ORIGINAL ARTICLE

Assessment of the impact of different N terminal pro brain natriuretic peptide thresholds on echocardiography services

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Abstract

Aims   N terminal pro brain natriuretic peptide (NT-proBNP) is considered a rule-out test for patients with suspected heart failure. The NT-proBNP thresholds recommended for echocardiography by the European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) are based on small studies of patients with heart failure and left ventricular (LV) systolic dysfunction (LVSD). The purpose of our study was to examine the relation between NT-proBNP and LVSD in a larger number of patients with symptoms suggestive of heart failure in a non-acute setting.
Methods and results   One thousand patients with suspected chronic heart failure underwent echocardiography within 6 months of NT-proBNP measurement. NT-proBNP was the strongest predictor of any form of LVSD in univariate (OR 2.52, 95% CI 2.19–2.91, *P* value < 0.001) and multivariate (OR 2.73, 95% CI 2.32–3.21, *P* value < 0.001) analyses. Negative predictive value (NPV) of NT-proBNP for impaired LV systolic function (ejection fraction 35–49%) was 98% at 125 pg/mL (the ESC threshold), 93% at 400 pg/mL (the NICE threshold), 91% at 1000 pg/mL and 90% at 2000 pg/mL. Corresponding values for severe LVSD (ejection fraction <35%) were 100%, 99%, 98% and 96%. The number of patients per 1000 with suspected chronic heart failure requiring echocardiography at each threshold was 851, 543, 324, and 182, respectively.
Conclusions   N terminal pro brain natriuretic peptide thresholds recommended by ESC and NICE result in large numbers of patients with suspected chronic heart failure being referred for echocardiography. Raising the NT-proBNP threshold would improve access to echocardiography with minimal negative impact on the clinical performance of this cardiac biomarker.

Keywords   NT-proBNP; Chronic heart failure; Heart failure with reduced ejection fraction

Introduction

Heart failure is a common and complex clinical syndrome of symptoms and signs caused by impairment of the cardiac function as a pump delivering oxygenated blood to organs and tissues.[1] It is associated with reduced quality of life and increased mortality.[2] Diagnosis is often challenging because breathlessness is a feature of so many other medical conditions, particularly obesity and chronic lung disease, which frequently coexist.

Natriuretic peptides are biomarkers released from myocardium in response to overall level of cardiac decompensation related to fluid overload, ischaemia, and neurohormonal activation.[1,2] Measurement is recommended in the assessment of patients presenting with symptoms suggestive of heart failure, mainly to rule out rather than rule in a diagnosis, although the thresholds below which heart failure can be safely ruled out and above which further diagnostic testing by echocardiography is required are not universally agreed. The European Society of Cardiology (ESC) recommends an N terminal pro brain natriuretic peptide (NT-proBNP) threshold of 125 pg/mL in the non-acute setting in order to rule out heart failure and that patients with higher values be referred for echocardiography.[2] National Institute for Health and Care Excellence (NICE) advises in their Chronic Heart Failure Guideline that an NT-proBNP <400 pg/mL in an untreated person

makes a diagnosis of heart failure less likely; that people with suspected heart failure and NT-proBNP 400 to 2000 pg/mL should have specialist assessment and transthoracic echocardiography within 6 weeks; and that because very high levels of NT-proBNP carry a poor prognosis, people with NT-proBNP >2000 pg/mL should be seen by a specialist and have echocardiography within 2 weeks.[1] Both NICE and ESC recommend higher NT-proBNP thresholds for ruling out heart failure in the acute setting.[1,3]

Taylor *et al*. in a small study of 304 patients in primary care, 104 of whom had a confirmed diagnosis of heart failure, endorsed the ESC threshold for referral although only 12 of their heart failure patients had left ventricular systolic dysfunction (LVSD) on echocardiography.[4] Verdu *et al*. studied 220 patients with suspected heart failure in a primary care setting and concluded that the best NT-proBNP cutpoint for ruling out heart failure was 280 pg/mL.[5] A diagnosis of heart failure was confirmed in 52 of their patients, only 16 of whom had LVSD.[5] Others have suggested that age stratified thresholds may considerably improve the ability of NT-proBNP to rule out LVSD in primary care.[6,7] Hildebrandt *et al*., in a pooled analysis of 5508 patients from 10 studies, found the best thresholds for ruling out heart failure were 50 pg/mL for those <50 years, 75 pg/mL for 50–75 years old and 250 pg/mL for those over 75.[8] Higher age-adjusted NT-proBNP thresholds of 900 pg/mL for patients aged 50 to 75 years and 1800 pg/mL for those over 75 years have been recommended for patients presenting with acute heart failure.[9,10] NT-proBNP level is also elevated in patients with renal impairment, but no optimal diagnostic threshold for heart failure has been determined.[11,12]

