ST2 Assay for Chronic Heart Failure and Heart Transplant Rejection

Policy Number: 2.04.130  Last Review: 8/2017  
Origination: 8/2015  Next Review: 8/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for ST2 Assay for Chronic Heart Failure and Heart Transplant Rejection. This is considered investigational.

When Policy Topic is covered
n/a

When Policy Topic is not covered
The use of the Presage® ST2 Assay to evaluate the prognosis of patients diagnosed with chronic heart failure is considered investigational.

The use of the Presage® ST2 Assay to guide management (pharmacological, device-based, exercise, etc.) of patients diagnosed with chronic heart failure is considered investigational.

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, is considered investigational.

Description of Procedure or Service

<table>
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<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tr>
<td>Individuals: With chronic heart failure</td>
<td>Interventions of interest are: Soluble suppression of tumorigenicity-2 assay to determine prognosis and/or to guide management</td>
<td>Comparators of interest are: Standard prognostic markers, including B-type natriuretic peptide levels</td>
<td>Relevant outcomes include: Overall survival, Morbid events, Hospitalization</td>
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<tr>
<td>Individuals: With heart transplantation</td>
<td>Interventions of interest are: Soluble suppression of tumorigenicity-2 assay to determine prognosis and to predict acute cellular rejection</td>
<td>Comparators of interest are: Endomyocardial biopsy for predicting acute cellular rejection</td>
<td>Relevant outcomes include: Overall survival, Morbid events, Hospitalizations</td>
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</table>
Clinical assessment and noninvasive imaging of chronic heart failure (CHF) can be limited in accurately diagnosing patients with heart failure (HF) because symptoms and signs can poorly correlate with objective methods of assessing cardiac dysfunction. For management of HF, clinical signs and symptoms (eg, shortness of breath) are relatively crude markers of decompensation and occur late in the course of an exacerbation. Thus, circulating biomarkers have potential benefit in HF diagnosis and management. A new protein biomarker, referred to as soluble suppression of tumorigenicity-2 (sST2), has elicited interest as a potential aid to predict risk and manage therapy of CHF. Soluble ST2 is also proposed for use in patients after heart transplant.

For individuals who have CHF who receive sST2 assay to determine prognosis and/or to guide management, the evidence includes correlational studies of the Presage ST2 Assay with physiologic and clinical outcomes. Relevant outcomes are overall survival, morbid events, and hospitalization. Most of the evidence is from reanalysis of existing randomized controlled trials and not from studies specifically designed to evaluate the predictive accuracy of sST2. In some studies, but not all, sST2 provided incremental prognostic information above that of standard clinical exam and B-type natriuretic peptide (BNP) levels. There is no evidence that sST2 provides clinically actionable information that can be used to improve outcomes. Thus, there is insufficient evidence to conclude that sST2 improves outcomes compared with standard care using either BNP or N-terminal pro B-type natriuretic peptide measurements. No evidence was identified on the use of the sST2 assay to guide management of patients diagnosed with CHF. The evidence is insufficient to determine the effects of the technology on health outcome.

For individuals who have heart transplantation who receive sST2 assay to determine prognosis and predict acute cellular rejection, the evidence includes a small number of retrospective observational studies on the Presage ST2 Assay. Relevant outcomes are overall survival, morbid events, and hospitalization. One retrospective study (N=241) found that sST2 levels were associated with acute cellular rejection and mortality; another study (N=26) found that sST2 levels were higher during an acute rejection episode than before rejection. No prospective studies were identified that provide high-quality evidence on the ability of sST2 to predict transplant outcomes. The evidence is insufficient to determine the effects of the technology on health outcome.

Heart Failure

HF is one among many cardiovascular diseases that comprises a major cause of morbidity and mortality worldwide. The term heart failure refers to a complex clinical syndrome that causes impairment of the heart’s ability to move blood through the circulatory system.(1) In the United States, approximately 600,000 individuals are estimated to be living with chronic HF.(2) HF is the leading cause of hospitalization among people older than age 65 years, with direct and indirect costs estimated at about $37 billion annually in the United States.(2) Although survival has improved with treatment advances, the absolute mortality rates of HF remain at about 50% within 5 years of diagnosis.
Heart failure can be caused by disorders of the pericardium, myocardium, endocardium, heart valves or great vessels, or metabolic abnormalities. Individuals with HF may exhibit a wide range of LV anatomy and function. Some have normal LV size and preserved ejection fraction (EF); others have severe LV dilatation and depressed EF. However, most patients present with key signs and symptoms that are secondary to congestion in the lungs from impaired LV myocardial function. These include dyspnea, orthopnea, and paroxysmal dyspnea. Other symptoms include weight gain due to fluid retention, fatigue, weakness, and exercise intolerance that also are secondary to diminished cardiac output.

