Clinical Investigations

Clinical Utility of Three B-Type Natriuretic Peptide Assays for the Initial Diagnostic Assessment of New Slow-Onset Heart Failure

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ABSTRACT

Background: In patients suspected of new slow-onset heart failure, data on the comparative diagnostic performance of automated B-type natriuretic peptide (BNP) assays are scarce.

Methods and Results: Two hundred patients referred to a heart failure outpatient diagnostic facility underwent standard diagnostic work-up including echocardiography. The reference standard for the diagnosis of heart failure was an expert panel conclusion. N-terminal pro-BNP on Elecsys and BNP on Axsym and Centaur machines were measured in a single batch. Data were available for 172 patients; 51 had heart failure (29.7%). All 3 tests had high c-statistic values. An intermediate-risk subset of 111 patients (34% with heart failure) was created by excluding patients with very high or very low probability based on history and physical examination, the subgroup most in need of an additional test. Applying different thresholds for ruling heart failure in or out, the positive predicted values in this "gray zone" group were 75%, 76%, and 72%, respectively, and the negative predictive values 83%, 71%, and 85%, with the remaining 50% of patients having ~18% probability of heart failure.

Conclusion: In practice, a valid diagnosis in patients suspected of slow-onset heart failure remains elusive for many in the absence of echocardiographic imaging. (*J Cardiac Fail 2011;17:729–734*)

Key Words: Diagnostic research, natriuretic peptides.

Measurement of B-type natriuretic peptides (BNP) is useful in the diagnostic assessment of patients suspected of heart failure and recommended by the 2008 European Society of Cardiology (ESC) Heart Failure guideline.[1] They are particularly useful in settings with limited access to other diagnostic tests, such as echocardiography, notably in primary care. BNP and the biologically inactive N-terminal counterpart (NT-proBNP) peptide assays are readily available with fully automated immunoassay as well as point-of-care testing methods.

Data on the comparative performance of 3 popular automated assays in patients suspected of new slow-onset heart failure are lacking. Our aim was to assess the comparative diagnostic accuracy and utility of NT-proBNP measured with the Roche assay, BNP measured with the Abbott assay, and BNP with the Bayer assay in patients suspected of new slow-onset heart failure in primary care on top of the preceding tests (signs and symptoms, history, physical examination).[2] We were particularly interested, as a measure of utility, in the predicted values of the 3 BNP tests in those patients where the clinical picture is unclear.

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See page 734 for disclosure information.

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Methods

Patient Population

The first 200 patients included in a larger study, the Utrecht Heart Failure Organisation—Initial Assessment (UHFO-IA),[3] had their blood drawn for assessment of BNP by the 3 assays. The UHFO-IA recruited patients suspected of heart failure by their general practitioner (GP). The only exclusion criteria were a previous diagnosis of heart failure or acute signs and symptoms demanding immediate treatment. The objective was to include patients where the GP could neither immediately and safely rule out nor diagnose heart failure, ie, patients in need of additional diagnostic work-up. Patients were referred to rapid access heart failure outpatient diagnostic facilities available in 8 hospitals. All patients underwent standard diagnostic work-up including electrocardiogram (ECG), laboratory measurements, chest x-ray, spirometry, and echocardiography. The reference ("gold") standard for the diagnosis of heart failure was the decision of an expert panel consisting of a cardiologist, a pulmonologist, and a GP. The panel based their decision on the results of all diagnostic tests: medical history, anamnesis, physical examination, laboratory values, ECG, spirometry, chest x-ray, echocardiography, and 6 months of clinical follow-up data (eg, to monitor the effect of targeted therapy). The panel did not receive the BNP results, to prevent incorporation bias, because one of the aims of the original study was to assess the added diagnostic value of BNP in these patients. The final decision of the panel was made following the criteria for heart failure of the 2008 ESC guideline[1] and more recently explicitly for patients suspected of heart failure by the Heart Failure Society of America 2010 heart failure guideline.[4]

This study was approved by the Medical Ethical Committee of the St Antonius Hospital, Nieuwegein, The Netherlands.

