# Supplemental Material

**Table S1. International Statistical Classification of Diseases-10th Revision (ICD-10) codes used to define cardiovascular death.**

| Diagnosis | Version | Code |
|---|---|---|
| Ischemic Heart Disease | ICD-10 | I20* I21* I22* I23* I24* I25* |
| Heart Failure & cardiomyopathy | ICD-10 | I10* I11* I12* I13* I14* I15* I16* I42* I255 J81 I50* I517 |
| Valvular heart disease | ICD-10 | I34* I35* I36* I37* |
| Cardiac arrest (due to cardiac condition) | ICD-10 | I462 |
| Ventricular tachycardia and ventricular fibrillation | ICD-10 | I470 I472 I4901 I4902 |
| Acute stroke (ischemic, non-ischemic and hemorrhagic) | ICD-10 | I60*, I161*, I63* I64* I65*, I166*, I67* I68* I69* G46* |
| Cardiogenic shock | ICD-10 | R570 |
| Thromboembolism | ICD-10 | I26* I82* |
| Peripheral vascular disease | ICD-10 | I70* I71* I72* I73* I74* I75* I76* I78* I79* I79* |
| Infective endocarditis | ICD-10 | I33* I38* |

*All digits after omitted

**Table S2. Baseline characteristics of AF and HF phenotype groups according to the composite outcome (HF hospitalization or cardiovascular death) at 2.5 years.**

| **Baseline Characteristic** | **Neither AF nor HF (N=488)** | | **AF only (N=354)** | | **HF only (N=369)** | | **AF plus HF (N=405)** | |
|---|---|---|---|---|---|---|---|---|
| | Without Event (N=452) | With event (N=36) | Without Event (N=299) | With event (N=55) | Without Event (N=277) | With event (N=92) | Without Event (N=277) | With event (N=128) |
| **Clinical characteristics** | | | | | | | | |
| Age, median, (IQR) | 65 (56–73) | 70 (65–79) | 70 (61–78) | 79 (69–85) | 68 (59–76) | 72 (57–79) | 74 (67–81) | 75 (67–81) |
| Female sex, n (%) | 205/452 (45) | 17/36 (47) | 120/299 (40) | 30/55 (55) | 98/277 (35) | 30/92 ((33) | 107/277 (39) | 37/128 (29) |
| Race, n (%) | | | | | | | | |
| Caucasian | 306/452 (68) | 26/36 (72) | 253/299 (85) | 49/55 (89) | 209/277 (75) | 55/92 (59) | 239/277 (86) | 101/128 (79) |
| Asian | 92/452 (20) | 8/36 (22) | 29/299 (10) | 2/55 (4) | 44/277 (16) | 19/92 (21) | 18/277 (7) | 12/128 (9) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Afro-Caribbean | 53/452 (12) | 2/36 (6) | 17/299 (6) | 3/ 55 (5) | 24/277 (9) | 18/92 (20) | 19/277 (7) | 15/128 (12) |
| Other | 1/452 (0.2) | - | - | 1/55 (2) | - | - | 1/277 (0.4) | - |
| Heart Rhythm, n (%) | | | | | | | | |
| Sinus Rhythm | 452/452 (100) | 36/36 (100) | - | - | 277/277 (100) | 92/92 (100) | - | - |
| Paroxysmal AF | - | - | 178/299 (60) | 17/55 (31) | - | - | 137/277 (49) | 47/128 (37) |
| Persistent AF | - | - | 57/299 (19) | 19/55 (35) | - | - | 66/277 (24) | 34/128 (27) |
| Permanent AF | - | - | 52/299 (17) | 17/55 (31) | - | - | 59/277 (21) | 43/128 (34) |
| Atrial Flutter | - | - | 12/299 (4) | 2/55 (4) | - | - | 15/277 (5) | 4/128 (3) |
| BMI, kg/m², median, (IQR)) * | 29 (25–33) | 29 (25–33) | 29 (26, 33) | 27 (23–32) | 28 (25–32) | 28 (24–32) | 29 (25–33) | 29 (26–33) |
| Systolic BP, mmHg , median, (IQR) | 126 (113–140) | 131 (111–145) | 130 (118–145) | 123 (109–135) | 122 (110–137) | 120 (106–130) | 121 (110–140) | 119 (106–134) |
| Heart rate/min, median, (IQR) | 68 (61–78) | 73 (60–89) | 68 (58–80) | 71 (59–88) | 72 (63–81) | 74 (62–83) | 76 (63–90) | 77 (64–89) |

