Title: Comparison of BNP and NT-proBNP in patients with heart failure and reduced ejection fraction

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ABSTRACT

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

Methods: Eligibility criteria in PARADIGM-HF included New York Heart Association (NYHA) functional class II-IV, left ventricular ejection fraction (LVEF) ≤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 (AF). Estimated glomerular filtration rate (eGFR) <30 ml/min/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 approximately 6.25:1. This ratio varied considerably according to rhythm (AF 8.03:1; no AF 5.75:1) and with age, renal function and body mass index but not with LVEF. Each peptide was similarly predictive of death (all-cause, cardiovascular, sudden and pump failure) and heart failure hospitalization e.g. cardiovascular death: BNP HR 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 HFrEF appears to be greater than generally appreciated, differs between patients with and without AF and increases substantially with

increasing age and decreasing renal function. These findings are important for comparison of natriuretic peptide concentrations in HFrEF.

Abbrevations

proBNP = Pro B-type natriuretic peptide

BNP = B-type natriuretic peptide

NT-proBNP = N-terminal proBNP

HFrEF = Heart failure and reduced ejection fraction

NYHA = New York Heart Association

LVEF = left ventricular ejection fraction

AF = Atrial fibrillation

MI = Myocardial infarction

BMI = Body mass index

ACE = Angiotensin converter enzyme

ARB = Angiotensin receptor blocker

MRA = Mineralocorticoid receptor antagonist

SBP = Systolic blood pressure

eGFR = estimated glomerular filtration rate

CV = cardiovascular

SD= standard deviation

PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial

Val-HeFT = Valsartan Heart Failure Trial

What is new?

- Although measurements of BNP and NT-proBNP 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 PARADIGM-HF was approximately 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 LVEF. We also found that the NT-proBNP to BNP varied according to heart rhythm (AF 8.03:1; no AF 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.

INTRODUCTION

Pro B-type natriuretic peptide (proBNP) is secreted by cardiomyocytes in response to stretch and is quickly cleaved into two circulating fragments - the biologically active 32-amino acid C-terminal B-type natriuretic peptide (BNP) and the inert 76-amino acid N-terminal (amino-terminal) pro-B-type natriuretic peptide (NT-proBNP).[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 two 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 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 or not). Although clinical trials apply different threshold values for inclusion of patients with and without atrial fibrillation, 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 non-fatal and a variety of fatal outcomes in HFrEF. We performed these analyses using data from the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF) 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 upon 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 (NYHA) functional class II-IV with a left ventricular ejection fraction (LVEF) ≤40% receiving recommended treatment for HFrEF including an angiotensin converter enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), a beta-blocker (unless contraindicated) and a mineralocorticoid receptor antagonist (MRA), 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 atrial fibrillation. The key exclusion criteria included

intolerance of an ACE inhibitor or ARB, a history of angioedema, symptomatic hypotension, a systolic blood pressure (SBP) <100 mmHg at screening (<95 mmHg at randomization), an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^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. Presence of atrial flutter or fibrillation was based on the rhythm present on the screening ECG. History of diabetes was based on investigator reported diagnosis of diabetes, irrespective of HbA1c 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 degrees Celsius. On the same day, samples were shipped on dry ice to the closest of six 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, NTproBNP 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 endpoint was a composite of cardiovascular death or heart failure hospitalization; we analyzed this, its components (cardiovascular death and heart failure hospitalization), the two 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 standard deviations 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, NYHA class, heart failure duration, prior heart failure hospitalization, body mass index (BMI), creatinine, LVEF, heart rate, atrial fibrillation (AF), myocardial infarction (MI), stroke and diabetes 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, NYHA class, BMI, heart rate, systolic blood pressure, creatinine, prior heart failure hospitalization, heart failure duration, AF, MI, stroke and diabetes. 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 Harrell's C-statistic.[12] P-values < 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 (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% vs 19%) and Caucasian (69% vs 62%) and fewer had an ischemic etiology (57% vs 64%) or history of myocardial infarction (38% vs 49%) [Table 1]. Patients with a median NT-proBNP/BNP ratio >6.25 also had worse kidney function (eGFR: 62 mL/min per 1.73 m^2 vs 70 mL/min per 1.73 m^2 in patients with NT-proBNP/BNP ratio ≤6.25) and more had a history of AF (40% vs 28%) as well as AF on their screening ECG (36% vs 15%) [Table 1]. The NT-proBNP/BNP ratio decreased in patients treated with sacubitril/valsartan (Supplementary figure 1).

NT pro BNP/BNP ratio according to baseline rhythm and interaction with other characteristics

In patients without atrial fibrillation, the median BNP was 329 (IQR 210-574) pg/ml and the median NT-proBNP was 1938 (1127-3750) pg/ml; in patients with atrial fibrillation 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 atrial fibrillation, the linear correlation between log BNP and log NT-proBNP was 0.83; in patients in atrial fibrillation 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 atrial fibrillation, compared to 8.03 (IQR 5.88-10.80):1 in patients with atrial fibrillation; 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 obese patients, 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 atrial fibrillation 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).

