ORIGINAL ARTICLE

Soluble ST2 Monitoring Provides Additional Risk Stratification for Outpatients With Decompensated Heart Failure

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Introduction and objectives. The novel biomarker ST2 provides diagnostic information in a variety of clinical settings. The objective was to determine whether measurement of the soluble ST2 (sST2) concentration improves risk stratification in outpatients with decompensated heart failure (HF).

Methods. The concentrations of sST2 and N-terminal probrain natriuretic peptide (NT-proBNP) and a heart failure severity score (HFSS), based on Framingham criteria, were determined at baseline and 2 weeks later in 48 outpatients with decompensated hf. The ratio of the value of each variable at week 2 relative to baseline was determined. Patients were followed for 1 year and cardiac events (i.e. death, HF admission and heart transplantation) were recorded.

Results. By 1 year, 56% of patients had experienced a cardiac event. The sST2 ratio was significantly lower in patients who did not have a cardiac event (0.6 [0.39] vs. 1.39 [0.92]; *P*<.001). After multivariable adjustment, the sST2 ratio remained an independent predictor of risk (odds ratio=1.054; 95% confidence interval, 1.01-1.09; *P*=.017). The optimum cut-point for the sST2 ratio determined by receiver operating curve [ROC] analysis was 0.75; this accounted for 25% of the change in sST2 by week 2. Among patients with an sST2 ratio >0.75 and a baseline NT-proBNP level >1000 ng/L, 72% had a cardiac event (*P*=.018), while no events occurred in patients with marker values below these reference levels.

Conclusions. Determination of the sST2 concentration in serial samples provided additional risk stratification in outpatients with decompensated HF. Repeated measurement of sST2 may aid clinical decision-making.

Key words: *Heart failure. Prognosis. NT-proBNP. ST2.*

La monitorización de ST2 soluble proporciona una estratificación del riesgo adicional en pacientes ambulatorios con insuficiencia cardiaca descompensada

Introducción y objetivos. El ST2 es un nuevo biomarcador que aporta información diagnóstica en varios contextos clínicos. Nuestro objetivo fue examinar si la monitorización de las concentraciones de ST2 soluble (sST2) mejora la estratificación del riesgo de los pacientes ambulatorios con insuficiencia cardiaca descompensada.

Métodos. Se determinaron las concentraciones de sST2 y de NT-proBNP, así como la puntuación de gravedad de la insuficiencia cardiaca (Heart Failure Severity Score [HFSS]), basada en los criterios de Framingham, en la situación basal y al cabo de 2 semanas en 48 pacientes ambulatorios con insuficiencia cardiaca descompensada. Para todas las variables, se calcularon los cocientes de los valores determinados a las 2 semanas respecto a los valores basales. Se efectuó un seguimiento durante 1 año y se registraron los episodios cardiacos (muerte, ingreso por insuficiencia cardiaca, trasplante de corazón).

Resultados. Al cabo de 1 año, el 56% de los pacientes había sufrido un episodio cardiaco. El cociente de sST2 fue significativamente inferior en los pacientes que no habían presentado ningún episodio cardiaco (0,6 ± 0,39 frente a 1,39 ± 0,92; p < 0,001). Tras introducir un ajuste multivariable, el cociente de sST2 continuó siendo un factor predictivo independiente para el riesgo (*odds ratio* = 1,054; intervalo de confianza del 95%, 1,01-1,09; p = 0,017). El valor de corte óptimo del cociente de sST2 obtenido mediante el análisis de la curva ROC fue 0,75;

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ABBREVIATIONS

HF: heart failure
HFSS: heart failure severity score
LVEF: left ventricular ejection fraction
NT-proBNP: N-terminal probrain natriuretic peptide
NYHA: New York Heart Association

con ello se explicaba un 25% del cambio de sST2 a las 2 semanas. De los pacientes con un cociente de sST2 > 0,75 y un valor basal de NT-proBNP > 1.000 ng/l, un 72% sufrió episodios cardiacos (p = 0,018); no hubo ningún episodio en los pacientes con concentraciones de marcadores inferiores a esos valores de referencia.

