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CURRENT OPINION

# Do we need another heart failure biomarker: focus on soluble suppression of tumorigenicity 2 (sST2)

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## Introduction: why use biomarkers in the care of our heart failure patients?

Managing patients with heart failure is no easy task. For those of us who delve in the daily 'fray' of heart failure, there are a number of situations where appropriate use of biomarkers may lead to better treatment:

(1) In patients presenting with dyspnoea, how sure are we of the diagnosis of heart failure?
(2) What treatments can I safely start in the hospital?
(3) How do I know the appropriate time to discharge a patient?
(4) Who is at high risk for early readmission and what can I do to prevent it?
(5) How do I decide what dose of known cardiac medications to treat with in the clinic?
(6) How do I determine if some of the newer heart failure drugs and devices are appropriate-and cost effective—for my patient?

Biomarkers exist in part to help answer the above questions. Biomarkers used for diagnosis should be either sensitive OR specific and much of the value may actually be on the low end to 'rule out' disease. In this regard a B-type natriuretic peptide (BNP) level under 100 pg/ml or an Nt-proBNP level $< 300$ pg/ml, rules out acute heart failure in more than 9 out of 10 cases. A good biomarker is a surrogate for underlying pathophysiologic abnormalities, and hence is often prognostic. However, in clinical practice 'what to do about the biomarker value' is often the make-or-break question.[1] The biomarkers that are here to stay are those that we can act on: personalize treatment in such a way that we might start a certain treatment or titrate that treatment using the changing levels of the biomarker. Of course all this should remain within the scope of clinical presentation of the patient along with physician equipoise as well as other, adjunctive tests.

## What biomarkers have we used?

The major biomarkers used for heart failure are the natriuretic peptides (NPs): both BNP and Nt-proBNP are useful in diagnosis and ruling out acute heart failure, can be used for risk stratification, and based on the upcoming results of the GUIDE IT trial, may soon be used for outpatient titration of cardiac medications.[2–6] In the hospital we already use NPs as a rough guide to volume management—using diuretics to help achieve a transition from a high 'wet' NP level toward a more euvolemic 'dry' NP may allow us to send a patient home fully decongested. While this is somewhat simplified, it has worked well in our practice. Additionally, a discharge NP level appears to be something we can use to follow the patient as they transition to the outpatient setting, both as a gauge when possible heart failure decompensation occurs, as well as a way to manage the patient's medications. But NPs have their problems. They are affected not only by conditions such as renal dysfunction, obesity, atrial fibrillation and anaemia, and levels can be elevated in HFpEF, HFrEF, pulmonary hypertension and right heart failure. Thus the level of NP should never be used as a stand-alone test, but rather as an important adjunct to clinical judgment and other tests. The same can be said for any test.

## Cardiac troponins

While cardiac troponins are mainstays in the evaluation of chest pain, their role in heart failure is yet to be fully ascertained.[7–9] Clearly prognostic in patients presenting with acute decompensated heart failure, there are as of yet no algorithms for additional treatment strategies based on troponin levels. With high sensitivity assays virtually all

Patients with acute decompensated heart failure will have levels above the 99th percentile for the specific assays. The questions that still need to be answered are:

(1) What level of elevation should one be suspicious of for a Type I NSTEMI as the cause of heart failure?

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(2) Should we target specific anti-ischemic agents (nitrates or ranolazine for example) towards rising troponins, and if so, what delta troponin value should we use?
(3) Can we use troponins to help identify the aetiology of heart failure such as infiltrative (amyloidosis) or inflammatory cardiomyopathy?
(4) What will the role of hs-Troponin levels be in ambulatory heart failure in relation to sST2 and Natriuretic peptides

## Procalcitonin (PCT)

PCT is a robust indicator of bacterial infection that is released early in response to bacteria and in amounts correlated to the severity of infection.[10] Levels decrease as effective therapy is instituted and may in fact help guide the duration of antibiotic treatment.[11] The BACH study demonstrated the potential usefulness in patients admitted with dyspnoea.[12] PCT and BNP used together were able to separate most patients who had heart failure, pneumonia, or both. In addition, in patients who had low levels of PCT but were treated with antibiotics had a worse prognosis than those not given antibiotics. Those with high PCT levels and not given antibiotics also had a poor prognosis. The IMPACT trial is underway to test the hypothesis that in patients with dyspnoea, PCT can be used to guide treatment.

## So do we need another biomarker?

The pathway to validation of a new biomarker is long and arduous. For the care and management of patients with heart disease very few biomarkers have successfully traversed this path since NPs and troponin. sST2 is one such biomarker that has jumped through all the 'hoops' expected from a biomarker that is ready for clinical use. Extensive clinical research studies have clearly demonstrated the utility of sST2 as a biomarker,[13] there is an food and drug administration (FDA) cleared and validated assay available[14] and it is noted in the 2013 American heart association (AHA) Heart Failure Guidelines. In our experience it is the ONLY new, approved, and available biomarker that can be of value today in taking care of patients with both acute and chronic heart failure. We have used sST2 clinically for the past years and will present our experience here.

