Dynamic Risk Stratification using Serial Measurements of Plasma Concentrations of Natriuretic Peptides in Patients with Heart Failure

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Running Title: Repeated NT-proBNP, mortality and chronic heart failure

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Abstract

Background: Prognostic models for patients with chronic heart failure are generally based on a single assessment but treatment is often given with the intention of changing risk; re-evaluation of risk is an important aspect of care. The prognostic value of serial measurements of natriuretic peptides for the assessment of changes in risk is uncertain.

Aims: To evaluate the prognostic value of serial measurements of plasma amino-terminal pro-brain natriuretic peptide (NT-proBNP) during follow-up of out-patients with chronic heart failure (CHF).

Methods: Patients diagnosed with CHF between 2001 and 2014 at a single out-patient clinic serving a local community were included in this analysis. NT-proBNP was measured at the initial visit and serially during follow-up. Only patients who had one or more measurements of NT-proBNP after baseline, at 4, 12 and/or 24 months were included.

Results: At baseline, amongst 1,998 patients enrolled, the median age was 73 (IQR: 64-79) years, 70% were men, 31% were in NYHA class III/IV, 58% had a reduced ejection fraction and 77% had NT-proBNP >400 pg/ml. Median follow-up was 4.8 (IQR 2.5-8.6) years. Serial measurements of NT-proBNP improved prediction of all-cause mortality at 3 years (c-statistic=0.71) compared with using baseline data only (c-statistic=0.67; $p<0.001$) but a model using only the most recent NT-proBNP had an even higher c-statistic (0.72; $p<0.001$). Similar results were obtained based on long-term prediction of mortality using all available follow-up data.

Conclusions: Serial measurement of NT-proBNP in patients with CHF improves prediction of all-cause mortality. However, using the most recent value of NT-proBNP has similar predictive power as using serial measurements.

Introduction

Plasma concentrations of N-terminal pro B-type natriuretic peptide (NT-proBNP) are strongly associated with prognosis in patients with chronic heart failure (CHF). [1-5] Prognostic models of CHF are generally based on a single assessment but in clinical practice risk varies over time as disease progresses, complications and co-morbidities develop and treatment that is intended to reduce risk is implemented. In clinical practice, health professionals evaluate risk serially. In clinical trials, the effect of treatment on NT-proBNP has often predicted outcome, [6] although this may not be true for some interventions such as beta-blockers. Recently the use of repeated measurements of NT-proBNP for predicting outcome have been studied for some chronic and acute setting (Supplementary Table S1). However, the prognostic value of serial measurements of natriuretic peptides for the assessment of changes in long-term risk in clinical practice has rarely been investigated and the value of doing so is uncertain. Some risk markers will be relatively fixed (eg:- age, sex and aetiology of disease) but other will be dynamic and fluctuate (for example, renal function). If serial measurements of NT-proBNP are more strongly related to prognosis than a single baseline value, it may be a dynamic marker that can be used to track risk.

The purpose of the present study was to investigate the relationship between all-cause mortality and repeated measurements of NT-proBNP compared with a single baseline or most recent value of NT-proBNP.

Methods

Study Population

Patients referred to a community heart failure clinic (Kingston-upon-Hull, UK) for the assessment of heart failure symptoms were invited to participate. A history and examination were performed, and patients underwent electrocardiography, echocardiography and had routine haematology and biochemical investigations. If heart failure was confirmed, patients were offered serial follow-up in the heart failure clinic. NT-proBNP was measured at baseline, and then at approximately 4 months, 12 months and yearly thereafter. Only patients who had one or more follow-up measurements of NT-proBNP were included in this analysis.

Samples for the measurement of NT-proBNP were collected in ethylene-diamine-tetra-acetic tubes, spun at 3000 r.p.m for 15 minutes in a cooled (4°C) centrifuge and the plasma was

stored at -80°C until batch analysed using the Elecsys proBNP assay (Roche Diagnostics, Basel, Switzerland).

