Novel biomarkers in Acute HF

By

Mohamed Abdel Ghany Karim
Assistant professor of cardiology, Assuit University

Potential Uses of Biomarkers in HF

- Diagnosis: Does this patient have heart failure or something else?
- Risk Stratification/Triage: Does this patient need hospitalization? Should they be referred for transplant, LVAD, or palliative care?
- Selection of Therapy: What should I do to make this patient better?
- Titration of Therapy: Should I keep doing what I’m doing or should I do something else?
Pathophysiologic factors leading to alterations in levels of biomarkers

- BNP or B-type natriuretic peptide is produced mostly by cardiac ventricles in response to stress/strain/stretch on the myocardium
- BNP’s half-life is approximately 20 minutes, and it is cleared primarily by neutral endopeptidase and natriuretic peptide (NP) receptors
- NT-proBNP has a half-life of 1 to 2 hours and is more dependent on renal filtration for elimination

BNP (NT-proBNP) in HF
Biomarkers

Biomarkers for Prognosis or Added Risk Stratification

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF.</td>
<td>MODIFIED: Current recommendation emphasizes that it is admission levels of natriuretic peptide biomarkers that are useful.</td>
</tr>
</tbody>
</table>
Table 2. Natriuretic peptides cut points for the diagnosis of heart failure

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>HF is unlikely</th>
<th>HF is possible but other diagnoses need to be considered</th>
<th>HF is very likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>All</td>
<td>&lt; 100 pg/ml</td>
<td>100-500 pg/ml</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>&lt; 50</td>
<td>&lt; 300 pg/ml</td>
<td>300-450 pg/ml</td>
</tr>
<tr>
<td></td>
<td>50 - 75</td>
<td>&lt; 300 pg/ml</td>
<td>450-900 pg/ml</td>
</tr>
<tr>
<td></td>
<td>&gt; 75</td>
<td>&lt; 300 pg/ml</td>
<td>900 - 1800 pg/ml</td>
</tr>
</tbody>
</table>

HF, heart failure

Negative predictive Value = 90 %

ACCURACY IS 90 %
GUIDing Evidence Based Therapy
Using Biomarker Intensified Treatment
GUIDE-IT

Christopher M. O'Connor, MD
Professor of Medicine
Chief of Cardiology
Director, Duke Heart Center

Duke Clinical Research Institute

Objectives

- The primary objective GUIDE IT is to determine the efficacy of a strategy of biomarker-guided therapy compared with usual care on the composite endpoint of time to cardiovascular death or first heart failure (HF) hospitalization in high risk patients with left ventricular systolic dysfunction.
BNP confounders

<table>
<thead>
<tr>
<th>Higher NP Levels than Expected</th>
<th>Lower NP Levels than Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age*</td>
<td>Obesity</td>
</tr>
<tr>
<td>ACS*</td>
<td>Flash pulmonary edema</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Pericarditis/tamponade</td>
</tr>
<tr>
<td>RV dysfunction*</td>
<td>Genetic polymorphisms</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>“Burned-out” cardiomyopathy</td>
</tr>
<tr>
<td>Pulmonary hypertension*</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism*</td>
<td></td>
</tr>
<tr>
<td>Anemia/high output states*</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation*</td>
<td></td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; NP = natriuretic peptide; RV = right ventricle.
*Denotes likely elevation from ventricular stretch.
ST2

- ST2 is a member of the interleukin-1 receptor family. It is found both as a trans-membrane form as well as a soluble form in serum.
- ST2 is the receptor for interleukin-33 (IL-33), which is an IL-1-like cytokine secreted by living cells in response to cell damage.
- The interaction of IL-33 and ST2 has been proved to be cardioprotective, reducing myocardial fibrosis, cardiomyocyte hypertrophy, apoptosis, and improving myocardial function.

IL-33 interactions with transmembrane receptor, ST2L, and soluble decoy receptor, sST2.
ST 2 level not affected by

- Age
- SEX
- BMI
- AF
- Renal function
- Anemia

> 35

= Risk
**ST 2 level is not a diagnostic marker of HF**

- Severe sepsis
- Disseminated cancer
- Liver fibrosis

It is elevated in almost every one with AHF
It is very prognostic in AHF
- short term
- long term

**ST2 Concentrations and Mortality Rates**
ST2 levels drawn on admission are highly predictive of future heart failure admissions, more so than B-type natriuretic peptide.