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, i.e. 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. 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 NYHA 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 to 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 two 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, 50-75 years and >75 years, the thresholds recommended are 450, 900 and 1800 pg/ml, respectively. 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 atrial fibrillation, 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 atrial fibrillation, compared to 5.75:1 in those not in atrial fibrillation. 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 atrial fibrillation as in those without. Consequently, for example, the NT-proBNP/BNP ratio in the oldest patients was approximately 10:1 for those in atrial fibrillation compared with around 6.5:1 in participants in sinus rhythm (compared with approximately 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 approximately 10:1 for those in atrial fibrillation compared with around 7:1 in participants in sinus rhythm (compared to patients with the highest eGFR where the ratio was approximately 6.5:1 in patients in atrial fibrillation compared with around 5:1 in those not in atrial fibrillation).

In contrast to the guidelines, most, but not all, trials have set different natriuretic peptide inclusion thresholds for patients with and without atrial fibrillation. However, the AF versus no AF multiplication factor for NT-pro BNP, versus BNP, varies two-fold from 1.5:1 to 3:0 in ongoing and recently completed trials; our data suggest that this factor is 1.4 (i.e. 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 were 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 is 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 patients without heart failure.[22-24] The first large analysis of this type was carried out by the Valsartan Heart Failure Trial (Val-HeFT) 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 i.e. 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 i.e. 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 standard deviation increase in peptide concentration of approximately 1.3-1.4 for all events other than pump failure death where the hazard ratio was 1.6-1.7. 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 models including other recognized prognostic variables. The two 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/1.73m^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 utilized in clinical trial inclusion criteria. Moreover, this ratio is quite different in patients with atrial fibrillation (8.03:1) compared to those without (5.75:1). At present, guidelines do not differentiate between atrial fibrillation and sinus rhythm and in the trials that do, the multiplication factor used is 1.5-3.0, higher than the 1.4-fold higher rate found in the current analyses. In both atrial fibrillation 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 atrial fibrillation and around 6.5:1 in those not in atrial fibrillation. Thus, there is no single, simple, conversion ratio for these two peptides.

