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Direct Comparison of B-Type Natriuretic Peptide (BNP) and Amino-Terminal proBNP in a Large Population of Patients with Chronic and Symptomatic Heart Failure: The Valsartan Heart Failure (Val-HeFT) Data

Serge Masson,[1]* Roberto Latini,[1,2] Inder S. Anand,[3] Tarcisio Vago,[4] Laura Angelici,[1] Simona Barlera,[1] Emil D. Missov,[5] Aldo Clerico,[6] Gianni Tognoni,[7] and Jay N. Cohn,[5] on behalf of the Val-HeFT Investigators

Background: **The B-type or brain natriuretic peptides (BNP) and the amino-terminal probrain natriuretic peptide (NT-proBNP) are good markers of prognosis and diagnosis in chronic heart failure (HF). It is unclear, however, whether differences in their biological characteristics modify their clinical correlates and prognostic performance in HF. This work aimed to provide a direct comparison of the prognostic value of BNP and NT-proBNP in patients with chronic and stable HF.**

Methods: **We measured BNP and NT-proBNP at baseline in 3916 patients enrolled in the Valsartan Heart Failure Trial. To identify the variables associated with both peptides, we conducted simple and multivariable linear regression analyses. We used Cox multivariable regression models to evaluate the independent prognostic value for all-cause mortality, mortality and morbidity, and hospitalization for HF. Prognostic performance was assessed by pairwise comparisons of the area under the curve of receiver-operator characteristic curves.**

Results: **NT-proBNP and BNP had similar relationships with age, left ventrical ejection fraction, and internal diameter and creatinine clearance. Either peptide ranked as the first independent predictor of outcome after adjustment for major confounding clinical characteristics. ROC curves were almost superimposable for all-cause mortality (area under the curve (SE): BNP 0.665 (0.011) vs NT-proBNP 0.679 (0.011); $P = 0.0734$), but NT-proBNP was superior to BNP for predicting mortality and morbidity ($P = 0.032$) or hospitalization for HF ($P = 0.0143$). Overall sensitivity and specificity ranged from 0.590 to 0.696.**

Conclusions: **The natriuretic peptides BNP and NT-proBNP showed subtle differences in their relation to clinical characteristics and prognostic performance in a large population of patients with chronic and stable HF. They were the most powerful independent markers of outcome in HF.**

The B-type or brain natriuretic peptides (BNP) are good markers of prognosis and for diagnosis of chronic heart failure (HF)[8] *(1, 2)*. It has been suggested that they may be useful as surrogate markers of therapeutic efficacy in clinical trials of patients with chronic HF *(3, 4)*.

[1] Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy.
[2] Department of Medicine, New York Medical College, Valhalla, NY.
[3] Cardiology Section, Veterans Affairs Medical Center, Minneapolis, MN.
[4] Laboratorio di Endocrinologia, Ospedale "Luigi Sacco", Milan, Italy.
[5] Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN.
[6] Laboratory of Cardiovascular Endocrinology and Cell Biology, Consiglio Nazionale delle Ricerche, Institute of Clinical Physiology, Pisa, Italy.
[7] Consorzio Mario Negri Sud, S. Maria Imbaro, Chieti, Italy.
* Address correspondence to this author at: Istituto di Ricerche Farmacologiche "Mario Negri", via Eritrea 62, 20157 Milan, Italy. Fax 39-023-320-0049; e-mail masson@marionegri.it.

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[8] Nonstandard abbreviations: HF, heart failure; BNP, B-type or brain natriuretic peptide; NT-proBNP, amino-terminal probrain natriuretic peptide; LV, left ventricular; LVEF, left ventricular ejection fraction; LVIDd, left ventricular diameter in diastole; AUC, area under the curve; Val-HeFT, Valsartan Heart Failure Trial; LVIDd/BSA, LV diameter in diastole adjusted for body surface area; M&M, mortality and morbidity; eGFR, estimated glomerular filtration rate; BMI, body mass index; CI, confidence interval.

BNP and the amino-terminal fragment of BNP (prohormone NT-proBNP) are secreted in equimolar amounts in response to mechanical or neurohormonal stimulation. Both peptides are reliably measured in clinical practice. Whereas BNP is a natriuretic and diuretic hormone, the biological role of NT-proBNP, if any, is not well understood. These peptides also differ with regard to their biological half-life, in vitro stability, and mechanisms involved in their clearance *(5)*. However, there is no compelling evidence in favor of either peptide in terms of indicators of clinical severity *(6–8)*, screening for left ventricular (LV) dysfunction in the general population *(9)*, diagnosis *(10–13)*, or prognosis *(8, 14, 15)*. In particular, a study in a large and representative population of patients with chronic HF is required to examine and compare the prognostic value of BNP and NT-proBNP in a setting that would allow sufficient statistical power to examine subgroups of patients according to their clinical characteristics.

In the Valsartan Heart Failure (Val-HeFT) trial, blood samples were collected at the time of entry into the study in a large population of patients with chronic and symptomatic HF, yielding one of the largest plasma banks collected for this disease. The clinical utility of several neurohormones, including BNP, has already been evaluated in this trial *(16–19)*. In this study, we carried out a direct comparison of the 2 natriuretic peptides in this large population in relation to the severity of the disease and clinical outcome.

Materials and Methods

STUDY DESIGN AND PATIENTS

Val-HeFT was a randomized, placebo-controlled, double-blind, parallel-arm multicenter trial. A total of 5010 patients with stable, symptomatic HF, who were on prescribed HF therapy and who had LV ejection fraction (LVEF) of <40% and LV diameter in diastole adjusted for body surface area (LVIDd/BSA) of ≥2.9 cm/m^2, were enrolled in the study. Results of the main trial have been presented in detail previously *(20)*.

MEASUREMENT OF NATRIURETIC PEPTIDE CONCENTRATIONS

Blood samples were collected at study entry by venipuncture in evacuated plastic tubes containing EDTA dipotassium salt. Blood samples were centrifuged at 3500*g* for 10 min at 4 °C immediately after collection, and plasma samples were stored at −70 °C. BNP (IRMA Shionogi) and NT-proBNP (ECLIA Elecsys 2010 analyzer, Roche Diagnostics) were measured by commercially available assays in plasma samples never thawed before. Norepinephrine, plasma renin activity, and C-reactive protein were determined, as previously described *(17, 19)*. The intraassay CVs were 2.9% and 3.9% for NT-proBNP and BNP, respectively. Corresponding interassay CVs were 3.9% and 4.7%. In 81 age-matched, healthy volunteers, the 95th percentile concentrations were 121 and 76 ng/L, for NT-proBNP and BNP, respectively.

STATISTICAL METHODS

We performed all statistical analyses both NT-proBNP and BNP concentrations measured at baseline in all patients (n = 3916). We compared concentrations of NT-proBNP or BNP according to clinical characteristics by means of the Wilcoxon rank-sum test because the normality of the distribution was not satisfied. We assessed the correlation between baseline concentrations of BNP and NT-proBNP with the Pearson correlation coefficient test.

