SYSTEMATIC REVIEW

Could Renin-angiotensin System Inhibitors Reduce Fibrosis in Rheumatic Heart Disease by Inhibiting Soluble Suppression of Tumorigenicity 2 (sST2)?: Systematic Review

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ABSTRACT

Introduction: Fibrosis and valvular thickening are clinical signs of rheumatic heart disease (RHD), which can cause significant hemodynamic disturbances. Fibrogenesis is associated with immune processes, there is a sensitive biomarker of cardiac fibrosis called soluble suppression of tumorigenicity 2 (sST2). Soluble ST2 is affected by angiotensin II and cardiomyocyte stretch. It is hypothesised that inhibiting the angiotensin II pathway can reduce cardiac fibrosis through sST2 inhibition by renin-angiotensin system inhibitors, but clinical trials in the RHD population are limited. Thus, this study will systematically review other heart disease populations with a fibrogenesis process similar to RHD. **Materials and methods:** We conducted a data search on online databases: PubMed, ScienceDirect, and Google Scholar. Data screening and selection process using PRISMA flowchart. We assessed the quality of articles using the GRADE method. **Results:** 770 articles were obtained and 8 of them were relevant. The use of sacubitril/valsartan compared to valsartan or enalapril was shown to significantly reduce sST2 levels at the end of the study ($p< 0.05$) and improved the risk of morbidity, mortality, hospitalisation, and echocardiographic outcomes. Objective parameters that showed sST2 reduction indirectly reduced cardiac fibrosis were decreased left ventricular end-diastolic volume index ($p= 0.02$), left ventricular end-systolic volume index ($p= 0.045$), left atrial volume index ($p< 0.001$), and mitral E/e' ratio ($p= 0.001$). **Conclusion:** Although this study did not directly utilize the RHD patient population, therapy using renin-angiotensin system inhibitors may reduce the incidence of cardiac fibrosis through the sST2 inhibition pathway in conditions with similar pathogenesis.
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Keywords: Angiotensin II, Cardiac fibrosis, Renin-angiotensin system inhibitors, Rheumatic heart disease, sST2

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INTRODUCTION

Rheumatic heart disease (RHD) has a significant impact, particularly in developing countries, where it affects 80% of the population and shows a higher incidence of mortality and morbidity rates among young adults (1). Globally, RHD impacts over 15.6 million people and causes 350,000 deaths each year (2). The problem with this disease is the relatively expensive treatment and long duration of therapy. One of the most common manifestations of RHD is fibrosis and thickening of the heart valves (3). Chronic inflammation damages more than one heart valve, resulting in significant hemodynamic disruptions (3).

The fibrosis process begins with an episode of acute rheumatic fever due to Group A Streptococcus (GAS) infection. The fibrogenesis that occurs involves immunological factors such as cytokines, connective tissue growth factors, and activators of fibrosis (2). Previous research has indicated that the suppression of tumorigenicity 2 (ST2) presents a sensitive cardiac biomarker that reflects the progression of cardiac fibrosis including RHD (4).

ST2 is part of the interleukin-1 family, also known as interleukin 1 receptor-like 1 (IL1RL-1). ST2 has two main isoforms, the transmembrane receptor (ST2L) and soluble ST2 (sST2) (5). Physiologically, ST2L binds to IL-33, thus causing cardioprotective effects as a response of living cells to damage. Conversely, sST2 competes with ST2L to bind to IL-33, which has fibrogenesis effects.

Biomechanical stress induces both ST2L and sST2 in cardiomyocytes and fibroblasts (6).

Angiotensin II is acknowledged as a contributor to cardiac fibrosis due to its ability to trigger sST2 binding with IL-33. This results in elevated cardiac workload, leading to cardiomyocyte stretching and scarring (2). Conversely, stretching of cardiomyocytes also triggers sST2 production, exacerbating fibrosis. Ultimately, RHD will progress to rheumatic heart failure (7). There is a hypothesis that Angiotensin Converting Enzyme Inhibitors (ACEIs) can inhibit sST2 due to its association with angiotensin II (2). In several clinical trial studies, Renin-angiotensin system inhibitors including ACEIs, Angiotensin receptor blockers (ARBs), and Angiotensin receptor-neprilysin inhibitors (ARNI) can reduce sST2 in heart failure patients (8).

