USE OF N-TERMINAL NATRIURETIC PEPTIDE IN A REAL-WORLD SETTING OF PATIENTS ADMITTED WITH ACUTE DYSPNOEA AND THE IMPLICATION FOR TRIAGING PATIENTS IN THE EMERGENCY DEPARTMENT

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ABSTRACT

The aim of this review is to determine, among patients admitted with dyspnoea, the proportion of patients that can be excluded from having acute decompensated heart failure (ADHF) due to low N-terminal of the prohormone brain natriuretic peptide (NT-proBNP), below diagnostic cut-off, and to examine the diagnostic value of NT-proBNP in patients with high NT-proBNP levels, above cut-offs. Patients ≥40 years of age who were acutely admitted with dyspnoea were included. Of 654 patients, 194 (30%) had NT-proBNP below rule-out (<35 pmol/l ≈296 pg/ml), 157 (24%) had intermediate levels of NT-proBNP, and 303 (46%) had NT-proBNP above age-adjusted rule-in values. The negative predictive value of NT-proBNP below rule-out was 99.5% for ADHF. A severe non-cardiac condition was the primary complaint in 88 of the 157 patients with intermediate levels of NT-proBNP, and these were not considered to have ADHF. Thereby, 372 patients (56.9% of 654) were left for examination of ADHF. Certain ADHF was present in 166 (45%), plausible in 85 (23%), and no ADHF in 121 (32%). Receiver-operating characteristics (ROC) analysis for NT-proBNP to identify certain ADHF resulted in an area under the curve (AUC) of 0.69 (95% CI: 0.64-0.74, p<0.001). ROC analysis of patients with current atrial fibrillation (Afib)/flutter (AFL) resulted in AUC of 0.58 (95% CI: 0.48-0.68, p=0.8) to diagnose certain ADHF. In patients admitted with dyspnoea, low NT-proBNP levels will safely rule out ADHF in 30%. We conclude that rule-in values for NT-proBNP are inappropriate to diagnose ADHF, and in patients with Afib or AFL there is no added diagnostic value of NT-proBNP.

Keywords: Heart failure, diagnosis, natriuretic peptides.

BACKGROUND

High values of the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) and BNP are seen among patients with acute decompensated heart failure (ADHF), and these biomarkers are reported to improve diagnostic accuracy in the emergency room.[1-3] For triage patients, rule-out and rule-in cut-off values have been proposed, dividing patients into three groups with a low, indeterminate, and high probability of having ADHF.[4,5] There is a general consensus that rule-out levels will exclude ADHF.[6] However, there is a lack of studies illustrating which proportion of patients will be triaged by rule-out levels alone in patients with acute dyspnoea.[7] Furthermore, the diagnostic value of NT-proBNP in the remaining patients with elevated NT-proBNP has not been described. The objectives of this study were to examine the prevalence of NT-proBNP rule-out levels in a cohort of patients admitted with dyspnoea, and to assess whether NT-proBNP can provide further value for diagnosing ADHF in patients not excluded due to a low NT-proBNP. Furthermore, we examined what factors affect the diagnostic ability of NT-proBNP.

METHODS

Patients and Study Design

Patients admitted to medical departments at Bispebjerg Hospital were screened prospectively at 180 days. We screened all patients ≥40 years of age, admitted within the last 24 hours to medical departments with a primary complaint of dyspnoea, reported by the admitting physician. The study included patients referred from a general practitioner, patients admitted with ambulance after an emergency call, or patient self-direction to the emergency department. Exclusion criteria for screening was estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2, since measurement of NT-proBNP is not recommended for diagnostic purposes in patients with severe renal dysfunction.[1,3] Patients with current acute coronary syndrome were also excluded. After affirmation from The Ethics Committee, no patient consent was required since all study diagnostic procedures were considered to be part of the routine medical care.

NT-proBNP Values to Rule out ADHF

In accordance with guidelines, NT-proBNP rule-out value was 35 pmol/l and rule-in values were defined as 50, 100, and 200 pmol/l for ages 40-49, 50-75, and >75 years, respectively. Intermediate values were defined as a NT-proBNP level between rule-in and rule-out values.[4,5] NT-proBNP ruled out a diagnosis of ADHF in one of two ways: 1) all patients with NT-proBNP below rule-out; 2) all patients admitted with a primary severe non-cardiac condition and intermediate NT-proBNP levels. A primary severe non-cardiac condition was defined as prior diagnosis of chronic obstructive pulmonary disease (COPD), with documented severe COPD in stable condition with a forced expiratory volume <50% and/or the use of home oxygen prior to admission, prior documented primary or secondary pulmonary malignancy, current diagnosis of pneumonia confirmed in chest X-ray, and current diagnosis of acute pulmonary embolism or current anaemia with a haemoglobin <6 mmol/L at admission.

