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## Usefulness of Soluble Concentrations of Interleukin Family Member ST2 as Predictor of Mortality in Patients With Acutely Decompensated Heart Failure Relative to Left Ventricular Ejection Fraction

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### Abstract

The aim of the present study was to determine whether the risk of mortality associated with the concentration of soluble ST2 (sST2) differs in patients with acutely decompensated heart failure with preserved ejection fraction (HFpEF) compared to patients with systolic heart failure. We prospectively enrolled 447 patients with acutely decompensated heart failure. Blood samples were collected at presentation to determine the sST2 concentration. HFpEF was defined as symptoms or signs of acutely decompensated heart failure and left ventricular ejection fraction of  $\geq 50\%$  on the echocardiogram. The patients were followed up for 1 year, and the vital status was obtained for all. The sST2 concentrations were greater in the patients with systolic heart failure ( $n = 250$ ) than in those with HFpEF ( $n = 197$ ) at 0.55 versus 0.38 ng/ml ( $p < 0.001$ ). Receiver operating characteristic curve analyses showed different cutoff point values for sST2 for the prediction of 1-year mortality in patients with HFpEF ( $>0.35$  ng/ml) and systolic heart failure ( $>0.56$  mg/ml). These cutoff points had similar prognostic accuracy (area under the curve of 0.69 vs 0.73;  $p > 0.05$ ). In the adjusted analyses that included amino terminal B-type natriuretic peptide concentrations, elevated sST2 concentrations were associated with a greater mortality risk in both populations (HFpEF, per ng/ml, hazard ratio 1.41, 95% confidence interval 1.14 to 1.76,  $p = 0.002$ ; and systolic heart failure, per ng/ml, hazard ratio 1.20, 95% confidence interval 1.10 to 1.32,  $p < 0.001$ ). The determination of the sST2 concentration improved the clinical risk prediction compared to amino terminal B-type natriuretic peptide, as assessed by both the improved C-statistic and an improvement in the net reclassification index and integrated discrimination improvement analyses. In conclusion, in the present multicenter study, sST2 concentrations were lower in patients with HFpEF; however, sST2 remained an independent predictor of mortality, regardless of the left ventricular ejection fraction.

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In addition to the natriuretic peptides, other biochemical markers have been examined for prognostication in heart failure. Among these is the soluble form of the interleukin-1 receptor member, ST2. A biomarker suggested to potentially reflect ventricular remodeling and fibrosis,<sup>1–3</sup> soluble ST2 (sST2) represents an attractive candidate marker for understanding heart failure biology. Moreover, concentrations of the marker represent a

powerful prognostic variable in those with acutely decompensated heart failure.<sup>4-8</sup> However, the value of sST2 as a biomarker of risk as a function of acutely decompensated heart failure with preserved ejection fraction (HFpEF) versus systolic heart failure has not been specifically examined. Thus, in a cohort of patients with acutely decompensated heart failure, we evaluated the effects of left ventricular function on the concentrations of sST2, the associations between the cardiac structure and function and sST2, and the prognostic meaning of sST2 in those with HFpEF versus systolic heart failure.

## Methods

The study population consisted of subjects from 3 previously reported prospective clinical trials of acutely decompensated heart failure from Boston, Massachusetts, Linz, Austria, and Murcia, Spain.<sup>9-11</sup> These trials had compatible inclusion/exclusion criteria and had used similar clinical and laboratory testing, including sST2, troponin T, amino terminal B-type natriuretic peptide (NT-proBNP), and C-reactive protein. For the purposes of the present study, 447 patients with acutely decompensated heart failure had data available and were considered (209 from Boston, Massachusetts; 131 from Linz, Austria; and 107 from Murcia, Spain). The ProBNP Investigation of Dyspnea in the Emergency Department study was a prospective, blinded study of NT-proBNP testing performed in Boston, Massachusetts, that examined 599 subjects with dyspnea in the emergency department. All patients with acutely decompensated heart failure from Boston were eligible for the present analysis. The Linz study had included 137 patients with dyspnea who had presented to the emergency department and had a final diagnosis of acutely decompensated heart failure. Of these patients, 131 had complete data and were included in the present study. The final source of data for the present analysis was a prospectively gathered group of subjects from a Spanish cohort study of patients with a diagnosis of acutely decompensated heart failure consecutively admitted to the University Hospital of Virgen de la Arrixaca from September 1, 2006 to February 28, 2009. During that period, 107 subjects with sST2 data on admission were available for analysis and were included in the present study. The patients from each study group were followed up for 1 year, and the vital status was obtained for all.

