

ST2 Assay for Chronic Heart Failure

Policy Number: AHS – G2130 – ST2 Assay for Chronic Heart Failure	Prior Policy Name and Number, as applicable:
Initial Presentation Date: 05/23/2016	
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I. Policy Description

Heart failure (HF) comprises a major cause of morbidity and mortality worldwide. HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood (Yancy et al., 2013).

Suppression of tumorigenicity 2 (ST2) is a marker of cardiomyocyte stress and fibrosis that provides incremental value to natriuretic peptides for risk stratification of patients with a wide spectrum of cardiovascular diseases (Bayes-Genis, Zhang, & Ky, 2015).

II. Related Policies

Policy Number	Policy Title
AHS-G2050	Cardiovascular Disease Risk Assessment
AHS-G2150	Cardiac Biomarkers for Myocardial Infarction
AHS-M2025	Genetic Testing for Inherited Cardiomyopathies and Channelopathies

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

1. The use of the Presage® ST2 Assay to evaluate the prognosis of patients diagnosed with chronic heart failure **DOES NOT MEET COVERAGE CRITERIA.**
2. The use of the Presage® ST2 Assay to guide management (pharmacological, device-based, exercise, etc.) of patients diagnosed with chronic heart failure **DOES NOT MEET COVERAGE CRITERIA.**

3. The use of the Presage® ST2 Assay in the post cardiac transplantation period, including, but not limited to, predicting prognosis and predicting acute cellular rejection, **DOES NOT MEET COVERAGE CRITERIA.**

IV. Scientific Background

HF is a complex clinical syndrome resulting from any structural or functional impairment of ventricular filling or ejection of blood, including disorders of the pericardium, myocardium, endocardium, heart valves, great vessels, or certain metabolic abnormalities (W. Colucci, 2020). Most patients with HF have symptoms due to impaired left ventricular (LV) myocardial function (W. Colucci, Dunlay, Shannon, 2020; Yancy et al., 2013). The most common symptoms of HF are dyspnea and fatigue, which may limit exercise tolerance and fluid retention. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema, dyspnea, or fatigue (W. Colucci, Dunlay, Shannon, 2020). Heart failure is often a progressive condition, beginning with predisposing factors and leading to the development and worsening of clinical illness (Colucci, 2021; W. Colucci, Dunlay, Shannon, 2020).

No single diagnostic test for HF exists because it is largely a clinical diagnosis based on a careful history and physical examination. However, biomarkers of cardiovascular diseases have been developed for diagnosis and prognosis, and the use of several biomarkers is now considered the standard of care. ST2 is a marker of cardiomyocyte stress and fibrosis that adds additional value to natriuretic peptides, resulting in a risk stratification of patients with a wide spectrum of cardiovascular diseases (Bayes-Genis et al., 2015).

ST2 is part of the interleukin-1 receptor family with two isoforms, soluble ST2 (sST2) and ST2L. ST2 is the receptor of the IL-33 cytokine that can be secreted by living cells in response to cellular stress and mechanical strain. IL-33 binds the receptor complex of ST2L and IL-1R accessory protein and reduces myocardial fibrosis, prevents cardiomyocyte hypertrophy, reduces apoptosis, and improves myocardial function. The cardioprotective effects of IL-33 are specifically through the ST2L receptor. However, sST2 may also bind IL-33, blocking the interaction between IL-33/ST2L. This eliminates the cardioprotective effects of the IL-33/ST2L interaction (Pascual-Figal & Januzzi, 2015). Experimentally, this leads to cardiac hypertrophy, fibrosis, and ventricular dysfunction (Januzzi, Mebazaa, & Di Somma, 2015)

One of the main proprietary tests used to assess ST2 levels is the Presage Assay by Critical Diagnostics. This assay was approved by the FDA on December 9, 2011. According to the FDA, “The Critical Diagnostics Presage® ST2 Assay kit is an in vitro diagnostic device that quantitatively measures ST2 in serum or plasma by enzyme-linked immunosorbent assay (ELISA) in a microtiter plate format. The Presage® ST2 Assay is indicated to be used in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure”. The manufacturer claims a measuring range of 3.1 ng/mL of soluble ST2 to 200 ng/mL, and the data based on 1100 samples supports this claim. These 1100 samples found coefficient of variation of under 5%, a linear curve, and a $r^2=0.99$ (FDA, 2011).