It is difficult to escape the view that previous studies have based their NT-proBNP thresholds for ruling out heart failure on relatively small numbers of patients with heart failure and even smaller numbers of patients with LVSD. Against this background, the purpose of our study was to examine the relation between NT-proBNP and LVSD in a larger number of patients presenting with symptoms suggestive of heart failure in a primary care (non-acute) setting. We have been able to do so because general practitioners in Dumfries and Galloway are encouraged to measure NT-proBNP as part of the diagnostic work up of patients with suspected heart failure.[13] Specifically, we wanted to determine the sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of different NT-proBNP cut points for LVSD in a primary care setting.

Methods

The study population comprised adult patients with suspected chronic heart failure who had NT-pro BNP measured in Dumfries and Galloway Royal Infirmary, a district general hospital serving the population of Dumfries and Gal-

loway in south west Scotland, between November 2014 and February 2017. We included patients whose NT-proBNP was requested by a general practitioner or at outpatient clinic review provided they had an echocardiogram within 6 months of their NT-proBNP result, serum creatinine within one month and no previous diagnosis of heart failure. We excluded patients who had their NT-proBNP measured following an emergency medical admission and patients under 18 years of age. When patients had more than one measurement of NT-proBNP we chose the result that was closest to their echocardiogram. We used the British Society of Echocardiography guideline to classify left ventricular systolic function (LVSF) as normal/low normal [left ventricular ejection fraction (EF) ≥ 50%], impaired (EF 36–49%) or severely impaired (EF ≤ 35%).[14] We also documented the presence or absence of atrial fibrillation (AF) or flutter.[15,16]

Three thousand one hundred and 15 patients had NT pro-BNP level checked during the period of study. We excluded 1954 patients with no recent echocardiogram, 156 patients with suspected acute heart failure, and 5 patients under 18 years of age, leaving a total of 1000 patients with suspected chronic heart failure for analysis. Most (76.9%) of the 1954 patients with no recent echocardiogram had NT-proBNP level <400 pg/mL indicating a low risk of LVSD. When we excluded all patients with NT-proBNP <400 pg/mL and compared the BNP distribution of those who had and did not have an echocardiogram within 6 months, we found no significant differences between the two groups (χ^2 5.03, *P* = 0.08), suggesting that those who had a recent echocardiogram were likely to be representative of the population from which they were derived.

Statistical methods

Demographic statistics including mean, median, and standard deviations, where appropriate, were obtained for all cases and sub-groups. Testing across groups was performed using Kruskal–Wallis and Mann–Whitney *U* procedures, and ordinal logistic regression models were employed to assess the respective influence of other variables at different levels of NT-proBNP and different degrees of LVSD. Sensitivity, specificity, PPV and NPV, and receiver operator characteristic curves were produced for each of the given scenarios. Analysis was performed on either IBM SPSS v26.0, VassarStats (RRID:SCR_010263) or MedCalc v19.5.

Results

Baseline characteristics

One thousand patients with suspected chronic heart failure underwent echocardiography within 6 months of an

NT-proBNP measurement. Baseline clinical characteristics of those with normal LV systolic function, impaired LV systolic function, and severe LVSD are shown in *Table 1*. Half (50.4%) were male. The average age of the entire cohort was 72.8 years. Estimated glomerular filtration rate was more than 60 mL/min in 64.5%. Only a few patients were younger than 50 (n = 35) or had estimated glomerular filtration rate <30 mL/min (*n* = 30). AF or flutter were present in 187 (18.7%) patients. One hundred and twenty-eight (12.8%)

had impaired LV systolic function and 86 (8.6%) had severe LVSD. Median NT-proBNP in those with normal LVSF was 359 pg/mL [inter-quartile range (IQR) = 163–931]. NT-proBNP was significantly higher in those with impaired LV systolic function (median = 1126, IQR = 397–2899 pg/mL) and severe LVSD (median = 3067, IQR = 1390–6795 pg/mL) (*Figure 1*).