The patients were characterized as having HFpEF if their left ventricular ejection fraction was  $\geq 50\%$ , as estimated using echocardiography and Simpson's biplane method.<sup>12,13</sup> The concentrations of sST2 were measured using an enzyme-linked immunosorbent assay (Medical and Biological Laboratories, Woburn, Massachusetts) on blood specimens frozen at  $-80^{\circ}\text{C}$ . In addition, NT-proBNP was measured using a validated, commercially available immunoassay (Elecsys ProBNP, Roche Diagnostics, Indianapolis, Indiana) using an established method.

The normally distributed data are presented as the mean  $\pm$  SD and the non-normally distributed data as the median and interquartile range. Differences in the baseline characteristics were compared using Student's *t* test for continuous variables and the chi-square test for categorical variables. The Mann-Whitney *U* test was used to compare continuous variables in states of non-normality. The Kruskal-Wallis test was performed to assess and compare the sST2 concentrations across the New York Heart Association (NYHA) functional class. The sST2 results were log-transformed to establish normality, and univariate Spearman correlation was used to evaluate the magnitude and significance of the relations among the continuous variables. To evaluate the characteristics of the sST2 concentrations as a predictor of death in patients with either HFpEF or systolic heart failure, several methods were used. The patients were grouped into tertiles, and the frequency of mortality relative to the increasing sST2 concentrations was calculated as a function of HFpEF and systolic heart failure. Receiver operating characteristic curve analyses with death at 1 year were also performed, and the area under the curve was estimated. The added

predictive ability of sST2 compared to NT-proBNP for the detection of events was evaluated using the C-statistic, net reclassification improvement, and integrated discrimination improvement analyses. Net reclassification improvement and integrated discrimination improvement were performed with the biomarkers kept as dichotomous variables, as described by Pencina et al,<sup>14</sup> such that the categories of probability for events are defined according to a prognostication scheme of the Heart Failure Survival Score.<sup>15</sup> To identify the independent predictors of death at 1 year, we performed multivariate Cox proportional hazards analyses using forward stepping. Variables were retained if their univariate p value was <0.05 and were entered into a multivariate model. Only those variables with significant p values were retained in the final multivariate model. The cumulative incidence of death was estimated using the Kaplan-Meier method, and the log-rank statistic was used for comparisons. All p values <0.05 were accepted as statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences, version 15.0, for Windows (SPSS, Chicago, Illinois). Receiver operating characteristic curve analysis was performed using MedCalc statistical software, version 10.4, for Windows (MedCalc Software, Mariakerke, Belgium).

## Results

A total of 447 subjects were included in the present analysis. The distribution of clinical characteristics and laboratory parameters as a function of left ventricular ejection fraction are listed in Table 1. The sST2 concentrations correlated with several clinical characteristics and laboratory parameters (Table 2). Moderate significant positive correlations were observed between sST2 and C-reactive protein, troponin T, and NT-proBNP (all  $p < 0.001$ ). The sST2 concentrations also correlated weakly with the left ventricular ejection fraction ( $r = -0.12$ ;  $p = 0.01$ ). Thus, patients with systolic heart failure had higher sST2 concentrations (median 0.55 ng/ml, interquartile range 0.30 to 1.03, vs median 0.38 ng/ml, interquartile range 0.26 to 0.79;  $p < 0.001$ ). When patients were categorized as a function of the NYHA functional class, the median sST2 concentrations were higher in those with worse symptoms, regardless of their left ventricular ejection fraction. Thus, of the patients with an ejection fraction  $\geq 50\%$  ( $n = 197$ ), those with NYHA class II had a median ST2 level of 0.28 ng/ml (interquartile range 0.17 to 0.36), NYHA class III, a median ST2 level of 0.43 ng/ml (interquartile range 0.30 to 0.84), and NYHA class IV, median 0.49 ng/ml (interquartile range 0.29 to 0.96 ( $p = 0.001$ )). Of those with an ejection fraction  $< 50\%$  ( $n = 250$ ), those with NYHA class II had a median ST2 level of 0.33 ng/ml (interquartile range 0.19 to 0.72), NYHA class III, median ST2 level of 0.59 ng/ml (interquartile range 0.31 to 1.01), and NYHA class IV, median ST2 level of 0.63 ng/ml (interquartile range 0.35 to 1.38;  $p < 0.001$ ).

