SUPPLEMENTARY MATERIAL

**Table 1 of the supplementary material**

Multivariable Cox Regression Analysis for Risk of All-cause, Cardiovascular and Heart Failure-related Death Including Inflammation Biomarkers (hs-CRP and ST2)a. For Cardiovascular Death and Heart-failure Related Death Competitive Risk Method Has Been Used

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All-cause death** | **Cardiovascular Death** | **HF-related death** |
|  | **HR** | **95%CI** | ***P* Value** | **HR** | **95%CI** | ***P* Value** | **HR** | **95%CI** | ***P* Value** |
| Age | 1.04 | 1.03-1.06 | <.001 | 1.04 | 1.02-1.05 | < .001 | 1.04 | 1.02-1.06 | < .001 |
| Female  | 0.69 | 0.55-0.89 | .003 | – | – | – | – | – | – |
| Ischemic etiology of HF | – | – | – | – | – | – | – | – | – |
| LVEF | 1.01 | 1.00-1.02 | .04 | – | – | – | – | – | – |
| NYHA functional class | 1.48 | 1.21-1.81 | <.001 | – | – | – | – | – | – |
| eGFR, mL/min/1.73 m2 | – | – | – | – | – | – | – | – | – |
| Diabetes mellitus | 1.33 | 1.08-1.64 | .007 | 1.40 | 1.05-1.85 | .02 | – | – | – |
| ACE inhibitor or ARB treatment | 0.69 | 0.50-0.95 | .03 | – | – | – | 0.61 | 0.38-1.00 | .05 |
| Beta-blocker treatment | 0.70 | 0.51-0.97 | .03 | – | – | – | – | – | – |
| Sodium | – | – | – | 0.93 | 0.89-0.98 | .003 | 0.94 | 0.89-0.99 | .01 |
| Hemoglobin | 0.93 | 0.88-0.99 | .03 | – | – | – | – | – | – |
| NT-proBNPb | 1.31 | 1.15-1.50 | < .001 | 1.32 | 1.11-1.57 | .002 | 1.32 | 1.10-1.57 | .003 |
| hs-CRP | – | – | – | – | – | – | – | – | – |
| ST2§ | 1.20 | 1.08-1.33 | .001 | 1.17 | 1.00-1.36 | .05 | – | – | – |
| Aβ40b | 1.21 | 1.08-1.35 | .001 | 1.17 | 1.01-1.35 | .04 | 1.13 | 0.93-1.37 | .22 |

aN=678.

bNT-proBNP, hs-CRP and Aβ40 as log (NT-proBNP), log (hs-CRP) and log(Aβ40), per 1 standard deviation.

95%CI, 95% confidence interval; Aβ40: amyloid-beta 1-40 peptide; ACE inhibitor: angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula equation); HF: heart failure; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP: N-terminal pro-B-type natriuretic peptide; ST2, soluble suppression of tumorigenicity-2.

ST2§ per every 10 mL; *P*-value for the quadratic form of ST2 = .01 for all-cause death and *P* = .06 for cardiovascular death.

**Table 2 of the supplementary material**

Measurements of Performance of the Models For All-cause, Cardiovascular and Heart Failure-Related Death at 5 Years. For Cardiovascular Death and HF-Related Death Competitive Risk Method Has Been Used