## What is sST2?

ST2 is a member of the interleukin 1 receptor family also known as interleukin 1 receptor-like 1 (IL1RL-1).[15,16] ST2 stands for 'suppression of tumorigenicity 2'. It was discovered in 1989[16] but only in 2002 Weinberg *et al*[17] reported that it can be expressed by cardiac cells in response to myocardial stress, drawing attention of researchers to a role in the cardiovascular system. ST2 has two main isoforms: transmembrane or cellular (ST2L) and soluble or circulating (sST2) form.[17] ST2 is the receptor for interleukin-33 (IL-33), which is an IL-1-like cytokine that is secreted by living cells in response to cell damage. The interaction of IL-33 and sT2L has been proved to be cardioprotective in experimental models, reducing myocardial fibrosis, cardiomyocyte hypertrophy and apoptosis. This cardioprotective action occurs exclusively through the ST2L receptor and not through the soluble form. In fact when the soluble receptor is shed in cases of cardiac 'distress, sST2 avidly binds to IL-33 competing with ST2L, blocking the IL-33/ST2L system and eliminating the cardioprotective effects described above. Therefore, sST2 is considered a decoy receptor.[18]

As we began using sST2 in the hospital and the heart failure clinic, I would often be asked: Why should we use sST2 when our present way of managing heart failure is sufficient? The answer is both simple and complex. Take the example of patients presenting with acute heart failure. Most are treated exactly the same-meaning intravenous followed by oral diuretics followed by discharge. Some patients do fine; some are readmitted within 30 days; other die. The discouraging fact here that it is difficult up front to tell which patient will suffer which fate. High BNP levels (above the dry BNP) correlates with volume overload, which is often obvious to the physician. However, our experience thus far suggests that sST2 levels give us insight into the state of heart failure far beyond the state of intravascular volume or physical exam findings. While it is certainly additive to what NPs bring to the table, we believe that sST2 might potentially be looked at as the HbA1c of heart failure (*Figure 1*); in other words, the sST2 value has inputs from wall stress, inflammation, macrophage activation (fibrosis) and a number of still-to-be determined stimuli. Just as better glucose control drops HbA1c levels into a better prognostic range, better control of heart failure appears to lower sST2 levels.

Thus far, the level of sST2 does not appear to be significantly affected by age, sex, BMI, aetiology of heart failure, atrial fibrillation and anaemia. Unlike almost any cardiac biomarker in use, sST2 does not appear to be significantly affected by renal function. The fact that sST2 has the lowest intra-individual variation and smallest relative change value compared to other biomarkers makes it suitable for accurate serial measurements.[19] Finally, in the outpatient setting, an sST2 value of 35 ng/ml appears to be the level that one should aim for in therapy.[20]

## Using sST2 in the hospital

Our experience with sST2 in patients admitted to the hospital with acute decompensated heart failure conforms to data permeating the literature. It is a powerful predictor of short-term and long-term adverse events. In the PRIDE study the prognostic utility of sST2 was additive to that of NT-proBNP, such that patients with elevation of both markers had the highest 1-year mortality rate (almost 40%).[21] This relationship of sST2 with death emerged soon after enrolment in the study and remained significant out to 4 years from presentation. In fact, high sST2 levels reclassified risk of death in patients with low-NP levels. Conversely, in patients with an sST2 value below the median concentration, NT-proBNP $>$1,000 pg/mL was not a predictor of 1-year mortality.

It is noteworthy to comment on the comparison of ST2 measurements with other biomarkers in the setting of acute decompensated heart failure (ADHF). In a study with 5306 patients carried out by the Global Research on Acute Conditions Team, among a great number of biomarkers measured at admission in patients with ADHF, sST2 emerged as the strongest biomarker with the ability to reclassify death risk beyond a clinical model. sST2 was the best predictor of both 30-day and 1-year mortality.[22] For a biomarker to be useful in