B-Type Natriuretic Peptide Measurements

Blood samples were taken and specimens of plasma were stored at −70°C. At the end of the study, NT-proBNP and BNP levels were measured for all patients in a single batch after the frozen specimens were thawed at the Saltro laboratories in Utrecht, The Netherlands. NT-proBNP was measured with an automated noncompetitive immunoradiometric assay (Roche, Mannheim, Germany) on an Elecsys 1010 analyzer. For plasma BNP measurements, the automated Abbott Axsym BNP immunoassay (Abbott, Park, Illinois, USA) and Advia Centaur BNP immunoassay (Siemens Healthcare Diagnostics, Deerfield, Illinois, USA) were used. Total coefficients of variation are reported to be 4.4%, 5.5% and 0.8%, respectively.[5] Results are given in pg/mL.

Data Analysis

The ability of a BNP assay diagnostic test to discriminate between patients with and without heart failure was assessed by means of the c-statistic (area under the receiver operating characteristic curve). The c-statistic is a rank order measure of discrimination combining sensitivity and specificity; specifically, the c-statistic represents the probability of a random patient with heart failure having a higher value of plasma BNP compared with a random patient without heart failure.[6] To assess the calibration we performed a goodness-of-fit test, the Hosmer—le Cessie (HLC) test,[7] in which a smaller P value indicates larger difference between observed and expected probabilities of heart failure. Additionally, we computed predicted values, taking the 25th and 75th percentiles of BNP values to respectively "rule out" and "rule in" heart failure as an arbitrary example to enable comparison of the 3 BNP assays. In daily practice, the cutoffs ruling out and diagnosing heart failure are chosen by the physician, taking into account the individual patient for whom the decision has to be made.

One other algorithm we assessed was published by the ESC in its 2008 guideline: Heart failure is unlikely when BNP <100 pg/mL (NT-proBNP <400 pg/mL), whereas heart failure is likely when BNP >400 pg/mL (NT-proBNP >2,000 pg/mL).[1]

To gain more insight into the utility of the 3 tests, we selected those patients for whom the test would be considered to be most appropriately indicated, ie, as additional diagnostic test in patients where there is still diagnostic uncertainty after history taking and physical examination. To that end, we computed the predicted probability of heart failure for all patients based on a multivariate logistic regression model and selected the group of patients with <80% probability and >10% probability. The multivariate model used age, history of myocardial infarction, coronary artery bypass graft or percutaneous coronary intervention, use of a loop diuretic, displaced ictus cordis, lung crackles, irregular pulse, pulse rate, heart murmur suggestive of mitral regurgitation, and elevated jugular venous pressure to predict the presence of heart failure. This model was derived from all of the 721 patients from the main study, where the analyses took the natural hierarchy according to daily practice (starting with easily obtainable items from history taking) into account. Variables were allowed in the model only if they had additional value (based on the likelihood ratio test) to items already included in the model.[3] More than 80% probability of heart failure present after history taking and physical examination would constitute the arbitrary threshold of not needing additional diagnostic tests, and vice versa, <10% is the arbitrary threshold of not needing additional diagnostic tests because heart failure is discarded from the differential diagnosis. In the 10%—80% probability of heart failure group, we computed the predicted values of the 3 BNP tests.

All statistical calculations were performed with R, version 2.10 (http://www.r-project.org/).

Results

Of the 200 samples, 28 were lost due to technical or organizational reasons, eg, insufficient amount of blood, ID label unreadable, or lost. There were no relevant differences between patients with and without plasma samples (data not shown); consequently, all analyses were performed on 172 patients. The mean age of the 172 patients was 70.2 years and 66% were female (Table 1). Heart failure was diagnosed by the panel in 51 patients (29.7%), of whom 41% had an ejection fraction as estimated by echocardiography of ≥45%—50%. All patients had ≥1 complaints compatible with heart failure. Physical examination signs compatible with heart failure were more common among patients with heart failure. In Table 2 and Figure 1 the uni- and bivariate measures of the 3 BNP tests are presented. As expected, the distribution off all BNP assays was skewed to the right; therefore, we used the log-transformed values in all computations. The Pearson correlation coefficient on the log scale was lowest for NT-proBNP with BNP on Axsym (0.84) and highest for NT-proBNP with BNP on Centaur (0.90).