Prospectively collected clinical data and blood samples from a single heart failure clinic were used in this study. The primary outcome of interest was all-cause mortality. Data for deaths were collected from the hospital's electronic systems, supplemented by information from patients, discharge letters and their family doctors.

Prior to inclusion, all patients provided written informed consent for their data to be used and the study was carried out in accordance with the Helsinki Declaration II and the European Standards for Good Clinical Practice. Ethical approval was granted by the Hull and East Yorkshire Local Research Ethics Committee.

Statistical methods

Continuous variables are presented as medians and the inter-quartile ranges and categorical variables are expressed as percentages. Correlations between the repeated NT-proBNP measurements were assessed with scatter plots and Pearson's correlation coefficients. The assumptions of Cox regression model, such as the proportional hazards and linearity were assessed.

Two main analyses were conducted. Firstly, the association between NT-proBNP measurements and survival at three years was studied and the predictive value of NT-proBNP was assessed. The strategy included analysis of the relation between outcome and: (a) baseline NT-proBNP; (b) repeated NT-proBNP measurements as a time-dependent covariate using an extended Cox regression model [7]allowing for different patients having different numbers of NT-proBNP measurements at varying time-points and (c) only the most recent NT-proBNP.

Secondly, a robust joint modelling of longitudinal and survival data [8] was used to evaluate the association between all repeated NT-proBNPs and time to all-cause mortality. The aim was to assess whether there was any association between the repeated of plasma NT-proBNP and outcome. The patients who had at least two measures of NT-proBNP used in the first analysis plus further available NT-proBNP measurements were included in this analysis. The joint model is effectively a two-stage process. First, an analysis of the longitudinal data for NT-proBNP over time is performed using a linear mixed effects model. In the second stage, a Cox

proportional hazard model is used for survival data. These two stages are linked through shared random effects to evaluate the association between the values of NT-proBNP and time to all-cause mortality.

For the longitudinal sub-model the random effects of both intercept and slope were included to allow variations in each individually. Baseline age, sex, estimated glomerular filtration rate (eGRF) were used as the fixed effects, and an interaction between time and heart rhythm was included. For the Cox-regression sub-model, pre-specified baseline variables included age, sex, and eGFR were used. Individual patient prediction was conducted according to the trajectory of NT-proBNP. Statistical analysis was carried out using R version 3.0.1 and Stata software package. The two-tailed level of statistical significance was set at $p<0.05$.

Results

Of 1,998 patients with at least two measurements of NT-proBNP, 70% were men. At baseline, their median age was 73 (IQR: 64-79) years, 31% were in NYHA class III/IV and 77% had NT-proBNP >400 $ng.L^{-1}$. Overall three-year mortality for patients with at least two measurements was 12.7%.

Patients who died at 3 years were older and more likely to be men, have ischaemic heart disease (IHD) and more severe symptoms, more likely to have atrial fibrillation, COPD and had a lower eGFR, systolic BP and haemoglobin, and higher heart rate and NT-proBNP than those who survived. Patients who survived were more likely to be prescribed beta-blockers and ACEi/ARBs (Table 1).

There were strong positive linear correlations between baseline log(NT-proBNP) and each of repeated measurements of log(NT-proBNP) at 4 months, 12 months and 24 months regardless of heart rhythm (supplementary Table S2). Patients in atrial fibrillation had a consistently higher and patients in sinus rhythm consistently had lower median plasma NT-proBNP at all time-points. Correlations were stronger for closer time-points (Figure 1, supplementary Table S2).

Baseline NT-proBNP, time-dependent covariate NT-proBNP and most recent NT-proBNP were all significant predictors of all-cause mortality at 3 years (Table 2) ($p<0.0001$ for all). Serial measurements and the most recent NT-proBNP were better predictors of prognosis than were baseline values. Similar results were obtained when the models were adjusted for

age and sex.

