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Review article

Prognostic potential of ST2 in patients with chronic heart failure

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Abstract Heart failure is a complex clinical syndrome with underlying structural and/or cardiac dysfunction, with an inability to adequately oxygenate tissue and maintain overall metabolism and represents one of the leading causes of morbidity and mortality in developed countries, with a significant incidence in low-income countries. So far, only natriuretic peptides have been used clincally to diagnose and monitor heart failure and are currently considered a "gold standard" in the treatment and monitoring of patients with heart failure. Soluble suppression of tumorigenicity 2 (sST2) belongs to the group of myocardial remodelling biomarkers and it was documented that it may provide additional value in the diagnosis, prognosis and stratification of risks in heart failure. sST2 is a member of the interleukin-1 receptor family and most likely represents a cardiomyocyte product in response to myocardial stress, resulting in the accelerated fibrosis and detrimental remodeling of the heart. sST2 may be easily measured in plasma and is minimally affected by patient characteristics: age, obesity, cause of heart failure and anaemia. There is a strong deal of evidence that ST2 may be a strong prognostic biomarker, which provides independent and additive prognostic information for patients with chronic heart failure. Will it be able to replace natriuretic peptides as in monitoring of heart failure future research future research is warranted.

Kew words sST2, heart failure, biomarkers, natriuretic peptides, cardiac remodeling

Introduction

Heart failure is a complex clinical syndrome with underlying structural and/or cardiac dysfunction, with an inability to adequately oxygenate tissue and maintain overall metabolism. It is defined as a complex mechanical and neurohumoral syndrome manifested by haemodynamic congestion associated with dyspnoea, orthopnea, paroxysmal nocturnal dyspnoea or peripheral oedema, in the presence of objective evidence of cardiac dysfunction. The basic pathophysiological phenomenon described in the "cardiovascular disease continuum" is the activation of two very powerful compensatory systems: renin-angiotensin-aldosterone system and sympathetic nervous system. Their synergistic activation is a neurohormonal response to the onset of heart failure, but at the same time has a share in the development of the disease. With this activation, a vicious cycle of numerous adverse reactions begins, with the final remodelling of the myocardium and progressive loss of cardiac function[1,2]. Heart failure is one of the leading causes of morbidity and mortality in developed countries, with a significant incidence in low-income countries. In addition to being a significant medical problem, heart failure is also important from the economic point of view of any health insurance. Patient treatment costs account for 2-3% of total healthcare expenditures in high-income countries, and experts estimate that these expenditures will increase by more than 200% over the next 20 years[3,4].

Biomarkers in chronic heart failure

So far, only two biomarkers, B-type natriuretic peptide (BNP) and pro-BNP (NT-proBNP) have been used in clinical work to diagnose and monitor heart failure and are currently considered a gold standard in the treatment of patients with heart failure. However, due to their "deficiencies" in the presence of associated diseases (obesity, kidney disease and atrial fibrillation), these biomarkers may have false positive or false negative values. Such „deficiencies" in the interpretation and use-value of natriuretic peptides are the focus of many researchers because there is a need for the detection of new, potentially better and more informative biomarkers. New generations of biomarkers, alone or in addition to natriuretic peptides and/or other clinical and echocardiographic parameters could be used to monitor patients with heart failure[5,6].

The most significant pathophysiological mechanisms described are known to be responsible for the onset and progression of heart failure: myocardial stress, myocardial remodelling, cardiomyocyte damage, oxidative stress, inflammation, neurohumour activation and renal

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dysfunction[7,8]. Biomarkers reflecting myocardial remodeling are: galectin-3, soluble suppression of tumorigenicity (sST2), syndecan-1, growth differentiation factor 15 (GDF-15), matrix metalloproteinases (MMP) 2, 3, 4, 8 and 9 and tissue inhibitor of matrix metalloproteinases 1 (TIMP1). It is expected that some biomarkers (sST2, GDF-15) are not associated with only one particular pathophysiological category, because pathogenic mechanisms cannot be strictly separated one from another, but intertwine with each other[8,9]. The multimarker approach is superior to the method of determining individual concentrations of biomarkers, but a further prospective study is necessary to determine what is the best combination[8,9]. It has been estimated that in addition to prognostic significance, the markers of remodelling may also play a significant role in finding the most adequate treatment for these patients.

Soluble suppression of tumorigenicity 2 (sST2) belongs to the group of myocardial remodelling biomarkers and, although not routinely used in clinical practice, it may provide additional value in the diagnosis, prognosis and stratification of risks of heart failure. As a marker of myocardial fibrosis and remodelling, it was successfully added to conventional methods for the treatment of patients with heart failure and in their prognosis (ACC/AHA guidelines, evidence level II, class b)[10,11].

