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ABSTRACT

Soluble suppression of tumorigenicity-2 (sST2) is a biomarker widely investigated during the last few years. Its role has become clear in pathological conditions such as fibrosis and inflammation. From translational research to laboratory medicine, considerable efforts have been made to elucidate the features of sST2 biomarker and to consider its contribution to HF management. In this review, we summarized the results from recent works concerning sST2, and particularly we focused on the interest of sST2 in conditions for which classical biomarkers value interpretation is misleading. Indeed, despite other HF biomarkers, sST2 was proved to be independent from common comorbidities such as renal dysfunction and hypertension. Thus, sST2 showed promise for a combined strategy with natriuretic peptides, mainly for specific categories of patients. Particular attention was paid to findings on sST2 in HF with preserved ejection fraction (HFpEF), a form of HF for which reliable and specific biomarkers are awaited. Finally, a place is reserved to sST2 kinetics from basal to follow up values in order to improve clinical decision making and to customize patient treatments.

1. Introduction

The role of soluble suppression of tumorigenicity-2 receptor (sST2) in inflammation and fibrosis has been well defined, but its contribution as a biomarker in the diagnosis and prognosis of heart failure (HF) has yet to be elucidated [1,2]. In 2016, the European Society of Cardiology (ESC) deemed research on sST2 and other novel HF biomarkers inconclusive for utility in clinical practice. The plasma concentration of natriuretic peptides (NPs) is the most widely used laboratory test for the HF initial diagnosis (class IIa, level C). Nevertheless, a multimarker approach is more informative than a single biomarker approach [3]. The latest ACC/AHA guidelines from April 2017 and AHA statement from the same year focused on biomarkers in the prevention, assessment, and management of HF. Biomarkers of myocardial fibrosis, such as sST2, galectin-3 (Gal-3), and high-sensitivity cardiac troponin (hs-cTn), are considered mainly predictive of hospitalization and death in HF patients and additive to NPs in their prognostic value [4–6]. Those findings raised interest in alternative biomarkers 1/ to add complementary information to NP markers and 2/ to better stratify the risk in specific subpopulations of HF patients. Finally, in the comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure (August 2017), sST2 is responsible for providing additional value for short- and long-term prognosis, regardless of the left ventricular ejection fraction (LVEF) [7,8]. Moreover, the usefulness of sST2 value to adapt therapies to improve clinical outcomes was underlined [9]. In the same year, two *meta*-analyses by Aimo *et al.* provided exhaustive studies supporting the predictive value of sST2 in patients with both acute (AHF) or chronic heart failure (CHF) [10,11].

This review aimed to examine the impact of the sST2 biomarker in improving the medical care of several HF subpopulations with common comorbidities (renal disease, hypertension, or metabolic disorders) as well as the elderly population. Additionally, increasing evidence has supported the concept that the value of sST2 over other HF biomarkers was that sST2 is independent of other factors such as arterial hypertension, renal dysfunction, obesity, or age, both in the case of a single or a serial measurement strategy [12]. Consistently, patients classified as having HF with a preserved ejection fraction (HFpEF) are commonly older than HF patients with a reduced ejection fraction (EF $<$ 50%) (HFrEF) and often with comorbidities [13,14]. The role of sST2 in HFpEF, comorbidities, and the proinflammatory state triad is thus becoming clear. We also focused on the sST2 strategy for HF serial measurements for the prognosis and guided therapy with more studies leading to improved clinical decision making and customized patient treatments [15]. The on-going clinical studies on sST2 conducted globally are listed in Table 1.

Table 1
On-going clinical studies on sST2.

Type	Title	NCT N°	Institution	Characteristics	Enrollment	Intervention	Outcomes	Status
Prevention	Comparison of lipophilic vs hydrophilic statins on HF patients	NCT03255044	Ain Shams University, Egypt	RCT, open	60	Atorvastatin (40 mg) vs. Rosuvastatin (20 mg)	Cardiac markers change from baseline to end of trial; NT-proBNP, sST2	Recruiting
	Effect of dietary approaches to stop hypertension eating pattern on cardiometabolic markers in AHF patients	NCT03538990	University of Georgia Clinical and Translational Research Unit, USA	POC	30	DASH Eating Pattern	Change in cardiometabolic marker levels between calibration and DASH diet intervention phase at baseline, 3 weeks, 6 weeks – sST2 is included as one of the markers	Recruiting
	A clinical research of Qi deficiency and blood stasis syndrome	NCT02875639	University of Traditional Chinese medicine, Henan, China	RCT, double blind	180	QISHEN YIQI DRIPPING vs. placebo	Difference in plasma levels of sST2, Gal-3, PT, APTT, FBg, TT, TnT, CK, GLUT-1, GLUT-4, H-FABP between baseline and 3 months.	Recruiting
	High-intensity interval training as treatment strategy for HFpEF patients:	NCT03184311	University Hospital Basel, Switzerland	RCT, single blind	98	HIT vs. usual care	Change in disease-specific biomarkers at baseline to 12 weeks; NT-proBNP, renine, AT-2, UCN-2, Osteopontin, sST2, Gal-3, GDF-15, Copeptin, Big-Endothelin-1, PlGF/sFlt-1, Hs-CRP, IL-6 and IGF-BP7	Not yet recruiting
Prediction	Prognostic value of sST2 in cardiac surgery on long term morbimortality	NCT03887767	CHU Montpellier, France	ROC	158		1 year mortality rate Number of rehospitalisation, cardiac events and stroke	To end at July 2019
	Correlational study on the biomarkers application to the prediction and diagnosis of CD	NCT02179047	Taipei City Hospital, Taiwan	POC	120	Coronography	Correlational study on the biomarkers application to the prediction and diagnosis of CD	Completed
	Evaluation of sST2 in patients receiving primary PCI with STEMI	NCT02830217	Wuhan Asia Heart Hospital, China	POC	500	Primary PCI	Rate of stent restenosis at 1-year, rate of recurrence of MI at 1-year, rate of readmission due to HF at 1- year, mortality at 1-year.	Recruiting
	The role of cardiac mechanics, circulating biomarkers and frailty in aortic stenosis in predicting outcomes after aortic valve intervention	NCT02856620	Montreal Heart Institute, Quebec, Canada	POC	450		Levels of NT-proBNP, hs-TnT, sST2, hs-CRP, GDF-15	Recruiting
	Frailty syndrome in daily practice of interventional cardiology ward	NCT03209414	Zabrze Medical University of Silesia, Polland	POC	1000		sST2 as a marker for frailty	Recruiting
Drug Therapy	Sacubitril/Valsartan (LCZ696) in patients with AHLVH and HFpEF: Clinical, haemodynamic and neurohumoral effects	NCT03928158	National Medical Research Center for Cardiology, Moscow, Russian Federation	RCT, open	60	LCZ696 vs. Enalapril	Difference in sST2 plasma levels between 24 weeks after baseline and at baseline	Not yet recruiting
	Personalized prospective comparison of ARNi with ArB in patients with NP elevation	NCT02682719	St Michael's Hospital, Dublin, Ireland	RCT, double blind (The PARABLE Study)	250	LCZ696 vs. valsartan or placebo	Change in markers of fibrosis (sST-2) from baseline, 9 months, 18 months	Unknown
Treatment safety	Rivaroxaban once daily versus dose-adjusted Vitamin K antagonist on the biomarkers in ADHF and AF	NCT03490994	Yonsei University College of Medicine Seoul, Republic of Korea	RCT, open (ROAD HF-AF)	150	Rivaroxaban vs. VKA	TAT complex, PAI-1, hsCRP, NT-proBNP, sST2, Gal-3, cystatin C, NGAL, NAG change from baseline to day7 or discharge and 1–6 months after discharge	Recruiting