1,998 patients with baseline and follow-up values for NT-proBNP (N=10,362) were included in the joint-modelling analysis, of whom 770 (39%) died. The median (IQR) follow-up time was 4.8 (2.5-8.6) years. The minimum follow-up time was 0.3 years and the maximum was 13.7 years.

There was a strong association between serial NT-proBNP values as a time-dependent covariate and all-cause mortality (Supplementary Table S3). A unit increase in log(NT-proBNP) corresponded to a 3.76 - fold increase in the risk for death (95%CI: 3.15-4.56, P<0.0001). The hazard ratios (HR) decreased when the most recent measurement of NT-proBNP was excluded (HR: 3.01 (2.20-3.21)). The HR of log(NT-proBNP) in the joint model was approximately twice as high as the model including only the baseline data. However, the Cox regression using only the most recent measurement of NT-proBNP gave a HR very similar to that in the joint model (HR: 3.73 (3.20-4.34)), with a higher z value of 16.89 (p<0.0001). A significant interaction between the time and baseline SR (p=0.01) was observed.

Figure 2 shows an example of the dynamic change in predicted risk based on an increasing number of NT-proBNP measurements. At baseline, the patient's NT-proBNP was high, decreasing quickly and becoming stable from 2 years onward. The graphs show that the probabilities for survival gradually improved as NT-proBNP decreased. Supplementary Figures S1 and S2 show a patient who died and another who had a plasma NT-proBNP persistently <500ng/L.

Discussion

To the best of our knowledge, this is the first paper to apply joint-modelling to study the dynamic association between serial measurements of NT- proBNP and survival. It suggests that NT-proBNP is a useful measurement for monitoring changes in prognosis, and presumably reflects the combined effects of disease progression, response to therapy and, for some, recovery of cardiac function. [9] Clearly, there must be a relationship between changes in and values of NT-proBNP but the most recent value of NT-proBNP conveys the most important prognostic information.[10] Our results cannot be taken as evidence that pursuing a particular target for NT-proBNP is the correct approach, as confirmed by the recent GUIDE-IT trial.[11]Basing clinical decisions on a single measurement is simple and has several other

advantages. Previous measurements may not be available. Measuring change is also complex. It is not clear whether absolute or relative change is more important or the rate of change, and therefore the timing of samples, or what value should be used as the reference point from which change is measured; values may go up as well as down and the change between the first and most recent test may be very different from the change between the two most recent ones.

Hopefully, one day, the aim will be to return values of NT-proBNP observed in patients with heart failure back into the normal range for the healthy population, although, despite implementation of guideline-recommended therapies, this rarely occurred in this cohort of patients. Further advances in the treatment of heart failure may increase the proportion of patients that achieve a normal value for NT-proBNP and if associated with control of symptoms and a good prognosis, this might be termed 'remission' of heart failure. [12]

Numerous studies have shown the prognostic value of natriuretic peptides for patients with chronic heart failure and various other medical conditions. [12, 10, 13-20] However, they have not proved consistently valuable for assessing prognosis in acute heart failure (Supplementary Table S1_A). [21-25, 26-27] Curiously, this may reflect their ability to track changing prognostic risk rather than their failure. A patient with decompensated heart failure, left untreated, is near to death. Treatment will usually reduce NT-proBNP and improve prognosis. If natriuretic peptides were good prognostic markers in the acute setting, this would imply that they did not track with changing prognosis. In this setting, changes in natriuretic peptides might possibly provide additional information to achieved values, [24, 28] but when patients enter a more stable chronic phase of their illness our results are likely to apply.

Few studies [10, 14, 17] have examined the relationship of changes in natriuretic peptides and outcome in out-patients with chronic heart failure [Supplementary Table S1_B]. In a small sample of patients with much fewer measurements of NT-proBNP and over a much shorter time-frame, we found similar results.[16] In a study of 2975 elderly adults without heart failure in whom NT-proBNP had been measured twice, 2-3 years apart, the second measurement further improved prediction of incident heart failure and cardiovascular death. [29] However, the possibility that baseline values added nothing to the follow-up value was not explored.

