Comparison of Brain Natriuretic Peptide (BNP) and Amino-Terminal ProBNP for Early Diagnosis of Heart Failure

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Background: We compared the diagnostic accuracy of brain natriuretic peptide (BNP) and amino-terminal proBNP (NT-proBNP) for diagnosis of preclinical and mild heart failure (HF).

Methods: We assayed plasma NT-proBNP and BNP in 182 healthy controls and in a prospective cohort of 820 HF patients divided according to the American Heart Association/American College of Cardiology classification. These included 86 patients in stage A [mean (SE) ejection fraction 61% (1%); mean (SE) age 47 (2) years], 255 in stage B [65% (2%); 62 (1) years], 420 patients in stage C [35% (1%); 68 (1) years] and 59 in stage D [25% (1%); 74 (1) years]. Diagnostic accuracies of BNP and NT-proBNP were evaluated by ROC analysis, and a multivariate linear regression model was applied to predict HF staging.

Results: Median BNP and NT-proBNP concentrations increased from stage A to D 57-fold and 107-fold, respectively. Both assays were accurate (*P* <0.001) in separating stage B from controls or stage A, and stage C from controls or stage A or B. NT-proBNP was more accurate (*P* <0.001) than BNP in differentiating stage C from stages A and B patients and controls and was a better predictor of HF classification in a model including age, sex, and renal function (*P* <0.001).

Conclusions: Monitoring BNP or NT-proBNP enabled identification of asymptomatic patients at risk for the development of HF. NT-proBNP showed better accuracy than BNP for identifying mild HF.

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The role of natriuretic hormones in identification of asymptomatic ventricular dysfunction remains to be clarified *(1, 2)*. Brain natriuretic peptide (BNP)[3] and amino-terminal pro–brain natriuretic peptide (NT-proBNP) assays have been confirmed to be useful *(2)* for screening of heart disease *(3)*, stratification of patients with heart failure (HF) *(4, 5)*, detection of left ventricular systolic and/or diastolic dysfunction *(2)*, and differential diagnosis of dyspnea *(6, 7)*. The use of BNP and NT-proBNP for ruling out noncardiac dyspnea in HF assessment was proposed by recent American and European guidelines *(8–11)*.

Because BNP and NT-proBNP show different biochemical and physiological characteristics, monitoring BNP and NT-proBNP may give different clinical results *(1, 2, 12, 13)*. A few studies have shown conflicting results regarding the diagnostic accuracy of BNP and NT-proBNP in patients with chronic stable *(14–25)* and acute *(26–35)* HF. These studies show wide heterogeneity of the BNP and NT-proBNP immunoassays used, clinical characteristics of patients, clinical end-points, and clinical standards used for HF diagnosis, but all of the studies used the New York Heart Association (NYHA) classification for the stages of HF.

The American Heart Association/American College of Cardiology (AHA/ACC) task force for the diagnosis and

[3] Nonstandard abbreviations: BNP, brain natriuretic peptide; NT-proBNP, amino-terminal pro–BNP; HF, heart failure; NYHA, New York Heart Association; AHA/ACC, American Heart Association/American College of Cardiology; EF, ejection fraction; ECLIA, electrochemiluminescence immunoassay; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; c-s, c-statistic; NS, not significant.

management of chronic HF has proposed a new classification, updated in 2005 (11), focusing on the preclinical evolution of the disease. In this classification, stage A includes asymptomatic patients at risk for developing HF with no structural cardiac involvement, stage B includes asymptomatic patients at risk for developing HF with structural cardiac involvement, stage C includes patients with past/current symptoms of HF associated with structural heart disease, and stage D includes symptomatic patients with end-stage disease requiring specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care. This classification is intended to complement the NYHA classification, which primarily gauges the severity of symptoms in stage C or D patients.

Our aim was to compare the diagnostic accuracy of BNP and NT-proBNP assays across a wide variety of patient populations, from asymptomatic individuals with clinical conditions that put them at risk for HF (AHA/ACC stage A–B), to patients with no, mild, or severe symptoms associated with mild-to-severe systolic dysfunction (C–D).

Materials and Methods

PATIENTS

From February 1998 to January 2006 we prospectively evaluated 820 consecutive patients referred to our cardiovascular medicine department for the evaluation of risk or presence of HF. The diagnosis of HF was determined in accordance with the ESC and AHA/ACC recommendations (9–11). Cardiac morphology and function were assessed by 2-dimensional echocardiography. All patients were stratified according to AHA/ACC classification. Stage C and D patients were stratified according to NYHA class and left ventricular ejection fraction (EF) (9–11). Diagnosis of HF and classification of AHA/ACC HF stages A through D, determined by history, symptoms, and physical and instrumental findings for the assessment of structural myocardial involvement, were established by expert cardiologists blind to BNP and NT-proBNP findings.

A control group, n = 182 healthy individuals, was free from disease and denied drug intake during the 4 weeks before the study. In controls ≥50 years old, an echocardiogram and an effort stress test were performed to exclude asymptomatic heart disease.

The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by our Institutional Ethics Committee. Informed consent was obtained from all participants enrolled in the study.

BNP AND NT-PROBNP ASSAYS

Blood was collected between 8 AM and 9 AM from study participants after they had fasted overnight and rested in a supine position for 20 min. Immediately after collection, samples (8–10 mL) were placed in ice-chilled disposable polypropylene tubes containing aprotinin (500 000 IU/L

of plasma) and EDTA (1 g/L of plasma). Plasma samples were obtained shortly after venipuncture by centrifugation at 1500g for 15 min at 4 °C and, if not assayed immediately, were frozen and stored at −20 °C in 0.5-mL aliquots in polypropylene tubes. Both assays were performed within 1 month of sample collection.