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|---|---|---|---|---|---|---|---|---|
| Ejection fraction, %, median, (IQR) | 61 (57–68) | 60 (54–71) | 62 (57–68) | 58 (54–68) | 47 (38–59) | 39 (29–52) | 49 (40–58) | 40 (27–52) |
| Ejection fraction <50%, n (%) | - | - | - | - | 158/267 (59) | 66/90 (73) | 141/262 (54) | 91/126 (72) |
| Previous diagnosis of stable HF | - | - | - | - | 99/277 (36) | 53/92 (58) | 123/277 (44) | 80/128 (63) |
| Symptomatic HF | | | | | | | | |
| NYHA II HF, n (%) | - | - | - | - | 118/277 (43) | 25/92 (25) | 120/275 (44) | 39/126 (31) |
| NYHA III HF, n (%) | - | - | - | - | 52/277 (19) | 32/92 (32) | 65/275 (24) | 46/126 (37) |
| NYHA IV HF, n (%) | - | - | - | - | 11/277 (4) | 9/92 (9) | 16/275 (6) | 15/126 (12) |
| LBBB, n (%) | 6/452 (1) | 0/36 (0) | 5/299 (2) | 1/55 (2) | 15/277 (4) | 11/92 (12) | 12/277 (4) | 10/128 (8) |
| **Medical history, n (%)** | | | | | | | | |
| Diabetes | 195/452 (43) | 17/36 (47) | 59/299 (20) | 16/55 (29) | 113/277 (41) | 53/92 (58) | 66/277 (24) | 46/128 (36) |
| Hypertension | 299/452 (66) | 23/36 (64) | 167/299 (56) | 38/55 (69) | 166/277 (60) | 54/92 (59) | 130/277 (47) | 69/128 (54) |
| Coronary artery disease | 206/452 (46) | 18/36 (50) | 50/299 (17) | 8/55 (15) | 155/277 (56) | 48/92 (52) | 88/277 (32) | 56/128 (44) |

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|---|---|---|---|---|---|---|---|---|
| Hyponatremia (Na <135 mmol/L)* | 71/445 (16) | 6/36 (17) | 30/272 (11) | 13/55 (24) | 46/274 (17) | 25/92 (27) | 28/270 (11) | 29/127 (23) |
| Severe valvular heart disease | 9/452 (2) | 0/36 (0) | 8/299 (3) | 9/55 (16) | 7/277 (3) | 5/92 (5) | 21/277 (8) | 20/128 (16) |
| HF hospitalization at presentation | - | - | - | - | 15/277 (5) | 8/92 (9) | 4/277 (1) | 12/128 (9) |
| **Laboratory measurements** | | | | | | | | |
| eGFR mL/min/1.73m$^2$, (CKD-EPI), median, (IQR) | 81 (64–95) | 66 (43–86) | 75 (62–88) | 56 (42–75) | 75 (57–91) | 59 (44–77) | 66 (47–82) | 56 (40–78) |
| NT-proBNP pg/mL, median, (IQR) | 192 (68–558) | 968 (250–2478) | 485 (167–1191) | 2580 (1204–6465) | 659 (218–2067) | 1801 (522–4752) | 1279 (461–3330) | 2793 (1220–6314) |
| NT-proBNP ≥125pg/ml, n (%) | 266/452 (59) | 32/36 (89) | 240/299 (80) | 55/55 (100) | 225/277 (81) | 87/92 (95) | 256/277 (92) | 126/128 (98) |
| NT-proBNP groups, n (%) | | | | | | | | |
| <300pg/mL | 276/452 (61) | 10/36 (28) | 119/299 (40) | 2/55 (4) | 88/277 (32) | 11/91 (12) | 50/277 (18) | 6/128 (5) |

