Serial Sampling of ST2 Predicts 90-Day Mortality Following Destabilized Heart Failure

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ABSTRACT

Background: To prospectively determine the prognostic utility of serial sampling of the interleukin-1 receptor family member, ST2, for predicting 90-day mortality in patients with heart failure (HF) admitted to a Veteran Affairs Medical Center.

Methods and Results: A total 150 patients hospitalized with acutely destabilized HF were followed at the Veteran Affairs Healthcare System in San Diego, CA. Multiple cardiac-related parameters were measured including ST2, B-type natriuretic peptide (BNP), NT-proBNP, and blood urea nitrogen (BUN). Plasma samples were collected at 6 time points between admission and discharge. Biomarker concentrations were correlated to survival at 90 days. Uni- and multivariate analyses were used to identify prognostic variables. From admission to discharge, percent change in ST2 was strongly predictive of 90-day mortality: those patients whose ST2 values decreased by 15.5% or more during the study period had a 7% chance of death, whereas patients whose ST2 levels failed to decrease by 15.5% in this time interval had a 33% chance of dying.

Conclusions: Percent change in ST2 concentrations during acute HF treatment is predictive of 90-day mortality and was independent of BNP or NT-proBNP levels. ST2 may provide clinicians with an additional tool for guiding treatment in patients with acute destabilized HF. (*J Cardiac Fail 2008;14:732−738*)

Key Words: ST2, B-type natriuretic peptide, Pro-B-type natriuretic peptide, heart failure.

Genomic and proteomic discovery programs have identified many clinically useful gene products, some of which may be measured for prognostic purposes.[1] One gene characterized in this fashion is ST2, which was originally identified in an in vitro model by examining mRNA transcripts upregulated when neonatal rat cardiac myocytes were subjected to mechanical stretch.[2] Subsequently, several investigators have shown that the protein product of the ST2 gene is increased in a number of pathologic conditions, including asthma, myocardial infarction, and heart failure (HF).[3,4] The ST2 gene codes for a transmembrane receptor, originally identified as an interleukin 1−related ''orphan receptor,'' because the natural ligand was unknown. Recently, Schmitz et al demonstrated that interleukin-33 is the natural ligand for the ST2 receptor.[5]

A truncated version of the ST2 receptor is produced by alternative promoter splicing and 3′ processing[6−8] and is subsequently secreted into circulation. This soluble form is detected in the serum of patients early after acute myocardial infarction,[9] and inversely correlates with ejection fraction.[4] It has been postulated that the volume overload engendered by poor cardiac pump function causes stretching of the myocardial fibers,[10] which then serves as a signal for nearby cells and the myocytes themselves to, among other things, upregulate ST2 production.[4] Sanada et al demonstrated that the soluble form of ST2 acts as a decoy receptor to block the interleukin 33−mediated effects on the transmembrane ST2 receptor.[11]

Shimpo et al demonstrated that baseline ST2 concentrations predict 30-day mortality in patients after acute myocardial infarction.[9] In the setting of chronic outpatient HF, Weinberg et al used multivariate analysis to show that change in ST2 levels over a 2-week period predicted outcome that was independent of B-type natriuretic peptide (BNP).[4] In each of these studies, the subjects evaluated did not have acutely destabilized HF. Recent data suggest a role

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for ST2 measurement in the prognosis of acutely destabilized HF,[12] but no studies have been conducted looking at serial ST2 measurements over the treatment course of acute HF. Accordingly, we collected serial blood samples for measurement of ST2 levels in the setting of hospitalized HF patients to determine if changes in concentrations of this biomarker would be useful in predicting 90-day outcomes.

