REVIEW ARTICLE

Plasma Soluble Suppression of Tumorigenicity-2 Level with Colchicine in Coronary Artery Disease

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ABSTRACT
Recently, suppression of tumorigenicity 2 (ST2) of the interleukin 1 receptor family has become an important biomarker in cardiovascular disease, more precisely in coronary artery disease. This review discusses two isoforms of ST2: the membrane-bound ST2L and its soluble form, sST2. Specifically, the interaction between sST2 and IL-33 is quite important; while IL-33 exerts actions to induce inflammatory responses, sST2 acts as a decoy receptor in suppressing such actions and reflects myocardial stress. High circulating levels of sST2 have been associated with poor clinical outcomes of CAD, and increased risks for MACE and all-cause mortality have been mainly seen in patients with type 2 diabetes mellitus. Despite this, the long-term prognostication of sST2 has remained largely unexplored, with very few data available in the literature regarding its predictive value in large cohorts with extended follow-up periods. Other issues are that colchicine may further exert an additive salutary effect on the cardiovascular component in gout-either directly or indirectly through regulation of sST2 levels. Placebo-controlled studies revealed that colchicine reduced inflammatory markers, thereby reducing the rate of MACE in CAD patients.Thus, the possible integration of sST2 measurement into clinical practice might finally translate into some real improvement in risk stratification and the management strategy in CAD patients. Therefore, large prospective studies will be needed to fully delineate the relationship of sST2 with CAD outcomes and its relationship to possible treatments, including colchicine. This review thus discusses the need for more research studies in defining the role of sST2 as a biomarker in cardiovascular health for further improvement in CAD patient management outcomes.

Keywords: Suppression of Tumorigenicity 2, Coronary artery disease, Colchicine, Cardiovascular risk, Myocardial stress, Plasma Soluble ST2.
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INTRODUCTION

Suppression of tumorigenicity 2 (ST2) is a member of the interleukin 1 (IL-1) receptor family and is formally known as interleukin 1 receptor-like 1 (IL1RL-1). It was first described in 1989 but remained an orphan receptor mainly related to immune and inflammatory diseases for years. ST2 was reported to be expressed in cardiac cells in response to myocardial stress, and interleukin 33 (IL-33) was reported to be the ligand of ST2 . Since then, its role in cardiovascular diseases has been of great concern. The ST2 gene is located on human chromosome 2q12 and encodes two main protein isoforms: transmembrane receptor (ST2 L) and truncated soluble receptor (sST2). The interaction between IL-33 and ST2 L mediates anti-inflammatory and antifibrotic effects.1 Coronary artery disease (CAD) is a common heart disease characterized by insufficient blood and oxygen supply to the myocardium. It is caused by atherosclerosis and atherosclerotic plaque rupture leading to arterial occlusion or obstruction of smaller branches of coronary arteries by material dislodged from the plaque. Inflammatory activation and dysfunction of the coronary endothelium is a key link in the development of atherosclerosis, as well as being strongly associated with an increased risk of cardiovascular events . Currently, CAD remains the leading cause of death worldwide and is a major source of global cardiovascular disease morbidity, mortality, and economic burden on health.3

Management

Clinically, management of diet as well as lifestyle and usage of statins as well as antiplatelet drugs are mainly used as prophylactic treatment for CAD . Although antiplatelet aggregation, lipid regulation to stabilize plaque and control of risk factors have reduced the cardiovascular risk of patients to some extent , the annual risk of major cardiovascular events is still as high as 3% , so CAD is still in urgent need of intervention with novel therapy regimens. Colchicine has been reported to have potential application in cardiovascular disease.4
significantly reducing major adverse cardiovascular events (MACE) in patients with CAD , and is expected to be a new drug for second-level prevention of CAD. Colchicine

