ST2 & Treatment Guidance In Heart Failure

Alan S. Maisel MD FACC
Professor of Medicine, University of California, San Diego, Director, CCU and Heart Failure Program
San Diego VA Medical Center
Objectives of Biomarker Testing in Heart Disease

**Diagnosis**
- To establish or refute a diagnosis
- To understand the underlying pathophysiologic processes

**Risk**

**Stratification/Screening**
- To determine the presence or severity of disease
- To detect adverse consequences

**Monitoring/Therapeutic Guidance**
- To facilitate selection of an appropriate therapeutic intervention

Many biomarkers may be risk factors themselves; therefore, may be potential targets of therapy

HF, heart failure.

Wetterson, Maisel AJM in press
Expression of ST2 in Cardiomyocytes

- In a study to identify novel pathways in cardiac myocyte mechanotransduction, DNA microarray technology was applied to cultured cardiac myocytes subjected to mechanical overload.

- Of the 7000 gene transcripts of known function, ST2 was extremely up-regulated in this model.

Weinberg et al, Circulation, 2002
Soluble ST – 2
ST-2: Suppressor of tumorigenicity 2 (IL-1 receptor-like-1)
Member of Interleukin-1 receptor family
membrane bound receptor: ST-2L (Profibrotic signaling)
soluble truncated form: sST-2 (Decoy receptor)
IL-33: Interleukin 33, Binds to ST-2L & Inhibits Profibrotic signaling
sST-2 binds IL-33 & inhibition of ST-2L profibrotic signaling → Fibrosis

Interleukin-33 (IL-33)
sST2L Decoy Receptor

Pro-fibrotic Signaling
ST2 plays a role in reducing cardiomyocyte hypertrophy and fibrosis.

Abnormalities in ST2 experimentally result in severe cardiac remodeling and heart failure.

Intact sST2

sST2 knock out
## Biological Variation Summary

<table>
<thead>
<tr>
<th>Marker</th>
<th>Duration</th>
<th>CV (_1)</th>
<th>RCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK</td>
<td>2 mths</td>
<td>30%</td>
<td>82%</td>
</tr>
<tr>
<td>BNP</td>
<td>2 mths</td>
<td>50%</td>
<td>138%</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>2 mths</td>
<td>33%</td>
<td>92%</td>
</tr>
<tr>
<td>hs-cTnI</td>
<td>2 mths</td>
<td>14%</td>
<td>63%</td>
</tr>
<tr>
<td>hs-cTnI</td>
<td>9 mths</td>
<td>28%</td>
<td>73%</td>
</tr>
<tr>
<td>hs-cTnT</td>
<td>1 mths</td>
<td>31%</td>
<td>87%</td>
</tr>
<tr>
<td>Gal-3</td>
<td>2 mths</td>
<td>20%</td>
<td>61%</td>
</tr>
<tr>
<td>sST2</td>
<td>1.5 mths</td>
<td>10.5%</td>
<td>30%</td>
</tr>
<tr>
<td>sST2</td>
<td>2 mths</td>
<td>11%</td>
<td>30%</td>
</tr>
</tbody>
</table>

- sST2 has the lowest intra-individual variation and smallest relative change value compared to other biomarkers

Wu, 2013, accepted Am. Heart J.
# Reference Analysis and Cut-point Selection

<table>
<thead>
<tr>
<th>Level</th>
<th>Primary Reference Cohort</th>
<th>Confirmation Reference Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>20.9 (9.3)</td>
<td>22.4 (8.7)</td>
</tr>
<tr>
<td>Min</td>
<td>1.8</td>
<td>3.2</td>
</tr>
<tr>
<td>25&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>14.5</td>
<td>16.7</td>
</tr>
<tr>
<td>50&lt;sup&gt;th&lt;/sup&gt; percentile (median)</td>
<td>18.8</td>
<td>20.9</td>
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<tr>
<td>75&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>25.2</td>
<td>26.1</td>
</tr>
<tr>
<td>90&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>34.2</td>
<td>32.9</td>
</tr>
<tr>
<td>95&lt;sup&gt;th&lt;/sup&gt; percentile*</td>
<td>37.9</td>
<td>37.3</td>
</tr>
<tr>
<td>99&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>49.7</td>
<td>51.0</td>
</tr>
<tr>
<td>Max</td>
<td>66.3</td>
<td>119.6</td>
</tr>
<tr>
<td>N</td>
<td>490</td>
<td>3,450</td>
</tr>
</tbody>
</table>

