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ORIGINAL ARTICLE

New York Heart Association class versus amino-terminal pro-B type natriuretic peptide for acute heart failure prognosis

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Abstract

Background: The prognostic value of the New York Heart Association classification (NYHAC) in acutely decompensated heart failure (ADHF) is unknown.

Objectives: We sought to determine the relative value of NYHAC among patients with concomitantly measured amino-terminal pro-B type natriuretic peptide (NT-proBNP) at presentation with ADHF.

Materials and methods: NYHAC was determined for 720 patients with ADHF and 1-year mortality status was examined. Cox-proportional hazards analysis compared the prognostic accuracy of NYHAC with other ADHF risk measures.

Results: NYHAC had a significant univariate association with 1-year mortality status (HR 1.41, 95% confidence interval (CI) 1.03–1.94; $p = 0.03$) but was not a significant predictor of death in a multivariable model that included NT-proBNP (HR 2.14; 95% CI 1.65–2.81, $p < 0.001$).

Conclusions: In contrast to objective measures such as NT-proBNP, the NYHAC appears to provide limited prognostic information among individuals with ADHF.

Keywords: *Acute decompensated heart failure; NYHA; prognosis; NT-proBNP; natriuretic peptides*

Introduction

With the growing epidemic of heart failure (HF), tools to assess rapidly the severity and prognsosis of this morbid disease state are greatly needed. The New York Heart Association (NYHA) classification is a widely used method for the assessment of disease severity among patients with chronic HF and is commonly applied to predict response to HF therapy. As such, the NYHA classification has emerged as a popular eligibility criterion for clinical trial enrolment in patients with chronic systolic and non-systolic HF (Cleland et al. 2005, Bardy et al. 2005, Young et al. 2004, Ahmed et al. 2006, Scrutinio et al. 1994) and has been recommended for risk assessment in this context (Fonarow et al. 2005, Senni et al. 2006, Levy et al. 2006). However, the systematic assessment of the prognostic accuracy of the NYHA classification in patients with acutely decompensated HF (ADHF) remains uncertain.

Natriuretic peptide testing, including that for B-type natriuretic peptide (BNP) and its amino-terminal

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cleavage fragment (NT-proBNP), has recently been established as a powerful tool for mortality risk assessment across the entire spectrum of HF, including those individuals with ADHF (Berger et al. 2002, Maisel et al. 2004, Miller et al. 2007). Although both BNP and NT-proBNP have been shown to correlate with NYHA symptom severity, significant natriuretic peptide concentration overlap across the NYHA groups has been observed (Januzzi et al. 2005, Maisel et al. 2002). We therefore undertook the present study to address the primary hypothesis that natriuretic peptide testing would provide a more accurate assessment of mortality risk than the NYHA classification among individuals with ADHF. In addition, we analysed the prognostic accuracy of natriuretic peptide testing and NYHA classification in patients with ADHF segregated by the presence of normal or reduced left ventricular systolic function.

Methods

Baseline and follow-up information from the International Collaborative of NT-proBNP (ICON), a multicentre registry of trial data assessing the role of NT-proBNP for the diagnosis of ADHF were utilized for this study (Januzzi et al. 2006). The ICON study population consists of patients from three previously reported prospective clinical trials of NT-proBNP testing from Christchurch, New Zealand, Barcelona, Spain and Boston, MA, USA (Januzzi et al. 2005, Lainchbury et al. 2003, Bayes-Genis et al. 2004). Each trial enrolled unselected patients presenting to the emergency department with ADHF. In addition, previously unpublished data from patients in a HF registry at the University Hospital of Maastricht, the Netherlands were included.

All data sources had compatible inclusion/exclusion criteria, and all studies collected similar clinical information, including standard demographics, medical history, drug therapy, presenting symptoms and signs, physical examination, radiographic studies (typically plain chest radiographs), electrocardiography results and results of haematology, blood chemistry and NT-proBNP testing; statistical analysis of the four sites demonstrated no heterogeneity with respect to outcomes (Januzzi et al. 2006).