NT-proBNP was measured by the Elecsys® 2010 analyzer (Roche Diagnostics) (12, 13) and BNP was measured with the 2-site IRMA method (Shionoria BNP), as described previously (12, 13). The analytical performance of electrochemiluminescence immunoassay (ECLIA) and IRMA methods, as tested in our laboratory, was previously reported in detail (12, 13). Total imprecisions were 4.0% (103 ng/L) and 3.8% (601 ng/L), respectively. For BNP, total imprecision was 11.0% (5 ng/L) and 9.0% (58 ng/L), respectively. The person executing and reading the tests was blind to clinical diagnosis.

STATISTICAL ANALYSIS

Statistical analysis was carried out using the SPSS 12.0 software (SPSS). Because BNP and NT-proBNP values do not show gaussian distribution in healthy individuals or in patients with HF (1, 2, 12, 13), natural logarithmic transformation of data was used for statistical analysis. Both the original (using nonparametric tests) and the logarithmically transformed (using parametric tests) data were used for statistical analysis, but only the results obtained with parametric tests after log transformation were reported here, because the parametric approach showed the same trend but with greater statistical power than the respective nonparametric tests. Differences among independent groups were analyzed by ANOVA. Linear regression analysis was performed to assess the relationship among peptides and other variables. The diagnostic accuracy of BNP and NT-proBNP was quantified in terms of area under the ROC curves. A significant difference in the area under the curve (AUC) defined the increment in predictive power between different models. ROC curve analysis furnished optimum cutoff values of BNP and NT-proBNP concentrations (at the point of ROC corresponding to maximal sum of specificity and sensitivity), as well as corresponding sensitivity, specificity, and positive and negative predictive value (PPV and NPV, respectively).

The statistical significance of AUC differences between BNP and NT-proBNP findings for each comparison were also computed by comparing AUC values and the SE.

To tease out the influence of age, sex, and renal function (estimated creatinine clearance by the Cockroft–Gault formula) as confounders of the relationship with NT-proBNP and BNP vs HF classification, a multiple logistic regression model was also used. The overall c-statistic (c-s) of the model was computed to assess the respective influence of either NT-proBNP or BNP. $P < 0.05$ was considered significant.

Table 1. Demographic and clinical characteristics of patients classified according to the AHA/ACC heart failure classification scheme.[a]

	Stage A (86 patients)	Stage B (255 patients)	Stage C (420 patients)	Stage D (59 patients)
Age, (years)	47 (2)	62 (1)	67 (1)	74 (1)
Sex, % males	56	50	54	77
BMI	27 (1)	28 (1)	27 (1)	25 (2)
HT, (%)	90	73	47	39
Diabetes, (%)	10	13	26	25
IHD, (%)	0	12	40	49
AF, (%)	4	17	41	72
CrCl <60 mL/min, %	4	17	41	72
EF, (%)	61 (1)	65 (4)	32 (1)	26 (1)
BNP, (ng/L)	11 (5–19)	20 (10–40)	165 (52–378)	404 (182–1012)
NT-proBNP, (ng/L)	43 (26–85)	88 (43–224)	1136 (379–2824)	4394 (1467–10 184)

[a] Age [mean (SE)], body mass index [BMI; mean (SE)], arterial hypertension (HT), creatinine clearance by Cockroft–Gault formula, ischemic heart disease (IHD), atrial fibrillation (AF), left ventricular EF [mean (SE)], BNP and NT-proBNP values (median, 25th–75th percentile) in patients (pts) classified according to AHA/ACC classification *(11)*.

Results

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

Characteristics of patients in various HF stages, as well as corresponding BNP and NT-proBNP concentrations, are summarized in Table 1. The stage A group included 86 patients [mean (SE) age 47 (2) years, range 15–84 years] who had normal left ventricular systolic and diastolic function but were affected by risk factors and/or clinical conditions prone to HF, including arterial hypertension and diabetes mellitus, but had no evidence of cardiac structural involvement at echocardiographic evaluation. The stage B group included 255 patients [age 62 (1) years, range 25–90 years] with structural alterations (including left ventricular hypertrophy and/or diastolic dysfunction) but without HF symptoms or left ventricular systolic dysfunction. Associated clinical conditions were arterial hypertension, diabetes mellitus, ischemic heart disease, and cardiac valve abnormalities. The stage C and D group included 479 patients [age 68 (1) years, range 24–94 years; 77% males] with a history of symptoms of HF and an EF <50% [mean (SE) 32% (1%)]; 420 patients were in stage C with past or current symptoms of HF associated with underlying structural heart disease [age 67 (1) years, range 24–94 years], and 59 patients were in stage D with symptomatic end-stage disease requiring specialized treatment strategies [age 74 (1) years, range 41–91 years)]. Underlying cardiac diseases in the C and D patients were idiopathic dilated cardiomyopathy in 230 patients (48%), ischemic cardiomyopathy in 199 patients (42%), and cardiomyopathy secondary to other diseases in 50 patients (10%) [including systemic arterial hypertension (n = 15), cardiac valve abnormalities (n = 14), cardiotoxicity after chemotherapy (n = 5), myopathies (n = 4), diabetes mellitus (n = 3), alcohol consumption (n = 3), myocarditis (n = 3), congenital cardiac abnormalities (n = 1), amyloidosis (n = 1), and chronic constrictive pericarditis (n = 1)]. NYHA classification of the stage C and D patients was NYHA I, 54 patients, 12%; NYHA II, 224 patients, 47%; NYHA III, 137 patients, 29%; and NYHA IV, 59 patients, 12%.

