Circulation: Heart Failure

ORIGINAL ARTICLE

Comparison of BNP and NT-proBNP in Patients With Heart Failure and Reduced Ejection Fraction

Rasmus Rørth, MD; Pardeep S. Jhund, MBChB, MSc, PhD; Mehmet B. Yilmaz, MD; Søren Lund Kristensen, MD, PhD; Paul Welsh, PhD; Akshay S. Desai, MD, MPH; Lars Køber, MD, DMSc; Margaret F. Prescott, PhD; Jean L. Rouleau, MD; Scott D. Solomon, MD; Karl Swedberg, MD, PhD; Michael R. Zile, MD, PhD; Milton Packer, MD; John J.V. McMurray, MD

BACKGROUND: Both BNP (B-type natriuretic peptide) and NT-proBNP (N-terminal pro B-type natriuretic peptide) are widely used to aid diagnosis, assess the effect of therapy, and predict outcomes in heart failure and reduced ejection fraction. However, little is known about how these 2 peptides compare in heart failure and reduced ejection fraction, especially with contemporary assays. Both peptides were measured at screening in the PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure).

METHODS: Eligibility criteria in PARADIGM-HF included New York Heart Association functional class II to IV, left ventricular ejection fraction ≤40%, and elevated natriuretic peptides: BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL (for patients with HF hospitalization within 12 months, BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL). BNP and NT-proBNP were measured simultaneously at screening and only patients who fulfilled entry criteria for both natriuretic peptides were included in the present analysis. The BNP/NT-proBNP criteria were not different for patients in atrial fibrillation. Estimated glomerular filtration rate <30 mL/min per 1.73 m^2 was a key exclusion criterion.

RESULTS: The median baseline concentration of NT-proBNP was 2067 (Q1, Q3: 1217–4003) and BNP 318 (Q1, Q3: 207–559), and the ratio, calculated from the raw data, was ≈6.25:1. This ratio varied considerably according to rhythm (atrial fibrillation 8.03:1; no atrial fibrillation 5.75:1) and with age, renal function, and body mass index but not with left ventricular ejection fraction. Each peptide was similarly predictive of death (all-cause, cardiovascular, sudden and pump failure) and heart failure hospitalization, for example, cardiovascular death: BNP hazard ratio, 1.41 (95% CI, 1.33–1.49) per 1 SD increase, $P<0.0001$; NT-proBNP, 1.45 (1.36–1.54); $P<0.0001$.

CONCLUSIONS: The ratio of NT-proBNP to BNP in heart failure and reduced ejection fraction appears to be greater than generally appreciated, differs between patients with and without atrial fibrillation, and increases substantially with increasing age and decreasing renal function. These findings are important for comparison of natriuretic peptide concentrations in heart failure and reduced ejection fraction.

Key Words: age ■ angiotensin ■ atrial fibrillation ■ chronic kidney disease ■ heart failure ■ natriuretic peptides ■ neprilysin ■ obesity

ProBNP (pro B-type natriuretic peptide) is secreted by cardiomyocytes in response to stretch and is quickly cleaved into 2 circulating fragments—the biologically active 32-amino acid C-terminal BNP (B-type natriuretic peptide) and the inert 76-amino acid NT-proBNP (N-terminal pro-BNP).[1,2] Both fragments are routinely used to aid diagnosis of heart failure, predict outcomes, and to monitor the effects of therapy.[3–6] Despite their wide use, few studies have compared these 2 peptides in patients with chronic heart failure and although considered interchangeable, even things as fundamental as how their concentrations relate to each other in patients with heart failure are essentially unknown.[7,8] We have analyzed how the concentrations of BNP and NT-proBNP compare

Correspondence to: John J.V. McMurray, MD, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Pl, Glasgow, G12 8TA, United Kingdom. Email john.mcmurray@glasgow.ac.uk

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.119.006541.

For Sources of Funding and Disclosures, see page 9.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- Although measurements of BNP (B-type natriuretic peptide) and NT-proBNP (N-terminal pro-BNP) are now routinely made in clinical practice, very little is known about how the values of each should be compared.
- Overall, the ratio of NT-proBNP to BNP in the PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) was ≈6.25:1, substantially higher than the ratio commonly used in current guidelines and clinical trials.
- Furthermore, this ratio varied considerably with age, renal function, and body mass index, although not with left ventricular ejection fraction. We also found that the NT-proBNP to BNP ratio varied according to heart rhythm (atrial fibrillation 8.03:1; no atrial fibrillation 5.75:1), a finding not previously reported and not considered in current guidelines.

WHAT ARE THE CLINICAL IMPLICATIONS?

- There is no single, simple, conversion ratio of NT-proBNP to BNP and factors such as atrial fibrillation, age, and renal function need to be taken into account.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin convertering enzyme
AF	atrial fibrillation
ARB	angiotensin receptor blocker
BMI	body mass index
BNP	B-type natriuretic peptide
eGFR	estimated glomerular filtration rate
HFrEF	heart failure and reduced ejection fraction
IQR	interquartile range
LVEF	left ventricular ejection fraction
NT-proBNP	N-terminal proBNP
PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial
proBNP	pro B-type natriuretic peptide
Val-HeFT	Valsartan Heart Failure Trial

in patients with heart failure and reduced ejection fraction (HFrEF), and whether certain patient characteristics and comorbidities influence the circulating levels of these peptides differently. In particular, we focused on heart rhythm (atrial fibrillation [AF] or not). Although clinical trials apply different threshold values for inclusion of patients with and without AF, the ratio for patients with different rhythms varies greatly between studies. We have also examined whether age, renal function, and body mass index as factors affect the concentration of each natriuretic peptide differently. In addition, we compared the predictive value of each peptide for nonfatal and a variety of fatal outcomes in HFrEF. We performed these analyses using data from the PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) in which patients with HFrEF were randomized to treatment with either enalapril or sacubitril/valsartan. Both BNP and NT-proBNP were measured in most patients at screening in PARADIGM-HF.[9]

METHODS

Data, materials, and statistical analyses are available on request from a third party.