*Cutpoint concentration for assessment of risk in patients with heart failure was selected at the ~95<sup>th</sup> percentile of normal

1. Lu et al. 2010 Clinica Chimica Acta
2. Coglianese et al. 2012 Clinical Chemistry
Single ST2 Cut-point:

> 35 ng/ml = RISK
ST2 not affected by

- Age
- Sex
- BMI
- Etiology of HF
- Atrial Fibrillation
- Anemia
In a cohort of 879 heart failure patients ST2 did not show any correlation with renal function whereas NT-proBNP concentrations increased significantly with decreasing renal function.
sST2 is NOT a diagnostic marker of AHF

- Severe sepsis
- Inflammatory disease
- Disseminated cancer
- Liver or other organ fibrosis

- It is elevated in almost everyone with AHF
- It is very prognostic in AHF
  - Short-term
  - Long-term
- Risk can be mitigated by lowering level
Mortality Risk Increases With ST2 Levels

One-year mortality exceeded 50% in the highest decile.

Additive Value of ST2 to NT-proBNP: Acute HF

Patient would have been classified as moderate risk with only NT-proBNP, but is considered high risk with the addition of ST2.

In my shop, most of the ADHF patients are being treated the same way

- Tune up with diuretics-iv for 2-3 days, then a new oral dose
- A bit of education
- Push patient out the door & wave good-bye
Why aren’t we using biomarkers?

- Are they too expensive?
- Aren’t they available everywhere now?
- Don’t they help us understand pathophysiology?
Changes one might consider on the basis of a biomarker prior to discharge

- Extra hospital time
- One week follow up
- Home nursing
- Telemonitoring
- More aggressive titration of medications
Patient A
- Male, 65y
- admitted AHF
- Rales, edema
Echo: EF 30%
- NYHA II-III
Felt better after 5 liters diuresed

Patient B
- Male, 58y
- Admitted AHF
- Rales, edema
- Echo EF 35%
- NYHA III
- Felt better after 5 liters diuresed

V3 voltage 1088µV
QRS duration 150ms

V3 voltage 2000µV
QRS duration 190ms
Patient A

- **NT-proBNP**: 1274 ng/mL
- **ST2**: 25 ng/mL

- Good clinical outcome.
- Evolved towards NYHA II
- No hospital admissions after 3 years.

Patient B

- **NT-proBNP**: 1100 ng/mL
- **ST2**: 65 ng/mL

- Admitted 3 times in 4 months.
- Sudden death at night

**Risk increased:**

- **NT-proBNP > 1720**
- **ST2 > 35**
**ST2 and Admissions Over 6 Months**

- R² = 0.49968

**BNP and Admissions Over 6 Months**

- R² = 0.07332

Wettersson, Maisel AJM-2016
ST2 and BNP for HF Admission

Frequent-Flyer Index

AUC 0.917
AUC 0.625
Patient: H.V.

75 y.o; HFrEF; medics increased
Toprol: 100mg
Hydralazine 100+ mg
Digoxin: 25 mg

No readmissions over One Year
Patient: E.D.

24 y.o; BM HFrEF; titrated meds: Bumex: 4mg
Toprol: 50 mg
Hyralazine: 25mg
Imdur: 30mg

No readmissions over one year
Patient: B.H.

