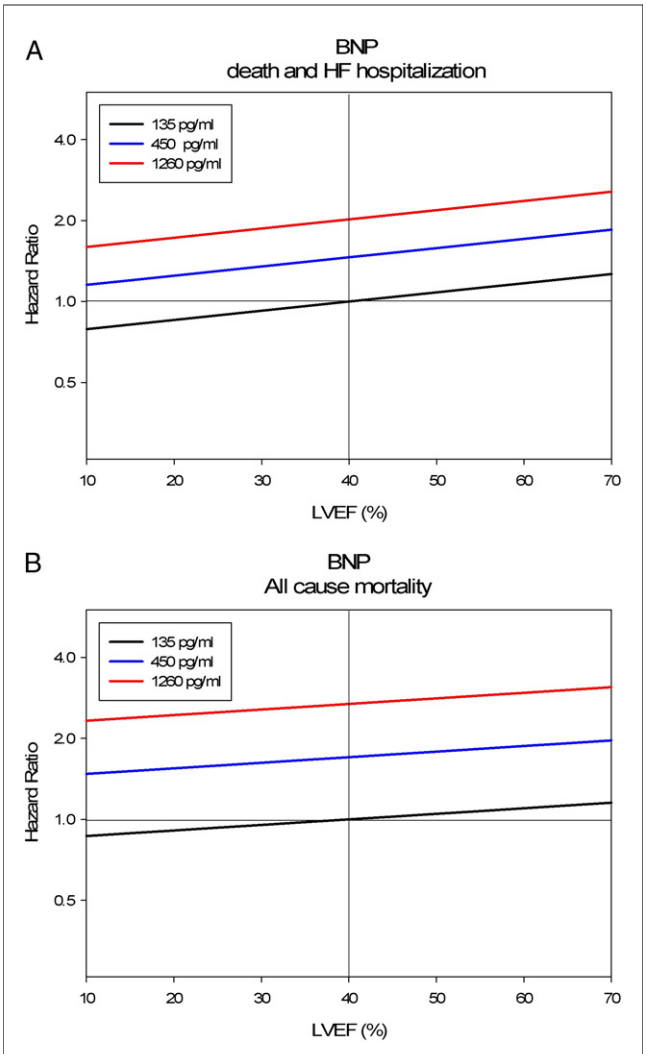


**Figure 5** **Risk Estimates of LVEF on Outcome**

Risk on the y axis is shown as hazard ratio, for the primary endpoint (death and HF hospitalization) **(A)** and for all-cause mortality alone **(B)** for specific levels of BNP. The same division in 3 BNP groups was used (low group: 0 to 250 pg/ml, median 135 pg/ml; middle group: 251 to 750 pg/ml, median 450 pg/ml; and high group: >750 pg/ml, median 1,260 pg/ml), and the curves were constructed using these median values in the 3 groups. Abbreviations as in Figures 1 and 2.

assumed that morbidity and mortality in HFPEF patients was lower than in HF patients with reduced LVEF (6,29). The present findings indicate, however, that first, for a given BNP level, which would suggest a similar severity of HF, the associated risk is the same, and this was true for patients with low, intermediate, and high BNP levels. In other words, if patients truly have HFPEF (confirmed by an elevated BNP level), their prognosis is not better than for HF patients with reduced LVEF. Second, it supports the notion, that (elevated) BNP levels could be used as an (additional) inclusion in HFPEF trials, as has been suggested elsewhere (13,16). By using such criteria in HFPEF, patients who do not really have HF can be excluded, thereby increasing the proportion of patients with true HF (and a poorer prognosis), and the likelihood of getting a positive result in trials assessing the effect of HF treatment. In addition, the use of biomarkers such as BNP (and NT-proBNP) to select HF patients for targeted HF treatment is attractive, because they can be measured relatively easily in everyday clinical practice, in contrast, for example, to state-of-the-art echocardiographic measurements to assess diastolic function (30).