Study Design and Patients

The background, design, and results of PARADIGM-HF are published previously.[9–11] In brief, 8399 patients in New York Heart Association functional class II to IV with a left ventricular ejection fraction (LVEF) ≤40% receiving recommended treatment for HFrEF including an ACE (angiotensin convertering enzyme) inhibitor or ARB (angiotensin receptor blocker), a β-blocker (unless contraindicated) and a mineralocorticoid receptor antagonist, if indicated, were enrolled. Patients were required to have a plasma BNP ≥150 pg/mL (or NT-proBNP ≥600 pg/mL), or a BNP ≥100 pg/mL (or NT-proBNP ≥400 pg/mL) if there had been a hospitalization for heart failure within the past 12 months. There was no difference in entry BNP or NT-proBNP requirement for patients with or without AF. The key exclusion criteria included intolerance of an ACE inhibitor or ARB, a history of angioedema, symptomatic hypotension, a systolic blood pressure <100 mm Hg at screening (<95 mm Hg at randomization), an estimated glomerular filtration rate (eGFR) <30 mL/(min·1.73 m^2) and a serum potassium level >5.2 mmoL/L at screening (>5.4 mmoL/L at randomization). Patients were randomized to sacubitril/valsartan (formerly known as LCZ696) or enalapril. The presence of atrial flutter or fibrillation was based on the rhythm present on the screening ECG. History of diabetes mellitus was based on investigator reported diagnosis of diabetes mellitus, irrespective of hemoglobin A1c level at screening. The trial was approved by the ethics committee at each study center. All the patients provided written informed consent.

Natriuretic Peptide Measurements

Blood was collected at the screening visit. Plasma was isolated and immediately frozen at −20°C. On the same day, samples were shipped on dry ice to the closest of 6 designated regional laboratories affiliated with the central laboratory run by Quintiles Durham, NC (now IQVIA). The same assay kits were used to measure each peptide at each site. Specifically, NT-proBNP was measured using the Roche Elecys proBNP assay (Roche Diagnostics, Indianapolis, IN) and BNP using

the Advia Centaur assay (Siemens Healthcare Diagnostics, Tarrytown, NY) as described previously.[10,11]

Outcomes

The median follow-up time in PARADIGM-HF was 27 months. The primary end point was a composite of cardiovascular death or heart failure hospitalization; we analyzed this, its components (cardiovascular death and heart failure hospitalization), the 2 major modes of cardiovascular death (sudden death and death due to worsening heart failure/pump failure) and all-cause mortality. We investigated the relationship between BNP and NT-proBNP and compared their predictive value for the outcomes described above. We also looked at the ratio of NT-proBNP to BNP and how different clinical characteristics affected this ratio.

Statistical Analyses

Baseline characteristics are described by use of proportions for categorical variables and means with SD or medians with quartiles for continuous variables. Differences in baseline characteristics between patients with a NT-proBNP/BNP ratio above or below the median were tested by use of a χ^2 test for categorical variables and ANOVA or Kruskal Wallis test for continuous variables. The relationship between BNP and NT-proBNP was assessed using the Pearson correlation coefficient. Multivariable linear regression models were used to explore the association between age, sex, New York Heart Association class, heart failure duration, prior heart failure hospitalization, body mass index (BMI), creatinine, LVEF, heart rate, AF, myocardial infarction, stroke and diabetes mellitus, and NT-proBNP/BNP ratio. Cox proportional hazard models were used to compare the risk of all-cause mortality, modes of death (cardiovascular, sudden, and pump failure) and heart failure hospitalization according to level of BNP and NT-proBNP at baseline. The Cox regression models were adjusted for age, sex, treatment effect, race, region, LVEF, New York Heart Association class, BMI, heart rate, systolic blood pressure, creatinine, prior heart failure hospitalization, heart failure duration, AF, myocardial infarction, stroke, and diabetes mellitus. The assumption of linearity in relation to outcomes in multivariable linear regression and Cox proportional hazard models was tested for age, LVEF, BNP, and NT-proBNP. Log (−log [survival]) curves were used to evaluate the proportional hazard assumption. Model discrimination was tested by use of the Harrell C statistic.[12] $P<0.05$ were considered significant. Analyses were performed by use of Stata version 15 and R version 3.5.1.

RESULTS

Baseline Characteristics

Of all patients enrolled, 6438 (77%) fulfilled both the BNP and NT-proBNP requirements at screening, and they were included in this substudy. The baseline characteristics of patients in PARADIGM-HF have been described in detail.[9,11]

Association Between BNP and NT-proBNP and Influence of Baseline Characteristics

In the overall cohort, the median BNP was 318 (interquartile range [IQR], 207–559) pg/mL and the median NT-proBNP was 2067 (IQR, 1217–4003) pg/mL. There was a linear correlation between log BNP and log NT-proBNP with a correlation coefficient of 0.81 (Figure 1A). The median NT-proBNP/BNP ratio in the overall study population was 6.25 (IQR, 4.52–8.81):1. The NT-proBNP/BNP ratio was consistent across deciles of BNP (Figure 2A). Patients with a median NT-proBNP/BNP ratio >6.25 were older (mean age 66 years compared with 61 years in patients with NT-proBNP/BNP ratio ≤6.25), more were women (23% versus 19%) and white (69% versus 62%), and fewer had an ischemic cause (57% versus 64%) or history of myocardial infarction (38% versus 49%; Table 1). Patients with a median NT-proBNP/BNP ratio >6.25 also had worse kidney function (eGFR, 62 versus 70 mL/min·1.73 m^2 in patients with NT-proBNP/BNP ratio ≤6.25) and more had a history of AF (40% versus 28%) as well as AF on their screening ECG (36% versus 15%; Table 1). The NT-proBNP/BNP ratio decreased in patients treated with sacubitril/valsartan (Figure I in the Data Supplement).

NT-proBNP/BNP Ratio According to Baseline Rhythm and Interaction With Other Characteristics

In patients without AF, the median BNP was 329 (IQR, 210–574) pg/mL, and the median NT-proBNP was 1938 (1127–3750) pg/mL; in patients with AF, the median BNP was 295 (IQR, 203–520) pg/mL, and the median NT-proBNP was 2480 (1517–4519) pg/mL. Among patients not in AF, the linear correlation between log BNP and log NT-proBNP was 0.83; in patients with AF, it was 0.79 (Figure 1B and 1C). The NT-proBNP/BNP ratio varied considerably according to AF status: 5.75 (IQR, 4.23–7.95):1 in patients without AF, compared with 8.03 (IQR, 5.88–10.80):1 in patients with AF; this difference was consistent across all BNP deciles (Figure 2B and Figure 2C). In both rhythm groups, the ratio increased with increasing age and decreasing kidney function, was lower among patients with obesity, but was constant across the range of LVEF included in the trial (Figure 3).

Independent Predictors of the NT-proBNP/BNP Ratio

In multivariable linear regression analyses, older age, male sex, higher creatinine, and AF were significantly associated with a higher NT-proBNP/BNP ratio (there was also a weak association with stroke). Conversely, obesity and history of myocardial infarction were associated with a lower NT-proBNP/BNP ratio (Table 2).