Conclusiones. La obtención de muestras para la determinación seriada del sST2 proporciona una estratificación del riesgo adicional en los pacientes ambulatorios con insuficiencia cardiaca descompensada. Las determinaciones repetidas del sST2 podrían ser útiles para la toma de decisiones clínicas.

Palabras clave: *Insuficiencia cardiaca. Pronóstico. NT-proBNP. ST2.*

INTRODUCTION

ST2 is emerging as a novel biomarker for patient stratification in different clinical settings. In the cardiovascular field, ST2 was first identified in the conditioned medium of cultured myocytes. When mechanical strain was applied to cultured rat cardiac myocytes, the ST2 gene was the most highly induced among thousands of genes analyzed by genomic screening.[1] Under the induction of separate promoters, the ST2 gene expresses two unique proteins: soluble ST2 (sST2), the circulating form of ST2, and ST2L, which is the transmembrane form that signals through a complex involving IL-33[2].[3] The cardiac role of ST2 remains to be entirely elucidated; however, experimental disruption of the ST2 gene in a murine model resulted in severe cardiac hypertrophy, fibrosis, and heart failure (HF), relative to wild type animals.[2]

Several reports have already evaluated the prognostic importance of a single baseline measurement of sST2. Circulating sST2 concentrations were elevated in the early phase of myocardial infarction and in patients presenting to the emergency department with acute dyspnea of cardiac origin.[1,4] More recently, our group found that increased sST2 levels were associated with higher risk of suffering sudden death in a cohort of ambulatory patients with HF.[5] Whether serial monitoring of sST2 levels correlates with long-term prognosis in patients with symptomatic HF is unknown.

The aim of this study was to determine the value of serial sST2 measurements, obtained at baseline and after 2 weeks, for predicting 1-year outcome in outpatients with signs and symptoms of destabilized HF who attended a structured HF clinic.

METHODS

Forty-eight ambulatory patients who attended 2 HF clinics with recently destabilized HF were included in the study. An objective HF severity score (HFSS) based on Framingham criteria was used to diagnose destabilized HF. Major criteria were assigned a value of 1, and minor criteria were assigned a value of 0.5. A total score of 2 or more was taken to indicate destabilized HF[6,7] (Table 1). Patients HFSS were assessed at enrollment (baseline) and after two weeks of intensified diuretic treatment. This study is a post-hoc analysis from a previous study designed to assess usefulness of novel biomarkers for heart failure monitoring.[7]

All patients had symptomatic HF (New York Heart Association [NYHA] class II-IV), impaired left-ventricular systolic function (left-ventricular ejection fraction [LVEF] ≤40% by echocardiography), and all had been treated with β-blockers at the maximum tolerated dose during the previous 3 months. Exclusion criteria have been described elsewhere[7] and included: acute coronary syndrome within the

TABLE 1. **Heart Failure Severity Score (HFSS)**

	Value
Major criteria	
Paroxysmal nocturnal dyspnea	1
Basal crackles	1
Hepatojugular reflex positive	1
Third heart sound present	1
Minor criteria	
Orthopnea	0.5
Reduction in exercise tolerance	0.5
Resting sinus tachycardia	0.5
Jugular venous pressure >4 cm	0.5
Hepatomegaly	0.5
Peripheral edema	0.5

last three months; pending cardiac transplant or revascularization; severe valvular disease eligible for surgical repair; or end-stage pulmonary, hepatic or renal diseases. The local Ethics Committee approved this study and each patient provided informed consent.

Biochemical Analysis

Serum samples were obtained from venipuncture at baseline and after 2 weeks. Concentrations of sST2 were determined using enzyme-linked immunosorbent assay (Medical & Biological Laboratories Co., Woburn, MA) as previously described[8]. This assay uses monoclonal antibodies to human sST2 for both capture and detection and had an inter-assay coefficient of variation of 17.5%. In this analysis, NT-proBNP levels were measured by electrochemiluminescence immunoassay using an Elecsys 2010 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) with a total imprecision lower than 3%.