NYHA class designation was assigned at the time of enrolment by a study clinician who was blinded to the results of NT-proBNP testing, and NYHA symptom severity was judged consistent with definitions used in the parent text describing the scale. The diagnosis of ADHF was determined as described in each study (Januzzi et al. 2005, Lainchbury et al. 2003, Bayes-Genis et al. 2004). Of the 1256 patients in ICON, 720 (57%) were diagnosed with ADHF and comprise the cohort analysed in this report.

Baseline data

Historical information, physical findings and the results of routine diagnostic testing obtained during the initial presentation were considered. Estimated glomerular filtration rate values were calculated by the modified diet in renal disease (MDRD) equation (Levey et al. 1999). Individuals with a left ventricular ejection fraction <50% were considered to have systolic HF while individuals with an ejection fraction above this value were considered to have HF with preserved systolic function.

Blood samples for the measurement of NT-proBNP concentration were obtained at the time of enrolment. NT-proBNP was measured using a validated, commercially available immunoassay (Elecsys® proBNP, Roche Diagnostics, Indianapolis, IN, USA), using established methodology.

Endpoints

The primary endpoint of this analysis was 1-year mortality. Death information was ascertained from hospital medical records, death certificates and telephone follow-up with referring physicians.

Statistical analysis

Data are presented as mean ± SD for continuous, normally distributed variables and as medians with interquartile ranges (IQR) for non-normally distributed variables.In order to maintain consistency with prior reports, we categorized patients into two groups based on presentation NT-proBNP level (≥5180 ng l^{-1} vs <5180 ng l^{-1}), as prior analyses had determined this to be an appropriate cut-off point for predicting shorter-term mortality in ADHF (Januzzi et al. 2006).

Differences in baseline variables among individuals in each NHYA class were assessed with analysis of variance. Univariate screening of baseline variables was used to identify candidate independent predictors of 1-year mortality using χ^2 testing for categorical variable and Wilcoxon's rank sum for continuous variables. Multivariable analysis with forward step-wise logistic regression and bootstrapping, including all candidate variables with a univariable p-values ≤0.10, was performed to identify independent predictors of 1-year mortality. Results are presented as hazard ratios (HR) or odds ratios (OR) with 95% confidence intervals (CI). In this model, we controlled for variation in observed baseline variables and survival rates between the four contributing clinical centres. Survival curves were calculated using the Kaplan–Meier method and differences between the curves were evaluated using the log-rank statistic. Aside from the p-value used for regression variable selection specified above, a p-value of <0.05 was considered significant for all analyses.

Results

Baseline characteristics

Of the 720 patients with ADHF studied, 55 (7.6%) had NYHA class II symptoms, 348 (48.4%) had NYHA class III symptoms, and 317 (44.0%) had class IV symptoms. Baseline characteristics as a function of NYHA class are presented in Table 1. Higher NYHA class (> functional class II) on presentation was associated with higher likelihoods of prior HF and obstructive pulmonary disease. Rising NYHA class was associated with increasing prevalence of HF symptoms by history including orthopnoea and paroxysmal nocturnal dyspnoea. Similarly, with

Table 1. Baseline characteristics among 720 subjects with acutely decompensated heart failure as a function of New York Heart Association (NHYA) class.