Simple linear regression analyses were carried out to evaluate the relationship between baseline concentrations of BNP or NT-proBNP (expressed as log-transformed data) and clinical characteristics as continuous variables when appropriate. The assumptions underlying the linear regression models, such as linearity, normality, and homoscedasticity, were satisfied for all the independent continuous variables, except for creatinine and bilirubin, which were transformed on a logarithmic scale.

Multivariable linear regression analyses were carried out to determine the variables independently associated with NT-proBNP or BNP, expressed as continuous log-transformed concentrations. In the final models, only variables statistically significant at the univariate analysis ($P < 0.05$) were included. β regression coefficients and their significance from multiple linear regression analysis are reported.

The relationship between NT-proBNP or BNP and these variables was also explored by dividing them into quartiles and assessing differences by means of the Kruskal–Wallis test.

Cox multivariable regression models were used to evaluate the independent prognostic value of baseline NT-proBNP and BNP (entered as categorical variables below and above the median concentration) on all-cause mortality, on mortality and morbidity (M&M), and on hospitalization for HF alone. Mean follow-up time was 23 months. The model included all the demographic, clinical, and echocardiographic variables, considered as categorical, that had a significant univariate relationship with outcome. To check for possible biases resulting from the arbitrary choice of median concentration, we also carried out the same Cox multivariate analysis with continuous variables where appropriate. We checked the assumption of proportional hazard with the log[-log(survival)] plot and by the time-dependent covariate test. Also, we used the martingale residuals plot to evaluate whether a specific time-independent continuous covariate might be entered directly into the model, or if a transformation was necessary. To ease the interpretability of these results, hazard ratios have been computed for intervals of 50 ng/L of BNP and 500 ng/L of NT-proBNP.

To assess the incremental prognostic value of NT-proBNP or BNP with respect to clinical variables, we

Table 1. Plasma concentrations of NT-proBNP or BNP according to baseline clinical characteristics.

Variable	Category, n	NT-proBNP, n (ng/L)	*P* value[a]	BNP, n (ng/L)	*P* value[a]
Overall (n = 3916)		895 (375–1985)		99 (41–242)	
Age, years (n)	<70 (2767)	721 (300–1547)	*<0.0001*	82 (34–204)	*<0.0001*
	≥70 (1149)	1477 (706–2883)		156 (68–313)	
Sex	Females (777)	984 (406–2291)	*0.0147*	95 (36–229)	*0.1129*
	Males (3139)	876 (368–1940)		100 (42–245)	
NYHA	II (2412)	745 (318–1553)	*<0.0001*	84 (36–189)	*<0.0001*
	III (1423)	1194 (516–2767)		132 (50–315)	
	IV (77)	2379 (904–5332)		261 (98–629)	
LVIDD, cm	<6.8 (1818)	740 (301–1721)	*<0.0001*	78 (33–196)	*<0.0001*
	≥6.8 (2098)	1029 (459–2181)		123 (51–272)	
LVEF, %	≥27 (2054)	674 (292–1495)	*<0.0001*	80 (33–182)	*<0.0001*
	<27 (1860)	1172 (523–2524)		134 (54–303)	
BMI, kg/m^2	>22 (3504)	827 (355–1816)	*<0.0001*	95 (39–223)	*<0.0001*
	≤22 (412)	1728 (793–3620)		194 (58–407)	
Diabetes	No (2887)	858 (357–1937)	*0.0037*	94 (39–238)	*0.0081*
	Yes (1029)	984 (426–2189)		114 (49–249)	
Atrial fibrillation	No (3450)	799 (338–1819)	*<0.0001*	93 (38–234)	*<0.0001*
	Yes (466)	1596 (912–3141)		141 (72–286)	
Ischemic etiology	No (1653)	859 (322–1978)	*0.0114*	84 (28–218)	*<0.0001*
	Yes (2263)	916 (404–1988)		110 (51–254)	
Background therapy					
Diuretics	No (591)	528 (259–1073)	*<0.0001*	64 (31–126)	*<0.0001*
	Yes (3325)	976 (412–2175)		110 (43–258)	
Digoxin	No (1246)	726 (335–1592)	*<0.0001*	90 (41–223)	*0.0568*
	Yes (2670)	987 (399–2141)		105 (41–250)	
ACE inhibitor	No (269)	885 (369–1956)	*0.0070*	98 (40–240)	*0.0197*
	Yes (3647)	1081 (471–2389)		119 (54–272)	
Beta-blockers	No (2490)	948 (384–2075)	*0.0006*	104 (41–247)	*0.2403*
	Yes (1426)	796 (355–1753)		93 (41–232)	
Sitting SBP, mm Hg	≥121 (1982)	811 (359–1801)	*<0.0001*	91 (37–244)	*0.0002*
	<121 (1934)	974 (391–2159)		109 (44–260)	
Sitting heart rate, bpm	<72 (1717)	812 (359–1816)	*0.0008*	101 (42–234)	*0.9263*
	≥72 (2199)	941 (385–2138)		98 (39–248)	
Bilirubin, μmol/L	<10.26 (1713)	665 (309–1425)	*<0.0001*	76 (33–173)	*<0.0001*
	≥10.26 (2196)	1113 (471–2411)		129 (49–296)	
Creatinine, μmol/L	<107 (1932)	665 (293–1418)	*<0.0001*	76 (33–180)	*<0.0001*
	≥107 (1978)	1186 (502–2600)		134 (54–294)	
Aldosterone, ng/L	<101 (1897)	837 (359–1886)	*0.0046*	97 (42–234)	*0.5986*
	≥101 (1952)	953 (391–2065)		102 (39–250)	
PRA, ng/mL/h	<5.26 (1917)	948 (407–2050)	*0.0018*	119 (52–272)	*<0.0001*
	≥5.26 (1975)	845 (341–1922)		82 (33–207)	
Norepinephrine, ng/L	<394 (1928)	731 (314–1501)	*<0.0001*	78 (33–184)	*<0.0001*
	≥394 (1970)	1104 (469–2530)		129 (52–298)	
CRP, mg/L	<3.23 (1876)	755 (329–1627)	*<0.0001*	86 (38–207)	*<0.0001*
	≥3.23 (1915)	1057 (430–2404)		115 (44–278)	

Concentrations presented as median (Q1-Q3).
[a] Wilcoxon rank-sum test.

evaluated a separate addition of NT-proBNP or BNP to a model based on demographic, clinical, and echocardiographic variables with the likelihood-ratio test with 1 degree of freedom.

To compare the predictive value of BNP and NT-proBNP, ROC curves were generated for the main outcomes. Exploratory analyses were also carried out to compare the prognostic value of both natriuretic peptides for the 2 main adjudicated causes of death, sudden death from cardiac causes and death because of pump failure *(20)*. Pairwise comparisons of the areas under the curve (AUC) were conducted, following the procedure of Hanley and McNeil *(21)*.

All endpoints were adjudicated by an independent Endpoint Committee, blind to study treatment. All tests were made at a 2-sided, 5% significance level. Statistical

analyses were performed with SAS 8.2 (SAS Institute, Inc.).