During the 1 year of follow-up, 117 patients (26%) died. The median concentration of sST2 were significantly greater among the deceased than among the survivors (median 0.80 ng/ml, interquartile range 0.42 to 1.83, vs median 0.38 ng/ml, interquartile range 0.24 to 0.72;  $p < 0.001$ ). This pattern of higher ST2 concentrations in those who died remained for patients with HFpEF (median 0.57 ng/ml, interquartile range 0.26 to 1.28, vs 0.35 ng/ml, interquartile range 0.22 to 0.66;  $p < 0.001$ ) and those with systolic heart failure (median 0.98 ng/ml, interquartile range 0.57 to 2.48, vs median 0.42 ng/ml, interquartile range 0.26 to 0.78;  $p < 0.001$ ; Figure 1). To evaluate the optimal prognostic accuracy of the sST2 concentrations for the prediction of 1-year mortality, we performed receiver operating characteristic curve analyses as a function of the left ventricular ejection fraction. The sST2 concentrations had an area under the curve for patients with HFpEF that was comparable to that for patients with systolic heart failure (Table 3). On multivariate Cox regression analysis, we found that elevated sST2 levels, as a quantitative variable, were associated with a greater risk of 1-year mortality for patients with HFpEF (per ng/ml, hazard ratio 1.41, 95%

confidence interval 1.14 to 1.76,  $p = 0.002$ ) and for those with systolic heart failure (per ng/ml, hazard ratio 1.20, 95% confidence interval 1.10 to 1.32,  $p < 0.001$ ; Table 4). In addition, tertile analyses of sST2 concentrations revealed that a graded increase occurred in the 1-year mortality rate with increasing concentrations of sST2 in both groups of acutely decompensated heart failure (Figure 2). The Kaplan-Meier survival analysis showed an early diverging rate of mortality according to sST2 cutoff values throughout the 1 year of follow-up for the entire cohort (sST2  $\geq 0.53$  ng/ml [ $n = 201$ ], 35% vs sST2  $< 0.53$  ng/ml [ $n = 246$ ], 12%; log-rank test,  $p < 0.001$ ), as well as after stratification by left ventricular ejection fraction (HFpEF, sST2  $\geq 0.35$  ng/ml [ $n = 114$ ], 31% vs sST2  $< 0.35$  ng/ml [ $n = 83$ ], 9.6%; log-rank test,  $p < 0.001$ ; and systolic heart failure, sST2  $\geq 0.56$  ng/ml [ $n = 121$ ], 37% vs sST2  $< 0.56$  ng/ml [ $n = 129$ ], 14%; log-rank test,  $p < 0.001$ ).

The added predictive ability of sST2 compared to NT-proBNP for the detection of events was evaluated using the C-statistic, net reclassification improvement, and integrated discrimination improvement analyses. The addition of the sST2 concentration to NT-proBNP improved the C-statistic and both net reclassification improvement and integrated discrimination improvement, regardless of the left ventricular ejection fraction (Table 5).

## Discussion

In the present study, we have provided novel data on the relation between the sST2 concentrations and the clinical and biochemical characteristics of hospitalized patients with acutely decompensated heart failure considered as a function of preserved versus impaired left ventricular ejection fraction. The rationale for such an analysis was the biologic and clinical significance of sST2 as a potential marker of ventricular remodeling and prognosis in patients with acutely decompensated heart failure.<sup>1–8,16</sup> Basic science studies have suggested a pivotal biologic role for sST2 in the process of ventricular remodeling in the context of ventricular pressure or volume overload. In addition, the concentrations of sST2 appear to predict a clinical phenotype vulnerable to remodeling, and are prognostically meaningful in the context of acutely decompensated heart failure.<sup>1–8,17</sup> Because remodeling is a meaningful process in most forms of heart failure,<sup>18</sup> our hypothesis was that if the sST2 values reflect the risk of remodeling, they would be—as a consequence—prognostically important across the wide spectrum of left ventricular function in our cohort.

Consistent with our primary hypothesis, in the present multinational pooled analysis, regardless of the left ventricular ejection fraction status, we found that the sST2 concentrations correlated significantly with several prognostically and biologically meaningful biomarkers involved in deleterious remodeling. Clinically, the sST2 values were associated with heart failure symptom severity. Furthermore, the sST2 concentration was an independent predictor of 1-year mortality in patients with acutely decompensated heart failure from either HFpEF or systolic heart failure, irrespective of the presence of natriuretic peptides in the analysis. With sST2 in the model, NT-proBNP was not a predictor of death in those with HFpEF.

