Biomarkers in Heart Failure: The Old and The New

Nancy K. Sweitzer, MD, PhD
Professor of Medicine
Chief of Cardiology
Director, Sarver Heart Center
University of Arizona, Tucson, AZ
Editor in Chief, Circulation: Heart Failure

Case

• RM is a 56 yo male. He was admitted to the hospital 2 weeks ago with his first episode of HF, and is sent to you for post-discharge f/u.
• Non-ischemic, LVEDD 69 mm, EF 25%, normal RV fxn
• ECG with NSR@102 bpm, LVH, QRS 100 ms
• On ASA, lisinopril 10, metoprolol succinate 12.5, simvastatin
• Weight 105 kg, BP 124/76, HR 96, JVP 16 cm H2O, 2/6 HSM, +S3
• BUN 18, Creatinine 1.2, eGFR 56
Case

- RM is a 56 yo male. He was admitted to the hospital 2 weeks ago with his first episode of HF, and is sent to you for post-discharge f/u.
- Non-ischemic, LVEDD 69 mm, EF 25%, normal RV fxn
- ECG with NSR@102 bpm, LVH, QRS 100 ms
- On ASA, lisinopril 10, metoprolol succinate 12.5, simvastatin
- Weight 105 kg, BP 124/76, HR 96, JVP 16 cm H2O, 2/6 HSM, +S3
- BUN 18, Creatinine 1.2, eGFR 56
- NT-proBNP 2200
- sST2 44

What Makes a Good Biomarker?

- A measurable phenomenon that allows:
  - Detection of Preclinical Disease
  - Diagnosis
  - Risk Stratification
  - Treatment Selection and Monitoring
The Promise of Biomarker Guided Tx

- Instead of empiric uptitration of therapy, if a physiologic target or marker could be used, we might be more able to prescribe the right therapy, at the right time, at the right dose, in the right patient.

The Breathing Not Properly Study

The Breathing Not Properly Study


The Breathing Not Properly Study

What Makes a Good Biomarker?

• A measurable phenomenon that allows:
  – Detection of Preclinical Disease
  – Diagnosis
  – Risk Stratification
  – Treatment Selection and Monitoring

Assay Characteristics
What Makes a Good Biomarker?

• A measurable phenomenon that allows:
  – Detection of Preclinical Disease
  – Diagnosis
  – Risk Stratification
  – Treatment Selection and Monitoring

Guide-IT

Felker et al, JAMA 2017; 318:713-720
BNP as a Biomarker

<table>
<thead>
<tr>
<th></th>
<th>Y</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of Preclinical Disease</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Risk Stratification</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Treatment Selection and Monitoring</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Biomarker Studies

![Graph showing biomarker studies over time]
Defining New biomarkers

Charting a Roadmap for Heart Failure Biomarker Studies

Tariq Ahmad, MD, MPH,⁎; Mona Fuzzat, Posand,⁎; Michael J. Pencina, PhD,⁎; Nancy L. Geller, PhD,⁎; Faez Zannad, MD, PhD; John G.F. Cleland, MD,⁎; James V. Snider, PhD,⁎; Stephan Blankenberg, MD,⁎; Kirkwood F. Adams, MD,⁎⁎; Rita F. Redberg, MD, MPH;⁎; Jae B. Kim, MD,⁎; Alice Mascette, MD,⁎; Robert J. Mentz, MD,⁎; Christopher M. O'Connor, MD,⁎⁎; G. Michael Felker, MD, MHS,⁎; James L. Januzzi, MD,⁎†

Ahmad et al, JACC:HF 2014, adapted from van Kimmenade and Januzzi
Risk Stratification

- 100s of biomarkers with demonstrated association with event risk in HF
- Rarely significantly better than BNP
- Almost none with any ability to guide therapeutic decisions

ST2

- Suppression of Tumorigenicity 2 (ST2)
- Member of the IL-1 receptor-like family of proteins
- Immune biology worked out in the 1990s
- Comes in 2 forms – membrane bound (ST2L) and soluble, circulating form (sST2)
- 2002: ST2 the most highly-induced gene in response to mechanical strain a microarray screen
Dieplinger et al., 2014 Clinica Chimica Acta p59

**Cardioprotection**

**Antihypertrophic**

**Antifibrotic**

**Fibroblast**
ST2 Risk Stratification in Acute HF

- PRIDE study
- 599 patients presenting to the MGH ED with dyspnea
- 35% adjudicated to have dyspnea due to HF
- Non-HF dx included COPD, pneumonia, ACS, PE, bronchitis.

