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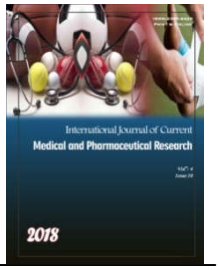


# PERSPECTIVE OF ST2 AS A CARDIAC BIOMARKER

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**ABSTRACT**

Heart failure [HF] has high morbidity and mortality. Once it sets in, it shortens the survival hence its treatment should be aimed at delaying the cardiac mortality. The pharmacotherapy should target the basic pathology of HF which consists of myocardial stretch, remodeling and fibrosis. Hormones of Renin Angiotensin Aldosterone system and Catecholamines are responsible for cardiac remodeling and fibrosis. The release of cardiac biomarkers natriuretic peptides [NPs] neutralize the myocardial stretch and reduce the volume overload but do not regress the process of remodeling and fibrosis. Hence they carry better diagnostic than prognostic specificity. Specific biomarkers of remodeling and fibrosis are soluble circulating form of suppression of tumerogenicity-2[sST2] and galectin-3. Like NPs, sST2is not affected by age, body mass index and renal insufficiency. In serial estimation, sST2 stands as a specific biomarker than Glalectin-3 for prognosis and risk stratification. High sST2 levels prompt the clinician to initiate the therapies like high dose of beta blockers, ACE inhibitors and Angiotensin receptor blockers, directed against the cardiac remodeling and fibrosis which result in to better cardiac outcome. Though the levels of sST2 get affected by certain inflammatory and immune diseases, still sST2 stands as a specific prognostic cardiac biomarker at present.



## INTRODUCTION

Heart failure [HF] is associated with severe morbidity and mortality. Once the HF sets in, survival of the patient gets compromised. Mortality rate of these patients is around 50% at the end of 5years[1] about 75% patients of HF have hypertension which is the commonest etiology for HF. The other causes for HF are ischemic heart disease with or without myocardial infarction, metabolic and non-metabolic cardiomyopathy, valvular and inflammatory heart diseases.[2]

### *Cardiac remodeling, fibrosis and HF*

Cardiac remodeling is the result of myocardial stress arising due to any factor which is responsible for inducing pressure over load, hypertrophy, dilatation or inflammation of myocardium. It alters the ventricular physiological and pathological morphology. It is divided in to early and late remodeling phases.[3]

Early phase [within 72hours] remodeling changes relates more to the acute myocardial injury, triggering responses involving Rennin Angiotensin Aldosterone [RAAS] system and Catecholamines to compensate for cardiac hypofunction and to maintain cardiac output by inducing peripheral vasoconstriction, myocardial stimulation and retention of sodium and water to increase the circulating volume. The release of natriuretic peptides like ANP and BNP try to correct the volume overload and sodium retention by their natriuretic, diuretic and vasodilatory action so as to reduce myocardial stress. They also inhibit the secretion of rennin and aldosterone. Early phase cardiac remodeling also comprises neutrophil infiltration, activation of matrix metalloproteinases in the extracellular matrix degrading intermyocyte collagen resulting in to myocyte slippage, ventricular wall thinning and dilatation.[3]

Late phase [after 72 hours] cardiac remodeling involves cardiomyocyte hypertrophy, increased release of Transforming growth factor[TGF beta]-1 resulting in to fibroblast proliferation and transformation of macrophages in to myofibroblast, activation of Tissue inhibitor of metalloproteinases [TIMPs] type I and III, collagen synthesis and resulting in to fibrosis. RAAS activated increased synthesis of aldosterone also contributes to the process of myocardial fibrosis. Fibrosis affects both the infarcted and non-infarcted myocardium. It is an attempt at remodeling to compensate for the distending forces and to prevent further cardiac deformity.[3]

Cardiac remodeling is an effort to compensate for HF. But in the due course myocardium cannot maintain the cardiac output and enters in to the phase of decompensated HF with fully manifested clinical signs and symptoms of HF. Fall in the left ventricular ejection fraction and rise in the left ventricular end

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diastolic volume and diastolic dysfunction predict the poor prognosis.[4,5]