Methods

This prospective study was designed to determine the prognostic utility of serial measurements of ST2 in patients admitted to the San Diego Veterans Affairs Medical Center with a clinical diagnosis of acute decompensated heart failure between July 2002 and December 2005 (the VA Effect of Therapy Study[13]). Patients younger than age 18 or unable to provide informed consent were excluded from participation. After obtaining written informed consent, data were obtained from verbal conversations with the patients and a review of their electronic medical records. Samples were obtained from venipuncture (potassium EDTA), specimens were centrifuged, and plasma was immediately frozen (−70°C). Blood was collected at admission and discharge, as well as up to 4 consecutive days between admission and discharge. After discharge from the hospital, patients were reevaluated through review of their electronic medical records or via telephone conversations to evaluate the primary end point of 90-day mortality. The diagnosis of HF was based on a number of parameters including, but not limited to, BNP, ejection fraction, and pulmonary edema. Patients were subsequently stratified according to the New York Heart Association (NYHA) guidelines, with most patients (92%) falling into Class III or IV.

Of the 200 patients enrolled in the study, 50 patients were excluded from analysis because ST2 was measured at only 1 time point, leaving a final sample of 150 patients. The 50 patients who were excluded were discharged before serial samples could be obtained and thus were not included in the data analysis because this study was designed to evaluate serial sampling of ST2 in a hospital setting.

Concentrations of ST2 were determined using an enzyme-linked immunosorbent assay (Medical & Biological Laboratories Co, Woburn, MA). This assay uses 2 monoclonal antibodies recognizing epitopes on human ST2 for both capture and detection, and has an interassay coefficient of variation of 14%. Samples were stored at −70°C before analysis. Because they were subjected to a single freeze-thaw cycle, it was necessary to validate that ST2 was stable through at least 1 freeze thaw cycle. ST2 stability was established by comparing the ST2 levels in fresh samples with results from samples subjected to 2 freeze-thaw cycles. BNP and NT-proBNP concentrations were measured using the Biosite-Triage assay (Biosite-Triage; San Diego, CA) and the Roche ProBNP assay (Roche Diagnostics; Indianapolis, IN), respectively. Blood urea nitrogen (BUN) levels from admission and discharge samples were measured using the Beckman LX20 autoanalyzer (Beckman Coulter, La Brea, CA).

Echocardiograms were performed by certified sonographers and interpreted by a cardiologist who was blinded to biomarker levels. Left ventricular (LV) systolic and diastolic volumes and ejection fraction were derived from biplane apical views using the modified Simpson's rule algorithm.[14] Patients classified with LV dysfunction had any or all of the following: LV segmental wall motion abnormalities (with or without systolic or diastolic abnormalities), LV systolic dysfunction defined by an ejection fraction <50%, or diastolic dysfunction. Diastolic dysfunction was determined using Doppler measurements of mitral inflow and Doppler tissue imaging of the mitral annulus, as previously described by Redfield et al.[15] Subjects whose measurements were borderline or suggestive of, but not definitive for, diastolic dysfunction were classified as indeterminate.

Statistical Analyses

ST2 values across freeze-thaw cycles were reported as geometric means and evaluated with paired *t*-tests and Pearson's correlation. Continuous variables were represented with medians and interquartile ranges, and graphed over time as geometric means and standard errors. Frequencies of categorical variables were expressed as percentages and compared with Fisher exact tests, with age (>65 years) and ejection fraction (<35%) treated as nominal variables. Receiver operating characteristic (ROC) curve analysis for predicting 90-day mortality was performed for the remaining continuous variables: baseline and percent change (first to last sample) in ST2, BNP, NT-proBNP, and BUN. Potential prognostic cut points for the stronger of baseline or percent change in each of these 4 parameters were identified as the point on the ROC curve nearest the top left corner, and their respective sensitivities and specificities were calculated. Comparisons between ROC curves were made using methods for correlated curves.[16] Fisher exact tests were used to identify significant univariate predictors of mortality. These predictors were then entered in a multivariate logistic regression analysis. Patient characteristics were subjected to reverse stepwise removal, whereas biomarkers were forced into the final multivariate model. Group differences in log-transformed ST2 concentrations at various time points were tested using *t*-tests for independent samples.

Results

Stability of ST2

Variation in ST2 levels between fresh samples and each freeze-thaw cycle was minimal. Geometric means after 0, 1, and 2 freeze thaw cycles were 0.57, 0.58, and 0.54 ng/mL, respectively. The difference between 0 and 1 cycle or between 0 and 2 cycles was not statistically significant ($P = .45$ and $P = .22$, respectively). The correlations between 0 and 1 cycle ($r = 0.998$, $P < .001$) and between 0 and 2 cycles ($r = 0.991$, $P < .001$) were high.