RCT = Randomized Controlled Trial; NT-proBNP = N Terminal-pro Brain Natriuretic Peptide; sST2 = soluble Suppression of Tumorigenicity-2 receptor; AHF = Advanced Heart Failure; POC = Prospective Observational Cohort ; DASH = Dietary Approaches to Stop Hypertension; Gal-3 = Galectin-3; PT = Prothrombin Time; APTT = Activated Partial Thromboplastin Time; FBg = Fasting Blood glucose; TT = Thrombin Time; TnT Troponin T; CK = Creatine Kinase; GLUT-1 = Glucose Transporter 1 ; .GLUT-4 = Glucose Transporter type 4; H-FABP = Heart-Fatty Acid Binding Protein; HFpEF = Heart Failure with preserved Ejection Fraction; HIT = High-Intensity interval Training; AT-2 = Angiotensin-II; UCN-2 = Urocortin-2; GDF-15 = Growth Differentiation Factor 15; PlGF/sFlt-1 = Placental Growth Factor/Soluble Fms-like tyrosine-kinase 1; Hs-CRP = High-sensitivity C-reactive protein; IL-6 = Interleukin 6; IGF-BP7 = Insulin-like growth factor-binding protein 7; ROC = Retrospective Observational Cohort; CD = Cardiovascular Diseases; PCI = Percutaneous Coronary Intervention; STEMI = Acute Myocardial Infarction ST Elevation; MI = Myocardial Infarction; AHLVH = Advanced Hypertensive Left Ventricular Hypertrophy; *ARNi* = angiotensin receptor-neprilysin inhibitor; ARB = Angiotensin II receptor blocker; NP = Natriuretic Peptide; ADHF = Acute Decompensated Heart Failure; AF = Atrial Fibrillation; TAT = Thrombin-AntiThrombin; PAI-1 = Plasminogen Activator Inhibitor-1; NGAL = Neutrophil Gelatinase Associated Lipocalin; NAG = N-Acetyl-β-D-Glucosaminidase.

2. Biological variability of sST2 and analytical concerns

Knowledge about the biological variability, as well as the measurement system performance of biomarkers, is necessary to identify significant changes in the state of patients during follow up. Thus, the concept of reference change values (RCVs) combining within-subject biological variation and analytical variation is the most appropriate. A biomarker with low biological variability and an index of individuality < 0.6 allows the consideration of clinically relevant minor changes in marker measurements, and it is more suitable to monitor patients serially [16,17]. Previous studies on healthy subjects reported RCVs of sST2 lower (close to 30%) than those of NPs, notably 60% for N-terminal-pro brain natriuretic peptide (NT-proBNP) and 90% for brain natriuretic peptide (BNP) [18]. In CHF patients, the RCV of sST2 remained lower than that of BNP (43% vs. 105%, respectively), and they were similar in different studies. Furthermore, the index of individuality was determined to be close to 0.25 for sST2, 0.91 and 1.01 for NT-proBNP and galectin-3 (Gal-3), respectively [19,20]. With low RCVs and individuality index values, sST2 seems to be the best candidate for monitoring and guided therapy. To date, four commercial assays to measure sST2 have been mostly used: the MBL assay (Siemens, Saint Denis, France), R&D ELISA kit (R&D Systems, Minneapolis, MN, USA), Presage ELISA kit (Critical Diagnostics, San Diego, CA, USA) and Aspect Plus assay on Aspect Plus reader point of care (Critical Diagnostics, San Diego, CA, USA). Although it is difficult to determine which kit is superior, the lack of concordance between assays complicates clinical interpretation and comparison. The main problem among commercially available ELISA kits is related to standards that are different in content and purity. Some kits use cell lysate preparations, whereas others use purified proteins. Additionally, the ratio of available epitopes to the mass of protein might vary with each purification of the standard during production processes. On the other hand, the epitopes recognized by anti-sST2 monoclonal antibodies are not the same in the different ELISA kits. Therefore, to date, no supporting evidence exists to measure “free sST2”, “complexed sST2” or both [16]. The sST2 level is widely measured using the Presage ST2 assay, which is the only method cleared by U.S. Food and Drug Administration (FDA) and labeled with the CE (Conformitée Européenne) mark. Several studies have demonstrated that the results from the newly developed Aspect Plus ST2 rapid test and Presage ST2 ELISA assay were well correlated at the proposed cut-off value of 35 ng/mL [21,22]. This was expected because the two systems used the same monoclonal antibody with the difference that the ASPECT-PLUS ST2 Test is based on the sandwich monoclonal lateral flow immunoassay (LFI). This technology allows us to deliver a result in approximately 20 min with within-run and total imprecision CVs < 17%, entirely adequate for the point-of-care format. While waiting for automatization of this parameter, the Aspect Plus system appears today to be the most adapted for bedside results and clinical practice.

