



Soluble ST2 and Soluble Markers of Fibrosis: Emerging Roles for Prognosis and Guiding Therapy

Justin Sharim¹ · Lori B. Daniels^{1,2}

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Abstract

Purpose of Review Biomarkers of cardiac fibrosis closely track the disease state that gives rise to heart failure. The purpose of this review is to highlight recent data on the use of soluble ST2, galectin-3, and procollagen, three markers of cardiac fibrosis, for aiding with prognostication, and to explore the use of these biomarkers for guiding therapy.

Recent Findings Soluble ST2, galectin-3, and procollagen are prognostic in both acute and chronic heart failure, and data are emerging as to their potential uses for guiding therapies. Mortality benefit from exercise, cardiac resynchronization therapy, statin use, as well as anti-fibrotic therapies such as aldosterone antagonism may vary based upon levels of these fibrosis markers.

Summary Soluble ST2, galectin-3, and procollagen provide independent prognostic information for heart failure morbidity and mortality. Markers of cardiac fibrosis may also help identify the subsets of patients who are most likely to benefit from various therapies. However, further studies are needed prior to formalizing individual patient care algorithms guided by fibrosis biomarkers.

Keywords Fibrosis · Heart failure · Biomarkers · Guided therapy

Introduction

Whereas some biomarkers in heart failure such as the cardiac troponins and the natriuretic peptides are reflective of myocyte injury and stretch, respectively, biomarkers of cardiac fibrosis more closely track the disease state that gives rise to heart failure. In this review, we cover the biology and measurement of three soluble markers of fibrosis and discuss the evidence behind their emerging roles in prognostication as well as their potential roles in guiding therapy. While many markers of cardiac fibrosis exist, we focus here on soluble ST2, galectin-3, and procollagen based upon their greater wealth of clinical data and potential for use in the clinical arena.

Soluble ST2

Biology

As a member of the interleukin-1 (IL-1) receptor family of proteins [1], suppression of tumorigenicity-2 (ST2) is involved in T cell-mediated inflammatory responses in a number of conditions including autoimmune diseases, asthma, sepsis, and fibroproliferative disorders [2]. Two distinct isoforms of ST2 exist: ST2 ligand (ST2-L), the transmembrane form, and soluble ST2 (sST2), the soluble form, both of which are produced by alternative splicing of the ST2 gene [2].

In the heart, ST2-L and its ligand, IL-33, are thought to play a role in the inflammatory response and in fibrosis within myocardial tissue [3]. IL-33 and ST2-L signaling mitigates adverse cardiac remodeling after cardiac injury and stress by reducing fibrosis, hypertrophy, and apoptosis [4, 5]. Thus, ST2-L is thought to play a cardioprotective role in cardiac disease. sST2, however, competes with ST2-L for IL-33, acting as a “decoy receptor,” thus attenuating the beneficial effects of ST2-L/IL-33 signaling [5]. As such, higher levels of sST2 are associated with more adverse cardiac remodeling and increased fibrosis.

In contrast to its transmembrane counterpart, sST2 is readily found in the circulation, and its serum level can be

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✉ Lori B. Daniels
lbdaniels@ucsd.edu

Justin Sharim
jdsharim@health.ucsd.edu

¹ Division of Cardiovascular Medicine, University of California, San Diego, La Jolla, CA, USA

² Sulpizio Cardiovascular Center, UC San Diego Health, 9452 Medical Center Drive, La Jolla, CA 92093-7411, USA

measured with ELISA assays [1, 6]. Unlike other cardiac biomarkers such as the natriuretic peptides and cardiac troponins, sST2 is minimally affected by renal function [7•]. Moreover, intra-individual variability of sST2 is lower than that of natriuretic peptides [8]. This low intra-individual variability of sST2 and its minimal variation in response to renal dysfunction render sST2 a reliable biomarker for measurement in chronic heart failure to monitor disease course and cardiac response to therapies as well as for prognostication [1].

