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Soluble ST2 – a new biomarker in heart failure

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Summary

Cardiovascular biomarkers play an essential role in the diagnosis, risk stratification and treatment of patients with cardiac diseases and in particular heart failure patients. However, the accuracy of most biomarkers is limited by confounding comorbidities, rendering their interpretation difficult. The relatively new biomarker sST2 (soluble suppression of tumourigenicity 2) is said to reflect myocardial wall stress and activation of the fibrosis pathway and to be less dependent on common confounders. Elevated sST2 levels in acute heart failure patients predict both rehospitalisation and mortality. Chronic heart failure patients who have sST2 levels responsive to medical treatment have a better outcome. However, elevated sST2 levels in the absence of heart failure or heart disease are not uncommon and limit its use for diagnostic purposes in a general non-heart failure population. This review reflects the presentations and discussion by the participants at the first meeting of the Swiss working group on cardiovascular biomarkers held in September 2018 in Zurich, Switzerland. It also highlights current Swiss experience with sST2 and indicates areas of uncertainty, in particular the need to identify the exact pathway of sST2 in cardiac disease and specify its clinical implications for subgroups of heart failure and non-heart failure patients.

Key words: biomarkers, cardiovascular biomarkers, soluble ST2, sST2, heart failure, Swiss working group

Introduction

Biomarkers such as troponin or brain natriuretic peptides play an important role in the diagnosis and treatment of various heart conditions, and in particular in the management of heart failure patients. ST2 (suppression of tumourigenicity 2) has evolved as a new cardiovascular biomarker for assessing acute heart failure and predicting the outcome of chronic heart failure (American Heart Association statement on Biomarkers in Heart Failure) [1]. This article summarises insights and discussion points from the first meeting of the Swiss working group on cardiovascular biomarkers held on September 4th 2018 in Zurich, Switzerland. The main focus was the diagnostic and prognostic importance of cardiovascular biomarkers (with an emphasis on ST2) for patients with cardiovascular disease. All authors were presenting participants at the meeting. The slides presented and references are summarised in the text below. A list of all attendees can be found in Appendix 1.

Heart failure – a rapidly advancing field

Heart failure represents the end stage of all cardiac diseases, irrespective of the underlying pathology. The number of patients with heart failure has increased in the last decades and it is currently the most prevalent cardiac disease [2]. Ironically, the increase in the number of heart failure patients is the price to be paid for successes achieved in advanced treatment of cardiac diseases such as acute coronary syndrome, valvular heart disease and cardiomyopathies [3–5]. Despite all therapeutic achievements, severe heart failure is associated with a grim prognosis and mortality rates often exceed those of cancer [6].

The increasing number of patients with heart failure is, however, also a result of successes in improvement of heart failure treatment. Medical therapy is the cornerstone of heart failure management: the use of angiotensin coenzyme inhibitors, beta-blocking agents and aldosterone antagonists has led to improved survival of heart failure patients (CONSENSUS; MERIT-HF, RALES [7–9],); these drugs thus have class 1A recommendations in the recent guidelines for heart failure therapy [10]. The latest advance in medical treatment was achieved with the use of valsartan/sacubitril in the PARADIGM-HF study [11]. In addition to medical treatment, cardiac resynchronisation therapy [12] and implantable cardioverter defibrillators [13, 14], as well as the use of telemonitoring [15], have im-

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Table 1: Factors influencing levels of cardiovascular biomarkers (adapted by permission from: Nishimura M, Brann A, Chang KW, Maisel AS. The confounding effects of non-cardiac pathologies on the interpretation of cardiac biomarkers. Curr Heart Fail Rep. 2018 Jul 10 [Epub ahead of print]).