Initial evaluation of a patient in whom HF is suspected is typically based on clinical history, physical examination, and chest radiograph. Because people with HF may present with signs and symptoms that are relatively nonspecific, for example dyspnea, an accurate diagnosis can be a challenge. Therefore, noninvasive imaging studies, such as echocardiography and radionuclide angiography, are used to quantify to pump function of the heart, thus identifying or excluding HF in patients with characteristic signs and symptoms. These tests can also be used to assess prognosis by determining the severity of the underlying cardiac dysfunction. However, clinical assessment and noninvasive imaging methods can be limited in accurately evaluating patients with HF because symptoms and signs can be poorly correlated with objective methods of assessing cardiac dysfunction. Thus, invasive procedures such as cardiac angiography or catheterization are used in selected patients with presumed HF symptoms to determine the etiology (ie, ischemic vs nonischemic) and physiologic characteristics of the condition.

Patients with HF may be treated using a number of interventions. Lifestyle factors such as the restriction of salt and fluid intake, monitoring for increased weight, and structured exercise programs are beneficial as components of self-management. A variety of medications are available to treat HF. These include diuretics (eg, furosemide, hydrochlorothiazide, spironolactone), angiotensin converting enzyme inhibitors (eg, captopril, enalapril, lisinopril), angiotensin receptor blockers (eg, losartan, valsartan, candesartan), β-blockers (eg, carvedilol, metoprolol succinate), and vasodilators (eg, hydralazine, isosorbide dinitrate). Numerous device-based therapies also are available. Implantable cardioverter defibrillators reduce mortality in patients with an increased risk of sudden cardiac death. Cardiac resynchronization therapy improves symptoms and reduces mortality for patients who have disordered LV conduction evidenced by a wide QRS complex on electrocardiogram. Ventricular assist devices are indicated for patients with endstage HF who have failed all other therapies and are also used as a bridge to cardiac transplantation in selected patients.

**HF Biomarkers**

Because of limitations inherent to usual assessment of suspected HF patients, a number of objective disease biomarkers have been investigated to diagnose HF and assess patient prognosis, with the additional goal of using biomarkers to guide
therapy. They include a number of proteins, peptides, or other small molecules whose production and release into the circulation reflect the activation of remodeling and neurohormonal pathways that lead to LV impairment. Examples include BNP, its analog NT-proBNP, troponin T and I, renin, angiotensin, arginine vasopressin, C-reactive protein, and norepinephrine.

BNP and NT-proBNP are considered the reference standard for biomarkers in assessing HF patients. They have had substantial impact on the standard of care for the diagnosis of HF and are included in the recommendations of all major societies including the American College of Cardiology, European Society of Cardiology, and the Heart Failure Society of America. Although natriuretic peptide levels are not 100% specific for the clinical diagnosis of HF, elevated values for either BNP or NT-proBNP in the presence of clinical signs and symptoms reliably identifies the presence of structural heart disease due to remodeling and heightened risk for adverse events. Natriuretic peptides also can help in determining prognosis of HF patients, with elevated blood levels portending poorer prognosis.

In addition to diagnosing and assessing prognosis of HF patients, blood levels of BNP or NT-proBNP have been proposed as an aid for managing patients diagnosed with chronic HF. Levels of either biomarker rise in response to myocardial damage and LV remodeling, whereas they tend to fall as drug therapy ameliorates symptoms of HF. Evidence from a large number of randomized clinical trials (RCTs) that compared BNP- or NT-proBNP-guided therapy to clinically guided adjustment of pharmacologic treatment of patients with chronic HF has been compiled in recent systematic reviews and meta-analyses (MA). However, these analyses have not consistently reported a benefit for BNP-guided management. The largest meta-analysis to date was a patient-level MA that included 2686 patients from 12 RCTs. This MA showed that NT-proBNP-guided management was associated with significant reductions in all-cause mortality and HF-related hospitalization compared with clinically guided treatment. Although BNP-guided management in this MA was not associated with significant reductions in these parameters, differences in patient numbers and characteristics may explain the discrepancy. A second patient-level MA included 11 RCTs and 2000 patients randomized to natriuretic peptide-guided pharmacologic therapy or usual care. These results show that among patients 75 years of age or younger with chronic HF, most of whom had impaired LVEF, natriuretic peptide-guided therapy was associated with significant reductions in all-cause mortality compared with clinically guided therapy. Natriuretic-guided therapy also was associated with significant reductions in hospitalization due to HF or cardiovascular disease.