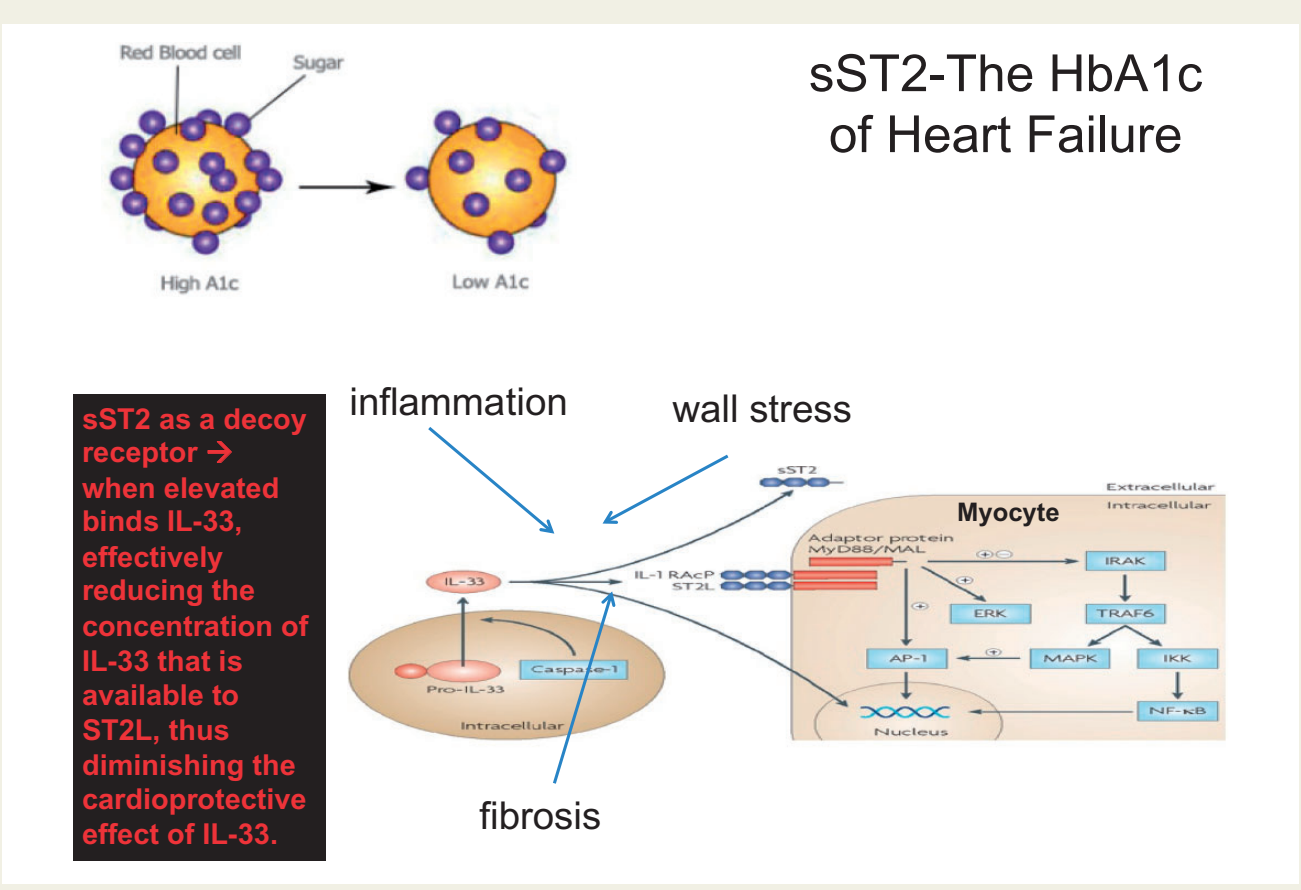


**Figure 1** sST2 the HbA1c of heart failure.

risk stratification and in guiding treatment in ADHF, the values must change in appropriate directions with appropriate treatment. The biologic variation and the low index of variation of ST2 make it a good candidate for monitoring and possibly guiding therapy in ADHF.[17] One of the first studies to assess serial measurements of sST2 was carried out by our group using an Research Use Only (RUO) sST2 assay.[23] In this study sST2 was measured on a daily basis in patients admitted with ADHF. We demonstrated that this biomarker changes quickly in response to effective treatment. When values did not decrease or even increased, there was a high probability of dying by six months

More recently, similar results were obtained by Manzano *et al*[24], using the newer, validated Presage® ST2 Assay. They found that median concentrations of sST2 decreased from 62 to 44 ng/mL and those patients with persistent elevation on Day 4 had a higher risk of death. Finally, Breidthardt *et al*[25] observed that sST2 values significantly decreased from admission to 48 h, especially in those with favourable outcomes, with a median reduction of 42% in survivors vs. 25% in non-survivors.

Of note, there are significant differences between the commercially available RUO assays and the validated (CE Mark and FDA cleared) Presage ST2 Assay.[26,27] The most notable difference is absolute sensitivity. The Presage ST2 Assay is several fold more sensitive, which allows accurate measurement of ST2 across the entire naturally occurring concentration range. And has been tested to verify that it is not effected potential interfering substances, such as heparin.

## Our experience with sST2 in the ADHF patient

*Figure 2* depicts the value of both BNP and sST2 measured in the setting of acute heart failure as part of the clinical routine. We then looked for heart failure admission three months before and three months after the admission. Data were extrapolated if patient had not been followed by us for the entire six months. sST2 levels are strongly correlated to previous and post admissions, even more so than BNP. We also demonstrated a robust area under the ROC curve for heart failure admissions for sST2, as compared to BNP. This is now being referred to as a 'frequent flyer index'.

*Figure 3*, depicts a patient whose sST2 levels decreased using a combination of diuretics and angiotensin converting enzyme (ACE) inhibitors. This patient who was obese had low BNP levels at admission and throughout treatment. Thus, obesity precluded us using the NP level but not the level of sST2

*Figure 4* demonstrates that while sST2 levels were initially decreased secondary to vigorous diuretic treatment, low levels were unable to be maintained. This was likely due to the inability to up titrate medications because of hypotension. He had two subsequent admissions.