The largest c-statistic, the measure of discriminating ability between heart failure present versus heart failure absent, was found for the NT-proBNP test (0.86), but no

Table 1. Characteristics of Patients Suspected of Heart Failure (HF) and According to the Presence or Absence of HF

	All Participants (n = 172)		HF Present (n = 51)		HF Absent (n = 121)		Intermediate Probability of HF (n = 111; 38 HF)	
	n	%	n	%	n	%	n	%
Age, y, mean (SD)	70.2	(11.3)	75.4	(9.7)	68	(11.2)	74.4	(8.3)
Female	113	65.7	30	58.8	83	68.6	71	64.0
Complaints								
Shortness of breath	103	59.9	41	80.4	62	51.2	76	68.5
Fatigue	121	70.3	40	78.4	81	66.9	79	71.2
Ankle swelling	83	48.3	31	60.8	52	43.0	54	48.6
Orthopnoea or paroxysmal nocturnal dyspnoea	58	33.7	23	45.1	35	28.9	35	31.5
History								
Never smoked	67	39.0	17	33.3	50	41.3	48	43.2
Hypertension	88	51.2	28	54.9	60	49.6	62	55.9
Diabetes	29	16.9	13	25.5	16	13.2	25	22.5
Stroke or TIA	15	8.7	9	17.6	6	5.0	11	9.9
Atrial fibrillation	8	4.7	3	5.9	5	4.1	8	7.2
MI, PCI, or CABG	9	5.2	7	13.7	2	1.7	7	6.3
COPD	47	27.3	16	31.4	31	25.6	33	29.7
Medication								
ACEI or AT2 blocker	52	30.2	22	43.1	30	24.9	40	36.0
Loop diuretic	61	35.5	32	62.7	29	24.0	49	44.1
β-Blocker	49	28.5	15	29.4	34	28.1	30	27.0
Physical examination and other test results								
BMI, kg/m^2, mean (SD)	29.5	(5.4)	28.5	(5.1)	29.9	(5.4)	28.9	(5.3)
Pulmonary rales	26	15.1	14	27.5	12	9.9	19	17.1
Elevated jugular venous pressure	15	8.7	11	21.6	4	3.3	9	8.1
Laterally displaced apex beat	16	9.3	14	27.5	2	1.7	8	7.2
Peripheral edema	48	27.9	20	39.2	28	23.1	31	27.9
eGFR, mL/min/m^2, mean (SD)	62.9	(15.0)	58.6	(15.4)	64.8	(14.4)	62	(14.6)
Ejection fraction >0.45−0.50 on echocardiogram	130	75.6	20	39.2	110	90.1	81	73.0

TIA, transient ischemic attack; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; AT2, angiotensin II; BMI, body mass index; eGFR, estimated glomerular filtration rate by the Modification of Diet in Renal Disease formula.

statistically significant differences were found between any of the tests (Table 2).

For the utility of the 3 tests, we selected the patients of intermediate risk of heart failure after history taking and physical examination (>10% and <80%). This subset contained 111 patients, of whom 38 (34.2%) had heart failure; the characteristics are presented in Table 1. Application of the 3 BNP tests in these patients resulted in loss of

Table 2. Univariate Measures and Diagnostic Accuracy of 3 BNP Assays for the Diagnosis of Heart Failure (n = 172; Prevalence of Heart Failure 29.7%)

	NT-proBNP	Axsym-BNP	Centaur-BNP
All patients			
Geometric mean	24.8	18	13.2
Median (25th−75th percentile)	16 (7−55)	14 (8−34)	10 (5−26)
Patients with heart failure			
Geometric mean	129.5	61.3	50.4
Median (25th−75th percentile)	185 (28−470)	85 (26−288)	58 (18−222)
Patients without heart failure			
Geometric mean	12.4	10.7	7.5
Median (25th−75th percentile)	12 (6−22)	12 (6−18)	7 (4−14)
c-Statistic (95% CI)	0.86 (0.80−0.92)	0.82 (0.73−0.90)	0.83 (0.76−0.91)
HLC *P* value for calibration	.051	<.001	.005
PPV > 75th percentile (95% CI)	0.81 (0.67−0.92)	0.74 (0.59−0.86)	0.77 (0.61−0.88)
NPV < 25th percentile (95% CI)	0.89 (0.75−0.97)	0.84 (0.69−0.93)	0.88 (0.75−0.96)
PPV BNP >400 pg/mL, NT-proBNP >2,000 pg/mL (n)	1/1	5/5	3/3
NPV BNP <100 pg/mL, NT-proBNP <400 pg/m (95% CI)	0.76 (0.69−0.82)	0.81 (0.73−0.87)	0.80 (0.73−0.86)
Applied in 111 patients at intermediate risk of heart failure and 34.2% prevalence			
c-Statistic (95% CI)	0.86 (0.73−0.89)	0.79 (0.68−0.90)	0.81 (0.71−0.91)
PPV > 75th percentile (95% CI)	0.75 (0.57−0.89)	0.76 (0.56−0.90)	0.72 (0.53−0.86)
NPV < 25th percentile (95% CI)	0.83 (0.59−0.96)	0.71 (0.48−0.89)	0.85 (0.62−0.97)
PPV BNP >400 pg/mL, NT-proBNP >2,000 pg/mL (n)	na (N = 0)	3/3	2/2
NPV BNP <100 pg/mL, NT-proBNP <400 pg/m (95% CI)	0.71 (0.61−0.79)	0.76 (0.66−0.84)	0.76 (0.66−84)