Heart failure and infection

- 20% of hospitalized AHF patients
- If pneumonia untreated, hospital mortality may be up to 20% (versus 5%)
- Use of procalcitonin to guide initiation and duration of antibiotic treatment in patients with ARIs was effective in reducing antibiotic failure.
Use of procalcitonin for the diagnosis of pneumonia in patients presenting with a chief complaint of dyspnoea: results from the BACH (Biomarkers in Acute Heart Failure) trial

Alan Maisel1,2†, Sean-Xavier Neath3, Judd Landsberg1,2, Christian Mueller1, Richard M. Nowak4, W. Frank Peacock5, Piotr Ponikowski6, Martin Möckel7, Christopher Hogan8, Alan H.B. Wu9, Mark Richards10, Paul Clifton1, Gerasimos S. Filippatos11, Salvatore Di Somma12, Inder Anand13, Leong L. Ng14, Lori B. Daniels9, Robert H. Christenson15, Mihael Potocki1, James McCord1, Garrett Terracciano16, Oliver Hartmann17, Andreas Bergmann18, Nils G. Morgenthaler7, and Stefan D. Anker7,19
Assessment of procalcitonin levels may be considered in patients with AHF with suspected coexisting infection, particularly for the differential diagnosis of pneumonia and to guide antibiotic therapy.

**HIGH-SENSITIVITY TROTONIN IN AHF**

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclude type I MI (ACS)</td>
<td>Data not clear yet whether you can guide therapy</td>
</tr>
<tr>
<td>Rising/falling pattern</td>
<td>Drops with Entresto</td>
</tr>
<tr>
<td>Signs/symptoms of ischemia</td>
<td></td>
</tr>
<tr>
<td>Imaging evidence</td>
<td></td>
</tr>
<tr>
<td>May rise and fall even without MI</td>
<td></td>
</tr>
<tr>
<td>Acute HF → rise</td>
<td></td>
</tr>
<tr>
<td>Treatment of HF → fall</td>
<td></td>
</tr>
<tr>
<td>Tn &gt; 99th percentile → worse outcome</td>
<td></td>
</tr>
<tr>
<td>Regardless of type I MI/ACS</td>
<td></td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; HF = heart failure; MI = myocardial infarction; Tn = troponin.
• **Galectin-3** is another promising biomarker, associated with the cumulative development of fibrosis and apoptosis in cardiac remodelling.

• ACC/AHA have given a Class IIb recommendation for measurement of galectin-3 in ADHF (level of evidence A) and chronic HF (level of evidence B), for the purpose of risk stratification and prognostication in HF patients, stages C–D.

---

**Does Galectin-3 identify a specific HF Phenotype?**

• **Low Galectin 3** = “Non-remodeling” HF  
  • Relatively good prognosis  
  • Likely to be responsive to traditional treatments  
• **High Galectin 3** = “Remodeling” HF  
  • Relatively poor prognosis  
  • May need earlier referral for advanced HF therapies  
  • Should we consider specific anti-remodeling agents?
**Growth differentiation factor-15**

- Growth differentiation factor-15 is a stress-response cytokine that is a distant member of the transforming growth factor (TGF)-beta family.
- In cardiomyocytes, GDF-15 is produced and released in the setting of oxidative stress or in response to stimulation with cytokines or angiotensin II.
- Increased GDF-15 has been associated with worse outcomes and new-onset HF in the general population, and with worse outcomes in patients with ACS as well as acute and chronic HF.

**Conclusions**

- Biomarkers in conjunction with the clinical and physical assessment can provide greater diagnostic accuracy than the physical assessment alone.
- The natriuretic peptides are the best-established and best-evaluated markers to help in the proper diagnosis and exclusion of HF.
- sST2, hsTn, and PCT will likely soon join the NPs as biomarkers routinely measured in heart failure patients in various settings.
Thank you