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Disclosures

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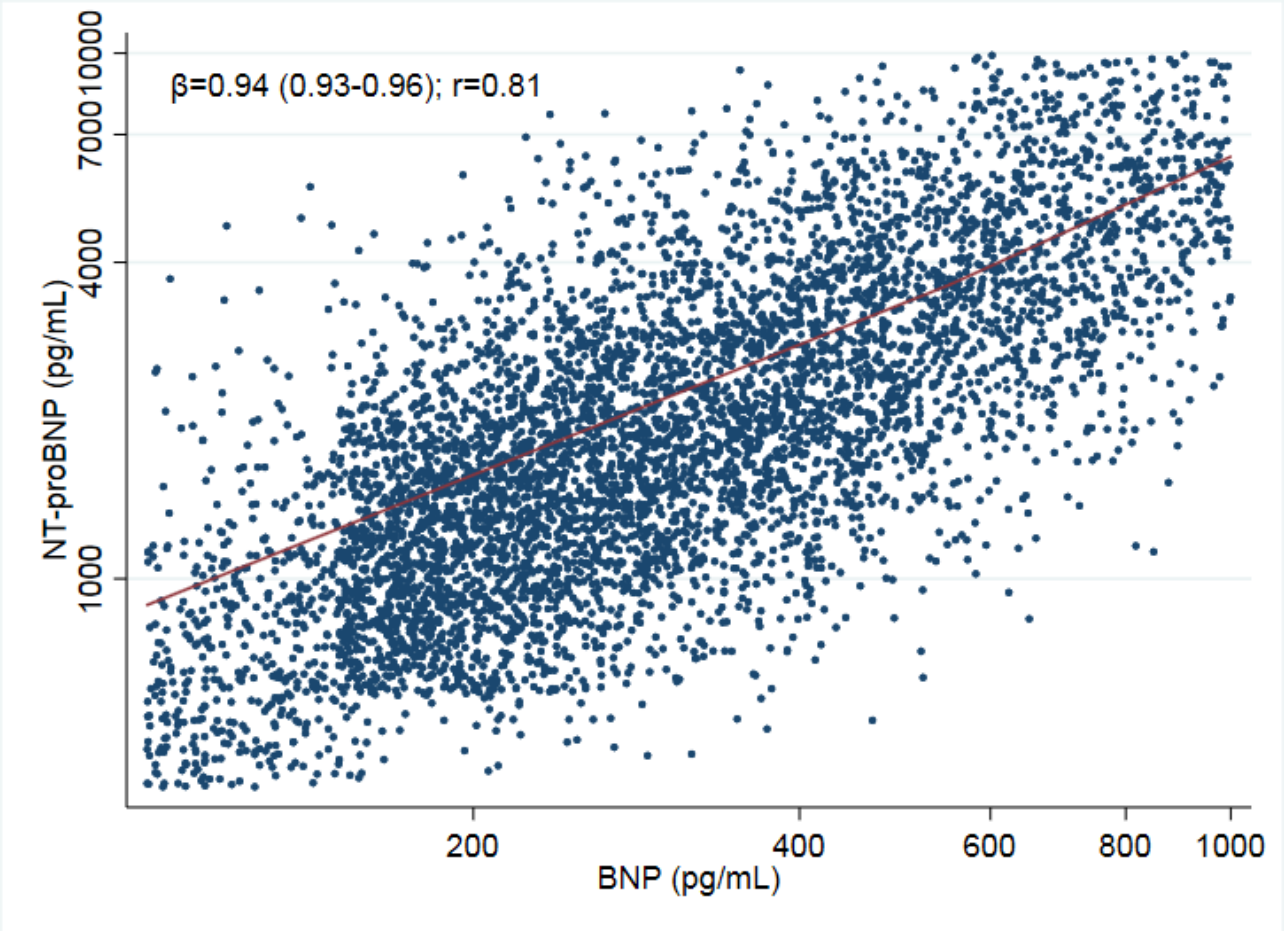
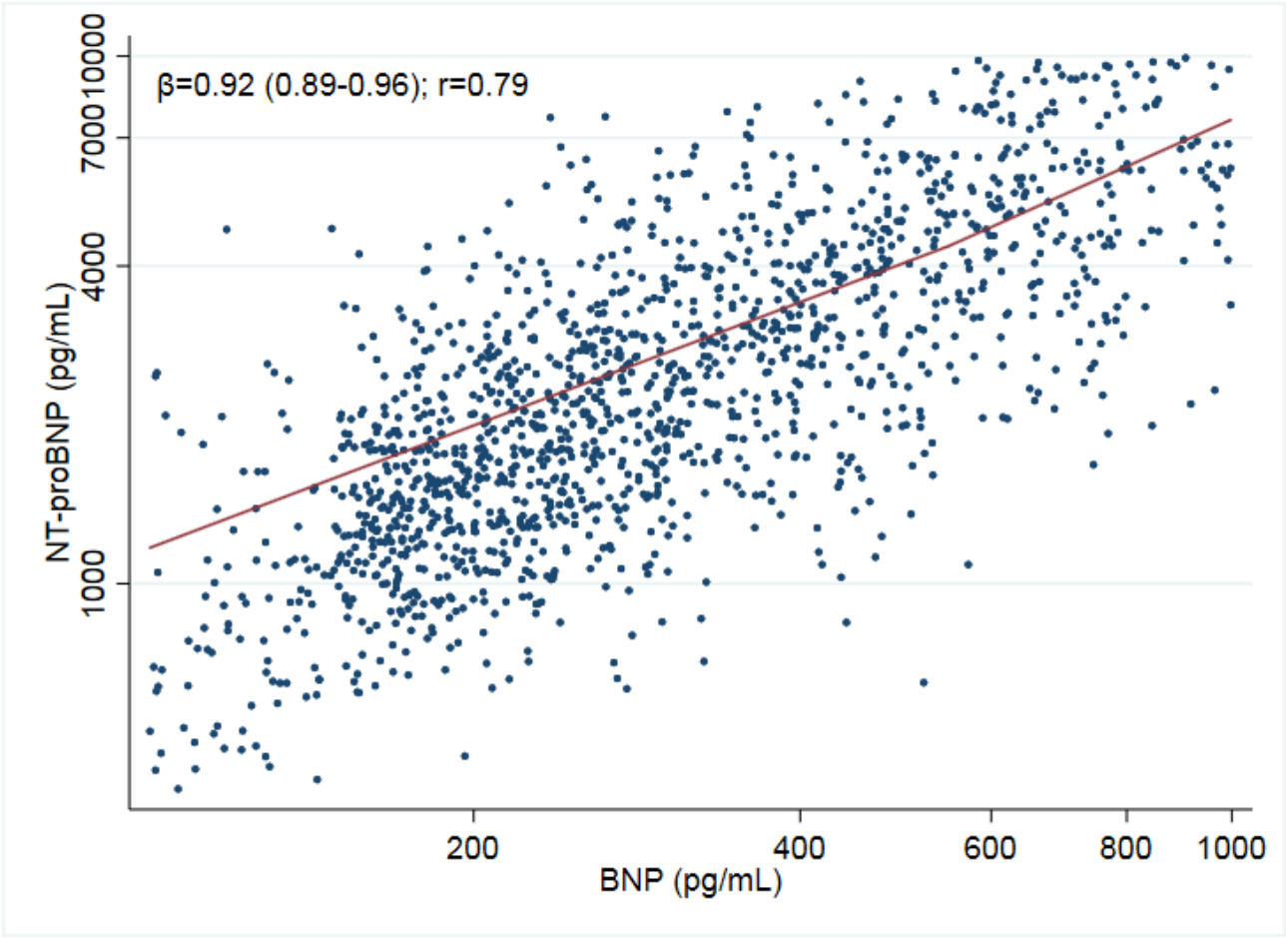
Figure 1: NT-proBNP and BNP levels in all patients (A), in patients with (B) and without (C) atrial fibrillation:

A:



B:


β=0.92 (0.89-0.96); r=0.79
NT-proBNP (pg/mL)
1000
4000
7000
10000
200
400
600
800
1000
BNP (pg/mL)