Clinical Follow-up

Patients were followed for one year and the one-year status was obtained in clinical visits (HF admissions, urgent cardiac transplantation) or by phone interview for all patients. The primary endpoints were cardiovascular death, hospital admission for HF, or urgent cardiac transplantation.

Statistical Analysis

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Variables not normally distributed are expressed as median (interquartile range [IQR]), and natural logarithmic transformation was used for statistical analysis. Normally distributed continuous variables are expressed as mean (standard deviation) (SD). Differences between groups were analyzed using the unpaired *t* test. Frequencies of categorical variables were expressed as numbers (percentage) and compared using Fisher exact test. Correlations between variables were assessed using Pearson's test. Differences in NYHA classification were tested by ANOVA analysis. Repeated measures analysis was used to study sST2 changes at week 2. A week-2 / baseline ratio (obtained by dividing results of week two by those at baseline) was determined for sST2, HFSS, and NT-proBNP. The independent prognostic value of sST2 ratio was assessed by entering in a multivariable Cox regression analysis that included age, sex, LVEF, and those variables with $P<.1$ in univariable analysis. A 2-sided P value less than .05 was considered statistically significant. All data analysis was performed using SPSS 14.0 software (SPSS Inc., Chicago, IL).

RESULTS

Twenty-six (56%) of the 48 patients experienced a cardiac event at one-year follow-up: 13 deaths, 10 admissions for HF, and 3 urgent cardiac transplants. The characteristics of patients with and without events are shown in Table 2. There were no differences in baseline HFSS or NT-proBNP between the groups. By contrast, there were significant differences in NT-proBNP and HFSS ratios between patients with and without events (P=.011 and P=.012, respectively; Figure 1).

The median sST2 concentration for the group as a whole was 0.27 ng/mL (IQR, 0.16-0.47) at baseline and 0.23 ng/mL (IQR, 0.11-0.30) at week 2. sST2 concentration at baseline showed a positive correlation with clinical assessment measured as HFSS (r=0.353; P=.014) and as NYHA functional class (r=0.372; P=.009). Table 3 shows the sST2 concentrations in patients with and without events at baseline and week 2, the absolute and relative sST2 changes, and the sST2 ratio. The sST2 concentration was not significantly different in patients with and without events at baseline (0.23 vs 0.31 ng/mL; P=.12) or week 2 (0.23 vs 0.22 ng/mL; P=.43). No significant associations were found between sST2 and other clinical variables, including the cumulative dose of loop diuretics at 2 weeks (P=.146; r=0.215).

Patients without events showed a significant sST2 reduction from baseline to week 2 as compared to patients with events when values were expressed as absolute (–0.10 vs +0.02 ng/mL; P=.002) or relative (–32% vs +18%, P<.001) change. Consequently, the sST2 ratio was significantly lower in the group of patients without events as compared with the group with events (0.60 vs 1.39; P<.001; Figure 1). Notably, the sST2 ratio was also significantly lower among decedents than among survivors (n=13; 1.51 [IQR, 0.70-2.84] vs 0.76 [IQR, 0.32-1.07]; P=.024) and in the combined endpoint of death plus urgent heart transplantation (n=16; 1.51 [IQR, 0.69-2.3] vs 0.76 [IQR, 0.32-1.02]; P=.010). Moreover, the sST2 ratio showed a positive correlation with changes in NT-proBNP (r=0.523; P<.001) and HFSS (r=0.566; P<.001).