The pathogenesis process described above has similar pathogenesis with heart diseases that involve fibrosis such as hypertension, myocardial infarction, and heart failure. In heart failure patients there is an increase in sST2 due to cardiomyocyte stretching which indicates left ventricular stress (7). Clinical trials investigating the effects of renin-angiotensin system inhibitors on sST2 in RHD are limited, and it is unclear whether these agents could be novel therapies targeting sST2. Therefore, we investigated these effects in other heart diseases with a similar pathogenesis to RHD. This study aims to establish a basis for the development of future clinical trials.

MATERIALS AND METHODS

Data sources and searches

The study utilised PubMed, ScienceDirect, and Google Scholar databases to obtain relevant scientific articles. The selected scientific articles were published between 2013 and 2023, with the last article search conducted in October 2023. The search used terms related to Renin-angiotensin system inhibitors including ACEI, ARB, and ARNI. In many sources, ARNI is also known as Sacubitril/Valsartan. Additionally, the search included keywords such as sST2, RHD, and cardiac fibrosis.

Eligibility and study selection

Articles with randomized controlled trial (RCT), non-RCT and observational study designs were included as data sources. We selected English and Indonesian language articles published within the last decade. Articles should contain interventions and controls of either renin-angiotensin system inhibitors with placebo or with intergroups but compared which is most effective. Articles must report sST2 levels as an outcome and focus in a heart disease that has a similar pathogenesis to RHD. There is no restriction on the type of heart disease, as long as it involves the same pathogenesis as RHD, it is eligible.

The primary outcome of the study is the reduction of sST2 levels from baseline to post-intervention. The secondary outcome is fibrosis improvement, assessed by clinical or supportive examinations. Clinical improvement conditions and supporting markers such as decreased mortality risk, morbidity, and hospitalisation incidence will be assessed. The enhancement of cardiac structure via echocardiographic investigation and other supporting outcomes that are relevant to disease improvement can be used as secondary outcomes. In order to prevent the possibility of bias, this research has not included trials in which renin-angiotensin system inhibitors were used in combination with other types of drugs.

Risk of bias and quality of evidence

To determine the quality of an article we use a system adapted from Cochrane's collaboration called GRADE (Grade of Recommendations, Assessment, Development, and Evaluations) (9). This method is widely used to assess the quality of a systematic review to a guideline. The first assessment starts from the study de-sign rating, the "high" rating is given to RCT studies, while observational studies receive a "moderate" rating. The rating can be downgraded or upgraded. Articles can be downgraded if there is a risk of bias, inconsistency of results, indirectness of evidence, imprecision of results, and publication bias. Meanwhile, it can be upgraded if there is a large magnitude of effect, confounding factors that do not affect the studied treatment effect, and dose-response gradient. The final step is to assess the final results and make recommendations according to the quality of evidence that has been made.

RESULTS

Search results

The study found 770 articles from three online databases search, with 738 remaining after eliminating duplicates. To determine relevance, a preliminary screening of article titles and abstracts was conducted, with 28 articles meeting the eligibility criteria. Eligibility was determined by assessing appropriate titles and abstracts and reading the full text of the article. Twenty articles were excluded: two due to being in Russian and Chinese, one due to being a review article, three due to inaccessibility of full text, and 14 due to unsuitable intervention or control groups that combined with other drugs, which were excluded from the criteria in this study. Eight articles

were eligible to be used as the source of data (see Fig. 1).