C:

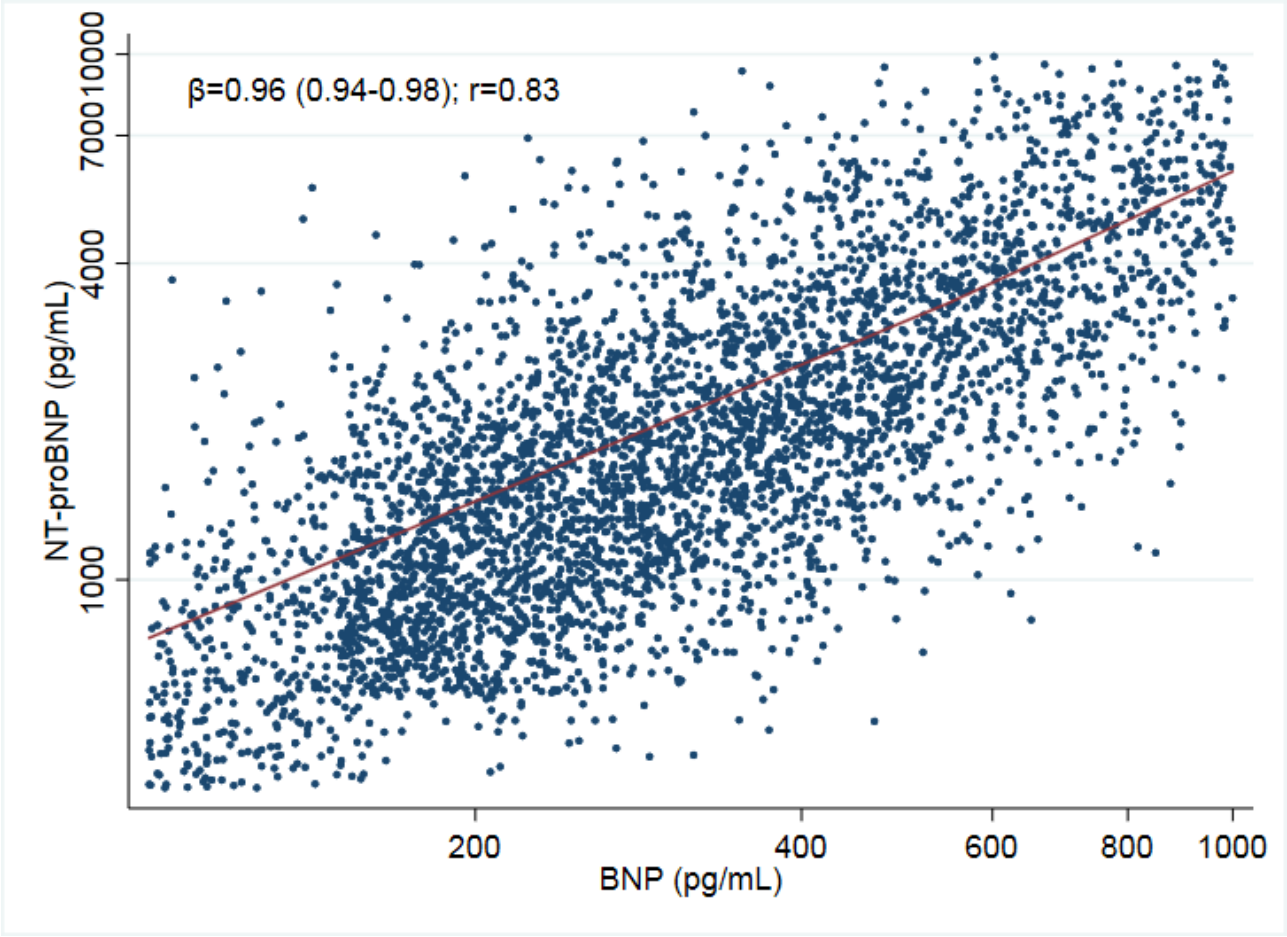