Patient Characteristics, ST2, BNP, and BUN Values

Detailed patient characteristics are shown in Table 1. By the end of the 90-day study period, 126 patients were alive and 24 had died, yielding a mortality rate of 16%. Of the additional 50 subjects not included in the data analysis, 48 were alive and 2 died, yielding a mortality rate of 4% ($P = .032$). The overall 200 patient cohort mortality rate was 13%.

Almost all the study patients were male, with 61% being older than age 65. Seventy-three percent of the patients presented with worsening of previously diagnosed HF, and the spectrum of disease spanned the entire range of severity, with most patients falling in the NYHA Classes III-IV. Using analysis of variance, the underlying etiology of congestive HF had no statistically significant impact on either

Table 1. Patient Characteristics

n	150		
Demographics (%)		Continuous Variables* Median (Interquartile Range)	
Age >65 y	61	First BNP	635 (304–1501)
Gender (% male)	99	Last BNP	399 (174–400)
Race		First ST2	0.177 (0.086–0.344)
White	77	Last ST2	0.103 (0.043–0.219)
Black	15	First BUN	24 (16–41)
Hispanic	6	Last BUN	25 (17–47)
Asian	2	First NT-proBNP	5,878 (2297–11,918)
		Last NT-proBNP	3,580 (1379–10,102)
History (%)			
CHF new	9.3	Cause of CHF (%)	
CHF worse	73.3	Hypertension	15.3
Other diagnosis	17.3	Ischemia	28.7
CHF systolic	72.0	Idiopathic	56.0
CHF diastolic	63.0		
CAD	63.3	Number of patients at each time point	
MI	36.7	1st time point	150
CRI	30.0	Day 2	133
COPD	28.0	Day 3	110
DM	53.3	Day 4	78
HTN	75.3	Day 5	56
Edema	56.0	Last time point	150
Wheezing	28.0		
Murmurs	41.0		
EF >35%	65.8		
NYHA class at admission:			
Class 2	6.0		
Class 3	50.0		
Class 4	42.0		
Not classified	2.0		
NYHA class at discharge:			
Class 2	51.4		
Class 3	31.3		
Class 4	9.3		
Not classified	8.0		

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CHF, congestive heart failure; CAD, coronary artery disease; MI, myocardial infarction; CRI, chronic renal insufficiency; DM, diabetes mellitus; HTN, hypertension; EF, ejection fraction; NYHA, New York Heart Association.
*Interquartile ranges (25%–75%).

baseline or percent change values for ST2, nor any of the other measured biomarkers (data not shown).

The median length of stay was 4 days (interquartile range 3–7), with a mean of 5.77 days (SD 7.44). ST2 values could not be obtained for all patients at all time points, with the greatest deficits being at Days 4 and 5. The majority of patients had their first time point drawn at admission, whereas in 16 patients the Day 2 ST2 level served as their first measured time point, because they did not have ST2 levels measured on admission.

ST2, BNP, NT-proBNP, BUN, and Prognosis

ROC analysis was used to eliminate those continuous variables whose area under the curve (AUC) failed to reach statistical significance. ROC analysis was also used to identify prognostic cut points for those parameters that yielded the strongest and most statistically significant capacity for predicting 90-day mortality, namely changes in ST2, NT-proBNP, and BNP, as well as baseline BUN and NT-proBNP. Baseline BNP and NT-proBNP levels were statistically significant, with AUCs of 0.629 (95% CI 0.513–0.746; $P = .05$) and 0.738 (95% CI 0.635–0.841; $P \leq .001$), respectively, whereas baseline ST2 and change in BUN were not, with respective AUCs of 0.583 (95% CI 0.447–0.718; $P = .201$) and 0.590 (95% CI 0.467–0.714; $P = .162$). The percent change in ST2 had an AUC of 0.783 (95% CI 0.690–0.877; $P \leq .001$), which was identical to baseline BUN concentrations (AUC 0.783 [95% CI 0.690–0.877; $P \leq .001$]), and almost identical to percent change in NT-proBNP (AUC 0.781 [95% CI: 0.665–0.897; $P \leq .001$]), whereas the percent change in BNP had an AUC of 0.671 (95% CI 0.555–0.787; $P = .008$). ROC curves for the 4 strongest predictors are shown in Fig. 1. Of the 4 strongest predictors, the only notable statistical difference was that NT-proBNP had a significantly higher AUC as compared with BNP ($P = .011$).

