E-ISSN: 3078-4514 | P-ISSN: 3105-1316
Vol. 2, No. 2, 2025
DOI: 10.71295/JHDT.2025.02.2.07

LITERATURE REVIEW

Cardiac Effects of sST2 Receptors: A Literature Review

Gulana Aghayeva*, Gulnaz Dadashova, Terane Cavadova

Institute of Cardiology, Baku, Azerbaijan.

Corresponding Author: *Gulana Aghayeva, Email: doctorgulane@yahoo.com*

Received: 01/12/2025 **Revised:** 05/12/2025 **Accepted:** 06/12/2025

Abstract

Continuous identification of new parameters and biomarkers is essential for improving the clinical assessment of patients with heart failure (HF). In recent years, the ST2 protein has emerged as a promising biomarker in cardiovascular diseases. ST2 is a member of the interleukin-1 receptor family and exists in two main isoforms: the membrane-bound ST2L and the soluble form, sST2. While ST2L exerts cardioprotective activity, sST2 blocks the ST2L–IL-33 interaction, promotes fibroblast activation, and contributes to myocardial fibrosis, thereby diminishing the beneficial effects of ST2L. Consequently, sST2 has gained attention as a clinically relevant biomarker and therapeutic target in heart failure and cardiac remodelling. This review summarizes preclinical and clinical evidence regarding the cardiac effects of sST2 receptors and discusses their therapeutic implications. Current findings indicate that modulation of the sST2 pathway may reduce ventricular remodelling, fibrosis, and overall HF risk, presenting a promising direction for future therapies.

Keywords: sST2 receptor, Cardiac fibrosis, Heart failure, Ventricular remodelling, Biomarker.

Introduction

Chronic heart failure (HF) represents a complex clinical syndrome and remains a major medical and socioeconomic challenge in industrialized nations [1]. It is estimated that HF affects up to 2% of the adult population in developed countries [2]. The condition substantially reduces quality of life, is one of the most common causes of hospital admission, and carries a 5-year mortality rate that surpasses several common malignancies [3–5]. Although diagnostic and therapeutic strategies for HF have advanced significantly, overall prognosis remains unfavourable. Therefore, the search for new biomarkers and predictive tools continues in order to refine risk stratification and tailor treatment approaches.

sST2, a member of the IL-1 receptor family, has gained recognition as both a biomarker and a potential therapeutic target in heart failure and post-infarction remodelling. When ST2L binds IL-33, it triggers anti-inflammatory, anti-fibrotic, and cardioprotective pathways. Conversely, the soluble form, sST2, neutralizes IL-33, inhibits this signalling cascade, enhances fibroblast activation, and promotes myocardial fibrosis. ST2 expression is also induced by mechanical strain on cardiac tissue, providing valuable insight into processes such as remodelling and fibrosis [6].

Elevated sST2 levels have been documented in HF, post-MI remodelling, and hypertrophic cardiomyopathy, and are widely used as indicators of adverse ventricular remodelling. Numerous studies have investigated its prognostic utility in acute [7] and chronic decompensated HF [8].

This review is based on a systematic search of PubMed, Scopus, and Web of Science for the years 2010–2025 using keywords such as “ST2 receptor,” “sST2,” “IL-33/ST2L,” “cardiac fibrosis,” “heart failure,” and “ventricular remodelling.” Both preclinical animal studies and human clinical investigations were included.

Discussion

Cardiovascular diseases, including HF, remain the leading cause of morbidity and mortality in industrialized countries [9]. Despite advances in pathophysiological understanding and biomarker discovery, HF continues to contribute to substantial morbidity and mortality. Continuous efforts are therefore directed toward

identifying biomarkers that may provide early prognostic insight and assist in therapeutic decision-making. Among these biomarkers, the ST2 protein stands out due to its involvement in inflammatory and fibrotic pathways, making it a promising tool for monitoring treatment and disease progression in HF [10].

According to the literature, ST2 concentrations are significantly higher in HF patients compared with healthy individuals [11]. In the PRIDE study (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department), sST2 levels were measured in approximately 600 patients presenting with dyspnea. Both HF and non-HF individuals were included. The study demonstrated notably elevated sST2 levels in patients whose dyspnea was caused by HF, and sST2 concentrations correlated strongly with mortality in both groups. Patients who died during follow-up exhibited significantly higher baseline sST2 concentrations.