Table 2 shows the number of patients with normal LVSF, impaired LV systolic function, and severe LVSD at different NT-proBNP thresholds. An ESC threshold of 125 pg/mL

Table 1 Baseline characteristics of all patients

	Normal LVSF	Impaired LVSF (EF 36–49%)	Severe LVSD (EF ≤35%)	All patients
All patients	786	128	86	1000
Age years (mean ± SD)	72.2 ± 11.4	75.2 ± 9.4	75.2 ± 10.4	72.8 ± 11.1
<50 years (%)	32 (4.1)	1 (0.8)	2 (2.3)	35 (3.5)
50–75 years (%)	410 (52.2)	53 (41.4)	37 (43.0)	500 (50.0)
>75 years (%)	344 (43.8)	74 (57.8)	47 (54.7)	465 (46.5)
Male (%)	371 (47.2)	79 (61.7)	54 (62.8)	504 (50.4)
Female (%)	415 (52.8)	49 (38.3)	32 (37.2)	496 (49.6)
eGFR >60 mL/min (%)	530 (67.4)	67 (52.3)	48 (55.8)	645 (64.5)
eGFR 30-60 mL/min (%)	240 (30.5)	53 (41.4)	32 (37.2)	325 (32.5)
eGFR <30 mL/min (%)	16 (2.0)	8 (6.3)	6 (7.0)	30 (3.0)
Atrial fibrillation or flutter (%)	139 (17.7)	26 (20.3)	22 (25.6)	187 (18.7)

EF, ejection fraction; eGFR, estimated glomerular filtration rate; LVSD, left ventricular systolic dysfunction; LVSF, left ventricular systolic function.

Figure 1 Box plot of N terminal pro brain natriuretic peptide (NT-proBNP) levels in patients with normal left ventricular systolic function, impaired left ventricular systolic function and severe left ventricular systolic dysfunction.
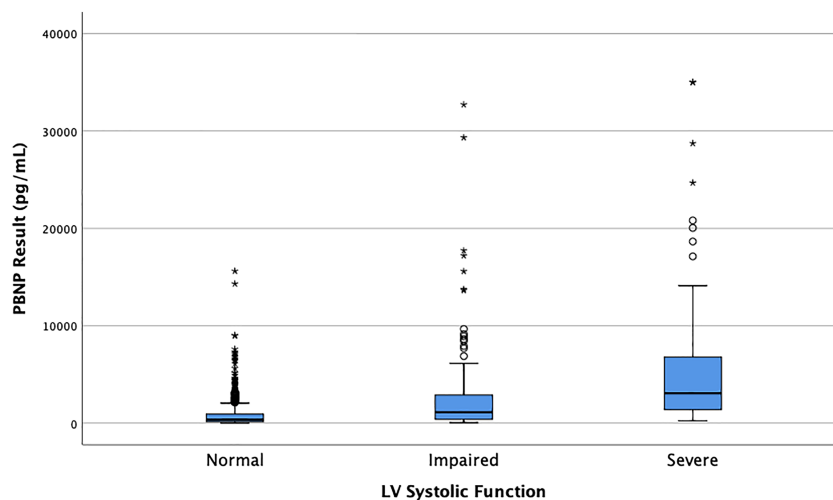
Table 2 Left ventricular systolic function at different NT-proBNP thresholds

	Normal LVSF	Impaired LVSF (EF 36–49%)	Severe LVSD (EF ≤35%)	All patients
All patients	786	128	86	1,000
NT-proBNP <125 (% of row)	146 (98.0)	3 (2.0)	0 (0.0)	149 (100.0)
NT-proBNP <280 (% of row)	330 (94.0)	19 (5.4)	2 (0.6)	351 (100.0)
NT-proBNP <400 (% of row)	420 (91.9)	34 (7.4)	3 (0.7)	457 (100.0)
NT-proBNP <1000 (% of row)	605 (89.5)	61 (9.0)	10 (1.5)	676 (100.0)
NT-proBNP <2000 (% of row)	705 (86.2)	82 (10.0)	31 (3.4)	818 (100.0)
NT-proBNP ≥2000 (% of row)	81 (44.5)	46 (25.3)	55 (30.2)	182 (100.0)

LVSD, left ventricular systolic dysfunction; LVSF, left ventricular systolic function; NT-proBNP; N terminal pro brain natriuretic peptide.

