SUPPLEMENTARY DATA

Study outcomes

The primary study outcome was cardiovascular mortality and the secondary study outcome was all-cause mortality. Vital status and causes of death were assessed by review of the clinical databases, hospital records, or direct contact with patients or relatives. For patients who could not be contacted by telephone we accessed the electronic medical records of the hospital and of the primary care health system and determined vital status and causes of death. A death was considered to be from a cardiovascular cause when it was due to progression of heart failure (HF) (worsening HF or treatment-resistant HF in the absence of another cause), sudden cardiac death (any unexpected death, witnessed or not, of a previously stable patient with no evidence of worsening HF or any other known cause of death), acute myocardial infarction, stroke, procedural (postdiagnostic or posttherapeutic), and other cardiovascular causes (eg, rupture of an aneurysm, peripheral ischemia, or aortic dissection). Two board-certified cardiologist investigators blinded to the patients' clinical, echocardiographic and biochemical data adjudicated the outcome.

Biochemical studies

Serum insulin growth factor-1 (IGF-1) was measured by an ELISA method (R & D systems). The interassay and intraassay coefficients of variation were 4.0% and 8.3%. The lower limit of detection was 26 pg/mL. Serum insulin-like growth factor binding protein 2 (IGFBP2) was measured by an ELISA method (Abcam). The inter-assay and intra-assay coefficients of variation were 5.7% and 3.9%. The lower limit of detection was 8.2 pg/mL. In addition, N-terminal pro-B-type natriuretic peptide (NT-proBNP) was determined using an immunoelectrochemiluminescence assay and the Modular Analytics E 170 system. This assay has less than 0.001% cross-reactivity with bioactive brain natriuretic peptide, and in the constituent studies in this

report, with interassay coefficients lower than 6%.[1] Finally, serum troponin T was measured in a subgroup of 219 patients by using highly sensitive troponin (hsTnT) (Troponin T hs STAT, Roche Diagnostics). The lower detection limit of the assay was 5 ng/L and the interassay coefficient was 4.6%.

Serum creatinine levels were analyzed using the creatinine (CREA) method with a Dimension Clinical Chemistry System (Siemens, Newark, New Jersey, United State), using a modification of the kinetic Jaffe reaction described by Larsen[2] with picrate as the reactant.

Statistical analysis

The analyses were performed in all patients and in patients classified according to the absence or presence of chronic kidney disease (CKD). Normality was demonstrated by the Shapiro-Wilks or Kolmogorov-Smirnov tests. Nonnormally distributed variables were examined after logarithmic transformation. Multivariable linear regression models were performed, adjusting for covariables significant in univariable analyses. For the linear regression models, the assumption of normality of residuals was checked by the Kolmogorov-Smirnov test and graphic analysis of the P-P plots. Multicollinearity was defined as variance inflation factor > 2 or tolerance < 0.50 with model reduction in case any variable showed evidence of multicollinearity. Optimal cutoff values for predicting the outcomes of interest were determined by performing receiver-operating characteristic (ROC) curve analysis followed by calculation of the Younden J statistic.

The cumulative incidence of all-cause death was estimated by the Kaplan-Meier method; unadjusted differences were assessed with log-rank tests. Univariable and multivariable Cox or competing risk regression models (Fine-Gray) with adjustment for noncardiovascular death were used to calculate hazard or subhazard ratios and corresponding 95% confidence intervals for the risk of all-cause mortality or cardiovascular mortality, respectively. Patients without outcome were censored at the date of their last follow-up. To determine whether the association of IGFBP2 and IGF-1 with the outcomes of interest

differed by the presence of CKD with decreased estimated glomerular filtration rate (eGFR), quantitative interaction analyses were performed by Cox or competing risk regression analyses in models including IGFBP2 or IGF-1 as continuous variables, CKD with decreased eGFR (yes/no), and their respective interaction terms. In addition, qualitative interaction analyses were performed by Cox or competing risk regression analyses in models including IGFBP-1 or IGF-1 (≤ or > cutoff as determined in ROC analyses), CKD with decreased eGFR (yes/no) and their respective interaction terms. The baseline characteristics considered as covariables were identified as significant in univariable competing risk regression and Cox analyses for cardiovascular or all-cause mortality, respectively (tables 1 and 2 of the supplementary data), followed by a backward stepwise selection with minimization of the Akaike information criterion and the *P* value set at .15 for elimination. Following this procedure, the variables selected in all patients for the cardiovascular death outcome were: age, New York Heart Association (NYHA) class, eGFR, NT-proBNP (log_2), hemoglobin, chronic obstructive pulmonary disease, ischemic cardiomyopathy, and treatment with diuretics. The variables selected for the all-cause death outcome were: age, NYHA, eGFR, NT-proBNP (log_2), hemoglobin, body mass index, diabetes mellitus, peripheral vasculopathy, and chronic obstructive pulmonary disease. In non-CKD patients, the following variables were selected according to the previous procedure, although they were included in 3 different models due to the low number of cardiovascular death outcomes: *a)* age and sex*; b)* NYHA class and serum sodium, and *c)* ischemic heart disease and NT-proBNP (log_2). In CKD patients, the following variables were considered according to the previous procedure: age, NYHA class, ischemic heart disease, eGFR and NT-proBNP. In addition, a second model included the following clinically relevant covariables significant in univariable analyses that were not selected in the previous model: hemoglobin, diabetes mellitus, and treatment with angiotensin converting enzyme inhibitors /angiotensin receptor antagonists. The proportional subhazard and hazard assumptions were verified using Schoenfeld's residuals for each model. If violated, standard Cox or competing risk

regression analyses were extended including time varying covariates for each variable that did not satisfy this assumption.