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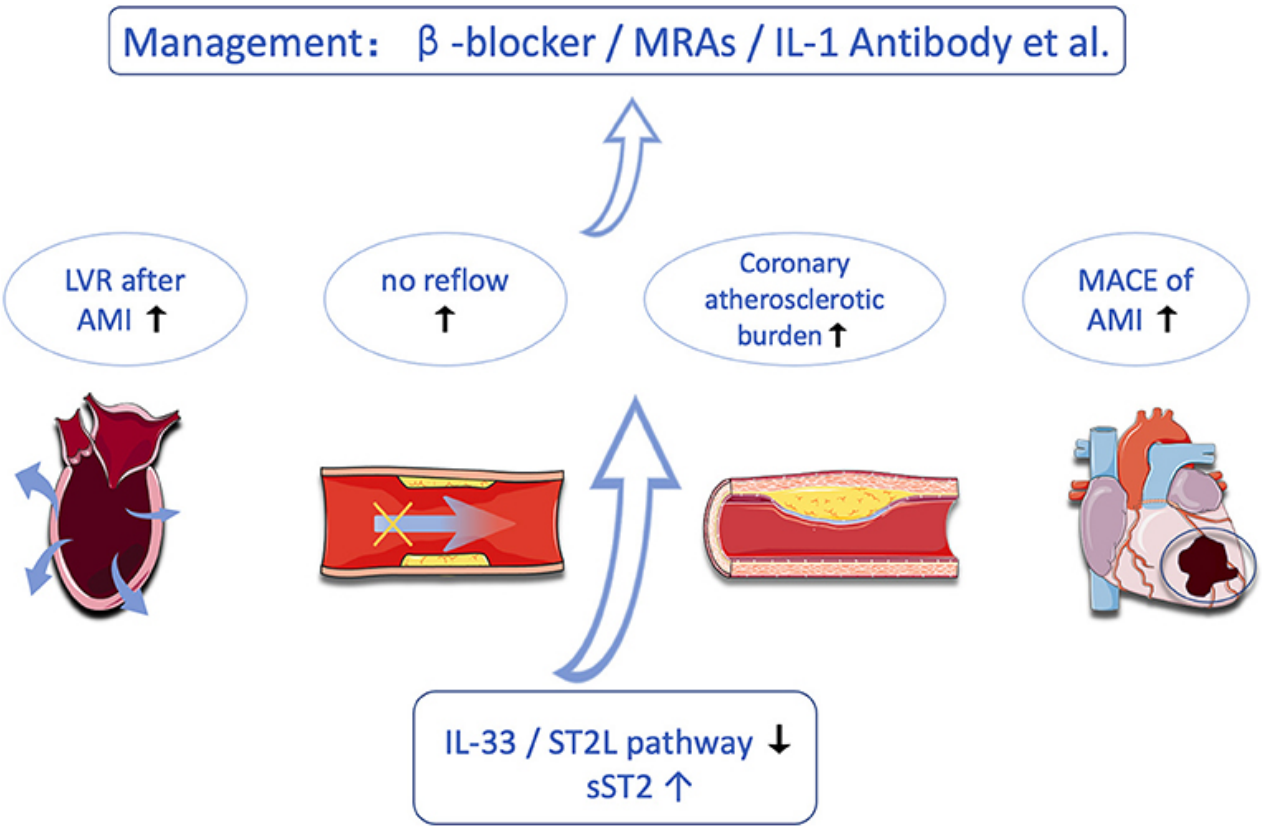