Biology and pathophysiology of sST2

Soluble suppression of tumourigenicity 2 (sST2) is a member of the interleukin-1 (IL-1) receptor family and it is now known that the concentration of circulating form of ST2 reflects cardiovascular stress and fibrosis. It was first identified in 1989 as a member of the interleukin-1 (IL-1) receptor family, also known as the interleukin-1 receptor (IL1RL-1)[12]. It has been documented that sST2 most likely represents a cardiomyocyte product in response to myocardial stress, which turned researchers' attention to its role in the cardiovascular system[13]. It is known that the human ST2 gene is located on the 2nd chromosome (locus 2q12) and is part of a larger cluster of IL-1 genes. Its primary role is to encode at least three isoforms by processing the same mRNA so as to distinguish three ST2 isoforms[14].

Shortly after ST2 was detected in plasma, a functional ligand for the transmembrane isoform of ST2 (ST2L), interleukin-33 (IL-33)[15], was also detected. This IL-33/ST2L signalling is first described in the context of inflammation and immune processes, in particular in relation to mast cell regulation and CD4 pT-helper type 2 cells, as well as the production of Th2-associated cytokines[15]. This observation has been demonstrated in numerous studies on immune diseases such as asthma, pulmonary fibrosis, rheumatoid arthritis, collagen vascular diseases, sepsis, trauma, malignancies, fibroproliferative diseases, helminth infections and ulcerative colitis. In fact, much of the information about this marker comes from studies on these autoimmune diseases, before recognizing its role in the cardiovascular system[15,16].

In essentially inflammatory diseases, IL-33 operates as an „alarm" that signals the presence of tissue damage to local immune cells after exposure to pathogens, stress caused by trauma or death caused by necrosis[17]. IL-33/ST2L signalling leads to the transcription of inflammatory genes and ultimately to the formation of Th2-associated cytokines/chemokines and the triggering of the immune system response, which is a positive effect. On the other hand, when sST2 binds to IL-33, the inhibition of IL-33/ST2L signalling is promoted, resulting in the accelerated fibrosis. Therefore, increased concentrations of sST2 reduce the systemic biological effects of IL-33[17-20].

In the heart, IL-33, which is produced primarily by myocardial fibroblasts, binds to the transmembrane isoform of ST2 (ST2L), and this complex (IL-33/ST2L) activates numerous intracellular signal cascades, leading to an increase in nuclear factor (NF)-KB and a decrease in myocardial fibrosis, cardiomyocyte hypertrophy and apoptosis, ultimately improving myocardial function[21, 22]. On the other hand, this cardiac signalling strongly antagonises angiotensin II and phenylephrine-induced cardiomyocyte hypertrophy, reflecting the cardioprotective effect of this signalling[23]. In the case of cardiomyocyte damage, specifically in the case of heart failure, the release of a soluble isoform of ST2, which competes with transmembranous isoform for the IL-33 ligand, is increased. The interaction of this soluble receptor with IL-33 and the forming of IL-33/sST2 signalling blocks positive IL-33/ST2L signalling and, as a result, eliminates the cardioprotective effects of IL-33[24]. In myocardial hypoxia, IL-33 reduces cardiomyocyte apoptosis and the addition of sST2 (from damaged cardiomyocytes) reduces this beneficial effect of IL-33[25]. The protective effects of IL-33 may be limited by the neurohormonal factor endothelin-1 (whose release from damaged cells is increased during hypoxia), which increases sST2 expression and inhibits IL-33 signalling through the P38 MAPK system[26-28]. Although the main sources of sST2 are cardiac fibroblasts and cardiomyocytes in the case of stress or injury, non-cardiac sources are additionally described. Endothelial cells from the macrovascular (aortic and coronary) and microvascular cardiac systems can additionally synthesize and secrete sST2. The contribution of this extracardiac production to the total circulating ST2, in the pathophysiology which involves heart failure and other cardiac diseases, is not yet fully understood[29-32].

The recommended limit value for sST2 is 35 ng/mL. One of the advantages of sST2 is that, unlike other cardiac biomarkers, primarily natriuretic peptides, sST2 is minimally affected by patient characteristics such as age, obesity, cause of heart failure and anaemia[33]. Specifically, renal impairment has a significant impact on natriuretic peptide and troponin levels, while sST2 levels are affected to a far lesser degree[34].