Finally, *Figure 5* demonstrates a high sST2 level at admission with the inability to bring the level down with medications. He had six admissions in the past year, and will now be started on Entresto. Note the variability in the BNP levels.

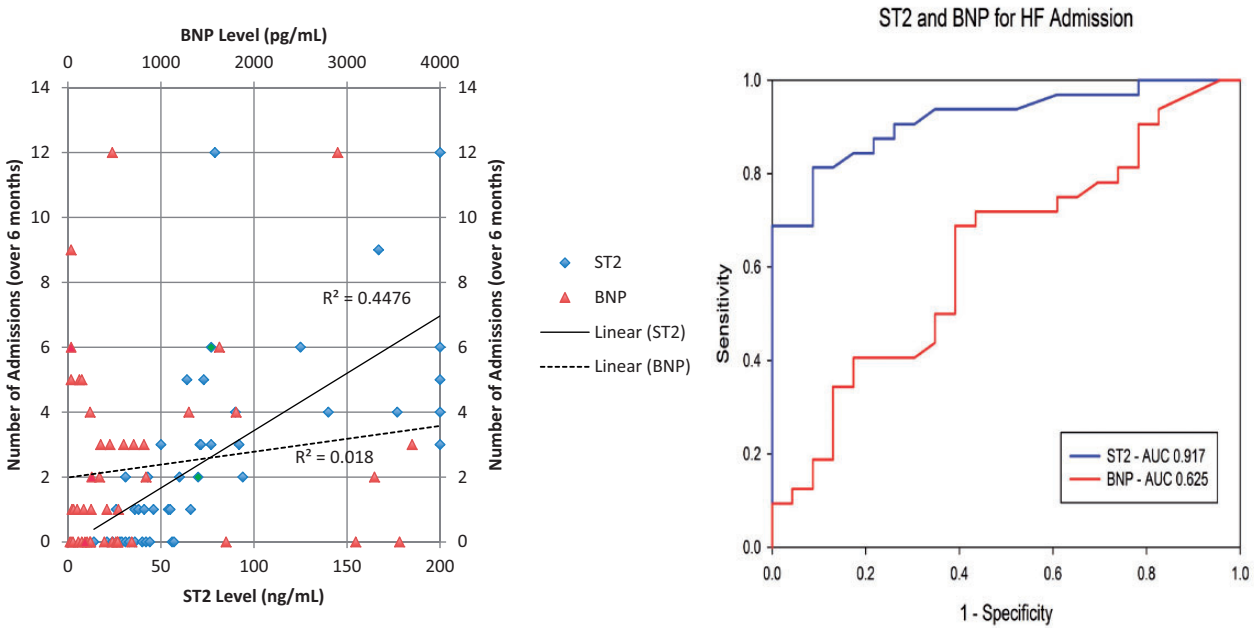


**Figure 2** Relationship of admission ST-2 levels and previous and future admissions.

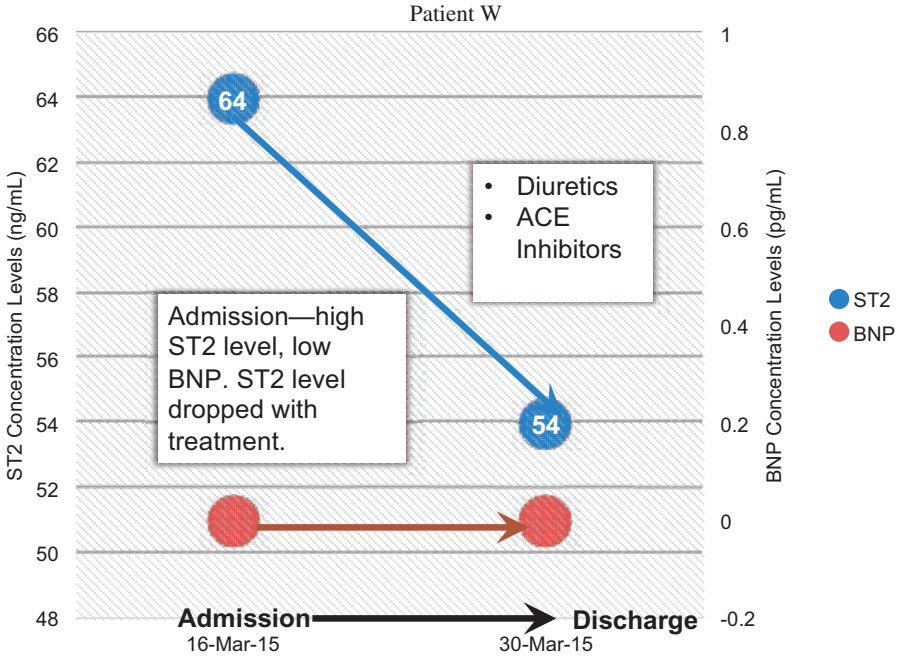


**Figure 3** Dropping ST2 levels during hospitalizations.

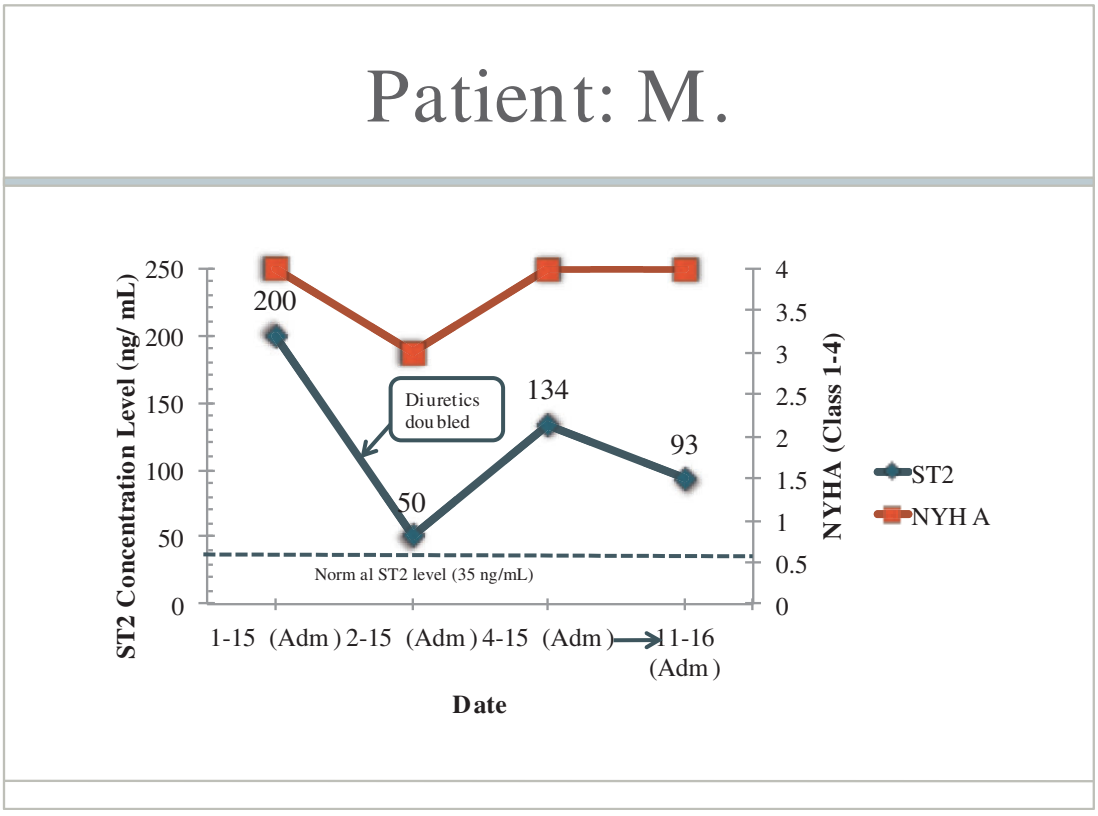


**Figure 4** Failure to drop ST2 levels.

## Early lessons learned using sST2 in ADHF

(1) sST2 levels when elevated in patients admitted for ADHF, point to a very sick patient, even when NP levels are either not high, or after they decrease during treatment.
(2) sST2 levels will fall rapidly with hospital treatment, but if levels are still high at discharge they are still at risk.
(3) A level that falls less than 25% from admission may benefit from more aggressive treatment. We are beginning to drive sST2 levels down by adding medications such as spironolactone while in the hospital.
(4) Elevated sST2 levels are strongly predictive of future heart failure admissions, and characterize the 'frequent fliers' better than NPs

## Value of soluble ST2 in chronic heart failure and use in the clinic

While many physicians use NP levels as a means of 'personalizing' outpatient treatment for heart failure, it is still a class IIb indication. The GUIDE IT trial, which should be completed soon, is a large randomized trial of targeting levels of NT-proBNP to under 1000 pg/ml vs. standard of care.[28]

