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/m2) | 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/1.73m2) | 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

Supplemental table S1

Table: S1\_A

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Acute HF** | **Type of study** | **HF phenotype** | **Number of patients** | **NP measurements** | **Potential modifiers of BNP** | **Findings** |
| **Bettencourt et al 2004** (1) | Observational | ADHF | 182 | Measured every day until discharge | Length of stay  Heart rate  Volume overload signs  No ACEi  Higher discharge NYHA | Patients who were readmitted had higher NT-proBNP  *Changes in NT-proBNP were associated with mortality and readmission* |
| **Logeart et al 2003** (2) | Observational; | ADHF | 114 | Measured every day until discharge | High LV filling pressures | High pre-discharge BNP is a strong independent marker of death or readmission after decompensated HF. Those with value <300pg/mL had lowest readmission rates.  *Patients with the greatest decrease in BNP had the best outcome* |
| **O’Brien et al 2003** (3) | Observational | ADHF | 96 | At admission, discharge |  | Pre-discharge rather than admission BNP concentration is better predictor of death/readmission with HF.  *NO* association between magnitude/direction of change in NT-proBNP and occurrence of death/hospitalisation |
| **Gackowski et al 2004** (4) | Observational | ADHF | 95 | At admission, after 24 hours, and 7th day/at discharge. |  | Serial measurements of BNP plasma levels provide incremental prognostic information over clinical and echocardiographic data in high-risk populations |
| **Cheng et al, 2000** (5) | Observational | ADHF | 72 | Within 24 hours of admission and prior to discharge | NYHA classification | Patients who died or were readmitted tended to have increase in BNP during hospitalisation, those who had successful treatment tended to have decreases in their BNP concentration during hospitalisation  A final BNP level <430pg/ml had a strong negative predictive value for 30 day readmission. |
| **Greene et al, 2015**(6) | ASTRONAUT | ADHF  EF <40%, BNP >400pg/mL  NT-roBNP >1600pg/ml | 1,351 | Measured at admission, 5 days and 1m | Weight loss / decongestion, renal dysfunction, AF | NT-proBNP 1 month post-discharge but not during admission predicted cardiovascular readmission/decompensation but not all cause mortality. |
| **Maisel et al, 2013** (7) | Observational study, monitoring daily concentrations of BNP | ADHF | 163 | Peri-discharge then daily until day 60. |  | Correlations between BNP measurements weakened over time.  Hazard ratio per unit increase of BNP was 1.84. Upward trending BNP corresponded to risk increase of 59.8% and downward trending BNP corresponded to risk decrease of 39.0%. |
| **Wu et al, 2006** (8) | Observational study of multiple studies |  |  |  |  | For inpatient monitoring, serial BNP/NT-pro BNP measurements are useful for detecting short-term improvements with diuretics. BNP/NT-proBNP concentrations double in patients with stable HF who suddenly decompensate. |

Table: S1\_B

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Chronic HF** | **Type of study** | **HF phenotype** | **Number of patients** | **NP measurements** | **Potential modifiers of BNP** | **Findings** |
| **Masson et al 2008** (9) | Placebo arm of Val-HF | LVEF <40% | 1,742 | Baseline & at 4 months |  | Achieved NT-proBNP more important than change |
| **Anand et al 2007**(10) | RCT Val-HF | LVEF<40% | 4,305 | Baseline, to 4 months and 12 months | Valsartan caused a sustained reduction in BNP regardless of trend | BNP changes over time are associated with corresponding changes in subsequent mortality and morbidity  *% change are relevant for morbidity and mortality* |
| **Zile et al, 2006**(11) | RCT PARADIGM-HF | LVEF <35%  BNP >100pg/ml  NT-proBNP>400pg/ml | 2,080 | Baseline, 1 month and 8 months | Sacubitril/valsartan nearly twice as likely as enalapril to reduce NT-proBNP to values < 1,000pg/ml | Percent reduction from baseline similarly important, regardless of treatment.  Risk of primary endpoint was 59% lower in patients with a fall in NT-proBNP to <1,000pg/ml than in those without such a fall. |
| **Kubanek et al 2009**(12) | Observational | LVEF<45% | 361 | Baseline, 4th month and 6th month |  | Plasma NT-proBNP levels are the strongest predictor of mortality and first unplanned CV hospitalisation.  NT-proBNP levels after optimization of pharmacotherapy better predict subsequent mortality and CV hospitalization events than baseline values or change between baseline and follow-up |
| **Gardner et al, 2007**(13) | Prospective observational | LVEF <35% | 112 | Baseline and at 4 months |  | NT-proBNP above the median and a change in NT-proBNP concentration over a 4 month period were independent predictors of mortality in patients with advanced heart failure |
| **O’Hanlon et al, 2006** (14) | Observational study, evaluating intra-individual variability of BNP and NT-proBNP | Stable HF patients | **45** | 1 hour apart on day 1, then at one week**.** |  | Large intra-individual variability in clinically stable HF patients, both within 1 hour and in samples taken 1 week apart.  Care needs to be taken when interpreting changes in natriuretic peptide levels when monitoring a patient’s response to therapy/assessing clinical status. |
| **Wu et al, 2006** (8) | Observational study, monitoring daily concentrations of BNP |  |  |  |  | In long term outpatient monitoring, changes in BNP-NT-proBNP do not exceed their normal biological variance. |

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Table S2: Correlations between log(NT-proBNP) measurements at baseline, 4, 12 and 24 months