Table 2. Demographic and clinical characteristics of Stage C and D patients classified according to NYHA classification and left ventricular ejection fraction value [EF; mean ± (SE)].[a]

	NYHA I–II EF > 35–50% (139 patients)	NYHA I–II EF < 35% (138 patients)	NYHA III–IV EF > 35–50% (51 patients)	NYHA III–IV EF < 35% (151 patients)
Age, years	61 (1)	62 (1)	68 (2)	70 (1)
Sex, % males	79	80	77	74
BMI	27 (1)	27 (1)	27 (1)	26 (1)
Diabetes, (%)	24	20	23	30
IHD, (%)	37	32	45	52
CrCl <60 mL/min, %	21	28	43	59
AF, (%)	5	12	18	15
EF, (%)	41 (1)	27 (1)	41 (1)	25 (1)
BNP, (ng/L)	59 (23–135)	208 (82–290)	342 (183–608)	399 (179–775)
NT-proBNP, (ng/L)	408 (184–1128)	1324 (568–2357)	3122 (1187–6746)	2994 (1269–6467)

[a] Age [mean ± (SE)], body mass index [BMI; mean ± (SE)], creatinine clearance by Cockroft–Gault formula, ischemic heart disease (IHD), atrial fibrillation (AF), BNP and NT-proBNP values (median, 25th–75th percentile) in stage C/D patients (pts) classified according to NYHA class and EF value.
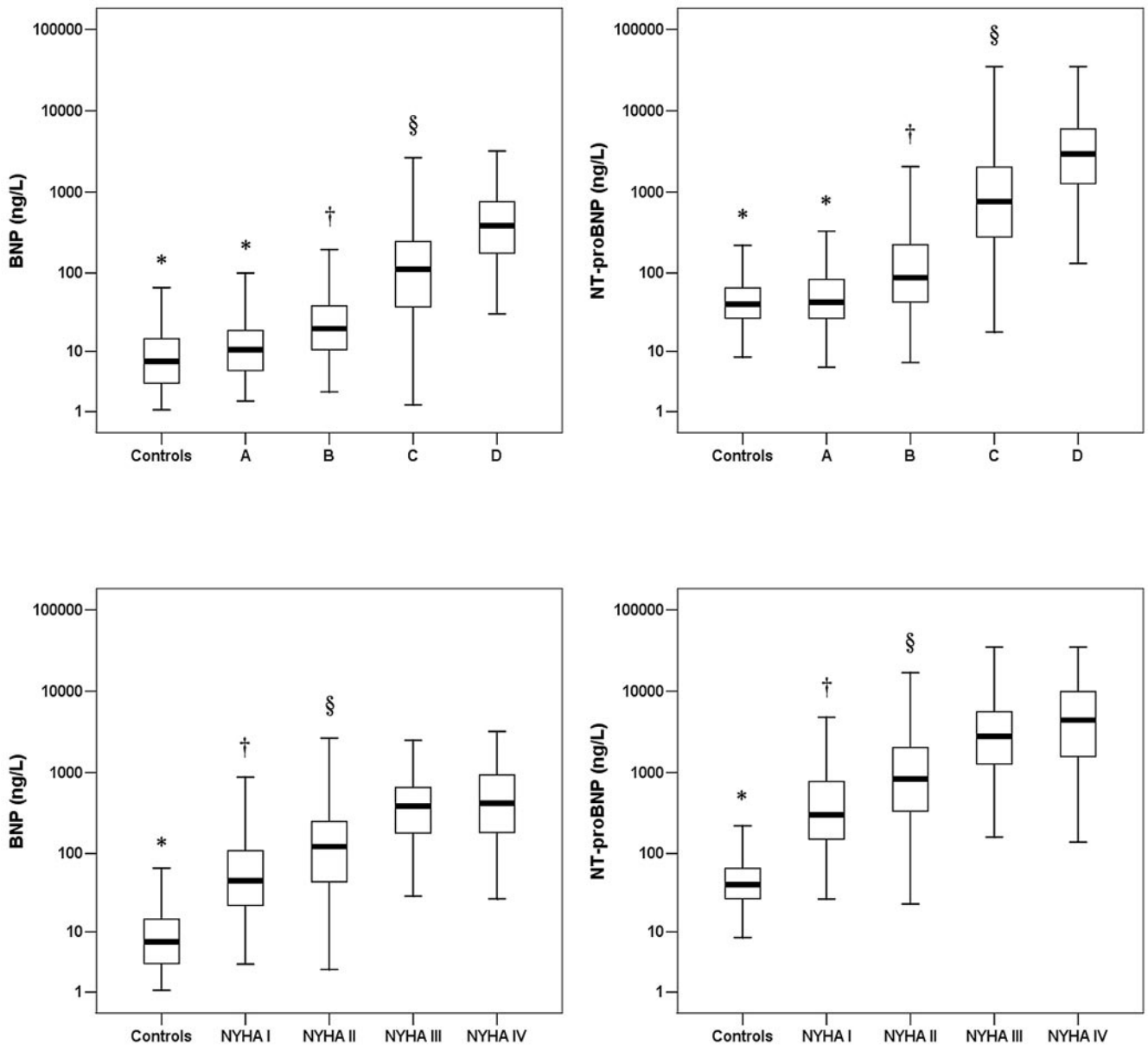
Fig. 1. Plasma BNP (*left*) and NT-proBNP (*right*) concentrations in (*top panel*) 182 controls and 820 patients with stages A–D of HF and controls; (*bottom panel*) 479 stage C–D patients grouped according to NYHA class.

The 10th, 25th, 50th (median), 75th, and 90th percentiles are indicated as *boxes* and *lines*. Note that the peptide concentrations are reported in log scale. Significant differences among different stages are also reported: *top panels*, * = P <0.001 vs B, C, D; † = P <0.001 vs C, D; § = P <0.001 vs D; *bottom panels*, * = P <0.001 vs NYHA I, II, III, IV; † = P <0.001 vs NYHA II, III, IV; § = P <0.001 vs NYHA III, IV.