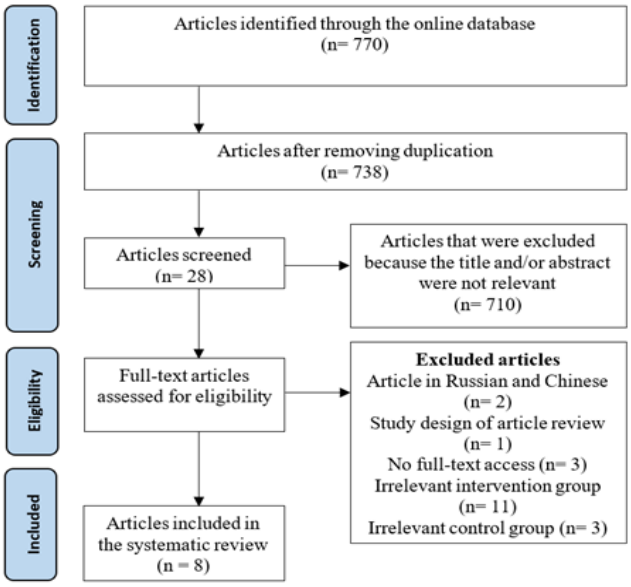

Fig. 1: PRISMA Flowchart

Study characteristics

The demographic findings from the eight articles indicate a male patient majority with 4584 cases compared to 1846 cases for females. Additionally, 1529 subjects did not provide gender data (Table I). The age range of the population with heart failure is over 60 years. The spectrum of heart failure in this study was heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), and acute decompensated heart failure (ADHF). The intervention group in seven out of eight articles was ARNI (sacubitril/valsartan), while only one article used valsartan. In the ARNI intervention group, ACEI or ARB was used as the control group. Placebo was used as the control in the valsartan intervention group (refer to Table II).

Table I: Demographic Data

No	Author, Years	Sample	Gender		Age [Mean (Group)]	Disease
			Male	Female		
1.	Cunningham, Jonathan W., et al., 2020 (8)	1135	549	586	73.5 ± 7.8 (Sacubitril/valsartan); 73.6 ± 8.3 (Valsartan)	HFpEF
2.	Anand, Inder S., et al., 2014 (10)	1650	1290	360	63 ± 12	Heart Failure
3.	Zile, Michael R., et al., 2019 (11)	1776	1444	332	67 ± 10 (Sacubitril/valsartan); 67 ± 10 (Enalapril)	HFrEF
4.	Myhre, Peder L., et al., 2022 (12)	410	309	101	67.3 ± 9.0	HFrEF
5.	Morrow, David A., et al., 2019 (7)	694	506	188	61 (Sacubitril/valsartan); 63 (Enalapril)	ADHF
6.	Zile, Michael R., et al., 2016 (13)	301	131	170	70.9 (Sacubitril/valsartan); 71.2 (Valsartan)	HFpEF
7.	O'Meara, Eileen, et al., 2018 (14	1529	-	-	67 ± 10	HFrEF
8.	Desai, Akshay S., et al., 2019 (15)	464	355	109	67.8 (Sacubitril/valsartan); 66.7 (Enalapril)	HFrEF