Diagnostic Examinations for Patients with Elevated NT-proBNP

For patients in which ADHF was not ruled out by a low NT-proBNP value, clinical characteristics were recorded, including medical history, symptoms, signs, medication use, electrocardiography, chest X-ray, standard blood tests, and echocardiography. The Framingham Criteria for the Clinical Diagnosis of Congestive HF were evaluated at admission in all patients.[8] A new echocardiography was performed within 72 hours after admission, unless the patient was documented to have known cardiac dysfunction (left ventricular ejection fraction [LVEF] <40% and/or severe valvular heart disease) within the past year. In patients with rapid supraventricular tachycardia, an echocardiogram was performed as soon as the heart rate dropped below 100 beats per minute. The presence of ADHF was evaluated in both patients with reduced and preserved ejection fraction.

Diagnosis of ADHF in Patients not Ruled-out by NT-proBNP

In recognition of the inherent difficulty of deciding a diagnosis of ADHF, the diagnosis of ADHF was based on two criteria: 1) a prospective physician consensus based diagnosis by use of echocardiography and clinical information; and/or 2) the modified Framingham criteria.[8] Hence 'Certain ADHF' was accepted if one and two were positive, indicating that ADHF was the major clinical problem for the patient, 'Plausible ADHF' was labelled if one or two were positive, reflecting that ADHF was a possible part of the problem, and 'No ADHF' was conceived if one and two were negative, implying that ADHF was not the cause of the hospital admission.

The physician-based consensus diagnosis of ADHF required is accepted by at least two out of three physicians. The first physician was the examining senior consultant who, unaware of the NT-proBNP level, had judged ADHF as the most important working diagnosis. The second physician was a dedicated study physician, with knowledge of the clinical, echocardiographic, and NT-proBNP results at discharge. The third physician was a senior HF specialist who was consulted in case the study physician's diagnosis differed from the clinical physician's diagnosis. The third physician had all available clinical information and echocardiography results, but was unaware of the patient's NT-proBNP level (8% of the cases).

NT-proBNP Analysis

NT-proBNP analysis was performed on the routine blood samples drawn within 1-2 hours from primary presentation (emergency department or hospital ward). Some patients presenting with

very severe dyspnoea did receive acute treatment before blood samples were drawn. NT-proBNP analysis was performed with a commercially available immunoassay (Elecsys NT-proBNP, Roche Diagnostics, pmol/l) using a Cobas e 411 according to established methods. Our laboratory reports an inter-run coefficient of variation of <2.0%.

Echocardiography

Echocardiography was performed by either clinical or study indication. Recordings were analysed off-line by a study physician. In accordance with guidelines, LVEF was assessed by the biplane modified Simpson's measurement. In case of poor echocardiographic window, LVEF was assessed with eyeballing.[9] Diastolic dysfunction was not routinely assessed in all patients. Valvular disease was assessed in all patients. Severe aortic stenosis was defined as an aortic valve area ≤1 cm^2 assessed by the continuity equation. The proximal isovelocity surface area method or vena contracta were used to assess mitral regurgitation. Severe mitral regurgitation was as an effective regurgitant orifice area ≥0.4 cm^2 and/or vena contracta ≥6 mm with moderate or severe left ventricular (LV) volume overload. Aortic regurgitation was assessed using vena contracta. Severe aortic regurgitation was defined as a vena contracta ≥6 mm with moderate or severe LV volume overload.[10]