The optimal cut point for percent change in ST2 corresponded to a 15.5% decrease in ST2 levels (sensitivity 70%, specificity 73%). Those patients whose ST2 values decreased by 15.5% or more during the study period had a 7% chance of death, whereas those whose ST2 levels failed to decrease by at least 15.5% in this interval had a 33% chance of dying. Patients who died during the 90-day follow-up period tended to have increasing concentrations of ST2 while they were in the hospital, whereas those who survived during follow-up tended to have decreasing ST2 concentrations (Fig. 2). Thus these groups did not differ in ST2 concentrations at baseline ($P = .22$), but ST2 concentrations were elevated in subsequent observations

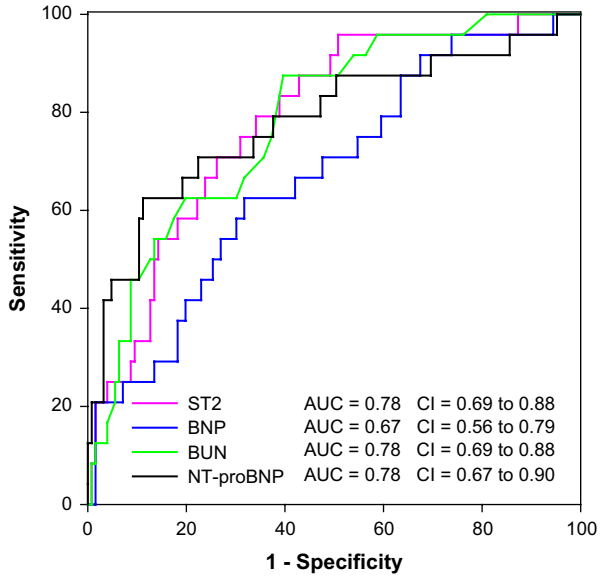

Fig. 1. Receiver operator characteristic curves for predicting 90-day mortality. Blood urea nitrogen (BUN) is plotted from baseline values, whereas ST2, B-type natriuretic peptide (BNP), and NT-proBNP are plotted as the percent change from first to last sample.

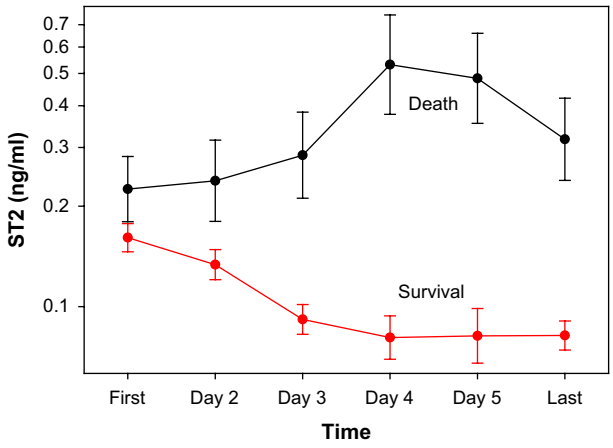

Fig. 2. Plot of ST2 concentrations (geometric means and standard errors) at serial time points in patients who survived as compared with those who died within 90 days. The groups did not differ in ST2 concentrations at baseline ($P = .22$), but were elevated in subsequent observations for those who died within 90 days by Day 2 ($P = .03$) and thereafter ($P < .001$ for each).

for those who died within 90 days by Day 2 ($P = .03$) and thereafter ($P < .001$ for each). Figure 2 shows data on all patients including those without 5 observations. This figure is similar to what is observed if only patients with complete data through 3, 4, or 5 days are evaluated which all show significant group by time interactions ($P < .001$ for all, data not shown).