The additional value of the combination of biomarkers for risk prediction of the outcomes of interest was assessed with Harrell's c-statistics and the integrated discrimination (IDI) and the continuous net reclassification indexes. Harrell's c estimates were calculated using the Stata package "somersd". The variances for the net reclassification and IDI estimates were calculated using bootstrapping (1000 resamples).

Values are expressed as mean ± SD or median [interquartile range], and categorical variables as numbers and percentages. Robust standard errors were calculated by using the stata option vce (cluster center), considering the clustering effect of the enrollment of patients in 2 different multidisciplinary HF units. Statistical significance was set as a 2-sided *P* of.05. The statistical analyses were performed by using SPSS (15.0 version) and STATA (12.1 version) software.

REFERENCES

1. Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J.* 2006;27:330-337.

2. Larsen K. Creatinine assay by a reaction-kinetic principle. *Clin Chim Acta*. 1972;41:209-217.

Table 1 of the supplementary data

Baseline clinical characteristics of heart failure patients categorized according to the occurrence of death

	Cardiovascular mortality				All-cause mortality			
	No (n = 588)	Yes (n = 98)	SHR (95%CI)	*P*	No (n = 509)	Yes (n = 177)	HR (95%CI)	*P*
Age, y	65.4 ± 12.0	74.0 ± 8.9	1.06 (1.06-1.07)	**< .001**	64.3 ± 11.9	73.5 ± 9.2	1.06 (1.04-1.08)	**< .001**
Female sex	189 (32.1)	35 (35.7)	1.04 (0.72-1.52)	.83	167 (32.8)	57 (32.2)	0.85 (0.35-2.02)	.71
BMI, kg/m^2	28.0 [25.1-31.4]	27.4 [23.3-32.1]	0.98 (0.96-0.99)	**.039**	28.1 [25.2-31.6]	27.1 [23.9-32.6]	0.97 (0.94-0.99)	**.006**
Sodium, mmol/L	139 ± 3.4	138 ± 4.0	0.93 (0.86-0.99)	**.033**	139 ± 3.4	138 ± 3.9	0.95 (0.89-1.00)	.06
Potassium, mmol/L	4.3 ± 0.5	4.3 ± 0.6	0.93 (0.73-1.41)	.92	4.3 ± 0.5	4.4 ± 0.6	1.09 (1.02-1.16)	**.014**
Hemoglobin, g/dL	13.4 ± 1.8	12.2 ± 2.1	0.71 (0.62-0.81)	**< .001**	13.5 ± 1.8	12.4 ± 2.0	0.72 (0.59-0.88)	**.002**
eGFR, mL/min/1.73m^2	66.1 ± 24.7	49.8 ± 25.2	0.98 (0.97-0.98)	**< .001**	67.4 ± 24.4	53.6 ± 25.4	0.98 (0.97-0.98)	**< .001**
NYHA class								
III-IV	130 (22.1)	54 (55.1)	3.19 (2.02-5.03)	**< .001**	96 (18.9)	88 (49.7)	2.70 (1.62-4.49)	**< .001**
HF duration, mo	7.0 [2.0-45.6]	19.0 [3.0-47.4]	1.00 (0.99-1.00)	.97	6.0 [1.9-40.6]	14.5 [2.8-52.1]	1.00 (1.00-1.00)	**< .001**
Hospitalization in the previous 3-mo	325 (55.3)	60 (61.2)	1.37 (0.77-2.44)	.29	273 (53.6)	112 (63.3)	1.58 (1.16-2.17)	**.004**

LVEF, %	40.6 ± 18.0	39.7 ± 16.4	0.99 (0.98-1.01)	.24	39.8±17.8	42.3 ± 17.6	0.99 (0.97-1.03)	.89
NT-proBNP (log_2), pg/mL	1400 [663-2789]	2855 [1741-7527]	1.46 (1.31-1.62)	**< .001**	1294 [634-2572]	2495 [1398-5120]	1.45 (1.24-1.71)	**< .001**
Ischemic heart disease	164 (27.9)	50 (51.0)	2.80 (2.72-2.89)	**< .001**	147 (28.9)	67 (37.9)	1.68 (1.33-2.14)	**< .001**
Comorbidities								
Hypertension	416 (70.7)	84 (85.7)	2.01 (1.05-3.85)	**.036**	352 (69.2)	148 (83.6)	1.73 (0.97-3.08)	.07
Atrial fibrillation	162 (27.6)	35 (35.7)	1.12 (0.95-1.31)	.17	125 (24.6)	72 (40.7)	1.39 (1.19-1.62)	**< .001**
Diabetes mellitus	181 (30.8)	51 (52.0)	2.70 (2.60-2.79)	**< .001**	155 (30.5)	77 (43.5)	2.04 (1.81-2.30)	**< .001**
Hypercholesterolemia	319 (54.3)	58 (59.2)	1.22 (1.12-1.32)	**< .001**	277 (54.4)	100 (56.5)	1.09 (0.97-1.23)	.15
Peripheral vascular disease	50 (8.5)	13 (13.3)	1.75 (1.74-1.76)	**< .001**	36 (7.1)	27 (15.3)	2.37 (2.19-2.55)	**< .001**
COPD	78 (13.3)	22 (22.4)	1.85 (1.59-2.14)	**< .001**	58 (11.4)	42 (23.7)	2.23 (2.16-2.31)	**< .001**
Treatments								
ACEIs/ARBs	535 (91.0)	84 (85.7)	0.63 (0.15-2.63)	.53	463 (91.0)	156 (88.1)	0.78 (0.28-2.16)	.63