Statistical Analysis

Baseline characteristics are reported in percent, mean and standard deviation, or median and interquartile range (IQR), as appropriate. Univariate comparisons across diagnostic categories were performed using a non-parametric test for trend. To obtain an index of the overall diagnostic performance of NT-proBNP, to diagnose ADHF, receiver-operating characteristic (ROC) curves were generated, as was the area under the curve (AUC) with 95% confidence interval (CI). Clinical characteristics independently associated with NT-proBNP levels were determined by multivariable linear regression analysis. Candidate variables were included in the initial linear regression model if associated with log-NT-proBNP in a univariate analysis (p≤0.1). Candidate variables tested in univariate analyses have all previously been reported to be correlated to NT-proBNP level. Backward elimination with an elimination criterion of a p-value of >0.05 was then used to create the final linear regression model. Assumptions of the multivariable linear regression model were satisfied. To examine if NT-proBNP would maintain any diagnostic value after knowing the echocardiogram, we added LVEF and severe valvular heart disease to the model. To identify characteristics that could affect the diagnostic ability of NT-proBNP, covariates in the final multivariable model were checked for interaction with ADHF using a likelihood ratio test. To obtain an index of diagnostic performance of NT-proBNP across characteristics interacting with ADHF, ROC curves were generated and AUCs were compared. Statistical analysis was performed using Stata software, version 11.2. A value of p<0.05 was considered to indicate statistical significance.

RESULTS

Population and Initial Triaging by use of NT-proBNP

A total number of 824 patients had been admitted with dyspnoea during the 180 days of screening and 654 patients were eligible for diagnostic workup. The difference of 170 (21%) patients were lost due to missing NT-proBNP (n=105) or echocardiography (n=65). Patients with missing NT-proBNP were younger (68 years versus 72 years, p<0.01) but same gender (female gender 60% versus 52%, p=0.1) compared to eligible patients. Reasons for missing echocardiograms among the 65 patients were: death within 72 hours of admission in 15 patients (23%); a decision to stop diagnostic procedures due to poor prognosis, or transfer to another hospital in 38 (58%) patients; patients who rejected any diagnostic procedures or unexpectedly left the department, in 12 patients (18%).

Of the 654 eligible patients, 194 (30%) had NT-proBNP below rule-out level. Of note, one patient had certain ADHF and preserved LVEF but was excluded due to NT-proBNP below rule-out. Hence, the negative predictive value of using an NT-proBNP cut-off at 35 pmol/l was 99.5% (193/194). NT-proBNP above rule-in was present in 303 (46%) patients, and 157 patients (24%) had intermediate NT-proBNP. A severe non-cardiac condition was the primary complaint in 56% (88/157) of the patients with intermediate NT-proBNP levels, and these were therefore not considered to have ADHF. Thus, 69 patients (44%) with intermediate NT-proBNP levels and all 303 patients with NT-proBNP above rule-in (Figure 1) were included in the analysis for examination of ADHF and the added value of NT-proBNP.