Characteristic	NYHA II ($n=55$)	NYHA III ($n=348$)	NYHA IV ($n=317$)	p-Value
Age (years), mean ± SD	72.1 ± 13.7	75.1 ± 11.8	75.1 ± 11.1	0.45
Male gender, %	56.4	49.1	53	0.66
Body mass index (kg m–2), mean ± SD	25.9 ± 4.3	26.8 ± 6.1	27.2 ± 5.8	0.08
African ethnicity, %	7.3	1.4	1.9	0.34
Prior history, %				
Hypertension	60	58	64.4	0.56
Coronary artery disease	47.3	54	52.4	0.21
Prior myocardial infarction	30.9	34.8	34.8	0.38
Prior heart failure	40	50	56.2	0.05
COPD or asthma	16.4	28.2	31.9	<0.001
Loop diuretic use, %	47.3	60.4	62	0.002
Symptoms/signs, %				
PND	12.7	26.4	39.7	<0.001
Orthopnoea	27.3	46.4	58.6	<0.001
Lower extremity oedema	40	47.4	47.3	0.62
Chest pain	43.6	33.7	32.5	0.06
Cough	23.6	30.2	34.7	0.002
Fever	1.8	5.7	4.7	0.89
Physical examination				
Pulse, mean ± SD	86.7 ± 23.6	92.0 ± 26.0	95.8 ± 26.5	0.01
Jugular venous distension, %	43.6	53.7	48.3	0.63
Wheezing on lung exam, %	3.6	12.7	20.8	<0.001
S3 gallop, %	7.3	6.9	7.3	0.3
Lower extremity oedema, %	45.5	59.5	53.9	0.34
ECG findings, %				
Sinus rhythm	65.5	60.9	57.7	0.72
Atrial fibrillation or flutter	25.5	35.6	35.6	0.49
Left bundle branch block	18.2	14.9	17.4	0.82
Chest radiography findings, %				
Interstitial oedema	27.3	27	48.3	<0.001
Alveolar oedema	10.9	9.5	14.8	0.005
Pleural effusion	21.8	25.6	26.2	0.58
Diagnostic testing				
Glucose (mg dl–1), mean ± SD	136.7 ± 94.5	136.9 ± 79.0	158.2 ± 82.9	<0.001
Haemoglobin (g dl–1), mean ± SD	11.6 ± 3.5	12.8 ± 3.0	12.6 ± 5.6	0.59
Creatinine (mg dl–1), mean ± SD	1.4 ± 0.5	1.3 ± 0.6	1.3 ± 0.7	0.81
EGFR (ml min–1 1.73 m–2), mean ± SD	58.3 ± 26.9	61.1 ± 24.7	60.2 ± 27.4	0.69
Troponin-T (ng ml–1), mean ± SD	0.3 ± 1.0	0.2 ± 1.0	0.1 ± 0.4	0.41
NT-proBNP (ng l–1), median (IQR)	3512 (1395–8588)	5610 (2260–11001)	6196 (2757–13295)	<0.001
Systolic heart failure, %	50	59	51.9	0.67
Mortality, %				
60-Day mortality	9.1	11.5	13.9	0.05
1-Year mortality	20	30.7	33.8	0.001

COPD, chronic obstructive pulmonary disease; EGFR, estimated glomerular filtration rate; PND, paroxysmal nocturnal dyspnoea; NT-proBNP, amino-terminal pro-B type natriuretic peptide.

higher NYHA symptom severity, results of objective testing (chest radiography and NT-proBNP) were more consistent with more severe HF.

One-year survival status and NYHA class

The overall 1-year mortality rate among individuals presenting with ADHF was 31.5% (225/720). When considered as a function of NYHA class at the time of index presentation, mortality rates were: 20.1% for class II, 30.7% for class III and 33.3% for class IV (Figure 1). Rates of death were significantly higher among individuals presenting with both class III and class IV symptoms when compared with individuals presenting with NYHA class II symptom severity ($p = 0.008$ for class II vs III, $p < 0.001$ for class II vs class IV). However there was no significant difference between the cumulative mortality rates of individuals with NYHA class III compared with those with class IV (30.7% vs 33.8%, $p = 0.78$) symptoms.

NYHA and outcomes: subgroup analysis by left ventricular function

Comprehensive echocardiographic data defining left ventricular ejection fraction during the index hospital encounter was available in 655/720 (91%) individuals. Among these individuals, 55% had left ventricular systolic dysfunction while the remaining 45% had ADHF with preserved left ventricular systolic function.

The relationships between NYHA symptom severity, rates of 1-year mortality and ventricular function are shown in Figure 1. Among individuals with ADHF and left ventricular systolic dysfunction, the highest mortality rate (35%) was observed among those with NYHA class III symptoms while patients with class II had significantly lower rates of death (16%, $p < 0.001$ vs class II). Although numerically lower, those with class IV symptoms were not statistically different in their death rate at 25% ($p = 0.09$ vs class II).