would require that 851/1000 (85.1%) patients with suspected heart failure undergo echocardiography but would miss only three patients with impaired LV systolic function or severe LVSD. A threshold of 280 pg/mL recommended by Verdu *et al*. would require echocardiography for 649/1000 (64.9%) patients and would miss 19 with impaired LV systolic function and two with severe LVSD. Corresponding figures for the NICE threshold of 400 pg/mL are 543/1000 (53.4%) echocardiograms, missing 34 impaired LV systolic function and three severe LVSD. The number of echocardiogram per 1000 patients with suspected chronic heart failure at NT-proBNP thresholds of 1000 and 2000 pg/mL decrease to 324 and 182, respectively, albeit at the cost of more patients with impaired LV systolic function and severe LVSD who are missed (*Table 2*). Conversely, the number and percentage of patients with LVSD increases as NT-proBNP increases, but only exceeds 50% when NT-proBNP is greater than 2000 pg/mL. Even then 81/182 (44.5%) patients had normal LVSF in our study.

Predictors of elevated N terminal pro brain natriuretic peptide

Interval logistic regression was performed to assess for factors independent of LVSD that are associated with elevated NT-proBNP (*Table 3*). The presence of AF or flutter was strongly associated with elevated NT-proBNP in both univariate (OR 5.64, 95% CI 4.21–7.54) and multivariate (OR 5.50, 95% CI 4.06–7.46) analyses (*Table 3*). Elevated NT-proBNP was also predicted by increasing age, male gender, and im-

paired renal function in both univariate and multivariate analyses.

Predictors of left ventricular systolic dysfunction

Raised NT-proBNP was the strongest predictor of all forms of LVSD in both univariate (OR 2.52, 95% CI 2.19–2.91) and multivariate (OR 2.73, 95% CI 2.32–3.21) analyses (*Table 4*). LVSD was also predicted by increasing age, male gender, and impaired renal function but not by AF or flutter in univariate analyses, and by the absence of AF or flutter in multivariate analyses (*Table 4*). Receiver operator characteristic curves for NT-proBNP as predictor of LVSD showed an area under curve of 0.792 ($P < 0.001$) for any form of LVSD and 0.893 ($P < 0.001$) for severe LVSD (*Figure 2*).

N terminal pro brain natriuretic peptide as a rule out test for left ventricular systolic dysfunction

Sensitivity, specificity, and negative and positive predictive values are shown in *Tables 5* and *6*. Negative predictive value (NPV), which is the probability a person with a negative test result did not have impaired LV systolic function at different NT-proBNP thresholds, was 98% at 125 pg/mL, 95% at 280 pg/mL, 93% at 400 pg/mL, 91% at 1000 pg/mL, and 90% at 2000 pg/mL. Corresponding figures for severe LVSD were 100%, 99%, 99%, 98%, and 96% (*Table 5*). NPV for an NT-proBNP threshold of 900 pg/mL in patients aged 50–75 years was 92% for impaired LV systolic function and 98% for severe LVSD. NPV for an NT-proBNP threshold of

Table 3 Predictors of elevated N terminal pro brain natriuretic peptide

| Variable	Single predictor model		Multivariate predictor model	
	Odds ratio [95% CI]	*P*	Odds ratio [95% CI]	*P*
Age	3.081 [2.47–3.85]	<0.001	2.297 [1.82–2.90]	<0.001
Male sex	1.400 [1.11–1.76]	0.004	1.363 [1.07–1.74]	0.014
eGFR	0.330 [0.27–0.41]	<0.001	0.369 [0.29–0.47]	<0.001
AF or flutter	5.638 [4.21–7.54]	<0.001	5.502 [4.06–7.46]	<0.001

AF, atrial fibrillation; CI, confidence interval; eGFR, estimated glomerular filtration rate.

Table 4 Predictors of left ventricular systolic dysfunction

Variable	Single predictor model		Multivariate predictor model	
	Odds ratio [95% CI]	*P*	Odds ratio [95% CI]	*P*
NT-proBNP	2.523 [2.19–2.91]	<0.001	2.728 [2.32–3.21]	<0.001
Increasing age	1.639 [1.23–2.17]	0.001	0.917 [0.66–1.26]	0.597
Male sex	1.828 [1.34–2.49]	<0.001	1.690 [1.20–2.36]	0.002
eGFR	0.574 [0.44–0.74]	<0.001	0.985 [0.73–1.32]	0.918
AF or flutter	1.370 [0.95–1.98]	0.092	0.490 [0.32–0.74]	0.001

AF, atrial fibrillation; CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP; N terminal pro brain natriuretic peptide.