3. sST2 and limitations of classical HF biomarkers

Evidence of noncardiac causes increasing the NP value and complicating the interpretation for the diagnosis and prognosis of cardiovascular outcomes has enhanced the interest in other biomarkers. It has emerged from several studies that sST2 is not influenced by age [23,24] or comorbidities such as renal dysfunction, which remain major biases for the interpretation of NP [25–27]. Furthermore, other confounding factors—e.g., inflammation state, hypertension, or metabolic dysfunctions—play an essential role in establishing the best biomarker strategy to adopt (Table 2) [28].

In a study recruiting patients with HF and other extracardiac pathologies, sST2 and other inflammation biomarkers (growth differentiation factor (GDF)-15, Gal-3) could not discriminate HF from pneumonia, chronic obstructive pulmonary disease (COPD) or sepsis. The concentration of sST2 increased considerably in patients with HF as well as in those with pneumonia, COPD, or sepsis only. An even higher increase in the sST2 value was observed for the group of patients with both HF and pneumonia and those with HF and sepsis with median plasma concentrations 53-fold and ~70-fold higher, respectively, than that of healthy subjects. Interestingly, no relevant difference was found in the sST2 concentration between healthy controls and patients with renal disease ($p = 0.065$) [29]. This result confirmed that the sST2 biomarker is merely specific in the presence of inflammation-associated illnesses such as sepsis, pneumonia or COPD, and other biomarkers such as NT-proBNP are more adequate in the diagnosis of those associated HF pathologies. Nevertheless, as discussed later in this review, the inflammation state is part of HF pathology (e.g., HFpEF), and sST2 seems to be well positioned to reflect the pathology progression and provide complementary information on prediction and monitoring. Moreover, sST2 was recently investigated among other novel biomarkers (GDF-15, soluble urokinase plasminogen activator receptor (suPAR) and heart-type fatty-acid binding protein (H-FABP)) for the diagnosis of patients with CHF associated with ischemic and dilated cardiomyopathy. The sST2 level was increased in both categories of patients compared with controls, whereas no significant correlation was found with the age, arterial hypertension, and estimated glomerular filtration rate (eGFR). Finally, a clear increase in biomarkers, including sST2, was demonstrated according to the HF severity estimated by NYHA stage [30]. In line with these findings, Bayes-Genis *et al.* reported on patients with both renal dysfunction and HF at different severity stages. Although at very low eGFR, the sST2 serum concentration tended to increase ($r = -0.09$; $p < 0.006$ in multivariate correlation analysis), NT-proBNP showed more remarkable correlation ($r = -0.37$, $p < 0.001$). Indeed, for more severe HF (NYHA functional class III-IV), sST2 appeared to be less related to renal function than NT-proBNP and, thus, was the preferential marker to use [25]. More recently, Plawecki *et al.* confirmed the independence of sST2 from eGFR and age and included sST2 in a multimarker strategy for cardiovascular (CV) risk stratification of nondialyzed chronic kidney disease (CKD) patients [31]. End-stage renal disease (ESRD) is a major issue in public health and is often associated with HF in these patients. Thus, the correct combination of biomarkers is important to discriminate hemodialyzed (HD) patients at high risk of future cardiovascular events from the others. A combination of cardiac biomarkers (cTnI and NT-proBNP) in association with the inflammatory marker C-reactive protein (CRP) was proven to predict cardiovascular risk in HD patients within two years, and the results showed a good prognostic value of these markers for the short-term follow up [32]. More recently, sST2 and Gal-3 provided independent and incremental prognostic values in HD patients when using different statistical models to predict all-cause death [33]. Unlike sST2 protein (48 kDa), NT-proBNP is a small molecule (8.4 kDa) filtered by the glomerulus that was influenced by alterations in GFR or hemodialysis filtration (HDF) treatments. The lack of a significant difference in the sST2 plasma concentration before and after HDF confirmed the interest of this biomarker for ESRD patients [34]. Furthermore, the promising role of the sST2 biomarker was demonstrated in a cohort of hypertensive HF patients (77 subjects) showing a good correlation between sST2 and several echocardiography indicators. Although this finding needs to be confirmed in a larger cohort, sST2 was a better circulating biomarker than NT-proBNP in assessing HF secondary to hypertensive heart disease [35]. Notably, sST2 provided a diagnostic aid of stable HF in hypertensive patients despite NT-proBNP, mainly contributing to diastolic abnormality information [36]. The independence of diabetes mellitus, as well as elderly and metabolic disorders, were all investigated to improve the risk of death prediction in the HF subpopulation. However, to our knowledge, the results are not always in agreement [23,24,37].

