Mini Review

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Clinical relevance of sST2 in cardiac diseases

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Abstract: ST2 has two main isoforms, ST2L and soluble isoform of ST2 (sST2), by alternative splicing. The interaction between interleukin (IL)-33 and the transmembrane isoform ST2L is up-regulated in response to myocardial stress and exerts cardio-protective actions in the myocardium by reducing fibrosis, hypertrophy and enhancing survival. The circulating isoform sST2, by sequestering IL-33, abrogates these favorable actions and will be elevated as a maladaptive response to cardiac diseases. Indeed, circulating sST2 concentrations correlate with a worse phenotype of disease including adverse remodeling and fibrosis, cardiac dysfunction, impaired hemodynamics and higher risk of progression. In patients with acute and chronic heart failure, sST2 concentrations are strongly predictive of death, regardless of the cause and left ventricle (LV) ejection fraction, and contribute relevant information in addition to other prognosticators and biomarkers, as natriuretic peptides or troponins. sST2 also retains prognostic information in the setting of acute myocardial infarction (AMI) and predicts cardiovascular death and risk of heart failure (HF) development in these patients. sST2 could also be a promising tool to stratify the risk of sudden cardiac death (SCD) in patients with depressed LV ejection fraction. Therefore, sST2 represents a clinically relevant biomarker reflecting pathophysiological processes and contributing predictive information in the setting of several cardiovascular diseases, and especially in patients with HF.

Keywords: biomarkers; coronary disease; heart failure; ST2.

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Introduction

ST2 is a member of the interleukin-1 receptor family, formally known as interleukin 1 receptor like 1 (IL1RL-1). There are two main isoforms: a transmembrane receptor (ST2L) and a truncated soluble receptor that is detected circulating in serum soluble isoform of ST2 (sST2) [1]. Currently, ST2 represents a clinical relevant biomarker as experimental research has suggested a pathophysiological role in cardiac diseases and studies conducted in different populations have found a relevant prognostic value for ST2.

IL-33/ST2L is a cardio-protective system but sST2 abrogates this favorable effect

In 2005, Schmitz et al. identified interleukin-33 (IL-33) as the ligand of ST2 [2]. IL-33 is an IL-1-like cytokine that can be secreted by most cells in response to damage [3]. Experimental research conducted in cardiac cells subjected to biomechanical strain, as well as animal models of myocardial infarction (MI) and pressure overload, have demonstrated that the IL-33/ST2L system is upregulated in response to myocardial stress [3–5]. This upregulation appears to be a defensive response, as the interaction between IL-33 and ST2L has been demonstrated to be cardio-protective (Figure 1). Indeed, IL-33 reduced myocardial hypertrophy, fibrosis, expression of natriuretic peptides, ventricular dysfunction and premature mortality in mice subjected to overt pressure overload of ventricles by aortic banding [4]. In a rat model of MI-reperfusion injury, IL-33