Patients were stratified according to the disease severity by NYHA classification with corresponding BNP and NT-proBNP concentrations (Table 2). EF values were 35%–50% for 190 patients and <35% for 289 patients. Therefore, stage C and D patients were further divided into 4 groups according to NYHA class and EF: (*a*) 139 with no/mild symptoms (NYHA I–II) and mild systolic dysfunction (EF 35%–50%), (*b*) 138 with no/mild symptoms (NYHA I–II) and severe systolic dysfunction (EF <35%), (*c*) 51 with severe symptoms and mild systolic dysfunction, and (*d*) 151 with severe symptoms and severe systolic dysfunction.

Patient medications included monotherapy or polytherapy with calcium blockers, β-blockers, diuretics, or angiotensin-converting enzyme inhibitors; 58% of stage A patients and 10% of stage B patients were free of medications. All stage C and D patients were treated with restriction of water and sodium intake and multidrug treatment (furosemide, 72% of patients; angiotensin-converting enzyme inhibitor or angiotensin-receptor blockers, 90%; carvedilol/bisoprolol, 63%; spironolactone, 49%) not stopped at the time of the study, for obvious ethical reasons. In stage D patients, blood sampling for BNP and NT-proBNP assays was obtained at hospital admission,

before the initiation of inotropic and vasodilatory intravenous support. The control group included 182 healthy individuals [mean (SE) age 60 (2) years, range 18–85 years; 56% males].

PEPTIDE CONCENTRATIONS IN CONTROLS AND PATIENTS STRATIFIED ACCORDING TO STRUCTURAL STAGES A–D AND NYHA CLASSIFICATION

Log-transformed concentrations of plasma BNP and NT-proBNP were significantly correlated (logNT-proBNP = 1.67 + 1.05 logBNP, n = 992, R =0.945, P <0.0001). Both BNP and NT-proBNP concentrations increased progressively (P <0.001) from stage A to stage D (Fig. 1, *top panel*), whereas no difference was found between controls and stage A concentrations. NT-proBNP showed a greater increase than BNP values (P <0.001). Compared with controls, median NT-proBNP concentrations increased by 28- and 107-fold in stages C and D, respectively, and BNP concentrations increased 20- and 57-fold, respectively. Similar progressive increases in plasma concentrations were observed when BNP and NT-proBNP were plotted according to NYHA classifications in C and D patients (Fig. 1, *bottom panel*). For both assays the control group concentrations were significantly lower (P <0.001) than those in patients at all NYHA stages. Furthermore, for both assays significant differences (P <0.001) were found among all NYHA class values.

EVALUATION AND COMPARISON OF DIAGNOSTIC ACCURACY OF BNP AND NT-PROBNP ASSAYS: DIAGNOSIS OF EARLY ASYMPTOMATIC HF

Both BNP and NT-proBNP did not show significant diagnostic accuracy for differentiating stage A patients from controls [Table 3 and Fig. 2, *top left panel*, BNP, mean (SE): ROC AUC 0.604 (0.038) vs NT-proBNP: AUC 0.531 (0.038)]. The diagnostic accuracies of both BNP and NT-proBNP were significant (P <0.001), and comparable, for separating stage B patients from controls [Fig. 2, *top center panel*, BNP, AUC 0.768 (0.022) vs NT-proBNP: AUC 0.750 (0.023)] and stage A patients [Fig. 2, *top right panel*, BNP, AUC 0.679 (0.031) vs NT-proBNP: AUC 0.696 (0.030)].

Both BNP and NT-proBNP showed significant (P <0.001) and comparable accuracy in diagnosing mild left ventricular diastolic dysfunction [153 patients (60%) with altered relaxation, early-to-late phase ratio <1, deceleration time >220 ms, isovolumetric relaxation >110 ms] in stage B patients [BNP: AUC 0.761 (0.026), cutoff 21 ng/L, sensitivity 49%, specificity 88%, PPV 55%, NPV 73% vs NT-proBNP: AUC 0.748 (0.027), cutoff 21 ng/L, sensitivity 60%, specificity 82%, PPV 53%, NPV 77%, not significant (NS)].

EVALUATION AND COMPARISON OF DIAGNOSTIC ACCURACIES OF BNP AND NT-PROBNP ASSAYS: DIAGNOSIS OF SYMPTOMATIC HF

The diagnostic accuracies of both BNP and NT-proBNP were significant in patients with symptomatic HF

Table 3. Comparison of the diagnostic accuracy between BNP and NT-proBNP assays.[a]