4. sST2 and the multimarker approach

A panel of biomarkers can be applied to better reflect the complexity of HF and various pathophysiological pathways. NT-proBNP is a marker of volume overload and congestion, whereas sST2 responds to

Table 2
Causes of confusing factors for the biomarker level.

Non-cardiac	Natriuretic peptides	sST2	Ref.
Advanced age	↗↗	↔	23, 24, 31, 65
Renal dysfunction	↗↗	↔	21, 23–27, 29, 31
Chronic obstructive pulmonary disease	↔	↗	21, 29
Severe infection (including pneumonia and sepsis)	↗	↗↗	21, 29
Diabetes	↗	↔	34
Obesity, BMI ($> 35\ kg/m^2$)	↘↘		23, 28
Hypertension	↗	↔	30
Cancer	↔	↗↗	16

cardiac fibrosis, inflammation, and remodeling. Thus, NT-proBNP and sST2 produce incremental information reflecting diverse pathophysiological pathways implicated in highly complex HF pathology while assessing the risk stratification strategy. The results from the PRIDE study on patients with acute dyspnea demonstrated the role of both sST2 and NT-proBNP in a multimarker approach. The additive value of sST2 contributed mainly to predicting the 1-year mortality risk in all subjects, as well as in those with AHF. Interestingly, patients with a low value of sST2 and elevated NT-proBNP were less likely to have AHF than those with elevated sST2 (58% vs. 81%, respectively; $p = 0.007$). Nevertheless, an elevation in both markers determined the highest rates of death [38]. A strong correlation was also found between sST2 and the mid-regional pro-adrenomedullin (MR-proADM) marker ($R = 0.59$, $p < 0.001$) in a large cohort of patients hospitalized for acute decompensated heart failure (ADHF). MR-proADM is also considered a highly useful marker for a combined strategy. The association of these two biomarkers was the best combination to be included in the risk prediction model individually or with NP and CRP [39,40]. By contrast, Mueller *et al.* proved the lack of contribution in the diagnosis capability and prognostic accuracy by adding sST2 or Gal-3 to BNP in the AHF emergency setting. However, in another study, sST2 and NT-proBNP were found to predict equally long-term mortality. ROC analysis used to predict the 1-year all-cause mortality showed that the combination of NT-proBNP and sST2 values (AUC = 0.732) was better than each parameter taken separately [41,42]. The findings included a high number of CHF patients (1081) and a prolonged period (13 years) of follow up (KAROLA study), showing that the sST2 value increased the prognostic assessment of cardiovascular disease compared with standard biomarkers. In this work, plasma sST2 concentrations independently predicted mortality but not cardiovascular events specifically [43]. This conclusion suggested that the predictive value of sST2 is not linked to myocardial and wall stress but rather to acute vascular stress in the context of cardiovascular events and confirmed the interest for the synergic biomarkers approach. In another population with stable CHF, sST2 showed additive prognostic value when combined with biomarkers implicated in collagen remodeling [44]. Beyond their current role as a diagnostic or prognostic marker, personalized medicine is suggested with the contribution of a panel of biomarkers. For the first time, greater than 40 biomarkers were recently included in an AHF retrospective analysis to differentiate responders from nonresponders to pharmacological therapy. sST2 was among the biomarkers for which the baseline high level was related to a better treatment response to rolofylline. This approach allows the study of subpopulations with different clinical characteristics, such as disease severity or comorbidities, and targeting those that benefited from treatment. In this work, the immunoassay to measure the sST2 concentration was developed by Alere. This research assay has not been standardized to the commercialized assays used in research or for clinical use. Furthermore, the extent to which the Alere assay correlates with the commercial assay has not been entirely characterized [45]. A summary of the main studies using a multimarker strategy is presented in Table 3.

5. sST2 and HFpEF

The inflammatory response and/or immune activation as a marker of disease progression in HF patients were recently stated [46]. As already mentioned, subclinical inflammatory processes are considered important factors in the progression of HF, and enhancement of sST2 secretion confirmed the involvement of this process in HF patients. Particularly, proinflammatory cytokines such as TNF-alpha or IL-6 provoke sST2 release as well as hemodynamic stress and cardiomyocyte strain in the case of congestive HF [47]. The IL-33/ST2 system is upregulated in cardiomyocytes and fibroblasts in response to cardiac injury. The soluble ST2 receptor binds to IL-33 and competes with the ST2 transmembrane isoform receptor, thereby eliminating the cardioprotective effects [48]. An inflammatory state is often responsible for cardiomyocyte hypertrophy and/or collagen deposit in the interstitial space, and it has recently been shown to be often predictive of incident HFpEF but not HFrEF. HFpEF represents half of HF patients, and it is mostly characterized by quasi-normal systolic function (EF > 50%) and concerns commonly elderly patients, mostly women, and often subjects presenting comorbidities. It is a multifactorial condition whose pathophysiology is not fully unrevealed, although a deep relationship with inflammatory processes appears clear [49]. Plasma biomarkers that reflect changes in collagen, titin, and the profibrotic milieu could be used to improve the diagnostic criteria for HFpEF and prognostic assessment. Thus, changes in biomarkers, such as sST2, may detect the earliest transition to HFpEF. Elevated sST2 levels reflect profibrotic changes in HFpEF, and these are associated with mechanical alteration, particularly of the left atrium [50]. Nevertheless, the correlation between sST2 levels and HFpEF has not yet been fully established mainly because of some significant drawbacks. However, this biomarker, considering previously discussed properties, is a favorite candidate. In an AHF cohort, two subsets of HFrEF and HFpEF patients were investigated to enhance the prognostic information with the association of sST2 and BNP. The good performance of the two biomarkers in the prognostication of any-cause mortality and readmission for AHF at six months was more apparent for the HFrEF group than the HFpEF group. The restricted number of the last group of patients (39%) and use of a research-only method for sST2 measurements introduced a bias to definitely conclude on this point [51]. Similarly, higher sST2, hsCRP, and cystatin-C (Cyst-C) for HFpEF, a lower level of NT-proBNP, and high-sensitive troponin T (hs-TnT) and hemoglobin for HFrEF reflected two different HF pathophysiological pathways. No important differences were found in the prognostic value of biomarkers in HFpEF vs. HFrEF [52]. More recently, in a network study involving an extensive set of 92 biomarkers of various pathophysiological pathways, the authors discriminated between the biomarker profile specifically for HFrEF (NT-proBNP, GDF-15, interleukin-1 receptor type 1 and activating transcription factor 2) related to cellular proliferation and metabolism and those specific for HFpEF related to inflammation and extracellular matrix reorganization (integrin subunit beta-2 and catenin beta-1). No important sST2 protein–protein correlation resulted in any of the two types of HF pathology. Cardiovascular-related proteins were measured simultaneously in 1-μl plasma samples with an original approach based

