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ST2 in Heart Failure: Where Does This New Marker Fit in?

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Abstract A member of the interleukin-1 receptor family, soluble ST2 (sST2), is a powerful marker of myocyte strain and vascular stress in heart failure and acute coronary syndrome, as well as numerous other cardio-pulmonary disease states. It is clinically useful in both the emergency department and hospital setting for predicting disease prognosis and mortality. Together with patient-specific characteristics, sST2 also has an increasing role to play as a tool to guide therapeutic interventions. We will discuss where this important new biomarker fits in now and its promise for the future.

Keywords Biomarkers · Heart failure · Soluble ST2 · Emergency department · Hospital medicine

Introduction

Cardiac biomarkers have added considerably to the evaluation and management of patients in the emergency department (ED) setting. Across several diagnoses, including acutely decompensated heart failure (ADHF) and acute coronary syndromes (ACS, including unstable angina pectoris [UAP] and acute myocardial infarction [MI]), biomarkers such as the natriuretic peptides and troponins may considerably augment clinical acumen; biomarkers may assist not only in identifying correct diagnosis but may be also useful for assessing severity of disease, and thus prognosis. Prognostication using biomarkers may be helpful to the ED physician for not only deciding on triage in this setting, but also may assist in identifying specific treatment opportunities for the hospital-based physician.

Beyond B-type natriuretic peptide (BNP), its amino-terminal pro-peptide equivalent (NT-proBNP) and the troponins, several other biomarkers have been evaluated for use in patients with ADHF and ACS. Notably, a substantial growth in the understanding of the interleukin (IL)-1 receptor family member ST2 points to its considerable value for risk stratification in cardiovascular diseases relevant to the ED and hospital specialist. In recognition, recent clinical practice guidelines for HF have given a Class IIb (level of evidence A) level of support for the measurement of cardiac biomarkers for additional risk stratification in patients with acute HF [1], a recommendation certain to strengthen as the understanding of ST2 is evolving rapidly.

This review will focus on studies describing measurement of the soluble form of ST2 (sST2) in ED and hospital-based patients, and specifically will discuss potential role(s) of this novel biomarker.

sST2 Biology

As noted, ST2 is a protein whose sequence best aligns with the IL-1 receptor family. ST2 was originally described as playing an important role in allergic and immunologic diseases, as it plays an important role in T-helper cell Type 2-mediated tolerance. Additionally, ST2 appears to play a role in atherogenesis; both ST2 and its subsequently described ligand, IL-33, are found in endothelial cells, and in atherosclerosis-prone animals, abnormalities in the ST2/IL-33 system led to

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accelerated atherosclerosis [2]. Clinically, regulation of the *ST2* gene is linked to severity of coronary atherosclerosis [3], while elevated concentrations of sST2 have been described to predict onset of systolic hypertension, linked to arterial stiffness, which is related, in part, to atherosclerosis [4].

The link between ST2 and vascular disease is important; however, a role in myocardial disease was subsequently described that is of substantial importance. In seminal work by the lab of Richard Lee, substantial transcription of the *ST2* gene was described following mechanical strain in cardiac myocytes [5]. Subsequently, a pivotal role for ST2 in myocardial remodeling and fibrosis has been elucidated.

The interaction between ST2 and IL-33 is now recognized as an important component of the process of cardiac fibrosis and hypertrophy. In vitro studies have shown IL-33, released by endothelial cells and fibroblasts in response to stretch, to be an important ligand for its receptor ST2 [6, 7]. ST2 exists in at least two forms: the membrane-bound ST2 ligand (ST2L) and the circulating, soluble form, sST2; given the identical structure, sST2 binds IL-33 as well as ST2L, and is thus thought to be a 'decoy' receptor, an endogenous 'off switch.' Biologically, the interaction between IL-33 and ST2L is that of a favorable, anti-fibrotic system. Indeed, ST2-knockout mice have greater degrees of myocyte hypertrophy and myocardial fibrosis than wild-type mice, due to an inability of IL-33 to bind ST2L. Conversely, administration of high concentrations of IL-33 decreased the degree of myocyte hypertrophy and fibrosis in wild-type mice but did not attenuate the hypertrophic phenotype in ST2-deficient mice. In fact, ST2-deficient mice, regardless of the presence of IL-33, developed dilated and hypertrophied left ventricles, reduced ejection fraction, and increased mortality, suggesting an important role for ST2/IL-33 signaling in adverse cardiac remodeling [8]. Additional studies in rat myocytes have elucidated a mechanism whereby intact ST2 attenuates the anti-apoptotic effects of IL-33, thereby helping to mediate states of myocardial stress [9]. Supporting its role as a decoy receptor to compete for IL-33, experimental administration of high concentrations of sST2 in laboratory animals mimics the appearance of an ST2L-deficient state, with comparable myocardial hypertrophy, fibrosis, remodeling, and higher risk for death.