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| NT-proBNP | Median with IQR for groups: all patients/AF/SR groups | The number of patients in each group | Correlations co-efficients for log(NT-proBNP) measured at various times (p<0.0001 for all) | | |
| Baseline | 4 months | 12 months |
| Baseline | All: 1,108 (448-2613)  AF: 1,878 (1026-3527)  SR: 828 (311-2080) | 1998  614  1384 |  |  |  |
| 4 months | All: 969 (393-2109)  AF: 1,530 (880-2816)  SR: 694 (297-1670) | 1314  426  888 | 0.82  0.70  0.83 |  |  |
| 12 months | All: 863 (354-1981)  AF: 2,952 (1649-2952)  SR: 586 (272-1380) | 1168  355  813 | 0.74  0.57  0.75 | 0.84  0.73  0.83 |  |
| 24 months | All: 825 (318-1928)  AF: 2,862 (1412-2862)  SR: 606 (253-1510) | 930  251  679 | 0.68  0.55  0.68 | 0.79  0.70  0.79 | 0.83  0.74  0.86 |

Abbreviations: AF: Atrial fibrillation; SR: Sinus rhythm.

Supplemental table S3: Survival models for all-cause mortality for long-term prediction\*

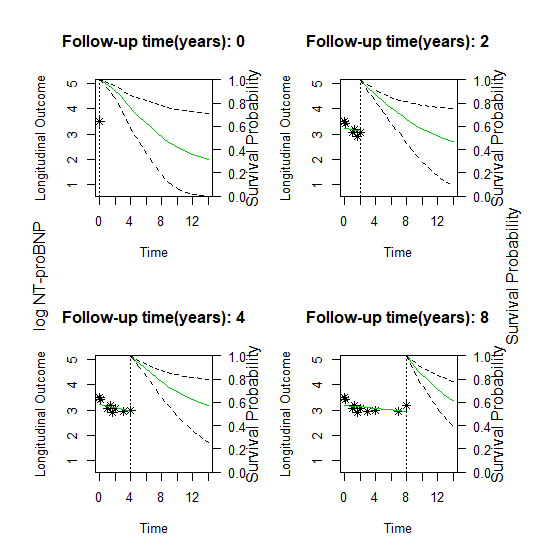
|  |  |  |  |
| --- | --- | --- | --- |
|  | Log(NT-proBNP) | | |
| HR (95%CI) | z-statistic | p-value |
| Starting from baseline | | | |
| Cox regression for baseline data | 1.81 (1.58 - 2.08) | 8.56 | <0.0001 |
| Joint modelling for all follow-up | 3.76 (3.15 - 4.56) | 13.24 | <0.0001 |
| Joint modelling for all follow-up excluding last data | 3.01 (2.20 - 3.21) | 11.07 | <0.0001 |
| Starting from most recent data | | | |
| Cox regression for most recent data | 3.73 (3.20-4.34) | 16.89 | <0.0001 |

\*The models were adjusted for pre-specified baseline age, sex and eGFR (Estimated glomerular filtration rate).

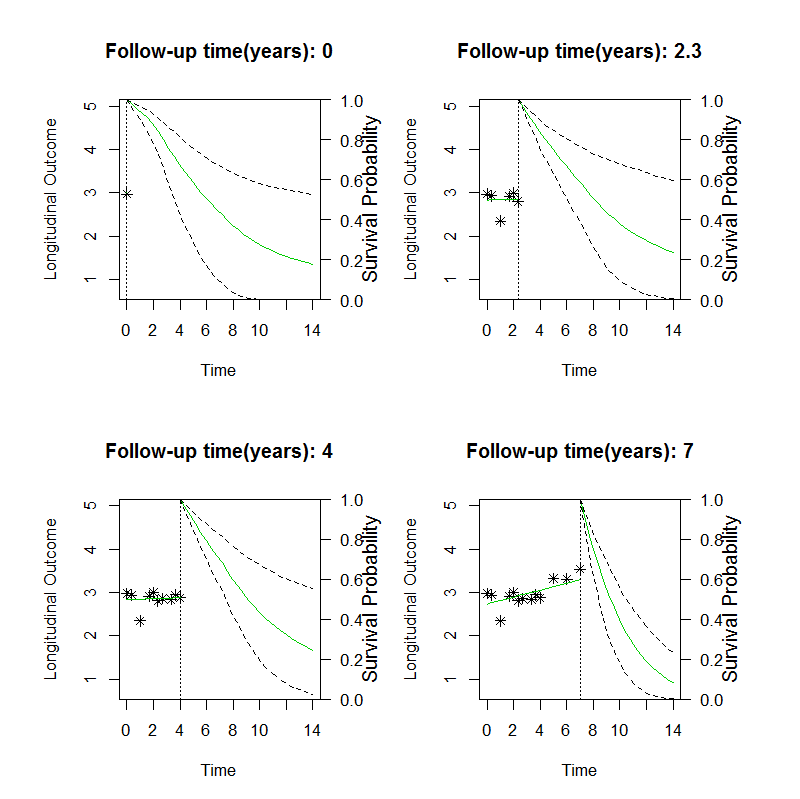




Figure 1: Relationship (showing lines of identity) between baseline log(NT-proBNP) and other measurements of log(NT-proBNP) at 4 months, 12 months and 24 months for patients who had SR (the top row), and not SR (the bottom row).



**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.



**Figure S1:** Dynamic survival probabilities with 95% CI based on serial measurements of NT-proBNP for a patient whose values rose. 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.



**Figure S2:** Dynamic survival probabilities with 95% CI based on serial measurements of NT-proBNP for a patient with lower and fairly stable measurements. 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.