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro−B-type natriuretic peptide; geometric mean, exponential of the mean of log-transformed mean; c-statistic, area under the receiver operating characteristic curve, a measure of discrimination, with a value of 1 representing perfect discrimination, 0.5 equivalent to flipping a coin; CI = confidence interval; PPV, positive predicted value; NPV, negative predicted value.

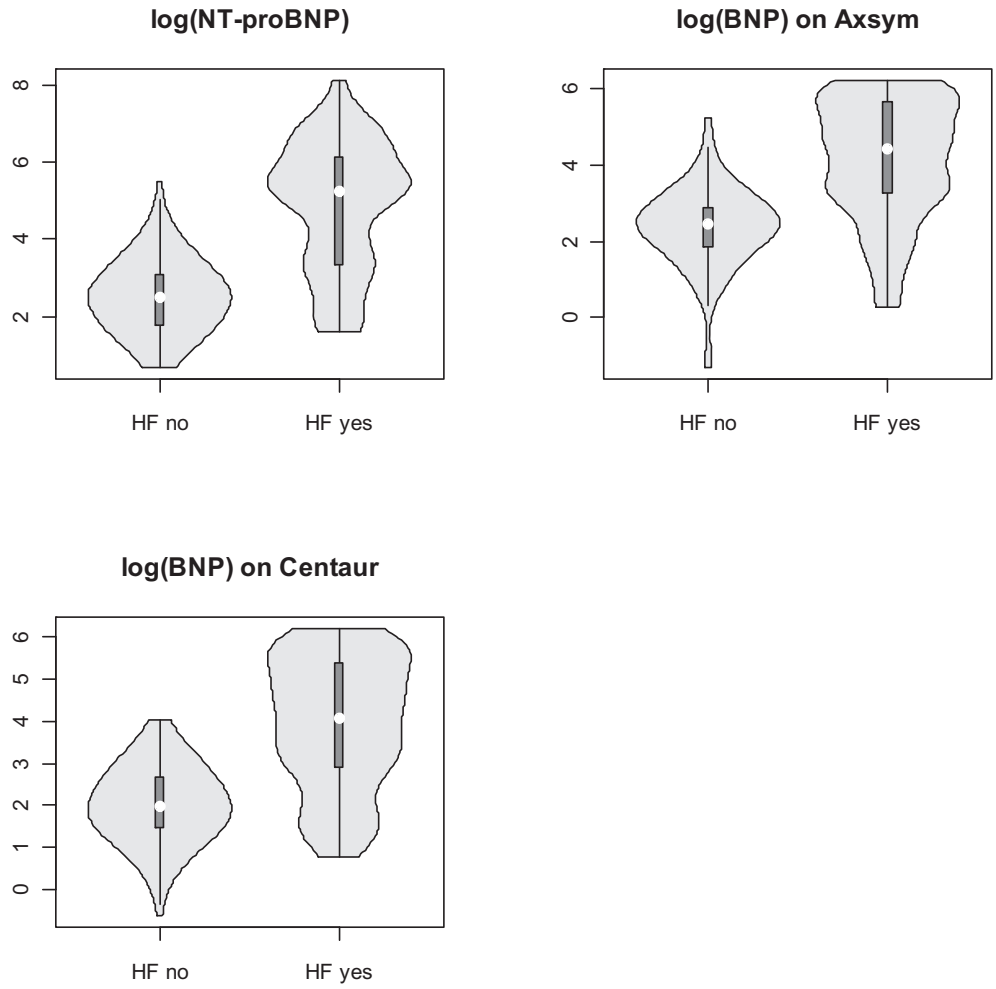

Fig. 1. Kernel density plot (violin plot) plus boxplot for patients with and without heart failure (HF) on a log scale. Top left: NT-proBNP; top right: BNP on Axsym; bottom left: BNP on Centaur.