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|---|---|---|---|---|---|---|---|---|
| 300–999pg/mL | 99/452 (22) | 8/36 (22) | 91/299 (30) | 10/55 (18) | 78//277 (28) | 21/91 (23) | 71/277 (26) | 16/128 (13) |
| 1000–1999pg/mL | 38/452 (8) | 6/36 (17) | 48/299 (16) | 10/55 (18) | 40//277 (14) | 16/91 (18) | 51/277 (18) | 28/128 (22) |
| ≥2000pg/mL | 39/452 (9) | 12/36 (33) | 41/299 (14) | 33/55 (60) | 71//277 (26) | 43/91 (47) | 105/277 (38) | 78/128 (61) |
| Sodium mmol/L, median, (IQR) * | 138 (136–140) | 138 (136–140) | 139 (137–141) | 139 (135–141) | 138 (136–140) | 137 (134–140) | 139 (137–141) | 138 (135–140) |
| Urea mmol/L, median, (IQR) * | 5.5 (4.4–7.0) | 6.4 (5.0–10.3) | 5.6 (4.6–6.9) | 6.9 (5.8–9.1) | 5.8 (4.5–7.2) | 7.8 (5.7–11.8) | 6.3 (4.9–8.8) | 9.2 (6.1–13.1) |
| Hemoglobin g/L, median, (IQR) * | 134 (121–145) | 119 (109–134) | 137 (124–148) | 124 (105–137) | 131 (118–144) | 122 (105–139) | 130 (116–142) | 121 (110–136) |
| **Pharmacotherapy, n (%)** | | | | | | | | |
| Beta-blocker | 247/452 (55) | 18/36 (50) | 153/299 (51) | 29/55 (53) | 173 /277 (63) | 59/92 (64) | 161/277 (58) | 68/128 (53) |
| ACE-inhibitors or ARB | 223/452 (49) | 18/36 (50) | 137/299 (46) | 24/55 (44) | 164/277 (59) | 51/92 (55) | 138/277 (50) | 61/128 (48) |
| NOAC | 9/452 (2) | 0/36 (0) | 133/299 (44) | 25/55 (45) | 6/277 (2) | 3/92 (3) | 133/277 (48) | 57/128 (45) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Warfarin | 4/452 (1) | 1/36 (3) | 65/299 (22) | 13/55 (24) | 8/277 (3) | 5/92 (5) | 72/277 (26) | 38/128 (30) |
| Diuretic | 83/452 (18) | 14/36 (39) | 59/299 (20) | 24/55 (44) | 97/277 (35) | 30/92 (33) | 135/277 (49) | 41/128 (32) |
| MRA | 6/452 (1) | 0/36 (0) | 5/299 (2) | 4/55 (7) | 23/277 (7) | 22/92 (24) | 20/277 (7) | 24/128 (19) |
| Complex device (ICD or CRT) | 4/452 (1) | 1/36 (3) | 2/299 (1) | 3/55 (5) | 14/277 (5) | 12/92 (13) | 20/277 (7) | 18/128 (14) |

ACE, Angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRT, cardiac resynchronization therapy; eGFR, estimate glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist; Na, sodium; NOAC, Novel oral anticoagulant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VKA, vitamin K antagonist.

* Baseline data were missing in 3.6% of the study population for BMI, 2.4% for hemoglobin, 2.8% for urea and sodium.

**Table S3**. **Outcomes stratified according to AF and HF phenotype groups.**

| **Patient Group** | **Composite outcome** | **HF Hospitalization** | **Cardiovascular Death** | **All-Cause Mortality** |
|---|---|---|---|---|
| | Events/person-yrs (incidence/100 person-yrs) | Events/person-yrs (incidence/100 person-yrs) | Events/person-yrs (incidence/100 person-yrs) | Events/person-yrs (incidence/100 person-yrs) |
| **Entire Cohort** | 310/3381 (9.2) | 202/3686 (5.5) | 168/3657 (4.6) | 254/3657 (7.0) |
| **Neither AF nor HF** | 36/1135 (3.2)) | 18/1190 (1.5) | 22/1160 (1.9) | 40/1159 (3.4) |
| **AF only** | 55/775 (7.1) | 34/826 (4.1) | 32/819 (3.9) | 47/819 (5.7) |
| **HF only** | 91/759 (12.1) | 59/824 (7.2) | 52/828 (6.3) | 66/828 (8.0) |
| **AF plus HF** | 128/722 (17.7) | 91/846 (10.8) | 62/850 (7.3) | 101/850 (11.9) |