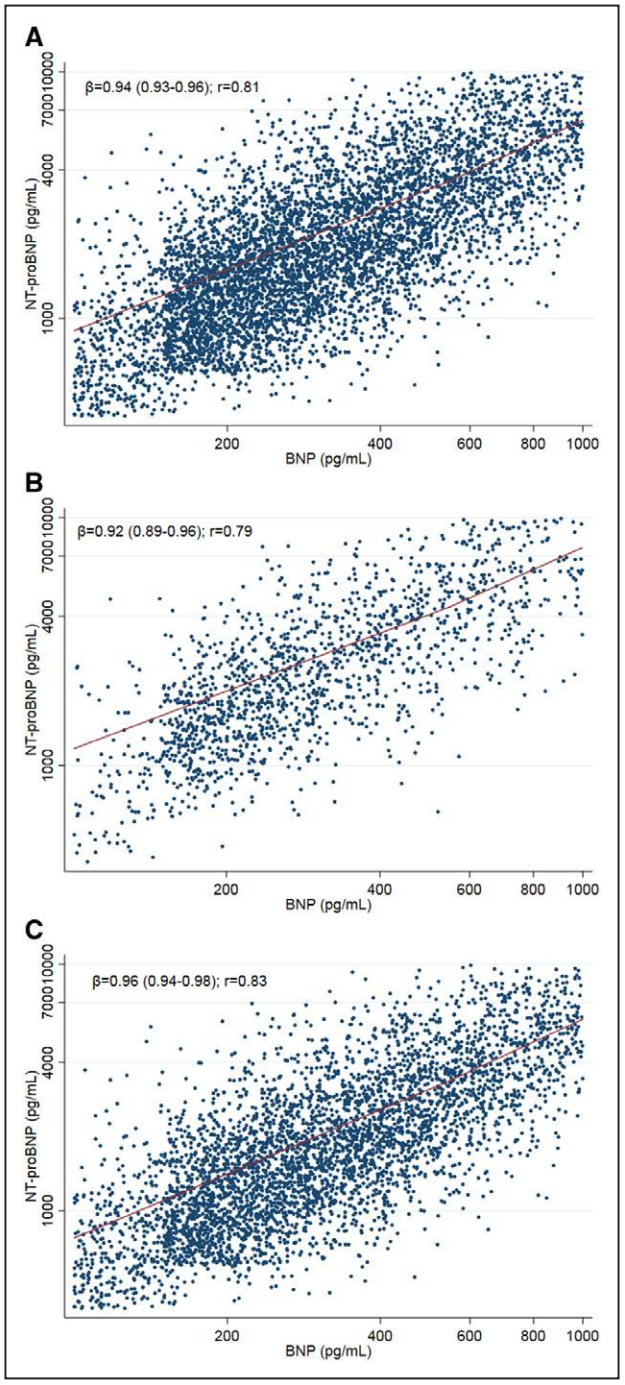

Figure 1. NT-proBNP (N-terminal pro-B-type natriuretic peptide) and BNP (B-type natriuretic peptide) levels.
A, All patients; (B) patients with atrial fibrillation, and (C) patients without atrial fibrillation.

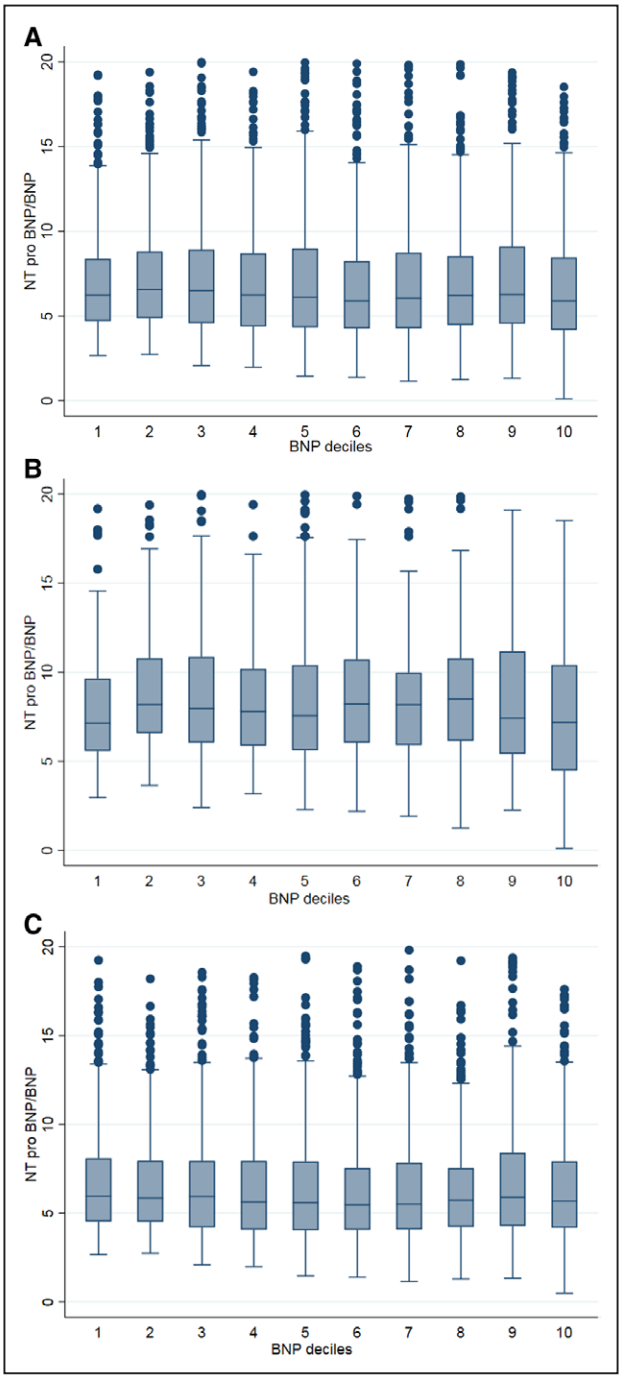

Figure 2. Ratio of NT-proBNP (N-terminal pro-B-type natriuretic peptide) to BNP (B-type natriuretic peptide; NT-proBNP/BNP) according to decile of BNP.
A, All patients; (**B**) patients with atrial fibrillation, and (**C**) patients without atrial fibrillation.

Prognostic Value of NT-proBNP and BNP

Higher concentrations of each of NT-proBNP and BNP were associated with a higher risk of death from any cause, cardiovascular death, sudden death and pump failure death, as well as heart failure hospitalization (Table 3). The ratio of NT-proBNP/BNP was not associated with risk of any of these outcomes. The added discriminatory power, that is, the ability to better separate patients at higher risk from those at lower risk, of NT-proBNP and BNP is outlined in Table 4. Each peptide provided incremental prognostic information when added to multivariable models including other recognized prognostic factors. The performance of NT-proBNP and BNP in each of these multivariable predictive models was similar.