The optimal cut point for percent change in BNP was a decrease of 10% (sensitivity 63%, specificity 67%). If the BNP concentration decreased by 10% or more, there was a 10% chance of death, whereas if it did not there was a 27% chance of dying. The optimal cut point for percent change in NT-proBNP corresponded to a decrease of 3% (sensitivity 71%, specificity 23%). If the NT-proBNP concentration decreased by 3% or more, there was a 7% chance of death, whereas failing to do so incurred a 38% chance of dying.

Finally, 2 possible cut points can be noted for BUN in Fig. 1. One represents a value of 26 mg/dL, the other a value of 40 mg/dL. Because a BUN of 26 mg/dL (sensitivity 88%, specificity 60%) is close to the high end of the normal range, the higher cut point corresponding to a BUN of 40 mg/dL (sensitivity 63%, specificity 80%) was selected for further analysis. Patients who did not achieve a reduction in their BUN levels ≤40 mg/dL had a 38% chance of dying, whereas those who did had a 92% chance of survival.

Univariate analyses were performed on potential prognostic variables. As shown in Table 2, percent change in ST2 and BNP were both significant ($P < .001$ and $P = .01$, respectively). Other significant predictors included age >65 years, baseline BUN >40 mg/dL, decrease in NT-proBNP of <3%, wheezing, murmurs, history of coronary artery disease and of myocardial infarction. In the multivariate analysis, the only parameters to reach statistical significance (Table 3) were decrease in ST2 < 15.5% ($P = .007$), BUN >40 mg/dL ($P = .042$), and decrease in NT-proBNP of <3% ($P = .030$). As shown in Fig. 3,

Table 2. Univariate Analysis of Predictors of Death

	Variable Present	Variable Absent	
Predictor Variable	% Mortality	% Mortality	*P* Value
Age >65 y	21.7	6.9	.021
Decrease ST2 < 15.5%	33.3	7.1	<.001
Decrease BNP <10.0%	26.8	9.6	.010
BUN >40 mg/dL	37.5	8.2	<.001
Decrease NT-proBNP <3%	37.8	6.7	<.001
EF <35%	22.5	11.7	.124
Male gender	16.2	0	1.000
Exam S3	10.5	16.2	.739
Rales	17.6	10.6	.335
Wheezing	32.1	11.6	.016
Murmurs	26.8	11.1	.023
Edema	16.7	10.3	.569
Ascites	12.5	15.6	1.000
CAD	21.1	7.3	.036
MI	25.5	10.6	.022
Hypertension	15.9	16.7	1.000
Atrial fibrillation	15.7	16.2	1.000
Diabetes	18.8	12.9	.377
Chronic renal insufficiency	24.4	12.4	.088
COPD	21.4	13.9	.321
Obesity	9.3	18.7	.219
CHF systolic	16.7	15.1	1.000
CHF diastolic	17.5	14.5	.808

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CHF, congestive heart failure; CAD, coronary artery disease; MI, myocardial infarction; HTN, hypertension; COPD, chronic obstruction pulmonary disease.

a combination of these 3 variables had an additive effect on predicting mortality: of patients who had a combination of BUN ≤40 mg/dL, an ST2 decrease of ≥15.5%, and an NT-proBNP decrease of ≤3%, 1.6% of them died, whereas of patients who had a BUN >40 and did not attain either a decrease in ST2 of at least 15.5% or a decrease in NT-proBNP of at least 3%, 72.7% of them died. Using logistic regression, none of the interactions among the categories of ST2, NT-proBNP, and BUN was statistically significant (all $P > .7$), indicating that these effects are additive and not synergistic.

Nonparametric analysis of the relationship between these 4 variables revealed a weak but significant correlation between % change ST2 and % change BNP ($r = 0.409$, $P < .001$), % change NTproBNP ($r = 0.491$, $P < .001$), and baseline BUN, although the strongest association was between % change BNP and % change NTproBNP ($r = 0.724$, $P < .001$), and between baseline BNP and baseline NTproBNP ($r = 0.780$, $P < .001$).