	Male gender	Age	Obesity	Non white	Renal impairment	During dialysis	Sepsis	Afib
Troponin	↑	↑	↑	↑	↑	↓	↑	↑
(NTpro)BNP	↓	↑	↓	↓	↑	↓	↑	↑
PCT	n/a	n/a	↑	n/a	↑	↓	↑	n/a
sST2	↑	↑	<->	<->	<->	<->	↑	<->

Afib = atrial fibrillation; NTproBNP = N-terminal brain natriuretic peptide; PCT = procalcitonin; sST2 = soluble suppression of tumourigenicity 2; ↑ = biomarker elevated by factor; ↓ = biomarker reduced by factor; <-> = no influence; n/a, not applicable as not known.

proved survival in heart failure patients. Improved survival has also been achieved in heart failure patients with underlying valvular disease. Treatment of severe aortic r stenosis using transcatheter aortic valve replacement rather than surgical replacement is beneficial also in patients with reduced ejection fraction [16, 17]. In heart failure patients with severe mitral regurgitation, catheter interventions have had mixed results: the use of MitraClip in the MITRA-FR study did not reduce the incidence of rehospitalisation or cardiac death, whereas percutaneous mitral valve repair dramatically increased survival and reduced heart failure-induced rehospitalisation in the COAPT study [18, 19].

Biomarkers in heart failure patients: strengths and limitations

Biomarkers such as troponin, C-reactive protein or natriuretic peptides play an important role in the diagnosis, treatment and prognosis of heart failure patients [20, 21]. The currently most widely used biomarkers are the natriuretic peptides. B-type natriuretic peptide (BNP) accurately diagnoses heart failure in patients presenting with dyspnoea and predicts future events in these patients when a cut-off level of 100 ng/ml is used [22]. For N-terminal B-type natriuretic peptide (NT-proBNP), an age-independent cut-off level of 300 pg/ml has a 98% predictive value to exclude acute heart failure [23]. Use of BNP levels to titrate heart failure therapy has improved outcomes in patients <75 years of age with heart failure and a reduced ejection fraction (HFrEF) [24, 25]. Like BNP, NTproBNP can be used to diagnose heart failure and predict heart failure events [26, 27]. However, although management of heart failure patients guided by NT-proBNP levels had an impact on medical therapy, it did not reduce mortality or morbidity in the PRIMA study [28]. Furthermore, the recent randomised controlled GUIDE-IT trial was terminated early as it failed to show an improved outcome when HFrEF patients were treated according to NT-proBNP levels [29].

Biomarkers alone or in combination play an important role in the management of heart failure, but their accuracy is limited by several factors (table 1) [30]. Many of these confounders, in particular renal impairment [31, 32], obesity [33]and/or atrial fibrillation [34], are present in the majority of heart failure patients and can lead to short-term changes in biomarker levels independently of heart failure. Furthermore, genetic alterations may have an impact on production of natriuretic peptides of up to 30% [35]. Thus, a biomarker with similar diagnostic and prognostic power to natriuretic peptides but not affected by typical confounders is highly desirable.

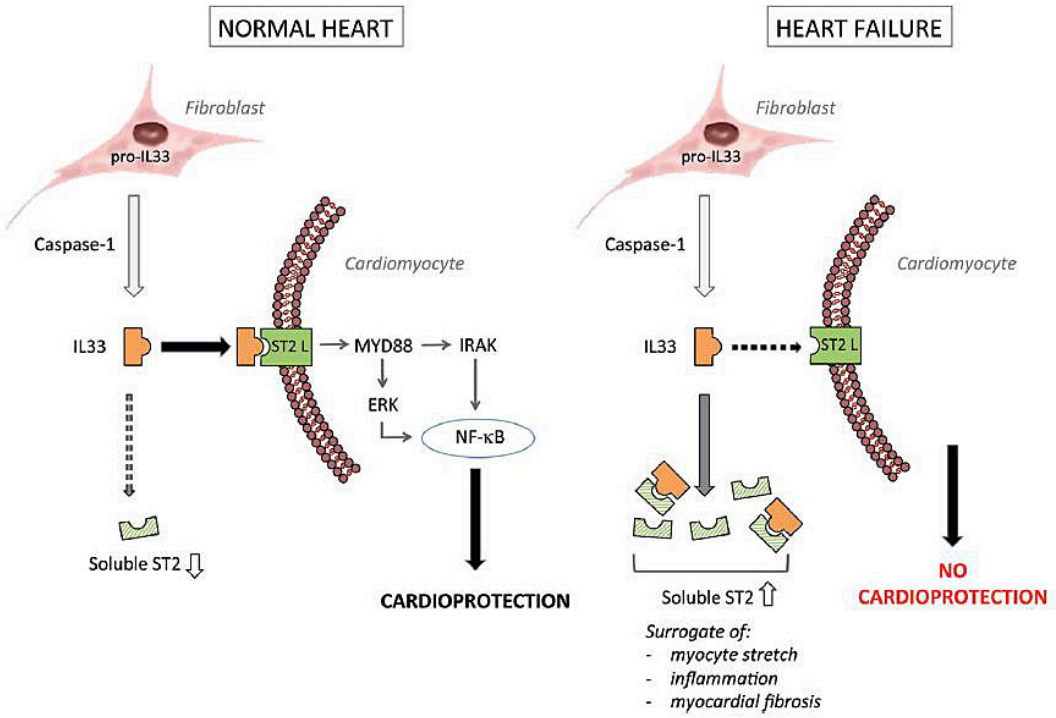
ST2 (suppression of tumourigenicity 2)