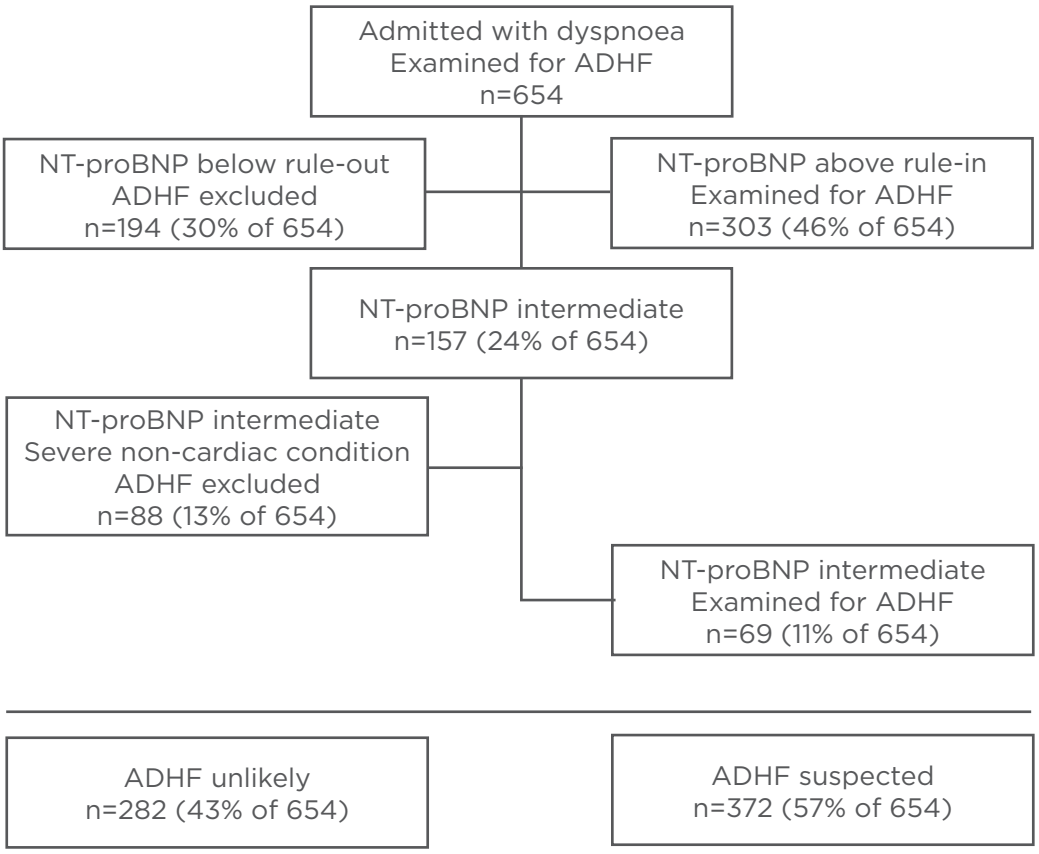

Figure 1: Flowchart of diagnostic workup in the study using NT-proBNP level.
'Rule-out' NT-proBNP defined as 35 pmol/L; 'Rule-in' NT-proBNP defined as >50, >100, and >200 pmol/L for ages 40-50, 50-75, and >75 years, respectively.
ADHF: acute decompensated heart failure; NT-proBNP: N-terminal of the prohormone brain natriuretic peptide.

Diagnosis of ADHF in Patients not ruled out by NT-proBNP

Among the 372 included patients, certain ADHF was decided in 45% (166/372), plausible ADHF in 23% (85/372), and no ADHF in 32% (121/372). Comparisons of the clinical characteristics at presentation are shown in Table 1. With increasing ADHF probability (no, plausible, or certain), several significant associations with clinical characteristics were found. Of the 121 patients without ADHF 10% had a history of HF and 19% atrial fibrillation (Afib), but these conditions were decided unimportant compared to the primary non-ADHF complaint that had caused hospitalisation. Patients with ADHF were more likely to be men and have a medical history of HF, ischaemic heart disease, or hypertension. LVEF decreased with increasing ADHF probability, and current Afib/flutter (AFL) and severe valvular disease was more prevalent. Patients with decreasing ADHF probability were more likely to have a history of COPD and a chest X-ray with signs of COPD. Current smoking was equally frequent among the three patient groups. Patients with lower ADHF probability had higher NT-proBNP level, C-reactive protein level, higher body temperature, and more often pneumonia on chest X-ray.

Diagnostic Value of NT-proBNP

Patients with certain ADHF (n=166) had a median NT-proBNP concentration of 597 pmol/l (IQR 260-1,350), patients with plausible ADHF (n=85) had a median NT-proBNP concentration of 301 pmol/l (IQR 153-577), and patients with no ADHF (n=121) had a median NT-proBNP concentration of 213 pmol/l (IQR 113-563) ($p<0.001$ for trend). ROC analyses using NT-proBNP showed AUC of 0.69 (95% CI; 0.64-0.74, $p<0.001$), for differentiating certain ADHF from plausible/no ADHF. ROC analysis for differentiating certain/plausible ADHF from no acute HF showed AUC of 0.66 (95% CI; 0.60-0.72, $p=0.002$). If the diagnosis of ADHF was based only on the study physician, the AUC was

0.68 (95% CI; 0.63-0.73, p=0.001); when based only on the clinical physician, the AUC was 0.65 (95% CI; 0.60-0.71, p=0.003) (p=0.5 for AUC difference).

Factors Associated with NT-proBNP and Diagnosis of Acute HF

In multivariable linear regression analysis certain ADHF, but not plausible ADHF, was independently associated with NT-proBNP (Table 2). If the echocardiographic information about LVEF and severe valvular disease was entered into the model, there was no association of ADHF with NT-proBNP level. Of note, an interaction was found for ADHF and current Afib/AFL showing only an association between current Afib/AFL and NT-proBNP level in patients without ADHF (p=0.04). We therefore examined the performance of NT-proBNP to diagnose certain ADHF from plausible/no ADHF in patients with sinus rhythm and found a significant but modest association (AUC of 0.71 with 95% CI: 0.64-0.78). The same analysis in patients with Afib/AFL showed no diagnostic performance of NT-proBNP to diagnose certain ADHF (AUC of 0.58 with 95% CI: 0.48-0.68) (p=0.04 for AUC difference).