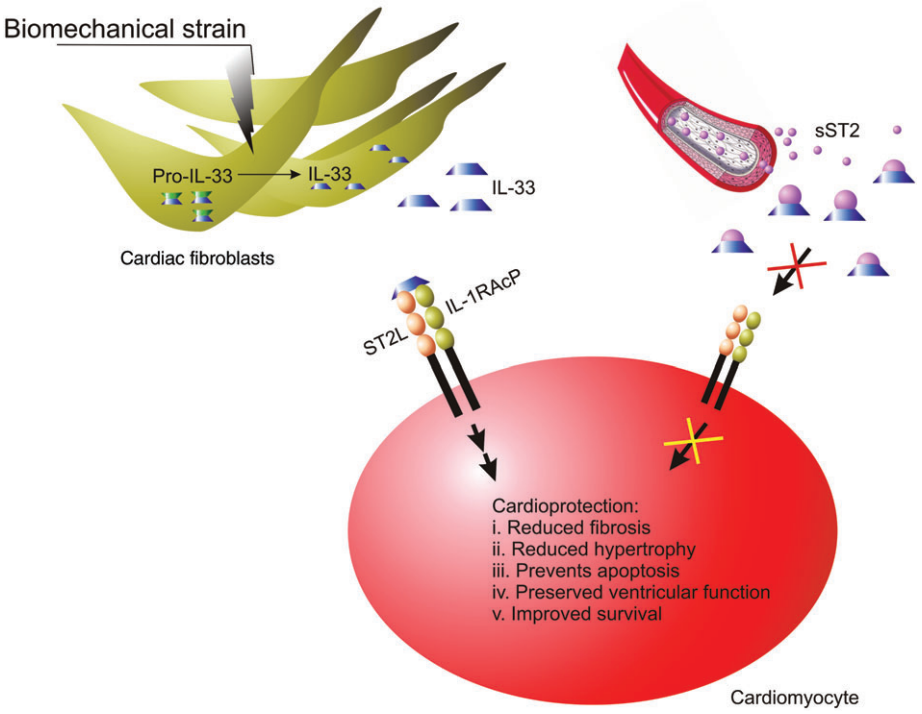

Figure 1: IL-33/ST2 system in the cardiac response to biomechanical strain.
The IL-33/ST2 system is a recently described cardiac fibroblast-myocyte signaling system. This signaling pathway serves an antihypertrophic and cardio-protective mechanism in the face of biomechanical overload. IL-33 is produced by mechanically loaded cardiac fibroblasts. IL-33 binds to its receptor complex composed of ST2L and the IL-1 receptor accessory protein (IL-1RAcP). The interaction of IL-33 with ST2L leads to cardio-protection. The binding of IL-33 to its receptor, could be abrogated by the decoy and circulating receptor sST2. In the extracellular environment, sST2 might bind free IL-33, thereby effectively decreasing the concentration of IL-33 that is available for ST2L binding and reducing the cardio-protective effect of IL-33.

treatment reduced infarct size, fibrosis and apoptosis, as well as improved ventricular dilation, contractile function and survival [6]. These beneficial effects of IL-33 are specifically mediated through the ST2L receptor, as blocking the ST2L receptor eliminated the cardio-protective effects of IL-33 [4, 6].

The circulating isoform, sST2, is able to bind with high affinity to IL-33, which results in interruption of the interaction between IL-33/ST2L, with consequent abrogation of their cardio-protective effect (Figure 1). Indeed, the treatment with sST2 reversed in a dose-dependent manner the antihypertrophic effect of IL-33 in cardiomyocytes stimulated with angiotensin II or phenylephrine [4]. In the presence of hypoxia, IL-33 reduced apoptosis of cardiomyocytes but addition of sST2 decreased this beneficial effect [6]. These data suggest that the sST2 acts as decoy receptor that may sequester IL-33 and, thereby, modulate IL-33/ST2L cardiac signaling. However, the source of sST2 is not well established and, even produced by both cardiac fibroblasts and cardiomyocytes in response to injury or stress, a non-myocardial production from endothelial cells has also been suggested [7, 8]. The latter is an area of interest, which deserves further investigation.

sST2 as a maladaptive response

Elevated concentrations of circulating sST2 in human are associated with relevant pathophysiological processes in heart diseases. A link between sST2 and phenomena as myocardial stretch, fibrosis, adverse remodeling, inflammation, impaired hemodynamics and vascular diseases has been described in experimental and human studies.

In patients suffering acute myocardial infarction (AMI), circulating concentrations of sST2 were elevated early and correlated with adverse cardiac remodeling as measured with magnetic resonance [9]. In this study, Weir et al. showed an sST2 inverse correlation with left ventricle (LV) ejection fraction and a positive correlation with infarct volume index at baseline and 24 weeks post-AMI. The relationship between sST2 and adverse remodeling after AMI is also supported by the results of our group in an experimental model of AMI, where the myocardial

expression of sST2 was rapidly upregulated during the first 4 weeks and correlated with the ongoing processes of fibrosis and inflammation [5]. As a further step in the progression of adverse remodeling to overt heart failure (HF), among patients with an acute coronary syndrome (ACS) (MERLIN-RIMI36 trial), those with higher circulating sST2 concentrations have a higher rate of development of HF, in the early- and long-term follow-up [10].

Therefore, higher sST2 levels are associated with a phenotype of adverse remodeling prone to HF development. By supporting it, sST2 also identified a more adverse phenotype in hypertensive patients, with more LV hypertrophy and HF [11]. Increased sST2 plasma level also correlated significantly with impaired parameters of cardiac structure, function and hemodynamics in dyspneic patients with acute HF [12]. In these patients, sST2 correlated with several echochardiographic parameters: ventricles exhibited a more dilated structure with lower systolic function, and hemodynamics were impaired with higher intra-cardiac, pulmonary and venous pressures. Zielinski et al. also support the correlation between sST2 and impaired hemodynamics in patients with HF who underwent pulmonary artery catheter-guided therapy; in these patients, higher sST2 levels identified a worse response of hemodynamics to early therapy [13].