Results

BASELINE CONCENTRATIONS OF NT-PROBNP AND BNP AND ASSOCIATION WITH CLINICAL VARIABLES

The median (25th-75th percentiles) concentration of NT-proBNP at baseline was 895 (375–1985) ng/L (n = 3916). Corresponding values for BNP were 99 ng/L (41–242). Pearson coefficient of correlation between baseline concentrations of NT-proBNP and BNP was 0.77 ($P < 0.0001$).

Plasma concentrations of NT-proBNP and BNP according to baseline clinical characteristics are presented in Table 1. NT-proBNP and BNP were significantly higher in older patients, and in patients with more symptomatic HF, more dilated LV and more severe LV dysfunction, lower body mass index (BMI), lower sitting arterial blood pressure, HF of ischemic etiology, or atrial fibrillation at study entry. The concentration of both peptides was also higher in patients with increased laboratory markers (creatinine and bilirubin) and neurohormones (plasma renin activity, norepinephrine, and C-reactive protein). There were no relevant differences between the univariate clinical correlates of NT-proBNP or BNP, except for beta-blocker use, sitting heart rate, and plasma aldosterone concentration (all nonsignificant for BNP).

Baseline log-transformed NT-proBNP or BNP concentrations correlated with age, LVEF, and LVIDd, with r^2 ranging from 0.02 to 0.12 ($P < 0.0001$, variables as continuous data). Fig. 1 compares the relationship between median NT-proBNP or BNP and these variables, categorized by quartiles. The trend was similar for both natriuretic peptides.

The strongest continuous relationship was found between log-transformed estimated glomerular filtration rate (eGFR) and NT-proBNP (Pearson CV −0.34, $P < 0.0001$) or BNP (−0.21, $P < 0.0001$). The relationship between median concentrations of NT-proBNP or BNP and eGFR showed a steeper increase of NT-proBNP compared with BNP in patients with reduced renal function (Fig. 2). However, the number of patients with eGFR <30 mL/min/m^2 was limited in this study (n = 59, 1.5% of the population).

The clinical variables that were independently associated with baseline concentrations of BNP or NT-proBNP (expressed as log-transformed data) were largely common to both peptides, with the exception of the use of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers (Table 2). Whereas NT-proBNP was independently associated with ACE inhibitors (positive relation) and beta-blockers (negative relation), no such associations were found with BNP. The factors with the strongest association were age, ischemic etiology, presence of atrial fibrillation, LV ejection fraction, and internal diameter.

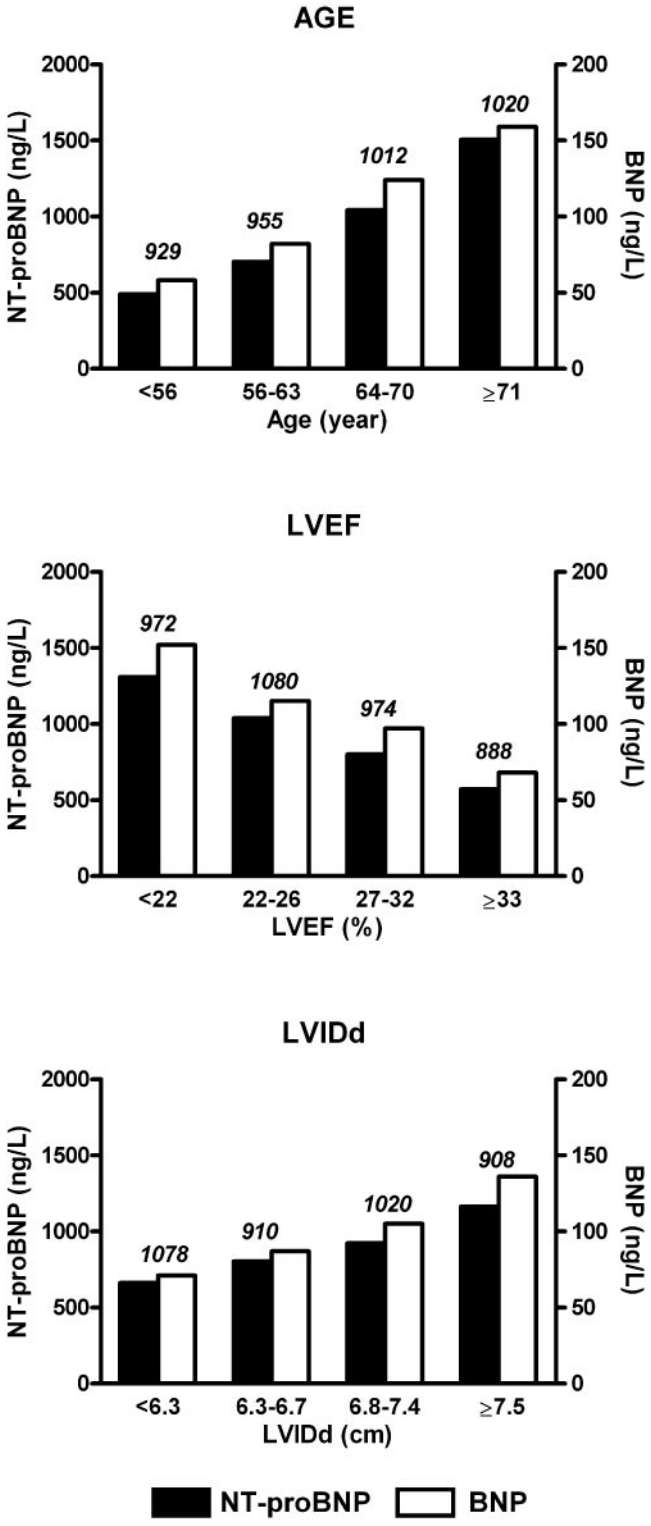


Fig. 1. Median concentrations of baseline NT-proBNP and BNP by quartiles of age, LVEF, and LVIDd.

Differences of median concentrations among quartiles were evaluated by the Kruskal–Wallis test and were significant for age, LVEF, and LVIDd for both peptides (all with $P < 0.00001$). Vertical scale is different for NT-proBNP (*black bars*) and BNP (*white bars*). The number of patients in each category is shown *above bars*.

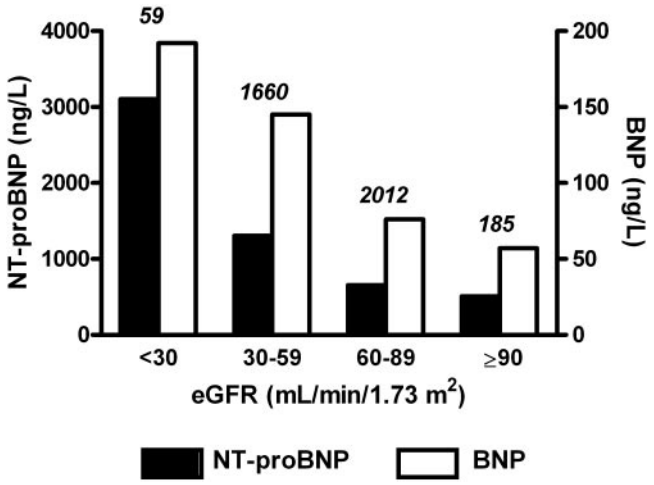


Fig. 2. Median plasma concentrations of NT-proBNP and BNP according to eGFR.

eGFR categories are based on the National Kidney Foundation classification of renal function. Vertical scale is different for NT-proBNP (*black bars*) and BNP (*white bars*). The number of patients in each category is shown *above bars*.