Thus, the ST2 system plays a pivotal role in both vascular and myocardial disease, which likely explains the powerful prognostic links between abnormalities in ST2 and outcomes in HF and ACS.

Measurement of sST2

Several enzyme-linked immunosorbent assays (ELISAs) for the measurement of sST2 exist. Most suffer from low sensitivity and poor precision and are to be considered as research use only; data regarding such research ELISAs should thus be regarded with caution. Only one method for sST2 measurement has received regulatory approval for clinical use in the United States, Europe, and Asia with an upper reference limit of 35 ng/mL as abnormal, a value associated with risk in a number of studies. Due to its high sensitivity, the assay can detect concentrations of sST2 in 100 % of normal subjects [10]. A near-patient method for measuring sST2 based on this FDA-approved ELISA is on the near horizon, as are automated methods for its assessment.

When measured in normal patients, values for sST2 are generally higher in men, increase with age, are associated with prevalent diabetes and hypertension, and also predict incident hypertension. Intriguingly, despite biological links with allergic and immunologic disorders, including reactive airways disease, sST2 values in normal subjects are not associated with prevalent asthma [10]. Unlike natriuretic peptides, sST2 values are not significantly affected by body mass index or renal insufficiency; additionally, the biological variability of sST2 is considerably lower than that of the natriuretic peptides, troponin, or galectin-3, which suggests that sST2 may be useful for longitudinal monitoring of patients with serial measurement [11].

sST2 in ADHF

sST2 elevation carries important prognostic implications for patients with HF. First described in patients with severe, chronic HF, Weinberg et al. found sST2 to be correlated with baseline BNP levels and predictive of subsequent mortality or transplantation, independent of proatrial natriuretic peptide (proANP) [12]. Studies in ADHF soon followed. In the seminal ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study of ED patients with dyspnea due to both ADHF and non-cardiac causes, Januzzi et al. demonstrated important findings regarding sST2: they found graded relationship between sST2 concentration and likelihood of ADHF diagnosis [13]; NT-proBNP was a stronger predictor for the presence of ADHF, while sST2 concentrations (measured with a research use only ELISA) were linear with ADHF symptoms, suggesting a link between sST2 and HF severity. Indeed, among all the clinical and biomarker data available in the PRIDE study database, sST2 concentrations $\geq$0.20 ng/mL were among the strongest predictor of death at 1-year follow-up in both ADHF patients (hazard ratio [HR] 9.3, 95 % CI 1.3–17.8; $P = 0.03$) and all patients as a whole (HR 5.6, 95 % confidence interval [CI] 2.2–14.2; $P < 0.001$). Interestingly, sST2 was independently prognostic to NT-proBNP: thus low values for both

markers were associated with the best prognoses, while elevation of both markers was conversely associated with the highest mortality rates at 1 year. Those with low NT-proBNP values but elevated sST2 concentrations had intermediate risk, suggesting the utility of a multi-marker approach for prognostication [13].

In a subsequent analysis, Shah and colleagues [14] described the echocardiographic phenotype of patients with elevated sST2 concentrations. Among patients from the PRIDE study undergoing echocardiography following admission, higher sST2 concentrations were independently associated with a broad range of cardiac structural and functional abnormalities and clinical findings all consistent with a more decompensated HF phenotype, prevalent systolic and diastolic abnormalities, and more predispositions to ventricular remodeling (Table 1).