If positive, the guidelines favouring NP guided therapy will likely be implemented. In our own practice, we routinely order an sST2 level along with the BNP level in our ambulatory clinic patients. This is based on sound evidence from the literature below.

Daniels *et al* [29] did an excellent job of summarizing the many clinical cohorts of chronic heart failure, demonstrating a clear prognostic capability of ST2 levels in the ambulatory setting. Numerous studies demonstrate the symbiotic relationship between sST2 and the NPs with regards to prognosis.[30–32] In fact, studies have demonstrated that the combination of sST2 and NT-proBNP have a performance similar to the Seattle Heart Failure Model.[33,34] sST2 appears to trump all other biomarkers except NPs in the ambulatory heart failure setting. Recently, Gruson *et al* evaluated the value of sST2 in addition to NPs (BNP, NT-proBNP, and $proBNP_{1\text{-}108}$) and conventional risk factors such as age, LV ejection fraction, and estimated glomerular filtration rate. ST2 was the strongest predictor of cardiovascular death.[30]

While Galectin 3 is an another robust marker of fibrosis, it does not change significantly during the course of treatment. Head-to-head comparison of these two biomarkers revealed that sST2 was superior to galectin-3 in risk stratification and reclassification of patients.[35] (It is noteworthy that in the Barcelona study, the performance of sST2 was not influenced by renal function, as observed with NT-proBNP. The inclusion of ST2 along with other biomarkers improved the prediction in patients with renal failure even more than in the whole population.[36] Thus in patients with renal impairment, the sST2 level may even be a better marker to follow than the natriuretic peptides.