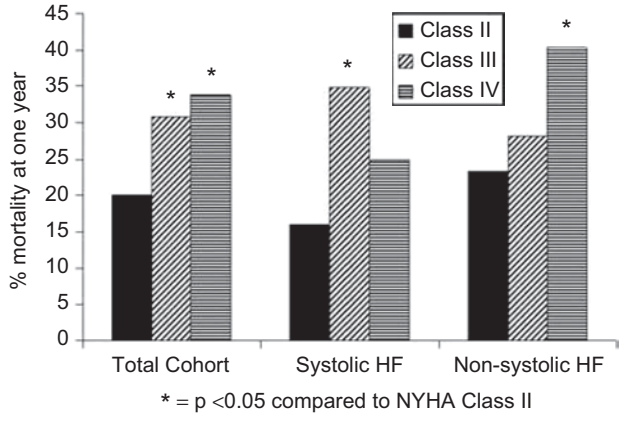

Figure 1. One-year mortality as a function of the New York Heart Association (NYHA) class among the total cohort and then among individuals stratified by left ventricular systolic function. HF, heart failure.

In contrast, the highest mortality rate among individuals with ADHF and preserved left ventricular systolic function was observed among those presenting with NYHA class IV symptoms, with a preserved trend of higher mortality rates paralleling higher NYHA classification (23%, 28%, and 40% for classes II, III, and IV, respectively; $p < 0.001$).

Cox proportional multivariable modelling was performed to determine factors independently associated with mortality status at 1 year among all subjects with ADHF, as well as in those with ADHF in the presence of impaired and preserved left ventricular systolic function (Table 2). Although NYHA class had an overall association in univariate analyses with 1-year mortality status (HR 1.41, 95% CI 1.03–1.94; $p = 0.03$), it was not a significant predictor of death in the multivariable model for all ADHF subjects (HR 1.12, 95% CI 0.90–1.41; $p = 0.29$), those with systolic dysfunction (HR 1.34, 95% CI 0.97–1.87; $p = 0.08$) or those with preserved left ventricular function (HR 0.86, 95% CI 0.62–1.21; $p = 0.41$).

One-year survival status and NT-proBNP level

The relationship between index presentation NT-proBNP level and mortality status at 1 year is shown in Figure 2A.

Table 2. Multivariable predictors of 1-year mortality status among all individuals presenting with acutely decompensated heart failure (ADHF), as well as a function of systolic and non-systolic mechanism of failure.

Characteristic	HR (95% CI)	*p*-Value
All individuals presenting with ADHF		
NT-proBNP >5180 pg ml^{-1}	2.14 (1.65–2.81)	<0.001
Serum creatinine	1.31 (1.09–1.59)	0.005
Tobacco use	1.18 (1.01–1.37)	0.03
Age	1.03 (1.02–1.05)	<0.001
History of hypertension	0.69 (0.52–0.92)	00.01
NYHA class	1.12 (0.90–1.41)	00.29
ADHF with impaired systolic function		
NT-proBNP >5180 pg ml^{-1}	2.43 (1.49–3.97)	<0.001
Serum creatinine	1.51 (1.23–1.85)	<0.001
Tobacco use	1.21 (0.96–1.52)	0.10
Age	1.01 (0.99–1.03)	00.26
History of hypertension	0.58 (0.39–0.88)	00.009
NYHA class	1.34 (0.97–1.87)	00.08
ADHF with preserved left ventricular systolic function		
NT-proBNP >5180 pg ml^{-1}	2.19 (1.32–3.64)	0.002
Serum creatinine	1.01 (0.66–1.58)	0.94
Tobacco use	1.23 (0.96–1.58)	0.79
Age	1.06 (1.03–1.10)	<0.001
History of hypertension	0.93 (0.55–1.56)	00.79
NYHA class	0.86 (0.62–1.21)	00.41

HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association; NT-proBNP, amino-terminal pro-B type natriuretic peptide.