Table 1. Baseline Characteristics According to Median NT-proBNP/BNP Ratio

	NT-proBNP/BNP Ratio ≤6.25	NT-proBNP/BNP Ratio >6.25	*P* Values
Patients, n (%)	3219 (50)	3219 (50)	
BNP, pg/mL, median [Q1,Q3]	333 (213–565)	307 (202–554)	0.002
NT-proBNP, pg/mL, median [Q1,Q3]	1406 (902–2448)	2983 (1830–5469)	<0.0001
Age, y, mean±SD	61±11	66±11	<0.0001
Female sex, n (%)	624 (19)	742 (23)	0.0003
White, n (%)	1992 (62)	2220 (69)	<0.0001
Ischemic cause, n (%)	2066 (64)	1837 (57)	<0.0001
HF duration, n (%)			0.5598
0–1 y	987 (31)	968 (30)	
>1–5 y	1218 (38)	1260 (39)	
>5 y	1014 (32)	991 (31)	
NYHA class, n (%)			0.0109
I	8 (0.2)	19 (0.6)	
II	2065 (64)	1966 (61)	
III	1087 (34)	1181 (37)	
IV	56 (2)	50 (2)	
Body mass index, Kg/m^2 n (%)			<0.0001
<18.5 kg/m^2	42 (1)	96 (3)	
18.5–24.9 kg/m^2	898 (28)	1048(33)	
25–29.9 kg/m^2	1256 (39)	1170 (36)	
30–34.9 kg/m^2	674 (21)	604 (19)	
≥35 kg/m^2	344 (11)	296(9)	
Ejection fraction, %, mean±SD	29±6	29±6	0.5341
Heart rate, beats/min, mean±SD	73±13	75±13	<0.0001
Atrial fibrillation or flutter on ECG, n (%)	490 (15)	1167 (36)	<0.0001
SBP, mm Hg, mean±SD	128±17	128±17	0.905
eGFR , mL/min/1.73m^2, median [Q1,Q3]	70 (58–84)	62 (50–74)	<0.0001
Creatinine, µmol/L, median [Q1,Q3]	91 (79–10)	99 (84–118)	<0.0001
eGFR <60 mL/min/1.73m^2, n (%)	876 (27)	1423 (44)	<0.0001
Jugular venous distension, n (%)	323 (10)	303 (9)	0.29
Edema, n (%)	669 (21)	732 (23)	0.06
Rales, n (%)	244 (8)	304 (9)	0.01
Third heart sound, n(%)	325 (10)	303 (9)	0.36
Medical history, n (%)			
Myocardial infarction	1580 (49)	1239 (38)	<0.0001
Stroke	244 (8)	311 (10)	0.0029
Atrial fibrillation	891 (28)	1562 (49)	<0.0001
Hypertension	2239 (70)	2326 (72)	0.017
Diabetes mellitus	1127 (35)	1094 (34)	0.39
Medication, n (%)			
ACEI	2504(78)	2498 (78)	0.8574
ARB	724 (22)	729 (23)	0.8815
β-blockers	3006 (93)	2979 (93)	0.1883
Diuretics	2538 (79)	2681 (83)	<0.0001
MRA	1847 (57)	1727 (54)	0.0026
Digoxin	868 (27)	1084 (34)	<0.0001
Antiplatelets	1947 (60)	1650 (51)	<0.0001
CRT P+D	211 (7)	236 (7)	0.2203
ICD	495 (15)	459 (14)	0.2066

ACEI indicates angiotensin convertering enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CRT P+D, cardiac resynchronization therapy pacemaker and defibrillator; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and SBP, systolic blood pressure.

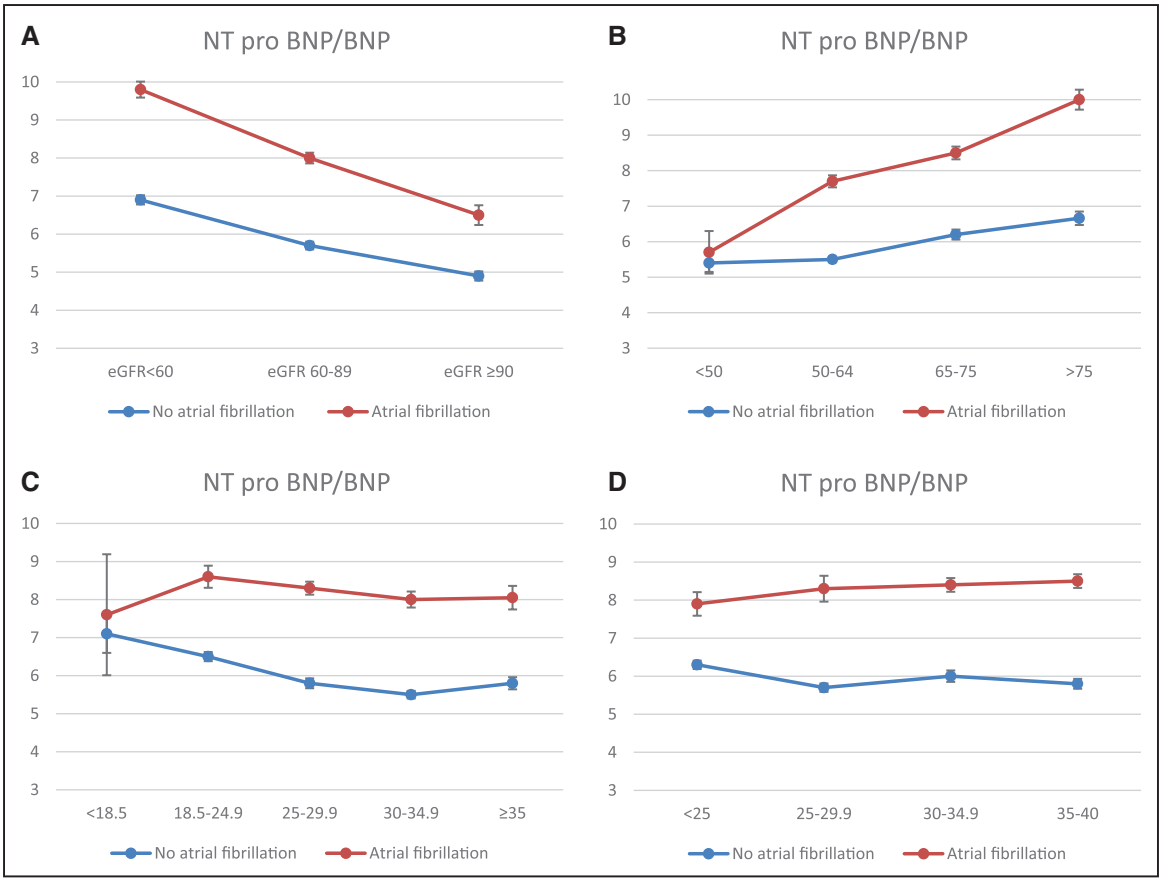

Figure 3. NT-proBNP (N-terminal pro-B-type natriuretic peptide)/BNP (B-type natriuretic peptide) ratio in patients with and without atrial fibrillation. According to categories of (A) estimated glomerular filtration rate (eGFR), (B) age, (C) body mass index (BMI), and (D) left ventricular ejection fraction (LVEF).