Patient-specific characteristics in patients with acute HF have also been linked to sST2 concentrations. In 2008, Rehman and colleagues examined sST2 values in a multicenter analysis of 346 subjects with ADHF, reporting sST2 values correlated with severity of HF symptoms, left ventricular (LV) ejection fraction ($r = -0.134$), creatinine clearance ($r = -0.224$), BNP ($r = 0.293$), NT-proBNP ($r = 0.413$), and C-reactive protein ($r = 0.429$), all at levels of statistical significance.

Importantly, in the study by Rehman and colleagues, in contrast to the natriuretic peptides, ST2 was not significantly correlated with age, hemoglobin, or BMI, and had no association with gender, prior episodes of HF, or the presence of atrial fibrillation. Moreover, there was no difference in sST2 concentrations among patients with HF due to ischemic etiologies versus non-ischemic etiologies, and the biomarker was equally predictive among patients with reduced and preserved ejection fraction (EF) [15]. This latter finding is of considerable importance, given the rise of HF with preserved EF (HFpEF) relative to that with reduced EF (HFrEF); in some analyses, HFpEF accounts for 50 % of hospitalized patients with HF, and as such, an understanding of how to risk stratify this important diagnosis is important. In this regard, Manzano-Fernandez et al. reported that sST2 concentrations were prognostic for death in both HFpEF (HR 1.41 per ng/mL, 95 % CI 1.14–1.76; $P = 0.002$) and HFrEF (HR 1.20, 95 % CI 1.10–1.32, $P < 0.001$) [16]. In subjects with both HFpEF and HFrEF, sST2 concentrations improved clinical risk prediction compared to NT-proBNP, as assessed by both improved C-statistic and an improvement in net reclassification index and integrated discrimination improvement analyses; notably, in those with HFpEF, sST2 was actually more prognostic than NT-proBNP for predicting death, knocking the natriuretic peptide out of the survival model entirely.

Beyond its favorable comparison to the natriuretic peptides, in a large comparative study of multiple established or emerging biomarkers, sST2 results provided the largest degree of reclassification (net reclassification improvement [NRI] = 10.3 %) beyond clinical variables for prognosticating death [17••]. This superiority notwithstanding, sST2 concentrations show considerable additive value, as this biomarker appears to provide 'orthogonal' information to many other biomarkers. As an example, Pascual-Figal and colleagues showed that the combination of NT-proBNP, highly sensitive troponin T (hsTnT), and sST2 provided incremental prognostic information for death in patients with ADHF, with each biomarker adding considerably to models of discrimination, calibration, and reclassification (see Fig. 1) [18••]. In this model, a HR of 2.64 ($P < 0.001$) was seen with each biomarker above its prognostic threshold.

Table 1 Predictors of sST2 in dyspneic patients from the PRIDE study [13]

Covariate	*T*	*P* value
NT-proBNP	3.31	0.009
RV systolic pressure	2.29	0.002
Transmitral E to tissue Doppler Ea ratio	−2.13	0.03
Tissue Doppler A wave peak velocity	2.11	0.05
LV ejection fraction	2.15	0.05
LV end-diastolic dimension	2.98	0.005
LV end-systolic dimension	2.57	0.01
Heart rate	2.59	0.01
Jugular venous distension	2.00	0.05

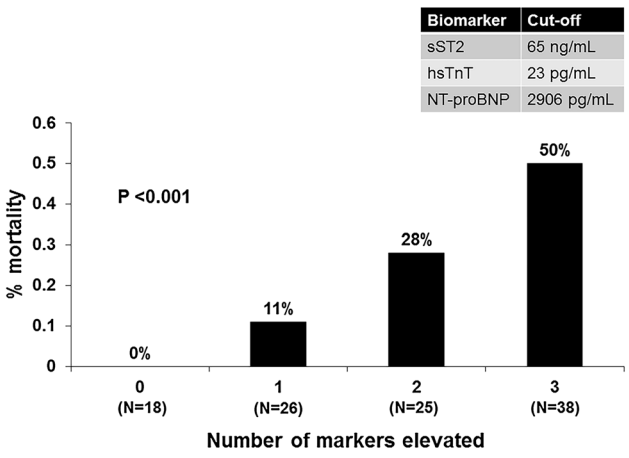

Fig. 1 Incorporation of sST2 together with hsTnT and NT-proBNP in a multi-marker strategy for risk prediction in ADHF. With each biomarker elevated, the risk for death approximately tripled. Data from [18••]