Furthermore, a meta-analysis involving more than 4,000 patients identified sST2 as an independent predictor of all-cause and cardiovascular mortality, as well as HF-related hospitalizations [12].

Conclusion

The soluble ST2 protein serves as an independent predictor of all-cause mortality in patients with heart failure. Inhibition or modulation of ST2-related pathways represents a promising therapeutic direction due to its central role in ventricular remodelling and fibrosis. Further studies are required to clarify optimal therapeutic strategies targeting sST2 in order to improve prognosis in HF populations.

References

1. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; ˇ Celutkien˙e, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur. Heart J. 2021, 42, 3599–3726.
2. Mosterd, A.; Hoes, A.W. Clinical epidemiology of heart failure. Heart 2007, 93, 1137–1146.
3. Bui, A.L.; Horwich, T.B.; Fonarow, G.C. Epidemiology and risk profile of heart failure. Nat. Rev. Cardiol. 2011, 8, 30–41.
4. Miller, K.D.; Siegel, R.L.; Lin, C.C.; Mariotto, A.B.; Kramer, J.L.; Rowland, J.H.; Stein, K.D.; Alteri, R.; Jemal, A. Cancer treatment and sur-vivorship statistics, 2016. CA Cancer J. Clin. 2016, 66, 271–289.
5. Giamouzis, G.; Kalogeropoulos, A.; Georgiopoulou, V.; Laskar, S.; Smith, A.L.; Dunbar, S.; Triposkiadis, F.; Butler, J. Hospitalization Epidemic in Patients with Heart Failure: Risk Factors, Risk Prediction, Knowledge Gaps, and Future Directions. J. Card. Fail. 2011, 17, 54–75.
6. Schmitz, J.; Owyang, A.; Oldham, E.; Song, Y.; Murphy, E.; McClanahan, T.K.; Zurawski, G.; Moshrefi, M.; Qin, J.; Li, X.; et al. IL-33, an Interleukin-1-like Cytokine that Signals via the IL-1 Receptor-Related Protein ST2 and Induces T Helper Type 2-Associated Cytokines. Immunity 2005, 23, 479–490.
7. Zhu, J.; Ruan, Z.; Zhu, L. Correlation between Serum LP-PLA2 and sST2 Levels and the Condition of Patients with Acute Heart Failure and Their Prognostic Value. Evid.-Based Complement. Altern. Med. 2021, 2021, 8267776.
8. Sun,Y.; Feng, L.; Hu, B.; Dong, J.; Zhang, L.; Huang, X.; Yuan, Y. Prognostic Value of 1 Adrenergic Receptor Autoantibody and Soluble Suppression of Tumorigenicity-2 in Patients with Acutely Decompensated Heart Failure. Front. Cardiovasc. Med. 2022, 9, 75.
9. Virani, S.S.; Alonso, A.; Benjamin, E.J.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Delling, F.N.; et al. Heart Disease and Stroke Statistics-2020 Update: A Report from the American Heart Association. Circulation 2020, 141, e139–e596.
10. Dieplinger, B.; Januzzi, J.L.; Steinmair, M.; Gabriel, C.; Poelz, W.; Haltmayer, M.; Mueller, T. Analytical and clinical evaluation of a novel high-sensitivity assay for measurement of soluble ST2 in human plasma—The Presage™ ST2 assay. Clin. Chim. Acta 2009, 409, 33–40.
11. Januzzi, J.L.; Peacock, W.F.; Maisel, A.S.; Chae, C.U.; Jesse, R.L.; Baggish, A.L.; O'Donoghue, M.; Sakhuja, R.; Chen, A.A.; van Kimmenade, R.R.; et al. Measurement of the Interleukin Family Member ST2 in Patients with Acute Dyspnea: Results From the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) Study. J. Am. Coll. Cardiol. 2007, 50, 607–613.
12. Mueller, C.; Laule-Kilian, K.; Christ, A.; Rocca, H.P.B.; Perruchoud, A.P. Inflammation and long-term mortality in acute congestive heart failure. Am. Heart J. 2006, 151, 845–850.