Discussion

This study was designed to evaluate a novel cardiac biomarker, ST2, as a potential predictor of mortality at 90 days in patients with acutely decompensated HF, requiring hospitalization. In 2002, Weinberg et al demonstrated that soluble ST2 mRNA transcription could be induced in neonatal rat cardiac myocytes subjected to mechanical strain, or given Il-1β or phorbol ester.[4] They also found increased

Table 3. Multivariate Analysis of Predictors of Death

		95% CI for OR		
	Odds Ratio	Lower	Upper	*P* Value
Decrease ST2 < 15.5%	4.54	1.55	13.33	.006
Decrease BNP <10%	1.15	0.36	3.63	.817
Decrease NT-proBNP <3%	0.19	0.06	0.61	.005
BUN >40	5.04	1.76	14.41	.001

CI, confidence interval; OR, odds ratio; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen.

levels of soluble ST2 in the serum of mice after experimental myocardial infarction, and in the serum of human patients 1 day after myocardial infarction.[4] Because interleukin-1 is one of the cytokines activated during the stress response associated with acute myocardial infarction,[2,17,18] these findings strengthen the notion that ST2 serves in modulating the immune response and mediates subsequent repair mechanisms. Although the primary source for ST2 production has not yet been uncovered, soluble ST2 protein has been shown to be secreted by cardiac myocytes when the cells are subjected to biomechanical overload.[9] It has also been postulated that the ST2 protein originates from multiple sources in response to the local inflammatory microenvironment generated by cell injury.[9]

Although the significance of these previous studies in relation to the pathophysiology of heart failure has yet to be established, it is plausible that the impaired regulation of these immune events might represent a precursor to the development of cardiac fibrosis, and thus subsequent progression of left ventricular dysfunction. In support of this, pro-inflammatory cytokines have previously been shown to participate in the development and progression of HF.[19,20]

Our results confirmed the hypothesis that increased ST2 expression was indeed predictive of mortality, whereas a decrease in ST2 expression was even more predictive of survival. Although the change in ST2 appeared to show a stronger relationship with outcome than either baseline or change in natriuretic peptides, we wanted to compare it with another known prognostic indicator of HF, renal function in the form of BUN. Because of inadequate cardiac output, patients with HF often develop prerenal azotemia, and may exhibit BUN to creatinine ratios in excess of 20:1.[21] As such, elevations in BUN could plausibly be used as a corollary of worsening HF, and might be predictive of subsequent mortality, whereas creatinine levels would not follow such a trend. Furthermore, because BUN was one of only two other variables in our study aside from change in ST2 to reach statistical significance in both univariate and multivariate analyses, this made it an attractive choice for such comparisons.[22] Although baseline BUN predicted 90-day mortality, it did not provide a means to monitor therapy as changes in BUN were not predictive. Clearly there is a need for biomarkers whose change during therapy predicts outcome.

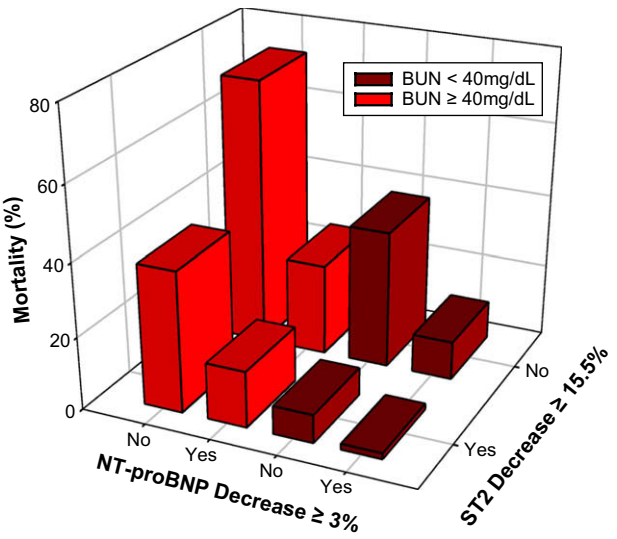

Fig. 3. Combined effect of blood urea nitrogen (BUN) ≥40, decrease in NT-proBNP ≤3%, and decrease in ST2 ≤ 15 on predicting mortality.