Table 1: Characteristics of patients with suspected acute decompensated heart failure.

Covariate	Certain ADHF (n=166)	Plausible ADHF (n=85)	No ADHF (n=121)	p Value
Demographics				
Age (years), mean (SD)	77 (12)	77 (12)	75 (11)	0.1
Male gender (%)	58%	41%	43%	<0.01
Body mass index (kg/m^2), mean (SD)	27.8 (6.5)	25.6 (5.9)	25.0 (5.3)	<0.001
Medical history				
Prior Heart Failure (%)	43%	26%	10%	<0.001
Hypertension (%)	51%	51%	45%	<0.001
Ischaemic heart disease (%)	29%	26%	16%	<0.01
Stroke (%)	14%	24%	16%	0.7
Diabetes (%)	24%	21%	15%	0.06
COPD (%)	25%	42%	54%	<0.001
Currently smoking (%)	31%	39%	41%	0.07
Clinical findings				
Respiration (breaths/min), mean (SD)	24 (7)	23 (9)	24 (6)	0.7
Temperature (Celsius), mean (SD)	36.0 (0.8)	36.7 (1.0)	36.9 (1.0)	<0.01
X-ray pneumonia (%)	11%	27%	31%	<0.001
Left ventricular dysfunction				
LVEF (%), mean (SD)	38 (15)	49 (14)	55 (11)	<0.001
Severe valvular disease (%)	19%	6%	3%	<0.001
Atrial fibrillation/flutter (%)	51%	29%	19%	<0.001
Biochemistry				
NT-proBNP (pmol/l), median (IQR)	597 (260-1350)	301 (153-577)	213 (113-563)	<0.001
eGFR (ml/min), median (IQR)	65 (47-77)	61 (78-42)	68 (49-85)	0.3
Haemoglobin (mmol/l), mean (SD)	8.0 (1.1)	7.8 (1.3)	7.8 (1.3)	0.1
C-reactive protein (mg/l), median (IQR)	16 (10-36)	22 (10-81)	58 (14-158)	<0.001

ADHF: acute decompensated heart failure; NT-proBNP: N-terminal of the prohormone brain natriuretic peptide; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; SD: standard deviation; IQR: interquartile range; COPD: chronic obstructive pulmonary disease.

Table 2: Multivariable correlations of clinical and echocardiographic indices with log NT-proBNP levels.

Covariate	Model without LVEF and Severe Valvular Disease			Model with LVEF and Severe Valvular Disease		
	Regression Coefficients (95% CI)		p Value	Regression Coefficients (95% CI)		p Value
Plausible ADHF (yes vs. no)	0.12	(-0.16 ; 0.40)	0.4	-0.08	(-0.34 ; 0.17)	0.5
Certain ADHF (yes vs. no)	0.73	(0.48 ; 0.97)	<0.001	0.09	(-0.16 ; 0.35)	0.5
Age	0.01	(0.00 ; 0.02)	0.04	0.01	(0.01 ; 0.02)	0.001
Current Afib/AFL (yes vs. no)	0.32	(0.09 ; 0.55)	0.006	0.34	(0.13 ; 0.54)	0.001
Haemoglobin	-0.15	(-0.23 ; -0.06)	0.001	-0.15	(-0.23 ; -0.07)	<0.001
Glomerular filtration rate	-0.01	(-0.01 ; -0.01)	<0.001	-0.01	(-0.01 ; 0.00)	<0.001
LVEF	------	----------	-------	-0.03	(-0.04 ; -0.02)	<0.001
Severe valvular disease (yes vs. no)	------	----------	-------	0.62	(0.31 ; 0.93)	<0.001

ADHF: acute decompensated heart failure; LVEF: left ventricular ejection fraction; Afib/AFL: atrial fibrillation/flutter; NT-proBNP: N-terminal of the prohormone brain natriuretic peptide; CI: confidence interval.

In a supplementary ROC analysis, a diagnosis of certain/plausible ADHF from patients with no ADHF, the AUC was 0.67 (95% CI: 0.60-0.73) for patients with sinus rhythm, and 0.51 (95% CI: 0.39-0.63) for patients with current Afib/AFL (p=0.03 for AUC difference). The AUC for current Afib/AFL was not statistically different from AUC=0.5 (no discriminatory ability) in either of the two analyses (p=0.1 and p=0.8, respectively) (Figure 2).