Soluble ST2 in Acute Heart Failure

Known to be triggered by myocardial stress, sST2 elevates during acute exacerbations of heart failure [1]. The Pro-Brain NP Investigation of Dyspnea in the Emergency Department (PRIDE) study examined sST2 levels in 593 patients presenting to the Emergency Department with undifferentiated dyspnea [9]. Although sST2 was not a marker well suited for diagnosis of heart failure, patients with a clinical diagnosis of heart failure were nonetheless found to have significantly higher levels of sST2 than those who presented with dyspnea due to another etiology [9]. Furthermore, sST2 levels during the hospitalization were strongly predictive of 1-year mortality in dyspneic patients both with and without acute heart failure, and this prognostic utility was complementary to that of NT-proBNP.

In another analysis providing longer-term follow-up of the PRIDE study, sST2 was found to be a significant predictor of 4-year mortality, even after adjustment for other clinical factors and biomarkers such as NT-proBNP [10]. The authors of this subanalysis also found higher sST2 levels to be associated with structural abnormalities on echocardiography. Higher sST2 levels were associated with higher right ventricular systolic pressure and hypokinesia, more severe tricuspid regurgitation, larger left ventricular end diastolic dimension, and lower left ventricular ejection fraction [10].

With respect to mortality, the findings of the PRIDE study and its subanalyses were corroborated in a recent meta-analysis of 10 studies encompassing 4835 patients, where sST2 measured during an acute exacerbation of heart failure was found to be predictive of cardiovascular outcomes at a median follow-up of 13.5 months [11••]. The meta-analysis also found both admission and discharge sST2 levels to be predictive of cardiovascular and all-cause mortality. Higher discharge sST2 levels further portended the risk of rehospitalization due to heart failure [11••].

Studies have also shown sST2 to be a dynamic marker, with changes in sST2 levels providing further prognostic information. In a study of 150 patients hospitalized for acute decompensated heart failure, Boisot and colleagues showed that the difference between discharge and admission sST2 levels was significantly predictive of 90-day mortality [12]. Patients who had a drop in sST2 level of at least 15.5% had a

90-day mortality of 7%, while those whose sST2 levels failed to fall at least this much had a 33% mortality. In a similar study, Manzano-Fernández and colleagues showed that in patients admitted with acute heart failure, the subgroup with the highest mortality at 2 years was those with sST2 that was elevated on admission and that failed to decrease during the course of their hospitalization [13]. Taken together, these results suggest that while sST2 does provide prognostic utility as a snapshot, dynamic changes in sST2 provide further information.

Finally, sST2 has been found to predict the future diagnosis of heart failure in ambulatory community-dwelling individuals who do not have a prior heart failure diagnosis. In a subanalysis of the Framingham Heart Study, Wang and colleagues analyzed sST2 levels in 3428 individuals in the general population and found that elevated sST2 levels were associated with future risk of death, heart failure hospitalization, as well as overall cardiovascular events [14]. These findings were corroborated by a study of 3915 elderly, community-dwelling individuals from the Cardiovascular Health Study (CHS), in whom higher sST2 levels were associated with incident heart failure as well as with cardiovascular death [15•]. sST2 was also associated with older age, African American race, and with traditional cardiovascular risk factors in the CHS [15•]. In a cross-sectional subanalysis of the Framingham Heart Study, Coglianesi and colleagues showed sST2 to be independently associated with the presence of diabetes as well as hypertension at the time of measurement [16]. In the general population, these data support the notion that sST2 levels reflect myocardial strain and thus are related to future onset of acute heart failure.

It is important to note that, to a much greater extent than with natriuretic peptides, [17], there is significant overlap in sST2 levels between healthy ambulatory patients without known cardiac disease and patients with diagnosed heart failure, as well as patients with inflammatory conditions such as chronic obstructive pulmonary disease [18, 19]. Thus, the utility of sST2 is primarily prognostic and not diagnostic [9, 19].