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All-cause death** | **Cardiovascular death** | **HF-related death** |
|  | **Reference**  | **Model with** | **Reference**  | **Model with**  | **Reference** | **Model with** |
|  | **Model\*** | **Aβ40†** | **Model\*** | **Aβ40†** | **Model\*** | **Aβ40†** |
| ***Discrimination*** |  |  |  |  |  |  |
| C-statistic§ | 0.742 | 0.753  |  |  |  |  |
|  | (0.720-0.775) | (0.729-0.778) |  |  |  |  |
|  | Reference | ‡*P* = .15 |  |  |  |  |
| AUC | 0.806 | 0.811  | 0.755 | 0.762 | 0.755 | 0.761 |
|  | (0.776-0.836) | (0.782-0.841) | (0.716-793) | (0.724-0.800) | (0.707-0.802) | (0.714-0.808) |
|  | Reference | ‡*P* = .20 | Reference | ‡*P* = .12 | Reference | ‡*P* = .23 |
|  |  |  |  |  |  |  |
| ***Calibration*** |  |  |  |  |  |  |
| H-L | Chi-square: 6.67 | Chi-square: 7.80 | Chi-square: 5.0  | Chi-square: 3.96 | Chi-square: 10.32  | Chi-square: 4.30 |
|  | *P* = .25 | *P* = .17 | *P* = .42 | *P* = .56 | *P* = .07 | *P* = .51 |
| Brier score | 0.1181 | 0.1168 | 0.0922 | 0.0913 | 0.0530 | 0.0529 |
| AIC | 5395 | 5382 | 3023 | 3018 | 1580 | 1580 |
| BIC | 5428 | 5419 | 3051 | 3052 | 1599 | 1604 |
| Likelihood ratio¶ | Reference | ‡*P* < .001 | Reference | ‡*P* = .02 | Reference | ‡*P* = .22 |
| ***Reclassification*** |  |  |  |  |  |  |
| NRI, % | Reference | 34.3 (22.1; 48.8) | Reference | 28.8 (13.5;44.9) | Reference | 29.0 (7.6; 49.8) |
|  |  | ‡*P* = .001 |  | ‡*P* < .001 |  | ‡*P* = .01 |

**\*Reference model:** age, sex, NYHA functional class, LVEF, ischemic etiology, diabetes, eGFR, hemoglobin, sodium, beta-blocker treatment, ACE inhibitor or ARB treatment, and NT-proBNP.

**†Model with Aβ40:** Reference model + Aβ40

**‡** *P* values versus reference model. §Uses the index of rank correlation, Somers Dxy, which already incorporates information of censored data.

‖Uses the D’Agostino-Nam version of the Hosmer-Lemeshow calibration test. ¶Used as an expression of global goodness of fit; a significant p value in this test means that adding a new variable to the model significantly improves the accuracy of the reference model.

Aβ40, amyloid-beta 1-40 peptide; ACE inhibitor: angiotensin-converting enzyme inhibitor; AIC, Akaike information criterion; ARB, angiotensin receptor blocker; AUC, area under the curve; BIC, Bayesian information criterion; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula equation); HF: heart failure; H-L, Hosmer–Lemeshow test; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