**ST2 Protein Biomarker**

A new protein biomarker, referred to as ST2 (suppression of tumorigenicity-2) has elicited interest as a potential aid to predict prognosis and manage therapy of chronic HF. This protein is a member of the interleukin-1 (IL-1) receptor family. It is found as a transmembrane isoform (ST2L) and a soluble isoform (sST2), both of which have circulating IL-33 as their primary ligand. ST2 is a unique biomarker that has pluripotent effects in vivo. Thus, binding between IL-33
and ST2L is believed to have an immunomodulatory function via T-helper type 2 lymphocytes and was initially described in the context of cell proliferation, inflammatory states, and autoimmune diseases.(18) However, the IL-33–ST2L signaling cascade also is strongly induced through mechanical strain of cardiac fibroblasts or cardiomyocytes. The net result is mitigation of adverse cardiac remodeling and myocardial fibrosis, which are key processes in the development of HF.(19) The soluble isoform of ST2 is produced by lung epithelial cells and cardiomyocytes and is secreted into the circulation in response to exogenous stimuli, mechanical stress, and cellular stretch. This form of ST2 binds to circulating IL-33, acting as a “decoy,” thus inhibiting the IL-33 associated antiremodeling effects of the IL-33–ST2L signaling pathway. Thus, on a biologic level, IL-33–ST2L signaling plays a role in modulating the balance of inflammation and neurohormonal activation and is viewed as pivotal for protection from myocardial remodeling, whereas sST2 is viewed as attenuating this protection. In the clinic, blood concentrations of sST2 appear to correlate closely with adverse cardiac structure and functional changes consistent with remodeling in patients with HF, including abnormalities in filling pressures, chamber size, systolic and diastolic function.(6,13,15)

An enzyme-linked immunosorbent (ELISA)–based assay is commercially available for determining sST2 blood levels (Presage® ST2 Assay, Critical Diagnostics, San Diego, CA).(16) The manufacturer claims a limit of detection of 1.8 ng/mL for sST2, and a limit of quantification of 2.4 ng/mL, as determined according to Clinical and Laboratory Standards Institute guideline EP-17-A. In 1 published study, a limit of detection of 2.0 ng/mL for sST2 was reported.(16) In the same study, the assay had a within-run coefficient of variation (CV) of 2.5% and a total CV less than 4.0%; demonstrated linearity within the dynamic range of the assay calibration curve; and, exhibited no relevant interference or cross-reactivity.

ST2 is not intended for use in diagnosis of HF, because it is a relatively nonspecific marker that is increased in many other disparate conditions that may be associated with acute or chronic manifestations of HF.(15,16) Although the natriuretic peptides, BNP and NT-proBNP, reflect different physiologic aspects of HF compared with sST2, they are considered to be the reference standard biomarker when used with clinical findings to diagnose, prognosticate, and manage HF and as such are the comparator to sST2.

**REGULATORY STATUS**

In December 2011, the Presage® ST2 Assay kit (Critical Diagnostics, San Diego, CA) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for use with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure. The assay had already received Conformite Europeenne (CE) Mark in January 2011. 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 soluble suppression of tumorigenicity-2 (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).

**Rationale**
This evidence review was originally created in January 2015 and has been updated with searches of the MEDLINE database. The original review also included a search of EMBASE. The most recent literature review was performed through March 23, 2017. Following is a summary of the key literature to date.

**Use of Soluble Suppression of Tumorigenicity-2 Levels to Determine Prognosis and/or to Guide Management of Chronic Heart Failure**

**Clinical Context and Test Purpose**
The purpose of biomarker testing in patients who have heart failure is to inform decisions about treatment goals and choice of treatment. This review evaluates whether the biomarker soluble suppression of tumorigenicity-2 (sST2) assay provides improved prognostic information compared with standardly used biomarkers.

The question addressed in this evidence review is: In individuals with chronic heart failure, does testing for sST2 levels change patient management decisions, especially choice of treatment, improve quality of life (QOL), and/or lead to improvements in health outcomes?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is patients with chronic heart failure.