Cardiac remodeling is a common mechanism for the progression of heart failure and involves multiple deleterious changes in the myocardium, including cardiomyocyte loss (by necrosis or apoptosis), left ventricular dilation, cardiomyocyte hypertrophy, fibroblast proliferation, and collagen accumulation.<sup>19</sup> Remodeling has been associated with a greater rate of adverse outcomes among patients with heart failure and has been a prime target for therapeutic strategies to reduce the risk in affected patients.<sup>20–23</sup> In addition to those with systolic heart failure, it has been well established that cardiac remodeling plays a crucial role in the pathophysiology and complications of HFpEF, including having an important effect on myocardial relaxation abnormalities.<sup>24,25</sup>

It is in this context that measurement of sST2 is relevant. Several experimental and clinical studies have demonstrated sST2 to be a biomarker of mechanical stress with a pivotal role in myocardial fibrosis. sST2 has a broad role in the body, including in inflammatory responses, atherosclerosis, autoimmunity, and cardiac remodeling.<sup>1-4,17,26</sup> Recently, interleukin-33 was identified as the ligand for sST2. Interleukin-33/ST2 signaling protects the myocardium under mechanical strain and acts as a biomechanically activated fibroblast-cardiomyocyte paracrine system to prevent cardiac hypertrophy and fibrosis. Sanada et al<sup>1</sup> recently suggested that sST2 abrogates this adaptative response in a dose-dependent manner by binding interleukin-33 and preventing signaling through the ST2 ligand. Moreover, Weinberg et al<sup>2</sup> showed that derangement of sST2 signaling leads to a phenotype quite consistent with myocardial remodeling. More recently, Weir et al<sup>3</sup> showed a relation between the sST2 levels and the cardiac remodeling parameters, including left ventricular ejection fraction, left ventricular end-diastolic volume, and myocardial infarct size, as well as with the plasma aldosterone level (which itself has strong profibrotic effects on the heart).

In a previous study,<sup>5</sup> we observed the important prognostic associations between sST2 and heart failure. However, because HFpEF could fundamentally differ from systolic heart failure, we wished to extend our initial observations by examining sST2 as a function of the left ventricular ejection fraction. We found—similar to findings reported with the natriuretic peptides—that the concentrations of sST2 were lower in those with HFpEF compared with those with systolic heart failure. This might be related to differences in wall stress—the trigger for both natriuretic peptide and sST2 release. Nonetheless, similar to natriuretic peptides, we found sST2 to be prognostically meaningful in those with HFpEF. Given the universally deleterious nature of remodeling in heart failure, our results lend internal consistency to the potential value of sST2 for directed antiremodeling therapies in those with heart failure, as has been previously suggested.<sup>3</sup>

The limitations of our study included that, as a pooled multinational analysis, it lacked predefined end points, despite the similar designs and goals of the respective data sources. Another consideration was the timing of sample collection. A pre-discharge sST2 value might have added stronger prognostic information; nonetheless, our results remain significant. Also, we lacked complete echocardiographic data for each subject. Although not easily feasible in such a large analysis, such data would have provided important correlates of cardiac structure and function with respect to the sST2 concentrations. We recently reported that the sST2 values correlate with important echocardiographic measures of remodeling, including myocardial relaxation abnormalities.<sup>8</sup> It also remains unclear whether the described association between the plasma sST2 concentrations, cardiac function parameters, and the prognosis of patients with heart failure reflects what is occurring at a cardiac level, or whether the sST2 concentrations reflect other pathologic processes, independent of cardiac function, such as pulmonary disease, as we have shown.<sup>27</sup> Mechanistic studies of myocardial expression and the secretion of sST2 are needed. We did not simultaneously measure interleukin-33 and therefore could not comment on the interleukin-33/sST2 ratio; however, this is a clear focus for future research of both heart failure and myocardial infarction. (Figure 3).