PROGNOSTIC VALUE OF BNP AND NT-PROBNP

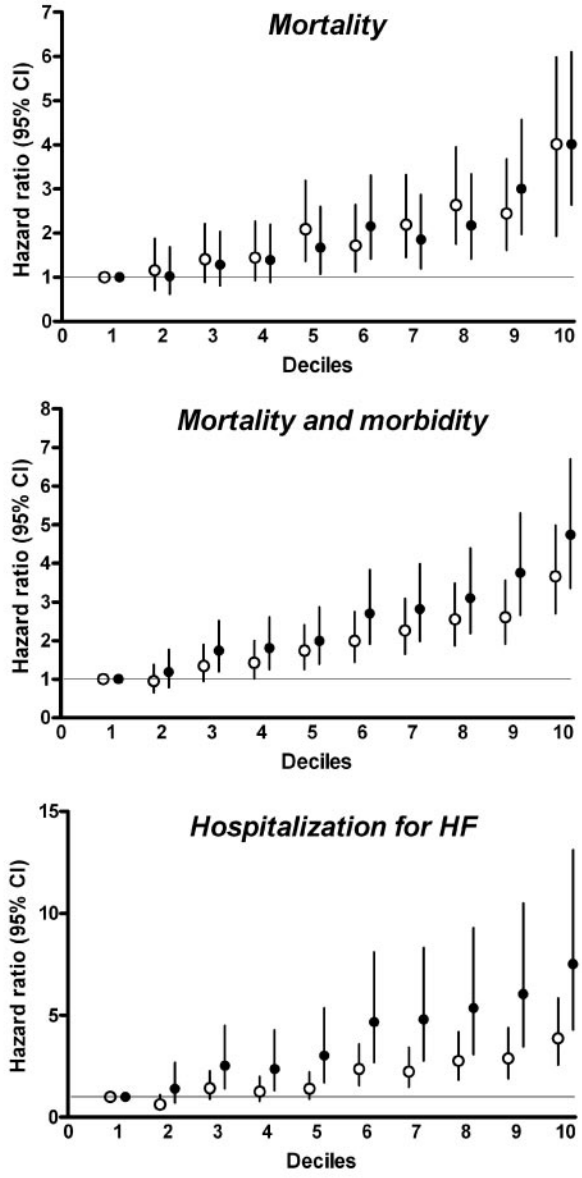
The adjusted hazard ratios for death, M&M, or hospitalization for HF according to baseline deciles of NT-proBNP and BNP are presented in Fig. 3. There was a similar progression in the probability of death with increasing plasma concentration of NT-proBNP or BNP, with hazard ratios in the tenth decile of 4.02 (2.63–6.11) and 4.02 (2.70–5.99), respectively. Corresponding values for M&M were 4.74 (3.36–6.70) and 3.67 (2.70–4.98). An apparent superiority of NT-proBNP over BNP for predicting the risk of hospitalization for patients with HF was observed across the whole range of concentrations. For instance, the relative risk of hospitalization for HF was higher in the tenth decile of NT-proBNP [7.51 (4.30–13.11)] compared with that of BNP [3.86 (2.56–5.84)], although 95% confidence intervals (CIs) always overlapped.

The independent prognostic values of baseline BNP or NT-proBNP were tested separately in Cox multivariable models that included the demographic, clinical, and echocardiographic variables with a statistically significant association with outcome at univariate analysis ($P < 0.05$). First, the natriuretic peptides and the other covariates were entered as categorical variables, dichotomized above or below the median value. In these models, NT-proBNP was the first predictor of outcome with hazard ratios (95% CI) of 2.07 (1.76–2.46) for mortality, 2.20 (1.92–2.51) for M&M, and of 2.66 (2.19–3.22) for hospitalization for HF (Fig. 4). Similarly, BNP resulted as the strongest independent predictor of mortality [1.87 (1.59–2.20)], M&M [2.05 (180–2.34)], and hospitalization for HF [2.48 (2.06–2.98)]. When the natriuretic peptides and appropriate covariates were considered as continuous variables, their prognostic value was consistent with the analysis based on median cutoff values. For instance, an increment of 500 ng/L of baseline NT-proBNP concentration corresponded to an increase of risk of 3.8% for mortality ($P < 0.0001$), whereas an increment of 50 ng/L of baseline BNP concentration corresponded to an increase of risk of 5.7% ($P < 0.0001$). Similarly, increases of risk for M&M were 3.5% and 5.4%, and 3.0% and 5.7% for hospitalization for HF, respectively ($P < 0.0001$ for all). Finally, the likelihood-ratio test showed that BNP or NT-proBNP provided significant incremental prognostic value for the prediction of all-cause mortality, M&M, and hospitalization for HF (all with $P < 0.0001$) compared with a model based on demographic, echocardiographic, and clinical variables.

The predictive values of NT-proBNP and BNP were compared by means of ROC curves (Table 3). The AUC (SE) for NT-proBNP (0.679 [0.011]) was marginally higher than for BNP (0.665 [0.001]; $P = 0.0734$) for predicting all-cause mortality. For M&M, NT-proBNP (AUC = 0.688 [0.009]) had a statistically significant higher predictive value than BNP [0.674 (0.009); $P = 0.0332$]. The same was

Table 2. Multivariable linear regression for the association with baseline $\log_e$ NT-proBNP, or $\log_e$ BNP.