DISCUSSION

The primary finding was that in a real-world setting of all comers with dyspnoea, NT-proBNP below rule-out levels will safely exclude acute HF in 30% of the patients. Secondly, we could not demonstrate any added diagnostic value of NT-proBNP in patients with Afib or AFL.

NT-proBNP and Diagnosis of ADHF

It is essentially important, but also difficult, to diagnose patients with dyspnoea in the acute setting. Dyspnoea is a frequent symptom leading to acute hospital admission, and extensive diagnostic work-up is often required. ADHF is predominantly a disease of the elderly, but its presentation is often complicated by multiple comorbidities that can also cause dyspnoea. In this context, ruling out ADHF in 30% of patients by use of NT-proBNP is useful since only one patient in our study had ADHF and NT-proBNP below rule-out value. This result could not have been foreseen, as the mean age was 77 years in our study, unlike another study that investigated much younger patients (mean age 57 years) and found 48% to have NT-proBNP below rule-out.[7] Rule-out levels are well established in current guidelines, but so far the clinical value of rule-in levels have yet to be clearly established,[1,2] and our study elucidates this matter. We find that NT-proBNP values above rule-in cannot be taken as a surrogate for ADHF because fewer than half of such patients had ADHF as the primary disorder responsible for their admittance. Further studies are needed to demonstrate if a fast track echocardiogram for patients with NT-proBNP above rule-in values will have a prognostic benefit.

Previous studies have reported NT-proBNP and BNP to be excellent at distinguishing patients with ADHF from patients without ADHF.[1-3] Since rule-out values are generally accepted, our study extended this concept by focusing on patients with NT-proBNP above rule-out values. This strategy obviously led to a lower diagnostic value, but the very low AUC (<0.80) does not justify any added value. In studies providing the evidence of the diagnostic ability of NT-proBNP and BNP, all patients did not undergo echocardiography.[1-3] Our data clearly establish that patients suspected of

ADHF with an elevated NT-proBNP should have an echocardiography performed, not only due to characterising the cardiac phenotype, but also due to guiding the physician in the difficult ADHF diagnosis in patients with a large burden of comorbidity that may increase NT-proBNP on its own.

Importance of Afib/AFL for Diagnostic Value of NT-proBNP

Covariates found to be independently associated with NT-proBNP in our study were well in accordance with previous studies, but importantly, an interaction between a diagnosis of ADHF and current Afib/AFL was found.[11-15] Current Afib/AFL primarily increased the NT-proBNP concentrations in patients without ADHF. This finding has been described earlier for both NT-proBNP and BNP, and higher cut-off values have therefore been proposed in patients with Afib/AFL.[14,16] However, in our study we found Afib to undermine the discriminatory ability of NT-proBNP. The clinical implication would be to omit NT-proBNP testing in patients with current Afib or AFL who should already have an indication for echocardiography. The prevalence of current Afib/AFL in patients with ADHF in our study (30-40%) was similar to other ADHF studies.[17-19] Other studies obtained higher diagnostic performance of NT-proBNP perhaps partly due to a much lower prevalence of Afib in patients without ADHF, but a direct comparison to our study containing only patients with high NT-proBNP is difficult. Several mechanisms are suspected to increase levels of NT-proBNP and BNP in Afib, including a primary increase in the secretion induced by the Afib per se, and/or a secondary increase in the secretion due to impaired cardiac function, LV wall stress, or increased LV filling pressures in the absence of overt ADHF.[20,21]

