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# ST2: A RISING STAR AS A BIOMARKER FOR HEART FAILURE - UNVEILING POTENTIAL AND ADDRESSING CHALLENGES

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**ABSTRACT**

Heart failure (HF) is a major global cause of death, accounting for approximately 32% of worldwide mortality, with a pronounced impact in developing nations like India. Despite various diagnostic techniques and protein biomarkers like BNP used in clinical practice, their prognostic utility remains limited, influenced by factors such as BMI and renal disease. Inconsistencies in trial outcomes emphasize the need for a more reliable HF biomarker. Among emerging markers, soluble suppression of tumorigenicity 2 (sST2) stands out for its potential in risk stratification. The sST2, a member of the interleukin 1 receptor family, offers promise due to its ability to integrate inflammation, fibrosis, and cardiac stress. The significance of sST2 as a biomarker in heart failure (HF) diagnosis and management, focusing on its detection, measurement techniques, advantages, limitations, and the development of novel assays. Several methods, like enzyme-linked immunosorbent assay (ELISA), automated immunoassays, and point-of-care testing devices, enable accurate quantification of sST2 levels in patient serum. Notably, a recent study introduced a DNA aptamer-based assay utilizing aptamer sS9_P, demonstrating its specificity and sensitivity in discriminating HF patients from healthy individuals. Despite its advantages, challenges such as lack of standardization, the multifactorial nature of HF, and cost-effectiveness need to be addressed. Standardization efforts, consideration of confounding factors, and economic evaluation are essential to optimize sST2 testing's utility in clinical practice. Combining aptamer and antibody-based assays shows potential to revolutionize heart failure diagnosis with rapid, point-of-care tools. Overall, sST2 emerges as a valuable biomarker offering insights into HF pathophysiology, prognosis, and therapeutic monitoring, with ongoing efforts focused on enhancing its clinical utility and addressing existing challenges.

## INTRODUCTION:

The recent reports in the medical field has revealed that heart failure (HF) is a leading cause of death globally and its prevalence continues to rise. According to estimates provided by the World Health Organization (WHO)[1], HF and other cardiovascular diseases claim roughly 32% of lives globally, with a heavier burden felt in developing countries like India. Consequently, there is a growing imperative to enhance early detection methods for HF to mitigate its associated morbidity and mortality rates.

Current diagnostic approaches encompass a range of techniques, including physical examinations2, electrocardiography[2], and blood analysis[3]. Additionally, various protein biomarkers, such as fibrinogen[4], apolipoproteins[5], cardiac troponin I (cTnI)[6], Galectin-3[7], N-terminal pro-peptide of B-type natriuretic peptide (BNP)[8], and C-reactive protein (CRP)[9], constitute a frequent tool in the clinical sphere. Despite their use, the effectiveness of these biomarkers in prognosis is still uncertain. One notable exception is BNP, which plays a crucial role in diagnosing or ruling out HF in both acute and ambulatory settings. Nevertheless, it's imperative to note that BNP levels can be fluctuated based on body mass index (BMI), renal diseases, and advanced age, potentially leading to inconclusive results, particularly in certain patient populations[10].

Moreover, the outcomes of numerous randomized prospective trials investigating traditional biomarker monitoring and therapy guidelines have yielded inconsistent results[11]. Consequently, there is a clear need for identifying a more reliable and superior biomarker to aid in risk stratification among HF patients.

ST2, a marker integrating inflammation, fibrosis, and cardiac stress, shows promise as a clinically relevant biomarker for disease progression due to its structural and functional similarity to the interleukin-1 receptor family. It exists in humans in two main forms: a soluble, circulating form (sST2) and a transmembrane form (ST2L)[12,13].

### The Rise of sST2:

The Food and Drug Administration (FDA) recently documented sST2 as a valuable tool for diagnosis in HF patients[14].

A large multicentric study (TRIUMPH) involving 496 patients demonstrated a strong association between elevated sST2 levels and increased risk of death or hospital readmission within a year[15].

These findings suggest that sST2 holds significant potential as a reliable biomarker for HF, offering improved accuracy and prognostic information compared to existing markers.

### ST2: Understanding the Molecule and its Role in HF

In the realm of cardiovascular research, the elucidation of molecular pathways underlying heart failure has been instrumental in shaping therapeutic strategies. Among these pathways, the scrutiny of ST2 has garnered significant attention. ST2L, one of the isoforms of ST2: a membrane-bound form binds with interleukin-33 (IL-33), evokes cytokine mediated regulation of inflammation and tissue repair. Upon binding to IL-33, ST2L initiates downstream signaling cascades, including the activation of NF-κB and MAPK pathways, ultimately modulating immune responses and promoting tissue homeostasis[16].

Conversely, sST2 behaves as a decoy receptor by sequestering IL-33, thereby antagonizing the protective effects mediated by the IL-33/ST2L axis[16]. Increased sST2 levels were evident in various pathological conditions, including heart failure, where it serves as a biomarker for adverse outcomes and disease progression[16]. In the context of heart failure, dysregulation of the IL-33/ST2 ratio plays a crucial role in perpetuating myocardial inflammation,

fibrosis, and remodeling. Experimental evidences suggest that the genetic ablation or pharmacological blockade of ST2 exacerbates cardiac dysfunction and adverse remodeling following myocardial injury, underscoring the cardioprotective role of ST2 signaling[12].