The ratio of NT-proBNP/BNP did not add prognostic information to the multivariable model for any outcome.

DISCUSSION

In patients with HFrEF, predominantly in New York Heart Association class II and III, the NT-proBNP to BNP ratio was 6.25:1, substantially higher than the ratio commonly applied in guidelines and clinical trials. For example, in the European Society of Cardiology guidelines, the rule-out threshold recommended is 35 pg/mL for BNP and for NT-proBNP is 125 pg/mL (ratio 3.6).[13] In the Canadian Cardiovascular Society guidelines, these thresholds are 50 pg/mL and 125 pg/mL, respectively (ratio 2.5), and in the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand the corresponding values are 100 pg/mL and 300 pg/mL (ratio 3.0).[14,15] No specific thresholds are recommended in US guidelines.[16] While it is possible that the relationship between NT-proBNP and BNP concentration is different than in patients with suspected heart failure compared with those with established HFrEF, one other sizeable study of patients in an emergency department reported a NT-proBNP to BNP ratio of 5.7, similar to what we calculated.[17] The NT-proBNP to BNP conversion ratio of between 3 and 4 to 1, used in recently completed and ongoing clinical trials in heart failure, is also substantially lower than the ratio we found in our study of HFrEF patients in which both peptides were measured in the same blood sample.

As reported previously, many of the clinical variables that influence the circulating concentration of each natriuretic peptide, particularly age and eGFR (which are clearly related), also influenced the ratio of the 2 peptides in the present study. The increase in ratio with declining renal function was particularly notable, in keeping the closer association between NT-proBNP and eGFR, compared with BNP and eGFR (probably because, unlike BNP, NT-proBNP is believed to be removed mainly or exclusively from the circulation by renal excretion). The variation in plasma concentrations in relation to other patient factors has been used as an argument for thresholds tailored to patient characteristics and the recent National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand guidelines recommend rule-in NT-proBNP thresholds stratified by age.[15] Specifically, for age <50 years, 50 to 75 years, and >75 years, the thresholds recommended are 450, 900, and 1800 pg/mL, respectively.

Table 2. Predictors of NT-proBNP, BNP, and the Ratio of NT-proBNP to BNP (Multivariable Model)

	NT-proBNP/BNP Ratio		Log_e NT-proBNP		Log_eBNP	
	β-Coef. (95% CI)	*P* Value	β-Coef. (95% CI)	*P* Value	β-Coef. (95% CI)	*P* Value
Age, +10 y	0.45 (0.34 to 0.56)	<0.001	0.03 (0.02 to 0.05)	<0.001	−0.04 (−0.05 to −0.02)	<0.001
Sex, female	1.33 (1.03 to 1.63)	<0.001	0.14 (0.09 to 0.19)	<0.001	−0.01 (−0.05 to 0.04)	0.78
NYHA class						
I	0.27 (−1.46 to −2.00)	0.76	−0.08 (−0.37 to −0.21)	0.54	−0.14 (−0.40 to 0.12)	0.29
II	Ref.		Ref.		Ref.	
III	0.06 (−0.18 to −0.30)	0.61	0.24 (0.20 to 0.29)	<0.001	0.24 (0.20 to 0.27)	<0.001
IV	−0.44 (−1.32 to −0.45)	0.33	0.43 (0.28 to 0.59)	<0.001	0.51 (0.38 to 0.65)	<0.001
BMI, kg/m^2						
<18.5	1.90 (1.10 to 2.70)	<0.001	0.41 (0.28 to 0.55)	<0.001	0.20 (0.08 to 0.32)	0.001
18.5–24.9	Ref.		Ref.		Ref.	
25–29.9	−0.72 (−1.00 to −0.45)	<0.001	−0.27 (−0.31 to −0.22)	<0.001	−0.19 (−0.23 to −0.14)	<0.001
30–34.9	−1.08 (−1.41 to −0.74)	<0.001	−0.43 (−0.49 to −0.38)	<0.001	−0.32 (−0.37 to −0.27)	<0.001
>35	−0.99 (−1.43 to −0.56)	<0.001	−0.53 (−0.61 to −0.46)	<0.001	−0.42 (−0.49 to −0.36)	<0.001
Creatinine, +1 log_e umol/L	4.16 (3.66 to 4.66)	<0.001	0.83 (0.74 to 0.91)	<0.001	0.33 (0.25 to 0.40)	<0.001
Ejection fraction, +1%	−0.01 (−0.03 to −0.01)	0.43	−0.02 (−0.02 to −0.02)	<0.001	−0.02 (−0.02 to −0.01)	<0.001
Systolic blood pressure, +1 mm Hg	−0.01 (−0.02 to −0.00)	0.02	0.00 (0.00 to 0.00)	0.14	0.00 (0.00 to 0.00)	0.66
Myocardial infarction, yes	−0.70 (−0.94 to 0.46)	<0.001	−0.16 (−0.20 to −0.12)	<0.001	−0.05 (−0.09 to −0.02)	0.004
Atrial fibrillation,* yes	2.05 (1.78 to 2.32)	<0.001	0.24 (0.19 to 0.29)	<0.001	−0.03 (−0.08 to −0.02)	0.11
Stroke, yes	0.43 (0.03 to 0.83)	0.04	0.04 (−0.03 to 0.11)	0.22	0.00 (−0.06 to 0.06)	0.97
Diabetes mellitus, yes	0.01 (−0.22 to −0.26)	0.91	0.0 (−0.04 to 0.04)	0.92	0.00 (−0.04 to 0.03)	0.92
Prior HF hospitalization yes	−0.03 (−0.26 to −0.21)	0.84	−0.05 (−0.09 to −0.01)	0.01	−0.06 (−0.10 to −0.03)	<0.001
HF duration						
0–1 y	Ref.		Ref.		Ref.	
>1–5 y	0.07 (−0.21 to −0.34)	0.63	0.05 (0.01 to 0.10)	0.03	0.07 (0.03 to 0.11)	0.001
>5 y	−0.24 (−0.55 to −0.06)	0.11	−0.04 (−0.09 to −0.01)	0.15	0.02 (−0.03 to 0.06)	0.42
Constant	−14.55 (−17.10 to −12.00)	<0.001	4.41 (3.98 to 4.84)	<0.001	5.26 (4.88 to 5.65	<0.001

β-Coef indicates β-coefficient; BMI, body mass index; BNP, B-type natriuretic peptide; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

*Atrial fibrillation or flutter on ECG at screening.