Beta-blockers	425 (72.3)	65 (66.3)	0.89 (0.77-1.03)	.12	379 (74.5)	111 (62.7)	0.75 (0.53-1.06)	.10
Diuretics	457 (77.7)	87 (88.8)	2.28 (2.28-2.29)	**< .001**	398 (78.2)	146 (82.5)	1.35 (0.77-2.36)	.29
MR blockers	335 (57.0)	49 (50.0)	0.97 (0.38-2.51)	.96	294 (57.8)	90 (50.8)	1.06 (0.49-2.31)	.88
Digoxin	182 (31.0)	34 (34.7)	1.04 (0.79-1.37)	.77	156 (30.6)	60 (33.9)	0.98 (0.71-1.36)	.91
Devices	147 (25.0)	17 (17.3)	0.68 (0.42-1.10)	.11	127 (25.0)	37 (20.9)	0.86 (0.61-1.23)	.42

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MR, mineralocorticoid receptor; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SHR, subhazard ratio; HR, hazard ratio. Unless otherwise indicated, quantitative variables are expressed as mean ± SD or as median [interquartile range] and categorical variables as No. (%). Significant *P* values are highlighted in bold.

Table 2 of the supplementary data

Baseline clinical characteristics of heart failure patients categorized according to the presence or absence of CKD with decreased eGFR (< 60 mL/min/1.73 m^2) and subcategorized according to the occurrence of cardiovascular death

	Patients with nondecreased eGFR				CKD patients with decreased eGFR			
	No (n = 360)	Yes (n = 36)	SHR (95%CI)	*P*	No (n = 228)	Yes (n = 62)	SHR (95%CI)	*P*
Age, y	63.5 ± 12.6	72.3 ± 8.2	1.05 (1.03-1.08)	**< .001**	68.5 ± 10.2	75.0 ± 9.1	1.06 (1.02-1.10)	**.002**
Female sex	110 (30.6)	9 (25.0)	0.69 (0.38-1.26)	.22	79 (34.6)	26 (41.9)	1.18 (1.71-1.95)	.53
BMI, kg/m²	28.0 [25.2-31.5]	27.8 [24.0-32.4]	0.99 (0.94-1.03)	.59	27.8 [24.9-31.3]	27.3 [22.9-32.0]	0.98 (0.93-1.03)	.47
Sodium, mmol/L	139 ± 3.2	138 ± 4.1	0.85 (0.83-0.87)	**< .001**	138 ± 3.7	139 ± 3.9	1.00 (0.94-1.06)	.92
Potassium, mmol/L	4.3 ± 0.5	4.4 ± 0.5	1.26 (0.59-2.71)	.56	4.4 ± 0.6	4.3 ± 0.6	0.83 (0.51-1.36)	.47
Hemoglobin, g/dL	13.7 ± 1.7	12.8 ± 2.1	0.75 (0.59-0.94)	**.015**	12.8 ± 1.9	11.8 ± 2.0	0.74 (0.64-0.86)	**< .001**
eGFR, mL/min/1.73 m²	82.1 ± 14.4	77.2 ± 10.2	0.98 (0.96-1.00)	.11	41.0 ± 14.5	33.9 ± 15.7	0.97 (0.95-0.99)	**< .0001**
NYHA class								
III-IV	78 (21.7)	18 (50.0)	2.74 (1.95-3.87)	**< .001**	52 (22.8)	36 (58.1)	3.27 (1.77-6.02)	**< .001**
HF duration, mo	7.0 (1.7-42.8)	5.5 (1.8-33.3)	0.99 (0.98-1.01)	.37	6.0 (2.0-48.0)	24.0 (6.0-50.3)	1.00 (0.99-1.00)	.88