Table 3
Summary of the clinical studies on sST2 and the multimarker approach.

First author, year (Ref. #)	Trial (population)/ Disease group	Patients, n	Prognostic (P), Diagnostic (D)- Primary end point /Follow up	Other markers	sST2 assay	sST2 results
Bayes-Genis A 2013([25])	Ambulatory patients (subgroup eGFR < 60 mL/min/1.73 m^2)	879	P-Death outcome	NT-proBNP	Presage ST2 assay	Significant long-term prediction in patients with renal insufficiency ($p < 0.001$)
Dupuy AM 2018([44])	CHF	182	P-42.3 M all-cause mortality	NT-proBNP, hs-cTnT, CRP, Gal-3, CTx/PIIINP ratio	Presage ST2 assay	Significant prognostic improvement in combination with CTx/PIIINP ratio ($p < 0.0001$)
Grande D 2017([24])	CHF	315	P-1Y cardiovascular death and HF related hospitalization	NT-proBNP, Gal-3	Presage ST2 assay	Significant HF risk stratification ($p < 0.001$)
Homsak E 2018([34])	ESRD patients	123	Effect of HDF in ESDR patients	NT-proBNP	Presage ST2 assay	Independent from HDF treatment, potential good risk stratifier in ESRD patients
Jin M 2017([41])	AHF (HFrEF only)	287	P-1Y all-cause mortality	NT-proBNP, Na	R&D Systems	Significant prediction equally to NT-proBNP and serum Na ($p < 0.049$)
Lichtenauer M 2017([30])	Coronary HF (ICM and DCM patients)	200	D and risk stratification	GDF-15, uPAR, H-FABP	R&D Systems	Promising for precise diagnostic in ICM and DCM patients
Liu LCY 2017([45])	PROTECT trial (AHF)	2033	P-3 M all-cause mortality	TNF-R1a, WAP-4C, total cholesterol, GDF-15, etc…	Alere TM Inc.	Significant in biomarker-based responder sum score to improve prognosis
Mueller T 2015([29])	HF (+non–cardiac conditions)	112	D	Gal −3, GDF-15	Presage ST2 assay	Not specific for a distinct disease group
Mueller T 2016([42])	AHF (+dyspnea)	137	P-1Y all-cause death	Gal- 3, BNP	Presage ST2 assay	Equally useful to Gal-3 and BNP for prediction
Obokata M 2016([33])	Hemodialysis patients	423	P-All-cause death and all-cause CV events	Gal-3, NT-proBNP,	M&B Laboratories	Independent and incremental prognostic value over NT-proBNP ($p < 0.001$)
Pfetsch V 2017([43])	KAROLA study (stable CHD)	1081	P-13Y cardiovascular and all-cause mortality	Cyst-C, NT-proBNP, hs-TnT, hs-TnI, MR-proANP, GDF-15	Presage ST2 assay	Significant for total mortality ($p < 0.0021$) but not for non-fatal CV events
Plawecki M 2018([31])	CKD patients	218	P-Risk stratification of CV events or/ and mortality	NT-proBNP, hs-TnT, CRP	Presage ST2 assay	Significant predictive in a multi-marker strategy based on Barcelona score ($p < 0.0001$)
Rehman SU 2008([23])	AHF	346	P-1Y follow up	NT-proBNP, hs-TnT, CRP, BNP	M&B Laboratories	Predictor of mortality ($p = 0.003$) and synergistic with NP ($p < 0.001$)
Wang YC 2013([36])	Hypertension cohort with EF $> 50\%$	107	D	NT-proBNP	R&D Systems	Independent biomarker of the presence of stable HF ($p < 0.001$)

eGFR: estimated Glomerular Filtration Rate; NT-proBNP: N Terminal-pro Brain Natriuretic Peptide; CHF: Chronic Heart Failure, M = Months; hs-cTnT: high-sensitive cardiac Troponin T; CRP: C-reactive protein; Gal-3: Galectin-3; CTx: C-terminal Telopeptide of type I collagen; PIINP: N-Terminal Propeptide of Type III collagen; Y = Year(s); HF: Heart Failure; ESRD: End-Stage Renal Disease; HDF: HaemoDialysis Filtration; AHF: Acute Heart Failure; HFrEF: Heart Failure with reduced Ejection Fraction; ICM: Ischaemic CardioMyopathy; DCM: Dilative CardioMyopathy; GDF-15: Growth and Differentiation Factor 15; uPAR: urokinase Plasminogen Activator Receptor; H-FABP: Heart Fatty-Acid Binding Protein; TNF-R1a: Tumor Necrosis Factor alpha Receptor 1 ; WAP-4C: Whey Acidic Protein four disulphide core domain protein HE4; BNP: Brain Natriuretic Peptide; Cyst-C: Cystatin C; TnI: Troponin I; MR-proANP: MidRegional pro-Atrial Natriuretic Peptide; CV: CardioVascular; CKD: Chronic Kidney Disease; EF: Ejection Fraction.