Comparison	Assay	AUC, mean (SE)	Diagnostic accuracy, P value	Cut-off, ng/L	Sensitivity, %	Specificity, %	PPV, %	NPV, %	BNP vs NT-proBNP comparison, P value
Stage A vs controls	BNP	0.604 (0.038)	NS	9	60	58	41	76	NS
	NT-proBNP	0.531 (0.038)	NS	55	44	69	41	63	
Stage B vs controls	BNP	0.768 (0.022)	P <0.001	13	69	67	75	61	NS
	NT-proBNP	0.750 (0.023)	P <0.001	70	60	81	82	60	
Stage A vs stage B	BNP	0.679 (0.031)	P <0.001	13	68	63	85	41	NS
	NT-proBNP	0.696 (0.030)	P <0.001	68	60	70	86	38	
Stage C vs controls	BNP	0.941 (0.009)	P <0.001	26	85	93	97	74	P <0.001
	NT-proBNP	0.974 (0.006)	P <0.001	122	93	95	97	87	
Stage C vs stage A	BNP	0.908 (0.013)	P <0.001	28	85	84	96	54	P <0.001
	NT-proBNP	0.956 (0.008)	P <0.001	195	86	93	98	61	
Stage C vs stage B	BNP	0.840 (0.015)	P <0.001	44	79	78	86	69	P <0.001
	NT-proBNP	0.880 (0.013)	P <0.001	264	82	80	86	75	
Stage C (NYHA I–II, EF 35%–50%) vs controls	BNP	0.870 (0.021)	P <0.001	21	75	88	81	84	P <0.001
	NT-proBNP	0.939 (0.015)	P <0.001	100	86	91	86	91	
Stage C (NYHA I–II, EF <35%) vs controls	BNP	0.960 (0.012)	P <0.001	26	89	93	90	93	P <0.05
	NT-proBNP	0.989 (0.006)	P <0.001	122	97	95	93	98	
Stage C (NYHA III–IV, EF 35%–50%) vs controls	BNP	0.997 (0.007)	P <0.001	38	95	97	89	99	NS
	NT-proBNP	1.000 (0.002)	P <0.001	158	100	98	93	100	
Stage C (NYHA III–IV, EF <35%) vs controls	BNP	0.995 (0.004)	P <0.001	38	98	97	97	99	NS
	NT-proBNP	0.999 (0.002)	P <0.001	220	98	100	100	99	

[a] Comparison by ROC analysis of BNP and NT-proBNP in differentiating stage A and B patients from the control group, stage A from the stage B, stage C from the control group and from stage A and B, and finally the stage C [with no/mild (NYHA class I–II) or severe (NYHA class III–IV) symptoms and mild (EF, between 35% and 50%) or severe (EF, <35%) left ventricular systolic dysfunction] from the control group.
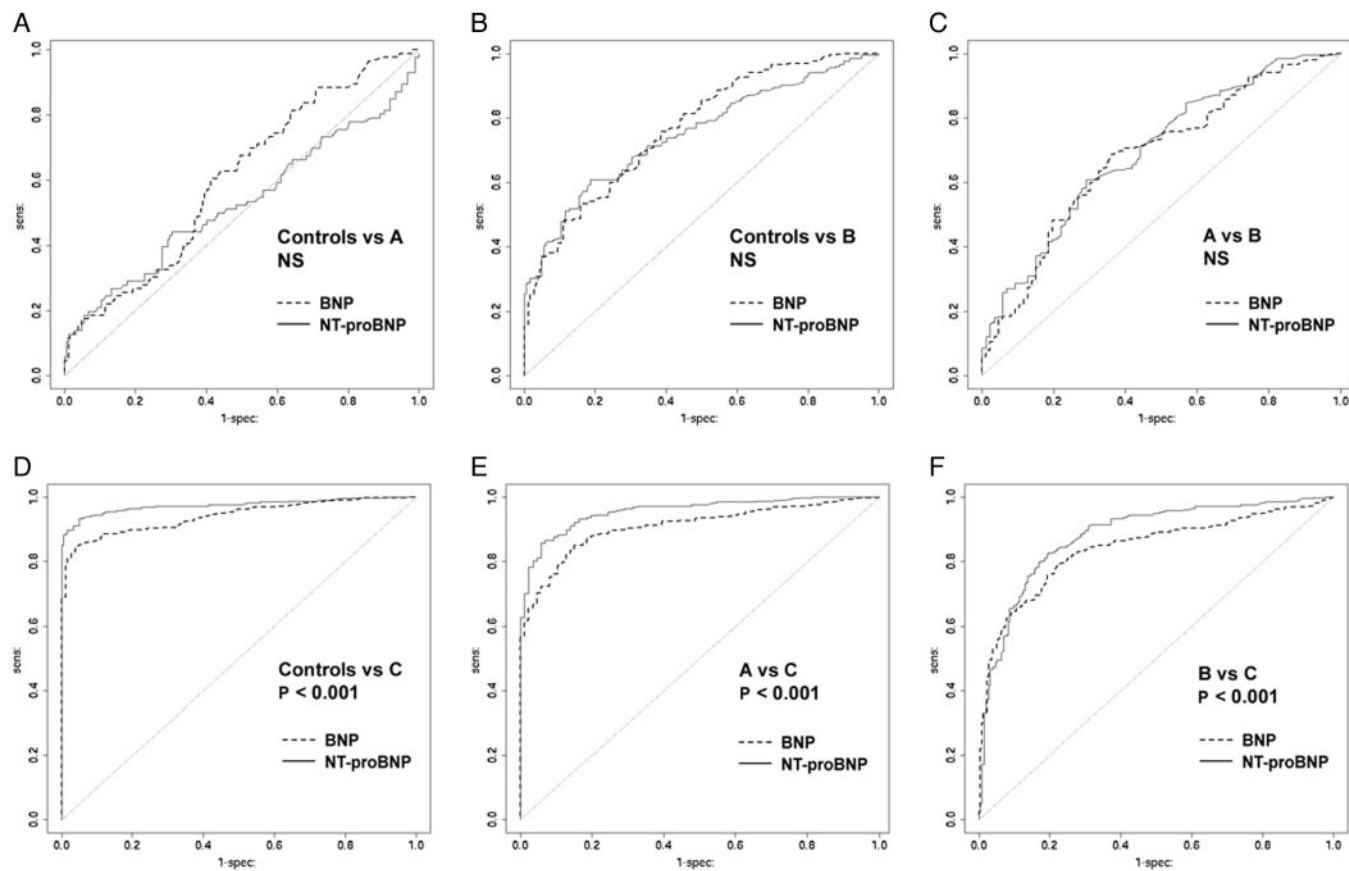
Fig. 2. ROC analysis of BNP and NT-proBNP in differentiating (*top panel*) stage A patients from controls (*left*), stage B from controls (*center*), stage A from stage B (*right*); (*bottom panel*), and stage C from controls (*left*), stage A (center), and stage B (*right*).