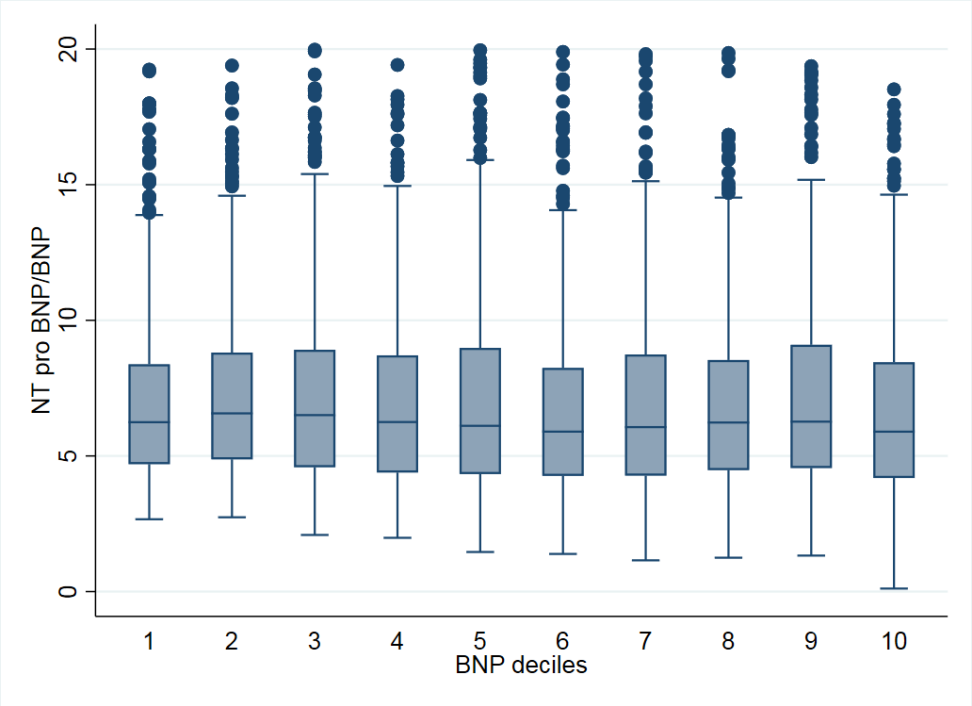
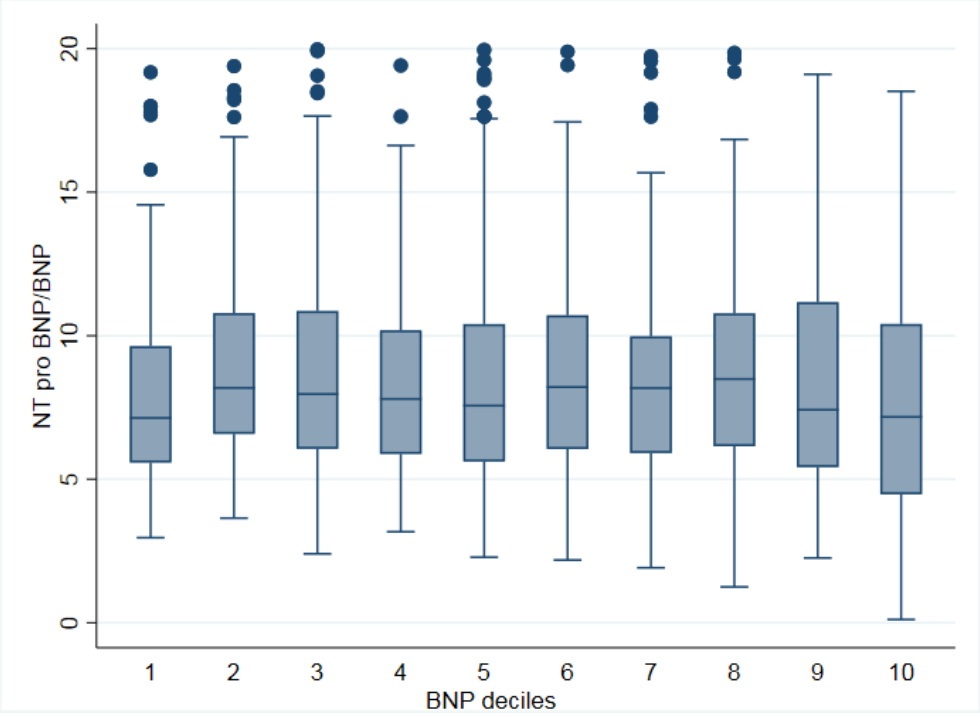