Similar stratification is not provided for BNP, with a single rule-in threshold of 400 pg/mL recommended.

Surprisingly, no major guideline differentiates between patients with and without AF, despite this arrhythmia clearly increasing natriuretic peptide levels.[18,19] We found that the NT-proBNP to BNP ratio was 8.03:1 in patients with AF, compared with 5.75:1 in those not in AF. It is unclear why the ratio should vary according to rhythm and the influence of the other clinical characteristics modifying natriuretic peptide concentrations was as powerful in patients with AF as in those without. Consequently, for example, the NT-proBNP/BNP ratio in the oldest patients was ≈10:1 for those in AF compared with around 6.5:1 in participants in sinus rhythm (compared with ≈5.5:1 in the youngest patients in both rhythm categories). In patients with the lowest eGFR values, the NT-proBNP/BNP ratio was also ≈10:1 for those in AF compared with around 7:1 in participants in sinus rhythm (compared with patients with the highest eGFR where the ratio was approximately 6.5:1 in patients in AF compared with around 5:1 in those not in AF).

In contrast to the guidelines, most, but not all, trials have set different natriuretic peptide inclusion thresholds for patients with and without AF. However, the AF versus no AF multiplication factor for NT-pro BNP, versus BNP, varies 2-fold from 1.5:1 to 3:0 in ongoing and recently completed trials; our data suggest that this factor is 1.4 (ie, 8.03/5.75).

In our study, both levels of BNP and NT-proBNP decreased with increasing BMI. However, the decrease in NT-proBNP levels was more pronounced. Thus, BMI was associated with a negative NT-proBNP/BNP ratio which is in accordance with previous literature.[20] It is unclear why levels of the natriuretic peptides are affected differently by BMI. As BNP, in contrast to NT-proBNP, is a substrate for neprilysin inhibition, a decrease in NT-proBNP/BNP ratio among patients treated with sacubitril/valsartan was expected.[21]

Few other studies have examined the NT-proBNP/BNP ratio, and most of these were small and involved

Table 3. Adjusted Hazard Ratios* for Outcomes of Interest According to 1 SD Increase of BNP or NT-proBNP

	No. of Events	HR (95% CI)	*P* Value
CV death/HF hospitalization	1757		
BNP (per 1 SD increase)		1.37 (1.31–1.43)	<0.0001
NT-proBNP (per 1 SD increase)		1.38 (1.32–1.45)	<0.0001
CV death	1089		
BNP (per 1 SD increase)		1.41 (1.33–1.49)	<0.0001
NT-proBNP (per 1 SD increase)		1.45 (1.36–1.54)	<0.0001
HF hospitalization	1034		
BNP (per 1 SD increase)		1.37 (1.29–1.46)	<0.0001
NT-proBNP (per 1 SD increase)		1.36 (1.28–1.45)	<0.0001
All-cause mortality	1328		
BNP (per 1 SD increase)		1.38 (1.30–1.45)	<0.0001
NT-proBNP (per 1 SD increase)		1.41 (1.33–1.49)	<0.0001
Sudden cardiac death	476		
BNP (per 1 SD increase)		1.32 (1.21–1.44)	<0.0001
NT-proBNP (per 1 SD increase)		1.35 (1.23–1.49)	<0.0001
Pump failure death	292		
BNP (per 1 SD increase)		1.60 (1.43–1.79)	<0.0001
NT-proBNP (per 1 SD increase)		1.66 (1.47–1.87)	<0.0001

BNP indicates B-type natriuretic peptide; CV, cardiovascular, HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

*All models were adjusted for age, sex, treatment effect, race, region, ejection fraction, NYHA class, body mass index, heart rate, systolic blood pressure, creatinine, prior heart failure hospitalizations, heart failure duration, atrial fibrillation, myocardial infarction, stroke, and diabetes mellitus.

patients without heart failure.[22–24] The first large analysis of this type was performed by the Val-HeFT (Valsartan Heart Failure Trial) investigators.[7] In a subgroup of 3916 participants with chronic ambulatory HFrEF, the median concentrations of BNP and NT-proBNP were 99 pg/mL and 895 pg/mL, respectively, that is, a ratio of 9.04:1. Presumably the difference in ratio reflects the older assays used in Val-HeFT. In a second and recent report from China, the ratio was more similar to what we found.[8] The Chinese investigators studied 1464 hospitalized patients. Of these, 58% had HFrEF, and the overall cohort was followed for a median period of 533 days. The median values of BNP and NT-proBNP were 375 pg/mL and 2029 pg/mL, respectively, that is, a ratio of 5.41:1.

We found that BNP and NT-proBNP were predictive of the clinical outcomes investigated with hazard ratios per 1 SD increase in peptide concentration of ≈1.3 to 1.4 for all events other than pump failure death where the hazard ratio was 1.6 to 1.7. For each outcome of interest, except heart failure hospitalization, the hazard ratio was slightly larger for NT-proBNP than BNP, but there was no significant difference for any outcome. Both peptides significantly improved the C-index when added to predictive

Table 4. C-Index for Predictive Model Without Natriuretic Peptides and for the Addition of Each of BNP and NT-proBNP, Separately

	C-Index $_{2\ year}$ (95% CI); *P* Value					
	CV Death or HF Hospitalization	CV Death	HF Hospitalization	All-Cause Mortality	Sudden Cardiac Death	Pump Failure Death
Baseline model*	0.63 (0.61–0.65)	0.64 (0.62–0.67)	0.65 (0.63–0.67)	0.63 (0.61–0.65)	0.66 (0.62–0.69)	0.71 (0.67–0.75)
+BNP	0.67 (0.65–0.68)	0.69 (0.66–0.71)	0.68 (0.66–0.70)	0.67 (0.65–0.69)	0.68 (0.65–0.72)	0.76 (0.72–0.79)
+NT-proBNP	0.66 (0.65–0.68); *P*=0.33†	0.68 (0.66–0.70); *P*=0.31†	0.68 (0.65–0.70); *P*=0.26†	0.66 (0.64–0.68); *P*=0.20†	0.68 (0.65–0.71); *P*=0.44†	0.76 (0.72–0.79); *P*=0.83†

BNP indicates B-type natriuretic peptide; CV, cardiovascular, HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

*Adjusted for age, sex, treatment effect, race, region, ejection fraction, NYHA class, body mass index, heart rate, systolic blood pressure, creatinine, prior heart failure hospitalizations, heart failure duration, atrial fibrillation, myocardial infarction, stroke, and diabetes mellitus. Addition of each of BNP or NT-proBNP improved the C-index significantly for all outcomes: *P*<0.0001 for each peptide and for each event, except sudden death (BNP, *P*=0.001; NT-proBNP, *P*=0.009).