Hospitalization in previous 3 mo	176 (48.9)	22 (61.1)	1.72 (0.89-3.35)	.11	149 (65.4)	38 (61.3)	0.96 (0.42-2.16)	.86
LVEF, %	41.6 ± 18.5	41.1 ± 17.2	0.99 (0.98-1.01)	.31	38.9 ± 17.0	38.9 ± 15.9	0.99 (0.98-1.00)	.23
NT-proBNP (log_2), pg/mL	1118 [501-2074]	2490 [1569-3882]	1.49 (1.34-1.65)	**< .001**	1900 [1061-4105]	4320 [1762-9132]	1.35 (1.21-1.51)	**< .001**
Ischemic heart disease	88 (24.4)	17 (47.2)	3.10 (1.32-7.29)	**.010**	76 (33.3)	33 (53.2)	2.21 (1.63-3.01)	**< .001**
Comorbidities								
Hypertension	237 (65.8)	31 (86.1)	2.63 (1.78-3.88)	**< .001**	179 (78.5)	53 (85.5)	1.30 (0.81-2.09)	.27
Atrial fibrillation	104 (28.9)	15 (41.7)	1.32 (0.69-2.50)	.40	58 (25.4)	20 (32.3)	1.09 (0.96-1.23)	.17
Diabetes mellitus	80 (22.2)	13 (36.1)	2.52 (1.75-3.64)	**< .001**	101 (44.3)	38 (61.3)	2.00 (1.47-2.72)	**< .001**
Hypercholesterolemia	179 (49.7)	20 (55.6)	1.29 (0.83-2.01)	.25	140 (61.4)	38 (61.3)	0.97 (0.86-1.10)	.64
Peripheral vascular disease	13 (3.6)	3 (8.3)	2.66 (0.80-8.84)	.11	37 (16.2)	10 (16.1)	1.08 (0.53-2.18)	.84
COPD	45 (12.5)	8 (22.2)	1.86 (0.86-4.05)	.12	33 (14.5)	14 (22.6)	1.78 (0.96-3.28)	.07
Treatments								

ACEIs/ARBs	329 (91.4)	34 (94.4)	1.81 (0.42-7.87)	.43	206 (90.4)	50 (80.6)	0.43 (0.29-0.63)	**< .001**
Beta-blockers	253 (70.3)	22 (61.1)	0.80 (0.23-2.78)	.73	172 (75.4)	43 (69.4)	0.86 (0.48-1.52)	.60
Diuretics	266 (73.9)	33 (91.7)	3.91 (0.43-35.5)	.23	191 (83.8)	54 (87.1)	1.36 (0.63-2.91)	.43
MR blockers	195 (54.2)	20 (55.6)	1.38 (0.75-2.56)	.30	140 (61.4)	29 (46.8)	0.72 (0.43-1.20)	.21
Digoxin	115 (31.9)	14 (38.9)	1.17 (0.68-2.03)	.57	67 (29.4)	20 (32.3)	1.00 (0.89-1.13)	.97
Devices	88 (24.4)	3 (8.3)	0.33 (0.10-1.06)	.06	59 (25.9)	14 (22.6)	0.81 (0.61-1.08)	.15

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blockers; BMI, body mass index; CKD, chronic kidney disease; COPD; chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HF, heart failure; LVEF, left ventricular ejection fraction; MR, mineralocorticoid receptor; NYHA, New York Heart Association; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SHR, subhazard ratio.

Unless otherwise indicated, quantitative variables are expressed as mean ± standard deviation or median [interquartile range] and categorical variables as No. (%). Significant *P* values are highlighted in bold

Table 3 of the supplementary data

Univariable linear regression analyses for the association of IGF-1 (log_2) with clinical parameters

	Parameter estimate	95%CI	*P*
Age, y	−0.01	−0.02 to −0.01	**< .001**
Female sex (no = 0, yes = 1)	−0.15	−0.25 to −0.05	**.004**
BMI, kg/m^2	−0.005	−0.01 to 0.004	.25
Serum sodium, mmol/L	−0.01	−0.02 to 0.003	.12
Serum potassium, mmol/L	0.05	−0.04 to 0.14	.31
Hemoglobin, g/dL	0.02	−0.01 to 0.05	.13
NT-proBNP (log_2), pg/mL	−0.01	−0.03 to 0.02	.58
eGFR, mL/min/1.73 m^2	−0.001	−0.003 to 0.001	.20
NYHA class III-IV (no = 0, yes = 1)	−0.15	−0.26 to −0.05	**.006**
HF duration, mo	−0.001	−0.002 to 0.001	.15
Hospitalization during previous 3 mo (no = 0, yes = 1)	0.17	0.08 to 0.27	**< .001**
LVEF, %			

Ischemic heart disease (no = 0, yes = 1)	−0.02	−0.13 to 0.08	.66
Hypertension (no = 0, yes = 1)	−0.08	−0.19 to 0.03	.16
Atrial fibrillation (no = 0, yes = 1)	−0.01	−0.12 to 0.10	.83
Diabetes mellitus (no = 0, yes = 1)	−0.08	−0.18 to 0.02	.12
Hypercholesterolemia (no = 0, yes = 1)	−0.009	−0.11 to 0.09	.86
Peripheral vascular disease (no = 0, yes = 1)	0.05	−0.12 to 0.22	.54
COPD (no = 0, yes = 1)	0.006	−9.13 to 0.14	.93
ACEIs/ARBs (no = 0, yes = 1)	0.13	−0.04 to 0.29	.13
Beta-blockers (no = 0, yes = 1)	0.12	0.02 to 0.23	**.022**
Diuretics (no = 0, yes = 1)	0.007	−0.11 to 0.13	.90
MR blockers (no = 0, yes = 1)	0.09	−0.004 to 0.19	.06
Digoxin (no = 0, yes = 1)	0.12	0.01 to 0.22	**.030**
Devices (no = 0, yes = 1)	−0.04	−0.15 to 0.08	.53

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blockers; BMI, body mass index; COPD; chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MR, mineralocorticoid receptor; NYHA, New York Heart Association; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

Significant *P* values are highlighted in bold.