After adjusting in a multivariable Cox regression model, sST2 ratio retained independent prognostic information (per decile: hazard ratio (HR), 1.054; 95% confidence interval [CI], 1.010-1.101; P=.017), as well as non-sinus rhythm (HR, 5.3; 95% CI, 1.7-17.3; P=.005), age (HR, 1.04; 95% CI, 1.003-1.087; P=.033), ischemic etiology (HR, 3.67;95% CI, 1.42-9.60; P=.007) and furosemide dose (per mg,

TABLE 2. **Patient Characteristics Sorted According to Outcome**

	No Events (n=22)	Events (n=26)	*P* Value
Age, mean (SD), y	62 (12)	62 (15)	.97
Sex, male, n (%)	19 (86)	19 (73)	.26
Arterial hypertension, n (%)	13 (59)	14 (54)	.72
Diabetes mellitus, n (%)	6 (27)	8 (31)	.79
Ischemic HF, n (%)	6 (27)	14 (54)	.06
NYHA class, mean (SD)	3.3 (0.6)	3.1 (0.6)	.40
Hemoglobin, mean (SD), g/L	136 (17)	130 (16)	.21
Serum creatinine, mean (SD), µmol/L	117 (30)	124 (27)	.38
Sinus rhythm, n (%)	16 (73)	9 (35)	.01
LVEDD, mean (SD), mm	65 (10)	65 (8)	.96
LVEF, mean (SD), %	26 (11)	29 (8)	.35
Therapy (baseline)			
ACEI or ARB, n (%)	22 (100)	26 (100)	1
β-blockers, n (%)	22 (100)	26 (100)	1
Furosemide, n (%)	22 (100)	26 (100)	1
Furosemide, mean (SD), mg/day	61 (31)	86 (51)	.08
Spironolactone, n (%)	13 (59)	18 (69)	.46
HFSS, baseline, mean (SD)	3.5 (1)	3.4 (1.1)	.62
HFSS ratio, week-2/baseline, mean (SD)	0.41 (0.4)	0.61 (0.35)	.012
NT-proBNP, ng/L	5156 [1817-13582]	5100 [2519-8351]	.75
NT-proBNP ratio, week-2/baseline, mean (SD)	0.67 (0.42)	0.97 (0.42)	.011

HFSS indicates heart failure severity score; LVEDD, left ventricle end diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Data are presented as mean (standard deviation), n (%), or median [IQR].

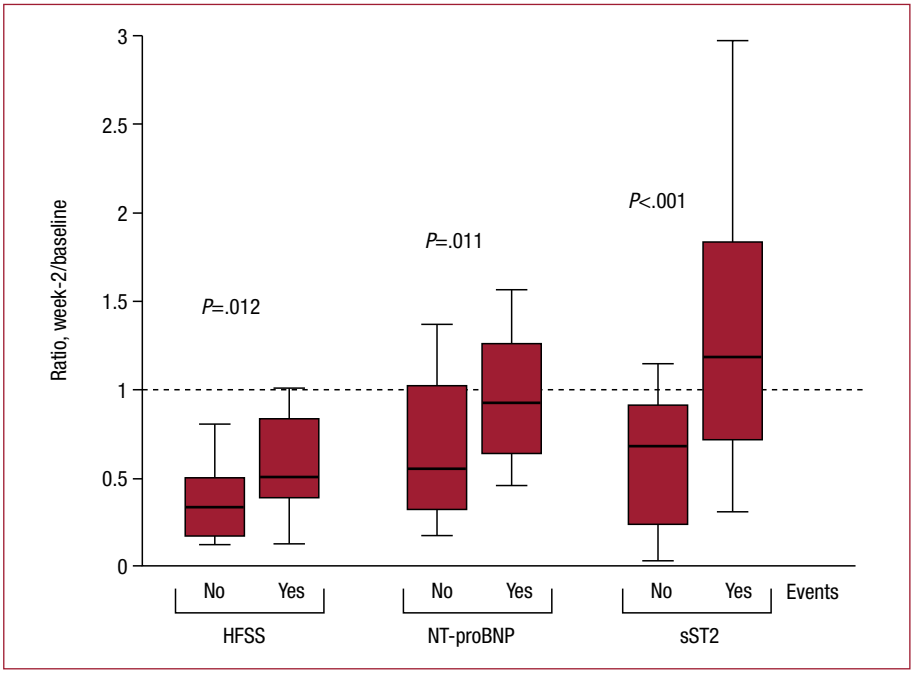

Figure 1. Box-plots showing the week 2/baseline ratios for Heart Failure Severity Score (HFSS), NT-proBNP, and sST2 in heart failure outpatients with and without events at one-year follow-up.