Soluble ST2 in Chronic Heart Failure

Multiple studies have supported the role of sST2 measurement in chronic heart failure prognostication and management. In a study of 588 outpatients with stable heart failure referred for echocardiography, Daniels and colleagues demonstrated a clinically significant relationship between sST2 levels and 1-year mortality (hazard ratio 15.11 *per 1 unit log ST2 increase*). Each increasing sST2 quartile was associated with an incremental increased risk of mortality at 1 year ($p = 0.01$); in fact, no patient in the study with an sST2 level below the median (19.8 ng/mL) died within 6 months [20]. Felker and colleagues later corroborated the findings of this study, similarly observing a significant association between ambulatory sST2

levels and composite outcome of death or heart failure readmission (hazard ratio for \log_2 ng/mL 1.48, $p < 0.0001$) [21].

sST2 levels are prognostic in both ischemic and nonischemic heart failure, including rarer etiologies. Among patients with ischemic heart failure, a subanalysis of the Controlled Rosuvastatin Multinational Trial (CORONA) study [22] of 1449 elderly patients with ejection fraction $\leq 40\%$ found that sST2 levels were predictive of both death and hospitalization even after adjustment for NT-proBNP and C-reactive protein [22, 23]. In a smaller study of 44 patients with arrhythmogenic right ventricular cardiomyopathy, sST2 levels were associated with both right ventricular strain and left ventricular function; moreover, patients with ventricular arrhythmias were found to have higher mean sST2 levels than those without ventricular arrhythmias (35 ± 13 ng/mL vs. 26 ± 7 ng/mL, $p = 0.009$) [24].

Finally, sST2 levels may provide insight into which subsets of heart failure patients may benefit most from therapies known to be beneficial in terms of both cardiovascular function and mortality. In a subanalysis of the EPHEsus trial [25] of patients with acute myocardial infarction, Weir and colleagues measured serial sST2 levels in the eplerenone (an aldosterone inhibitor) and placebo arms. They found that treatment with eplerenone resulted in no significant change in sST2 over time [26]. However, there was a positive interaction between sST2 level and benefit from eplerenone. In patients with lower-than-median sST2 levels, no difference in adverse remodeling was found between the eplerenone and placebo arms; however, in those with higher-than-median sST2 levels, there was less adverse left ventricular remodeling in those randomized to eplerenone compared with placebo. These results suggest that patients with high sST2 levels may benefit most from anti-fibrotic medications such as eplerenone.

Relationships between sST2 and other anti-fibrotic therapies have been evaluated as well. In the biomarker ancillary study of the Angiotensin-Nepriylsin Inhibition versus Enalapril in Heart Failure (PARADIGM-HF) trial [27], patients randomized to treatment with the angiotensin receptor-nepriylsin inhibitor (ARNI) sacubitril-valsartan had a greater reduction in sST2 levels than patients treated with enalapril [28, 29]. This reduction in sST2 was independently associated with reduced risk of outcomes, including cardiovascular death and heart failure rehospitalization. The relationship between treatment with sacubitril-valsartan and sST2 in patients with heart failure with preserved ejection fraction (HFpEF) is still under investigation; however, the Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction (PARAMOUNT) study [30] suggested that subjects with lower levels of sST2 were more likely to show reduction in left atrial volume with ARNI treatment [31]. Biomarker subanalyses from the phase 3 Angiotensin-Nepriylsin Inhibition in Heart Failure with

Preserved Ejection Fraction (PARAGON-HF) study of patients with HFpEF [32] are not yet reported.

Finally, the prognostic role of ST2 may extend into non-pharmacotherapeutic treatment as well. In the Cardiac Resynchronization Therapy for the Prevention of Heart-Failure Events (MADIT-CRT) study [33] of patients with mildly symptomatic heart failure and reduced ejection fraction (30% or less), elevated sST2 at baseline was independently associated with risk of death, heart failure, and ventricular tachycardia, even after adjusting for BNP levels [34]. However, it was the patients with lower sST2 levels who had the greatest risk reduction from cardiac resynchronization therapy (CRT).