Clinical Validity and Utility

Ky et al. conducted a multi-center prospective study to evaluate whether plasma ST2 levels predict adverse outcomes in 1,141 chronic heart failure outpatients. Patients in the highest ST2 tertile (ST2 > 36.3 ng/mL) had a “markedly increased” risk (hazard ratio 3.2) of adverse outcomes compared to the lowest tertile (≤ 22.3 ng/mL). The investigators concluded that “ST2 is a potent marker of risk in chronic heart failure and when used in combination with NT-proBNP offers moderate improvement in assessing prognosis beyond clinical risk scores” (Ky et al., 2011).

Broch et al. studied the association between sST2 and cause-specific outcome in 1449 patients enrolled in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA study). Soluble ST2 was measured in 1449 patients ≥ 60 years of age with left ventricular ejection fraction $\leq 40\%$ due to ischemic heart disease. ST2 remained associated with death due to worsening HF, hospitalization due to worsening HF, and hospitalization due to any CV cause, even after full adjustment for N-terminal pro brain natriuretic peptide and C-reactive protein. A cut-off point of 15.5% increase of sST2 was associated with hospitalization, but not with any other outcome. This increase became weakly associated with both the primary endpoint (cardiovascular events such as stroke) and hospitalization. The investigators concluded that “Soluble ST2 is associated with adverse outcomes in older patients with systolic, ischemic HF. In particular, sST2 is independently associated with worsening HF (Broch et al., 2012).

Wang et al. studied the prognostic value of three novel biomarkers induced by cardiovascular stress. The investigators measured sST2, growth differentiation factor-15, and high-sensitivity troponin I in 3,428 participants in the Framingham Heart Study. Multivariable-adjusted proportional hazards models were performed to assess the individual and combined ability of the biomarkers to predict adverse outcomes. The three new biomarkers were associated with death, major cardiovascular events, and heart failure, but not with coronary events. The investigators concluded that the findings demonstrated the prognostic value of the newer biomarkers in apparently healthy individuals (Wang et al., 2012).

Felker et al. studied the association of ST2 level with long-term clinical outcomes in ambulatory heart failure patients enrolled in the HF-ACTION study – a multicenter, randomized study of exercise training in HF. ST2 was analyzed in a subset of 910 patients with evaluable plasma samples and correlations and Cox models were used to assess the relationship among ST2, functional capacity, and long-term outcomes. ST2 was “modestly” associated with measures of clinical capacity, such as death or hospitalization from HF but did not add to any reclassification of risk, improve discrimination of risk, or lead to any reclassification improvements” (Felker et al., 2013).

Anand et al. evaluated the association between soluble ST2 (sST2) and patient outcomes. sST2 was measured at baseline (n=1650), 4 months (n=1345), and 12 months (n=1094) in Valsartan Heart Failure Trial. The authors observed that baseline sST2 (average of 28.7 ± 16.2 ng/mL) was nonlinearly associated with patient outcomes. However, only sST2 levels < 33.2 ng/mL were significantly related to patient outcomes when 23 other clinical variables were added to the regression model. The authors concluded that additional research is needed to determine whether monitoring ST2 levels can improve patient outcomes (Anand, Rector, Kuskowski, Snider, & Cohn, 2014).

Januzzi et al. conducted a retrospective study to assess sST2 as a prognostic marker after orthotopic heart transplantation (OHT) and as a test to predict acute cellular rejection. sST2 concentrations were measured in 241 patients following OHT. Elevated sST2 was associated with cellular rejection, with

highest rates of cellular rejection in the 4th sST2 quartile. No significant association between sST2 and antibody-mediated rejection or allograft vasculopathy was found. A sST2 level of ≥ 30 ng/mL was found to independently predict death over the 7-year follow-up with a hazard ratio of 2.1. The investigators concluded that sST2 levels are associated with the presence of cellular rejection and predict long-term mortality following OHT (Januzzi et al., 2013).