HR, 1.013; 95% CI, 1.003-1.023; *P*=.01); whereas LVEF, sex, baseline ST2 and ratios at week 2 of NT-proBNP and HFSS did not reach statistical significance.

The sST2 ratio showed an area under ROC curve of 0.772 (95% CI, 0.641-0.903; *P*<.001; Figure 2) with an optimal reference value of 0.75 (77% sensitivity, 59% specificity), which accounts for a

TABLE 3. **sST2 Concentrations and Changes at Week 2**

	No Events (n=22)	Events (n=26)	*P* Value
sST2 at baseline, ng/mL	0.31 [0.21-0.71]	0.23 [0.13-0.44]	.12
sST2 at week 2, ng/mL	0.22 [0.04-0.30]	0.23 [0.13-0.31]	.43
sST2 absolute change, ng/mL	–0.10 [–0.55 to –0.01]	+0.02 [–0.08 to +0.13]	.002
sST2 relative change, %	–32 [–77 to –9]	+18 [–28 to +83]	<.001
sST2 ratio, week-2/baseline	0.6 (0.39)	1.39 (0.92)	<.001

Absolute change = week 2-baseline.
Relative change = (week 2–baseline)/baseline.
sST2 ratio = week 2/baseline.
Data are presented as mean (standard deviation) or median [IQR].

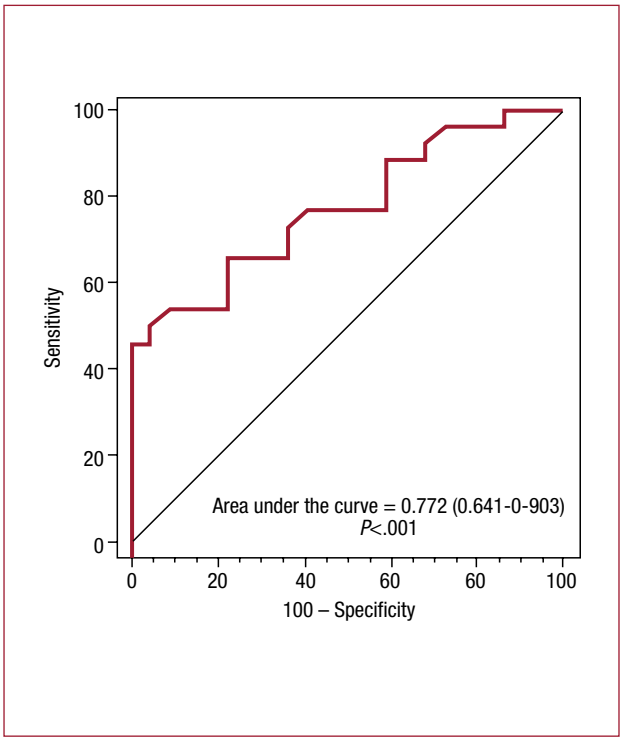

Figure 2. Receiver Operating Characteristics curve from the sST2 week 2/baseline ratios.

25% change in sST2 between baseline and week 2. Sixty-nine percent of patients with an sST2 ratio >0.75 had events, while only 32% of patients with an sST2 ratio ≤0.75 had an event (*P*=.011). After adjusting in the multivariable Cox regression analysis, this cutt-off point was also associated with a higher risk of adverse events (HR, 2.74; 95% CI, 1.11-6.83; *P*=.023). Because the NT-proBNP cut-point ≈1000 ng/L was previously suggested to be optimal for patient risk stratification,[9] this cut-point was examined in combination with the sST2 ratio at week 2. No events occurred when both markers were low, while 72% of patients with an sST2 ratio >0.75 and NT-proBNP >1000 ng/L had events (*P*=.018; Figure 3).