ST2 is part of the interleukin (IL)-1 receptor family and can be found on cardiac myocytes and fibroblasts. In experimental models, the interaction between IL-33 and ST2 appears to be protective, reducing fibrosis, hypertrophy and apoptosis [36, 37]. ST2 exists in two forms: a transmembrane isoform (ST2L), which is responsible for the cardioprotective action on fibroblasts, and a soluble form (sST2) [38]. It is the sST2 form that competes with ST2L, and by binding with IL-33 eliminates the cardioprotective pathway of the IL-33/ST2L interaction [37].(fig. 1 [39],). Whereas ST2 is certainly part of the myocyte wall, some studies have suggested that the vascular endothelial cell might be a prominent source of sST2 in cardiac patients [40]. All clinical conditions that increase wall stress, inflammation and macrophage activation increase sST2 and may therefore lead to an increase of cardiac fibrosis. However, since sST2 is also expressed by other organs and is elevated in various liver diseases [41], increased sST2 levels are not specific for heart failure.

Measurement of sST2

There are currently two laboratory tests available for measuring sST2 levels. One is manufactured by Critical Diagnostics® (the Presage Assay) of San Diego, California, USA. This enzyme-linked immunoassay (ELISA) is performed by specialised laboratories and can sim There are currently two laboratory tests available for measuring sST2 levels. One is manufactured by Critical Diagnostics® (the Presage Assay) of San Diego, California, USA. This enzyme-linked immunoassay (ELISA) is performed by specialised laboratories and can simultaneously analyse 96 samples. As duplicate samples from each patient are normally run, and control and calibration samples are included, sST2 levels of approximately 40 patients can be measured simultaneously. The second, bedside test (Point of Care Rapid Test) allows single patient measurements within 20 minutes. Both tests have similar lower and upper test limits (ELISA 2.4–200 ng/ml; POCT 12.5–257 ng/ml), but the bedside test has a somewhat larger repeat test variability (10.4–13.6% vs 4.0–6.4% with the ELISA). Nevertheless, these variabilities are still much smaller than the repeat test variabilities of BNP assays (up to 50%) [42]. The normal values for sST2 are age- and sex-dependent (table 2) [43]. The mean normal values for males are 24.9 ng/ml (95% nonparametric reference interval 8.6–49.3 ng/ml) and females 16.9 ng/ml (95% nonparametric reference interval 7.2–33.5 ng/ml) [44].This is important since the current cut-off level indicating good outcome in ambulatory heart failure patients is 35 ng/ml. Because of natural variation, 10–18% of men and 2–8% of women will thus have

Figure 1: The ST2 pathway (reprinted with permission from: Bayes-Genis A, Nunez J, Lupon J. Soluble ST2 for prognosis and monitoring in heart failure: The new gold standard? J Am Coll Cardiol. 2017;70(19):2389–92, with permission from Elsevier. ERK = extracellular signal-regulated kinases; IL33 = interleukin-33; IRAK = interleukin-1 receptor-associated kinase; MYD88 = myeloid differentiation primary response gene 88; NF = nuclear factor; ST2L = ST2 ligand.



values above this cut-off level in the absence of heart failure.