Lower sST2 levels also may predict mortality benefit from exercise therapy. In the Efficacy and Safety of Exercise Training in Patients with Chronic Heart Failure (HF-ACTION) trial, Felker and colleagues randomized 2331 patients with ejection fraction $\leq 35\%$ and NYHA class II-IV symptoms to either exercise testing or usual care and retrospectively analyzed 910 of those patients who had available plasma [21]. Those with lower sST2 levels were more likely to experience a benefit from exercise therapy with respect to both all-cause and cardiovascular mortality ($p = 0.016$ and 0.032 for ST2 \times treatment interaction, respectively). In contrast, patients with higher baseline sST2 levels were more likely to experience improvement in VO₂max after 3 months of exercise therapy.

Galectin-3

Biology

Galectin-3 (gal-3) is a member of the beta-galactosidase binding protein family expressed and secreted by macrophages [35], and is involved in cell adhesion, activation, chemoattraction, and apoptosis [36]. Gal-3 binds and activates fibroblasts, leading to deposition of collagen into the extracellular matrix and subsequently to progressive cardiac fibrosis [37, 38]. Studies have documented an association between gal-3 expression and a broad variety of sites of fibrosis, including hepatic fibrosis [39], renal fibrosis [40], and idiopathic pulmonary fibrosis [41]. In the heart, macrophage gal-3 expression has been implicated in myofibroblast proliferation, fibrogenesis, inflammation, and ventricular remodeling [37, 42].

Gal-3 is overexpressed in the rat heart failure model even prior to the development of overt heart failure [37]. Moreover, infusion of gal-3 into the pericardium of healthy rats independently led to cardiac fibroblast proliferation, collagen deposition, and subsequent left ventricular dysfunction [37]. In human subjects with aortic stenosis, those with depressed ejection fraction had significantly higher gal-3 levels than those whose ejection fraction was preserved [37]. Taken together,

these results suggest that gal-3 not only serves as a biomarker of disease state but also may have a direct causative role in the genesis of heart failure. Thus, gal-3 may be an indirect downstream target for current heart failure therapeutics and may serve as a potential direct target for future heart failure therapies.

Galectin-3 in Acute Heart Failure

Like sST2, the utility of gal-3 in heart failure is primarily prognostic and not diagnostic. In the Framingham Cohort Survey, higher levels of gal-3 were found to be associated with an increased risk of new-onset heart failure and were independently predictive of all-cause mortality, even after adjusting for several clinical factors including BNP [43, 44]. Similarly, in the Rancho Bernardo Study of 1393 community-dwelling older adults free from cardiovascular disease at baseline, higher gal-3 levels were independently associated with all-cause and cardiovascular mortality [45]. In this study, individuals with elevated levels of both gal-3 and NT-proBNP above the median had increased risk of death compared with those with only one marker elevated.

In patients after myocardial infarction, Asleh and colleagues showed that elevated gal-3 levels were associated with both mortality as well as new-onset heart failure [46]. Finally, in the PRIDE study [47], gal-3 was a stronger prognostic marker for 60-day mortality and for recurrent heart failure hospitalization than was NT-proBNP or apelin. Moreover, the combination of gal-3 with NT-proBNP provided additive prognostic ability when compared with NT-proBNP alone.

In the acute setting, gal-3 may thus be used in conjunction with other biomarkers such as the well-established natriuretic peptides to provide additive prognostic value [48, 49]. Independently, given its prognostic capabilities in the acute setting, gal-3 may play a role in predicting which patients may benefit most from close short-term monitoring after discharge from either the hospital or the Emergency Department [35, 50]. For instance, in the Relationship between Galectin-3 Serum Levels and Short- and Long-term Outcomes in Patients with Acute Heart Failure (GALA) study of 115 consecutive patients presenting to the Emergency Department for acute heart failure, gal-3 was predictive of 30-day mortality but not 1-year mortality (unlike NT-proBNP), even after adjustment for age and renal function [51]. These data suggest that gal-3 may have its greatest utility as a marker of short-term risk, though other larger studies have shown more robust long-term prognostic ability.