BNP dropped, but not ST-2

Graph showing:
- ST2 concentration levels from 7-15 (Adm) to 12-15 (Died)
- BNP concentration levels from 7-15 (Adm) to 12-15 (Died)
- Normal ST2 level (35 ng/mL)
- Lisinopril: 5mg, Bumex: 25mg/d
ST2 in Chronic, Ambulatory HF Cohorts

HR for risk of death at 1 year, with ST2 >35 ng/ml

Univariable

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barcelona</td>
<td>891</td>
<td>78</td>
<td>4.10 (2.22–7.57)</td>
</tr>
<tr>
<td>PHFS</td>
<td>1125</td>
<td>72</td>
<td>4.67 (2.83–7.71)</td>
</tr>
<tr>
<td>HF-ACTION</td>
<td>910</td>
<td>43</td>
<td>4.95 (2.72–9.01)</td>
</tr>
<tr>
<td>SDVA Echo HF</td>
<td>157</td>
<td>13</td>
<td>2.66 (0.89–7.95)</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, NYHA class, EF, GFR, diabetes, HTN, and smoking

Risk-Adjusted

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barcelona</td>
<td>876</td>
<td>76</td>
<td>3.07 (1.64–5.75)</td>
</tr>
<tr>
<td>PHFS</td>
<td>949</td>
<td>72</td>
<td>3.03 (1.55–5.92)</td>
</tr>
<tr>
<td>HF-ACTION</td>
<td>817</td>
<td>40</td>
<td>3.20 (1.66–6.17)</td>
</tr>
<tr>
<td>SDVA Echo HF</td>
<td>157</td>
<td>13</td>
<td>3.19 (0.99–10.28)</td>
</tr>
</tbody>
</table>

RE model

Adjusted for age, sex, NYHA class, EF, GFR, diabetes, HTN, and smoking

Daniels LB, Future Cardiol 2014
Additive value of sST2 and NT-proBNP

- Median NT-proBNP 852 pg/mL
- sST2 remained an independent predictor of risk even when adjusted for multiple covariates, including renal function and NT-proBNP
Serial ST2 Measurements
Categorize Responder Status

Decrease ≥50%
Decrease 25 – 49%
Increase or decrease <25%

Adjusted for ADHERE Risk Factors and BNP change.

Basel ADHF cohort
Changes in ST2 in Val-HeFT: placebo vs valsartan

Patients randomized to valsartan had less ↑ in ST2 levels over time.
Results from Val-HeFT

**Conclusion:** Change in ST2 over time was independently and significantly related to subsequent risks of mortality, 1st morbid event or HF hospitalization

- 72% had persistently low ST2
- 8% moved from high risk to low risk
- 20% had persistently high or transitioned to high ST2
ST2 Predicts Response to Treatment: Aldosterone Blockade in STEMI

- Eplerenone prevents adverse ventricular remodeling
- ST2 predicts which pts are most at risk...
- AND which pts will benefit most from aldosterone blockade


High and low ST2 separated at median.

→ Eplerenone attenuates remodeling more in pts with higher baseline ST2.
ST2 and Ventricular Tachycardia: Results from MADIT-CRT

- Multivariate analysis demonstrated that ΔST2 from baseline to 12 months was independently predictive for VT (HR 3.71 [95% CI 1.4-9.8]; p=0.008).

- In the 42% of the patients with an ST2 increase of more than 7.1% risk of VT increased by 2.25 fold (95% CI 1.2-4.1; p=0.008).

- ΔST2 remained predictive even after controlling for changes in BNP, LVEF, LVESV, and LVEDV (P=0.0048).
Patient: F.S.

68 y.o; HFpEF
Spironolactone: 25mg
Carvedilol: 25mg
Lasix: 60 mg

Normal ST2 level (35 ng/mL)

ST2 Concentration Level
(ng/mL)

Date
12-14 (Clinic) 4-15 (Clinic) 1-16 (Clinic)

No Admissions-1 year
Patient: K.E.

BNP still high but ST2 low-No readmissions in one year

Carvedilol: 12.5mg BLD
Eplerenone: 25mg
Lasix: 60 mg

Normal ST2 level (35 ng/mL)
Patient: S.V.

92 y.o HFrEF
Carvedilol: 25mg
Lasix: 20mg

Rising EF over one year
Patient: M.O.

Only transient decrease in ST2- too hypotensive to increase medications
Patient: H.H.

Lived in Mexico - poor diet and med compliance

80 y.o; EF 20%.

Normal ST2 level (35 ng/mL)
Patient: M.L.