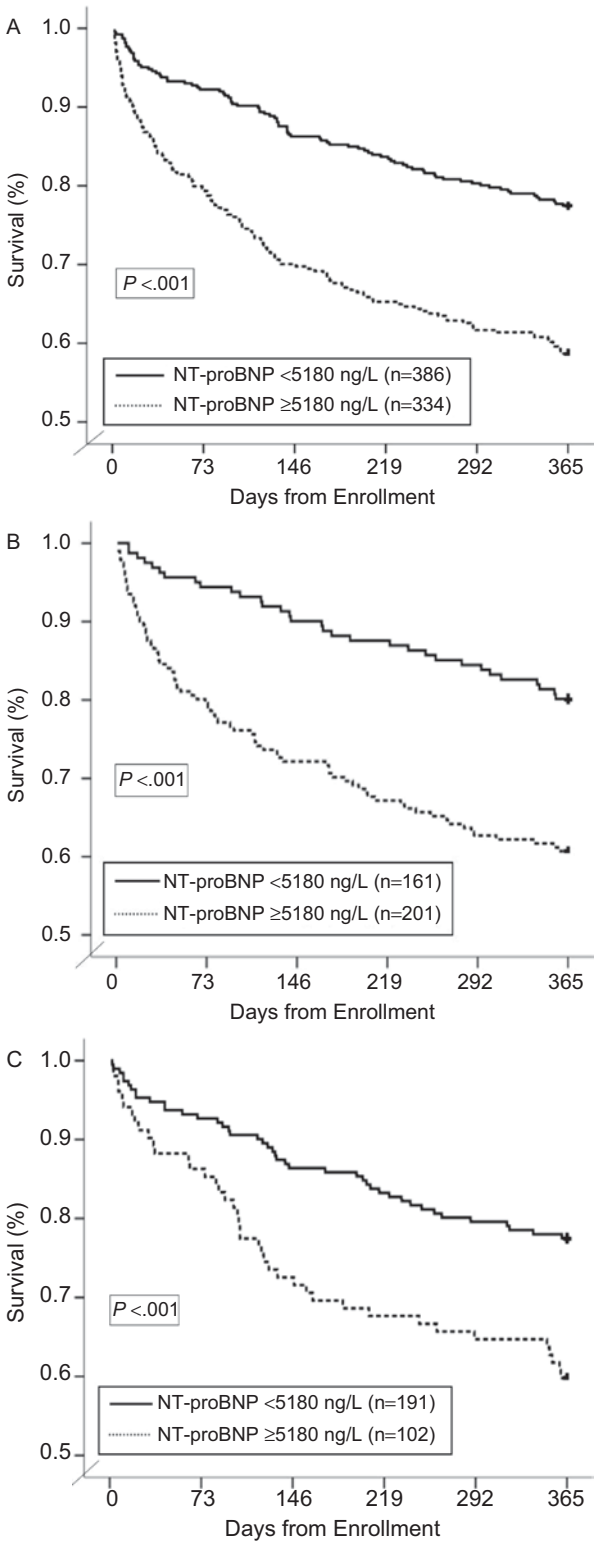

Figure 2. One-year mortality as a function of amino-terminal pro-B type natriuretic peptide (NT-proBNP) level at the time of index presentation among (A) 720 individuals with acutely decompensated heart failure, as well as a function of underlying (B) left ventricular systolic dysfunction or (C) preserved left ventricular function.

The cumulative 1-year mortality rate among individuals with a presenting NT-proBNP level of ≥5180 ng l^{-1} was 42% compared with 24% among individuals with an NT-proBNP level below this cut-off point (HR 2.6, 95% CI 2.0–3.3; $p < 0.001$).

NT-proBNP and outcomes: subgroup analysis by left ventricular function

The relationship between NT-proBNP and mortality among individuals with impaired or preserved left ventricular systolic function is detailed in Figure 2B and C. Among individuals with ADHF and left ventricular systolic dysfunction, those with an NT-proBNP ≥5180 ng l^{-1} had a 1-year mortality rate of 40% compared with a mortality rate of 22% ($p < 0.001$). Similarly, among ADHF patients with preserved left ventricular function, those with an NT-proBNP ≥5180 ng l^{-1} had a 1-year mortality rate of 43% compared with a mortality rate of 23% among individuals with an NT-proBNP value below this level ($p < 0.001$).

