ST2 as a Cardiovascular Biomarker

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ST2 and IL-33: Cardioprotective

- ST2: member of the Interleukin-1 receptor family
- Exists in two main isoforms
  - ST2L
  - Circulating sST2
- IL-33 binding to ST2L triggers cardioprotective effects.

Kakkar et al. Nat Rev Drug Discov 2008

Competitive Model of ST2/IL-33 Signaling

- sST2 acts as decoy receptor
- IL-33 can bind to sST2, reducing [IL-33] available to ST2L

ST2 in Heart Failure

Cardioprotection:
- Reduced fibrosis
- Reduced hypertrophy
- Preserved ventricular function
- Improved survival
ST2 is higher in patients with acute heart failure

ST2 is Associated with Symptom Severity

ST2 Predicts 30-Day Mortality after Acute Decompensation in HF (PRIDE Study)

After acute event:
- ST2 identifies patients at highest risk during first 30-days
- Prognostic value persists to 1 year and beyond.

ST2 Concentrations and 1-Yr Mortality in Acute HF:
As ST2 levels increase, so does risk...

One-Year mortality >50% for highest decile
**Mortality Associated with Elevated ST2: Multivariate**

In multivariable analysis (adjusted for age, vital signs, treatment at presentation, CRP and either NT-proBNP or BNP), an ST2 >median was independently predictive of death at one year.

**PRIDE: 1 Yr Mortality Risk Stratification**

Dyspnea: ST2 Has Best Prognostic AUC

All p-values <0.001 except where asterisked

Rehman SU et al. Clinica Chimica Acta 2008

**ST2 in Acute Decompensated HF Cohorts**

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

Univariable Risk-Adjusted

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>Sex</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>916</td>
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<td>2.48 (1.43-4.27)</td>
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<td>PRIDE</td>
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<td>METABOLIC</td>
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<td>1.64 (1.16-2.29)</td>
<td>0.001</td>
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<tr>
<td>Baseline</td>
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<td>-</td>
<td>2.48 (1.33-4.63)</td>
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</tbody>
</table>

Continued...

**ST2 in Chronic, Ambulatory HF Cohorts**

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

Univariable Risk-Adjusted

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>Sex</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>301</td>
<td>-</td>
<td>2.48 (1.27-4.92)</td>
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<tr>
<td>PRIDE</td>
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<td>METABOLIC</td>
<td>99</td>
<td>-</td>
<td>1.21 (0.99-1.46)</td>
<td>0.06</td>
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Continued...
**Predicting Short-Term Adverse Events: ST2 vs Natriuretic Peptides**

- Acute HF – pooled studies

ST2 gives an earlier and stronger signal for short-term adverse events than NPs.

**HFpEF**

- TIME-CHF – ST2 similarly predictive in HFpEF and HFrEF
- PARAMOUNT

**HFpEF vs HFrEF**

ST2 and 18m survival in HFpEF vs HFrEF

622 symptomatic HF patients

- ST2 equally predictive

**PARAMOUNT: HFpEF**

- Entresto vs Valsartan and short-term Δ in LA volume
- (6 to 9 months)

- ST2 < median predicts improved LA volume with LCZ696
Additive value of ST2 to NT-proBNP in long term prognosis

ST2 Levels: Monitoring and Response to Treatment

Short-Term Changes in ST2 are Associated With Long-Term Events in HF

ST2 as a Function of Events in Chronic HF
ST2 in Val-HeFT

- Val-HeFT (background):
  - 5010 patients with NYHA class II-IV HF
  - Randomized to valsartan or placebo
    - Valsartan associated with ↓ risk of mortality or HF hospitalization.
- ST2 Substudy: Do changes in ST2 levels over time provide additional prognostic information?
  - ST2 measured at baseline and at 4 months
  - 4 groups: Low-low, low-high, high-low, high-high
  - Based on cut-point of 35 ng/mL

Changes in ST2 in Val-HeFT: placebo vs valsartan

- Patients randomized to valsartan had less ↑ in ST2 levels over time

Results from Val-HeFT

- Fully adjusted hazard ratios after correction for 20 clinical variables.

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

Serial ST2 Measurements Predict Outcome: Basel ADHF Cohort

- 207 AHF patients in ED
- Samples at: presentation, Day 1, Day 2

ST2 “Non-Responders”

ST2 “Responders”
Serial ST2 Measurements for In-Patient Monitoring (SDVA): Mortality

ST2 Values Shown Using 1st Generation Research Assay.

N= 150
N=35
N=115

Serial ST2 Measurements Categorize Responder Status

Adjusted for ADHERE Risk Factors and BNP change.

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

ST2 “Non-Responders”

ST2 Levels Predict Response to Treatment: Beta-blockers

Baseline ADHF cohort

ST2 Predicts Response to Treatment: Aldosterone Blockade in STEMI

Eplerenone attenuates remodeling more in pts with higher baseline ST2.

High and low ST2 separated at median.
Predicting Reverse Remodeling: ST2-R2 score

- Developed in 304 HF pts with EF <40%
- Validated in 569 pts from 3 international HF cohorts, EF <40%:
  - Barcelona, TIME-CHF, PROTECT
- Followed 4 yrs for Δ EF, Δ LV size, mortality

### Dichotomized Variables Used for Score Construction

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>Assigned Points</th>
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</thead>
<tbody>
<tr>
<td>Non-ischemic etiology</td>
<td>6.33</td>
<td>5</td>
</tr>
<tr>
<td>No LBBB</td>
<td>5.56</td>
<td>4</td>
</tr>
<tr>
<td>ST2 &lt;48 ng/ml</td>
<td>2.96</td>
<td>3</td>
</tr>
<tr>
<td>Duration of HF &lt;12 Months</td>
<td>2.13</td>
<td>2</td>
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<tr>
<td>Beta Blocker treatment</td>
<td>1.89</td>
<td>2</td>
</tr>
<tr>
<td>Baseline LVEF &lt; 24%</td>
<td>1.52</td>
<td>1</td>
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</table>

**Dichotomized Variables**

- **Low Risk**: OR < 2
- **Medium Risk**: OR 2-3
- **High Risk**: OR > 3

#### ST2-R2 Score:

- Probability of Reverse Remodeling using ST2

- 2x ↑ likelihood of reverse remodeling if score is 12-14 vs 9-11
- 4x ↑ score 15-17 vs 9-11

**Improved NRI by 14.8%**

### Admission vs Discharge ST2 in Acute HF

- N=182 pts admitted with AHF; "real life population"
- Admission and d/c ST2 and NT-proBNP

#### Admission ST2 Level vs Discharge ST2 Level

- Discharge ST2 more predictive of outcomes

#### Admission vs Discharge ST2

- Discharge ST2 more predictive of outcomes
Discharge ST2 and NTproBNP

- Only 1 marker (+): Big gain in prognosis with +ST2 alone
- Only 1 vs Both Markers (+): Addition of +NTpro complementary primarily for composite outcome

ST2 in Monitoring and Treatment Response

- Early ST2 changes identify which acute HF patients respond to inpatient treatment
- Discharge levels most predictive of outcomes
- Change in ST2 over time predicts mortality and morbidity in chronic HF
- Predicts response to (and varies with) aldosterone blockade, beta-blockers, and diuretics

Algorithm for Using ST2 in Chronic HF

- ST2 is a powerful predictor of short-term mortality in acute & chronic HF and MI
- ST2 is useful in both HFpEF and HFrEF
- ST2 and natriuretic peptides are synergistic
- Changes in ST2 levels have important clinical implications
  - Admission and D/C levels give different info
  - Non-responders are at higher risk, and optimizing therapy can attenuate this