sST2 in ACS

Beyond those with ADHF, sST2 measurement provides prognostic value in patients with ACS. In a study of acute MI patients, sST2 levels rose during the first day after infarction and were maximally elevated at 12 h [19]; studies of later measurement of sST2 in ACS have shown that delayed measurement provides less robust prognostic information, informing the importance of early measurement in ischemic syndromes [20].

In an early study of ACS, baseline sST2 concentrations predicted death ($P = 0.0001$) or development of new HF ($P = 0.009$), and stratification of patients by ST2 quartiles showed a significant, graded association with death ($P = 0.001$) and the combined outcome of death and HF ($P = 0.001$) at 1-month follow-up [19]. Subsequently, in the Thrombolysis in Myocardial Infarction (TIMI)-28 trial, baseline sST2 performed well as a predictor of increased risk of cardiovascular death or subsequent HF in patients with acute ST-elevation MI, and was independent of NT-proBNP and related clinical factors, including age, hypertension, prior MI, and prior HF. After adjustment for NT-proBNP levels, ST2 levels above the median were associated with greater risk of heart failure or cardiovascular death (third quartile: OR 1.42; 95 % CI 0.68–3.57; fourth quartile: OR 3.57; 95 % CI 1.87–6.81; $P < 0.0001$ for trend), again highlighting the role of multiple, complementary biomarkers in risk-prediction modeling [21].

In the TIMI-36 trial of patients with non-ST segment elevation ACS, an sST2 concentration above 35 ng/mL was associated with risk for death/HF by 30 days (6.6 vs 1.6 %; $P < 0.001$) and 1 year (12.2 vs 5.2 %; $P < 0.001$). After adjusting for covariates, the risk for death/HF by 30 days and 1 year remained significant (HR 1.90 and 1.51, respectively; both $P < 0.05$). At both time points, baseline sST2 values added significant reclassification to a robust clinical and biomarker model [22].

Mechanistically, much as in HF, sST2 appears to predict post-infarction myocardial remodeling. In an animal model, Lax and colleagues showed that sST2 plays a pivotal role in tissue remodeling and left ventricular dysfunction after acute MI [23]; this phenotype curiously could be rescued with administration of IL-33 or treatment with mineralocorticoid receptor antagonists [24]. These data were recapitulated in a clinical study of acute MI patients, where sST2 concentrations were measured at baseline, 12, and 24 weeks after infarction. sST2 concentrations correlated significantly with LV ejection fraction at baseline ($r = -0.3$) and 24 weeks ($r = -0.23$) as well as infarct volume index at baseline ($r = 0.26$) and 24 weeks ($r = 0.22$), all at statistically significant levels. Through serial measurements, the investigators also showed that change in sST2 over time correlated with change in LV end-diastolic volume index ($r = -0.24$). Higher sST2 concentrations were associated with greater microvascular obstruction at the time of acute MI, as well as greater degree of transmural infarction (both of which are risk factors for remodeling), which supports the suggestion that elevated sST2 reflects a heightened risk for LV remodeling and plays an important role in infarct and ventricular remodeling post-MI [25]. Indeed, in this study, administration of mineralocorticoid receptor antagonist therapy in the form of eplerenone reduced LV remodeling exclusively in those with an elevated sST2 at baseline, supporting this concept.