Multivariable Cox hazard modelling demonstrated an index presentation NT-proBNP level of ≥5180 ng l^{-1} to be the strongest predictor of 1-year mortality among all subjects (HR 2.14, 95% CI 1.65-2.81; $p < 0.001$). A robust predictive accuracy of NT-proBNP was also observed within those with HF and systolic dysfunction (HR 2.43, 95% CI 1.49–3.97; $p < 0.001$) as well as those with HF and preserved systolic function (HR 2.19, 95% CI 1.32–3.64; $p = 0.002$).

Combination of NYHA and NT-proBNP

Finally, we assessed whether NYHA class designation added useful prognostic information following stratification based on an NT-proBNP level of 5180 ng l^{-1}. Within both NT-proBNP subgroups, there was a trend toward higher 1-year mortality with rising NYHA class (Figure 3); however, this trend reached statistical significance only among subjects with an index NT-proBNP <5180 ng l^{-1}. Specifically, those individuals with a NT-proBNP <5180 ng l^{-1} and NYHA class II symptoms had a significantly lower 1-year mortality (8%) compared with those individuals with similar NT-proBNP levels and higher NYHA class designation (19% and 26% for class III and IV, respectively).

Discussion

Our results demonstrate that natriuretic peptide testing is a more accurate method of determining prognosis than the NYHA classification among patients with ADHF, independent of left ventricular function. Specifically,

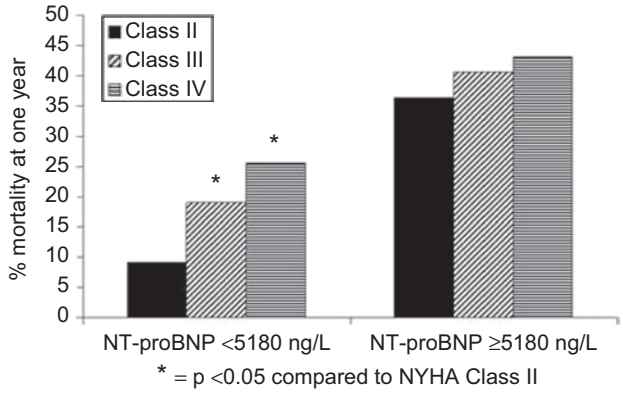

Figure 3. One-year mortality status as a function of amino-terminal pro-B type natriuretic peptide (NT-proBNP) level and New York Heart Association (NYHA) class among individuals with acutely decompensated heart failure.

NT-proBNP testing out-performed the time-honoured NYHA classification for prediction of 1-year mortality among patients with ADHF, performed well in the total cohort of patients with HF, and demonstrated equal value for risk stratification of HF with and without preserved ventricular systolic function. This latter finding is of particular importance given recent data describing the high incidence and prevalence of HF with preserved left ventricular function and the need for adequate tools to risk-stratify this population (Owan et al. 2006, Yancy et al. 2006). In contrast, NYHA class, although associated with 1-year mortality in univariable analysis, failed to retain significant prognostic utility when considered in a multivariable model including NT-proBNP level and other established prognostic variables.

The NYHA classification system was designed to provide clinicians with an objective method of describing functional capacity limitations due to symptoms of HF. Since the initial publication in 1928, the NYHA class system has undergone numerous revisions with the most recent update addressing the importance of integrating objective diagnostic testing results, rather than relying solely on subjective assessment, in the assignment of class. At the present time, the NYHA class remains a widely used method of characterizing HF severity in both clinical and research settings. Clinically, NYHA symptom severity is utilized for the evaluation and management of patients across a wide spectrum of HF presentations, from chronic stable to more acutely unstable patients, such as those in the present report (HFSA 2006, Radford et al. 2005).

A proposed relationship between NYHA class and prognosis stems from its original publication in which the authors assigned an anticipated response to therapy to each functional class. More recently, the prognostic value of the NYHA class system has been formally assessed. Specifically, Muntwyler *et al.* performed an assessment of potential prognostic factors in a large cohort of outpatients with chronic HF due to systolic dysfunction and found the presence of NYHA class III and IV symptoms to be independently associated with 1-year mortality (Muntwyler et al. 2002). Similar findings were reported by Scrutinio and colleagues who found NYHA class to be more tightly coupled with mortality than objective exercise capacity (peak oxygen consumption), age, or the presence of ventricular arrhythmia (Scrutinio et al. 1994). The prognostic utility of NYHA class among individuals with HF and preserved systolic function was recently demonstrated among individuals enrolled in the DIG trial of digoxin therapy for outpatient management of heart failure (Ahmed et al. 2006). In aggregate, the above work demonstrates that NYHA class is associated with long-term mortality status among individuals with chronic HF.