Clinical variables	$\log_e$ NT-proBNP		$\log_e$ BNP	
	β regression coefficients (SE)	*P* value	β regression coefficients (SE)	*P* value
Age (+1 year)	0.0254 (0.0016)	<0.0001	0.0183 (0.0020)	<0.0001
BMI (+1 kg/m²)	−0.0637 (0.0036)	<0.0001	−0.0585 (0.0046)	<0.0001
NYHA (III–IV)	0.2477 (0.0332)	<0.0001	0.2086 (0.0420)	<0.0001
LVEF (+1%)	−0.0300 (0.0024)	<0.0001	−0.0235 (0.0030)	<0.0001
LVIDD (+1 cm)	0.2052 (0.0185)	<0.0001	0.2416 (0.0023)	<0.0001
Ischemic etiology (yes)			0.2429 (0.0423)	<0.0001
Atrial fibrillation (yes)	0.5416 (0.0509)	<0.0001	0.2575 (0.0634)	<0.0001
SBP (+1 mmHg)			0.0029 (0.0011)	0.0109
Heart rate (+1 bpm)	0.0087 (0.0013)	<0.0001		
Digoxin (yes)			−0.1405 (0.0443)	0.0015
Diuretics (yes)	0.2343 (0.0455)	<0.0001	0.2636 (0.0575)	<0.0001
ACE inhibitors (yes)	0.1741 (0.0621)	0.0051		
Beta-blockers (yes)	−0.1419 (0.0340)	<0.0001		
Bilirubin (+1 $\log_e$ μmol/L)	0.3601 (0.0330)	<0.0001	0.4346 (0.0418)	<0.0001
Creatinine (+1 $\log_e$ μmol/L)	0.8119 (0.0747)	<0.0001	0.4811 (0.0946)	<0.0001



BNP (ng/L)	<16	16-31	32-50	51-70	71-98	99-138	139-201	202-286	287-442	>442
NT-proBNP (ng/L)	<173	173-304	305-454	455-647	648-895	896-1187	1188-1632	1633-2376	2377-3863	>3863

Fig. 3. Adjusted hazard ratios for outcome by deciles of baseline concentrations of BNP or NT-proBNP.

Hazard ratio and 95% CI for BNP (*open symbols*) and NT-proBNP (*closed symbols*), adjusted for clinical, demographic, and echocardiographic covariates with significant univariate relationship with outcome ($P < 0.05$). The first decile of each peptide is considered as the reference category. Number of patients for each decile was 379 to 399.

true for hospitalization for HF [0.685 (0.011) vs 0.665 (0.012); $P = 0.0143$]. For a given peptide, optimum cutoff points were similar for main outcomes (Table 3). The concentrations of BNP at 95% of sensitivity were 18, 17, and 14 ng/L for mortality, M&M, and hospitalization for HF, respectively (Table 3). Corresponding values for NT-proBNP were 202, 208, and 250 ng/L. The concentrations of BNP at 95% of specificity were 531, 490, and 546 ng/L for mortality, M&M, and hospitalization for HF, respectively. Corresponding values for NT-proBNP were 4643, 4367, and 5015 ng/L. In exploratory analyses, the prognostic values of both peptides were compared according to adjudicated causes of death: whereas NT-proBNP was similar to BNP in predicting sudden death [399 events, AUC = 0.619 (0.015) vs 0.627 (0.015); $P = 0.47$, Fig. 5], results superior to BNP for the prediction of death from pump failure [191 events, AUC = 0.749 (0.017) vs 0.703 (0.019); $P = 0.0003$].

When patients were divided into clinical subgroups, NT-proBNP retained statistical superiority over BNP in males ($P = 0.018$ for all-cause mortality; $P = 0.044$ for hospitalization for HF, Table 4), in patients older than 70 years ($P < 0.0001$ for all-cause mortality; $P = 0.023$ for hospitalization for HF), or in patients with eGFR of 30 and 59 mL/min/1.73 m^2 ($P = 0.017$ for all-cause mortality; $P = 0.036$ for hospitalization for HF). BNP and NT-proBNP, however, performed similarly in females, in patients <70 years, in patients with eGFR 60–89 mL/min/1.73 m^2, in patients with or without diabetes, and in 3 classes of BMI index (Table 4).

Discussion

Our findings indicate that the hormone BNP and the inactive amino terminal fragment NT-proBNP exhibited parallel changes with age, LVEF, and LV diameter in patients with chronic and symptomatic HF. These peptides were the first independent predictors of outcome after adjustment for major confounding baseline clinical characteristics. However, a head-to-head comparison of their prognostic value showed that NT-proBNP performed slightly better than BNP in predicting outcome, in particular for death from pump failure and hospitalizations for HF. These results were obtained in a large and relatively heterogeneous population of well-characterized patients enrolled in a multicenter international clinical trial. They extend the results of several previous studies performed on smaller cohorts of patients, and often in single centers *(7, 11–13, 15)*. The biological relevance of the present observations will have to be confirmed in different clinical and/or analytical settings.

Relationships between NT-proBNP, BNP, and clinical severity

In this study we investigated the association of various demographic, clinical, and echocardiographic variables and baseline concentrations of natriuretic peptides with univariate and multivariable models. We concluded that the set of variables associated with plasma concentrations of NT-proBNP or BNP was essentially the same, with the exception of the use of ACE inhibitors and beta-blockers.