**Table 3 of the supplementary material**

Clinical Characteristics and Treatment Relative to Period Inclusion (2006-2009 Vs 2010-2013)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **2006-2009**  | **2010-2013** | ***P*-value** |
|  | **N=643** | **N= 296** |  |
| Age, years | 66.0 ± 12.8 | 65.9 ± 12.2 | .95 |
| Male, n (%) | 464 (72.2) | 218 (73.6) | .64 |
| White, n (%) | 637 (99.1) | 294 (99.3) | .63 |
| Ischemic etiology, n (%) | 336 (52.2) | 139 (47.0) | .13 |
| HF duration, months | 26.7 (4.8–72) | 10 (2–55.5) | < .001 |
| LVEF, % | 33.3 ± 13.2 | 33.7 ± 13.2 | .67 |
| HFpEF (LVEF ≥ 50), n (%) | 82 (12.8) | 37 (12.5) | .91 |
| NYHA class III-IV, n (%) | 164 (25.5) | 49 (16.6) | .002 |
| Diabetes, n (%) | 231 (35.9) | 111 (37.5) | .64 |
| Hypertension, n (%) | 401 (62.3) | 193 (65.2) | .40 |
| Anemia, n (%)\*,\*\* | 297 (46.4) | 129 (45.2) | .75 |
| Renal insufficiency, n (%)#,\*\* | 404 (62.8) | 148 (50) | < .001 |
| Atrial fibrillation, n (%) | 133 (20.7) | 76 (25.9) | .08 |
| Cognitive impairment, n (%)†† | 18 (3.2) | 5 (2.1) | .44 |
| BMI, Kg/m2\*\* | 27.9 ± 5.2 | 27.2 ± 5.6 | .07 |
| eGFR, mL/min/1.73m2 | 53.3 ± 26.2 | 59.6 ± 27.6 | < .001 |
| Na, mmol/L\*\* | 139.1 ± 3.4 | 138.1 ± 3.7 | < .001 |
| Hemoglobin, g/dL\*\* | 12.9 ± 1.9 | 12.9 ± 1.9 | .79 |
| NT-proBNP, ng/L\*\*\* | 1180 (491–2726) | 1487 (698–3817) | .001 |
| Neprilysin, ng/mL | 0.65 (0.42–1.11) | 0.63 (0.36–1.29) | .035 |
| hs-CRP† | 3.74 (1.42–8.92) | 2.65 (1.05–6.7) | .20 |
| ST2§ | 39.5 (31.2–51.2) | 33.7 (28.7–41.5.9) | .007 |
| Treatment, n (%) |  |  |  |
|  ACE inhibitor or ARB | 590 (91.8) | 240 (81.1) | < .001 |
|  Beta-blocker | 578 (90) | 267 (90.2) | .88 |
|  MRA | 377 (58.6) | 175 (59.1) | .89 |
|  Loop diuretic | 596 (92.7) | 254 (85.8) | <.001 |
|  Digoxin | 277 (43.1) | 22 (26) | <.001 |
|  Ivabradine | 44 (6.8) | 54 (18.2) | <.001 |
|  Statins | 491 (76.3) | 211 (71.3) | .10 |
|  CRT | 51 (7.9) | 30 (10.1) | .26 |
|  ICD | 82 (12.8) | 46 (15.5) | .25 |

Data in mean ± standard deviation, median (interquartile range) or n (%); \*WHO (World Health Organization) criteria (< 13 g/dL in men and < 12 g/dL in women); #eGFR < 60 mL/min/1.73 m2; \*\*n= 925; \*\*\*n=903; †n=649; ††n=802. § n=686.

Aβ40, amyloid-beta 1-40 peptide; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula equation); HF, heart failure; HFpEF, heart failure with preserved ejection fraction; hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block. LVEF, left ventricular ejection fraction; MRA, mineralcorticoid recptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

**Table 4 of the supplementary material**

Multivariable Cox Regression Analysis for Risk of All-cause, Cardiovascular and Heart Failure-related Death in Patients With Left Ventricular Ejection Fraction < 50%. For Cardiovascular Death and HF-related Death Competitive Risk Method Has Been Used

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All-cause death** | **Cardiovascular Death** | **HF-related death** |
|  | **HR** | **95%CI** | ***P* Value** | **HR** | **95%CI** | ***P* Value** | **HR** | **95%CI** | ***P* Value** |
| Age | 1.05 | 1.03-1.06 | <.001 | 1.04 | 1.02-1.05 | <.001 | 1.04 | 1.02-1.06 | <.001 |
| Female  | 0.65 | 0.51-0.84 | <.001 | 0.69 | 0.48-0.98 | .04 | – | – | – |
| Ischemic etiology of HF | – | – | – | – | – | – | – | – | – |
| LVEF | – | – | – | – | – | – | – | – | – |
| NYHA functional class | 1.80 | 1.47-2.22 | <.001 | 1.37 | 1.02-1.85 | .04 | – | – | – |
| eGFR, mL/min/1.73 m2 | – | – | – |  |  |  | – | – | – |
| Diabetes mellitus | 1.32 | 1.07-1.62 | .009 | 1.45 | 1.08-1.95 | .01 | 1.75 | 1.17-2.63 | .007 |
| ACE inhibitor or ARB treatment | 0.57 | 0.41-0.78 | .001 | – | – | – | – | – | – |
| Beta-blocker treatment | 0.50 | 0.36-0.70 | <.001 | – | – | – | – | – | – |
| Sodium | – | – | – | 0.95 | 0.91-1.00 | .03 | – | – | – |
| Hemoglobin | 0.93 | 0.87-0.99 | .02 | – | – | – | 1.15 | 1.02-1.29 | .022 |
| NT-proBNP\* | 1.34 | 1.18-1.52 | <.001 | 1.50 | 1.26-1.78 | <.001 | 1.65 | 1.32-2.06 | <.001 |
| Aβ40\* | 1.24 | 1.11-1.38 | <.001 | 1.11 | 0.95-1.28 | .19 | 1.08 | 0.88-1.34 | .46 |

\*NT-proBNP and Aβ40 as log (NT-proBNP) and log (Aβ40), per 1 standard deviation.