Galectin-3 in Chronic Heart Failure

Gal-3 has also been shown to be of prognostic value when measured serially in an ambulatory setting. In a subgroup analysis of the Deventer-Alkmaar Heart Failure (DEAL-HF)

study, with heart failure In a subgroup analysis of the Deventer-Alkmaar Heart Failure study (DEAL-HF), gal-3 predicted mortality independent of NT-proBNP; gal-3 predicted mortality independent of NT-proBNP [52]. Similar to the PRIDE study, the combination of gal-3 and NT-proBNP improved prognostic ability compared with NT-proBNP alone [52]. Other studies of patients with chronic systolic heart failure have also shown gal-3 to be an independent predictor of all-cause mortality in multivariable analyses [43, 53].

In patients specifically with advanced heart failure, gal-3 also shows prognostic ability. Among those receiving a ventricular assist device, Milting and colleagues found higher gal-3 levels predict death from multi-organ failure. In this population, serial measurements did not improve prognostic ability over a single measurement, as the gal-3 level tended to remain stable over the 6-month period of measurement [54].

Given its prognostic ability in chronic heart failure, gal-3 levels may be able to assist and guide therapy in the ambulatory setting [35]. In a post hoc subanalysis of the CORONA trial [22], patients with lower gal-3 values (< 19 ng/mL) benefited from randomization to rosuvastatin with lower mortality and heart failure hospitalization rates, while those with higher gal-3 values failed to show benefit from rosuvastatin [55]. The reason for the beneficial effect of statins only in those chronic heart failure patients with low gal-3 levels is unknown, but may be due to low gal-3 identifying a subset of individuals with less myocardial fibrosis and more viable myocardium ripe for protection by statins. A similar pattern was seen in the PARAMOUNT study of HFpEF patients [31] where those subjects with gal-3 levels below the median (like sST2) showed a healthier left atrial volume response to sacubitril-valsartan therapy than those with gal-3 levels above the median. These data, however, must be taken in the context of the negative overall finding that gal-3 levels did not modify the response to sacubitril-valsartan for the primary endpoint, lowering of NT-proBNP levels.

Gal-3 was also evaluated in the biomarker ancillary study of PARADIGM-HF. In contrast to sST2, where both baseline level and changes in the biomarker were associated with outcomes, there was no relationship between gal-3 levels and outcomes [29]. In fact, gal-3 was the only one of the 8 markers of fibrosis to increase rather than decrease in both study arms at 8 months. The implications of this are unclear.

Like sST2, gal-3 was measured in the MADIT-CRT cohort, but with disparate findings for the two fibrosis markers. In contrast to the finding that subjects with low sST2 had the greatest risk reduction with CRT, the biggest benefit from CRT when stratified by gal-3 level occurred for those in the top quartile (65% reduction in the primary endpoint of heart failure event or death for the top quartile, compared with 25% decrease for all others) [56]. Also in contrast to sST2 [21], gal-3 levels were not useful for predicting response to exercise

training in randomized chronic heart failure patients within the HF-ACTION study [57].

As with all markers of fibrosis, further studies are needed to shed more light on what role, if any, gal-3 may have for guiding therapy in chronic heart failure.

Procollagen

Biology

Collagen scar formation is known to play an important role in fibrosis. Within cardiac tissue, collagen scar formation plays a large role in remodeling after myocardial infarction and the subsequent development of heart failure [35]. Soluble markers of collagen synthesis and turnover may be useful as biomarkers reflecting the extent of cardiac fibrosis. Procollagen type III amino-terminal propeptide (PIIINP) is a marker of collagen synthesis and is one of the most studied of these markers.

Procollagen in Acute Heart Failure

In the setting of acute myocardial infarction, PIIINP is elevated; moreover, higher PIIINP levels portend a greater likelihood of development of left ventricular dilation and heart failure after 1 year [58]. A sub-study of The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure (RALES) trial [59] found that in those with previously diagnosed heart failure hospitalized for an acute decompensation, higher levels of PIIINP were associated with poorer outcomes [60]. Fibrosis markers such as procollagen may also have a role in selecting patients for proven mortality-benefiting therapies. In the same study, PIIINP was reduced by aldosterone antagonism with spironolactone; however, only in those whose PIIINP levels were above the median did the reduction in PIIINP lead to an improvement in outcomes [60].