## Acknowledgments

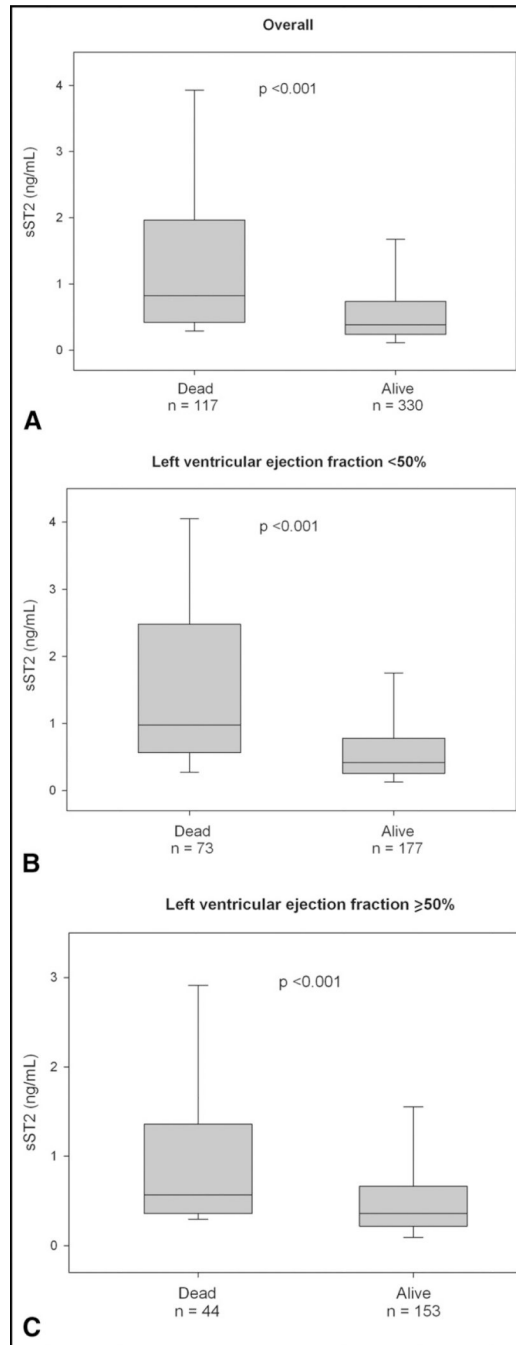
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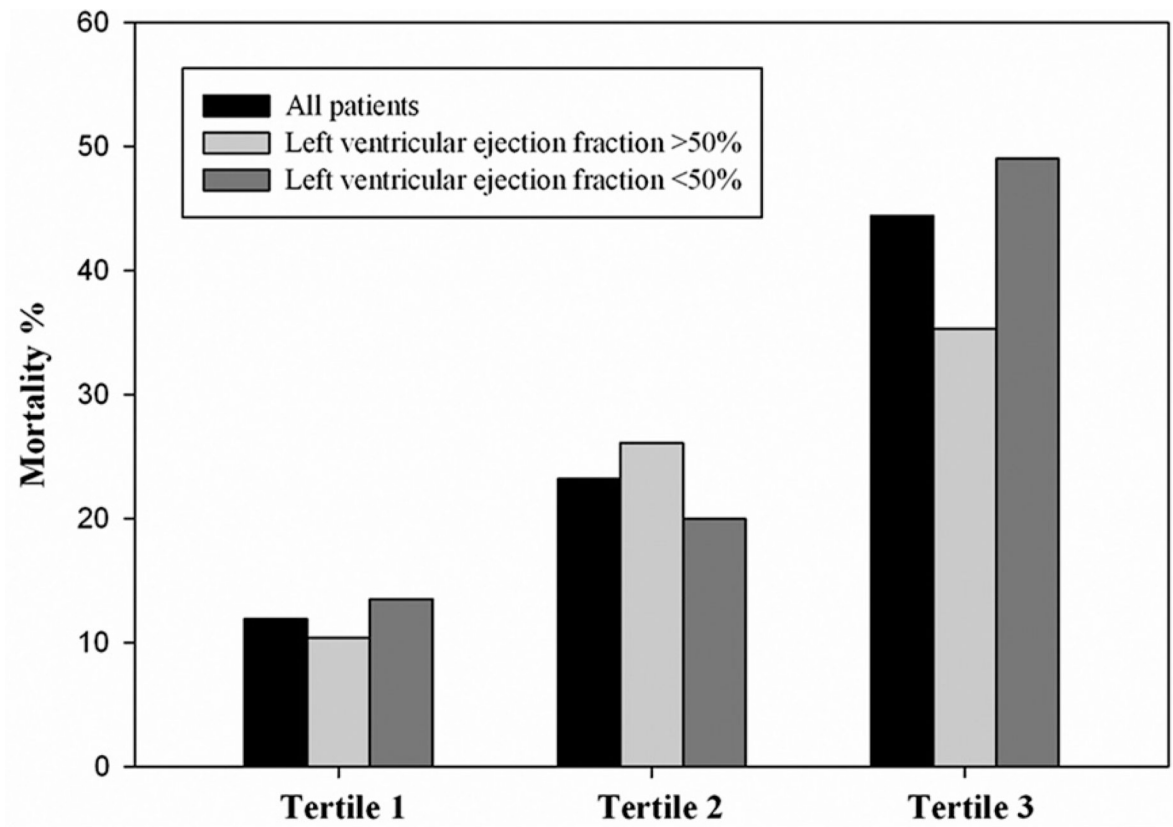
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**Figure 1.** Soluble ST2 values as function of 1-year mortality in (A) all patients and patients with (B) preserved and (C) reduced left ventricular ejection fraction.