Research progress on sST2 in the field of coronary heart disease.2

was found to reduce hs-CRP at 0.36 mg/L and mean leukocytes at 371.75/L in patients with CAD , implying that colchicine can reduce the inflammatory response in patients with CAD. Meta-analysis demonstrated that colchicine reduced MACE by approximately 27%–35%% , and this benefit was independent of the clinical phenotype of CAD . colchicine was also shown to significantly reduce the incidence of stroke by 75% and the incidence of ACS by 36% . This evidence suggests that colchicine has great potential in the treatment of CAD.[5] Colchicine, one of the oldest drugs still in use today, is derived from the dried bulb and seeds of the colchicum . It is a low-cost drug with a wide range of anti-inflammatory properties and is currently used in diseases such as gout and familial mediterranean fever . colchicine significantly reduces MACE and decreases the level of inflammatory markers in patients with CAD , and the benefit of MACE still holds after percutaneous coronary intervention . Nevertheless, the mechanism of action of colchicine in the treatment of CAD has not been elucidated, and it is difficult to determine its long-term efficacy and safety.6 Suppression of tumorigenesis-2 (ST2) is an interleukin-1 (IL-1) receptor family member that exists in two isoforms: membrane-bound (ST2L) and soluble isoform soluble suppression of tumorigenesis-2 (sST2) forms . IL-33 acts as an “alarm” to signal potential tissue stress or damage . IL-33 promotes the production of inflammatory cytokines and Th2 immune responses by signaling through a heterodimer receptor complex composed of ST2L and IL-1 receptor attachment proteins; sST2 is known to bind to IL-33, and it acts as a “decoy” receptor for IL-33 to inhibit IL-33/ST2L signaling. An increase in the circulating sST2 concentration attenuates the systemic biological effects of IL-33.[7] Therefore, sST2 has long been recognized as a marker of the activation of both inflammatory and hemodynamic overload. Subsequently, soluble sST2 has been shown to be a powerful independent prognosticator in patients with acute coronary syndrome (ACS) , as well as heart failure (HF) . However, it remains unclear whether sST2 is predictive of MACEs and all-cause death in long-term follow-up of CAD. In addition, type 2 diabetes mellitus (T2DM) is a known predictor of elevated sST2.8 Over the past two decades, biomarkers have become increasingly important tools that can help to improve patient prognosis. Numerous biomarkers have been identified for the diagnostic, prognostic and risk prediction of cardiovascular disease, but few have been adopted in clinical practice . The most extensively used cardiovascular biomarkers are natriuretic peptides for the diagnosis and prognosis of heart failure and cardiac troponins for the diagnosis of acute myocardial infarction. More in-depth experimental studies of the pathophysiology of atherosclerosis have identified a large number of molecules as potential prognostic biomarkers in cardiovascular disease.[9] To date, however, no marker has been shown to predict cardiovascular events with high accuracy. Therefore, the investigation of potential markers that can predict cardiovascular events is still of great value. Only 2 small studies have reported the prognostic value of sST2 in patients with CAD . sST2 and IL-33 were associated with mortality in patients with ST elevation myocardial infarction (STEMI) but not in patients with non-STEMI (NSTEMI) or stable angina pectoris (SAP). increased concentrations of sST2 to be an independent