Boman et al. assessed the prognostic value of ST2 on cardiovascular mortality. 159 patients were evaluated, but ST2 was not found to be significantly associated with cardiovascular mortality or all-cause mortality. Furthermore, no significant interaction of ST2 and N-terminal pro-hormone of brain natriuretic peptide /N-terminal pro-B-type natriuretic peptide was found (Boman, Thormark Frost, Bergman, & Olofsson, 2018).

Mueller et al. evaluated the prognostic and diagnostic value of sST2 (measured with Presage) for HF in an emergency setting (along with two other biomarkers, galectin-3 and BNP). 137 patients had dyspnea attributed to acute HF, and BNP was evaluated to have a 0.92 area under the curve (AUC) for the diagnosis of HF. For comparison, the AUC of sST2 was 0.63 and the AUC of galectin-3 was 0.57. Of these 137 patients, 41 died and 96 returned for follow-up. The AUC of BNP for the prediction of “all-cause mortality” was 0.72 similar to galectin-3 and sST2 (0.70 and 0.75, respectively). The authors concluded all three biomarkers to be approximately equally useful for prediction of all-cause mortality in patients with acute HF, but only BNP was found to be useful as a diagnostic aid in patients presenting with dyspnea (Mueller et al., 2016).

Stojkovic et al. (2018) published a study which concluded that GDF-15 is superior to sST2 in prediction of fatal arrhythmic events and all-cause mortality in dilated cardiomyopathy (DCM). 52 patients with DCM and left ventricular ejection fraction (LVEF) of under 50% were enrolled in the study, and only GDF-15 was found to be associated with increased risk of arrhythmic death or resuscitated cardiac arrest (hazard ratio: 2.1). Although ST2 was considered an independent predictor of “all-cause mortality”, only GDF-15 was significantly associated with all-cause mortality when LVEF, ST2, GDF-15, and NYHA functional class were considered (Stojkovic et al., 2018).

Tyminska et al. investigated the association of galectin-3 and soluble ST2 (sST2) with the development of heart failure, including “echocardiographic parameters of HF [heart failure] (ejection fraction, atrial and ventricular size, left ventricular hypertrophy, e' , and E/e') in patients with ST-segment elevation myocardial infarction (STEMI)...”. 117 patients were included, and the primary endpoint was “HF onset at one year follow up”. Mean baseline concentrations of sST2 (26.4 ng/mL) were increased at one year follow-up (31.4 ng/mL), and patients that reached the endpoint ($n = 43$) had a mean concentration of 33.1 ng/mL. Although sST2 was found to be a predictor of the primary endpoint in univariate logistic regression analysis, it was not significant in multivariate analysis (Tyminska et al., 2019).

Dimitropoulos et al. investigated the association of soluble suppression of tumorigenesis-2 (sST2) with endothelial function in patients with ischemic heart failure. A total of 143 patients with “table HF of ischemic etiology and reduced left ventricular ejection fraction (LVEF)” were included along with 77 controls. The authors found an increased level of sST2 in HF patients compared to controls (15.8 ng/mL compared to 12.5 ng/mL). Within the HF group, there was no association of LVEF with sST2. Overall, sST2 levels were found to be increased and associated with functional capacity in “patients with chronic HF of ischemic etiology”. Finally, the authors found an inverse association between flow-mediated dilation and sST2 levels, which the authors stated “highlight[ed] the interplay between the dysfunctional endothelium and HF pathophysiological mechanisms” (Dimitropoulos et al., 2020).

Hou et al. aimed to investigate the association between sST2 levels and clinical outcomes of high-risk heart failure. The primary endpoint was defined as all-cause mortality. A total of 150 patients were included; all-cause mortality occurred in 16 of the patients over the course follow-up. The authors found that all-cause mortality increased significantly above 34.98846 ng/mL by a factor of 16% to 5.33%. After adjusting the model for certain co-factors (age, gender, et al.), and after adding NT-proBNP, “the risk of all-cause death was increased by 2.5% and 1.9%, respectively, per ng/ml of sST2”. The authors identified the best sST2 cut-off for predicting all-cause mortality to be 43.42671 ng/ml, with an area under the curve of 0.72, sensitivity of 0.69, and specificity of 0.69. Risk of all-cause mortality was found to be 21.2% above this cutoff and 5.1% below it, with a corresponding hazard ratio of 3.30. The authors concluded that “Patients with sST2 levels more than 43.42671 ng/ml even after ICD implantation should therefore be monitored carefully” (Hou et al., 2020).