β=0.96 (0.94-0.98); r=0.83
NT-proBNP (pg/mL)
1000
4000
7000
10000
200
400
600
800
1000
BNP (pg/mL)

Figure 2: Ratio of NT-proBNP to BNP (NT-proBNP /BNP) according to decile of BNP: A) All patients. B) Patients with atrial fibrillation. C) Patients without atrial fibrillation.

A:



B:



C:

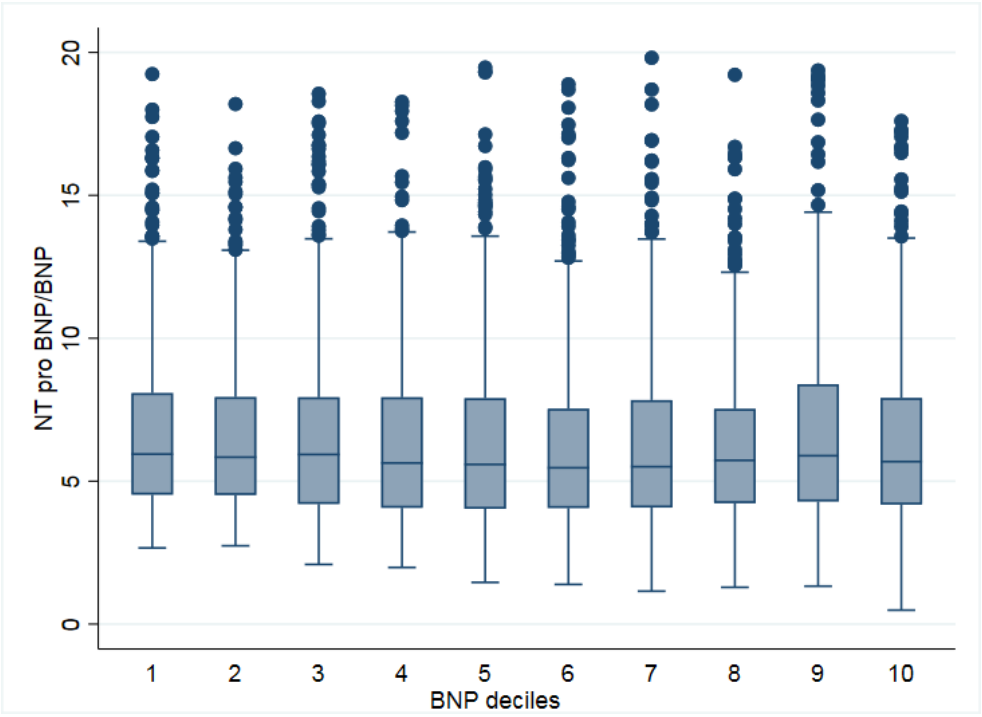
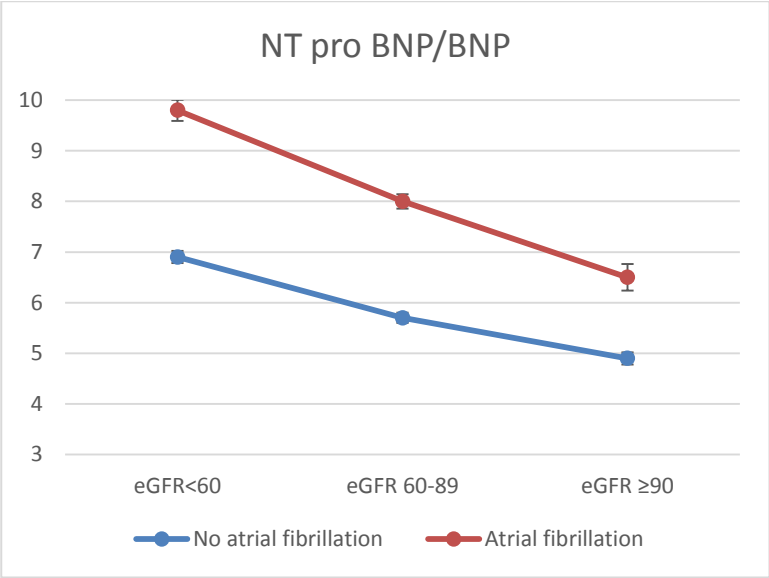
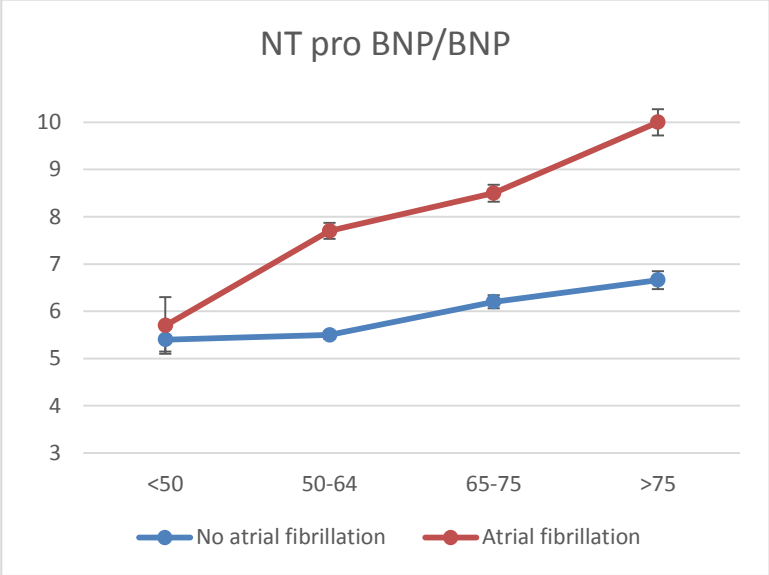

NT pro BNP/BNP
0
5
10
15
20
1
2
3
4
5
6
7
8
9
10
BNP deciles

Figure 3: NT-proBNP/BNP ratio in patients with and without atrial fibrillation, according to categories of: A) eGFR, B) age, C) BMI and D) LVEF