on the high throughput technique (Olink Proseek Multiplex CVD III kit; Olink Proteomics, Uppsala, Sweden) [53]. Several studies have shown that the concentration of sST2 assayed either at admission or discharge in ADHF in HFpEF was predictive of all-cause death, CV death, and the composite outcome of all-cause death or HF hospitalization. Wang et al. evaluated 107 hypertensive patients with LVEF > 50%. Among them, 68 presented with symptoms of HFpEF. The sST2 concentration was significantly lower in patients with E/e′ < 8 than in those with E/e′ from 8 to 15 to > 15. Multivariate analysis demonstrated that sST2 > 13.5 ng/ml was independently associated with the presence of HFpEF. Additionally, sST2 was measured in 70 coronary artery bypass grafting (CABG) patients stratified into three groups: control (no hypertension), hypertensive patients without HFpEF, and hypertensive patients with HFpEF. sST2 was higher in hypertensive patients without HFpEF than in control subjects, and the sST2 levels were raised in hypertensive patients with HFpEF (105.5 ± 31.4 vs. 82.0 ± 35.7 ng/ml; $p < 0.05$) [36,54]. The prognostic value of sST2 was observed in the acute dyspnea population presenting HFpEF. The authors showed that an increased concentration of sST2 was an independent predictor of intermediate-term mortality in this population [55]. In addition to NT-proBNP, the sST2 values did not correlate with the echocardiographic parameters of systolic and diastolic dysfunction in these patients, supporting the hypothesis of distinct pathophysiological mechanisms involved. More consistent results on the sST2 level and inflammation-driven pathologies came from the RELAX trial that enrolled 216 patients with HFpEF and excluded patients with DFG < 20 mL/min per 1.73 m^2. Among all pathologies, patients with high sST2 levels were likely to have diabetes mellitus ($p = 0.049$), hypertension ($p = 0.023$), atrial fibrillation ($p = 0.049$), renal dysfunction ($p < 0.0001$) and congestion ($p < 0.0001$). sST2 was precisely named as a systemic inflammation marker connecting proinflammatory comorbidities and HF severity-related systemic congestion in HFpEF patients [56]. The STOP-HF Clinic population included fragile elderly patients with comorbidities and mainly HFpEF (mean LVEF 58.8%). The prognostic power of sST2 in both univariate and multivariate analyses was superior to NT-proBNP, tumor marker cancer antigen 125 (CA125; a marker of systemic congestion in HF) and hs-cTnI for primary and secondary endpoints, all-cause mortality and HF-related hospitalization at 1 year [57]. In the PARAMOUNT trial (301 HFpEF patients only), a high sST2 baseline level together with Gal-3 reflected a profibrotic state that was correlated with the presence and severity of the disease [58]. Nevertheless, in the same year, the findings by French *et al.* regarding the CHF population determined that Gal-3 alone is the most accurate discriminator of risk among participants with HFpEF (AUC = 0.782; $p = 0.81$ vs. s ST2; $p = 0.029$ vs. troponin I; $p = 0.35$ vs. BNP) [59]. Functional studies have shown an emerging role for microRNAs, although no biomarker has been identified yet to differentiate systolic dysfunction and HFpEF conclusively. Indeed, while waiting for more conclusive responses, a panel of various biomarkers representing different aspects of the complex pathophysiology seems to be the most helpful solution (Table 4) [60,61].