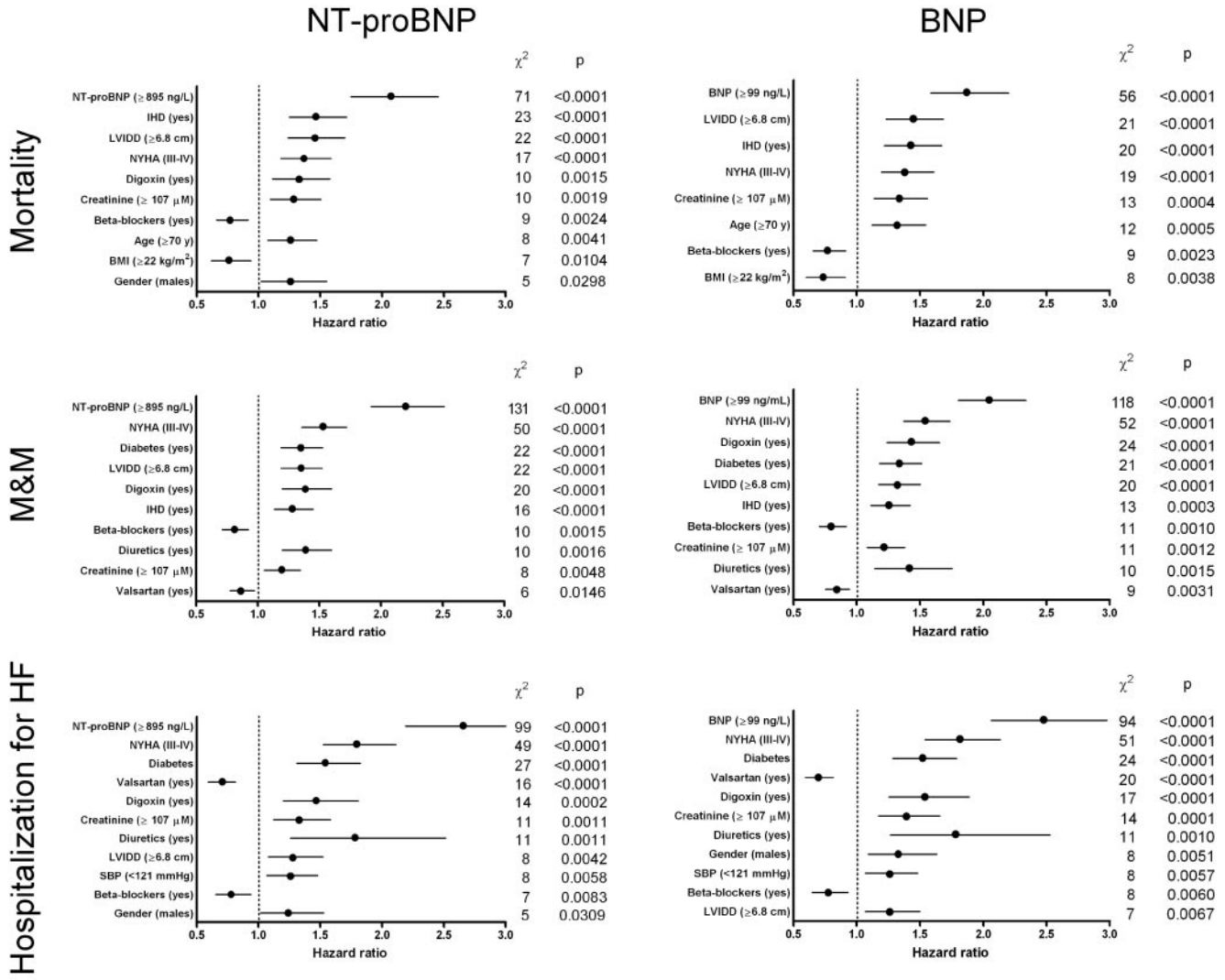


Fig. 4. Prognostic models for all-cause mortality, M&M, and hospitalization for HF based on Cox proportional hazard regression.

Analysis adjusted for baseline NT-proBNP or BNP and the demographic, clinical, and echocardiographic variables with a significant univariate relationship with outcome ($P < 0.05$). Data presented as hazard ratio and 95% CIs in decreasing order of χ^2.

The reason for this difference is unknown at present; however, recent studies have shown that the introduction of a beta-blocker (metoprolol) in patients with mild and stable HF raised the concentration of both C-terminal and N-terminal natriuretic peptides *(22–23)*. The strongest associations were found with age, ischemic etiology of

Table 3. Comparison of the prognostic performance of NT-proBNP and BNP for predicting outcome in patients with chronic heart failure.

	All-cause mortality, 758 events		Mortality and morbidity, 1194 events		Hospitalization for HF, 634 events	
	NT-proBNP	BNP	NT-proBNP	BNP	NT-proBNP	BNP
Optimal prognostic value, ng/L	1016	125	1007	125	1007	126
AUC (SE)	0.679 (0.011)	0.665 (0.011)	0.688 (0.009)	0.674 (0.009)	0.685 (0.011)	0.665 (0.012)
P value[a]	0.0734		0.0332		0.0143	
Sensitivity	0.666	0.636	0.658	0.621	0.699	0.648
Concentration at 95% sensitivity, ng/L	202	18	208	17	250	14
Specificity	0.600	0.620	0.630	0.650	0.590	0.620
Concentration at 95% specificity, ng/L	4643	531	4367	490	5015	546

AUC: area under the curve.

[a] *P* value for the comparison of AUC according to the test of Hanley and McNeil *(21)*.

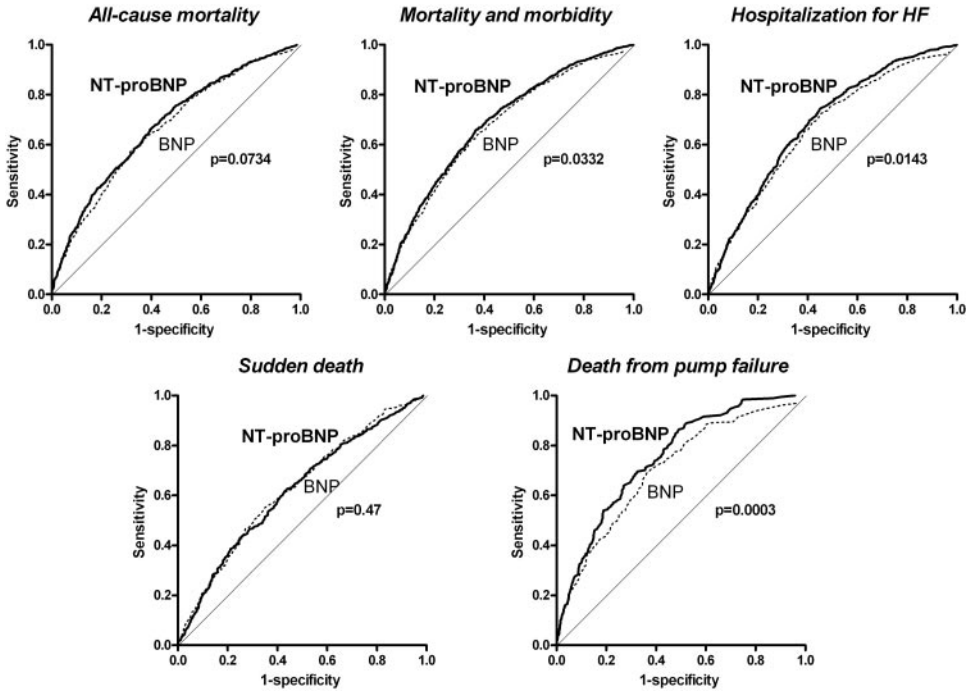


Fig. 5. ROC curves for NT-proBNP and BNP as markers of outcome.

NT-proBNP *as bold continuous lines*, BNP as *dashed lines*.

HF, presence of atrial fibrillation, LVEF, and LV internal diameter, as previously described *(24–26)*. Our data also concur with the conclusion of a comparative study performed in a large cohort of patients with stable ischemic heart disease in which LVEF, age, and renal function were the most powerful independent predictors of BNP and NT-proBNP *(8)*.

Among the continuous variables, the strongest association was found with renal function. Median concentrations of the natriuretic peptides increased progressively with renal dysfunction estimated as eGFR and categorized according to the classification of the National Kidney Foundation. This trend has been observed in patients presenting in emergency departments for dyspnea *(27)*. Decreased clearance from the kidney has been put forward to explain increased BNP in patients with HF *(28)*. Although the mechanisms of elimination of these 2 peptides might differ (BNP is mainly cleared by neutral endopeptidases and specific receptors, whereas renal excretion is currently regarded as the main clearance mechanism for NT-proBNP *(5)*, the increase of both peptides with lower eGFR suggests that the susceptibility of NT-proBNP concentrations to renal dysfunction was not, apparently, greater than that of BNP. We must remember, however, that the number of patients with severely compromised renal function (eGFR <30 mL/min/1.73 m^2) was limited in our study population, so this conclusion does not apply in such patients. This extends to previous

Table 4. Comparison of the area under the ROC curves of NT-proBNP and BNP for predicting outcome in selected clinical groups of patients with chronic heart failure.