**Interventions**
The intervention of interest is an sST2 assay cleared by the Food and Drug Administration (FDA).

**Comparators**
The comparators of interest are standard prognostic markers such as B-type natriuretic peptide (BNP) levels.

**Outcomes**
The primary outcome of interest is overall survival. Other relevant outcomes are cardiovascular mortality, QOL, and hospitalizations.

**Time**
The timing of survival outcomes are short-term (in-hospital and 30-day mortality) and longer term (eg, 1- and 5-year) mortality. The timing for other outcomes is also short-term (30-days) and longer term.
Setting
The assay could be used in the inpatient or the outpatient setting.

Correlational Studies
A number of clinical studies in which sST2 blood levels were determined using the Presage ST2 Assay have reported that there is an association between ST2 levels and adverse outcomes in patients diagnosed with chronic heart failure. A substantial body of biomarker evidence has been reported retrospectively from subsets of patients enrolled in randomized controlled trials (RCTs) of heart failure interventions. These RCTs include Val-HeFT (Valsartan Heart Failure Trial); HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training); CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure); and PROTECT (ProBNP Outpatient Tailored Chronic Heart Failure study). Although patients in these RCTs were well-characterized and generally well-matched between study arms, the trials were neither intended nor designed specifically to evaluate biomarkers as risk predictors. At present, no prospectively gathered evidence is available from an RCT in which sST2 levels were compared with levels of a natriuretic peptide (BNP or N-terminal pro B-type natriuretic peptide [NT-proBNP]) to predict risk for adverse outcomes among well-defined cohorts of patients with diagnosed chronic heart failure. Key results of larger individual studies are summarized in Table 1.

Findings of studies on the prognostic value of sST2 for chronic heart failure were pooled in a 2017 meta-analysis by Aimo et al. The meta-analysis included 7 studies, including post hoc analyses of RCTs, and calculated the association between the Presage ST2 Assay and health outcomes. A pooled analysis of 7 studies found that sST2 was a statistically significant predictor of overall mortality (hazard ratio [HR], 1.75; 95% confidence interval [CI], 1.37 to 2.22). Moreover, a pooled analysis of 5 studies found that sST2 was a significant predictor of cardiovascular mortality (HR=1.79; 95% CI, 1.22 to 2.63).

No evidence is available from randomized or nonrandomized controlled studies in which outcomes from groups of well-matched groups of patients managed according to serial changes in sST2 blood levels were compared with those managed according the reference standard of BNP or NT-proBNP levels.

Section Summary: Use of Soluble Suppression of Tumorigenicity-2 to Determine Prognosis and/or to Guide Management of Chronic Heart Failure
Several analyses, mainly retrospective, have evaluated whether sST2 levels are associated with disease prognosis, especially mortality outcomes. Studies mainly found that elevated sST2 levels were statistically associated with elevated risk of mortality. A pooled analysis of study results found that sST2 levels significantly predicted overall mortality and cardiovascular mortality. Several studies, however, found that sST2 test results did not provide additional prognostic information compared with BNP or NT-proBNP levels. In general, it appears that elevated sST2 levels predict higher risk of poor outcomes better than lower levels. The available evidence is limited by interstudy inconsistency and differences in patient
characteristics, particularly the severity of heart failure, its etiology, duration, and treatment. Furthermore, most of the evidence was obtained from retrospective analyses of sST2 levels in subsets of larger patient cohorts within RCTs, potentially biasing the findings. The evidence primarily shows associations between elevated sST2 levels and poor outcomes, but does not go beyond that in demonstrating a clinical connection among biomarker status, treatment received, and clinical outcomes.

Use of Soluble ST2 in Post Heart Transplantation Patients

Clinical Context and Test Purpose
The purpose of biomarker testing in patients who have had heart transplantation is to predict acute cellular rejection and provide information on prognosis to inform patient management decisions.

The question addressed in this evidence review is: In individuals who have had heart transplantation, does testing for sST2 levels reduce the need for endomyocardial biopsy, contribute to patient management decisions (eg, dosing of antirejection medications), and/or lead to improvements in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients who have had heart transplantation.

Interventions
The intervention of interest is an FDA-cleared sST2 assay.

Comparators
The comparator of interest for predicting acute cellular rejection is endomyocardial biopsy.

Outcomes
The primary outcomes of interest are OS and morbid events (ie, acute cellular rejection). Another outcome of interest is hospitalizations.

Time
The timing of survival outcomes are short-term (in-hospital and 30-day mortality) and longer term (eg, 1- and 5-year) mortality. The timing of acute cellular rejection is primarily within the first year after transplantation.