HFPEF is a large medical problem, which is increasing in prevalence in the Western world (2,4,31), but treatment for these patients is difficult. Although potentially interesting findings have been reported on the use of ACE inhibitors (32), ARB (33), and beta-blockers (34), no prospective randomized trial has shown a statistically significant beneficial effect on outcome, and none of these agents is recommended for HFPEF in current HF guidelines (1,35). In the largest study of HFPEF so far, with the ARB irbesartan (36), there was no effect whatsoever on the primary composite outcome of mortality or cardiovascular hospitalization, and median value of NT-proBNP was 341 pg/ml in that study (16). Somewhat unexpectedly, another substudy of that trial (37) showed that irbesartan was effective in patients with NT-proBNP below but not above the median, which contrasts with the findings from 2 other studies of HFPEF (32,38), in which the drug effects were slightly (but not significantly) better in patients with NT-proBNP levels above the median. Nevertheless, these findings from the large substudy with irbesartan (37) are intriguing. It cannot be excluded that activation of natriuretic peptides in HFPEF may reflect a (partly) different pathophysiology than in HF patients with reduced LVEF and reflect, for example, more cardiorenal dysfunction in HFPEF. Recently, data from another trial in HFPEF with the angiotensin receptor neprilysin inhibitor LCZ696 were published (38). Importantly, in that study, baseline NT-proBNP was used as an entry criterion (>400 pg/ml), which resulted in mean levels of around 800 pg/ml, and remarkably, change in NT-proBNP was in fact the primary endpoint of that study.

**Study limitations.** First, the number of patients studied was relatively small, particularly for those with HFPEF (LVEF ≥40%), and the number of patients with LVEF ≥45% or even ≥50% was even smaller. We chose a LVEF of 40% for practical purposes, and because many other large trials used this, but it may be argued that some of these patients do not have a (completely) preserved systolic function. Second, systematic echocardiographic evaluations to examine diastolic dysfunction (preferably with the use of a core lab) were not done. Although this would have been useful, BNP levels have been shown to correlate with indices of diastolic dysfunction (39,40). Nevertheless, it must be noted, that the diagnostic accuracy of natriuretic peptides appears to be less in patients with HFPEF than in those with HF and reduced LVEF (24,41). Third, serial measurements of BNP would have been interesting to assess further the prognostic association between BNP and LVEF, but these were not available.

## Conclusions

For a given BNP level, the prognosis in patients with HFPEF is similar as in those with reduced LVEF. These findings may have important implications in the management of HFPEF patients in everyday clinical practice and in the design of trials in HFPEF.