The prognostic value of natriuretic peptides appears similar for most if not all phenotypes of chronic heart failure. [13, 14, 16] However, for each of these phenotypes, plasma concentrations of NT-proBNP were relatively stable for most patients despite attempts to control symptoms and

deliver guideline-recommended therapy.

Previous analyses have often failed to take into account the possibility that serial measurements of NT-proBNP are highly correlated. [13-15] Joint modelling of longitudinal and survival data is useful since it reduces the bias in estimating the association between repeated measurements and time to event [8] and provides an updated individual survival probability when a new measurement of NT-proBNP becomes available.

Limitations: An important limitation is that joint modelling, currently, allows only one variable (NT-proBNP in this case) to be used serially in the model. In addition, we have not reported rates of ICD/CRT implantation at baseline, partly because implant rates were low, and partly because many patients had a device implanted during follow up. Furthermore, the c-statistics we report are invariably much less than 1 reflects the impact of other variables, such as renal function and co-morbidities, on outcome. However, the aim of the study was to explore whether the history of how the NT-proBNP reached its present value matters. We have therefore not used further complex modelling to include all possible variables in all possible models to maximise the value for c-statistics. Supplementary table S2 shows how we did not have data at every time point in each subject. However, one of the advantages of using joint modelling is that it can cope with missing values and does not require equal time intervals of longitudinal data. Further studies are needed to validate the findings.

Conclusions

In conclusion, serial measurement of NT-proBNP may be useful to monitor changes in prognostic risk but it is the last measured value that carries the most information. Reductions in NT-proBNP may indicate improving prognosis but it is the value achieved that indicates what the prognosis has improved to; in other words, what the prognosis actually is!

Figure legend

Figures 1: Relationship (showing lines of identity) between baseline log(NT-proBNP) and other measurements of log(NT-proBNP) at 4 months, 12 months and 24 months for patients who had SR (the top row), and not SR (the bottom row).

Figure 2: Dynamic survival probabilities with 95% CI based on various measurements of NT-proBNP for a patient whose values fell. The vertical dotted lines show the time point of the last log(NT-proBNP) measurement; prior values are shown to the left of the vertical line. The curves to the right are the survival probabilities incorporating all the NT-proBNP data to that point (x-axis: Time (years), y-axis: Longitudinal Outcome shows the observed values of log10(NT-proBNP) at each follow-up time point.

Supplementary Figure S1-S2: Dynamic survival probabilities with 95% CI based on various measurements of NT-proBNP for a patient (Figure S1 shows the patient who died and Figure S2 shows the patient who survived). The vertical dotted lines show the time point of the last log(NT-proBNP) measurement; prior values are shown to the left of the vertical line. The curves to the right are the survival probabilities incorporating all the NT-proBNP data to that point (x-axis: Time (years), y-axis: Longitudinal Outcome shows the observed values of log10(NT-proBNP) at each follow-up time point.