V. Guidelines and Recommendations

American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA, 2017) (Yancy Clyde et al., 2017)

In 2017, the ACC, AHA, and HFSA jointly updated evidence-based guidelines for the management of heart failure (HF). The ACC/AHA/HFSA stated that “Biomarkers of myocardial fibrosis, soluble ST2 receptor, and galectin-3 are predictive of hospitalization and death and may provide incremental prognostic value over natriuretic peptide levels in patients with HF.” The guidelines also note that “in patients with chronic HF, clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients” (Yancy Clyde et al., 2017).

American Heart Association (AHA) (Chow Sheryl et al., 2017; Cresci et al., 2019)

The AHA notes sST2 as an “emerging” biomarker that supports diagnosis of HF with preserved ejection fraction, a biomarker that may predict mortality and HF events, and a biomarker that correlates with left ventricular end-diastolic pressure. The AHA states that sST2 has numerous advantages as a biomarker, namely its concentration being unaffected by BMI, age, or renal function. SST2 is stated to correlate with HF prognosis as well. Overall, AHA states that out of the newer biomarkers (SST2, ST2, Gal-3, and GDF-15), “most appeal is driven by sST2” (Chow Sheryl et al., 2017).

A Scientific Statement published in 2019 also considered ST2 as the most “promising clinically”, but also mentioned the limitations in consistency and utility in most inflammatory mediators. The Statement notes several clinical studies focusing on sST2 that are in progress as of March 24, 2020 (Cresci et al., 2019).

Canadian Cardiovascular Society (CCS, 2017)

The CCS notes sST2 as a potential prognostic biomarker and states that “might be superior” to galectin-3. However, the CCS also remarks that it is “unclear” if using sST2 in HF to modify therapies improve clinical outcomes (CCS, 2017).

European Society of Cardiology (ESC) (Ponikowski et al., 2016)

The ESC states that “although there is extensive research on biomarkers in HF (e.g. ST2, galectin 3, copeptin, adrenomedullin), there is no definite evidence to recommend them for clinical practice.” (Ponikowski et al., 2016)

Heart Failure Association of the European Society of Cardiology (Crespo-Leiro et al., 2018)

The Heart Failure Association of the European Society of Cardiology published a position statement on Advanced Heart Failure (Crespo-Leiro et al., 2018) which states: “Post-transplant patients should undergo a pre-defined regimen of graft biopsies, titration of immunosuppressive and other therapies, rejection monitoring, assessment for infections, transplant coronary artery disease and/or cardiac allograft vasculopathy, immunosuppression side effects, and other potential complications including neoplasia, and co-morbidities that require comprehensive treatment.” However, the guideline does not mention sST2 regarding prognosis of post-transplant patients (Crespo-Leiro et al., 2018).

VI. State and Federal Regulations, as applicable

The Presage® ST2 Assay kit received 510(k) marketing clearance from FDA in December 2011. According to the FDA 510(k) Summary, the Presage® ST2 Assay is to be used in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic HF. The Presage® ST2 Assay kit is provided in a microplate configuration. The kit contains a ready-to-use 96-well microtiter plate coated with mouse monoclonal antihuman sST2 antibodies; a recombinant human sST2 standard calibrator (lyophilized); a standard diluent; an anti-ST2 biotinylated antibody reagent (mouse monoclonal antihuman sST2 antibodies) in phosphate-buffered saline; a sample diluent; a tracer concentrate and tracer diluent; a wash concentrate; a tetramethylbenzidine reagent; a stop solution; and 2 levels of controls provided in a sealed, lyophilized format (high and low control) (FDA, 2011)

Two other research products are available to assay sST2: the MBL ST2 ELISA kit (Medical and Biological Laboratories, MA) and the Human ST2/IL-1 R4 DuoSet® (R&D Systems, MN). They use different standards, different antibodies, different reagents and buffers and, thus, results are not comparable between them and the Presage® ST2 Assay. Furthermore, neither the MBL ST2 ELISA nor the Human ST2/IL-1 R4 DuoSet® assay has received FDA marketing approval. These assays are not considered in this Policy.

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
83006	Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1).

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

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