diagnostic ability compared with the full cohort without relevant changes between the tests (Table 2). The number of patients associated with application of the ''percentile'' rule-in and rule-out cutoff levels is presented in Table 3. At best, the prior probability of 34.2% increased to 75.9% when the test was positive (>75th percentile) and decreased to 18.0% when the test was negative (<25th percentile). Application of the ESC-based cutoff levels resulted in lower negative predicted values and very few patients in the rule-in category.

The only diagnosis other than heart failure that was systematically assessed was chronic obstructive pulmonary disease (COPD), defined as Global Initiative for COPD stage ≥2. Fifty-four patients were diagnosed with COPD (20 in patients with heart failure, 34 in patients without heart failure).

Discussion

BNP, whether it is measured with the NT-proBNP on the Roche Elecsys, BNP on the Bayer Centaur, or BNP on the Abbott Axsym, is a helpful diagnostic instrument in the assessment of new slow-onset heart failure. When comparing these 3 assays, the inference could be that most information regarding the diagnosis of heart failure is given by NT-proBNP, followed by BNP on the Centaur and least by BNP on the Axsym, but differences were small. The NT-proBNP showed marginally better discriminatory power for detecting heart failure, as demonstrated by the c-statistic of 0.86, the BNP on the Centaur and the Axsym scored 0.83 and 0.82, reespectively. There were no statistically significant differences on the nonparametric c-statistic scale.

The c-statistic can be interpreted as the probability that a test will rank a randomly chosen patient with heart failure higher than a randomly chosen patient without heart failure[6] (even if this situation would never emerge in practice). However, the predictive values have more practical use, because ultimately, a nonperfect diagnostic test should provide an indication of presence of disease expressed as a probability. Moreover we selected from our cohort only patients with diagnostic uncertainty after taking history taking and physical examination into account. Thus we excluded patients with very high (>80%) or very low (<10%) probability of heart failure, because these patients do not need an additional diagnostic test. We used different

Table 3. Utility of 3 BNP assays for the Diagnosis of Heart Failure Applied in 111 Patients at intermediate risk of heart failure and 34.2% prevalence

	Patients with Disease (n)	Patients without Disease (n)	Prevalence of Heart Failure	% of All Patients
"Percentile" guided				
>75th percentile				
NT-proBNP	24	8	75.0%	28.8%
Axsym-BNP	22	7	75.9%	26.1%
Centaur-BNP	23	9	71.9%	28.8%
<25th percentile				
NT-proBNP	3	15	16.7%	16.2%
Axsym-BNP	6	15	19.7%	18.9%
Centaur-BNP	3	17	15.0%	18.0%
25th–75th percentile				
NT-proBNP	11	50	18.0%	55.0%
Axsym-BNP	10	51	16.4%	55.0%
Centaur-BNP	12	47	20.3%	53.2%
ESC guideline[1]				
BNP >400 pg/mL (NT-proBNP >2,000 pg/mL)				
NT-proBNP	0	0	na	0%
Axsym-BNP	3	0	100%	2.7%
Centaur-BNP	2	0	100%	1.8%
BNP <100 pg/mL (NT-proBNP <400 pg/mL)				
NT-proBNP	30	73	29.1%	92.8%
Axsym-BNP	23	71	24.5%	84.7%
Centaur-BNP	23	73	24.0%	86.5%
BNP 100–400 pg/mL (NT-proBNP 400–2,000 pg/mL)				
NT-proBNP	8	0	100%	7.2%
Axsym-BNP	12	2	85.7%	12.6%
Centaur-BNP	13	0	100%	11.7%