Figure 2 Receiver operating characteristic curve for N terminal pro brain natriuretic peptide (NT-proBNP) as predictor of all forms of left ventricular systolic dysfunction (left panel) and severe left ventricular systolic dysfunction (right panel).
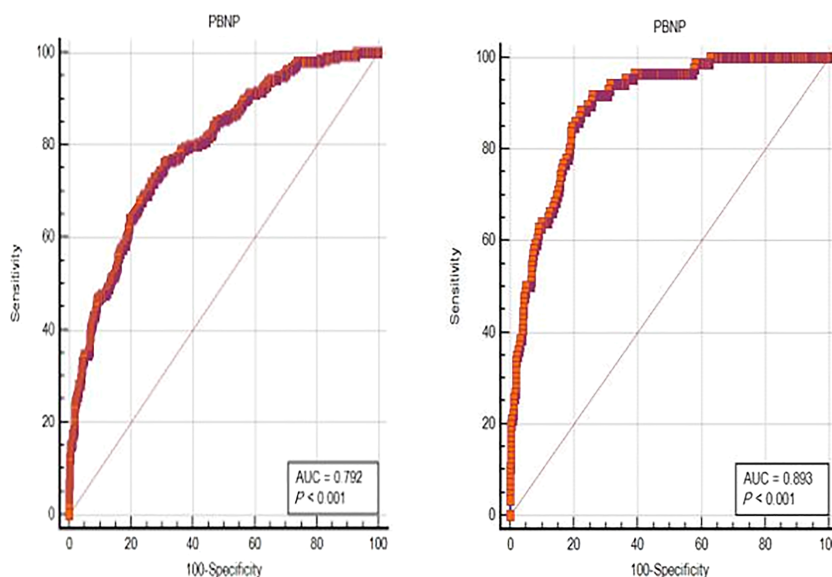
Table 5 Sensitivity, specificity, and positive and negative predictive values for LVSD at different NT-proBNP thresholds

All non-acute patients N = 1000		Impaired LVSF (EF 36–49%)	Severe LVSD (EF ≤35%)
No of patients		128	86
All ages, cutpoint of 125 pg/mL	Sensitivity (%)	97.7	100.0
	95% CI	92.9–99.4	94.7–100.0
All ages, cutpoint of 280 pg/mL	Specificity (%)	18.6	18.6
	95% CI	16.0–21.5	16.0–21.5
	PPV	0.17	0.12
	NPV	0.98	1.00
	Sensitivity (%)	85.2	97.7
	95%CI	77.5–90.6	91.1–99.6
	Specificity (%)	42.0	42.0
	95% CI	38.5–45.5	38.5–45.5
	PPV	0.19	0.16
All ages, cutpoint of 400 pg/mL	NPV	0.95	0.99
	Sensitivity [%]	73.4	96.5
	95% CI	64.8–80.7	89.4–99.1
	Specificity [%]	53.4	53.4
	95% CI	49.9–57.0	49.9–57.0
	PPV	0.20	0.18
	NPV	0.93	0.99
All ages, cutpoint of 1000 pg/mL	Sensitivity [%]	52.3	88.4
	95% CI	43.4–61.2	79.2–94.0
	Specificity [%]	77.0	77.0
	95% CI	73.8–79.8	73.8–79.8
	PPV	0.27	0.30
	NPV	0.91	0.98
All ages, cutpoint of 2000 pg/mL	Sensitivity [%]	35.9	64.0
	95% CI	27.8–44.9	52.8–73.8
	Specificity [%]	89.7	89.7
	95% CI	87.3–91.7	87.3–91.7
	PPV	0.36	0.40
	NPV	0.90	0.96

Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; EF, ejection fraction; LVSF, left ventricular systolic function; LVSD, left ventricular systolic dysfunction.