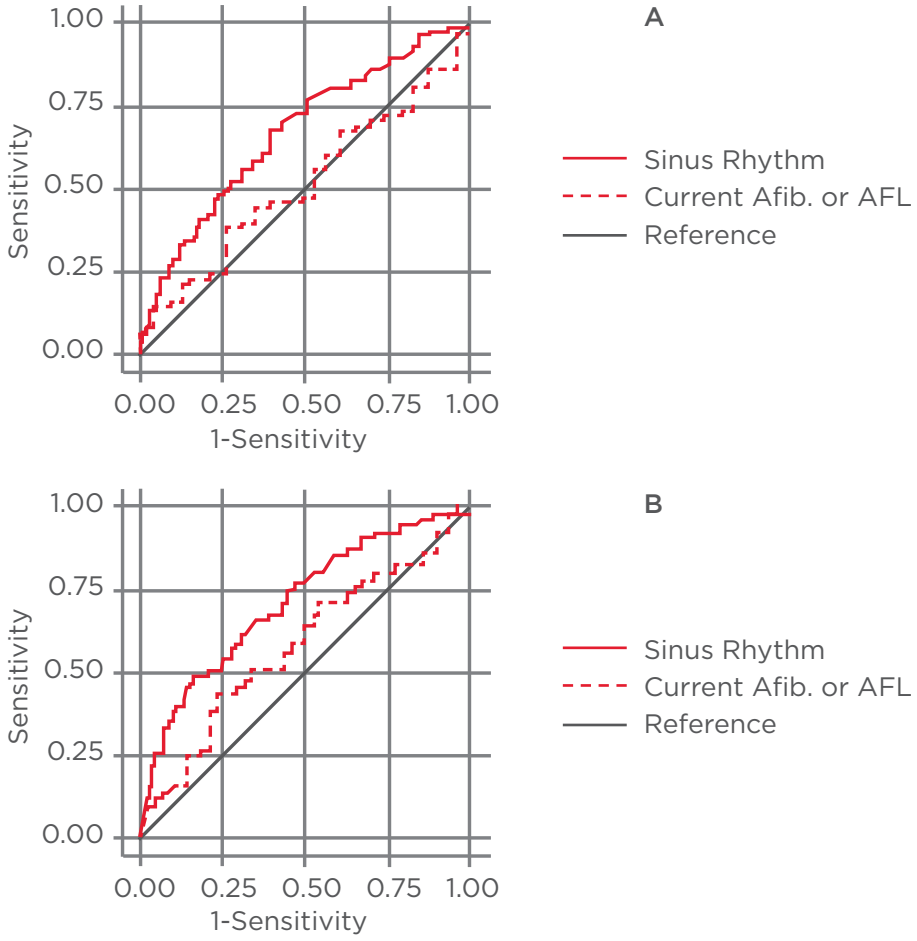

Figure 2: Receiver-operating characteristic curves for NT-proBNP as a continuous parameter in differentiating patients with certain ADHF from plausible/no ADHF (A), and differentiating patients with certain/plausible ADHF from no ADHF (B) according to presence of sinus rhythm (full line) or current atrial fibrillation or flutter (dashed line).

Strengths and Limitations

It is notoriously challenging to study acute dyspnoea patients. We believe it is a positive result to have performed a study under these conditions, which reflect a real-world setting. The fact that NT-proBNP is becoming a routine test in many countries makes the results of this study more applicable. It is a methodological limitation that the study physician was not blinded to NT-proBNP level.

However, we reduced this shortcoming by having objective criteria and two other NT-proBNP blinded physicians to resolve the final diagnosis. The effect of not having the study physician blinded to NT-proBNP would probably be a bias towards having a higher diagnostic value. However, there was no significant increase in the AUC when the study physician was compared to the physician without knowledge of NT-proBNP level, and in both cases AUCs were <0.7, indicating only a modest diagnostic value. A recent randomised study of BNP supports our finding.[22]

NT-proBNP analysis was performed on the routine blood samples drawn within 1-2 hours from primary presentation (emergency department or hospital ward), and we cannot rule out that early treatment with nitrates and diuretics, before blood sampling, could have influenced our results. The lack of a gold standard for ADHF is another limitation. We used the widely used Framingham criteria assessed at admission, to ensure conformity in the understanding of ADHF.[8,17-19,23] Missing data were problematic in the study since 21% of the patients had to be excluded. Patients with missing NT-proBNP were younger compared to all patients with available NT-proBNP. Inclusion of these patients could potentially have changed our results towards a higher diagnostic value for NT-proBNP. Patients with missing echocardiography and NT-proBNP above rule-out were similar in terms of age, gender, and NT-proBNP level, and we suspect that the inclusion of these patients in the analysis would have had only a minor influence on our results.

IMPLICATIONS

The implications of our results are that, in elderly patients admitted acutely with dyspnoea, NT-proBNP levels below rule-out provide the physician with a test that nearly rules out ADHF in 30% of patients. This information is useful when planning resources for an emergency department and allocation of echocardiographic capacity. The diagnostic value of NT-proBNP in patients with values above rule-out is limited and does not at present support triaging based on NT-proBNP to identify patients with ADHF. However, current Afib/AFL removes the limited added diagnostic value of NT-proBNP, and NT-proBNP testing seems almost pointless in these.

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