***Cardiac biomarkers***

The term biomarker is defined by National Institute of Health [NIH] in 2001 as a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathological process or pharmacological responses arising as a result of pharmacological interventions.[6]It is an indicator of disease trait, risk marker, clinical or preclinical presentations of disease state or its progression.[7]Cardiac biomarkers help in the assessment of risk factors in the patients of HF.[8,9]Several biomarkers have been investigated which help in the diagnosis and the prognosis of the patients of HF. These are -Brain natriuretic peptide [BNP],N-Terminal-proBNP [NT-proBNP], Galectin-3,Soluble endothelin, Growth differentiation factor-15, Copeptin, Suppression of tumerogenicity-2 [ST2].[10-15]

***ST2 -as a cardiac biomarker***

ST2 is a member of interleukin-1 [IL-1] receptor family, also known as IL-1 receptor like-1 [IL-1RL-1].ST2 stands for suppression of tumerogenicity 2. It was first discovered in 1989 and in 2002 it was reported that ST2 could be expressed from cardiac myocytes as a result of myocardial stress.[16,17]ST2 is a receptor for interleukin-33 [IL-33],a cytokine secreted by the damaged living cells.IL-33 is expressed more in lungs, spinal cord, brain and skin and low in spleen, lymph tissue, pancreas, kidney and heart.[18]ST2 system gets upregulated in cardiomyoctes and fibroblasts in response to cardiac injury. It exists mainly in two forms-a membrane bound ST2L and a soluble circulating form sST2. ST2L is composed of three extracellular immunoglobulin G domains, a single transmembrane domain and an intracellular domain. sST2 is a truncated soluble receptor, lacks transmembrane and intracellular domain hence moves freely and can be measured in the circulation.[18-20]In experimental studies it is shown that the binding of interleukin-33 [IL-33] to ST2L is cardioprotective which reduces myocardial fibrosis, cardiomyocyte hypertrophy, apoptosis and improves myocardial function. This cardioprotective effect results through ST2L receptor and not through sST2.[16,17,19]sST2 acts as a decoy receptor for IL-33 and in dose dependent manner blocks the cardioprotective effect of IL-33/ST2L combination.[18] Decoy receptor is a receptor which is able to recognize and bind to specific growth factors or cytokines efficiently,but it is not able to signal or activate the intended receptor complex. It acts as an inhibitor, binding a ligand and keeping it away from binding to its regular receptor.[21]There is a third isoform of ST2 which is produced in human by differential processing of a single copy which is expressed in many gastrointestinal organs labeled as ST2V.[18]

The main sources of sST2 are cardiac myocytes and fibroblasts. It rises in response to myocardial stress or injury. The other nonmyocardial sources are endothelial cells of macrovasculatures like coronary arteries and aorta and microvascular system of heart.ST2 is also associated with inflammatory and immune processes where Th2 associated cytokines play an important role in conditions like bronchial asthma, pulmonary fibrosis, collagen vascular diseases, rheumatoid arthritis, fibroproliferative disorders, ulcerative colitis, malignancy, trauma, sepsis and helminthic infections.[16,18]

***Serum levels of sST2 in other diseases***

Serum levels of sST2 were found to be high in patients of bronchial asthma and strongly related to the neutrophilic than the eosinophilic asthma.[22]In patients of systemic lupus erythematosus [SLE], the serum levels of sST2 were higher than in healthy controls and correlated well with the disease activity.[23]Similarly levels of sST2 were significantly higher in the patients of macrophage activation syndrome and in active systemic juvenile idiopathic arthritis [JIA]which were declined during the phase of remission.[24] Hong *et al* observed the raised levels of sST2in the patients of rheumatoid arthritis as compared with healthy controls which were reduced eventually after the administration of disease modifying anti rheumatic drugs [DMARDs][25]