**Table S4. C-Statistic of NT-proBNP as a continuous variable in each patient group for the composite outcome, its individual components i.e., HF hospitalization and cardiovascular death, and all-cause mortality.**

| Patient Group | Composite Outcome C-Statistic (95% CI) | *P* Value | HF Hospitalization C-Statistic (95% CI) | *P* Value | Cardiovascular Death C-Statistic (95% CI) | *P* Value | All-Cause Mortality C-Statistic (95% CI) | *P* Value |
|---|---|---|---|---|---|---|---|---|
| **Entire Cohort** | 0.74 (0.72 to 0.77) | <0.001 | 0.72 (0.69 to 0.75) | <0.001 | 0.76 (0.73 to 0.80) | <0.001 | 0.72 (0.69 to 0.75) | <0.001 |
| **Neither AF nor HF** | 0.73 (0.65 to 0.81) | <0.001 | 0.74 (0.64 to 0.84) | <0.001 | 0.74 (0.63 to 0.85) | <0.001 | 0.67 (0.59 to 0.76) | <0.001 |
| **AF only** | 0.82 (0.77 to 0.87) | <0.001 | 0.79 (0.72 to 0.85) | <0.001 | 0.86 (0.80 to 0.91) | <0.001 | 0.79 (0.73 to 0.85) | <0.001 |
| **HF only** | 0.66 (0.60 to 0.72) | <0.001 | 0.64 (0.57 to 0.71) | <0.001 | 0.71 (0.64 to 0.78) | <0.001 | 0.70 (0.63 to 0.77) | <0.001 |
| **AF plus HF** | 0.66 (0.61 to 0.70) | <0.001 | 0.61 (0.55 to 0.66) | <0.001 | 0.68 (0.62 to 0.75) | <0.001 | 0.65 (0.59 to 0.71) | <0.001 |

**Table S5. Optimal cut-point in the entire cohort and each patient group (Youden index) and important cut-offs with associated area under the ROC curve, sensitivity, specificity, positive predictive value and negative predictive value of NT-proBNP for the composite outcome (heart failure hospitalization or cardiovascular death).**