predictor of all-cause mortality in patients with stable CAD. Therefore, a large-sample study including patients with SAP and ACS is urgently needed to further demonstrate the predictive value of sST2 in CAD patients during long-term follow-up.10 sST2 might be a potential biological marker for mechanical overload in the heart. sST2 was shown to be markedly upregulated in mechanically stimulated cardiomyocytes. Furthermore, sST2 has been demonstrated to predict the outcomes in patients with HF . sST2 may be predictive in patients with ACS. According to research by Eggers KM, sST2 levels were elevated early in NSTE-ACS and predicted 1-year mortality . the serum levels of sST2, IL-33 and BNP were positively correlated with MACEs in patients with AMI after PCI . However, no studies have investigated the long-term value of sST2 in the prediction of MACEs or all-cause death in a large population of patients with CAD.[11]
The inflammatory hypothesis of atherosclerosis suggests that inflammatory cell signaling drives the formation, development, and eventual instability of atherosclerotic plaques. IL-33 was originally reported to be a modulator of inflammation that tips the balance toward CD4 + T helper-cell type 2-mediated immune responses. The effect of IL-33 on the function of foam cells indicated the protective role of IL-33 in atherosclerosis . sST2 acts as a decoy receptor for IL-33, thus blocking its protective effects.[12] sST2 is specifically expressed in arterial endothelial cells and is involved in the progression of atherosclerosis . sST2 could be a marker of plaque burden and a predictor of future cardiovascular events ; therefore, the IL-33-ST2 pathway deserves consideration. Although the above data suggest that sST2 plays a role in the prognosis of patients presenting with ACS, whether sST2 contributes to cardiovascular risk prediction in a large population of CAD patients during long-term follow-up remains uncertain.[13] To evaluate the prognostic value of a biomarker in CVD, researchers must demonstrate the elevated risk of cardiovascular events associated with higher levels of the new biomarker with adjustment for other established risk factors. The results should be presented as hazard ratios or relative risk estimates obtained by a Cox model and a probability value test of significance of the marker in multivariable models. According to our results, the adjusted HRs for MACEs and all-cause death were 1.36 and 2.01, respectively, in the Cox proportional hazards models after incorporating age, sex, and other clinically relevant covariates. Moreover, the follow-up time for the predictive value of sST2 was relatively short. Brown et al. assessed the prognostic value of sST2 for acute MI, ACS, and MACEs over a short-term follow-up of 30 days.14 The prognostic value of sST2 in patients with chest pain over a longer follow-up of 18 months . Two other reports were based on data from 3 clinical trials in patients with STEMI and provided data on the prognostic value of plasma sST2 for 30 days after MI for adverse events, while another study reported the prognostic performance over an average follow-up of 20 months . After a median follow-up of 6.4 years, a higher level of sST2 was significantly associated with all-cause death and MACEs and provided incremental prognostic value beyond traditional risk factors.[15]
Higher values of sST2 confer a markedly adverse prognosis characterized by excessive risk of MACEs and all-cause death over a long follow-up period. sST2 is a useful predictor of adverse clinical outcomes in patients with CAD, suggesting that elevation of sST2 might provide long-term prognostic information for CAD patients. In subgroup analysis depending on diabetes status, the diabetes group still had a significantly higher level of sST2, and it remained a significant predictor of MACEs and all-cause death in patients with and without T2DM after adjusting for age, sex and other confounders. The AUC of CAD patients with diabetes mellitus was significantly higher than in those without diabetes mellitus. In summary, measurement of sST2 should be considered part of the approach to risk stratification in CAD patients with and without diabetes during long-term follow-up. sST2 has a high predictive value for cardiovascular adverse events in CAD patients with diabetes, and these findings provide new evidence for the role of sST2.16
The term "Plasma Soluble Suppression of Tumorigenicity-2" (sST2) refers to a protein that can be measured in the blood and is associated with inflammation and cardiovascular diseases, including coronary artery disease (CAD). In the context of CAD, elevated levels of sST2 have been linked to poor outcomes and increased risk. Colchicine, a medication traditionally used to treat gout, has gained attention for its anti-inflammatory properties and potential benefits in cardiovascular disease.14

Potential Mechanisms

Inflammation: Colchicine may reduce inflammation, which could lead to lower levels of sST2 in plasma. This suppression may improve cardiovascular outcomes by reducing vascular inflammation associated with atherosclerosis.

Tumorigenicity and Cardiovascular Health: sST2 has been studied not only in cancer but also in cardiovascular contexts, where its elevated levels can indicate myocardial stress or damage.[7]

Declarations:

Ethics approval

Ethical approval was obtained by the ethical committee of Minia University, Faculty of Medicine.

Consent to participate

Informed written consent to participate in the study was obtained from all recruited patients.

Consent for publication

Not applicable.

Availability of data and materials:

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

AAmr Setouhi, K Maghraby, M. Abdelsayed, Hossam Eldin M. Mahmoud shared in the study idea, collection and analysis of data and finalizing the results.

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