(P <0.001). NT-proBNP showed greater diagnostic accuracy (P <0.001) than BNP for differentiating stage C patients from (*a*) controls [Table 3 and Fig. 2, *bottom left panel*, BNP, AUC 0.941 (0.009) vs NT-proBNP, AUC 0.974 (0.006)], (*b*) stage A patients [*bottom center panel*, BNP: AUC 0.908 (0.013) vs NT-proBNP: AUC 0.956 (0.008)], (*c*) stage B patients [*bottom right panel*, BNP: AUC 0.840 (0.015) vs NT-proBNP: AUC 0.880 (0.013)].

For stratification of patients according to NYHA class and EF values, the diagnostic accuracies of both BNP and NT-proBNP were significant (P <0.001), with NT-proBNP accuracy significantly better when patients with no or only mild current symptoms (NYHA classes I and II) were compared with controls (Table 3 and Fig. 3), irrespectively of EF [*top left panel* EF 35%–50%, BNP: AUC 0.870 (0.021) vs NT-proBNP: AUC 0.939 (0.015), P <0.001; *top right panel* EF <50%: BNP: AUC 0.960 (0.012) vs NT-proBNP: AUC 0.989 (0.006), P <0.05)].

When the patients with severe HF (NYHA classes III and IV) were considered, the 2 assays showed significant (P <0.001) and comparable diagnostic accuracy, irrespectively of EF [Table 3 and Fig. 3; *bottom left panel* EF 35%–50%: BNP: AUC 0.997 (0.007) vs NT-proBNP: AUC 1.000 (0.002), NS; *bottom right panel* EF <50%: BNP: AUC 0.995 (0.004) vs NT-proBNP: AUC 0.999 (0.002), NS].

PREDICTORS OF ACC-AHA CLASSIFICATION OF HF

Multivariate logistic regression showed a significant increase (P <0.01) in the c-s when BNP or NT-proBNP was separately added to the starting model including age, sex, and creatinine clearance, in predicting stage C vs control group, stage A, or stage B. The c-s values were always significantly higher for models including NT-proBNP than BNP: stage C vs healthy condition, starting model (age, sex, and creatinine clearance) c-s, 0.506, SE 0.037 (BNP c-s 0.713, SE 0.066 vs NT-proBNP c-s 0.877, SE 0.062; P <0.05); stage C vs stage A: starting model c-s 0.703, SE 0.037 (BNP c-s 0.798, SE 0.033 vs NT-proBNP c-s 0.876, SE 0.027; P <0.05); stage B vs stage C: starting model c-s 0.607, SE 0.031 (BNP c-s 0.702, SE 0.029 vs NT-proBNP c-s 0.804, SE 0.026; P <0.01).

Discussion

This study evaluated the diagnostic accuracy of B-type natriuretic peptides in a large spectrum of patients at risk for HF, either without or with structural myocardial involvement. Present findings confirm that BNP and NT-proBNP share a clinically relevant diagnostic accuracy in HF patients (*2*) and suggest a significant difference in diagnostic accuracy between BNP and NT-proBNP, depending on the type of population studied. Another
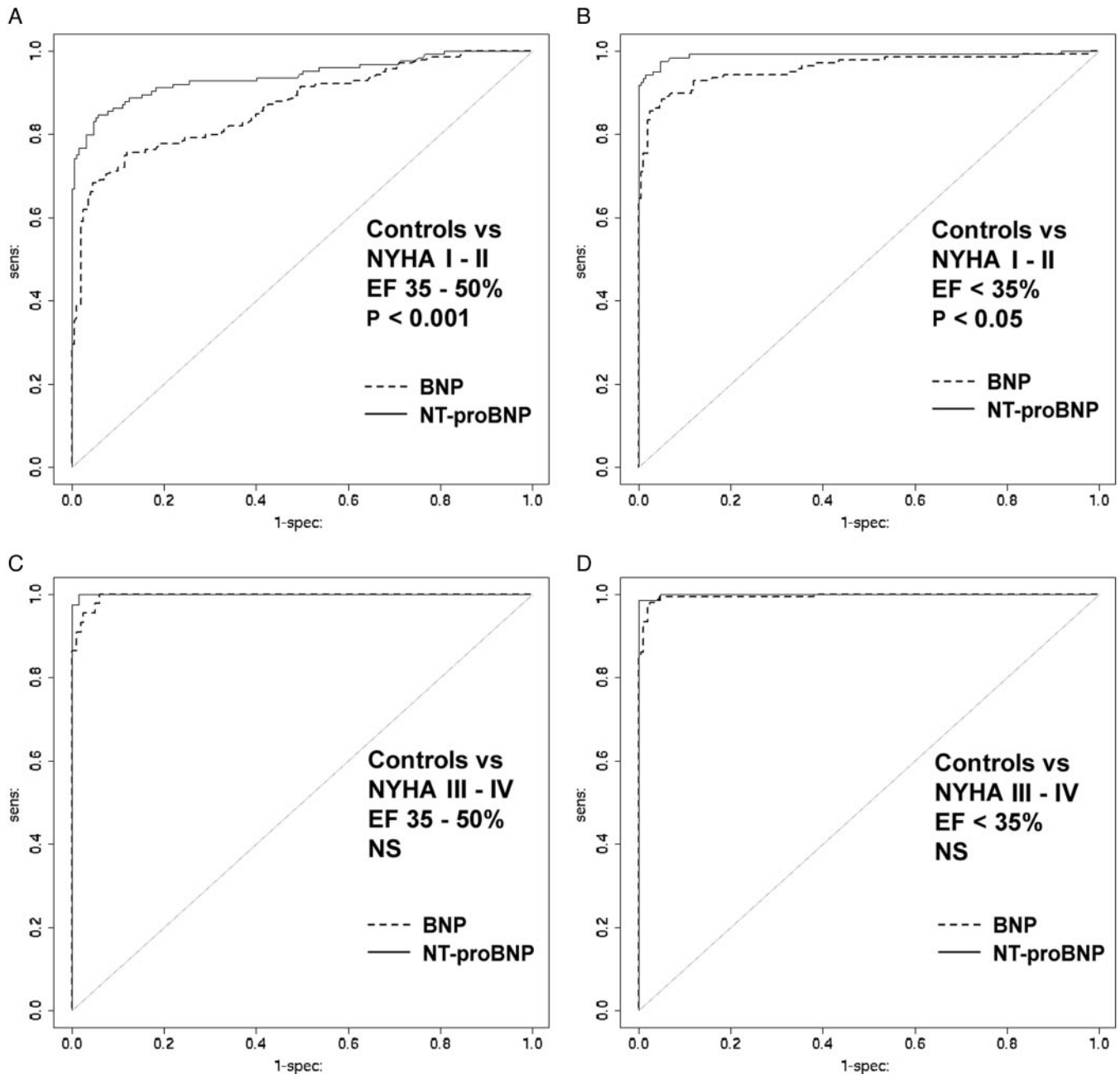
Fig. 3. ROC analysis of BNP and NT-proBNP corresponding to comparison between healthy controls and (*a*) patients with no or mild symptoms of HF (NYHA class I–II) and mild/moderate systolic dysfunction (EF between 35% and 50%; *top left panel*), (*b*) NYHA class I–II patients and severe systolic dysfunction (EF <35%; *top right panel*), (*c*) NYHA class III–IV patients with EF between 35% and 50% (*bottom left panel*), and (*d*) NYHA class III–IV patients with severe systolic dysfunction (EF <35%; *bottom right panel*).