DISCUSSION

This study shows that sST2, a novel biomarker of cardiac stretch, is a marker of increased risk for patients with destabilized HF in the ambulatory setting. sST2 changes correlated with clinical and NT-proBNP changes, but added prognostic information to these data. In consequence, serial sST2 monitoring emerges as a novel tool for prognostic guidance in HF.

Increased levels of sST2 have been associated with numerous human diseases including acute exacerbation of eosinophylic pneumonia, sepsis, and trauma.[10-12] Circulating sST2 concentration in the context of cardiac disease was first characterized in response to myocardial infarction.[1] Our study shows that during HF decompensation, baseline sST2 concentrations correlate with clinical indices of severity, such as NYHA functional class and the more objective HFSS derived from the Framingham criteria. Moreover, a reduction in sST2 level after two weeks, but not baseline sST2 levels, correlated with improvement in the clinical severity score and a reduction in NT-proBNP levels. Thus, sST2 appears to be a dynamic marker of HF that correlates well with clinical phenomena. All together, these factors make sST2 a potential marker for monitoring change in disease status and response to therapy.

The prognostic power of circulating sST2 concentration in patients with HF is not well understood. For ambulatory patients with HF, the only relevant data about sST2 come from a sub-analysis of the PRAISE-2 Trial (Prospective Randomized Amlodipine Survival Evaluation–2).[13] This study showed that change

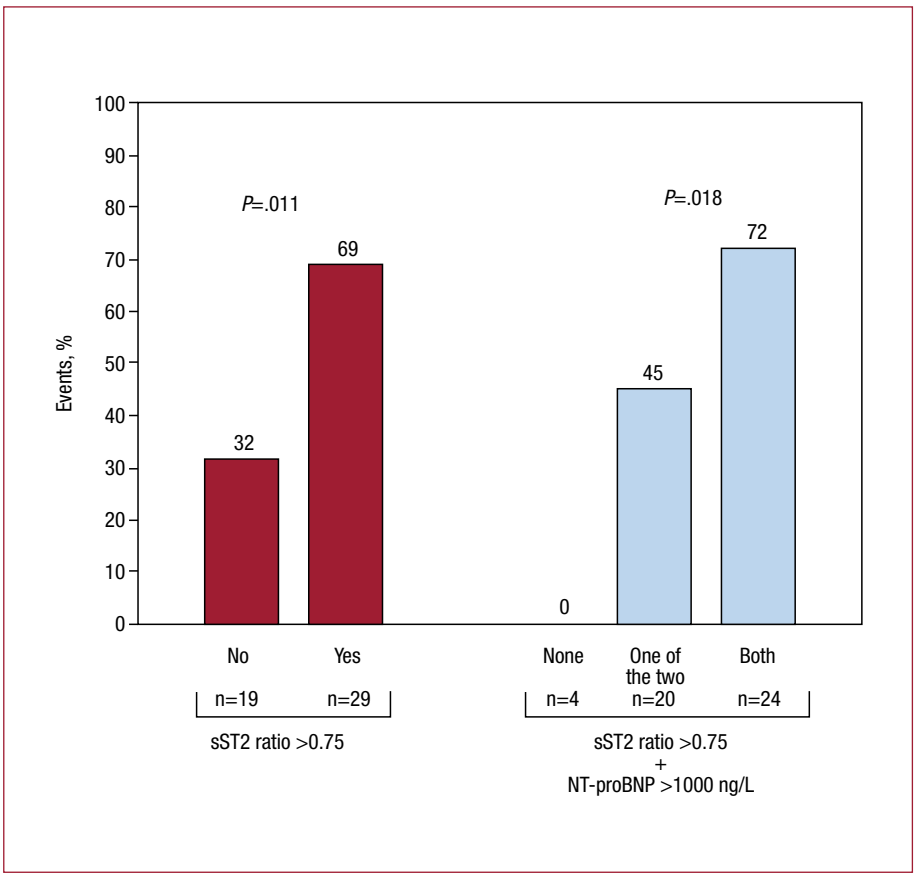

Figure 3. Bar graphs showing events according to sST2 ratio >0.75 alone and in combination with NT-proBNP concentration >1000 ng/L (at week 2).