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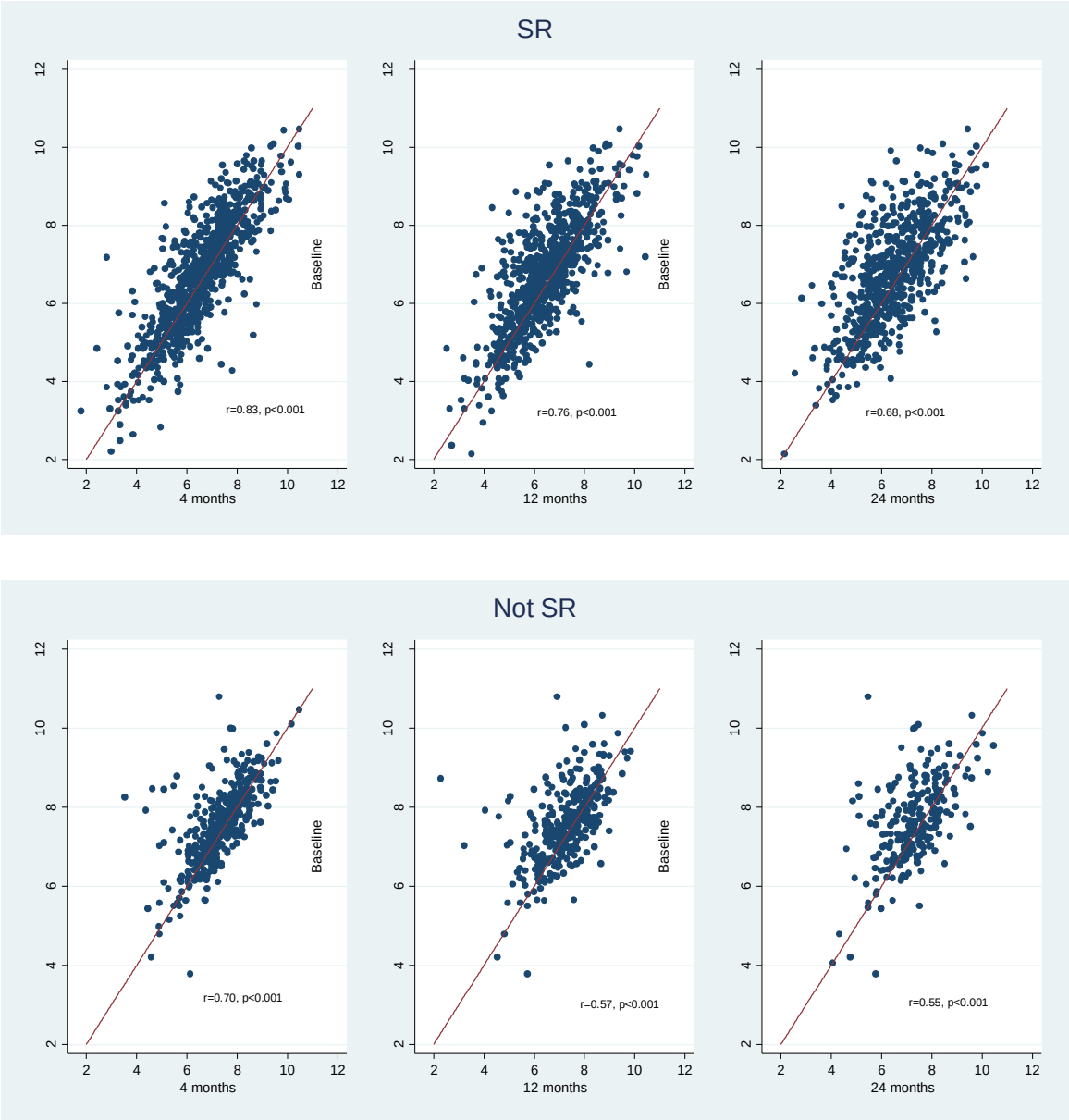

Figure 1: Relationship (showing lines of identity) between baseline log(NT-proBNP) and other measurements of log(NT-proBNP) at 4 months, 12 months and 24 months for patients who had SR (the top row), and not SR (the bottom row).