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### REFERENCES

1. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Eur J Heart Fail 2012;14:803–69.
2. Kindermann M, Reil JC, Pieske B, Van Veldhuisen DJ, Böhm M. Heart failure with normal left ventricular ejection fraction: what is the evidence? Trends Cardiovasc Med 2008;18:280–92.
3. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.
4. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260–9.
5. Paulus WJ, Van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth. J Am Coll Cardiol 2010;55:526–37.
6. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948–55.
7. Krum H, Abraham WT. Heart failure. Lancet 2009;373:941–55.
8. Holland DJ, Kumbhani DJ, Ahmed SH, Marwick TH. Effects of treatment on exercise tolerance, cardiac function, and mortality in heart failure with preserved ejection fraction: a meta-analysis. J Am Coll Cardiol 2011;57:1676–86.
9. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59:998–1005.
10. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. BMJ 2000;321:215–8.
11. Maeder MT, Kaye DM. Heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol 2009;53:905–18.
12. Persson H, Lonn E, Edner M, et al., for the CHARMES Investigators. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence: results from the CHARM Echocardiographic Substudy—CHARMES. J Am Coll Cardiol 2007;49:687–94.
13. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol 2007;50:2357–68.
14. Januzzi JL, Jr., Rehman SU, Mohammed AA, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular dysfunction. J Am Coll Cardiol 2011;58:1881–9.
15. Parekh N, Maisel AS. Utility of B-natriuretic peptide in the evaluation of left ventricular diastolic function and diastolic heart failure. Curr Opin Cardiol 2009;24:155–60.
16. Komajda M, Carson PE, Hetzel S, et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). Circ Heart Fail 2011;4:27–35.
17. Jaarsma T, Van der Wal MH, Hogenhuis J, et al. Design and methodology of the COACH study: a multicenter randomised Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure. Eur J Heart Fail 2004;6:227–33.
18. Jaarsma T, Van der Wal MH, Lesman-Leegte I, et al., for the COACH Investigators. Effect of moderate or intensive disease management program on outcome in patients with heart failure: Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH). Arch Intern Med 2008;168:316–24.
19. Hogenhuis J, Voors AA, Jaarsma T, et al. Anaemia and renal dysfunction are independently associated with BNP and NT-proBNP in patients with heart failure. Eur J Heart Fail 2007;9:787–94.
20. Jaarsma T, Lesman-Leegte I, Hillege HL, Veeger NJ, Sanderman R, Van Veldhuisen DJ. Depression and the usefulness of a disease management program in heart failure: insights from the COACH (Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure) study. J Am Coll Cardiol 2010;55:1837–43.
21. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 1999;28:964–74.
22. Dickstein K, Cohen-Solal A, Filippatos G, et al., for the ESC CPG. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Eur Heart J 2008;29:2388–42.
23. Grambsch PM, Therneau TM. Proportional hazards test and diagnosis based on weighted residuals. Biometrika 1994;81:515–26.
24. Maisel AS, McCord J, Nowak RM, et al., for the Breathing Not Properly Multinational Study Investigators. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction: results from the Breathing Not Properly Multinational Study. J Am Coll Cardiol 2003;41:2010–7.
25. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. JAMA 2006;296:2209–16.
26. Fonarow GC, Peacock WF, Phillips CO, et al., for the ADHERE Scientific Advisory Committee and Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 2007;49:1943–50.
27. DeFilippi CR, Christensen RH, Kop WJ, Gottdiener JS, Zhan M, Selinger SL. Left ventricular ejection fraction assessment in older adults: an adjunct to natriuretic peptide testing to identify risk of new-onset heart failure and cardiovascular death? J Am Coll Cardiol 2011;58:1497–506.
28. Postmus D, Van Veldhuisen DJ, Jaarsma T, et al. The COACH risk engine: a multistate model for predicting survival and hospitalization in patients with heart failure. Eur J Heart Fail 2012;14:168–75.
29. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004;43:317–27.
30. Franssen C, Paulus WJ. The future diagnosis of heart failure with normal ejection fraction: less imaging, more biomarkers? Eur J Heart Fail 2011;13:1043–5.
31. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail 2011;13:18–28.
32. Cleland JG, Tendera M, Adamus J, et al., for the PEP-CHF Investigators. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study. Eur Heart J 2006;27:2338–45.
33. Yusuf S, Pfeffer MA, Swedberg K, et al., for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–81.
34. van Veldhuisen DJ, Cohen-Solal A, Böhm M, et al., for the SENIORS Investigators. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). J Am Coll Cardiol 2009;53:2150–8.
35. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009;119:1977–2016.

36. Massie BM, Carson PE, McMurray JJ, et al., for the I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456–67.
37. Anand IS, Rector TS, Cleland JG, et al. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. Circ Heart Fail 2011;4:569–77.
38. Solomon SD, Zile MR, Pieske B, et al., for the PARAMOUNT Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387–95.
39. Grewal J, McKelvie R, Lonn E, et al. BNP and NT-proBNP predict echocardiographic severity of diastolic dysfunction. Eur J Heart Fail 2008;10:252–9.
40. Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. Circulation 2002;105:595–601.
41. O'Donoghue M, Chen A, Baggish AL, et al. The effects of ejection fraction on N-terminal ProBNP and BNP levels in patients with acute CHF: analysis from the ProBNP Investigation of Dyspnea in the Emergency Department. J Card Fail 2005;11:S9–14.

**Key Words:** heart failure ■ natriuretic peptides ■ preserved ejection fraction ■ prognosis.

**APPENDIX**

**For a supplementary table, please see the online version of this article.**