NT-proBNP estimate is the effect size for doubling of its concentrations in blood.

Table 4 of the supplementary data

Receiver operating characteristic (ROC) curve analyses in all patients

All patients (No. = 686)	Cardiovascular mortality	All-cause mortality
IGFBP2		
AUC	0.739	0.744
95% confidence interval	0.688-0.790	0.704-0.785
P value	*< .001*	*< .001*
Cutoff, ng/mL	686	686
Sensitivity, %	69.4	64.4
Specificity, %	71.4	76.0
IGF-1		
AUC	0.554	0.547
95% confidence interval	0.489-0.618	0.496-0.599
P value	*.09*	*.06*
Cutoff, ng/mL	80.3	80.3
Sensitivity, %	55.8	55.1

Specificity, %	51.4	53.1

AUC, area under the curve; IGF-1, insulin growth factor-1; IGFBP2, insulin growth factor binding protein-2.

Table 5 of the supplementary data

Association of IGFBP2 with cardiovascular mortality in patients with nondecreased eGFR (≥ 60 mL/min/1.73 m^2)

	IGFBP2 (log_2)*	IGFBP2 ≥ 564 ng/mL
Regression models, SHR (95%CI), *P*		
Univariate analyses	1.88 (1.82 to 1.94), < ***.001***	3.12 (2.65 to 3.68), < ***.001***
Multivariate analyses		
Baseline model[a]	1.44 (1.35 to 1.53), **< *.001***	2.02 (1.59 to 2.57), **< *.001***
Baseline model[b]	1.64 (1.46 to 1.85), < ***.001***	2.48 (2.29 to 2.67), < ***.001***
Baseline model[c]	1.45 (1.38 to 1.53), **< *.001***	2.11 (1.46 to 3.04), <***0.001***
Discrimination improvement		
Harrell's c, AUC (95%CI)		
Baseline model[a]	0.725 (0.635 to 0.815)	0.725 (0.635 to 0.815)
Baseline model[a] + IGFBP2	0.736 (0.650 to 0.821)	0.734 (0.648 to 0.820)
ΔAUC (95%CI), P	0.011 (−0.028 to 0.049), *.58*	0.009 (−0.029 to 0.047), *.65*
Baseline model[b]	0.740 (0.652 to 0.828)	0.740 (0.652 to 0.828)
Baseline model[b] + IGFBP2	0.773 (0.682 to 0.865)	0.760 (0.667 to 0.854)

ΔAUC (95%CI), P	0.033 (−0.002 to 0.069), *.07*	0.021 (−0.019 to 0.060), *.30*
Baseline model[c]	0.766 (0.686 to 0.845)	0.766 (0.686 to 0.845)
Baseline model[c] + IGFBP2	0.769 (0.687 to 0.851)	0.760 (0.674 to 0.847)
ΔAUC (95%CI), P	0.003 (−0.028 to 0.035), *.84*	−0.005 (−0.036 to 0.025), *.74*
Reclassification improvement		
IDI (95% CI), P		
Baseline model[a]	0.003 (−0.08 to −0.131), *.96*	0.007 (−0.020 to 0.052), *.72*
Baseline model[b]	0.015 (−0.013 to 0.070), *.48*	0.014 (−0.020 to 0.064), *.54*
Baseline model[c]	−0.001 (−0.027 to 0.037), *.99*	0.001 (−0.027 to 0.039), *.99*
Continuous NRI (95% CI), P		
Baseline model[a]		
Events	0.086 (−0.229 to 0.416), *.61*	0.222 (−0.082 to 0.541), *.16*
Nonevents	0.072 (−0.029 to 0.175), *.16*	0.394 (0.302 to 0.489), ***< .001***
All	0.158 (−0.173 to 0.504), *.37*	0.617 (0.298 to 0.949), ***< .001***
Baseline model[b]		
Events	0.278 (−0.020 to 0.592), *.07*	0.222 (−0.081 to 0.541), *.16*

Nonevents	−0.056 (−0.157 to 0.047), *.29*	0.313 (0.217 to 0.411), **< *.001***
All	0.222 (−0.093 to 0.552), *.18*	0.535 (0.217 to 0.868), ***.001***
Baseline model[c]		
Events	−0.056 (−0.367 to 0.271), *.75*	0.167 (−0.140 to 0.489), *.30*
Nonevents	0.050 (−0.051 to 0.153), *.34*	0.422 (0.331 to 0.515), **< *.001***
All	−0.006 (−0.333 to 0.336), *.98*	0.589 (0.269 to 0.924), < ***.001***

AUC, area under the curve; eGFR, estimated glomerular filtration rate; IDI, integrated discrimination index; NRI, net reclassification index; SHR, subhazard ratio;

Significant *P* values are highlighted in bold

[a] Baseline model: age, sex. The N in the final model was equal to 396

[b] Baseline model: New York Heart Association class, serum sodium. The N in the final model was equal to 394

[c] Baseline model: ischemic cardiomyopathy, N-terminal pro–B-type natriuretic peptide (log_2). The N in the final model was equal to 396