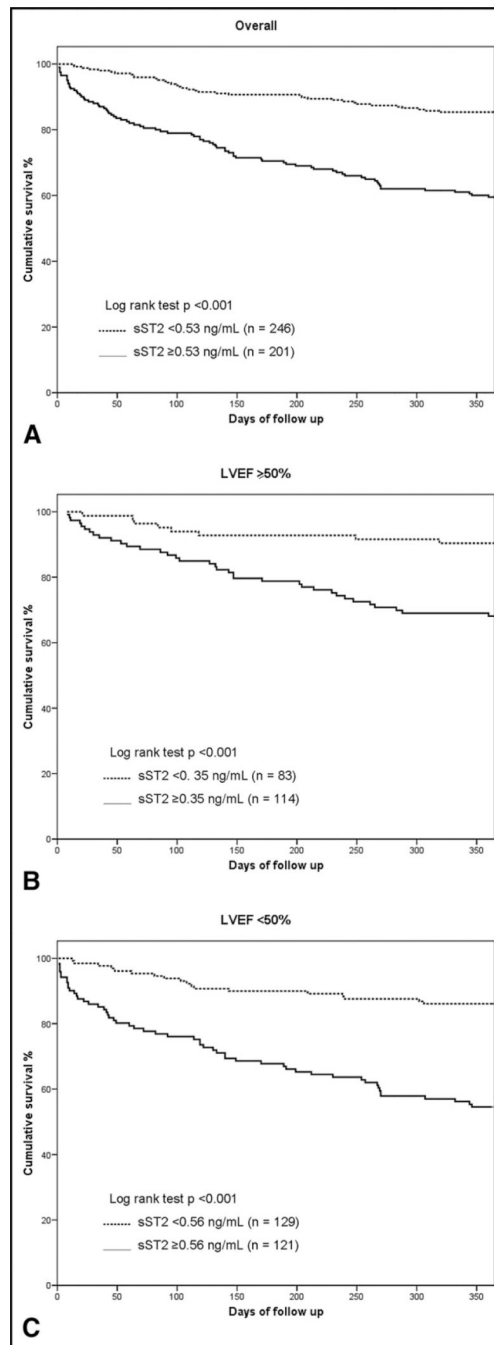


	Tertile			P value
	1 <sup>st</sup> ≤0.32 ng/mL	2 <sup>nd</sup> 0.33-0.71 ng/mL	3 <sup>rd</sup> ≥0.72 ng/mL	
All patients (n = 447)				
Mortality %	12	23	44	
Unadjusted Hazard Ratio*	1	2.04 (1.15-3.60)	4.77 (2.83-8.03)	<0.001
Adjusted Hazard Ratio	1	1.68 (0.94-3.00)	3.08 (1.78-5.34)	<0.001
Left ventricular ejection fraction ≥50% (n = 197)				
Mortality %	10	26	35	
Unadjusted Hazard Ratio*	1	2.67 (1.16-6.15)	4.07 (1.77-9.35)	0.004
Adjusted Hazard Ratio	1	2.63 (1.13-6.12)	4.18 (1.79-9.76)	0.004
Left ventricular ejection fraction <50% (n = 250)				
Mortality %	13	20	49	
Unadjusted Hazard Ratio*	1	1.38 (0.69-2.74)	2.28 (1.19-4.37)	<0.001
Adjusted Hazard Ratio	1	0.90 (0.40-2.04)	2.64 (1.29-5.41)	<0.001

Adjusted for age, body mass index, systolic blood pressure, diastolic blood pressure, prior heart failure, left ventricular ejection fraction, New York Heart functional class,  $\beta$ -blocker, Angiotensin-converting enzyme inhibitor, haemoglobin, leukocytes, estimated glomerular filtration rate, blood urea nitrogen, C-reactive protein (per mg/dL) and NT-proBNP.

**Figure 2.**

Tertile analysis comparing concentrations of sST2 relative to outcome in all subjects and those with preserved or impaired left ventricular ejection fraction. Univariate and multivariate Cox proportional hazard ratios for sST2 tertiles as predictors of 1-year mortality depicted.



**Figure 3.** Kaplan-Meier survival curves for 1-year mortality according to sST2 cutoff point values in (A) all patients and patients with (B) preserved and (C) reduced left ventricular ejection fraction.

**Table 1**

Characteristics of study patients as function of left ventricular ejection fraction