| NT-proBNP cut-off | Patient Group | AUC (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) |
|---|---|---|---|---|---|---|
| **Optimal cut-point (Youden index)** | | | | | | |
| 1079pg/ml | Entire Cohort | 0.70 (0.68 to 0.73) | 71% (66% to 76%) | 69% (67% to 72%) | 36% (32% to 39%) | 91% (89% to 93%) |
| 229pg/ml | Neither AF nor HF | 0.68 (0.61 to 0.75) | 81% (64% to 92%) | 55% (51% to 60%) | 13% (9% to 18%) | 97% (95% to 99%) |
| 1182pg/ml | AF only | 0.77 (0.71 to 0.83) | 78% (65% to 88%) | 75% (70% to 80%) | 36% (28% to 46%) | 95% (91% to 97%) |
| 1407pg/ml | HF only | 0.64 (0.58 to 0.70) | 60% (49% to 70%) | 68% (62% to 74%) | 39% (31% to 47%) | 84% (78% to 88%) |
| 2128pg/ml | AF plus HF | 0.62 (0.57 to 0.67) | 60% (51% to 69%) | 64% (58% to 69%) | 43% (36% to 51%) | 78% (72% to 83%) |
| **Important cut-offs** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 125pg/ml | Entire Cohort | 0.60 (0.59 to 0.62) | 97% (94% to 98%) | 24% (22% to 27%) | 23% (21% to 26%) | 97% (94% to 98%) |
| | Neither AF nor HF | 0.65 (0.59 to 0.71) | 89% (74% to 97%) | 41% (37% to 46%) | 11% (7% to 15%) | 98% (95% to 99%) |
| | AF only | 0.60 (0.58 to 0.62) | 100% (94 to 100%) | 20% (15% to 25%) | 19% (14% to 24%) | 100% (94% to 100%) |
| | HF only | 0.57 (0.53 to 0.60) | 95% (88 to 98%) | 19% (14% to 24%) | 28% (23% to 33%) | 91% (81% to 97%) |
| | AF plus HF | 0.53 (0.51 to 0.55) | 98% (95% to 100%) | 8% (5% to 11%) | 33% (28% to 38%) | 91% (72% to 99%) |
| 300pg/ml | Entire Cohort | 0.66 (0.64 to 0.68) | 90% (0.87 to 0.93) | 41% (38% to 44%) | 27% (24% to 30%) | 95% (93% to 96%) |
| | Neither AF nor HF | 0.67 (0.59 to 0.74) | 72% (55% to 86%) | 61% (56% to 66%) | 13% (9% to 18%) | 97% (94% to 98%) |
| | AF only | 0.68 (0.64 to 0.72) | 96% (88% to 100%) | 40% (34% to 46%) | 23% (18% to 29%) | 98% (94% to 100%) |
| | HF only | 0.59 (55 to 0.64) | 87% (78% to 93%) | 32% (26% to 38%) | 30% (24% to 36%) | 88% (80% to 94%) |
| | AF plus HF | 0.57 (0.54 to 0.60) | 95% (90% to 98%) | 18% (14% to 23%) | 35% (30% to 40%) | 89% (78% to 96%) |
| 1000pg/ml | Entire Cohort | 0.70 (0.67 to 0.73) | 73% (67% to 78%) | 67% (64% to 69%) | 34% (31% to 38%) | 91% (89% to 93%) |
| | Neither AF nor HF | 0.67 (0.58 to 0.75) | 50% (33% to 67%) | 83% (79% to 86%) | 19% (12% to 28%) | 95% (93% to 97%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | AF only | 0.74 (0.68 to 0.80) | 78% (65% to 88%) | 70% (65% to 75%) | 33% (25% to 41%) | 95% (91% to 97%) |
| | HF only | 0.62 (0.56 to 0.68) | 64% (54% to 74%) | 60% (54% to 66%) | 35% (28% to 42%) | 83% (78% to 88%) |
| | AF plus HF | 0.63 (0.59 to 0.68) | 83% (75% to 89%) | 44% (38% to 50%) | 41% (35% to 47%) | 85% (78% to 90%) |
| 2000pg/ml | Entire Cohort | 0.67 (0.64 to 0.70)) | 53% (48% to 59%) | 80% (78% to 83%) | 39% (35% to 44%) | 88% (86% to 90%) |
| | Neither AF nor HF | 0.62 (0.54 to 0.70) | 33% (19% to 51%) | 91% (88% to 94%) | 24% (13% to 38%) | 95% (92% to 96%) |
| | AF only | 0.73 (0.66 to 0.80) | 60% (46% to 73%) | 86% (82% to 90%) | 45% (33% to 57%) | 92% (88% to 95%) |
| | HF only | 0.61 (0.55 to 0.66) | 47% (36% to 57%) | 74% (69% to 79%) | 38% (29% to 47%) | 81% (75% to 85%) |
| | AF plus HF | 0.62 (0.56 to 0.67) | 61% (52% to 69%) | 62% (56% to 68%) | 43% (35% to 50%) | 78% (71% to 83%) |

**Table S6. Performance of important cut-offs at predicting the composite outcome evaluated using discrimination, calibration, and reclassification. An NT-proBNP cut-off of 300pg/ml was used as a reference for NRI with two risk levels were selected: >20% and <20% risk of the composite outcome.**