Setting
The assay could be used in the inpatient or the outpatient setting.

Observational Studies
Serum ST2 levels have been proposed as a prognostic marker post heart transplantation and as a test to predict acute cellular rejection (graft-versus-host disease). There is very little evidence available for these indications. Januzzi et al
(2013) retrospectively assessed sST2 levels in 241 patients post heart transplant. Over a follow-up of up to 7 years, sST2 levels were predictive of total mortality (HR=2.01; 95% CI, 1.15 to 3.51; p=0.01). Soluble ST2 levels were also associated with risk of acute cellular rejection, with a significant difference between the top and bottom quartiles of sST2 levels in the risk of rejection (p=0.003).

In study by Pascual-Figal et al (2011), 26 patients were identified with post cardiac transplantation and an acute rejection episode. Soluble ST2 levels were measured during the acute rejection episode and compared to levels measured when acute rejection was not present. Soluble ST2 levels were higher during the acute rejection episode (130 ng/mL) than during the nonrejection period (50 ng/mL; p=0.002). Elevated sST2 levels greater than 68 ng/mL had a positive predictive value of 53% and a negative predictive value of 83% for the presence of acute cellular rejection. The addition of sST2 levels to serum BNP resulted in incremental improvement in identifying rejection episodes.

**Section Summary: Use of Soluble ST2 in Post Heart Transplantation Patients**

Few studies are available and they are observational and retrospective. No prospective studies were identified that provide high-quality evidence on the ability of sST2 levels to predict transplant outcomes. One retrospective study (N=241) found that sST2 levels were associated with acute cellular rejection and mortality; another study (N=26) found that sST2 levels were higher during an acute rejection episode than before rejection.

**Table 1. Summary of Selected Clinical Studies of sST2 to Predict Outcomes in Chronic Heart Failure Patients**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Population, N</th>
<th>Mean Age, y</th>
<th>Study Description and Biomarkers</th>
<th>Primary End Points</th>
<th>Mean FU</th>
<th>Synopsis of Findings</th>
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<tr>
<td>Ky et al (2011)27</td>
<td>Ambulatory CHF (N=1141, 75% of Penn HF Study population)</td>
<td>56</td>
<td>Retrospective analysis of sST2 and NT-proBNP levels and their incremental usefulness over clinical SHFM</td>
<td>Mortality or cardiac transplant</td>
<td>2.8 y</td>
<td>- Elevated sST2 levels associated with increased risk (adjusted p=0.002) sST2 in plus NT-proBNP levels showed moderate improvement over SHFM in predicting outcomes (p=0.017)</td>
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<tr>
<td>Bayes-Genis et al (2012)28</td>
<td>Ambulatory decompensated HF (N=891)</td>
<td>70</td>
<td>Retrospective analysis of sST2 and NT-proBNP levels from consecutive series of patients</td>
<td>Mortality</td>
<td>2.8 y</td>
<td>- Elevated sST2 and NT-proBNP levels provided independent and additive prognostic information for elevated risk of mortality (p&lt;0.001)</td>
</tr>
<tr>
<td>Study</td>
<td>Population Description</td>
<td>Methodology</td>
<td>Follow-up Period</td>
<td>Findings</td>
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</table>
| Broch et al (2012)    | Ischemic CHF (N=1149, 30% of CORONA RCT)                         | Retrospective analysis of sST2 NT-proBNP, and CRP levels | 2.6 y            | Elevated sST2 levels independently associated with increased risk for mortality, hospitalization due to HF, or any CV hospitalization (p<0.001)  
|                       |                                                                  |                                                  |                  | sST2 did not provide additive prognostic information vs NT-proBNP       |
| Felker et al (2013)   | Ambulatory HF (N=910, 39% of HF-ACTION RCT)                      | Retrospective analysis of sST2 and NT-proBNP levels | 2.5 y            | Elevated sST2 levels independently associated with increased risk for mortality, hospitalization due to HF, or any CV hospitalization (p<0.000)  
|                       |                                                                  | Mortality, hospitalization, functional capacity   |                  | sST2 and NT-proBNP provided independent prognostic information         
|                       |                                                                  |                                                  |                  | sST2 did not provide additive prognostic information vs NT-proBNP       |
| Gaggin et al (2013)   | Recently decompensated CHF (N=151, 100% of PROTECT RCT)         | Retrospective analysis of sST2 and NT-proBNP levels | 0.8 y            | Elevated sST2 levels associated with increased risk for adverse CV outcome (p<0.001)  
|                       |                                                                  | Composi te outcome (worsening HF, hospitalization for HF, clinically significant CV events) |                  | sST2 and NT-proBNP did not provide independent prognostic information |
| Anand et al (2014)    | CHF (N=1650, 33% of Val-HeFT RCT)                               | Retrospective analysis of sST2, NT-proBNP, and other biomarker levels | 63               | Elevated sST2 levels independently associated with increased risk of poor outcomes (p<0.000)  
|                       |                                                                  | All-cause mortality and composite outcome (mortality, SCD with resuscitation, hospitalization for HF, or) |                  | Baseline sST2 levels did not provide substantial prognostic information when added to a clinical model that included NT-proBNP levels |
Summary of Evidence