Beyond ADHF and ACS in the ED Setting

While powerfully prognostic in cardiovascular disease states, sST2 has been described as being highly prognostic in a wide range of non-cardiovascular diseases [26•], including malignancy, trauma, and sepsis [27, 28]. Elevated soluble levels of ST2 have also been linked to various forms of pulmonary disease and airway inflammation [29, 30], including acute asthma exacerbation [31], eosinophilic pneumonia [32], and idiopathic pulmonary fibrosis [33], and sST2 is strongly prognostic in acute respiratory distress syndrome as well [34]; in cases where outcomes were available, sST2 concentrations were routinely linked to outcomes in each state. This suggests broad applicability for the ED specialist to judge risk across a wide range of diagnoses.

sST2 for In-hospital Monitoring and Therapy Decision-Making

As noted, baseline concentrations of sST2 at presentation are very strongly associated with increased mortality and risk for complications from HF, allowing for more refined risk stratification either alone or in conjunction with other biomarkers such as NT-proBNP. Emerging data suggest that serial monitoring of sST2 concentrations during in-hospital treatment may afford even greater information regarding risk.

Boisot and colleagues first reported the value of serial sST2 sampling in a VA-based population. In this analysis, sST2 levels collected serially at six time points between hospital admission and discharge and were correlated with 90-day mortality, and percent change in sST2 level predicted 90-day mortality. In particular, those whose ST2 values decreased by 15.5 % or more over the course of hospitalization had a lower mortality (7 % chance of death)

than the mortality of those whose ST2 values failed to decrease by 15.5 % (33 % chance of death) [35]. Concentrations of sST2 were more prognostic than BNP in this analysis.

Subsequently, in a small trial of hospitalized advanced stage ADHF patients, an sST2 value above 104 ng/mL during the first 48 h of admission to an intensive care unit strongly predicted risk for death, heart transplantation, or mechanical circulatory support (HR 5.53; $P < 0.001$), and was superior to NT-proBNP, galectin-3, or hsTnI [36]. In less severely ill subjects with ADHF, Manzano-Fernandez et al. reported experience from a single center trial in Spain. In this analysis of 72 hospitalized subjects, the median concentration of sST2 at presentation was 62 ng/mL, which decreased to 44 ng/mL by day 4 of hospitalization; both concentrations at presentation, as well as on day 4, were independent predictors of mortality, such that those with sST2 values at baseline and/or day 4 below 76 ng/mL (baseline) or 46 ng/mL (day 4) had lower risks for death [37]. Similarly, Breidthardt and colleagues reported dynamic change in sST2 value from admission to discharge was a stronger predictor of mortality than baseline values alone in 207 patients with ADHF. These findings all point towards the value of serial measurement of sST2, rather than relying on baseline assessment only.

Curiously, in the study by Breidthardt and colleagues, treatment with beta-adrenergic blockers appeared to attenuate the risk for mortality predicted by an elevated sST2 [38•]. These findings are reminiscent of those described previously by Gaggin and colleagues, who described the heightened value of beta-adrenergic blockers in those with elevated sST2 concentrations in chronic ambulatory HF [39•]. Recently, data suggested that elevated sST2 may also predict specific benefit from mineralocorticoid receptor antagonist therapy in those recently discharged for ADHF [40]. Taken together these data suggest that sST2 monitoring may not only predict risk but also may assist in therapy decision-making for the hospital-based physician.

Conclusion

It has been just over a decade since sST2 was "found in translation" [41] as a candidate cardiac biomarker, and in the period that has followed, sST2 has been shown to be among the most powerful biomarkers for predicting adverse outcome not only in those with ADHF but also chronic HF syndromes, ACS, and numerous other cardiopulmonary and critical care disorders. sST2 measurement has support in clinical practice guidelines, and a near-patient method for its measurement is on the near horizon, as are automated methods for its assessment.

Practically speaking, an sST2 should be measured as early as possible at the time of first evaluation for suspected ADHF or ACS; following treatment, a post-therapy value should be re-assessed; both the presenting sST2 value as well as serially measured concentrations provide important prognostic information, and may also afford useful information to guide therapy.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Mallick declares they have no disclosures to declare. Dr. Januzzi is supported in part by the Desanctis Clinical Scholar Endowment and the Hutter Family Chair in Medicine.

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by the author.

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highest event rate and an odds ratio of 6.77 ($P < 0.001$) compared with the lowest risk group. Beta-blocker therapy exerted a dose-related benefit across all groups, and sST2 measurement identified patients with HFrEF who may benefit most from higher BB doses.

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