main finding is that cutoff concentrations are dependent on the study population and/or on the reference group studied. Our results demonstrate that the measurement of BNP or NT-proBNP is useful in stratifying patients according to the HF stages as suggested by AHA/ACC guidelines *(11)*. In particular, both BNP and NT-proBNP showed diagnostic accuracy in separating out either asymptomatic ventricular impairment (stage B) vs controls or stage A patients. Moreover, BNP and NT-proBNP

assays enabled differentiation of those patients with no or mild symptoms of disease (stage C, NYHA class I–II) from controls or stage A–B patients. For these clinical conditions, our study suggests that NT-proBNP has a better diagnostic accuracy than BNP, including a model based on age, sex, and renal function.

We have chosen for the present study the ECLIA method for NT-proBNP and the IRMA method for BNP, although the latter is not commonly used. Indeed, a

previous multiassay comparison from our laboratory, between ECLIA NT-proBNP assay and several BNP immunoassays, indicated that the ECLIA NT-proBNP assay had a better diagnostic accuracy in detecting patients in the early stage of HF (NYHA class I–II), and that the IRMA BNP method showed better performance compared with other commercial immunoassays for BNP (12, 13). Results of several recent studies suggest that the diagnostic accuracy of BNP depends not only on the peptide measured but also on the platform used (2, 12, 13, 36–38). Commercial BNP immunoassays use different standard materials and antibodies, specific for different epitopes (2, 12, 13, 36–38). Therefore, BNP results may significantly vary dependent on the assay used (2, 12, 13, 36–38). On the other hand, all fully automated NT-proBNP assays, using standard materials and antibodies harmonized against the Roche system, should likely give more homogeneous results, although this has not yet been proven.

The findings of the present study confirm that cutoff concentrations depend on the method as well as on the population studied (2, 12, 13, 36–38). For this reason it is impossible to suggest a specific cutoff concentration as valid for all clinical settings. In particular, because of their high NPVs, low concentrations of BNP (<40 ng/L) and NT-proBNP (<160 ng/L) should be used as cutoffs to differentiate healthy individuals or asymptomatic patients (stage A–B or NYHA class I) from patients with symptoms of HF (i.e., for the rule-out; Fig. 2). More precise methods might show better diagnostic accuracy than IRMA compared with the ECLIA method. For this reason and for the differences in diagnostic accuracy among commercial BNP methods (12, 13), the cutoff concentrations found in the present study cannot be applied in other clinical settings, and findings on the IRMA assay might not be directly applicable to other BNP assays.