†Compared with BNP.

models including other recognized prognostic variables. The 2 peptides increased the C-index similarly for each outcome examined. Although there are many comparisons of the diagnostic performance of BNP and NT-proBNP, few studies have compared the prognostic value of BNP and NT-proBNP in patients with HFrEF. The Val-HeFT investigators found that NT-proBNP was a slightly but significantly better predictor of all-cause mortality and, especially, heart failure hospitalization. However, in the recent study from China mentioned above, the investigators reported that BNP and NT-proBNP were similarly predictive for all-cause death or transplantation. Again, these differences may reflect the much older assays used in Val-HeFT.

This study has several limitations. Most importantly, at enrollment, patients were required to have a plasma BNP ≥150 pg/mL (or NT-proBNP ≥600 pg/mL), or a BNP ≥100 pg/mL (or NT-proBNP ≥400 pg/mL) if there had been a hospitalization for heart failure within the past 12 months. Consequently, we do not know about the relationship between BNP and NT-proBNP at lower plasma concentrations. Similarly, patients with an eGFR <30 mL/(min·1.73 m^2) were excluded which is important, given the significant influence of renal function on natriuretic peptide levels. Because our patients were enrolled in a clinical trial, they were also, on average, younger than in the population at large and likely had less comorbidity. Lastly, we studied patients with HFrEF and the relationships described might be different in patients with heart failure and preserved ejection fraction and during acute decompensation as well as after acute myocardial infarction. Each of these factors limit the generalizability of our findings.

In summary, when measured simultaneously in patients with HFrEF, the ratio of NT-proBNP to BNP is 6.25:1, substantially larger than the ratio currently recommended in guidelines or used in clinical trial inclusion criteria. Moreover, this ratio is quite different in patients with AF (8.03:1) compared with those without (5.75:1). At present, guidelines do not differentiate between AF and sinus rhythm and in the trials that do, the multiplication factor used is 1.5 to 3.0, higher than the 1.4-fold higher rate found in the current analyses. In both AF and sinus rhythm, age and renal function had a strong influence on the NT-proBNP to BNP ratio which increased to 10:1 in the oldest patients with AF and around 6.5:1 in those not in AF. Thus, there is no single, simple, conversion ratio for these 2 peptides.

ARTICLE INFORMATION

Received August 26, 2019; accepted January 16, 2020.

Affiliations

BHF Cardiovascular Research Centre, University of Glasgow, United Kingdom (R.R., P.S.J., S.L.K., P.W., J.J.V.M.). Rigshospitalet Copenhagen University Hospital, Copenhagen (R.R., S.L.K., L.K.). Department of Cardiology, Faculty of Medicine, Dokuz Eylül University, Izmir, Turkey (M.B.Y.). Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA (A.S.D., S.D.S.). Novartis Pharmaceuticals Corporation, East Hanover, NJ (M.F.P.). Institut de Cardiologie de Montréal, Université de Montréal, Canada (J.L.R.). Department of Molecular and Clinical Medicine, University of Gothenburg, Sweden and National Heart and Lung Institute, Imperial College, London (K.S.). Medical University of South Carolina and Ralph H. Johnson Veterans Administration Medical Center, Charleston, SC (M.R.Z.). Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX (M.P.).

Sources of Funding

The PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) was funded by Novartis. Professor McMurray is supported by a British Heart Foundation Centre of Research Excellence Grant (RE/18/6/34217).

Disclosures

Dr McMurray's employer, University of Glasgow, was paid by Novartis for Dr McMurray's time spent as cochairman of the PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure). Dr Jhund reports receiving grant support from Boehringer Ingelheim and fees for serving on an advisory board from Cytokinetics. Dr Yilmaz has received institutional research grants from Novartis, Bayer, Amgen and has consulted Novartis, Bayer, Amgen via institutional contracts. Dr Welsh reports receiving research grants from AstraZeneca, Boehringer Ingelheim, and Roche. Dr Desai reports grants consulting fees from Novartis, Alnylam, and AstraZeneca, consulting fees from Abbott, Boehringer-Ingelheim, Regeneron, Biofourmis, Boston Scientific, Corvidia, DalCor Pharma, Relypsa. Dr Køber reports honoraria from Novartis and Astra Zeneca. Dr Prescott is an employee of Novartis Pharmaceuticals. Dr Rouleau reports grants and consulting fees from Novartis, and consulting fees from AstraZeneca. Dr Solomon reports grants paid to his institution for chairing PARAGON-HF from Novartis; grants paid to Brigham and Women's Hospital from Alnylam, Amgen, AstraZeneca, Bayer, Bellerophon, Bristol-Myers Squibb, Celladon, Cytokinetics, Gilead, Eidos, GlaxoSmithKline, Ionis, Lone Star Heart, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, Sanofi Pasteur, and Theracos; and consulting fees from Alnylam, Amgen, AOBiome, AstraZeneca, Bayer, Bristol-Myers Squibb, Cardiac Dimensions, Corvia, Cytokinetics, Daiichi Sankyo, Gilead, GlaxoSmithKline, Ironwood, Janssen, Merck, MyoKardia, Novartis, Quantum Genomics, Roche, Takeda, Tenaya, and Theracos. Dr Swedberg reports consulting for Novartis. Dr Zile reports grants and personal fees from Novartis for being a member of the PARAGON-HF Executive Steering Committee and a local investigator; personal fees from Abbott for serving on the executive committee of the GUIDE-HF (Hemodynamic-Guided Management of Heart Failure) trial; personal fees for consulting on product development from Boston Scientific; grants and personal fees for serving on the Executive Steering Committee and being a local investigator for the BeAT HF trial (Baroreflex Activation Therapy for Heart Failure Pivotal Trial) from CVRx; personal fees for serving on the eligibility committee of the SOLVE trial (Stimulation of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and Previously Untreatable Patients) from EBR; personal fees for serving on the Clinical Events Committee of the SIRONA trial (A Prospective, Multi-Center, Open-Label, Single-Arm Clinical Trial Evaluating the Safety and Efficacy of the Cordella Heart Failure System in NYHA Class III Heart Failure Patients) from Endotronics; personal fees for serving on the Executive Steering Committee of the CAPACITY HFpEF trial (A Study of the Effect of IW-1973 on the Exercise Capacity of Patients With Heart Failure With Preserved Ejection Fraction) from Ironwood; personal fees for serving on the data safety monitoring board of the Ertugliflozin trial (MK-8835/ PF-04971729) from Merck; grants and personal fees for serving on the executive steering committee of the Revamp Trial, Alleviate Trial, Link-HF trial (Link-HF, Phase II: Multisensor Noninvasive Telemonitoring System for Prediction of Heart Failure Exacerbation), and Intervene trial and being a local investigator from Medtronic; personal fees for consulting for product development from MyoKardia; and personal fees for serving on the eligibility committee of the RELIEVE trial (Reducing Lung Congestion Symptoms in Advanced Heart Failure) from V Wave. Dr Packer reports receiving consulting fees from AbbVie, Akcea, Actavis, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, Novo Nordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance. The other authors report no conflicts.