***Diagnostic and prognostic evaluation of sST2 in decompensated heart failure***

NPs are considered asagold standard for the diagnosis of acute heart failure with dyspnoea but they do not predict the risk stratification in these patients. As per recent studies sST2 is the most promising biomarker for the risk stratification for the patients of HF although its diagnostic value is not superior to NPs. Expression of sST2 from biomechanically loaded cardiomyocytes starts rising within one hour of generation of myocardial stress in acute myocardial infarction [MI][26-27]In 2011 the Conformite Europeenne [CE] Mark and the USA FDA approved the Presage sST2 assay for its use in assessing the prognosis in HF patients.[28]In the Pro-Brain Natriuretic peptide Investigation of Dyspnea in the Emergency Department[PRIDE] study the levels of sST2 were measured by Presage ST2 assay and were found to be higher in acute HF than in non-HF patients and it was a powerful predictor of the mortality. There was clear correlation between the sST2 levels and mortality, the higher the levels higher was the mortality. However for the diagnosis of heart failure NT-proBNP remained the best biomarker.[29,30]With the sub-analysis of PRIDE study it was inferred that rise ofsST2 was associated with the two fold increase in the mortality irrespective of other parameters including NPs. Unlike NPs levels of sST2 did not correlate with previous diagnosis of HF, cause of HF whether ischemic or nonischemic, atrial fibrillation, age and body mass index.[26,31]A prognostic biomarker should be unaffected by or be independent of traditional risk factors like age, body mass index [BMI] or serum creatinine. No significant correlation of age,BMI and creatinine was noted with sST2.Biomarkers like BNP and Galectin-3 get affected by these factors. ThussST2 stands as asuperior biomarker than BNP and Galectin-3.[32]Galectin-3 is a member of lectin family and is a beta galactosidase binding soluble protein. It is also a marker of myocardial fibrosis and remodeling like sST2.[33,34]Most of the studies regarding the prognostic value of sST2 and Galectin-3 are related to ischemic etiology or mixed ischemic but not about inflammatory etiology. David Binas *et al* studied the role of these biomarkers in dilated cardiomyopathy [DCM] with infective etiology. They found that higher levels of sST2 were predictor of all cause mortality and cardiac mortality which was not the case with Galectin-3.Though it is considered that sST2 relates to the myocardial remodeling and fibrosis, in case of DCM it was raised before the development of this pathologic process indicating that its rise is also related to hemodynamic stress.[35,36]It is found from the survival analysis that the levels of Galectin-3 are not useful is patients of non-ischemic HF. But Hu *et al* observed in their study that Galectin-3 levels were raised in non-ischemic cardiomyopathy

and were associated with adverse cardiac events in univariate analysis.[37]But Galectin-3 was considered not to be useful for serial measurements in chronic HF to predict risk stratification.[38]

sST2 is involved in the cardiac remodeling. This component of pathology of HF was studied by Shaha *et al* with the help of 2 dimensional echocardiography where the values of sST2 were correlated well with the left ventricular systolic and diastolic dimensions, left ventricular ejection fraction, right ventricular systolic pressure and also with the heart rate, jugular venous pressure and NT-proBNP.[39]In the PRIDE study median Presage sST2 values in the patients of acute decompensated heart failure were 42.7ng/ml which were found to be very high to the tune of 148ng/ml by Zilinski in the very sick patients of HF. In this study these high levels of sST2 were predictors of mortality but not the NT-proBNP or high sensitivity troponin.[40]Thus sST2stands as a strongest biomarker for the prediction of death risk beyond a clinical model. For the prediction of 30days and l year mortality sST2 emerges as a best biomarker.[41]

American college of cardiology foundation and American heart association recommended sST2 assay in patients of acute heart failure [AHF] for risk stratification.[42] C.G.Bahuleyan *et al* in their study found that in patients with HF having reduced ejection fraction, the concentration of sST2 at baseline and in serial estimation was significantly raised among the patients who had worsening of HF, adverse outcome, cardiac mortality and re-hospitalization than those without them.[43]In recent meta-analysis, sST2 is considered as a marker of myocardial fibrosis and remodeling and a strong predictor of cardiovascular outcome in both acute and chronic HF.[44,45]

Serial measurement of sST2 in acute HF guided for risk stratification,[38,46] for possible anticipation of adverse cardiac outcome [47,48]and for initiating the anti-remodeling therapy like beta blocker.[48]Using a new Presage assay for serial sST2 estimation in cases of chronic HF in studies like Controlled Rosuvastatin Multinational Trial in Heart Failure [ CORONA] study,[49] Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy [ PROTECT] study,[50] PROTECT study with anti-remodeling beta blocker therapy[51]and Valsartan Heart Failure Trial [VAL-HeFT] study[52], rising levels of sST2correlated well with the adverse cardiac outcome.[49-52]