| **NT-proBNP Cut-off** | | **Discrimination** | **Calibration** | | | | **Reclassification** | |
|---|---|---|---|---|---|---|---|---|
| | | C-Statistic | Brier Score | AIC | BIC | Likelihood Ratio | NRI (20%) | IDI |
| **125pg/ml** | Entire Cohort | 0.60 (0.58 to 0.61) | 0.12 (0.10 to 0.13) | 4425 | 4430 | *p*=0.013 | No change | 0.001 (*p*=0.040) |
| | Neither AF nor HF | 0.65 (0.60 to 0.70) | 0.06 (0.04 to 0.08) | 428 | 432 | *p*=0.076 | No change | 0.003 (*p*=0.120) |
| | AF only | 0.59 (0.57 to 0.61) | 0.11 (0.08 to 0.14) | 615 | 619 | *p*=0.101 | No change | -0.003 (*p*<0.001) |
| | HF only | 0.56 (0.53 to 0.59) | 0.13 (0.11 to 0.16) | 1050 | 1054 | *p*=0.270 | No change | 0.002 (*p*=0.298) |
| | AF plus HF | 0.53 (0.51 to 0.54) | 0.14 (0.12 to 0.16) | 1472 | 1476 | *p*=0.679 | No change | 0.0001 (*p*=0.734) |
| **300pg/ml** | Entire Cohort | 0.65 (0.63 to 0.66) | 0.11 (0.99 to 0.12) | 4364 | 4370 | Reference | Reference | Reference |
| | Neither AF nor HF | 0.66 (0.59 to 0.74) | 0.06 (0.41 to 0.08) | 428 | 432 | Reference | Reference | Reference |
| | AF only | 0.67 (0.64 to 0.70) | 0.90 (0.72 to 0.12) | 601 | 605 | Reference | Reference | Reference |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | HF only | 0.59 (0.55 to 0.62) | 0.13 (0.11 to 0.16) | 1047 | 1051 | Reference | Reference | Reference |
| | AF plus HF | 0.56 (0.54 to 0.58) | 0.14 (0.12 to 0.16) | 1463 | 1467 | Reference | Reference | Reference |
| **1000pg/ml** | Entire Cohort | 0.69 (0.66 to 0.71) | 0.10 (0.09 to 0.12) | 4345 | 4350 | *P*<0.001 | 0.08 (*p*=0.003) | 0.04 (*p*<0.001) |
| | Neither AF nor HF | 0.66 (0.58 to 0.74) | 0.06 (0.04 to 0.08) | 425 | 429 | *P*=0.017 | No change | 0.02 (*p*=0.013) |
| | AF only | 0.73 (0.68 to 0.78) | 0.09 (0.06 to 0.11) | 590 | 594 | *P*<0.001 | 0.12 (*p*=0.062) | 0.06 (*p*<0.001) |
| | HF only | 0.62 (0.57 to 0.67) | 0.13 (0.11 to 0.15) | 1043 | 1047 | *P*=0.008 | No change | 0.02 (*p*=0.014) |
| | AF plus HF | 0.62 (0.59 to 0.65) | 0.13 (0.11 to 0.15) | 1448 | 1452 | *P*<0.001 | 0.13 (*p*=0.002) | 0.04 (*p*<0.001) |
| **2000pg/ml** | Entire Cohort | 0.66 (0.63 to 0.69 | 0.11 (0.10 to 0.12) | 4372 | 4377 | *P*<0.001 | 0.03 (*p*=0.507) | 0.05 (*p*<0.001) |
| | Neither AF nor HF | 0.62 (0.54 to 0.70) | 0.06 (0.04 to 0.08) | 428 | 432 | *P*=0.014 | No change | 0.02 (*p*=0.028) |
| | AF only | 0.72 (0.66 to 0.78) | 0.08 (0.06 to 0.10) | 586 | 590 | *P*<0.001 | 0.10 (*p*=0.263) | 0.11 (*p*<0.001) |
| | HF only | 0.60 (0.55 to 0.65) | 0.13 (0.11 to 0.16) | 1046 | 1050 | *P*=0.008 | No Change | 0.02 (*p*=0.016) |
| | AF plus HF | 0.61 (0.56 to 0.65) | 0.14 (0.11 to 0.16) | 1458 | 1462 | *P*<0.001 | No Change | 0.03 (*p*=0.001) |