Variable	Overall (n = 447)	Left Ventricular Ejection Fraction		p Value
		≥50% (n = 197)	<50% (n = 250)	
Age (year)	73 ± 13	74 ± 12	72 ± 13	0.035
Men	290 (65%)	83 (42%)	207 (83%)	<0.001
Body mass index (kg/m <sup>2</sup> )	27 [24–31]	28 [25–32]	26 [23–30]	<0.001
Systolic blood pressure (mm Hg)	142 ± 32	149 ± 32	136 ± 31	<0.001
Diastolic blood pressure (mm Hg)	80 ± 18	79 ± 17	80 ± 19	0.46
Heart rate (beats/min)	92 ± 27	88 ± 27	96 ± 26	0.002
Hypertension	306 (69%)	148 (75%)	158 (63%)	0.007
Diabetes mellitus	183 (41%)	79 (40%)	104 (42%)	0.75
Coronary artery disease	202 (45%)	64 (33%)	138 (55%)	<0.001
Previous heart failure	239 (54%)	81 (41%)	158 (63%)	<0.001
Obstructive airway disease	103 (23%)	49 (25%)	54 (22%)	0.42
Current smoking	63 (14%)	22 (11%)	41 (16%)	0.11
Left ventricular ejection fraction (%)	46 (32–60)	60 (55–65)	34 (25–42)	<0.001
Admission New York Heart Association functional class				0.46
II	102 (23%)	45 (23%)	57 (23%)	
III	156 (35%)	63 (32%)	93 (37%)	
IV	189 (42%)	89 (45%)	100 (40%)	
Atrial fibrillation/flutter	189 (42%)	82 (42%)	107 (43%)	0.80
Medication				
β Blocker	233 (52%)	105 (53%)	128 (51%)	0.66
Angiotensin-converting enzyme	208 (47%)	71 (36%)	137 (55%)	<0.001
Angiotensin-receptor blocker	57 (13%)	34 (17%)	23 (9%)	0.011
Digoxin	104 (23%)	31 (16%)	73 (29%)	0.01
Loop diuretic	309 (69%)	124 (63%)	185 (74%)	0.012
Hemoglobin (g/dl)	12.7 ± 2.2	12.1 ± 2.3	13.1 ± 2.1	<0.001
Leukocytes (per 10 <sup>3</sup> )	8.7 (7.0–10.9)	8.6 (7.1–10.6)	8.7 (6.7–11.1)	0.79
Creatinine (mg/dl)	1.10 (0.83–1.50)	1.10 (0.82–1.49)	1.14 (0.88–1.56)	0.53
Estimated glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )	63 (43–86)	61 (40–83)	65 (45–90)	0.029
Blood urea nitrogen (mg/dl)	25 (18–34)	24 (18–33)	25 (18–35)	0.36
C-reactive protein (mg/dl)	3.5 (0.9–16.3)	5.2 (1–22)	2.65 (0.80–9.95)	0.013
Troponin T (ng/ml)	0.01 (0.01–0.04)	0.01 (0.01–0.037)	0.016 (0.01–0.062)	0.004
Plasma amino terminal B-type natriuretic peptide (pg/ml)	3,558 (1,646–9,250)	2,749 (1,344–6,634)	4,709 (2,099–11,159)	<0.001
Soluble ST2 (ng/ml)	0.47 (0.28–0.94)	0.38 (0.26–0.79)	0.55 (0.30–1.03)	<0.001

Data are presented as mean ± SD, median (quartiles), or n (%).

**Table 2**  
Correlations between soluble ST2 (sST2) and continuous covariates as function of left ventricular ejection fraction

Variable	Left Ventricular Ejection Fraction					
	Overall (n = 447)		≥50% (n = 197)		<50% (n = 250)	
	r	p Value	r	p Value	r	p Value
Age (years)	—	0.69	—	0.65	0.10	0.12
Body mass index (kg/m <sup>2</sup> )	—	0.23	—	0.94	—	0.42
Systolic blood pressure (mm Hg)	-0.10	0.040	—	0.47	-0.10	0.11
Diastolic blood pressure (mm Hg)	—	0.68	-0.11	0.13	—	0.59
Heart rate (beats/min)	0.20	<0.001	—	0.19	0.25	<0.001
Hemoglobin (g/dl)	-0.11	0.018	-0.12	0.09	-0.26	0.006
Leukocytes	0.23	<0.001	0.19	0.01	0.26	<0.001
Creatinine (mg/dl)	0.25	<0.001	0.18	0.015	0.30	<0.001
Estimated glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )	-0.23	<0.001	-0.18	0.01	-0.30	<0.001
Blood urea nitrogen (mg/dl)	0.26	<0.001	0.13	0.08	0.36	<0.001
C-reactive protein (mg/dl)	0.40	<0.001	0.36	<0.001	0.47	<0.001
Plasma amino terminal B-type natriuretic peptide (pg/ml)	0.41	<0.001	0.35	<0.001	0.43	<0.001
Troponin T (ng/ml)	0.31	<0.001	0.25	0.001	0.34	<0.001
Left ventricular end-systolic diameter (mm)	0.15	0.033	—	0.16	0.23	0.034
Left ventricular end-diastolic diameter (mm)	—	0.382	—	0.49	—	0.39
Right ventricular systolic pressure (mm Hg)	0.22	<0.001	0.16	0.08	0.27	<0.001