Table 6 Sensitivity, specificity, and positive and negative predictive values using age specific thresholds

	Normal LVSF	Impaired LVSF (EF 36–49%)	Severe LVSD (EF ≤35%)	All patients
Patients 50–75 years	410	53	37	500
With NT-proBNP <900 pg/mL (% of row)	346 (90.6)	30 (7.9)	6 (1.6)	382 (100.0)
Sensitivity % 95% CI		43.3	83.8	
		30.1–57.6	67.3–93.2	
Specificity 95% CI		84.4	84.4	
		80.4–87.7	80.4–87.7	
PPV		0.26	0.33	
NPV		0.92	0.98	
Patients ≥75 years	344	74	47	465
With NT-proBNP <1800 pg/mL (% of row)	278 (83.5)	42 (12.6)	13 (3.9)	333 (100.0)
Sensitivity % 95% CI		43.2	72.3	
		31.9–55.2	57.1–83.9	
Specificity % 95% CI		80.8	80.8	
		76.2–84.8	76.2–84.8	
PPV		0.33	0.34	
NPV		0.87	0.96	

CI, confidence interval; EF, ejection fraction; LVSD, left ventricular systolic dysfunction; LVSF, left ventricular systolic function; NPV, negative predictive value; NT-proBNP, N terminal pro brain natriuretic peptide; PPV, positive predictive value.

1800 pg/mL in patients >75 years was 87% and 96%, respectively (*Table 6*).

N terminal pro brain natriuretic peptide as a rule in test for left ventricular systolic dysfunction

Positive predictive value (PPV), the probability that a person with a positive test had impaired LV systolic function at different NT-proBNP thresholds, was 17% at 125 pg/mL, 19% at 280 pg/mL, 20% at 400 pg/mL, 27% at 1000 pg/mL, and 36% at 2000 pg/mL. Corresponding figures for severe LVSD were 12%, 16%, 18%, 30%, and 40% (*Table 5*). PPV for an NT-proBNP threshold of 900 pg/mL in patients aged 50–75 years was 26% for impaired LV systolic function and 33% for severe LVSD. PPV for an NT-proBNP threshold of 1800 pg/mL in patients >75 years was 33% and 34%, respectively (*Table 6*).

Discussion

Our study of 1000 patients with suspected chronic heart failure who underwent echocardiography within 6 months of NT-proBNP measurement confirms that NT-proBNP is an independent predictor of LVSD. Elevated NT-proBNP was in turn predicted by increasing age, male gender, the presence of AF and impaired renal function in both univariate and multivariate analyses. NPVs (the probability that a person with a negative test did not have LVSD) were never less than 90% for patients with NT-proBNP up to 2000 pg/mL while PPVs for severe LVSD (the probability that a person with a positive test did have severe LVSD) were never greater than 40% even in patients with NT-proBNP >2000 pg/mL.

The threshold for NT-proBNP below which heart failure with reduced ejection fraction can be reliably excluded is an area of ongoing research and guidelines differ in their recommendations.[17,18] Moreover, NT-proBNP sensitivity is not the only factor to be considered when setting thresholds as cost effectiveness and pressure on the echocardiography services at a time of great demand need to be taken into consideration. A low threshold ensures fewer cases are missed, at the expense of more patients undergoing echocardiography, a test with limited availability in many healthcare systems including the NHS.

The results of our study therefore raise a number of interesting questions regarding NT-proBNP as a rule-out or rule-in test for LVSD in patients suspected of having chronic heart failure, and the timing of echocardiography. The ESC threshold for echocardiography of NT-proBNP 125 pg/mL,[2] means that many patients will require this test. Only 149/1000 (14.9%) of patients presenting with suspected heart failure would not have been referred for echocardiogram, 98% of whom would not have had LVSD (NPV); while 851/1000 (85.1%) patients would have required an echocardiogram although only 17% of these would have had impaired LV systolic function and 12% severe LVSD (PPV). An NT-proBNP threshold of 280 pg/mL for echocardiography, as recommended by Verdu *et al*.,[5] would have led to fewer echocardiograms but otherwise yielded essentially similar results: 35.1% of patients with suspected heart failure would not have been referred for echocardiogram, 95% of whom would not have had LVSD; while 64.9% would have required an echocardiogram yielding 19% with impaired LV systolic function and 16% with severe LVSD.

If instead we were to adopt the NICE NT-proBNP threshold of 400 pg/mL,[1] this would mean that 457/1000 (45.7%) patients with suspected heart failure would not require

echocardiography, 93% of whom would not have LVSD; and that 543/1000 (54.3%) patients would undergo echocardiography yielding 20% with impaired LV systolic function and 18% with severe LVSD. NICE advise that patients with suspected heart failure and NT-proBNP between 400 and 2000 pg/mL should have specialist assessment and transthoracic echocardiography within 6 weeks.[1] Although NPVs in our study fell as NT-proBNP rose, as expected, our data still show a 91% and 98% probability that a patient with suspected heart failure and NT-proBNP <1000 pg/mL will not have impaired LV systolic function or severe LVSD. Corresponding NPVs for NT-proBNP <2000 pg/mL were 90% and 96%, respectively. Based on these findings, it could be argued that specialist assessment and transthoracic echocardiography within 6 weeks cannot be justified on the ability of this test to detect severe LVSD.