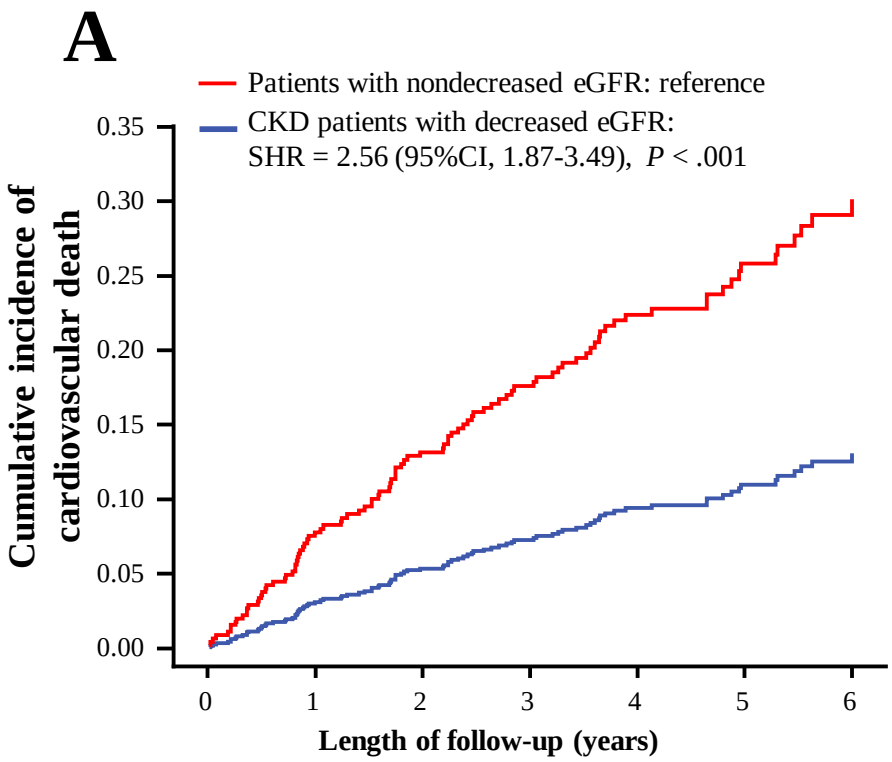
*Subhazard ratios (SHR) are effect sizes for doubling of serum IGFBP2.

FIGURE LEGENDS

Figure 1 of the supplementary data. Cumulative incidence curves represent unadjusted competing risk analyses (Fine-Gray model) for the risk of cardiovascular mortality (A) and Cox regression analyses for the risk of all-cause mortality (B) in HF patients classified according to the absence or presence of CKD with decreased eGFR (< 60 mL/min/1.73 m^2). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SHR, subhazard ratio; HR, hazard ratio.

Figure 2 of the supplementary data. Cumulative incidence curves represent unadjusted competing risk analyses (Fine-Gray model) for the risk of cardiovascular mortality in heart failure (HF) patients with nondecreased estimated glomerular filtration rate (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2) (A) and in patients with HF and chronic kidney disease with decreased eGFR (< 60 mL/min/1.73 m^2) (B) classified according to IGFBP2 (< or ≥ 686 ng/mL) in the whole population. 3D bar graphs depicting percentage of cardiovascular mortality when combining IGFBP2 (< or ≥ 686 ng/mL) with eGFR (< 30, 30-59, 60-90, > 90 mL/min/1.73 m^2) (C). SHR, subhazard ratio.

Figure 3 of the supplementary data. Cumulative incidence curves represent competing risk analyses (Fine-Gray model) for the risk of cardiovascular mortality in heart failure (HF) patients with nondecreased estimated glomerular filtration rate (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2) after adjustment by age and sex (A) serum sodium and NYHA class (B) and ischemic heart disease and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (log_2) (C) and in patients with HF and chronic kidney disease (CKD) with decreased eGFR (< 60 mL/min/1.73 m^2) after adjustment by age, NYHA, ischemic cardiomyopathy, eGFR and NT-proBNP (log_2) (D) and by hemoglobin, diabetes mellitus, treatment with angiotensin converting enzyme inhibitor or angiotensin II type 1 receptor blockers (E). HF patients were classified according to the IGFBP2 best cutoff value (Younden index) in each group (patients with nondecreased eGFR: 564 ng/mL; CKD patients with decreased eGFR: 726 ng/mL).