Besides correlating with stretch markers, sST2 also correlates with inflammation. In acute HF patients, Rehman et al. showed associations between sST2 and measures of inflammation, such as temperature, leukocyte count, and C-reactive protein (CRP) [14]. In addition, higher sST2 level was found in patients with shortness of breath attributable to HF plus concomitant inflammatory pulmonary disease compare to HF alone or to inflammatory pulmonary disease alone [15]. The association between inflammation and sST2 is an almost constant feature in correlation studies and, on the whole, inflammation seems to be a cornerstone of sST2 response. In fact, sST2 was originally identified as involved in autoimmune and inflammatory diseases through regulating T-helper cell type 2 responses [3].

Therefore, the increase of sST2 reported in acute heart diseases represents a maladaptative response that abrogates the beneficial effects of IL-33/ST2L system and results in a more adverse phenotype of disease, associated with an impaired disease progression: myocardial stretch, fibrosis, adverse remodeling, inflammation and worse hemodynamics.

Prognostic value of sST2

While the natriuretic peptides have received much focus in the past decade in diagnosing and risk-stratifying patients with HF, there is increasing interest in the role of other circulating biomarkers, such as sST2. Concentrations of sST2 have a relevant prognostic value in several acute and chronic cardiovascular diseases, based on numerous clinical studies published in recent years. The main findings are presented in the following paragraphs and are summarized in Tables 1 and 2.

In patients with acute dyspnea attended at the emergency department, serum sST2 concentrations are strongly predictive of mortality at 1 year in patients with acute HF as well as those without HF [16]. sST2 concentrations were significantly greater in patients with HF than those with non-HF dyspnea, but the performance of sST2 for acute HF diagnosis was significantly inferior to N-terminal of

Table 1: Prognostic value of sST2 in acute and chronic cardiac diseases.

Cardiac disease	Setting	Prognostic value	Comments
Acute HF [16–21]	Admission, emergency department monitoring	Death, CV death, HF re-hospitalization, response to therapy	Short- and long-term Repeated measures (4–5 days or discharge) could reclassify the risk for adverse events
Acute dyspnea [16]	Admission, emergency department	Death, CV death, readmissions	Short- and long-term HF and non-HF related dyspnea
STE MI [22, 23]	First 24 h	Death, CV death, HF	30-days and long-term
NSTE ACS [10]			Higher risk of HF development
Chronic HF [9, 24–30]	Out-patient monitoring	Death, CV death, SCD, HF hospitalization, response to therapy	Long-term Repeated measures (≥3 months) could reclassify the risk for adverse cardiovascular events and remodeling
Stable CAD [31]	Out-patient	Death, CV death	Long-term

The sST2 concentration of 35 ng/mL is the threshold recommended to identify a worse prognosis, by using the Presage ST2 Assay. CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; NSTE ACS, non-ST elevation acute coronary syndrome; SCD, sudden cardiac death; STE MI, ST elevation myocardial infarction.

Table 2: Summary of clinical studies.