For individuals who have chronic heart failure who receive the soluble suppression of tumorigenicity-2 (sST2) assay to determine prognosis and/or to guide management, the evidence includes correlational studies and a meta-analysis. Relevant outcomes are overall survival, quality of life, and hospitalization. Most of the evidence is from reanalysis of existing randomized controlled trials and not from studies specifically designed to evaluate the predictive accuracy of sST2. Studies have mainly found that elevated sST2 levels are statistically associated with elevated risk of mortality. A pooled analysis of study results found that sST2 significantly predicted overall mortality and cardiovascular mortality. Several studies, however, found that sST2 test results did not provide additional prognostic information compared with N-terminal pro B-type natriuretic peptide levels. Moreover, no comparative studies were identified on the use of the sST2 assay to guide management of patients diagnosed with chronic heart failure. The

<table>
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<tr>
<th>Study</th>
<th>Setting and Design</th>
<th>Results</th>
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<tr>
<td>Zhang et al (2015) [33]</td>
<td>De novo HF or decompensated CHF (N=1161)</td>
<td>Elevated sST2 levels independently associated with increased risk of all-cause mortality (p&lt;0.001) after adjustment for clinical risk factors and NT-proBNP levels</td>
</tr>
<tr>
<td>Dupuy et al (2016) [34]</td>
<td>HF for ≥6 mo (N=178)</td>
<td>Elevated sST2 levels independently associated with increased risk for all-cause mortality and CV mortality (p&lt;0.001)</td>
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<td></td>
<td>Prospective analysis of sST2, NT-proBNP, and other biomarker levels in patient sample from 1 center in France</td>
<td>In multivariate analysis, sST2 and CRP significantly associated with all-cause mortality and CV mortality</td>
</tr>
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</table>

CHF: chronic heart failure; CRP: C-reactive protein; CV: cardiovascular; FU: follow-up; HF: heart failure; IV: intravenous; NT-proBNP: N-terminal pro B-type natriuretic peptide; RCT: randomized controlled trial; SCD: sudden cardiac death; SHFM: Seattle Heart Failure Model; sST2: soluble suppression of tumorigenicity-2.

a Median.
Evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have heart transplantation who receive sST2 assay to determine prognosis and/or to predict acute cellular rejection, the evidence includes a small number of retrospective observational studies on the Presage ST2 Assay. Relevant outcomes are overall survival, morbid events, and hospitalization. No prospective studies were identified that provide high-quality evidence on the ability of sST2 to predict transplant outcomes. One retrospective study (N=241) found that sST2 levels were associated with acute cellular rejection and mortality; another study (N=26) found that sST2 levels were higher during an acute rejection episode than before rejection. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements
In 2013, the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) published joint evidence-based guidelines, informed by a systematic review of the literature, on the management of heart failure. The review states that soluble suppression of tumorigenicity-2 (sST2) is a biomarker for myocardial fibrosis that predicts hospitalization and death in patients with heart failure and provides additive prognostic information to natriuretic peptide levels. In the ambulatory heart failure setting, ACCF and AHA applied a class IIb recommendation and assigned a level B of evidence for the use of sST2 as an option to provide additive prognostic information to established clinical evaluation and biomarkers. The guidelines do not address other uses of sST2.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in April 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

References


7. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. Aug 2012;14(8):803-869. PMID 22828712


Billing Coding/Physician Documentation Information

83006 Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)

ICD-10 Codes

I50.1 Heart failure code range
I50.9

Additional Policy Key Words

N/A

Policy Implementation/Update Information

8/1/15 New Policy. Considered Investigational.
8/1/16 “Heart Transplant Rejection” added to policy title. No policy statement changes.
8/1/17 No policy statement changes.

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