in sST2 level was an independent predictor of mortality in a cohort of patients with established HF of non-ischemic origin. Our study is the first to provide data on the prognostic value of serial sST2 levels in outpatients with destabilized HF who require medical assistance in structured HF clinics but are not ill enough to require immediate hospitalization. Due to the limited availability of hospital beds for HF patients and the need to better identify those patients who most need close monitoring and assistance, structured HF care plans have evolved to address these issues. In this study, we found that a decrease in sST2 concentration at two weeks was predictive of a more benign outcome at one-year follow-up, while the absence of a reduction in sST2 in the first 2 weeks was associated with a higher risk of cardiovascular events.

The mechanism underlying the dynamic behavior of sST2 levels is likely to be multifactorial. First, the decrease in circulating levels of sST2 during the first 2 weeks might be a surrogate for reduced inflammation. HF is known to be a low-grade inflammatory disease and ST2 is expressed in mast cells and T helper 2 cells, in addition to cardiomyocytes,[1] and participates in inflammatory and immune responses.[14] On cells that express ST2, the presence of IL-33 leads to activation of a signaling pathway involving MyD88 and NF-κB.[15] It is possible that continued serial measurements of sST2 during follow-up would reveal an even greater decrease in sST2 concentrations in the event-free group. Second, sST2 might act as a sensor of the reduction in ventricular stress on the myocardium following treatment.

There is a need for novel biomarkers whose change during therapy is predictive of outcome. Natriuretic peptides have been studied extensively, and studies have shown that treating HF based on BNP or NT-proBNP[16,17] levels appears to reduce cardiovascular events as compared to clinically-guided treatment. In multivariable analysis, sST2 emerged as an important stratifier of risk in this population of HF outpatients. These data suggest that the subset of patients who received therapy sufficient to allow their

clinical condition to be considered stable but whose sST2 concentrations did not change significantly might be candidates for more aggressive diagnostic and therapeutic maneuvers.

Future studies that investigate the dynamics of sST2 in addition to natriuretic peptides will be able to determine whether a multi-marker approach is superior to a single-marker approach for identifying long-term events. Indeed, these preliminary data illustrate the potential for using the two markers in combination, with clinical relevance. Similarly, it has recently been reported that the combination of sST2 and NT-proBNP significantly improved risk stratification in patients with ST-elevation myocardial infarction, highlighting the prognostic value of multiple, complementary biomarkers.[18]

Limitations of our study include the relatively small number of patients, although the results are statistically sound in a homogeneous population that represents a subset of patients with severe systolic HF who received optimal treatment and had signs and symptoms of destabilization. Patients were obtained from specialized HF clinics included in heart transplant programs. This may explain the relatively young population with predominantly severe left ventricular systolic dysfunction. Additionally, due to the narrow inclusion criteria results might not be applicable to other clinical settings. Because it was not the purpose of this study to guide therapy using serial measurements of sST2, we do not know whether sST2 levels are useful for this purpose, but sST2 clearly emerged as a risk marker.

CONCLUSIONS

This study demonstrates that serial monitoring of sST2 concentrations (baseline and week 2) provides information for incremental risk stratification of outpatients with destabilized HF. Patients with a greater decrease in sST2 during the two-week measurement period had better outcomes at one year than did patients with smaller change in sST2, independent of NT-proBNP concentration. Future studies in larger, non-selected, patient cohorts will help to elucidate whether this novel biomarker can be used in clinical decision-making, and will evaluate the benefit of new therapies that lower sST2 concentration in high-risk subgroups.

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