Januzzi JL et al, 2007 JACC p607

Risk Stratification in Acute HF

Dyspnea Due to HF

Dyspnea Without HF

Januzzi JL et al, 2007 JACC p607
Risk Stratification in Acute HF

Risk Stratification in Chronic HF
Risk Stratification in Chronic HF

Bayes-Genis et al, Am J Cardiol p3A

Risk Stratification – Multiple Markers

Bayes-Genis et al, 2014 J Card Fail p25
Monitoring HF Treatment

ST2 in Treatment Monitoring

Anand IS et al, 2014 CircHF p418
ST2 in Therapy

Anand IS et al, 2014 CircHF p418

ST in Treatment Monitoring

Januzzi JL et al, 2015 Am J Cardiol p4A
## ST2 and Reverse Remodeling

### Table 1

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Reverse Remodeling N=104</th>
<th>No reverse remodeling N=200</th>
<th>Univariable Logistic Regression</th>
<th>Multivariable Logistic Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>p</td>
<td>OR</td>
</tr>
<tr>
<td>Galectin-3, ng/mL</td>
<td>16.3 (12.6-20.2)</td>
<td>16.5 (13.2-22.8)</td>
<td>0.77</td>
<td>0.42-1.42</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>1307 (703-2777)</td>
<td>2390 (1046-4289)</td>
<td>0.74</td>
<td>0.61-0.91</td>
</tr>
<tr>
<td>Hs-cTnT, ng/L</td>
<td>21.4 (7.5-32.8)</td>
<td>28.8 (14.5-48.5)</td>
<td>0.62</td>
<td>0.47-0.81</td>
</tr>
<tr>
<td>ST2, ng/mL</td>
<td>38.3 (32.47-5)</td>
<td>43.8 (33.59-9)</td>
<td>0.71</td>
<td>0.56-0.9</td>
</tr>
</tbody>
</table>

- Reverse remodeling defined as LVEF increase ≥ 15% or LVEF increase ≥ 10% + LVESDi reduction ≥ 20% or LVESVi reduction ≥ 40%.
- R2 group had HR 0.36 for death + HF hosp

## ST2 and Reverse Remodeling Score

### Table 2

<table>
<thead>
<tr>
<th>Multivariate logistic regression (N = 304)</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>β</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ischemic etiology</td>
<td>6.33</td>
<td>3.52–11.39</td>
<td>&lt; 0.001</td>
<td>1.845</td>
<td>5</td>
</tr>
<tr>
<td>No LBBB</td>
<td>5.56</td>
<td>2.37–13.05</td>
<td>&lt; 0.001</td>
<td>1.716</td>
<td>4</td>
</tr>
<tr>
<td>ST2 &lt; 48 ng/mL</td>
<td>2.96</td>
<td>1.62–5.39</td>
<td>&lt; 0.001</td>
<td>1.084</td>
<td>3</td>
</tr>
<tr>
<td>Duration of HF &lt; 12 months</td>
<td>2.13</td>
<td>1.18–3.84</td>
<td>0.01</td>
<td>0.754</td>
<td>2</td>
</tr>
<tr>
<td>β-Blocker treatment</td>
<td>1.89</td>
<td>0.52–6.86</td>
<td>0.34</td>
<td>0.634</td>
<td>2</td>
</tr>
<tr>
<td>Baseline LVEF &lt; 24%</td>
<td>1.52</td>
<td>0.81–2.88</td>
<td>0.20</td>
<td>0.421</td>
<td>1</td>
</tr>
</tbody>
</table>

Lupon J et al, 2015 Int J Cardiol p337
ST2-R2 Score

Lupon J et al, 2015 Int J Cardiol p337

BNP as a Biomarker

<table>
<thead>
<tr>
<th></th>
<th>BNP</th>
<th>ST2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of Preclinical Disease</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Risk Stratification</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Treatment Selection and Monitoring</td>
<td>✔</td>
<td></td>
</tr>
</tbody>
</table>
# Charting a Roadmap for Heart Failure Biomarker Studies

Tariq Ahmad, MD, MPH; Mona Fiuzat, PhD; Michael J. Pencina, PhD; Nancy L. Geller, PhD; Falez Zamad, MD, PhD; John G.F. Cleland, MD; James V. Snider, PhD; Stephan Blankenberg, MD; Kirkwood F. Adams, MD; Rita F. Redberg, MD, MPH; Jae B. Kim, MD; Alice Mascette, MD; Robert J. Mentz, MD; Christopher M. O'Connor, MD; G. Michael Felker, MD, MHS; James L. Januzzi, MD

---

## TABLE 3 Proposed Tier System for Quality of Biomarker Studies: The Paris Criteria

<table>
<thead>
<tr>
<th>Tier</th>
<th>Improved Diagnosis and Prognostication</th>
<th>Tailoring Therapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1</td>
<td>Satisfies criteria for tiers 2 and 3</td>
<td>Randomized, controlled trial in which biomarker levels determine therapeutic choices</td>
</tr>
<tr>
<td>Tier 2</td>
<td>Satisfies criteria for tier 3</td>
<td>Validates results in a representative cohort</td>
</tr>
<tr>
<td>Tier 3</td>
<td>Follows STARD statement</td>
<td>Shows differential effect of treatment based on biomarker levels in a retrospective analysis of randomized, controlled trials</td>
</tr>
</tbody>
</table>

AUC — area under the receiver-operating characteristic curve; STARD — Standards for Reporting of Diagnostic Accuracy.
Thank You!