Working the st2 down—doesn’t tolerate meds well keeping out of hospital

67 y.o. atrial fibrillation (afib); and HFrEF
Sacubitril / Valsartan Mechanism of Action

**Vasoactive Peptide System**
- ANP
- BNP
- CNP
  - Adrenomedulin
  - Bradykinin
  - Substance P (angiotensin II)

**Renin Angiotensin System**
- Angiotensinogen (liver secretion)
- Angiotensin I
- Angiotensin II
- AT<sub>1</sub> receptor

**Heart Failure**
- LCZ696

**Neprilysin**
- Inactive fragments

**Blood Pressure**
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↓ Aldosterone levels
- ↓ Fibrosis
- ↓ Hypertrophy
- Natriuresis/Diuresis

**LCZ696**
- Stable at pH 5-7
- Breaks apart after ingestion

**Valsartan**
- AT<sub>1</sub> receptor

**VASODILATION**
- ↑ Blood pressure
- ↑ Sympathetic tone
- ↑ Aldosterone
- ↑ Fibrosis
- ↑ Hypertrophy

**VASOCONSTRICION**
- LCZ696 is a novel crystalline complex consisting of the molecular moieties of valsartan and sacubitril in an equimolar ratio
HFrEF: New therapeutic approaches after the PARADIGM-HF study?

The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality. (COR: I; LOE: ACE: A)

The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema. (COR: I; LOE: ARB: A)

In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (COR: I; LOE: ARNI: B-R)

Reason for slow uptake

• In the united states it is quite costly and not always reimbursed
• In other countries it is reimbursed but still not always used. Why?
  – Some people feel they are stable on their current regimen
  – Don’t realize that they might still be at high risk
  – If we could demonstrate an increased risk, they would certainly want to mitigate this.
ST2 in Paradigm study
The Findings

• What they found was that baseline concentrations of sST2 were very prognostic for the primary endpoints of the study, cardiovascular death and heart failure hospitalizations.

• The other thing that they found was that treatment with sacubitril/valsartan caused a significant reduction in sST2 concentrations from baseline to follow-up. And at both follow-up time points, they found lower concentrations of ST2 versus enalapril where the change, there was not much change at all.
**Paradigm: ST2 Geometric Mean Change at 4 weeks and 8 mo Post-randomization Compared to Pre-Run in Baseline**

- **Sacubitril/valsartan**
- **Enalapril**

![Graph showing geometric mean serum ST2 levels over time](image)

- **Time (weeks)**
- **Geometric Mean Serum ST2 (ng/mL)**

**# obs**
- Sacubitril/valsartan: 1011, 969, 971
- Enalapril: 991, 971, 886

**P<0.0001**

**Note:** The graph compares the geometric mean serum ST2 levels over 4 weeks and 8 months post-randomization for patients treated with Sacubitril/valsartan and Enalapril. The data shows a significant decrease in ST2 levels over time for the Sacubitril/valsartan group compared to the Enalapril group.
ST2 Levels: Monitoring and Response to Treatment with Sacibatril/Valsartan

sST2 levels fell the most out of all the biomarkers tested
Patient: C.B.

44 v.o; BM HFrEF
Carvedilol: 25mg BLD
Hydralazine: 50mg BLD
Eplerenone: 25mg
Imdur: 30mg

Normal ST2 level (35 ng/mL)

LCS696 added
LCZ 696 is great drug but could use some help. sST2 could be that help

- If you are asymptomatic on ACE/ARB but your sST2 > 35 ng/ml, you are at risk for dying. They should be on LCZ696
- IF the sST2 drops on LCZ696, they will live longer.
- LCZ696 might even be titrated by sST2
- Eventually sST2 will prove valuable in HFpEF
TIME-CHF Study: HFpEF vs HFrEF
ST2 and 18m survival in HFpEF vs HFrEF