Study	Population and design	Main results	Additional findings
Januzzi et al. [16]	599 patients Acute dyspnea, PRIDE study Emergency Department Follow-up: 1-year	Subjects above the ST2 median had 11-fold greater odds for death (95% CI 5.5–21.4). AUC of 0.80 (95% CI 0.75–0.84) for 1-year mortality	The increment in either AUC from the addition of ST2 or NT-proBNP to each other was significant (both p=0.001)
Lassus et al. [17]	5306 patients Acute HF, MOCA study Emergency department Follow-up: 30-days and 1-year	sST2 added a NRI of 25.5% for predicting death at 30 days and 10.3% at 1 year, over a clinical prediction model	sST2 was on the top of a large list of biomarkers: NT-proBNP, BNP, CRP, MR-proANP, MR-proADM, TnI, TnT
Pascual-Figal et al. [19]	136 patients Acute decompensated HF Emergency department Follow-up: median 739 days	sST2 concentrations independently predicted mortality (median 739 days): per 10 ng/mL, HR 1.09, 95% CI 1.03–1.15. sST2, hsTnT and NTproBNP provided complementary information	For each marker elevated (0–3) adjusted analysis showed almost tripling the risk of death (HR 2.64, 95% CI 1.63–4.28). C-index, NRI and IDI improved
Ky et al. [24]	1141 patients Chronic HF, Ambulatory Follow-up: median 2.8 years	Patients in the highest ST2 tertile (ST2 >36.3 ng/mL) had a markedly increased risk of adverse outcomes compared to the lowest tertile (ST2 ≤22.3 ng/mL). The AUC for ST2 was 0.75 (95% CI 0.69–0.79)	Addition of ST2 and NT-proBNP to the Seattle HF model reclassified appropriately 14.9% of patients
Bayes-Genis et al. [25]	876 patients Chronic HF, Ambulatory Follow-up: median 4.2 years	Incorporation of ST2 into a full-adjusted model (including NT-proBNP) for all-cause mortality improved the C-statistic (0.77) and the NRI (9.4%, 95% CI 4.8–14.1)	On direct model comparison, ST2 was superior to Gal-3
Pascual-Figal et al. [29]	Case-control study: 36 cases of SCD and 63 control patients, with chronic HF and LVEF <45%.	Elevated sST2 concentrations were predictive of SCD (per 0.1 ng/mL, OR 1.39, 95% CI 1.09–1.78)	sST2 and NT-proBNP provide complementary information to predict SCD
Gaggin et al. [27]	151 patients Chronic HF, PROTECT study Follow-up: 1-year	sST2 independently added information in predicting total cardiovascular events (p<0.001). sST2 serial measurement every 3 months (> or ≤35 ng/mL) improved prediction	Time spent below 35 ng/mL predicted total CV events (HR 0.86 for each 10% of time spent below 35 ng/mL) and reverse myocardial remodeling (OR 1.22, 95% CI 1.04–1.43)
Anand et al. [26]	1650 patients Chronic HF, VAL-HEFT study Follow-up: 1-year	From baseline to 12 months, for a 1 ng/mL rise in sST2, the slope of lnHR increased significantly (β=0.028; 95% CI 0.020–0.035) for prediction of death or HF-related hospitalization	A decrease in sST2 was associated with little or no effect on lnHR. The concentration of 35 ng/mL is also supported as threshold value
Sabatine et al. [23]	1239 patients STEMI, CLARITY-TIMI 28 Follow-up: 30-days	sST2 was associated with a significantly greater risk of CV death or HF at 30 days (third quartile: OR 1.42; 95% CI 0.68–3.57; fourth quartile: OR 3.57; 95% CI 1.87–6.81), independent of risk factors and complementary to NT-proBNP	The combination of ST2 and NT-proBNP improved risk stratification and discrimination compared with TIMI Risk Score alone (c-statistic 0.86 vs. 0.82)
Kohli et al. [10]	4426 patients Non-STEACS, MERLIN-TIMI 36 Follow-up: 30-days and 1-year	sST2 predicted the composite of cardiovascular death and new or worsening HF at 30 days (HR 2.56, 95% CI 1.77–3.71)	sST2 predicted the composite of CV death and new or worsening HF also at 1 year (HR 1.67, 95% CI 1.32–2.11)
Dieplinger et al. [31]	1345 patients Stable coronary disease LURIC study Follow-up: median 9.8 years	sST2 was an independent predictor of all-cause mortality (HR 1.16 per 1-SD increase in log-transformed values; 95% CI 1.05–1.29)	The prognostic impact of sST2 was additive to NT-proBNP and hs-TnT. Patients with all three biomarkers elevated had the poorest outcome

CV, cardiovascular; HF, heart failure; IDI, integrated discrimination improvement; Non-STE ACS, non-ST elevation acute coronary syndrome; NRI, net reclassification improvement; SCD, sudden cardiac death; STE MI, ST elevation myocardial infarction.

the prohormone brain natriuretic peptide (NT-proBNP) [area under curve (AUC) of 0.74 vs. 0.94 in the same cohort] [16, 32]. sST2 lacked specificity for diagnosing HF, but provided powerful prognostic information. Indeed, the discrimination ability of sST2 to predict death showed an AUC higher than the observed in the same cohort with other biomarkers, such as natriuretic peptides, galectin-3, mid regional pro adrenomedullin (MR-proADM), BUN, troponin (Tn) or hemoglobin. In a multinational cohort of patients with acute HF, Lassus et al. reported that sST2 was again on the top of prognosticators for the prediction of 1-month and 1-year mortality; and exhibited higher predictive value than other biomarkers, such as NT-proBNP, BNP, CRP or troponins [17]. Of relevance, sST2 remains an independent predictor of mortality regardless of the cause of HF or the LV ejection fraction [18]. Another repeated finding, as reported by our group and others, is that the prognostic information provided by sST2 is in addition to that provided by other well stablished biomarkers, such as natriuretic peptides and troponins [19]. In small studies, it has been suggested that serial sST2 measures in the days following admission could improve the accuracy of mortality prediction [20] and changes during hospitalization could classify patients as responders or not, which was also predictive of 1-year mortality [21].