In chronic HF sST2 values were equally predictive of cardiovascular risk.[53]There was a strong association between high sST2 levels and accelerated cardiovascular mortality in chronic HF.[54]Barcelona study proved the superiority of sST2 over Galectin-3, though both are the markers of cardiac remodeling and fibrosis, in the risk stratification related to cardiac mortality, the high sST2 levels correlated well with high cardiac mortality.[55,56]Studies like Heart Failure: A Controlled Trial Investigating Outcome Of Exercise Training [HF-ACTION] study,[57]CORONA study,[49] and studies done by Gruson *et al*[58] and Daniels *et al* confirmed the role of sST2 in risk stratification and predicting the cardiac mortality.[59]

***Effect of pharmacotherapy of HF on biomarkers***

Treatment with drugs like beta blockers which prevent cardiac remodeling and drugs like ACE inhibitors, Angiotensin receptor blockers, aldesterone receptor antagonists like aldosterone and eplerenone which prevent cardiac remodeling and fibrosis is associated with lower sST2 levels. On the contrary drugs like Digoxin and Diuretics were associated with unaffected high sST2 levels as they do not affect the basic pathology of cardiac remodeling and fibrosis.[60]

In PROTECT study effects of beta blocker on serial measurements of sST2 were studied. Patients with high sST2 levels who received high dose of beta blockers benefited more with reduction in CV mortality than those who were put on low doses.[51]In trial like VAL-HeFT, sST2 levels were measured at base line, after 4months and at the end of 1st year in the patients of LV dysfunction who were on Valsartan. In these cases serial rise in sST2 from base line to end of 1st year was a significant predictor of CV events.[52]

Estimation of sST2 has a potential importance in case of HF like HbA1c is for diabetes mellitus. Serial rise in the levels of sST2 definitely guides to plan for the aggressive drug therapy to prevent myocardial remodeling and fibrosis and possible adverse cardiac events, as this biomarker is strong predictor of mortality. Rise in sST2 levels despite the adequate pharmacotherapy and worsening of clinical condition would help the clinician to initiate therapies like implantable cardiovascular defibrillator, cardiac resynchronization therapy, CardioMems implantation [pulmonary artery pressure monitoring] and left ventricular assist device to prevent or overcome the crisis.[61]

***Limitations and merits of sST2***

In cases of acute and chronic HF, high sST2 levels are related to adverse cardiac outcome. It has more of prognostic importance than diagnostic which can guide for the biomarker guided therapy to prevent cardiac remodeling and fibrosis. In comparison with NPs like ANP, BNP or NT-proBNP which specifically mirror the patho-physiological conditions of cardiac stretch in HF, sST2 does not completely show this specificity and hence lack diagnostic sensitivity. In the case DCM the sST2 levels correlated well with the myocardial stretch response. But sST2 not merely reflect cardiac stretch but is also involved in non cardiac conditions like immune and inflammatory response related diseases as described earlier. Levels of NPs and Galectin-3 get modified by factors like age, body mass index and serum creatinine levels.sST2 remains unaffected by these factors hence forms a better prognostic index and guide for risk stratification in cases of HF. So it is clear that sST2 is not only the independent prognostic biomarker and risk stratifier but it also outperforms clinical variables and other biomarkers and provides incremental prognostic value which is a very relevant issue in clinical practice.[28]

## CONCLUSION

Though many cardiac biomarkers are available, the NPs are considered as diagnostic and sST2 as the prognostic. NPs get affected by the factors like age, body mass index and serum creatinine and also they do not correlate with the prognosis. High sST2 levels correlate with the risk stratification and prognostic information. Levels of sST2 are not affected by the factors which impact NPs. Serial estimation of Galectin-3 levels do not correlate with the risk stratification like sST2.Even though the levels of sST2 are raised in some inflammatory and immunological disorders, at present it stands as the specific biomarker of prognosis of HF.

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