**Table S7. Univariate Cox proportional hazards models based on cut-offs with B coefficient and baseline hazard in the entire cohort.**

| NT-proBNP cut-off | B coefficient | 95% Confidence Interval | Standard Error | Z score | *p* value | Baseline Hazard |
|---|---|---|---|---|---|---|
| 125pg/ml | 2.08 | 1.48 to 2.69 | 0.31 | 6.79 | <0.001 | 0.03 |
| 300pg/ml | 1.78 | 1.39 to 2.15 | 0.19 | 9.20 | <0.001 | 0.05 |
| 1000pg/ml | 1.55 | 1.30 to 1.80 | 0.13 | 12.17 | <0.001 | 0.08 |
| 2000pg/ml | 1.40 | 1.18 to 1.63 | 0.11 | 12.32 | <0.001 | 0.11 |

**Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD Checklist for Prediction Model Development** (Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement).

| Section/Topic | | | Checklist Item | Page |
|---|---|---|---|---|
| **Title and abstract** | | | | |
| Title | 1 | D;V | Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted. | 1 |
| Abstract | 2 | D;V | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. | 3-4 |
| **Introduction** | | | | |
| Background and objectives | 3a | D;V | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | 6-7 |
| | 3b | D;V | Specify the objectives, including whether the study describes the development or validation of the model or both. | 6-7 |
| **Methods** | | | | |
| Source of data | 4a | D;V | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. | 7-8 |
| | 4b | D;V | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. | 7-8 Figure 1 |
| Participants | 5a | D;V | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centers. | 7-8 |
| | 5b | D;V | Describe eligibility criteria for participants. | 7-8 |
| | 5c | D;V | Give details of treatments received, if relevant. | n/a |
| Outcome | 6a | D;V | Clearly define the outcome that is predicted by the prediction model, including how and when assessed. | 9-10 |
| | 6b | D;V | Report any actions to blind assessment of the outcome to be predicted. | n/a |
| Predictors | 7a | D;V | Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured. | 11-13 |
| | 7b | D;V | Report any actions to blind assessment of predictors for the outcome and other predictors. | n/a |
| Sample size | 8 | D;V | Explain how the study size was arrived at. | 7-8 |
| Missing data | 9 | D;V | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. | 11-13 |
| Statistical analysis methods | 10a | D | Describe how predictors were handled in the analyses. | 11-13 |
| | 10b | D | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. | 11-13 |
| | 10c | V | For validation, describe how the predictions were calculated. | n/a |

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| | 10d | D;V | Specify all measures used to assess model performance and, if relevant, to compare multiple models. | 11-13 |
| | 10e | V | Describe any model updating (e.g., recalibration) arising from the validation, if done. | n/a |
| Risk groups | 11 | D;V | Provide details on how risk groups were created, if done. | 11 |
| Development vs. validation | 12 | V | For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors. | n/a |
| **Results** | | | | |
| Participants | 13a | D;V | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | Figure 1 |
| | 13b | D;V | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome. | Table 1 |
| | 13c | V | For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome). | n/a |
| Model development | 14a | D | Specify the number of participants and outcome events in each analysis. | 14<br>Figure 1 |
| | 14b | D | If done, report the unadjusted association between each candidate predictor and outcome. | Table 2 |
| Model specification | 15a | D | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point). | Table 2<br>Supplemental Materials Table 7 |
| | 15b | D | Explain how to use the prediction model. | 15-18 |
| Model performance | 16 | D;V | Report performance measures (with CIs) for the prediction model. | Supplemental Materials Table 5, Supplemental Materials Table 6 |
| Model-updating | 17 | V | If done, report the results from any model updating (i.e., model specification, model performance). | n/a |
| **Discussion** | | | | |
| Limitations | 18 | D;V | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data). | 22 |
| Interpretation | 19a | V | For validation, discuss the results with reference to performance in the development data, and any other validation data. | n/a |
| | 19b | D;V | Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence. | 18 |
| Implications | 20 | D;V | Discuss the potential clinical use of the model and implications for future research. | 20-21 |
| **Other information** | | | | |
| Supplementary information | 21 | D;V | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. | n/a |
| Funding | 22 | D;V | Give the source of funding and the role of the funders for the present study. | 23 |