Consistent with the data in acute HF, studies of patients with ambulatory chronic HF have demonstrated the prognostic ability of ST2 in the long-term follow-up, across a wide range of cohorts. sST2 concentrations improved the risk stratification for death, cardiovascular death and HF hospitalization, and added independent information over other biomarkers, including natriuretic peptides [24, 25]. In addition, when repeated measures are performed, those with elevated and/or rising sST2 values are at considerably higher risk for adverse outcomes, whereas a falling value may be reassuring [26, 27]. The prognostic impact of an elevated sST2 concentration is more significant for predicting HF-based events, and a greater benefit from addition or titration of aldosterone antagonists and β-blockers has been seen in those with elevated concentrations of sST2 [9, 28].

In the setting of AMI, early levels of sST2 in the first 24 h predict mortality, cardiovascular mortality and HF at 30 days [22]. In addition, as in acute HF, the predictive value of ST2 level was independent and complementary to natriuretic peptides; the combination of ST2 and NT-proBNP significantly improved risk stratification [23]. In patients with non-ST elevation ACS, sST2 was also predictive of cardiovascular death and HF at 30-days and 1-year [10]. In stable coronary disease, sST2 is also predictive of mortality and cardiovascular death independent of clinical variables and biomarkers [31]. In contrast to the prognostic value, in patients presenting to the emergency department with chest pain, the reported AUC for diagnosis of AMI or ACS was 0.579, and the ST2 clearly underperformed troponin in the diagnosis of AMI, with insufficient sensitivity and specificity [33, 34]. Nevertheless, while the low diagnostic performance; the prognostic performance was notable.

Of special interest is the potential utility of sST2 in predicting sudden cardiac death (SCD). A case-control study from our group suggested in 2009 that sST2 is associated with a higher risk of SCD in patients with severe LV systolic dysfunction, and adds prognostic information to natriuretic peptides [29]. This finding has been also supported recently in an analysis from the HF-ACTION study, where fibrosis markers and sST2 in particular improved risk stratification for SCD [30].

Analytical considerations

The Presage ST2 assay (Critical Diagnostics, San Diego, CA, USA) is the only method that has been cleared by the US Food and Drug Administration (FDA), as an aid in assessing prognosis of patients with chronic HF, and has received "Conformitè Europèenne Mark". Other assays have been extensively used as research assays, but results between assays are not comparable. The Presage ST2 assay [35, 36] measures sST2 concentrations in serum and plasma by ELISA and has several favorable characteristics: high in vitro stability of analyte, low intra- (<7%) and inter-assay (<9%) coefficients, low limit of detection (1.3 ng/mL) and no influence by fasting status. It is important to be aware that reference values are higher in males than females (4–31 ng/mL in a male sample and 2–21 ng/mL in a female sample of healthy blood donors [36]), but unaffected by age and body renal function.

sST2 lacks specificity to be useful as a diagnostic test, but it represents a powerful prognostic marker in several cardiovascular diseases. From the review of existing research using the Presage ST2 assay, the value of >35 ng/mL may be suggested as the threshold associated with a worse prognosis. When testing clinically, the biological variation of sST2 is low [37]: the reference change value was 30%, which compares very well with the 92% of N-terminal pro-B-type natriuretic peptide. It means that sST2 could be more useful as a serial marker of response to treatment than NT-proBNP, due to its lower biological variation.

Conclusions

sST2 represents a clinically relevant biomarker reflecting meaningfully pathophysiological processes in cardiac diseases. sST2 concentrations may be measured with reliable analytical precision and concentrations of sST2 are: 1) strongly prognostic for short- and long-term outcome; 2) predict risk for major adverse cardiovascular events, mainly HF-related events; 3) demonstrate substantial additional value over clinical variables and other biomarkers. Accordingly, the last ACCF/AHA guideline of 2013 has incorporated sST2 as a relevant marker of fibrosis, and recommends it as class IIb for additive risk stratification in patients with acutely decompensated HF (level of evidence A) or chronic HF (level of evidence B) [38].

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