Although data defining the prognostic value of the NYHA classification derived from the chronic HF population may be applicable to individuals with ADHF, objective data substantiating this notion are lacking. Indeed, while the NYHA classification is recommended to describe patients with ADHF, prior to this analysis, the prognostic performance of the NYHA classification system among such individuals had not been directly established. With the rising use of natriuretic peptides for risk assessment in HF comes the important comparison between NYHA and these objective prognostic biomarkers. However, natriuretic peptide values often demonstrate a considerable degree of overlap between NYHA symptom class, which often leads to clinician uncertainty as to which measure is accurate from a risk-assessment perspective (Januzzi et al. 2005, Maisel et al. 2002, Maron et al. 2004, Pfister et al. 2004). Our data suggest that among ADHF patients both with and without preserved left ventricular systolic function, NT-proBNP testing, a rapidly obtained, widely available, reliably reproducible, and relatively objective measurement out-performs the NYHA classification for mortality risk assessment and must be considered the standard by which other potential prognostic indices are assessed.

Several specific aspects of our findings deserve mention. First, NYHA class performed differently among individuals with left ventricular systolic dysfunction (highest mortality among NYHA class III subjects) and among those with preserved left ventricular function (highest mortality among NYHA class IV subjects). As the underlying pathophysiology of HF is rarely certain at the time of presentation, this presents a major limitation to the use of this method for accurate risk assessment. In contrast, NT-proBNP testing performed similarly well for prognostication in both categories of HF, making determination of underlying left ventricular function unnecessary at the time of presentation risk assessment. Second, it appears that NYHA class assessment retains

prognostic importance among individuals with low or intermediate NT-proBNP levels as we detected significantly less mortality among the relatively small subgroup (55/720, 8%) of individuals with an NT-proBNP <5180 ng l^{-1} and NYHA class II symptom severity than among those with similar NT-proBNP levels and more pronounced symptoms. These results indicate that the NYHA classification may provide additive information to NT-proBNP testing among individuals with low levels of this marker.

Several potential limitations of this study merit consideration. While NYHA symptom classification is the most widely used method to describe severity of HF symptoms, we did not compare NT-proBNP to other objective methods such as those suggested by Nohria and colleagues (2003) and others (Forrester et al. 1977, Killip & Kimball 1967), which include describing patients on the basis of signs of congestion and hypoperfusion. Although the merits of this latter approach are undeniable, we argue that the use of NT-proBNP as an objective risk measure that does not rely on history or physical examination would be of even greater value to the physician not skilled in such assessments, and is probably additive to such an approach. As well, in our report, none of these clinical factors were particularly common, or associated with mortality in the presence of NT-proBNP. Lastly, this analysis was confined to a comparison of NT-proBNP testing and NYHA classification designation performed at the time of index presentation. As such, we are unable to comment on the role of either serial NT-proBNP testing or repeat NYHA classification following disease-specific therapy for 1-year mortality risk prediction. Further study to address this uncertainty is underway.

In conclusion, we have provided data clarifying the comparative prognostic performances of the NYHA classification system and NT-proBNP testing for 1-year mortality prediction among individuals with ADHF. We have demonstrated several key limitations of the NYHA system for evaluating those with acutely symptomatic HF. Our data suggest that the NYHA classification is at best a weak measure of risk among patients with ADHF. In contrast, we have shown that NT-proBNP outperforms NYHA assessment for mortality prediction in those with ADHF. Thus, we conclude that risk assessment of individuals with ADHF should be more centred on the measurement of NT-proBNP level rather than the NYHA classification. The ramifications of this conclusion are not small. We suggest that future clinical trials addressing therapeutic management of ADHF patients should consider the use of NT-proBNP testing rather than the less objective NYHA classification for decisions regarding eligibility for enrolment, as NT-proBNP testing provides a more objective, powerfully prognostic measure of risk.

Declaration of interest

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