95%CI, 95% confidence interval; Aβ40, amyloid-beta 1-40 peptide; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula equation); HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

**Table 5 of the supplementary material.**

Multivariable Cox Regression Analysis for Risk of All-cause, Cardiovascular and Heart Failure-related Death Including Inflammation Biomarkers (hs-CRP and ST2)\*\* In Patients With Left Ventricular Ejection Fraction < 50%. For Cardiovascular Death and Heart-failure Related Death Competitive Risk Method Has Been Used.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All-cause death** | **Cardiovascular Death** | **HF-related death** |
|  | **HR** | **95%CI** | ***P* Value** | **HR** | **95%CI** | ***P* Value** | **HR** | **95%CI** | ***P* Value** |
| Age | 1.04 | 1.03-1.06 | <.001 | 1.04 | 1.02-1.05 | <.001 | 1.04 | 1.02-1.06 | <.001 |
| Female  | 0.68 | 0.52-0.89 | .005 | 0.69 | 0.48-0.98 | .04 | – | – | – |
| Ischemic etiology of HF | – | – | – | – | – | – | – | – | – |
| LVEF | – | – | – | – | – | – | – | – | – |
| NYHA functional class | 1.65 | 1.31-2.08 | <.001 | -- | -- | -- | – | – | – |
| eGFR, mL/min/1.73 m2 | – | – | – | – | – | – | – | – | – |
| Diabetes mellitus | 1.38 | 1.10-1.73 | .006 | 1.45 | 1.08-1.95 | .01 | 1.75 | 1.17-2.63 | .007 |
| ACE inhibitor or ARB treatment | 0.67 | 0.45-1.00 | .048 | – | – | – | – | – | – |
| Beta-blocker treatment | 0.57 | 0.39-0.84 | .004 | – | – | – | – | – | – |
| Sodium | – | – | – | 0.95 | 0.91-0.99 | .03 | – | – | – |
| Hemoglobin | 0.91 | 0.85-0.98 | .008 | – | – | – | 1.15 | 1.02-1.29 | .02 |
| NT-proBNP\* | 1.30 | 1.12-1.50 | .001 | 1.56 | 1.31-1.85 | <.001 | 1.65 | 1.32-2.06 | <.001 |
| hs-CRP | – | – | – | – | – | – | – | – | – |
| ST2§ | 1.05 | 1.01-1.10 | .02 | – | – | – | – | – | – |
| Aβ40\* | 1.24 | 1.10-1.40 | .001 | 1.11 | 0.96-1.29 | .17 | 1.08 | 0.88-1.34 | .46 |

\*NT-proBNP, hs-CRP and Aβ40 as log (NT-proBNP), log (hs-CRP) and log (Aβ40), per 1 standard deviation.

\*\*N=567.

ST2§, per every 10 mL; *P*-value for the quadratic form of ST2 = .207

95%CI, 95%confidence interval; Aβ40, amyloid-beta 1-40 peptide; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula equation); HF, heart failure; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide;; ST2, soluble suppression of tumorigenicity-2.

**Figure of the supplementary material.** Survival curves relative to median blood Aβ40 concentration in patients with left ventricular ejection fraction < 50%. A: Kaplan-Meier survival curves for all-cause death. B: cumulative incidence of cardiovascular death, taking into account other causes of non-cardiovascular of death as competitive risk event. C: cumulative incidence of heart failure-related death, taking into account other cardiovascular and non-cardiovascular causes of death as competitive risk event. Aβ40, amyloid-beta 1-40 peptide; HR, hazard ratio.