cutoff values for ruling in heart failure and ruling out heart failure, as proposed in the ESC guideline.[1] The chosen cutoff levels were the 75th and 25th percentiles, because no evidence-based levels exist for patients suspected of new slow-onset heart failure. For each test, the actual values were 7 and 55 for NT-proBNP, 8 and 34 for BNP on the Axsym, and 5 and 26 for BNP on the Centaur. In doing so we created an intermediate group for whom no diagnosis could be made, amounting to 55% of the patients, predominantly owing to the choice of cutoff levels. Add to this amount the false positives and false negatives, and the NT-proBNP, BNP on Axsym, and BNP on Centaur have, respectively, 64.9% (n = 72), 66.7% (n = 74), and 68.0% (n = 71) of patients not adequately categorized. One could argue that these figures are not very effective to reach a conclusion in a fair number of patients, but fortunately a practicing physician has more diagnostic tests at his or her disposal, notably (among others) signs and symptoms, course in time, ECG, and echocardiography.

The proposed cutoff levels from the ESC guideline appear to be too high, resulting in the majority of patients ending up in the rule-out category, reducing the negative predicted value.

Our results are in line with earlier reports. Recently, the analytical performance and diagnostic accuracy of immunoassays for BNP, including the 3 assays we report, were compared.[5,8] The general conclusion was that all automated BNP methods showed acceptable analytical performance and clearly differentiated between healthy individuals and heart failure patients. Because, however, results of one assay cannot be substituted for another, it is important to know which specific assay is being used in a specific institution. As mentioned before, this "test research" is not directly applicable to daily practice.[9] A study in patients with selection criteria comparable to our study, ie, patients suspected of new slow-onset heart failure, gave similar results comparing a point-of-care BNP test with the NT-proBNP assay.[10] The utility of the tests was assessed by their ability to prevent unnecessary referrals for echocardiography. The point-of-care test prevented 24% and NT-proBNP 25% unnecessary referrals with the use of the "single cutoff level" method. These results emphasize the ability of BNP to discriminate between heart failure present versus heart failure absent. The calibration, on the other hand, is not often reported. Where calibration is not an issue in a "one cutoff level" binary test, the interpretation in daily practice of a diagnostic test such as BNP would be ordinal by nature, eg, a BNP level twice the upper level of normal would have a different interpretation compared with a BNP level 10 times the upper level of normal. In the present study, all 3 BNP assays suffered from lack of calibration as single tests. Figure 2 illustrates the lack of differentiation in the lower 3 quintiles. It should be interesting to study whether recalibration can be accomplished by adding other tests, notably physical examination.

In the present study, consecutive patients were referred to the participating hospitals from primary care to reduce selection bias. Patients in need of urgent care were excluded; consequently, our study does not address the diagnosis of acute heart failure.

A point of interest is the absence of a "gold" standard diagnostic test for heart failure. The presence of heart

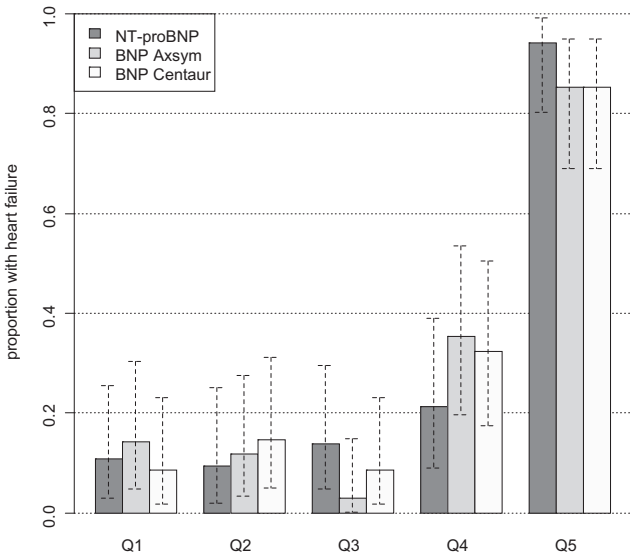

Fig. 2. Calibration of probability of heart failure by quintiles (Q) of 3 BNP tests, with 95% confidence intervals.

failure in our study was established by consensus evaluation using all available diagnostic information. This is an established method as reference standard.[11]

In patients suspected of new slow-onset heart failure, 3 common BNP assays (Roche NT-proBNP, Abbott Axsym BNP, and Bayer Centaur BNP) have similar and satisfactory diagnostic power when used as single tests. However, a valid diagnosis remains difficult in a substantial proportion of patients and there is room for improvement in the early diagnosis of heart failure in the absence of full echocardiographic imaging.

Disclosures

None.

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