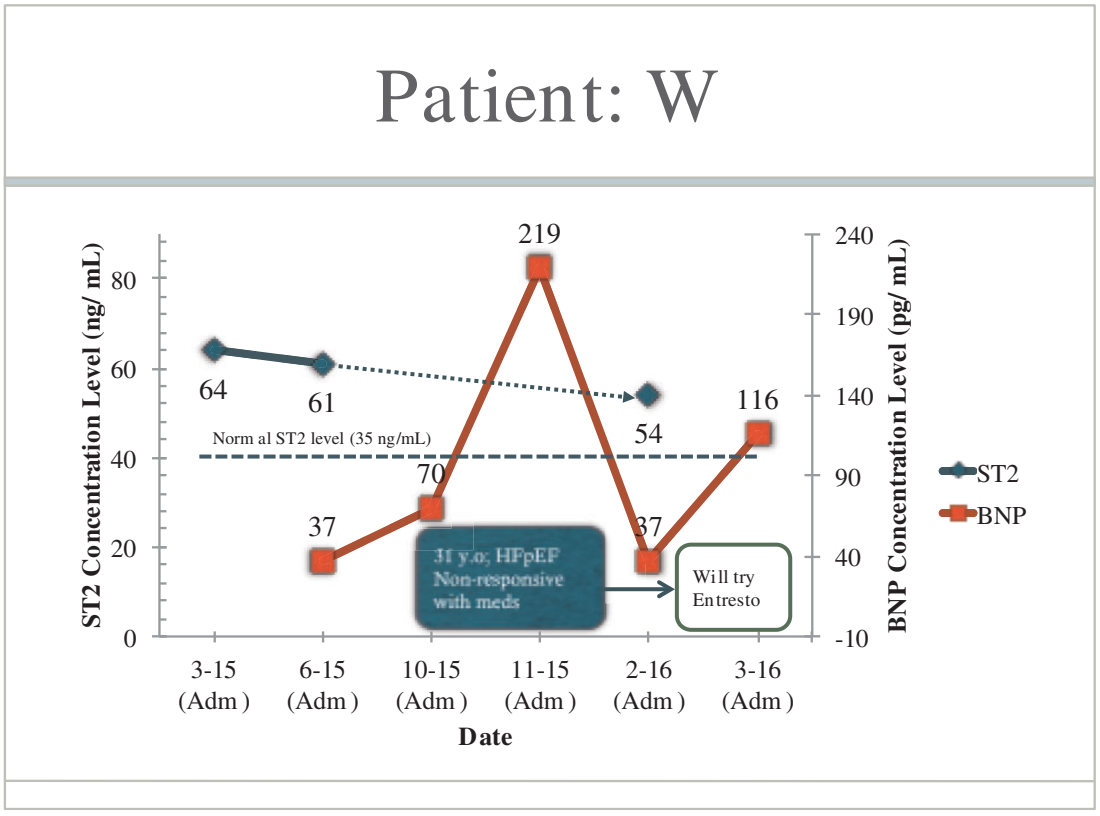


**Figure 5** Stability of sST2 levels to follow outpatient treatment as compared to BNP.

Right now, in our clinical setting, we have the availability of not only BNP and sST2 but troponins as well. A recent study by Miller *et al*[37] biomarkers were collected every 3 months over to years and analysed in relation to death/cardiac transplantation and heart failure an hospitalization. Time dependent analysis demonstrated that BNP cTnT, and sST2, along with clinical variables demonstrated a relationship to the endpoints in all biomarkers but Galectin 3.[37] Interestingly, only serial measurements of sST2 demonstrated incremental value in reclassifying patients. Finally, we had data from own institution to go on (*Figure 6*). We reported on 588 outpatients who were referred for echocardiography. High sST2 levels were independently associated with 1-year mortality, even among the subgroup of 429 patients with no history of HF. Importantly, no patient with an ST2 value below the median levels died in the first 6 months of follow-up

Sampling sST2 in the clinic depends on assay precision as well as the variability of the test result within the same patient. This biological variation of sST2 was recently assessed by Wu *et al*[17]. The study included 17 healthy subjects over a period of 8 weeks. They found that the reference change value for ST2 was 30%, much lower than observed with galectin-3 (60%) or NT-proBNP (92%). The index of individuality (a measure to evaluate whether serial measurements add significantly to a single assessment) for ST2 was 0.25, suggesting value from serial measurements. In comparison, the same index for galectin-3 was 1.0, indicating that galectin-3 is useless for serial measurements. These data suggest that soluble sST2 is a potential biomarker for monitoring and possibly guiding therapy in patients with HF.