Januzzi *et al*. have proposed using age-specific NT-proBNP thresholds for patients with suspected acute heart failure,[9] which we have applied to our data in *Table 6*. A threshold of 900 pg/mL in patients aged 50 to 75 would have meant 382/500 (76.4%) of patients presenting with suspected chronic heart failure would not have required an echocardiogram and that 92% of these would not have had LVSD (NPV); while 118/500 (23.6%) patients would have required an echocardiogram with 26% showing impaired LV systolic function and 33% severe LVSD (PPV). Corresponding percentages for a threshold of 1800 pg/mL in patients over 75 are that echocardiogram would not be required in 333/465 (71.6%), 87% of whom would not have LVSD (NPV); and that echocardiogram would be necessary in 132/465 (28.4%), with 33% showing impaired LV systolic function and 34% severe LVSD (PPV). NPV and PPV for these age-specific thresholds were not dissimilar to those recorded for the NICE threshold of 400 pg/mL when applied to all ages, suggesting that the main benefit of an age specific NT-proBNP threshold would be a need for fewer echocardiograms.

In addition to its importance as a screening tool for heart failure, NT-proBNP is considered a strong independent predictor of heart failure hospitalization and mortality both in the general population,[19,20] and in patients with advanced heart failure referred for possible cardiac transplantation.[21] It seems likely that studies such as these have led to the recommendation that patients with suspected heart failure whose NT-proBNP is greater than 2000 pg/mL should be seen by a specialist and have echocardiography within 2 weeks.[1] We did not address hospitalization or mortality in our study but note very low mortality in the general population study (3% at 1 year) for patients admitted to hospital for the first time with suspected heart failure and NT-proBNP >275 pg/mL,[20] and high mortality as expected (28% at 1 year) among those referred for cardiac transplantation whose NT-proBNP was greater than 1490 pg/mL.[21]

Strengths and limitations

This is large study of patients presenting to primary care with symptoms and signs of heart failure. The study was however of a retrospective design. Even though a sizeable cohort of patients was identified initially, nearly two thirds were excluded due to the time delay between NT-proBNP measurement and echocardiography, neatly illustrating that echocardiography is a limited resource. We acknowledge this as a limitation, as clinical data or peptide levels might be involved in the timing of echocardiography appointment, but note that the distribution of NT-proBNP among those who did and did not have an echocardiogram within 6 months was similar. This suggests that our study cohort was representative of the population from which it was derived. We recognize also that our findings are relevant only for systolic dysfunction in patients with suspected chronic heart failure as we excluded patients with suspected acute heart failure and did not analyse the relation between NT-proBNP and diastolic dysfunction in patients with heart failure with preserved ejection fraction. While all types of heart failure are of clinical importance, patients with severe LVSD tend to benefit the most from advanced heart failure therapies including sacubitril–valsartan, mineralocorticoid receptor antagonists, implantable cardiac defibrillators, cardiac resynchronisation therapies, LV assist devices, and cardiac transplantation.[22,23] It is therefore crucial to focus our limited resources on the early detection of these patients and the optimisation of their heart failure treatment.

Conclusions

In conclusion, our study has shown that the NT-proBNP thresholds recommended by ESC and NICE result in a large number of patients with suspected chronic heart failure being referred for echocardiography. Raising the NT-proBNP threshold would improve access to echocardiography with minimal negative impact on the clinical performance of this cardiac biomarker. To illustrate, a threshold of 1000 pg/mL would have a 91% negative predictive value for impaired LV systolic function and a 98% negative predictive value for severe LVSD. This is comparable with the negative predictive value of CT coronary angiography (CTCA) that led NICE to adopt CTCA as a first line investigation in excluding coronary artery disease in patients presenting with chest pain.[24] Reviewing the current NT-proBNP thresholds has never been more important due to the increased pressure on echocardiography services during the COVID-19 pandemic and expected increased demand on this precious resource in the post COVID-19 era.[25] The results of our study may therefore help in the assessment of the clinical application and cost effectiveness of current NT-proBNP thresholds for echocardiog-

raphy in patients with symptoms suggestive of chronic heart failure.

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