The role of sST2 in chronic heart failure

According to numerous studies and the AHA/ACC/Heart Failure Guidelines (Class II, Evidence Level B), sST2 is currently the most promising biomarker in risk stratification in patients with chronic heart failure, but it should be noted that sST2 is a prognostic and not a diagnostic marker. Serial sST2 measurements have proven to be

significant for the prediction in patients with heart failure, more specifically, that elevated values of this biomarker correlated with twice the risk of death or transplantation compared to a single, baseline sST2 measurement. Compared to other biomarkers, sST2 has proven to be superior to galectin-3 in risk stratification, that other markers are associated with an increase in general mortality, whereas only sST2 was associated with cardiovascular mortality[34]. The prognostic value of sST2 relative to natriuretic peptide concentrations (BNP, NT-proBNP and proBNP) and conventional risk factors (subject's age, left ventricular ejection fraction and glomerular filtration strength) was also analysed, with sST2 being the strongest predictor of cardiovascular death[35]. Highest sST2 concentrations have also been documented in patients with significant disease symptoms, with poorer NYHA functional class, lower ejection fraction and higher creatinine clearance values[34,35]. Studies conducted in recent years have been dominantly centred on the determination of sST2 in patients with heart failure and preserved ejection fraction because these patients showed superior measurements of sST2 concentrations to NT-proBNP measurements and that sST2 concentrations correlate positively with echocardiographic parameters of diastolic dysfunction[36].

Prognostic value of sST2 in chronic heart failure

There is still insufficient evidence that the measurement and monitoring of soluble sST2 concentrations could be a method for monitoring patients with chronic heart failure. Accordingly, it is assumed that the serial determination of this biomarker could indicate the course of heart failure and potentially help identify the myocardial remodelling phenotype. By a comparative analysis of the existing pathophysiological phenomena (left ventricular pathological remodelling, significant diastolic dysfunction, worsening of right ventricular function) and elevated sST2 concentrations in patients with chronic heart failure, it was concluded that there is an independent correlation between the studied variables. The final conclusion, based on a large number of studies, is that soluble form of ST2 could be used as a predictor for future complications in patients with heart failure: hospitalisation, arrhythmias, and fatal outcome.

The first prognostic evaluation of this biomarker was presented in[36] PRAISE-2 study, which involved a patient diagnosed with chronic heart failure, functional NYHA class III or IV of non-ischaemic aetiology. The study documented that when serial changes to sST2 concentrations were found to be significant for the prediction of the disease, elevated values correlated with twice the risk of death or transplantation, compared to a single baseline sST2 measurements. These initial results were confirmed in a Barcelona study in which sST2 and NT-proBNP concentrations showed a significant correlation with mortality compared to conventional risk factors. It is also important to note that patient's weight, renal function, gender and age had no impact on the concentration of sST2, whereas they affect the concentrations of NT-proBNP[37]. Another additional contribution of this study was the comparison of different biomarkers of fibrosis, primarily sST2 and galectin-3. The comparison of these two biomarkers showed that sST2 was superior to galectin-3 in risk stratification and that all other monitored biomarkers were associated with an increase in general mortality, whereas only sST2 was associated with cardiovascular mortality[38].

The next study, Muerte Subita en Insuficiencia Cardiaca (MUSIC), showed that sST2 is a good predictor of sudden cardiac death in patients with mild to moderate systolic heart failure. Concentrations of sST2 and NT-proBNP above the limit values were associated with a high rate of sudden cardiac death (71%), as opposed to a very low rate (4%) when both biomarkers were at concentrations below the lower limit[39]. The prognostic value of sST2 in addition to natriuretic peptides (NP) and conventional risk factors (age, left ventricular ejection fraction and glomerular filtration rate) was also recently confirmed, with sST2 being the strongest predictor of cardiovascular death[40]. The diagnostic role of sST2 in patients with heart failure and preserved ejection fraction (HFpEF) is also interesting, where the levels of sST2 are superior to NT-proBNP in identifying these patients, while the increase in sST2 levels was proportional to diastolic dysfunction parameters[41]. Subsequently,[42-44] a significant and direct correlation between sST2 and parameters which indicate the severity of HFpEF, E/e and the volume of the left atrium was also confirmed.

The most relevant results of serial measurements of sST2 concentrations were obtained from the results of three major studies: 1) Controlled Rosuvastatin Multinational Trial in Heart Failure, CORONA Study[45], 2) Pro-BNP Outpatient Tailored Chronic HF Therapy, PROTECT[46], and 3) Valsartan Heart Failure Trial, Val-HeFT Study[47].

In the CORONA study, soluble ST2 concentrations were measured in nearly 1.500 subjects with heart failure and previous left ventricular dysfunction[45]. The primary endpoint of the study was recorded in 28.2% subjects, such as cardiovascular death, non-fatal acute myocardial infarction or stroke, with a fatal outcome for 29.1% of study participants. Median concentrations of sST2 initially were 17.8 ng/ml, with an interquartile difference ranging from 13.0 to 25.0. Patients with the highest sST2 concentrations (>28.8 ng/ml) were older males who had a lower ejection fraction, a higher atrial fibrillation rate, and higher concentrations of NT-proBNP and C-reactive protein. Patients who experienced a decrease in sST2 concentrations after 3 months had a reduced risk of hospitalisation due to the disease progression and hospitalisation due to cardiovascular events[45].

