Supplementary material

Bloodstream Amyloid-beta (1-40) Peptide, Cognition, and Outcomes in Heart Failure

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] A Competitive Risk Method Was Used for Cardiovascular Death and Heart-failure Related Death

	All-cause death			Cardiovascular Death			HF-related death		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
Age	1.04	1.03-1.06	<.001	1.04	1.02-1.05	< .001	1.04	1.02-1.06	< .001
Female sex	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 m^2	–	–	–	–	–	–	–	–	–

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-proBNP[b]	1.31	1.15-1.50	< .001	1.32	1.11-1.57	.002	1.32	1.10-1.57	.003
hs-CRP	–	–	–	–	–	–	–	–	–
ST2[d]	1.20	1.08-1.33	.001	1.17	1.00-1.36	.05	–	–	–
Aβ40[c]	1.21	1.08-1.35	.001	1.17	1.01-1.35	.04	1.13	0.93-1.37	.22

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.

[a]N = 678.

[b]n = 678.

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

[d]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. A Competitive Risk Method Was Used for Cardiovascular Death and HF-Related Death

	All-cause death		Cardiovascular death		HF-related death	
	Reference	Model with	Reference	Model with	Reference	Model with
	Model[a]	Aβ40[b]	Model[a]	Aβ40[b]	Model[a]	Aβ40[b]
Discrimination						
C-statistic[d]	0.742	0.753				
	(0.720-0.775)	(0.729-0.778)				
	Reference	*P* = .15[c]				
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[c]	Reference	*P* = .12[c]	Reference	*P* = .23[c]
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[f]	Reference	*P* < .001[c]	Reference	*P* = .02[c]	Reference	*P* = .22[c]
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[c]		*P* < .001[c]		*P* = .01[c]

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.

[a]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.

[b]Model with Aβ40: Reference model + Aβ40

[c]*P* values vs reference model.

[d]Uses the index of rank correlation, Somers Dxy, which already incorporates information of censored data.

[e]Uses the D'Agostino-Nam version of the Hosmer-Lemeshow calibration test.

[f]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.

Table 3 of the supplementary material

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

	2006-2009	2010-2013	*P*
	N = 643	N = 296	
Age, y	66.0 ± 12.8	65.9 ± 12.2	.95
Male sex	464 (72.2)	218 (73.6)	.64
Caucasian	637 (99.1)	294 (99.3)	.63
Ischemic etiology	336 (52.2)	139 (47.0)	.13
HF duration, mo	26.7 [4.8–72]	10 [2–55.5]	< .001
LVEF, %	33.3 ± 13.2	33.7 ± 13.2	.67
HFpEF (LVEF ≥ 50)	82 (12.8)	37 (12.5)	.91
NYHA class III-IV	164 (25.5)	49 (16.6)	.002
Diabetes	231 (35.9)	111 (37.5)	.64
Hypertension	401 (62.3)	193 (65.2)	.40
Anemi[a,]	297 (46.4)	129 (45.2)	.75

Renal insufficiency[b,c]	404 (62.8)	148 (50)	< .001
Atrial fibrillation	133 (20.7)	76 (25.9)	.08
Cognitive impairment[f]	18 (3.2)	5 (2.1)	.44
BMI, Kg/m^{2}[,c]	27.9 ± 5.2	27.2 ± 5.6	.07
eGFR, mL/min/1.73m^{2}	53.3 ± 26.2	59.6 ± 27.6	< .001
Na, mmol/L[c]	139.1 ± 3.4	138.1 ± 3.7	< .001
Hemoglobin, g/dL[c]	12.9 ± 1.9	12.9 ± 1.9	.79
NT-proBNP, ng/L[d]	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[e]	3.74 [1.42–8.92]	2.65 [1.05–6.7]	.20
ST2[g]	39.5 [31.2–51.2]	33.7 [28.7–41.5.9]	.007
Treatment			
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

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.

Data are expressed as mean ± standard deviation, median [interquartile range] or n (%).