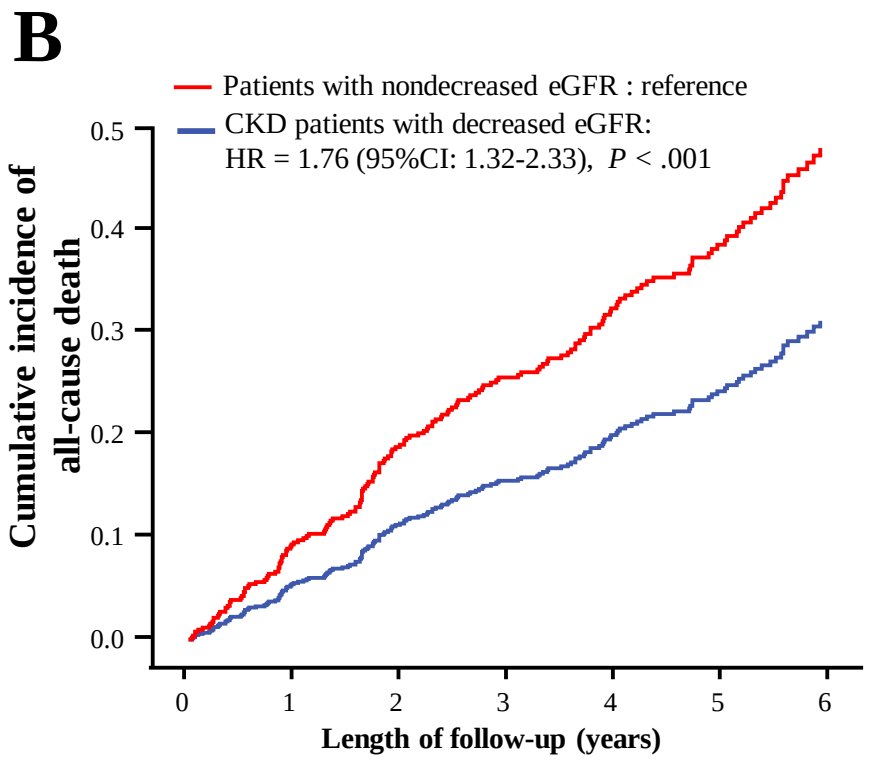
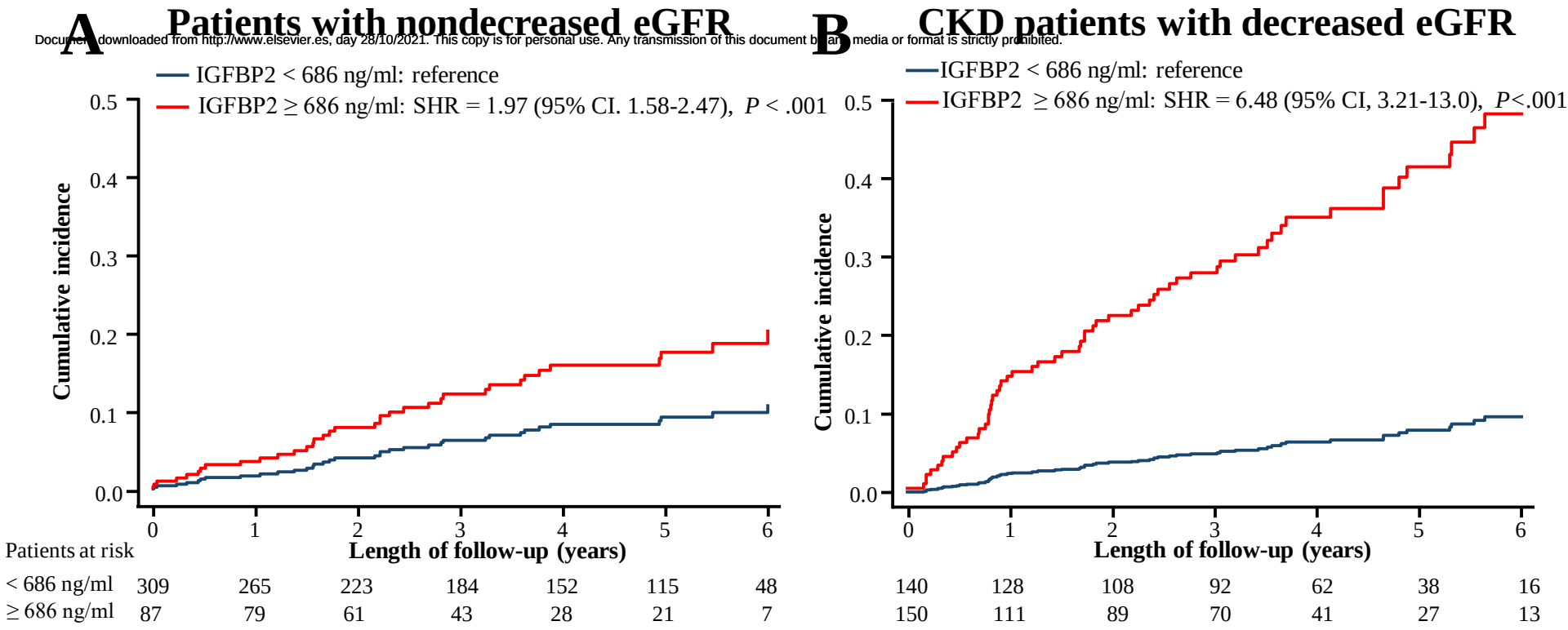