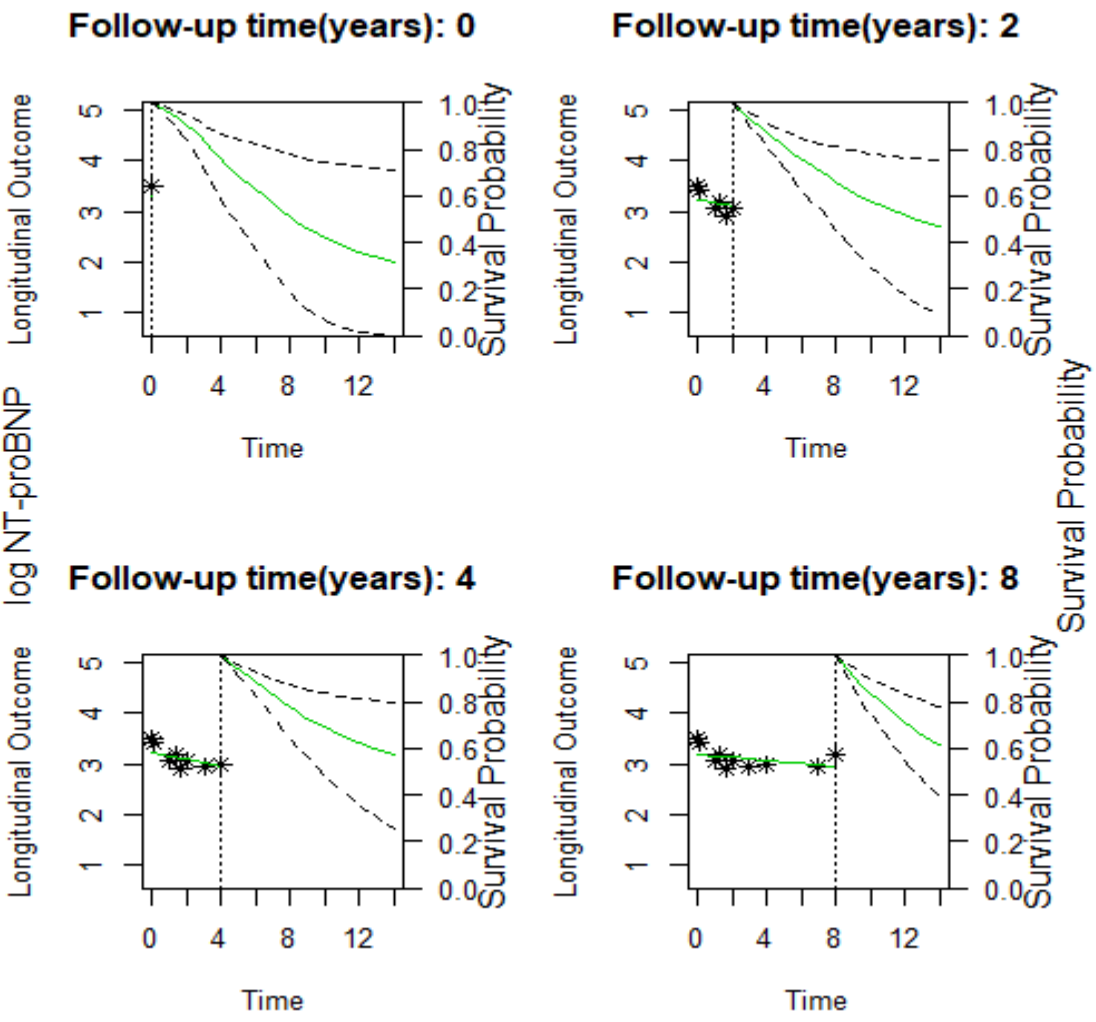

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Table1: Baseline patient characteristics