ROC analysis demonstrated that the % change in ST2 was equivalent to % change in NT-proBNP and that both of these biomarkers were better at predicting 90-day mortality than % change in BNP. In multivariate analysis, there was additive predictive power when % change in ST2, % change in NT-proBNP, and baseline BUN were analyzed together. These findings agree with Weinberg et al's conclusions from the Prospective Randomized Amlodipine Survival Evaluation (PRAISE)-2 trial, which showed that change in ST2 levels, but not the baseline ST2, was predictive of 30-day mortality in patients with chronic NYHA Class III-IV HF.[4] Our results confirmed that serial BNP measurements did not yield any independently prognostic information in the context of ST2 and other independent variables, although serial NT-proBNP measurements did.

Finally, the cut points we obtained for serial % changes in ST2 and NT-proBNP should be interpreted in the context of both analytic and biologic variability of the respective assays.[23] In the case of the ST2 assay, the interassay coefficient of variation in our study was 14%, so a decrease in ST2 of at least 15.5% could be regarded as clinically significant, even in light of such high interassay variability. With improved analytical performance, the predictive value of the ST2 assay would likely increase. The clinical utility of serial measurements of ST-2 would also depend on the biologic variability of this marker, which is currently unknown. For NT-proBNP, the interassay coefficient of variation was approximately 3%, which is the same as the cut point we obtained from ROC analysis for a changing value predicting 90-day mortality. From our clinical experience, we know that the biologic variability of NT-proBNP measurements within an individual is much greater than 3%, and that reference change values, the amount of change needed to indicate a pathologic event, may be as high as 23%.[24] As such, it is difficult to ascertain whether a decrease in NT-proBNP of 3% is truly clinically significant or if this relatively small change merely reflects adequate

therapy and a definitive downturn in NT-proBNP values; indeed, prior data suggest that a more plausible in-hospital NT-proBNP change might be 30% or more.[25]

Current guidelines for the treatment of HF are largely based on subjective clinical criteria, such as cardiac stress testing, echocardiography, and ultimately NYHA class. The need for more objective parameters is underscored by the vast body of research into cardiac biomarkers, and their potential use in this context.[26] The use of both BNP and NT-proBNP concentrations in guiding the treatment of HF in the outpatient setting has been investigated, and 2 studies show significantly improved outcomes when compared with the use of standard treatment protocols.[20,27] However, no prospective studies have been conducted looking at the use of biomarker-guided therapy in the inpatient setting. Our results suggest that serial ST2 measurements in this context may help to stratify patients according to their predicted mortality and further assist in guiding treatment. In addition, understanding the pathophysiology of elevations of ST2 in the context of acute decompensated HF may uncover novel approaches to treatment.

Limitations

The present study is hindered by a few unavoidable limitations. The number of patients in the study population was relatively small and consisted of subjects from a single VA Medical Center with a predominantly male patient base. This population also had a high incidence of cardiac disease with other significant comorbidities. Because of this, the results presented may not be applicable to other community settings. Because therapy was not guided by serial measurements of ST2 or NT-proBNP, we do not know if these biomarkers are useful for this purpose.

Assessment for 90-day outcome was largely performed on the electronic medical record, making it possible that certain events might not have been included in our analysis. However, the number of such missing events is likely to be negligible, because all study participants had primary care physicians within the VA Medical Center system, and most study subjects obtained their care solely through a single center. It is important to note that all of the events recorded from telephone follow-up were also contained in the electronic medical record.

Conclusions

In conclusion, serial measurements of a novel heart failure biomarker, ST2, added independent prognostic information among a population of patients undergoing therapy for destabilized HF. Whether used alone or together with NT-proBNP and/or BUN, ST2 was strikingly prognostic, with those subjects demonstrating a rise in ST2 during HF therapy suffering the worst short-term outcomes, independent of natriuretic peptide concentrations. The role of ST2, an emerging biomarker bridging the inflammatory and neurohormonal systems, appears promising in predicting outcomes in patients with destabilized HF, and may assist in clinical decision-making.

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