6. sST2 serial measurements and guided therapy

The relationship between basal and serial sST2 values was pointed out in relation to cardiac death and rehospitalization for HF worsening during the short and long follow up [62,63]. Notably, serial sST2 measurements allowed better prediction of cardiovascular admission or worsening of renal function in patients with pharmacologically optimized treatment for CHF compared with NT-proBNP [64]. The association of sST2 with repeated NT-proBNP measurements both in a short time during hospitalization (at least 3 measurements) and during a 1-year follow up (at least 5 measurements) guaranteed the prognosis accuracy [65–67]. Serial testing at multiple points during treatment revealed that lower sST2 concentrations were associated with reduced mortality and an improved functional status. By contrast, patients with persistently elevated sST2 levels at the follow up presented an increased mortality risk. In the *meta*-analysis already mentioned, sST2 at discharge, but not at admission, was predictive of HF rehospitalization during follow up [11]. Considering the important role of inflammation in HF pathology, several markers were used to follow ADHF patients during hospitalization. sST2, together with NT-proBNP and GDF-15 serial measurements, showed a good correlation, with a high level at admission followed by a sharp decrease up to discharge. Additionally, other inflammatory marker levels such as hsCRP or myeloperoxidase (MPO) did not significantly change after initially increasing [68]. Likewise, in patients with CHF, serial measurements of sST2 provided incrementally predictive value over time, particularly in combination with hs-cTn, reflecting myocardial injury [69,70]. The role of serial measurements of sST2 was thus established to identify ambulatory patients at highly increased risk despite the absence of clinical signs. Genetic factors can influence the values of repeated measurements, and this concern continues to gain importance in the field of HF. Genetic modifications were reported in relation to sST2 expression and changes in the IL-33/sST2 pathway; thus, genetic factors must be considered to interpret changes in marker expression and for an accurate prognostic value of sST2 [71]. However, the idea of a microRNA marker influencing sST2/IL-33 signaling needs more intensive studies. On the other hand, more sensitive assays are required to allow precise estimations of microRNA because many of them are often undetectable [72]. The utility of repeated measurements in prognostication and monitoring has been underlined. Obviously, a further step should establish the value of repeated sST2 measurements when used to guide therapy decisions. The idea is to first have a baseline sST2 value at admission, and then, after days 4/6, decide whether to intensify the therapy according to the sST2 cut-off of 35 ng/ml. Consequently, sST2 measurement is obtained before discharge to help physicians decide the optimal discharge timing, being more reasonable to delay discharge but to avoid readmission within the month. The 1-month discharge sST2 level allows monitoring and readapting patient therapy if necessary. Using biomarkers to predict the treatment response and to help physicians in tailoring therapy is a promising approach under intensive studies. Over the last decade, interest has arisen regarding biomarker-directed therapy (therapeutic choice and optimal dosing) and personalized medicine. As highlighted by Chow *et al.* (AHA SS 2017) among a panoply of biomarkers potentially used for guided therapy, sST2 appears to be the most suitable because of the analytical features previously discussed and—unlike NP—it is less influenced by other factors [5]. The importance of early sST2 changes obtained in the emergency department by measuring at admission and in the 1st 48 h was highlighted in the work of Breidthardt *et al.* A 33% decrease in the median sST2 level was observed during the 1st 48 h of in-hospital treatments; importantly sST2 levels decreased more significantly in survivors than in nonsurvivors. In Cox regression analysis, the percentage change of sST2 over the 1st 48 h predicted long-term mortality in univariate and multivariate analyses [73]. Gagging *et al.* demonstrated that elevation in sST2 might identify patients who are more likely to benefit from a higher beta-blocker dosage. Patients with a high baseline sST2 treated with low-dose beta-blockers had the highest cardiovascular event rate. Together with other classical and innovative biomarkers, sST2 was selected to identify subpopulations with a distinct treatment response in AHF [74]. Curinier *et al.* designed a study to prove the interest of sST2 measurement in real-time using the new generation point of care developed by Critical Diagnostic and now commercially available (CE mark) [75]. This apparatus, which is available in clinical laboratories, as well as in ambulatory services, allows decision making on the intensification treatment in the case of high values of sST2 (> 35 ng/ml). Likewise, it helps clinicians on the hospitalization discharge of patients. Table 5 summarizes the main works up to date.

Table 4
Summary of the clinical studies on sST2 and HFpEF.

First author, year (Ref. #)	Trial (population)/ Disease group	Patients, n (HFpEF, HFrEF)	Co-morbidities	Prognostic (P), Diagnostic (D)- Primary end point /Follow up	Other markers	sST2 assay	sST2 results
AbouEzzeddine OF 2017([57])	RELAX trial (HFpEF)	174 (174, 0)	DM, AF, RD	D- Association ST2 and proinflammatory comorbidities in HFpEF	NT-proBNP, aldosterone, ET-1, Cyst-C, creatinine, UA, PIIINP, CITP, hs-TnI, CRP	Presage ST2 assay	Marker of systemic inflammation in HFpEF and potentially of extracardiac origin
French B 2016([60])	CHF	1385 (106, 1141)		P-5Y follow up	Gal-3, TnI, BNP	Presage ST2 assay	Not significant in discriminating risk of adverse events
Frioes F 2015([53])	Prospective AHF cohort	195 (76, 119)	*	P-6 M all cause death or hospital readmission for HF	BNP	R&D Systems	Not significant in discriminating risk in HFpEF
Manzano-Fernàndez S 2011([8])	ADHF	447 (197, 250)		P-1Y follow up	NT-proBNP, Tn, CRP	M&B Laboratories	Not specific for HFpEF
Nagy AI 2018([50])	KaRen study (HFpEF)	86 (86, 0)	AF, Hypertension, DM, COPD Obesity	P-All-cause mortality or HF –related rehospitalization (18 M follow-up)	NT-proBNP	Presage ST2 assay	Sensitive marker of LA dysfunction in HFpEF ($p = 0.009$)
Najjar E 2019([7])	Different cohorts	193 (86, 86, 21 controls)		P-Death or HF hospitalization	NT-proBNP	Presage ST2 assay	More strongly associated with outcomes in HFpEF ($p = 0.046$)
Pacho C 2018([58])	STOP-HF Clinic study (HFpEF)	522 (522, 0)	HIVHD, DM, anaemia, RD, elderly	P-All-cause mortality or HF –related re-hospitalization at 30D and 1Y	NT-proBNP CA 125 hs-TnI	Presage ST2 assay	Better predictive marker in high risk HFpEF ($p = 0.001$)
Sanders-van Wijk S 2015([54])	TIME-CHF	622 (112, 458)	–	P-18-months overall and hospitalization-free survival	NT-proBNP hsCRP, Cyst-C hs-TnT, etc	Presage ST2 assay	No important differences in prognostic value in HFrEF vs.HFpEF
Shah KB 2011([56])	Prospective 5-center cohort	290 (200, 90)	acute dyspnoea	P-1Y mortality	NT-proBNP, MPO, cTnI, hsCRP	Presage ST2 assay	Independent predictor of intermediate-term mortality ($p = 0.03$)
Tromp J 2018([55])	BIOSTAT-CHF project	1544 (431, 718, 395 HFmrEF)	–	D	92 biomarkers	Olink Proseek Multiplex CVD III kit	Not specific for HEpEF
Zile MR 2016([59])	PARAMOUNT trial (HFpEF)	301 (301, 0)		D Changes in NT-proBNP	Gal-3, MMP-2, PIIINP	Presage ST2 assay	Good correlation with the presence and severity of disease