	Missing	All patients (n=1,998)	Survived at 3 years				Died at 3 years			
			Total (n = 1,744)	Not SR (n=527)	SR (n=1,217)	p-value*	Total (n = 254)	Not SR (n=87)	SR (n=167)	p-value*
Age (yrs)	1	73 (64-79)	72 (66-78)	74 (67-81)	70 (63-77)	<0.001	76 (70-82)	78 (72-83)	76 (69-82)	0.21
Men (n;%)	0	1,397 (70%)	1,215 (70%)	382 (72%)	833 (68%)	0.09	182 (72%)	66 (76%)	116 (69%)	0.28
IHD (n;%)	0	1,227 (61%)	1,062 (61%)	253 (48%)	809 (66%)	<0.001	165 (65%)	48 (55%)	117 (70%)	0.02
COPD (n;%)	0	214 (11%)	174 (10%)	45 (9%)	129 (11%)	0.19	40 (16%)	14 (16%)	26 (16%)	0.61
Diabetes (n;%)	0	494 (25%)	437 (25%)	127 (24%)	310 (25%)	0.54	57 (22%)	24 (28%)	33 (20%)	0.16
NYHA Class III/IV (n;%)	0	595 (31%)	491 (28%)	181 (34%)	310 (25%)	<0.001	104 (41%)	37 (43%)	67 (40%)	0.71
BMI (kg/m^2)	53	29 (25-32)	29 (25-32)	28 (25-33)	29 (25-32)	0.82	28 (24-31)	29 (24-30)	28 (23-31)	0.85
Heart Rate (bpm)	68	71 (60-84)	70 (60-83)	77 (66-90)	68 (59-79)	<0.001	77 (65-88)	80 (69-92)	75 (63-85)	0.09
Systolic BP (mmHg)	54	134 (118-152)	134 (118-152)	132 (117-149)	135 (119-153)	0.04	132 (116-150)	130 (112-149)	133 (117-151)	0.38
Oedema (> trivial)	225	443 (22%)	357 (20%)	166 (32%)	191 (16%)	<0.001	86 (34%)	32 (37%)	54 (32%)	0.74
NT-proBNP (ng/L)	0	1,108 (448-2,613)	1,023 (404-2,329)	1,758 (992-3,254)	741 (279-1,784)	<0.001	2,428 (941-5,532)	3,187 (1,548-5,700)	1,996 (774-5,208)	0.01
eGFR(4-variable) ($ml/min/1.73m^2$)	59	62 (48-76)	64 (51-77)	61 (48-74)	64 (52-78)	0.001	52 (35-67)	54 (35-68)	51 (37-65)	0.71
Haemoglobin (d/dL)	63	13.5 (12.3-14.6)	13.6 (12.4-14.7)	13.8 (12.6-15.0)	13.5 (12.4-14.6)	0.003	12.9 (11.6-14.4)	13.0 (11.8-14.5)	12.9 (11.5-14.3)	0.42
ACEi/ARB (n; %)	0	1,587 (79%)	1,399 (80%)	414 (79%)	985 (81%)	0.25	188 (74%)	65 (75%)	123 (74%)	0.86
Beta blocker (n; %)	0	1,253 (63%)	1,117 (64%)	325 (62%)	792 (65%)	0.17	136 (54%)	53 (61%)	83 (50%)	0.09
Diuretic (n; %)	0	1,516 (76%)	1,303 (75%)	426 (81%)	877 (72%)	<0.001	213 (84%)	78 (90%)	135 (81%)	0.07

Abbreviations: IHD: Ischaemic heart disease; COPD: Chronic obstructive pulmonary disease; NYHA Class: New York Heart Association classes; BMI: Body mass index; Systolic BP: Systolic blood pressure; eGFR: Estimated glomerular filtration rate; ACEi/ARB: Angiotensin-Converting enzyme inhibitors/angiotensin receptor blockers, SR: Sinus rhythm.

* Comparison between groups of patients with SR and not SR.

Table 2: Survival models using baseline log(NT-proBNP) only/adjusted for baseline age and sex; serial measurements of log(NT-proBNP); and most recent value of log(NT-proBNP) for all-cause mortality at 3 years

	Log(NT-proBNP)			
	HR (95%CI)	z-statistic	p-value	c-statistic (SE)
Baseline Cox model	3.05 (2.42-3.85)	9.42	<0.0001	0.67 (0.02)
Model adjusted for age and sex	2.57 (2.02-3.28)	7.62	<0.0001	0.69 (0.02)
Time-dependent Cox model	4.49 (3.54-5.70)	12.40	<0.0001	0.71 (0.02)
Model adjusted for age and sex	3.92 (3.04-5.06)	10.58	<0.0001	0.73 (0.02)
Most recent Cox model*	4.51 (3.57-5.71)	12.54	<0.0001	0.72 (0.02)
Model adjusted for age and sex*	4.11 (3.20-5.29)	11.04	<0.0001	0.72 (0.02)

* Models were generated using the same cohort but starting from the time of the most recent measurement of NT-proBNP