ST2 FOR THE CLINICIAN: THE TIME IS NOW

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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, etiology of heart failure, atrial fibrillation and anemia. 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. Finally, in the outpatient setting, an sST2 value of 35 ng/ml appears to be the level that one should aim for in therapy.

**OUR EXPERIENCE WITH sST2 IN THE ADHF PATIENT**

Figure 2 depicts a patient whose sST2 levels decreased using a combination of diuretics and 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 2 demonstrates that while sST2 levels decreased during hospitalization, they were still high (>35 ng/ml) at discharged and this was associated with a readmission ten days later, with even higher sST2 levels.

Finally, Figures 3 and 4 demonstrate the powerful predictive value of a high sST2 at admission. Even with a low BNP level, there was subsequent admissions and death.
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 sST2 IN CHRONIC HEART FAILURE AND USE IN THE CLINIC

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. biomarkers were collected every 3 months over two years and analyzed in relation to death/cardiac transplantation and heart failure 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.

Interestingly, only serial measurements of sST2 demonstrated incremental value in reclassifying patients. Finally, we had data from own institution to go on (Figure 5). 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.

![ST2 and BNP – Survival](image.png)

Figure 5
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 remodeling was felt to occur. In the Valsartan Heart Failure Trial (VAL-HeFT) an increase in sST2 concentrations from baseline to 12 months was an excellent predictor of events. Finally, the effects of medications on sST2 serial measurements in the PROTECT study were assessed. 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 6 demonstrates a patient whose discharge sST2 level was extremely high. He was placed on high doses of beta-blocker and hydralazine was started. His sST2 level has dropped significantly and within that time period did not have a readmission.

In Figure 7, adding spironolactone decreased sST2 to less than 35 ng/ml and the patient has been free of complications and readmission.

Figure 8 demonstrates that a high sST2 level in the clinic predicted subsequent admission, despite a relatively low BNP level.
Finally, Figure 9 demonstrates a patient where a high sST2 predicted two early readmissions. Once in clinic medications were added that decreased sST2 from 167 ng/ml to 73 ng/ml (greater than 50% response) and as of August 2015, has not had another admission.

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 U.S.), 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 versus 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, 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 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.

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