Fig. S1



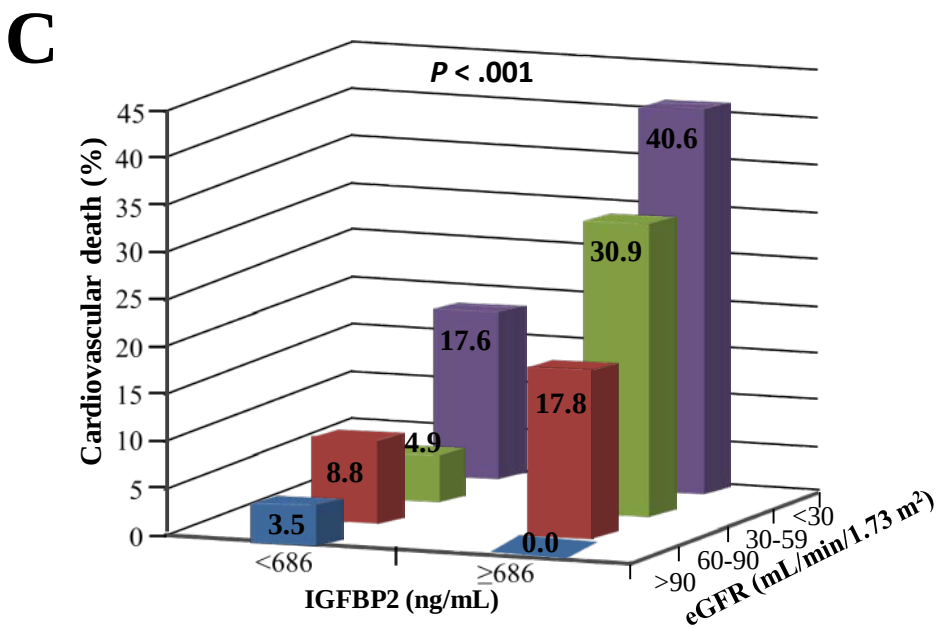


Fig. S2

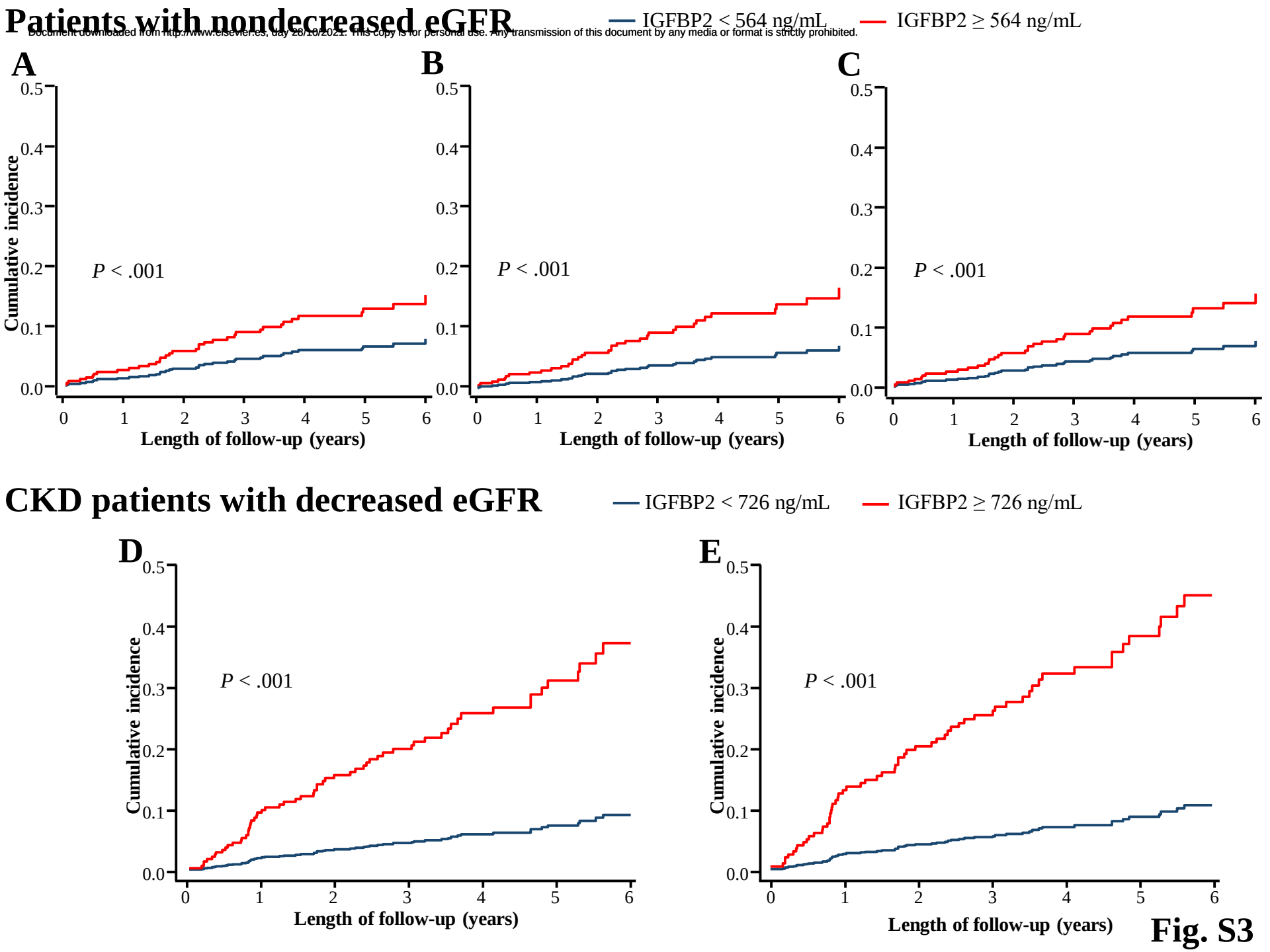


Fig. S3