## A cut point of 35 ng/ml appears to separate high-risk from low-risk patients

A number of studies all point to this level as the proverbial 'magic number' to strive for, much the same way we strive for NT-proBNP levels $< 1000$ pg/ml and BNP levels $< 100$ pg/ml. Januzzi *et al* determined in the PROTECT trial that the more time a patient spent with levels $> 35$ ng/ml the more cardiac remodelling was felt to occur.[30] In the Valsartan Heart Failure Trial (VAL-HeFT) an increase in sST2 concentrations from baseline to 12 months was an excellent predictor of events.[31] Finally, the effects of medications on sST2 serial measurements in the PROTECT study were assessed.[32] Those with elevated baseline sST2 concentrations who achieved higher beta-blocker doses had significantly lower risk of events than those titrated to lower beta-blocker dose. Those with low ST2 levels and high beta-blocker doses experienced the lowest rate of events.

## Examples of sST2 and BNP in our outpatient clinic

*Figure 7* demonstrates cases followed in our outpatient clinic

Patient H. This is a patient whose discharge sST2 level was extremely high. He was placed on high doses of beta-blocker and

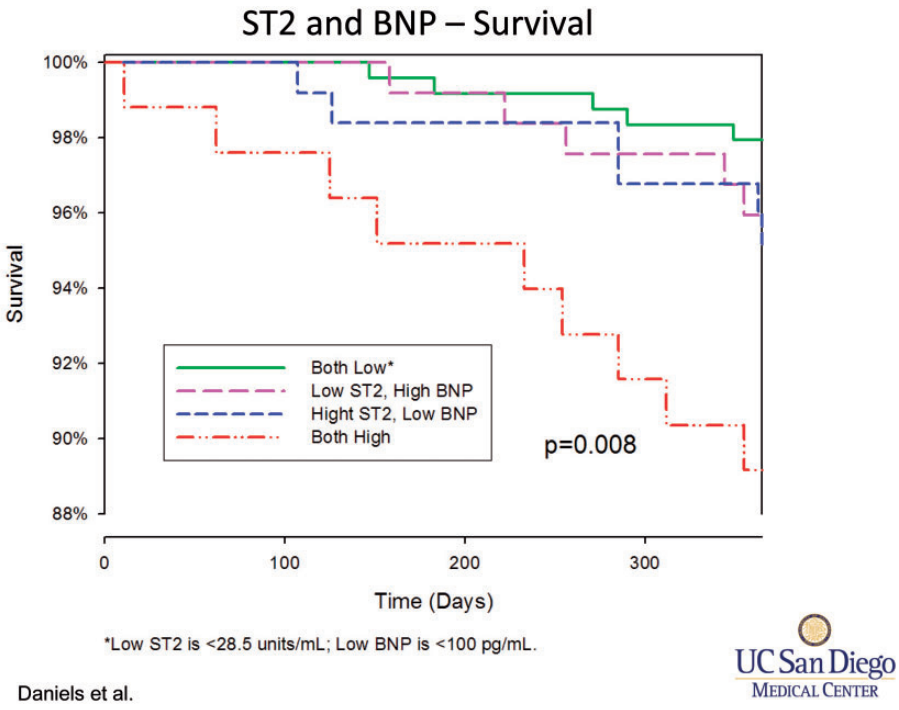


**Figure 6** Survival of patients referred for echocardiography based on sST2 and BNP.

hydralazine was started. His sST2 level has dropped significantly and within that time period did not have a readmission.

Patient K demonstrates a patient who had a low sST2 at discharge and this stayed low on medical treatment, with no readmissions in the next year. The BNP level remained high.

Patient C: This was a previously stable patient who recently decompensated with a doubling of sST2. He was admitted two days later, at which time Entresto was added. He stabilized and his sST2 decreased.

Patient B: We were unable to increase medications due to hypotension. The BNP level dropped but the sST2 remained high. In five months he had three admissions from clinic and then died.

## Lessons learned using sST2 in ambulatory heart failure clinic

(1) sST2 levels measured in the outpatient setting, will decrease as effective treatment is added.
(2) A level $<35$ ng/ml or a response of $>50\%$ decrease appears to be associated with improvement in symptoms and prognosis
(3) High sST2 levels in the outpatient setting are predictive of events, even when NP levels are low.

## The future of sST2 levels

If sST2 indeed turns into the HbA1c of heart failure, its value should increase exponentially in our management of patients with heart failure. Serial sST2 levels should allow us to titrate therapy and monitor the clinical state of the patient. In addition, since sST2 is such a strong marker of the risk of death, it would not be surprising to see a level be used to make decisions when patients are on the cusp of such therapies as ICD, CRT, CardioMems implantation and even left ventricular assist devices.

A discussion about the use of biomarkers would not be complete without mentioning the issue of surrogates for determining the therapy effectiveness of some of the newer heart failure drugs. Novartis's Entresto®, the brand name for its recently CE marked and FDA approved ARNI1 drug (previously known as LCZ696) and Servier's ivabradine drug Corlanor® (marketed by Amgen in the USA), also CE marked and FDA approved, while offering exciting potential benefits to heart failure patients—even being hailed 'game-changer' drugs by some—raises the thorny issue of cost vs. benefit. These new drugs are several times the cost of the generics that have become the mainstay of heart failure treatment, i.e. ACE inhibitors, angiotensin receptor blocker (ARBs), beta-blockers, etc. Pushback is therefore expected from payers.