Soluble ST2 in clinical settings

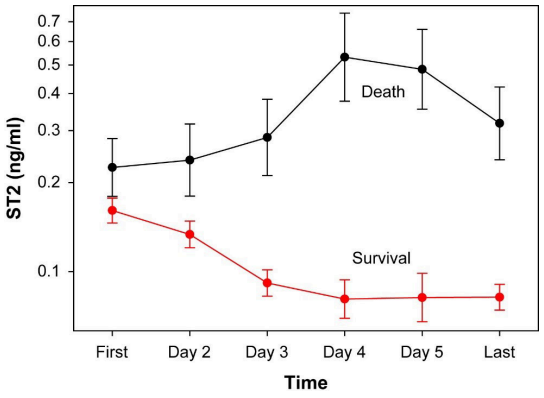
Acute heart failure

Soluble ST2 is not a diagnostic marker of acute heart failure and can be elevated in sepsis, disseminated cancer and fibrosis of other organs. Some of these conditions may mimic heart failure upon presentation. However, once the diagnosis of heart failure is made, 90% of the patients will have elevated levels of sST2. The higher the sST2 level in acute heart failure, the higher the mortality: mortality rate at one year was more than 50% for patients in the highest decile. And whereas the combination of elevated sST2 and a natriuretic peptide best predicted one year mortality, levels of natriuretic peptide failed to predict mortality in those with low sST2 levels [45, 46]. Levels of sST2 remained prognostic for up to 4 years [47]. The prognostic power appears to be valid for heart failure patients with preserved ejection fraction (HFpEF, ejection fraction >50%) as well as for those with reduced ejection fraction (<50%), but with different cut-off levels (HFpEF 35 ng/ml; HFrEF 48 ng/ml) [45, 49]. Several studies have underlined the importance of serial sST2 measurements [50, 51]. The absolute baseline sST2 value gives some prognostic information, but additional predictive value can be found in the pattern of sST2 levels over time. Very early sST2 changes (within 48 h) can separate responders to heart failure therapy from nonresponders, and those patients whose sST2 does not decrease over 90 days or even increases during hospitalisation have a higher likelihood of death than those with a relevant decrease (fig. 2) [50, 52, 53]. The results of

Table 2: Reference limits for sST2 levels (in ng/ml) according to age and sex (adapted with permission of the American Association for Clinical Chemistry, from Coglianese EE, Larson MG, Vasan RS, Ho JE, Ghorbani A, McCabe EL, et al. Distribution and clinical correlates of the interleukin receptor family member soluble ST2 in the Framingham Heart Study. Clinical Chemistry. 2012;58(12):1673–81.)

	Men, percentile				**Women, percentile**			
Age group, years	2.5th	50th	97.5th	99th	2.5th	50th	97.5th	99th
Empirical reference limits								
35–44	10.6	22.9	47.6	49.3	10.4	17.1	33.2	45.9
45–54	11.5	22.3	43.7	64.4	9.8	17.7	30.7	36.7
55–64	12.4	22.7	43.3	46.4	9.9	17.5	34.3	39.3
65–74	13.2	24.5	45.2	54.7	9.3	19.2	45.1	53.0
Quantile regression reference limits								
35–44	10.3	21.3	46.5	46.7	10.2	16.6	29.4	29.5
45–54	11.2	22.0	45.8	48.7	10.0	17.2	31.2	34.0
55–64	12.1	22.8	45.2	50.8	9.8	17.8	33.2	39.3
65–74	13.1	23.6	44.6	53.0	9.6	18.5	35.3	45.3

Figure 2: Plot of ST2 concentrations (geometric means and standard errors) at serial time points in patients who survived as compared with those who died within 90 days. The groups did not differ in ST2 concentrations at baseline (p = 0.22), but were elevated in subsequent observations for those who died within 90 days by Day 2 (p = 0.03) and thereafter (p <0.001 for each timepoint). Reprinted from: Boisot S, Beede J, Isakson S, Chiu A, Clopton P, Januzzi J, et al. Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure. J Card Fail. 2008;14(9):732–8, with permission from Elsevier.



individual studies were confirmed in a recently published meta-analysis [54]. Concentrations of sST2 proved to have prognostic value for all-cause and cardiovascular death, as well as the composite endpoint of all-cause death or hospitalisation for heart failure. Both admission and discharge sST2 values demonstrated prognostic efficacy. However, only discharge sST2 (but not admission sST2) was predictive of heart failure rehospitalisation during follow-up.