References

1. Clerico A, Recchia FA, Passino C, Emdin M. Cardiac endocrine function is an essential component of the homeostatic regulation network: physiological and clinical implications [Review]. Am J Physiol Heart Circ Physiol 2006;290:H17–29.
2. Clerico A, Emdin M. Diagnostic accuracy and prognostic relevance of the measurement of the cardiac natriuretic peptides: a review [Review]. Clin Chem 2004;50:33–50.
3. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction. JAMA 2002;288: 1252–9.
4. Koglin J, Pehlivanli S, Schwaiblmair M, Vogeser M, Cremer P, von Scheidt W. Role of brain natriuretic peptide in risk stratification of patients with congestive heart failure. J Am Col Cardiol 2001;38: 1934–41.
5. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004;110: 2168–74.
6. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347: 161–7.
7. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005; 95:948–54.
8. Adams KF, Lindenfeld J, Arnold JMO, Baker DW, Barnard DH, Baughman KL. Executive summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline. J Cardiac Fail 2006;12:10–38.
9. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115–40.
10. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:384–416.
11. Hunt SA; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol. 2005; 46: e1–82.
12. Prontera C, Emdin M, Zucchelli GC, Ripoli A, Passino C, Clerico A. Analytical performance and diagnostic accuracy of a fully-automated electrochemiluminescent assay of the N-terminal fragment of brain natriuretic peptide in patients with cardiomyopathy: comparison with immunoradiometric assay methods for brain natriuretic peptide and atrial natriuretic peptide. Clin Chem Lab Med 2004;42:37–44.
13. Clerico A, Prontera C, Emdin M, Passino C, Storti S, Poletti R, et al. Analytical performance and diagnostic accuracy of immunometricassays for the measurement of plasma BNP and NT-proBNP concentrations. Clin Chem 2005;51:445–7.
14. Seino Y, Ogawa A, Yamashita T, Fukushima M, Ogata K, Fukumoto H, et al. Application of NT-proBNP and BNP measurements in cardiac care: a more discerning marker for the detection and evaluation of heart failure. Eur J Heart Fail 2004;6:295–300.
15. Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK. Reliability of N-terminal proBNP assay in diagnosis of left ventricular systolic dysfunction within representative and high risk populations. Heart 2004;90:866–70.
16. Mikkelsen KV, Bie P, Moller JE, Ryde H, Videbaek L, Haghfelt T. Diagnostic accuracy of plasma brain natriuretic peptide and aminoterminal-proBNP in mild heart failure depends on assay and introduction of therapy. Scand J Clin Lab Invest 2005;65:633–47.
17. Pfister R, Scholz M, Wielckens K, Erdmann E, Schneider CA. Use of NT-proBNP in routine testing and comparison to BNP. Eur J Heart Fail 2004;6:289–93.
18. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Biochemical diagnosis of impaired left ventricular ejection fraction: comparison of the diagnostic accuracy of brain natriuretic peptide (BNP) and amino terminal proBNP (NT-proBNP). Clin Chem Lab Med 2004; 42:159–63.

19. Bhalla V, Isakson S, Bhalla MA, Lin JP, Clopton P, Gardetto N, et al. Diagnostic ability of B-type natriuretic peptide and impedance cardiography: testing to identify left ventricular dysfunction in hypertensive patients. Am J Hypertens 2005;18:73S–81S.

20. 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.

21. Costello-Boerrigter LC, Boerrigter G, Redfield MM, 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.

22. Mueller T, Gegenhuber A, Dieplinger B, Poelz W, Haltmayer M. Capability of B-type natriuretic peptide (BNP) and amino-terminal proBNP as indicators of cardiac structural disease in asymptomatic patients with systemic arterial hypertension. Clin Chem 2005;51:2245–51.

23. 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.

24. Hammerer-Lercher A, Ludwig W, Falkensammer G, Muller S, Neubauer E, Puschendorf B, et al. Natriuretic peptides as markers of mild forms of left ventricular dysfunction: effects of assays on diagnostic performance of markers. Clin Chem 2004;50:1174–83.

25. Vanderheyden M, Bartunek, Claeys G, Manoharan G, Beckers JF, Ide L. Head to head comparison of N-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in patients with/without left ventricular systolic dysfunction. Clin Biochem 2006; 39:640–5.

26. 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.

27. Alibay Y, Beauchet A, El Mahmoud R, Schmitt C, Brun-Ney D, Benoit MO, et al. Plasma N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in assessment of acute dyspnea. Biomed Pharmacother 2005;59:20–4.

28. 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.

29. Jefic D, Lee JW, Jefic D, Savoy-Moore RT, Rosman HS. Utility of B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide in evaluation of respiratory failure in critically ill patients. Chest 2005;128:288–95.

30. Ray P, Arthaud M, Birolleau S, Isnard R, Lefort Y, Boddaert J, et al. Comparison of brain natriuretic peptide and probrain natriuretic peptide in the diagnosis of cardiogenic pulmonary edema in patients aged 65 and older. J Am Geriatr Soc 2005;53: 643–8.

31. Bal L, Thierry S, Brocas E, Van de Louw A, Pottecher J, Hours S, et al. B-type natriuretic peptide (BNP) and N-terminal-proBNP for heart failure diagnosis in shock or acute respiratory distress. Acta Anaesthesiol Scand 2006;50:340–7.

32. Chien TI, Chen HH, Kao JT. Comparison of Abbott AxSYM and Roche Elecsys 2010 for measurement of BNP and NT-proBNP. Clin Chim Acta 2006;369:95–9.

33. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Diagnostic accuracy of B type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure. Heart 2005;91:606–12.

34. Gegenhuber A, Struck J, Poelz W, Pacher R, Morgenthaler NG, Bergmann A, et al. Midregional pro-A-type natriuretic peptide measurements for diagnosis of acute destabilized heart failure in short-of-breath patients: comparison with B-type natriuretic peptide (BNP) and amino-terminal proBNP. Clin Chem 2006;52:827–31.

35. 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.

36. Emdin M, Passino C, Prontera C, Iervasi A, Ripoli A, Masini S, et al. Cardiac natriuretic hormones, neuro-hormones, thyroid hormones and cytokines in normal subjects and patients with heart failure. Clin Chem Lab Med 2004;42:627–36.

37. Apple FS, Panteghini M, Ravkilde J, Mair J, Wu AH, Tate J, et al. Quality specifications for B-type natriuretic peptide assays. Clin Chem 2005;51:486–93.

38. Emdin M, Clerico A, Clemenza F, Galvani M, Latini R, Masson S, et al. Consensus document: recommendations for the clinical use of cardiac natriuretic peptides. Ital Heart J 2005;6:430–46.