Group	Patients, n	All-cause mortality			Hospitalization for HF		
		NT-proBNP	BNP	*P* value[a]	NT-proBNP	BNP	*P*[a]
Age, <70 years	2767	0.670 (0.014)	0.680 (0.013)	0.29	0.707 (0.014)	0.697 (0.014)	0.32
Age, ≥70 years	1149	0.660 (0.018)	0.611 (0.019)	<0.0001	0.619 (0.020)	0.587 (0.022)	0.023
Males	3139	0.684 (0.015)	0.665 (0.012)	0.018	0.0687 (0.013)	0.667 (0.013)	0.044
Females	777	0.662 (0.026)	0.667 (0.027)	0.81	0.671 (0.022)	0.665 (0.023)	0.70
eGFR 30–59 mL/min/1.73 m^2	1660	0.682 (0.015)	0.656 (0.015)	0.017	0.656 (0.016)	0.635 (0.017)	0.036
eGFR 60–89 mL/min/1.73 m^2	2012	0.650 (0.017)	0.657 (0.017)	0.60	0.674 (0.017)	0.661 (0.019)	0.22
Diabetes	1029	0.664 (0.020)	0.652 (0.020)	0.35	0.619 (0.020)	0.594 (0.021)	0.072
No diabetes	2887	0.683 (0.013)	0.669 (0.013)	0.14	0.707 (0.014)	0.669 (0.014)	0.40
BMI, <25 kg/m^2	1353	0.687 (0.017)	0.663 (0.017)	0.044	0.593 (0.075)	0.668 (0.074)	0.16
BMI, 25–30 kg/m^2	1734	0.678 (0.017)	0.661 (0.017)	0.17	0.656 (0.016)	0.635 (0.017)	0.099
BMI, >30 kg/m^2	829	0.619 (0.027)	0.643 (0.026)	0.19	0.674 (0.017)	0.661 (0.019)	0.29

[a] *P* value for the comparison of AUC according to the test of Hanley and McNeil *(21)*.

observations of patients with myocardial infarction and compensated renal dysfunction *(7)* and confirms recent studies that showed similar renal extraction of the 2 peptides in healthy volunteers and in patients with essential arterial hypertension *(29, 30)*.

PROGNOSTIC VALUE OF NT-PROBNP AND BNP IN HEART FAILURE

BNP and NT-proBNP are strong markers of outcome in chronic HF *(2, 17)*. The present analysis attests to their superiority compared with other variables, but also confirms the strength of several clinical variables (older age, diabetes, and lower LVEF) that have been powerful and independent predictors of mortality and morbidity in a large and contemporary population of patients with HF *(31)*. Few studies have directly compared the prognostic value of the 2 brain natriuretic peptides in patients with heart disease. Some have concluded that the 2 markers are substantially equivalent *(14, 15, 32)*. In patients with stable ischemic heart disease, Richards et al. *(8)* recently showed that both peptides independently predicted a composite clinical endpoint (1-year all-cause mortality or admission with HF) with almost overlapping, event-free survival curves. There are, however, some exceptions: BNP (but not NT-proANP or NT-proBNP) independently predicted sudden death in 382 patients with chronic HF *(33)*, whereas NT-proBNP (but not BNP) predicted symptom-free survival and postoperative outcome in patients with severe aortic stenosis *(34)*. Differences have also been observed in acute settings, for instance in response to short term exercise *(35)* or after intravenous infusion of Levosimendan *(36)*. In the present study, NT-proBNP performed better than BNP to predict death from pump failure and hospitalization for HF ($P = 0.0003$ and 0.0143 by univariate pairwise comparison, respectively). When patients were divided into clinical subgroups, NT-proBNP retained a statistical superiority over BNP in males, in patients over 70 years, or with eGFR of 30 to 59 mL/min/1.73 m^2. In univariate analysis, BNP and NT-proBNP performed similarly in females, in patients <70 years, or in patients with eGFR >60 mL/min/1.73 m^2. In addition, the prognostic value of BNP and NT-proBNP was similar in patients with or without diabetes and in different classes of BMI (lean, overweight, or obese). Several factors might, in principle, explain these differences. First, the longer estimated biological half-life of NT-proBNP compared with BNP (70 min vs ~20 min) *(37, 38)* renders the former less prone to short-term fluctuations that may confound the prognosis. This difference is corroborated by the relatively smaller intraindividual biological variation of NT-proBNP observed in patients with HF *(39)*. In the context of a large multicenter trial, preanalytical deviations from the protocol during blood collection, plasma processing, and storage would also have a greater detrimental impact on BNP than on NT-proBNP. Second, differences in the analytical performance of the methods used to measure BNP and NT-proBNP could influence their respective prognostic value, although the impact of assay imprecision on the performance of cardiac biomarkers for diagnosis seems not to be critical *(40)*. The IRMA used in the present study to measure BNP showed slightly higher analytical variability than the automated method for NT-proBNP; this could further reduce the prognostic performance of BNP. It is important to note that immunoreactive moiety detected by any given immunoassay depends on the combined influence of circulating forms of NT-proBNP and BNP, the degree and rate at which they are degraded from amino and/or C-terminals, and (most importantly) the epitope(s) to which polyclonal or monoclonal antibodies have been raised *(41)*. Indeed, recent studies demonstrated that the clinical results (including the reference interval and decisional cutoff values) of BNP and NT-proBNP assays are method-dependent *(42)*. For these reasons, the analytical performance and clinical accuracy of any single immunoassay should be assessed in each laboratory. Third, it cannot be excluded that different relationships between NT-proBNP or BNP and some clinical characteristics not considered in the present analysis might explain our data. Finally, the large study population (3916) might have revealed subtle differences in the prognostic performance of the 2 peptides not detectable in smaller populations.

The relatively modest prognostic accuracy of BNP and NT-proBNP in the present study (AUCs of 0.66 to 0.75, sensitivity and specificity of 0.590 to 0.696) might result from the fact that our population included only patients with stable, chronic, and symptomatic mild-to-moderate HF, with LV systolic dysfunction (LVEF <40%). Effective neurohormone suppression with background therapy might also have limited the prognostic performance of these markers.

In conclusion, we report a small, but statistically significant difference in the predictive value of 2 related natriuretic peptides in a well-characterized and large population of patients with chronic and symptomatic HF.