HFpEF: Heart Failure with preserved Ejection Fraction; HFrEF: Heart Failure with reduced Ejection Fraction; DM: Diabetes Mellitus; AF: Atrial Fibrillation; RD: Renal Dysfunction; NT-proBNP: N Terminal-pro Brain Natriuretic Peptide; ET1: Endothelin-1; Cyst-C: Cystatin C; UA: Uric Acid; PIIINP: N-Terminal Propeptide of Type III Collagen; CITP: Carboxy-terminal Telopeptide of Collagen Type I; hs-cTnI: high-sensitive cardiac Troponin I; CRP: C-reactive protein; CHF: Chronic Heart Failure; Gal −3: Galectin-3; TnI: Troponin I; BNP: Brain Natriuretic Peptide; ADHF: Acute Decompensated Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; LA: left atrial; HIVHD: Hypertension Ischemia valvular heart disease; CA 125: Cancer Antigen; MPO: Myeloperoxidase; HFmrEF : Heart Failure with middle range ejection fraction defined as having an LVEF of 40 to 49%; MMP-2: Matrix Metalloproteinase-2; 6 M: 6 months, 18 M: 18 months, 1Y: 1 year, 30D: 30 days

Table 5
Summary of clinical studies on sST2 and serial measurements.

First Author, year (Ref. #)	Trial (population) Disease group	Patients, n	Prognostic (P), Diagnostic (D) Primary end point /Follow up	Other markers	sST2 serial measurements / sST2 assay
Bahuleyan CG 2018[63]	HFrEF	141	P-1Y cardiac death and rehospitalization for worsening of HF		AD, DD, 1 M, 6 M, 12 M Presage ST2 assay
Boulogne M 2017[69]	AHF /CHF	75	P-CV cause death and unplanned admission	BNP, CRP, TNFα, IL-6, MPO, MR-proADM, Gal-3, GFD-15, PCT	AD, DD, 1 M (AHF);AD, 2 M (CHF) No specified ELISA
Breidthardt T 2013[74]	AHF	207	P-sST2 changes	BNP	AD, 2D Presage ST2 assay
Broch K 2012[67]	CORONA study (Ischemic HF)	1449	P-Composite CV death non-fatal MI or stroke	NT-proBNP, CRP	AD, 3 M Presage ST2 assay
Demissei B 2016[66]	PROTECT trial (AHF)	2033	P-1 M all-cause death, HF hospitalization or death, 6 M all-cause death	48 biomarkers (NT-proBNP, IL-6, MPO, proADM, etc)	AD, 3D, 7D, 14D Alere Inc, San Diego
Gaggin HK 2014[70]	PROTECT trial (CHF)	151	P-10 M changes in LVF	GDF-15, hs-cTnT, NT-proBNP	AD, 3 M, 6 M, 9 M Presage ST2 assay
Manzano-Fernández S 2012[64]	ADHF	72	P-2Y all-cause mortality	Hs-cTnT, NT-proBNP	AD, 4D Presage ST2 assay
Miller WR 2016[71]	CHF	180	P-2Y death and cardiac transplantation	Gal-3, cTnT, NT-proBNP	AD, 3 M, 6 M, 9 M, 12 M, 15 M, 18 M, 21 M, 24 M Presage ST2 assay
Piper S 2015[65]	Pharmacologically optimized CHF	50	P-6 M cardiovascular admission or worsening renal function	NT-proBNP	AD, 1 M, 3 M, 6 M R&D Systems
van Vark LC 2017[15]	TRIUMPH cohort (AHF)	496	P-1Y composite all-cause mortality and HF rehospitalization	NT-proBNP	AD, 2-4D, DD, 2–4 W; 3, 6, 9, 12 M Presage ST2 assay
Tang WH 2016[68]	ASCEND-HF (ADHF)	858	P-1–3 M death, HF hospitalization, all-cause worsening and death	NT-proBNP	AD, 48-72H, 1 M Presage ST2 assay

HFrEF: Heart Failure with reduced Ejection Fraction; AD: admission day/ baseline, DD: discharge day, 2-14D: days, 1 M: 1 month, 2–24 M: months, 2–4 W : weeks,1Y: 1 year, 2Y: 2 years; AHF: Acute Heart Failure, CHF: Chronic Heart Failure, BNP: Brain Natriuretic Peptide, CRP: C-Reactive Protein, TNFα: Tumor Necrosis Factor-A, IL-6: Interleukin-6, MPO: Myeloperoxidase MR-proADM: Mid regional pro-Adrenomedullin, Gal-3: Galectin-3, GDF-15: Growth and Differentiation Factor 15, PCT: Procalcitonin; CV: cardiovascular; MI: Myocardial Infarction; NT-proBNP: N Terminal-pro Brain Natriuretic Peptide; LVF: Left Ventricular Function hs-cTnT: high-sensitive cardiac Troponin T; ADHF: Acute Decompensated Heart Failure.

7. Conclusions

Heart failure is a complex disease in which various pathophysiological processes are involved over time. The interest of sST2 in prognosis has been increasingly consolidated, considering the biomarker alone or combined with other parameters [6]. This review focused on some subgroups of HF patients for whom the features of sST2 are more relevant, making it a first-choice biomarker. The independence from prevalent comorbidities in a highly frail population with HF is a potential advantage of sST2. Therefore, in line with this assumption, sST2 would be the ideal parameter to measure during HFpEF pathology, which is highly related to an inflammation state and to comorbid conditions. Thus, in serial measurements, sST2 appears to be a promising tool to optimize both the monitoring and treatment of this complex pathology. sST2 may be used to tailor specific therapies that will benefit the management of HF. Prospective randomized studies would be needed to confirm these associations. The potential value in considering sST2 levels to prompt aggressive treatment that allows a reduction in rehospitalization is a major medico-economic challenge.

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