Because sST2 changes rapidly with the underlying condition of the patient, is not affected by normal confounding factors, and has a single cut point, it may be ideally suited to help clinicians determine if these newer mediations are effective for each patient, are improving quality of life, and whether dosing needs to be titrated or changed.

The new reality of heart failure care is that while more treatment options have opened up, which can literally be a lifesaver for millions of patients, the burden on healthcare systems has skyrocketed. Biomarkers, and particularly sST2, could offer physicians and payers a way to bring treatment down to an individual patient level, providing

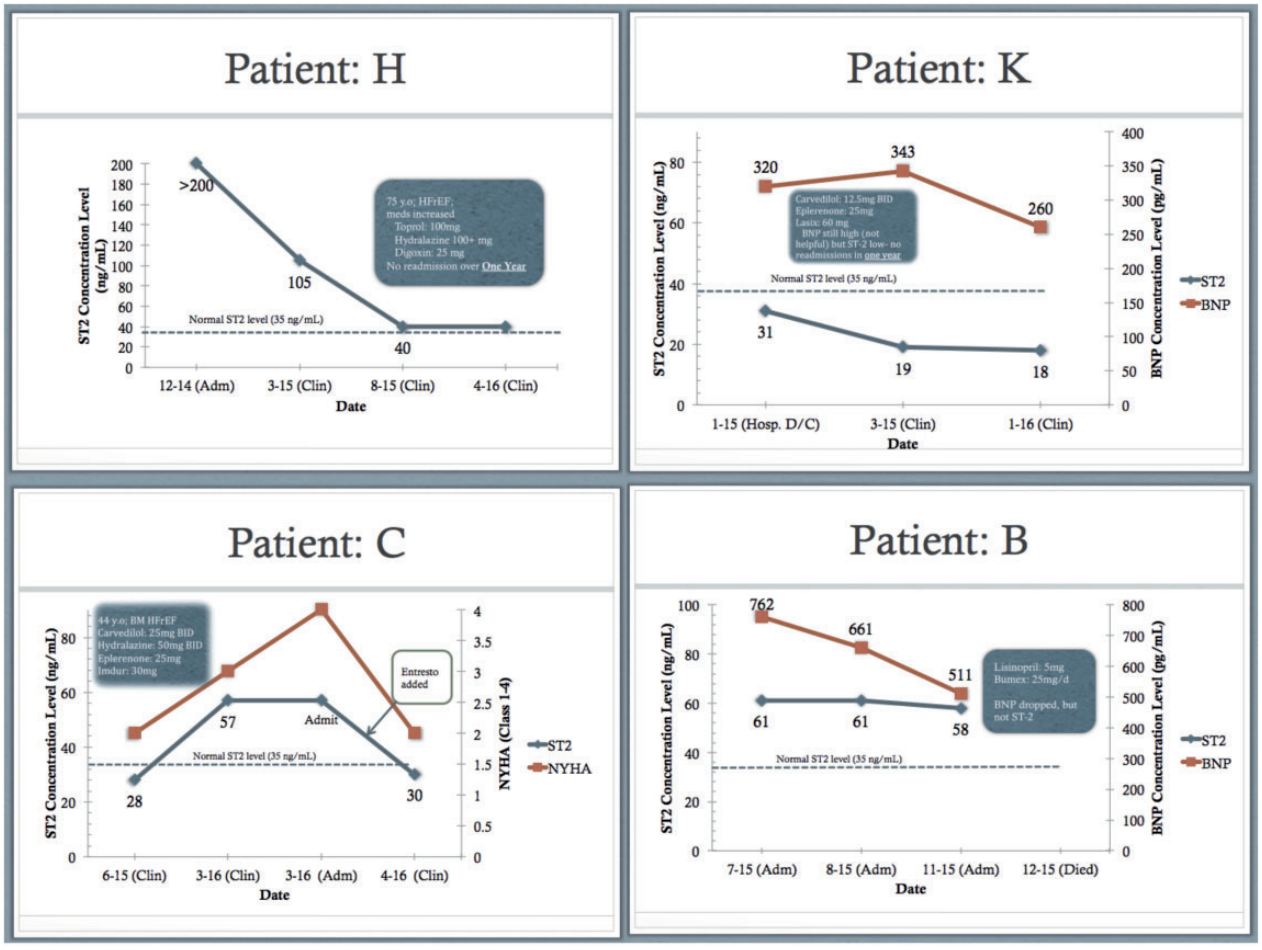


**Figure 7** Examples of ST2 monitoring during therapy.

good, affordable care to those in need and can benefit from these breakthroughs. For that and the many real-world examples shown above, sST2 has a very bright future in heart failure care.

**Conflict of interest:** A.M. Consultant: Alere, Critical Diagnostics, Sphingotec, Astute, Roche, ThermoFisher. S.D.: Assut, Novartis, Alere, Adrenomed, Spingothec, ThermoFisher.

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