Chronic heart failure

Soluble ST2 is also a strong predictor of future events in chronic heart failure. As in acute heart failure patients, prognostic information in chronic heart failure can be derived from both the baseline sST2 value and the pattern of sST2 levels over time. The level of sST2 (median 19.8 ng/ml) at the time of baseline echocardiography was predictive of one year mortality in patients with HFpEF, with no deaths in patients with sST2 below the median. A large body of evidence underlines the predictive value of sST2 values in HFrEF patients: sST2 is predictive of short-term (2 weeks) mortality or heart transplantation [55], or long-term (>2.5 years) occurrence of death, rehospitalisation or worsening of heart failure [48, 56]. In addition to prognosis, sST2 measurements identify patients with chronic heart failure who may particularly benefit from specific medical treatment. Patients with high sST2 (>35 ng/ml) and low doses of beta-blockers (<50 mg daily equivalent dose of metoprolol succinate) had an odds ratio of 6.77 for cardiovascular events within 10 months follow up compared to patients with low sST2 (<35 ng/ml) and higher doses of beta-blocker [57]. In the recent PRADIGM-HF trial, the reduction of sST2 within 1 month of treatment was an independent predictor of future cardiovascular events, and valsartan/sacubitril reduced sST2 to a greater extent than enalapril [58].

The Swiss experience

In a study performed by the University of Basel, levels of sST2 were measured in 207 patients with acute heart failure at presentation to the emergency department and again 48 hours later [53]. The impact of medical treatment, as well as of sST2 levels, were analysed for a period of 1 year. Levels of sST2 were higher in nonsurvivors than in survivors (median 180 vs 69 ng/ml), and the sST2 decrease was less pronounced in nonsurvivors (median −25% vs −42%). As in the study of Gaggin et al. described above [57], the study by Breidthardt et al. [53] also detected influences of medical treatment: in patients with a less pronounced sST2 decrease, adding beta-blocker treatment was associated with a significant decrease in 1-year mortality.

The University Hospital of Basel together with the Kantonsspital Aarau will analyse the predictive value of sST2 in patients who underwent noncardiac surgery and developed a perioperative myocardial infarction in a subgroup of a previously published cohort [59].

The Heart Clinic Zurich is studying patterns of sST2 and NTproBNP levels in all comers in a cardiology outpatient setting. In an interim analysis of 345 analysed pairs, 14% had a combination of elevated sST2 levels (median 58.2 ng/l) with normal (i.e., below the age-adjusted cutoff value) NTproBNP levels (median 228.4 ng/l). None of these patients had clinical signs of heart failure. These findings underscore the finding that, in a non-heart failure population, ST2 levels may be normal even when above the cutoff level of 35 ng/ml defined in the heart failure population. Further analyses to define this specific subgroup are pending.

Areas of uncertainty

Perhaps the biggest uncertainty is the exact pathomechanism of sST2 and its effects on the cardiovascular system. The rapid changes in sST2 levels within days of heart failure treatment initiation indicate that they do not represent an absolute amount of fibrosis in the heart, but rather the activation level of the fibrosis generating pathway [60]. And since this pathway can be activated by several cardiac and noncardiac triggers, we need to better understand why sST2 levels rise or fall, and what they really stand for.

The usability of sST2 in the general population remains a matter of debate. Use of multiple biomarkers (including sST2, growth differentiation factor-15 and high-sensitive troponin I), as opposed to single biomarkers, in over 3428 individuals of the Framingham heart study added prognostic value to standard risk factors for predicting death, overall cardiovascular events and heart failure [61]. However, in 8444 healthy persons from Finland, sST2 measurements did not improve long-term prediction of cardiovascular events, including heart failure or all-cause mortality [62].