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References

1. Clerico A, Emdin M. Diagnostic accuracy and prognostic relevance of the measurement of cardiac natriuretic peptides: a review. Clin Chem 2004;50:33–50.
2. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. Br Med J 2005;330:625.
3. Anand IS, Florea VG, Fisher L. Surrogate end points in heart failure. J Am Coll Cardiol 2002;39:1414–21.
4. Cohn JN, Quyyumi AA, Hollenberg NK, Jamerson KA. Surrogate markers for cardiovascular disease: functional markers. Circulation 2004;109:IV31–46.
5. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. Eur J Heart Fail 2004;15;6:257–60.
6. Masson S, Vago T, Baldi G, Salio M, De Angelis N, Nicolis E, et al. Comparative measurement of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in ambulatory patients with heart failure. Clin Chem Lab Med 2002;40:761–3.
7. Luchner A, Hengstenberg C, Löwel H, Riegger GAJ, Schunkert H, Holmer S. Effect of compensated renal dysfunction on approved heart failure markers: direct comparison of brain natriuretic peptide (BNP) and N-terminal pro-BNP. Hypertension 2005;46:118–23.
8. Richards M, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, et al. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischemic heart disease. J Am Coll Cardiol 2006;47:52–60.
9. Costello-Boerrigter LC, Boerrigter G, Redfield MR, Rodeheffer RJ, Urban LH, Mahoney DW, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. J Am Coll Cardiol 2006;47:345–53.
10. Hammerer-Lercher A, Neubauer E, Muller S, Pachinger O, Puschendorf B, Mair J. Head-to-head comparison of N-terminal pro-brain natriuretic peptide, brain natriuretic peptide, and N-terminal pro-atrial natriuretic peptide in diagnosing left ventricular dysfunction. Clin Chim Acta 2001;310:193–7.
11. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and N-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. J Am Coll Cardiol 2003;42:728–35.
12. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Head-to-head comparison of the diagnostic utility of BNP and NT-proBNP in symptomatic and asymptomatic structural heart disease. Clin Chim Acta 2004;341:41–8.
13. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T, et al. The diagnostic accuracy of plasma BNP and NT-proBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. Eur J Heart Fail 2005;7:537–41.
14. Alehagen U, Lindstedt G, Levin LA, Dahlstrom U. Risk of cardiovascular death in elderly patients with possible heart failure. B-type natriuretic peptide (BNP) and the aminoterminal fragment of ProBNP (N-terminal proBNP) as prognostic indicators in a 6-year follow-up of a primary care population. Int J Cardiol 2005;100:125–33.
15. Hülsmann M, Berger R, Mörtl D, Gore O, Meyer B, Pacher R. Incidence of normal values of natriuretic peptides in patients with chronic heart failure and impact on survival: a direct comparison of N-terminal atrial natriuretic peptide, N-terminal brain natriuretic peptide, and brain natriuretic peptide. Eur J Heart Fail 2005;7:552–6.
16. Latini R, Masson S, Anand I, Judd D, Maggioni AP, Chiang YT, et al. Effects of valsartan on circulating brain natriuretic peptide and norepinephrine in symptomatic chronic heart failure: the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2002;106:2454–8.
17. Latini R, Masson S, Anand I, Salio M, Hester A, Judd D, et al. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. Eur Heart J 2004;25:292–9.
18. Cohn JN, Anand IS, Latini R, Masson S, Chiang YT, Glazer R; Valsartan Heart Failure Trial Investigators. Sustained reduction of aldosterone in response to the angiotensin receptor blocker Valsartan in patients with chronic heart failure: results from the Valsartan Heart Failure Trial. Circulation 2003;108:1306–9.
19. Anand IS, Latini R, Florea VG, Kuskowski MA, Rector T, Masson S, et al. C-reactive protein in heart failure: prognostic value and the effect of Valsartan. Circulation 2005;112:1428–34.
20. Cohn JN, Tognoni G, and the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667–75.
21. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839–43.
22. Davis ME, Richards AM, Nicholls MG, Yandle TG, Frampton CM, Troughton RW. Introduction of metoprolol increases plasma B-type cardiac natriuretic peptides in mild, stable heart failure. Circulation 2006;113:977–85.
23. The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy: the randomized evaluation of strategies for left ventricular dysfunction pilot study. Circulation 2000;101:378–84.
24. Hogenhuis J, Voors AA, Jaarsma T, Hillege HL, Boomsma F, van Veldhuisen DJ. Influence of age on natriuretic peptides in patients with chronic heart failure: a comparison between ANP/NT-ANP and BNP/NT-proBNP. Eur J Heart Fail 2005;7:81–6.
25. Kjaer A, Hildebrandt P, Appel J, Petersen CL. Neurohormones as markers of right- and left-sided cardiac dimensions and function in patients with untreated chronic heart failure. Int J Cardiol 2005;99:301–6.
26. Luchner A, Hengstenberg C, Lowel H, Buchner S, Schunkert H, Riegger GA, et al. NT-proBNP in outpatients after myocardial infarction: interaction between symptoms and left ventricular function and optimized cut-points. J Card Fail 2005;11:21–7.
27. Chenevier-Gobeaux C, Claessens YE, Voyer S, Desmoulins D, Ekindjian OG. Influence of renal function on N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients admitted for dyspnoea in the emergency department: comparison with brain natriuretic peptide (BNP). Clin Chim Acta 2005;361:167–75.
28. Tsutamoto T, Wada A, Sakai A, Ishikawa C, Tanaka T, Hayashi M, et al. Relationship between renal function and plasma natriuretic peptide in patients with heat failure. J Am Coll Cardiol 2006;47:582–6.
29. Schou M, Dalsgaard MK, Clemmesen O, Dawson EA, Yoshiga CC, Nielsen HB, et al. Kidneys extract BNP and NT-proBNP in healthy young men. J Appl Physiol 2005;99:1676–80.
30. Goetze JP, Jensen G, Moller S, Bendtsen F, Rehfeld JF, Henriksen JH. BNP and N-terminal proBNP are both extracted in the normal kidney. Eur J Clin Invest 2006;36:8–15.
31. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJV, Swedberg KB, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006;27:65–75.
32. Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, et al. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. Circulation 2003;107:2786–92.
33. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, et

al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation 2002;105:2392–7.

34. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, et al. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. Circulation 2004;109:2302–8.

35. Wijbenga JA, Balk AH, Boomsma F, Man in 't Veld AJ, Hall C. Cardiac peptides differ in their response to exercise: implications for patients with heart failure in clinical practice. Eur Heart J 1999;20:1424–8.

36. Gegenhuber A, Mueller T, Firlinger F, Lenz K, Poelz W, Haltmayer M. Time course of B-type natriuretic peptide (BNP) and N-terminal proBNP changes in patients with decompensated heart failure. Clin Chem 2004;50:454–6.

37. Pemberton CJ, Johnson ML, Yandle TG, Espiner EA. Deconvolution analysis of cardiac natriuretic peptides during acute volume overload. Hypertension 2000;36:355–9.

38. Richards AM, Crozier IG, Holmes SJ, Espiner EA, Yandle TG, Frampton C. Brain natriuretic peptide: natriuretic and endocrine effects in essential hypertension. J Hypertens 1993;11:163–70.

39. Bruins S, Fokkema MR, Romer JW, Dejongste MJ, van der Dijs FP, van den Ouweland JM, et al. High intraindividual variation of B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with stable chronic heart failure. Clin Chem 2004;50:2052–8.

40. Kupchak P, Wu AH, Ghani F, Newby LK, Ohman EM, Christenson RH. Influence of imprecision on ROC curve analysis for cardiac markers. Clin Chem 2006;52:752–3.

41. Clerico A, Del Ry S, Giannessi D. Measurement of cardiac natriuretic hormones (atrial natriuretic peptide, brain natriuretic peptide, and related peptides) in clinical practice: the need for a new generation of immunoassay methods. Clin Chem 2000;46:1529–34.

42. Panteghini M, Clerico A. Understanding the clinical biochemistry of N-terminal pro-B-type natriuretic peptide: the prerequisite for its optimal clinical use. Clin Lab 2004;50:325–31.