In the Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy Study, PROTECT study on the chronic systolic heart failure[46], the prognostic significance of serial measurements of sST2 was confirmed while the additional analyses indicated that prolonged periods with sST2 concentrations <35 ng/mL predicted a decrease in diastolic diameter and left ventricular mass[46]. The results of the PROTECT study imply that the strongest cardiovascular risk factor, during a one-year monitoring period, is the time during which subjects had plasma sST2

values below 35 ng/mL. With the aim to provide cardiovascular risk stratification, the classification of patients according to the sST2 limit value is recommended to patients whose sST2 values are constantly <35 ng/mL, to patients whose concentrations are sometimes below 35 ng/mL and to patients whose sST2 concentrations never fall below 35 ng/mL. If patients had values of sST2 <35 ng/mL most of the period of monitoring, they had a statistically significant decrease in the left ventricular end-diastolic volume index. This finding suggests that there is a pathophysiological connection between sST2 concentrations and the pathological remodelling of the left ventricle, implying the potential significance of introducing this marker for biomonitoring of the structural changes in the left ventricle.

In the Valsartan Heart Failure Trial, VAL-HeFT study[47], sST2 was measured at the start of the study, after 4 months and after 1 year in 1,650 patients with left ventricular systolic dysfunction. Serial increases in sST2 concentrations were associated with new cardiovascular events[47]. The highest concentrations of this biomarker were observed in elderly subjects and men, as well as in those who had signs of congestion, atrial fibrillation or comorbidities. Researchers have documented the presence of a linear increase in risk, even in cases where sST2 concentrations were <35 ng/mL. It is assumed that the risk of an adverse cardiovascular event also exists when sST2 concentrations are >33.2 ng/mL and that the difference in the prognostic potential of these two benchmarks is practically negligible. Morbidity rates have been shown to increase with an increase in sST2 concentrations by 1 ng/mL, with similar results obtained when mortality and hospitalization rates were examined. The final conclusion of the study was that the concentrations of sST2 measured in patients within 12 months after randomization was the most important factor in risk stratification and as a prognostic indicator.

Conclusion

Having all the above in mind, we may conclude that there is a great amount of evidence that sST2 is a strong prognostic but not a diagnostic biomarker, which provides independent and additive prognostic information for patients with chronic heart failure. Therefore, in 2017, sST2 was included in the current guidelines of the American College of Cardiology/American Heart Association (ACCF/AHA), as Class II, Evidence Level B, for prediction purposes. However and based on the current knowledge, one can not claim with certainty that the measurements of the soluble form of ST2 will succeed in replacing BNP as the “gold standard” for monitoring heart failure.

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Sažetak

Prognostički potential ST2 kod pacijenata sa hroničnom srčanom slabošću

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Srčana insuficijencija predstavlja kompleksan klinički sindrom koje se manifestuje postojanjem poremećaja strukture i/ili funkcije srca, sa nemogućnošću adekvatne oksigenacije tkiva i održanja ukupnog metabolizma. Predstavlja jedan od vodećih uzroka morbiditeta i mortaliteta u razvijenim zemljama, sa značajnom incidencijom u zemljama sa niskim bruto nacionalnim dohotkom. Za sada se samo određivanje koncentracija natriuretskih peptida koristi za dijagnozu i monitoring pacijenata sa srčanom insuficijencijom i smatra se „zlatnim standardom".

Solubilna forma biomarkera sST2 pripada grupi biomarkera miokardnog remodelovanja i rezutatima brojnih studija je dokumentovano da može biti aditivni parametar u dijagnozi, prognozi i stratifikaciji faktora rizika kod pacijenata sa srčanom slabošću. sST2 pripada porodici receptora za interleukin-1 i najverovatnije nastaje kao proizvod sinteze i sekrecije u kardiomiocitima kao odgovor na stres miokarda, što dovodi do ubrzane fibroze i miokardnog remodelovanja.

sST2 se lako može meriti u plazmi i na njegovu koncentraciju minimalno utiču karakteristike pacijenata: starost, gojaznost, etiologija srčane insuficijencije i anemija. Dokumentovano je da ST2 može biti snažan prognostički biomarker koji omogućava nezavistan ili dodatni prognostički potencijal za pacijente sa hroničnom srčanom insuficijencijom. Da li će biti u stanju da zameni natriuretske peptide u monitoring pacijenata pokazaće buduća istraživanja.

Ključne reči: sST2, srčana insuficijencija, biomarkeri, natriuretski peptidi, miokardno remodelovanje