In the heart failure population, a growing body of literature underscores the prognostic value of elevated baseline sST2 levels (above 35 ng/ml) and the predictive value of changing sST2 levels during heart failure therapy. However, the absolute sST2 level in a given patient is less well understood. 35 ng/ml appears to separate heart failure patients with bad from those with favourable outcome. However, the linear increase of mortality with linear increase of sST2 did not allow definition of a clear cut-off level in the PARADIGM heart failure ST2 cohort [58]. And as multiple sST2 measurements offer incremental predictive pow-

er over a single sST2 measurement, the factors influencing the sST2 levels at a given point in time need to be understood better [51]. This holds particularly true for the interplay of sST2 with medical and non-medical therapeutic interventions, and how sST2 can be used to guide heart failure therapy. Until we have more answers in these clinically relevant areas of uncertainty, some of the authors feel that sST2 should only be used cautiously in clinical practice.

Conclusions

Biomarkers play an important role in the risk stratification, treatment and prognosis of heart failure patients. Soluble ST2 is a relatively new biomarker indicating myocardial wall stress and activation of the fibrosis pathway. Elevated sST2 levels in acute heart failure patients predict both recurrent hospitalization and mortality. In patients with chronic heart failure, sST2 levels that are responsive to medical treatment are associated with better outcome. However, elevated ST2 levels in the absence of heart failure or heart disease are not uncommon and limit its use for diagnostic purposes in a general non-heart failure population. Further studies need to identify the exact pathway of sST2 and specify its clinical implications for subgroups of heart failure and non-heart failure patients.

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Appendix 1 **List of the attendees of the meeting (in alphabetic order)**

Title	Name	First Name	Address	City
Cand. med.	Ammann	Camille	HerzKlinik Hirslanden	Zurich, CH
Dr. med.	Arrigo	Mattia	USZ Universitäres Herzzentrum	Zurich, CH
PD Dr. med.	Biaggi	Patric	HerzKlinik Hirslanden	Zurich, CH
Dr. med.	Blümel	Sena	Universitätsspital Zürich	Zurich, CH
PD Dr. med.	Breidthardt	Tobias	Universitätsspital Basel	Basel, CH
	Dumert	Werner	Bestbion	Köln, D
Ph.D.	Gawinecka	Joanna	Universitätsspital Zürich	Zurich, CH
Dr. med.	Hammerer-Lercher	Angelika	Kantonsspital Aarau AG	Aarau, CH
Dr.phil.nat.	Horn	Michael P.	Inselspital Bern, ZLM	Bern, CH
Prof. Dr. med.	Hullin	Roger	Centre hospitalier universitaire Vaudois	Lausanne, CH
PD Dr. med.	Hunziker Munsch	Lukas	Inselspital Bern	Bern, CH
Dr.sc.nat.	Imperiali	Mauro	Centro medicina di laboratorio Dr. Risch	Pregassona, CH
Dr. med.	Krull	Nora	Unilabs LAS Ticino	Breganzona, CH
Dr.	Lüscher	Dieter		Zurich, CH
Prof. Dr. med.	Maisel	Alan	University of California San Diego	San Diego, USA
Dr. med.	Mertens	Joachim C. P.	Universitätsspital Zürich	Zurich, CH
Prof. Dr. med.	Moccetti	Tiziano	Cardiocentro Ticino	Lugano, CH
Prof. Dr. med.	Müller	Christian	Universitätsspital Basel	Basel, CH
Prof. Dr. med.	Noll	Georg	HerzKlinik Hirslanden	Zurich, CH
Dr. med.	Pasotti	Elena	Cardiocentro Ticino	Lugano, Ch
Prof. Dr. med.	Risch	Lorenz	Labormedizinisches Zentrum Dr. Risch	Liebefeld, CH
Prof. Dr. med.	Ruschitzka	Frank	Universitätsspital Zürich	Zurich, CH
Dr.rer.nat.	Saleh	Lanja	Universitätsspital Zürich	Zurich, CH
Dr. med.	Scopigni	Francesca	Cardiocentro Ticino	Lugano, CH