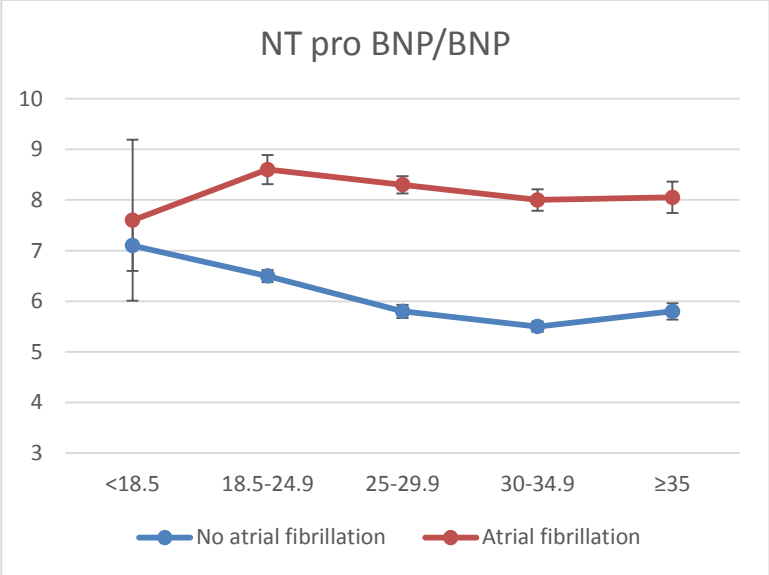
A:



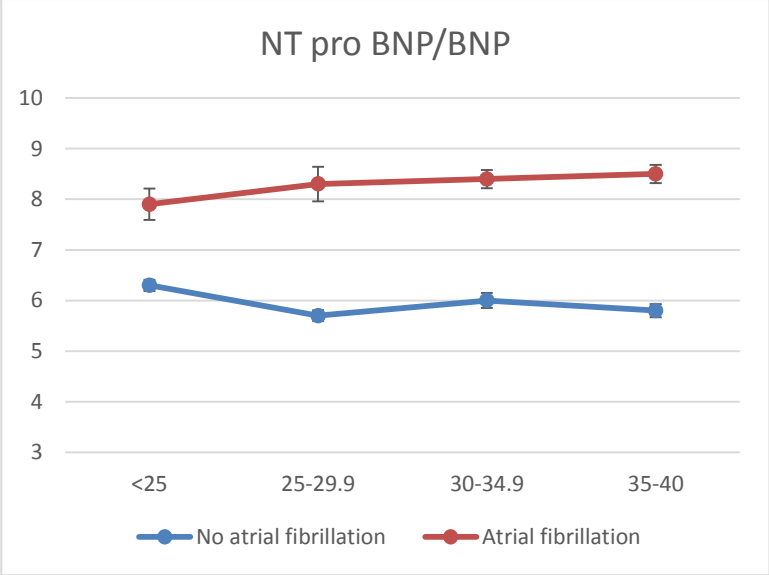
B:



C:


NT pro BNP/BNP
10
9
8
7
6
5
4
3
<18.5
18.5-24.9
25-29.9
30-34.9
≥35
No atrial fibrillation
Atrial fibrillation

D:


NT pro BNP/BNP
10
9
8
7
6
5
4
3
<25
25-29.9
30-34.9
35-40
No atrial fibrillation
Atrial fibrillation

Supplementary figure 1: NT pro BNP/ BNP ratio according to treatment allocation

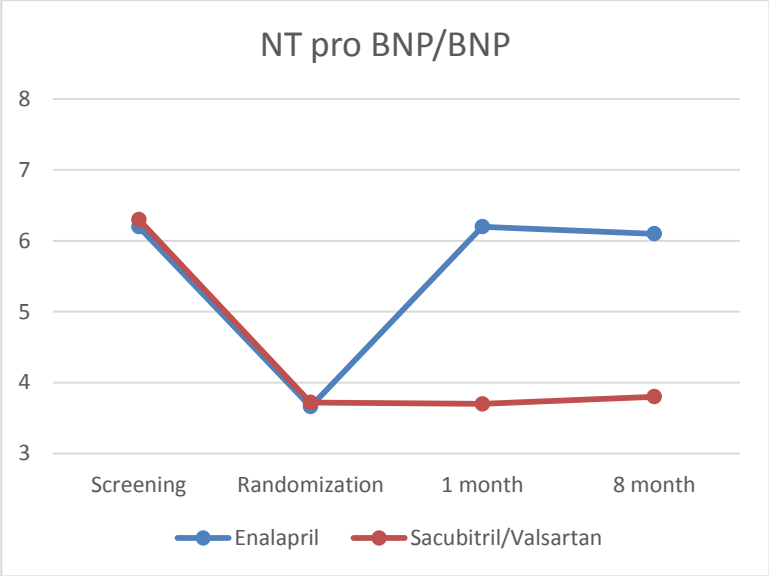


Table 1: Baseline characteristics according to median NT-proBNP/BNP ratio

	NT -proBNP/BNP ratio ≤6.25	NT-proBNP/BNP ratio >6.25	P-values
Patients, n (%)	3219 (50)	3219 (50)	
BNP, pg/mL	333 [213, 565.1]	307 [202, 554]	0.002
NT-proBNP, pg/mL,	1406 [902, 2448]	2983 [1830, 5469]	<0.0001
Age, 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 etiology, n (%)	2066 (64)	1837 (57)	<0.0001
HF duration, y, n (%)			0.5598
0-1	987 (31)	968 (30)	
>1-5	1218 (38)	1260 (39)	
>5	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, m^2/kg, median [Q1,Q3]			<0.0001
<18.5	42 (1)	96 (3)	
18.5-24.9	898 (28)	1048(33)	
25-29.9	1256 (39)	1170 (36)	
30-34.9	674 (21)	604 (19)	
≥35	344 (11)	296(9.)	
Ejection fraction (%)	29 ± 6	29 ± 6	0.5341
Heart rate, beats/min	73 ± 13	75 ± 13	<0.0001
Atrial fibrillation or flutter on ECG	490 (15)	1167 (36)	<0.0001
SBP, mmHg	128 ± 17	128 ± 17	0.905
eGFR, mL/min per 1.73 m^2	70 [58, 84]	62 [50, 74]	<0.0001
Creatinine; umol/L	91 [79, 107]	99 [84, 118]	<0.0001
eGFR, <60 mL/min per 1.73 m^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	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