**Table 3**

Performance of soluble ST2 (sST2) values for prediction of mortality at 1 year

Variable	AUC	95% CI	Cutpoint (ng/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All patients (n = 447)	0.71	0.67–0.76	0.53	0.69	0.64	0.41	0.85
Left ventricular ejection fraction $\geq 50\%$ (n = 197)	0.69	0.62–0.75	0.35	0.82	0.49	0.37	0.88
Left ventricular ejection fraction $< 50\%$ (n = 250)	0.73	0.67–0.79	0.56	0.76	0.62	0.42	0.88

AUC = area under the curve; CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

**Table 4**  
Univariate and multivariate Cox proportional hazards for soluble ST2 (sST2) as predictor of 1-year mortality

Variable	All Patients (n = 447)			Left Ventricular Ejection Fraction		
	Univariate			Multivariate		
	Hazard Ratio	p Value	Hazard Ratio	p Value	Hazard Ratio	p Value
Age (years)	1.006 (1.004–1.008)	<0.001	1.05 (1.03–1.07)	<0.001	1.07 (1.03–1.11)	<0.001
Body mass index (kg/m <sup>2</sup> )	0.94 (0.90–0.97)	0.001				
Systolic blood pressure (mm Hg)	0.985 (0.979–0.992)	<0.001	0.988 (0.982–0.994)	<0.001		0.986 (0.977–0.995)
Diastolic blood pressure (mm Hg)	0.981 (0.971–0.992)	0.001				
Previous heart failure	1.72 (1.18–2.50)	0.005				
New York Heart Association functional class	1.43 (1.12–1.82)	0.004				
β Blocker	0.68 (0.48–0.98)	0.038	0.66 (0.45–0.97)	0.035		0.56 (0.34–0.91)
Angiotensin-converting enzyme inhibitor	0.64 (0.44–0.93)	0.018				
Hemoglobin (g/dl)	0.87 (0.80–0.94)	<0.001				
Leukocytes (U)	1.07 (1.02–1.03)	0.003			1.13 (1.03–1.24)	0.008
Creatinine (mg/dl)	1.74 (1.43–2.12)	<0.001				
Estimated glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )	0.985 (0.979–0.992)	<0.001			0.98 (0.97–0.99)	0.012
Blood urea nitrogen (mg/dl)	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	<0.001		1.03 (1.01–1.04)
C-reactive protein (mg/dl)	1.006 (1.004–1.008)	<0.001				
Plasma amino terminal B-type natriuretic peptide (100 pg/ml)	1.003 (1.002–1.004)	<0.001	1.002 (1.001–1.003)	<0.001		1.002 (1.001–1.003)
Soluble ST2 (ng/ml)	1.74 (1.43–2.12)	<0.001	1.23 (1.13–1.34)	<0.001	1.37 (1.11–1.68)	0.003
Soluble ST2 greater than cutoff						
All patients (>0.53 mg/ml)	3.31 (2.23–4.89)	<0.001	2.43 (1.60–3.69)	<0.001		
Left ventricular ejection fraction ≥50% (>0.35 mg/ml)					3.26 (1.50–7.05)	0.003
Left ventricular ejection fraction <50% (>0.56 mg/ml)						2.94 (1.66–5.19)



**Table 5**

Soluble ST2 (sST2) concentration improved C-statistic and net reclassification improvement and integrated discrimination improvement

Variable	All Patients (n = 447)	Left Ventricular Ejection Fraction <50% (n = 250)	Left Ventricular Ejection Fraction ≥50% (n = 197)
Incremental value of biomarkers for detection of 1-year mortality assessed by C-statistic improvement			
C-statistic (model 1)	0.64	0.65	0.60
C-statistic (model 2)	0.71	0.74	0.68
Differences in C-statistic (95% CI)	0.07 (0.02–0.11)	0.08 (0.03–0.14)	0.08 (0.02–0.15)
p Value	0.002	0.08	0.01
Evaluating added predictive ability of model 2 plus model 1 for detection of events using net reclassification and integrated discrimination indexes			
Net reclassification improvement (95% CI)	0.56 (0.39–0.73)	0.71 (0.49–0.92)	0.47 (0.22–0.71)
Events correctly reclassified (%)	9%	26%	16%
Nonevents correctly reclassified (%)	48%	45%	31%
p Value	<0.0001	<0.0001	0.0002
Evaluating added predictive ability of model 2 plus model 1 for detection of events using net reclassification and integrated discrimination indexes			
Integrated discrimination improvement (95% CI)	0.04 (0.02–0.06)	0.07 (0.04–0.10)	0.04 (0.01–0.07)
Events change probability	3%	5%	3%
Nonevents change probability	–1.1%	–2.1%	–0.9%
p Value	<0.0001	<0.0001	0.004

Model 1 included NT-proBNP and model 2 included NT-proBNP and sST2.  
CI = confidence interval.