622 symptomatic HF patients

<table>
<thead>
<tr>
<th>Unit</th>
<th>HFpEF (n = 112)</th>
<th>HFrEF (n = 458)</th>
<th>Interaction P-value</th>
<th>Corrected interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP (log)</td>
<td>2.80 (0.54–14.39)</td>
<td>6.59 (3.21–13.52)</td>
<td>&lt;0.001</td>
<td>26.4 (0.35)</td>
</tr>
<tr>
<td>Symptom guided</td>
<td>0.27 (0.04–1.71)</td>
<td>4.45 (1.95–10.17)</td>
<td>&lt;0.001</td>
<td>12.5 (0.007)</td>
</tr>
<tr>
<td>NT-proBNP guided</td>
<td>4.76 (1.31–17.39)</td>
<td>2.53 (1.76–3.64)</td>
<td>&lt;0.001</td>
<td>25.1 (0.36)</td>
</tr>
<tr>
<td>hsTnT (log)</td>
<td>13.73 (1.53–123.02)</td>
<td>19.21 (6.91–53.44)</td>
<td>&lt;0.001</td>
<td>32.1 (0.78)</td>
</tr>
<tr>
<td>GDF15 (log)</td>
<td>12.18 (2.45–60.65)</td>
<td>5.84 (2.93–11.63)</td>
<td>&lt;0.001</td>
<td>25.2 (0.43)</td>
</tr>
<tr>
<td>ST2</td>
<td>1.08 (0.99–1.18)</td>
<td>1.01 (0.97–1.06)</td>
<td>0.56</td>
<td>0.4 (0.20)</td>
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<tr>
<td>P1NP</td>
<td>1.39 (0.71–2.72)</td>
<td>1.42 (0.99–2.04)</td>
<td>0.05</td>
<td>3.7 (0.99)</td>
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<tr>
<td>hsCRP (log)</td>
<td>2.17 (0.99–4.74)</td>
<td>2.20 (1.34–3.61)</td>
<td>0.002</td>
<td>9.6 (0.99)</td>
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<tr>
<td>IL6</td>
<td>15.89 (2.70–93.54)</td>
<td>2.93 (1.25–6.86)</td>
<td>0.01</td>
<td>6.1 (0.09)</td>
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<tr>
<td>sFLT (log)</td>
<td>1.89 (0.87–3.92)</td>
<td>2.40 (1.53–3.87)</td>
<td>0.009</td>
<td>1.6 (0.93)</td>
</tr>
<tr>
<td>PLGF (per 10 UI)</td>
<td>1.04 (0.94–1.15)</td>
<td>1.15 (1.09–1.21)</td>
<td>&lt;0.001</td>
<td>30.3 (0.08)</td>
</tr>
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<td>VREAA</td>
<td>1.05 (0.82–1.36)</td>
<td>1.13 (0.96–1.35)</td>
<td>0.009</td>
<td>6.9 (0.75)</td>
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<tr>
<td>Uric acid</td>
<td>0.81 (0.65–1.02)</td>
<td>0.85 (0.75–0.96)</td>
<td>0.009</td>
<td>6.9 (0.75)</td>
</tr>
<tr>
<td>Hb (per 10 UI)</td>
<td>1.04 (0.94–1.15)</td>
<td>1.15 (1.09–1.21)</td>
<td>&lt;0.001</td>
<td>30.3 (0.08)</td>
</tr>
<tr>
<td>Creatin (per 10 UI)</td>
<td>1.08 (1.02–1.15)</td>
<td>1.09 (1.05–1.13)</td>
<td>&lt;0.001</td>
<td>22.0 (0.81)</td>
</tr>
<tr>
<td>Cys-C</td>
<td>1.25 (0.89–1.75)</td>
<td>2.55 (1.83–3.54)</td>
<td>&lt;0.001</td>
<td>31.1 (0.003)</td>
</tr>
</tbody>
</table>

→ ST2 equally predictive
PARAMOUNT: HFpEF
sacubitril/valsartan vs valsartan and short-term Δ in LA volume
(6 to 9 months)

→ ST2 <median predicts improved LA volume with LCZ696

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

Alan S. Maisel¹* and Salvatore Di Somma ²
sST2 as a decoy receptor → when elevated binds IL-33, effectively reducing the concentration of IL-33 that is available to ST2L, thus diminishing the cardioprotective effect of IL-33.

Figure 1 sST2 the HbA1c of heart failure.