Procollagen in Chronic Heart Failure

In patients with chronic heart failure, PIIINP is an independent predictor of mortality [61]. In a recent study of patients with stable heart failure, PIIINP proved to be an independent predictor of mortality on both univariable and multivariable analysis when controlling for age as well as other cardiac biomarkers like gal-3 and sST2 [62]. Of note, this study also found that sST2 (but not gal-3) provided incremental prognostic information when added to the multivariable model. No difference was found when comparing PIIINP levels between patients with HFpEF and those with HFrEF, in contrast to gal-3 [63]. Taken together, these results suggest that each cardiac

biomarker indeed provides unique and at least some non-overlapping information.

Like the previous markers discussed, procollagen holds some promise for guiding therapy in chronic heart failure, though results are retrospective and not always consistent. In PARADIGM-HF, and similar to sST2, higher levels of PIIINP at baseline were associated with an increased rate of outcomes [29]. In addition, PIIINP decreased more in the sacubitril-valsartan than in the enalapril arm at 8 months. However, unlike sST2, this drop in PIIINP was not associated with improved outcomes.

In a recent small study of 60 patients who underwent CRT, those with a positive response to therapy at 6 months post-implantation (no hospitalization/death and an increase in ejection fraction of > 15%) had significantly lower pre-implantation PIIINP and procollagen type I C-terminal propeptide (PICP, another procollagen biomarker), when compared with those who were nonresponders [64]. These data suggest that patients with a lower degree of cardiac fibrosis—at least as measured by PIIINP—may have the greatest chance of reverse remodeling with CRT. Again, these results need to be digested in conjunction with the concordant sST2 and discordant gal-3 data, and point toward a more complex interplay between myocardial fibrosis and each individual marker of fibrosis than we are currently able to fully synthesize.

Conclusion

Markers of cardiac fibrosis give important prognostic information about the severity of heart failure and, in particular, provide significant incremental information in predicting mortality across multiple studies and cohorts. The critical next step is to home in on how to translate all of this biomarker potential into actionable clinical changes at the level of the individual patient—but this remains elusive. Currently, the data for biomarkers of fibrosis in aggregate are challenging to interpret due to paradoxical findings. Are patients with elevated markers of cardiac fibrosis those whom we should most aggressively target with goal-directed therapies, since they are at highest risk? Or should we be targeting the patients with low levels of fibrosis markers, since they may have less advanced fibrosis that is more likely to respond to treatment? The answer to this question is undoubtedly complex and probably depends upon both the marker(s) in question, as well as the specific therapy (i.e., CRT, exercise training, statins for those with less fibrosis as measured by sST2 and PIIINP; aldosterone inhibition for those with advanced fibrosis?). Potentially, an algorithm could be developed to detail an ideal pattern of various individual fibrosis biomarkers for optimal benefit from a given intervention—but this has not yet been elucidated. Until we gain a better, more detailed, and perhaps

individualized understanding of the nuances of these markers, it is difficult to propose costly high-stakes prospective studies of biomarker-guided therapy. Nonetheless, with each additional biomarker subanalysis, and in combination with basic science and translational work, we improve our understanding of the mechanisms of fibrosis that adds to our understanding of acute and chronic cardiovascular disease and the many factors that affect the readings we get from biomarkers of fibrosis. Ultimately, we hope this will translate into better individualized patient care and outcomes for our acute myocardial infarction and acute and chronic heart failure patients.

Compliance with Ethical Standards

Conflict of Interest Justin Sharim declares that he has no conflict of interest. Lori B. Daniels has received research supplies from Critical Diagnostics, has served as a consultant for Quidel and Roche, and has served on clinical endpoints adjudication committees for Abbott and Siemens.

Human and Animal Rights and Informed Consent This article is a review and does not contain any studies with human or animal subjects performed by any of the authors.

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