[a]World Health Organization criteria (< 13 g/dL in men and < 12 g/dL in women).

[b]eGFR < 60 mL/min/1.73 m^2.

[c]n = 925.

[d]n = 903;

[e]n = 649;

[f]n = 802.

[g]n = 686.

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%. A Competitive Risk Method Was Used for Cardiovascular Death and HF-related Death

	All-cause death			Cardiovascular Death			HF-related death		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
Age	1.05	1.03-1.06	<.001	1.04	1.02-1.05	<.001	1.04	1.02-1.06	<.001
Female sex	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 m^2	–	–	–				–	–	–
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

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.

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

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)[a] In Patients With Left Ventricular Ejection Fraction < 50%. A Competitive Risk Method Was Used For Cardiovascular Death and Heart-failure Related Death

	All-cause death			Cardiovascular Death			HF-related death		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
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 m^2	–	–	–	–	–	–	–	–	–
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[b]	1.30	1.12-1.50	.001	1.56	1.31-1.85	<.001	1.65	1.32-2.06	<.001
hs-CRP	–	–	–	–	–	–	–	–	–
ST2[c]	1.05	1.01-1.10	.02	–	–	–	–	–	–
Aβ40[b]	1.24	1.10-1.40	.001	1.11	0.96-1.29	.17	1.08	0.88-1.34	.46

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.

[a]N = 567.

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

[c]ST2, per every 10 mL; *P* value for the quadratic form of ST2 = .207.
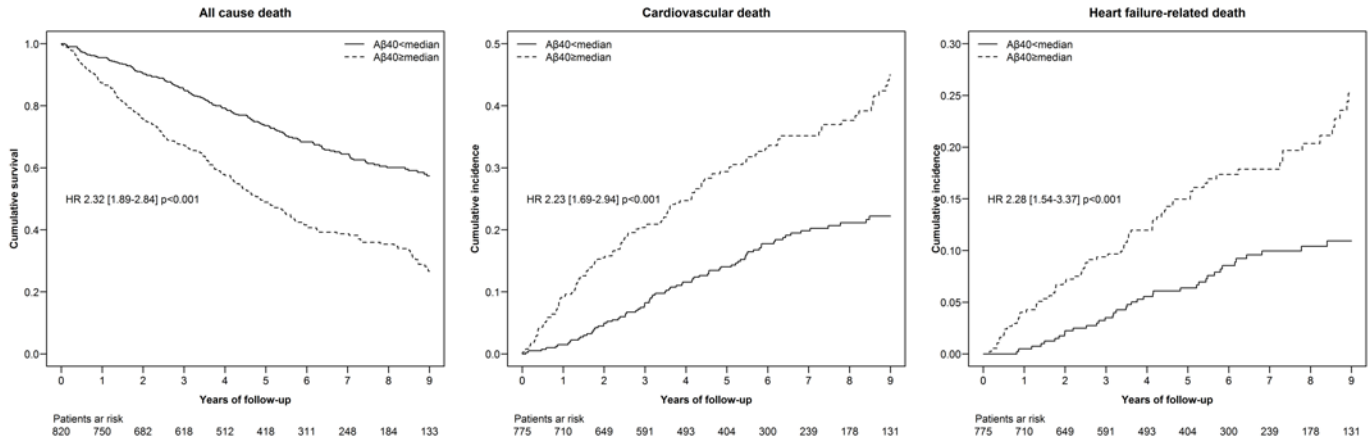
Figure of the supplementary material. Survival curves relative to median blood Aβ40 concentration in patients with left ventricular ejection fraction < 50%. A: Kaplan-Meier survival curves for all-cause death. B: cumulative incidence of cardiovascular death, taking into account other causes of noncardiovascular of death as competitive risk event. C: cumulative incidence of heart failure-related death, taking into account other cardiovascular and noncardiovascular causes of death as competitive risk event. Aβ40, amyloid-beta 1-40 peptide; HR, hazard ratio.