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 year)	0.45 (0.34-0.56)	<0.001	0.03 (0.02-0.05)	<0.001	-0.04 (-0.05--0.02)	<0.001
Sex (female)	1.33 (1.03-1.63)	<0.001	0.14 (0.09-0.19)	<0.001	-0.01 (-0.05-0.04)	0.78
NYHA class						
I	0.27 (-1.46-2.00)	0.76	-0.08 (-0.37-0.21)	0.54	-0.14 (-0.40-0.12)	0.29
II	Ref.		Ref.		Ref.	
III	0.06 (-0.18-0.30)	0.61	0.24 (0.20-0.29)	<0.001	0.24 (0.20-0.27)	<0.001
IV	-0.44 (-1.32-0.45)	0.33	0.43 (0.28-0.59)	<0.001	0.51 (0.38-0.65)	<0.001
BMI (kg/m2)						
<18.5	1.90 (1.10-2.70)	<0.001	0.41 (0.28-0.55)	<0.001	0.20 (0.08-0.32)	0.001
18.5-24.9	Ref.		Ref.		Ref.	
25-29.9	-0.72 (-1.00--0.45)	<0.001	-0.27 (-0.31--0.22)	<0.001	-0.19 (-0.23--0.14)	<0.001
30-34.9	-1.08 (-1.41--0.74)	<0.001	-0.43 (-0.49--0.38)	<0.001	-0.32 (-0.37--0.27)	<0.001
>35	-0.99 (-1.43--0.56)	<0.001	-0.53 (-0.61--0.46)	<0.001	-0.42 (-0.49--0.36)	<0.001
Creatinine (+1 log_e umol/L)	4.16 (3.66-4.66)	<0.001	0.83 (0.74-0.91)	<0.001	0.33 (0.25-0.40)	<0.001
Ejection fraction (+ 1 %)	-0.01 (-0.03-0.01)	0.43	-0.02 (-0.02--0.02)	<0.001	-0.02 (-0.02--0.01)	<0.001
Systolic blood pressure (+1 mmHg**)**	-0.01 (-0.02-0.00)	0.02	0.00 (0.00-0.00)	0.14	0.00 (0.00-0.00)	0.66
Myocardial infarction (Yes)	-0.70 (-0.94-0.46)	<0.001	-0.16 (-0.20--0.12)	<0.001	-0.05 (-0.09--0.02)	0.004
Atrial fibrillation* (Yes)	2.05 (1.78-2.32)	<0.001	0.24 (0.19-0.29)	<0.001	-0.03 (-0.08--0.02)	0.11
Stroke (Yes)	0.43 (0.03-0.83)	0.04	0.04 (-0.03-0.11)	0.22	0.00 (-0.06-0.06)	0.97
Diabetes (Yes)	0.01 (-0.22-0.26)	0.91	0.0 (-0.04-0.04)	0.92	0.00 (-0.04-0.03)	0.92
Prior HF hosp. (Yes)	-0.03 (-0.26-0.21)	0.84	-0.05 (-0.09--0.01)	0.01	-0.06 (-0.10--0.03)	<0.001
HF duration (Years)						
0-1	Ref.		Ref.		Ref.	

>1-5	0.07 (-0.21-0.34)	0.63	0.05 (0.01-0.10)	0.03	0.07 (0.03-0.11)	0.001
>5	-0.24 (-0.55-0.06)	0.11	-0.04 (-0.09-0.01)	0.15	0.02 (-0.03-0.06)	0.42
Constant	-14.55 (-17.10- -12.00)	<0.001	4.41 (3.98-4.84)	<0.001	5.26 (4.88-5.65	<0.001

*Atrial fibrillation or flutter on ECG at screening

BMI = body mass index

β-Coef. = beta-coefficient

HF = heart failure

NYHA = New York Heart Association

Table 3: Adjusted hazard ratios* for outcomes of interest according to 1 standard deviation increase of BNP or NT-proBNP.

	No. 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

CV = cardiovascular, HF = heart failure, SD= standard deviation

*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.

Table 4: C-index for predictive model without natriuretic peptides and for the addition of each of BNP and NT pro BNP, separately.

	CV death or HF hospitalization	CV death	HF hospitalization	All-cause mortality	Sudden cardiac death	Pump failure death
	C-index$_{2\ year}$ (CI95%); P-value					
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-pro BNP	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*

[†]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. 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