Table II: Outcome Data

No.	Author, Years	Intervention	Control	Outcome
1.	Cunningham, Jonathan W., et al., 2020 (8)	Sacubitril/valsartan 97/103 mg b.i.d follow-up at 16 and 48 weeks after randomisation [ARNI; n= 576]	Valsartan 160 mg b.i.d follow-up at 16 and 48 weeks after randomisation [ARB; n= 559]	After 16 weeks of randomisation, sacubitril/valsartan reduced sST2 by 4% (95% CI: 1% to 7%; p= 0.002) compared to valsartan alone, and this effect was sustained until 48 weeks (p= 0.02). Higher levels of sST2 were associated with an increased risk of cardiovascular mortality and heart failure hospitalisation, which remained statistically significant (RR: 1.15 per SD increase; 95% CI: 1.02 to 1.31; p= 0.03).
2.	Anand, Inder S., et al., 2014 (10)	Valsartan (no dose information) follow-up at 12 months after randomisation [ARB; n= 837]	Placebo [n= 813]	Valsartan significantly reduced the rate of increase in sST2 when compared to placebo (95% CI, -0.2 to 2.0; p< 0.0001). Increases in sST2 were linked to a significant increase in risk for all following outcomes (first morbid event, mortality, and hospitalisation) (p< 0.001), but decreases in sST2 were not linked to a significant decrease in risk.
3.	Zile, Michael R., et al., 2019 (11)	Sacubitril/valsartan 97/103 mg b.i.d follow-up at 8 months after randomisation [ARNI; n= 895]	Enalapril 10 mg b.i.d follow up at 8 months after randomisation [ACEI; n= 881]	Compared with enalapril, sacubitril/valsartan treatment decreased sST2 by -7% (95% CI, -9% to -4%; p< 0.05) Changes in sST2 from baseline to 8 months after randomisation reduce the risk of the primary outcome (composite of cardiovascular mortality or heart failure hospitalisation) (p< 0.001).
4.	Myhre, Peder L., et al., 2022 (12)	Sacubitril/valsartan 97/103 mg b.i.d follow-up at 24 weeks after randomisation [ARNI; n= 205]	Enalapril 10 mg b.i.d follow-up at 24 weeks after randomisation [ACEI; n= 205]	The median (IQR) concentration of sST2 at 24 weeks was 25 (20–32) ng/ml, corresponding to a −3% (−13% to +8%) change from baseline (p< 0.001) (sacubitril/valsartan compared to enalapril). Changes in sST2 are associated with changes in echocardiography parameters especially in left ventricular global longitudinal strain (LV GLS) (p= 0.010), but not significant in other parameters.
5.	Morrow, David A., et al., 2019 (7)	Sacubitril/valsartan 97/103 mg b.i.d follow-up at 1, 2, 4, and 8 weeks after randomisation [ARNI; n= 342]	Enalapril 10 mg b.i.d follow-up at 1, 2, 4, and 8 weeks after randomisation [ACEI; n= 352]	Treatment with sacubitril/valsartan resulted in a higher decrease in sST2 than enalapril. This resulted in a 9% higher decrease after 1 week (p< 0.001), which was maintained for 8 weeks.
6.	Zile, Michael R., et al., 2016 (13)	Sacubitril/valsartan 97/103 mg b.i.d follow-up at 12 and 36 weeks after randomisation [ARNI; n= 149]	Valsartan 160 mg b.i.d follow-up at 12 and 36 weeks after randomisation [ARB; n= 152]	There was no interaction between the responsiveness to sacubitril/valsartan therapy on change in sST-2 (interaction p= 0.99) at 36 weeks follow-up. There was an interaction between the responsiveness to sacubitril/valsartan therapy vs. valsartan on change in Left atrium volume at 36 weeks and sST-2 baseline values (interaction p= 0.07).
7.	O'Meara, Eileen, et al., 2018 (14)	Sacubitril/valsartan 97/103 mg b.i.d follow-up at 1 month and 8 months after randomisation [ARNI; n= 775]	Enalapril 10 mg b.i.d follow-up at 1 month and 8 months after randomisation [ACEI; n= 754]	Treatment with sacubitril/valsartan reduced sST2 levels compared to enalapril, resulting in statistically significant treatment differences at both 1 and 8 months (geometric mean -7%; 95% CI -9% to -4%; p< 0.001). sST2 increases at 1 month were associated with worse subsequent outcomes and decreased with better outcomes (Hospitalisation and cardiovascular death) (p= 0.012 and 0.009 for the 2 outcomes, respectively).

CONTINUE

Table II: Outcome Data (CONT.)

No.	Author, Years	Intervention	Control	Outcome
8.	Desai, Akshay S., et al., 2019 (15)	Sacubitril/ valsartan 97/103 mg b.i.d follow-up at 12 weeks after randomisation [ARNI; n= 231]	Enalapril 10 mg b.i.d follow-up at 12 weeks after randomisation [ACEI; n= 233]	Sacubitril/valsartan significantly reduced the sST2 when compared to enalapril (geometric mean 0.94; 95% CI 0.89 to 0.98; p= 0.006) after 12 weeks of randomisation.
				Greater reductions from baseline were seen among participants assigned to sacubitril-valsartan compared with those assigned to enalapril in left ventricular end-diastolic volume index (between-group difference, −2.0 mL/m^2; 95% CI, −3.7 to −0.3mL/m^2; p= 0.02), left ventricular end-systolic volume index (between-group difference, −1.6 mL/m^2; 95% CI, −3.1 to −0.03 mL/m^2; p= 0.045), left atrial volume index (between-group difference, −2.8 mL/m^2; 95% CI, −4.0 to −1.6 mL/m^2; p< .001), and mitral E/e' ratio (between-group difference, −1.8; 95% CI, −2.8 to −0.8; p= 0.001).

Risk of bias assessment

As previously discussed, articles with an RCT study design had an initial rating of "high". However, after review, 7 out of 8 articles had a final rating of "moderate". This is because the indirectness aspect was rated as serious for all articles. This is because this study took the outcome effect indirectly from other diseases that are not RHD. This reduces the quality because it did not come from the actual disease. Meanwhile, one article has a "low" rating due to serious inconsistencies. This is because the sST2 results in the article were inconsistent with the researcher's hypothesis, and the only article that was not significant when the other articles said it was. After further review, the sample used is very small compared to others, supported by the limitation of the study, which has a limited sample (Table III).