Moreover, clinical investigations have highlighted the prognostic utility of sST2 as a biomarker for risk assesment in heart failure patients. Higher incidence of appearance of sST2 in circulation have been associated with increased mortality, hospitalizations, and adverse cardiac events, independent of traditional risk factors and established biomarkers[15]. The burgeoning interest in targeting the IL-33/ST2 axis for therapeutic intervention underscores its potential as a druggable pathway in heart failure management. Strategies aimed at enhancing ST2L signaling or neutralizing sST2 hold promise for mitigating myocardial inflammation, fibrosis, and dysfunction, thereby offering novel avenues for improving clinical outcomes in heart failure patients.

**Detection Methods**

The detection and measurement of sST2 levels in the blood play a crucial role in cardiovascular medicine, particularly in heart failure management. Various techniques have been developed to accurately quantify sST2 levels, providing valuable insights into disease prognosis, risk stratification, and therapeutic monitoring. Among them Enzyme-linked immunosorbent assay (ELISA) a commonly employed technique for quantifying sST2 levels in clinical practice[17]. ELISA kits utilize specific antibodies against sST2 to capture and detect its presence in biological samples such as serum or plasma. This method offers high sensitivity and specificity, allowing for precise measurement of sST2 concentrations over a wide range of values[17]. For example, commercial ELISA kits like the Human ST2/IL-33R ELISA Kit, cat# RAB0281 (Sigma-Aldrich), Presage ST2 assay (Critical diagnostics, San Diego, USA), the Human ST2 ELISA Kit, cat# ab254505 (Abcam) and to name a few have been validated for the accurate quantification of sST2 levels in HF patients.

Additionally, point of care (POC) diagnostic tools have been developed to enable real-time measurement of sST2 levels at the bedside or in outpatient settings. These portable devices offer convenience and rapid turnaround time, allowing for immediate clinical decision-making based on sST2 measurements. For example, the AFIAS ST2 assay (Boditech Med Inc., Chuncheon, Korea) is a POC testing platform that utilizes fluorescence immunoassay technology to quantify sST2 levels in whole blood or plasma, providing actionable results in few minutes.

In a recent study by Gupta et al. (2024)[18], the sST2 level was measured using an aptamer (DNA) based assay. Through the Systematic Evolution of Ligands with Exponential Enrichment (SELEX) process, an aptamer named sS9_P was isolated from an aptamer library. This sS9_P aptamer exhibited a low nanomolar range dissociation constant (Kd) and a Limit of Detection (LOD) of approximately 4 ng. Employing the sS9_P aptamer in an Aptamer Linked Immobilized Sorbent Assay (ALISA), the team successfully quantified sST2 levels in the serum of 99 patients. Notably, the sS9_P aptamer displayed significant discrimination between HF patients and control group, with 83% specificity and 64% sensitivity. In contrast, an sST-2 antibody demonstrated a lower specificity (~44%) but a higher sensitivity (~87%). This investigation underscores the synergistic potential of aptamer and antibody-based assays, suggesting a combined strategy to develop POC diagnostic tools tailored to rapidly detect HF patients. This approach aligns with the broader discourse on techniques for measuring sST2 levels[18].

**Recent Advancements and Future Directions**

While sST2 holds immense promise, continued research is crucial to unlock its full potential:

- **Optimizing cut-off values:** Establishing standardized cut-off points for sST2 levels across diverse populations remains crucial for distinguishing healthy individuals, those at risk, and confirmed HF cases.
- **Integration into clinical practice:** Integrating sST2 testing into established HF management algorithms requires further exploration to determine its cost-effectiveness and impact on patient outcomes in real-world settings.
- **Understanding the mechanisms:** Elucidating the precise mechanisms by which sST2 contributes to HF pathogenesis could pave the way for targeted therapies aimed at interrupting the detrimental signaling pathways.
- **Novel applications:** Exploring the potential of sST2 in guiding treatment decisions, monitoring response to therapy, and identifying individuals who may benefit from advanced interventions like cardiac transplantation are promising avenues for future research.

## CONCLUSION

Heart failure (HF) is a global menace, responsible for a staggering 32% of global mortality, particularly burdening developing nations like India. Despite diagnostic advancements and the use of biomarkers like BNP, their predictive accuracy remains hampered by factors such as BMI and renal complications, necessitating more reliable indicators. The sST2 emerged as a beacon of hope, combining inflammation and fibrosis associated with cardiac health to offer deeper insights into HF dynamics. Precise quantification via ELISA and aptamer-based assays unveils sST2's potential, promising enhanced diagnostic accuracy. However, challenges such as standardization and cost-effectiveness persist, underscoring the need for collaborative efforts. The fusion of aptamer and antibody-based assays holds promise for rapid, point-of-care diagnostics, revolutionizing HF management. In conclusion, sST2 embodies a transformative paradigm in HF care, offering comprehensive understanding and personalized interventions, with ongoing endeavors aimed at optimizing its clinical utility and accessibility.

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