REFERENCES

1. Burnett JC Jr, Kao PC, Hu DC, Heser DW, Heublein D, Granger JP, Opgenorth TJ, Reeder GS. Atrial natriuretic peptide elevation

in congestive heart failure in the human. *Science*. 1986;231:1145–1147. doi: 10.1126/science.2935937
2. Hall C. NT-ProBNP: the mechanism behind the marker. *J Card Fail*. 2005;11(5 suppl):S81–S83. doi: 10.1016/j.cardfail.2005.04.019
3. Logeart D, Thabut G, Jourdain P, Chavelas C, Beyne P, Beauvais F, Bouvier E, Solal AC. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol*. 2004;43:635–641. doi: 10.1016/j.jacc.2003.09.044
4. Sugiura T, Takase H, Toriyama T, Goto T, Ueda R, Dohi Y. Circulating levels of myocardial proteins predict future deterioration of congestive heart failure. *J Card Fail*. 2005;11:504–509. doi: 10.1016/j.cardfail.2005.04.025
5. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, Aupetit JF, Aumont MC, Galinier M, Eicher JC, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol*. 2007;49:1733–1739. doi: 10.1016/j.jacc.2006.10.081
6. Fonarow GC, Peacock WF, Horwich TB, Phillips CO, Givertz MM, Lopatin M, Wynne J; ADHERE Scientific Advisory Committee and Investigators. Usefulness of B-type natriuretic peptide and cardiac troponin levels to predict in-hospital mortality from ADHERE. *Am J Cardiol*. 2008;101:231–237. doi: 10.1016/j.amjcard.2007.07.066
7. Masson S, Latini R, Anand IS, Vago T, Angelici L, Barlera S, Missov ED, Clerico A, Tognoni G, Cohn JN; Val-HeFT Investigators. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clin Chem*. 2006;52:1528–1538. doi: 10.1373/clinchem.2006.069575
8. Wang Y, Zhang R, Huang Y, Zhai M, Zhou Q, An T, Huang Y, Zhao X, Tian P, Zhang Y, et al. Combining the use of amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the prognosis of hospitalized heart failure patients. *Clin Chim Acta*. 2019;491:8–14. doi: 10.1016/j.cca.2018.12.025
9. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004. doi: 10.1056/NEJMoa1409077
10. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, et al; PARADIGM-HF Committees and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2013;15:1062–1073. doi: 10.1093/eurjhf/hft052
11. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, et al; PARADIGM-HF Committees Investigators. Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2014;16:817–825. doi: 10.1002/ejhf.115
12. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387. doi: 10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, et al; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200. doi: 10.1093/eurheartj/ehw128
14. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, et al. 2017 comprehensive update of the Canadian cardiovascular society guidelines for the management of heart failure. *Can J Cardiol*. 2017;33:1342–1433. doi: 10.1016/j.cjca.2017.08.022
15. Atherton JJ, Sindone A, De Pasquale CG, Driscoll A, MacDonald PS, Hopper I, Kistler PM, Briffa T, Wong J, Abhayaratna W, et al. National heart foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018. *Heart Lung Circ*. 2018;27:1123–1208. doi: 10.1016/j.hlc.2018.06.1042
16. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2013;62:e147–e239. doi: 10.1016/j.jacc.2013.05.019
17. Farnsworth CW, Bailey AL, Jaffe AS, Scott MG. Diagnostic concordance between NT-proBNP and BNP for suspected heart failure. *Clin Biochem*. 2018;59:50–55. doi: 10.1016/j.clinbiochem.2018.07.002
18. Kristensen SL, Jhund PS, Mogensen UM, Rorth R, Abraham WT, Desai A, Dickstein K, Rouleau JL, Zile MR, Swedberg K, et al. Prognostic value of N-terminal pro-B-type natriuretic peptide levels in heart failure patients with and without atrial fibrillation. *Circ Heart Fail*. 2017;10:e004409. doi: 10.1161/CIRCHEARTFAILURE.117.004409.
19. Richards M, Di Somma S, Mueller C, Nowak R, Peacock WF, Ponikowski P, Mockel M, Hogan C, Wu AH, Clopton P, et al. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients: results from the BACH Study (Biomarkers in ACute Heart Failure). *JACC Heart Fail*. 2013;1:192–199. doi: 10.1016/j.jchf.2013.02.004
20. Krauser DG, Lloyd-Jones DM, Chae CU, Cameron R, Anwaruddin S, Baggish AL, Chen A, Tung R, Januzzi JL Jr. Effect of body mass index on natriuretic peptide levels in patients with acute congestive heart failure: a ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) substudy. *Am Heart J*. 2005;149:744–750. doi: 10.1016/j.ahj.2004.07.010
21. Myhre PL, Vaduganathan M, Claggett B, Packer M, Desai AS, Rouleau JL, Zile MR, Swedberg K, Lefkowitz M, Shi V, et al. B-type natriuretic peptide during treatment with sacubitril/valsartan: the PARADIGM-HF Trial. *J Am Coll Cardiol*. 2019;73:1264–1272. doi: 10.1016/j.jacc.2019.01.018
22. Richards M, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton CM, Crozier IG, Yandle TG, Doughty R, et al; Christchurch Cardioendocrine Research Group; Australia-New Zealand Heart Failure Group. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischemic heart disease. *J Am Coll Cardiol*. 2006;47:52–60. doi: 10.1016/j.jacc.2005.06.085
23. Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton C, Turner J, Crozier IG, Yandle TG. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. *Circulation*. 2003;107:2786–2792. doi: 10.1161/01.CIR.0000070953.76250.B9
24. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. *J Am Coll Cardiol*. 2003;42:728–735. doi: 10.1016/s0735-1097(03)00787-3