Table III: GRADE Assessment

			Certainty Assessment					
No	Author, Years	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty
1	Cunningham, Jonathan W., et al., 2020 (8)	randomised trials	not serious	not serious	serious	not serious	none	⊕⊕⊕◯ Moderate
2	Anand, Inder S., et al., 2014 (10)	randomised trials	not serious	not serious	serious	not serious	none	⊕⊕⊕◯ Moderate
3	Zile, Michael R., et al., 2019 (11)	randomised trials	not serious	not serious	serious	not serious	none	⊕⊕⊕◯ Moderate
4	Myhre, Peder L., et al., 2022 (12)	randomised trials	not serious	not serious	serious	not serious	none	⊕⊕⊕◯ Moderate
5	Morrow, David A., et al., 2019 (7)	randomised trials	not serious	not serious	serious	not serious	none	⊕⊕⊕◯ Moderate
6	Zile, Michael R., et al., 2016 (13)	randomised trials	not serious	serious	serious	not serious	none	⊕⊕◯◯ Low
7	O'Meara, Eileen, et al., 2018 (14)	randomised trials	not serious	not serious	serious	not serious	none	⊕⊕⊕◯ Moderate
8	Desai, Akshay S., et al., 2019 (15)	randomised trials	not serious	not serious	serious	not serious	none	⊕⊕⊕◯ Moderate

DISCUSSION

The measurement of sST2 levels could indicate cardiac stress and remodelling in cardiovascular diseases such as heart failure, myocardial infarction, hypertension, and RHD (16). The association of sST2 with RHD is due to its association with the inflammatory process, immunology, response to cardiac injury, and angiotensin II. Renin-angiotensin system inhibitors, including ACEI, ARB, and ARNI are used to inhibit the process of sST2 binding to IL-33 (8).

According to the results of data analysis, two categories of medications were utilised as interventions, specifically ARNI (Sacubitril/valsartan) and ARB (Valsartan). The longest study, 48 weeks, with sacubitril/valsartan 97/103 mg b.i.d intervention reduced sST2 by 4% (p= 0.002) compared to control (valsartan 160 mg b.i.d) after 16 weeks follow-up and maintained up to 48 weeks follow-up (8). A significant reduction in sST2 after 8 months of treatment with sacubitril/valsartan compared to enalapril (p< 0.05) was also seen in the study with the largest sample size of 1776 patients (11). The ARB group, like the ARNI group, can also reduce sST2 after 12 months of observation compared to a placebo (p< 0.0001) (10).

A decrease in sST2 will certainly reflect the clinical improvement of the patient. Decreased sST2 is

associated with improved patient clinical outcomes (14). The secondary outcomes of this study will evaluate the following indicators: morbidity, mortality, hospitalisation, and echocardiography. Previous literature has demonstrated a correlation between decreased sST2 levels and lower risks of morbidity, mortality, and hospitalisation. Echocardiographic indicators provide objective evidence that a reduction in sST2 levels leads to a decrease in cardiac remodelling and an improvement in cardiac structure and function. The sacubitril/valsartan group showed a significant decrease in left ventricular end-diastolic volume index ($p= 0.02$), left ventricular end-systolic volume index ($p= 0.045$), left atrial volume index ($p< 0.001$), and mitral E/e' ratio ($p= 0.001$) compared to the enalapril group (15). sST2 is induced by cardiomyocyte stretching, which indicates ventricular wall stress. Sacubitril inhibits neprilysin, which degrades natriuretic peptides (NPs). In fact, NPs have cardioprotective effects, myocardial relaxation, improving afterload and preload. Thus, the effect of sacubitril may indirectly reduce sST2 through improving ventricular remodelling including cardiomyocyte stretching (17).

CONCLUSION

Renin-angiotensin system inhibitors have the potential to decrease the incidence of cardiac fibrosis through the sST2/IL-33 inhibition pathway, which is characterised by reduced sST2 levels and clinical improvements in terms of reduced risk of morbidity, mortality, hospitalisation, and improved cardiovascular structure and function. Although the RHD patient population was not directly utilised by this study, the effects that were examined may be used as a valid source of data for the development of future clinical trials.

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