Biomarkers of Heart Failure

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8th International Conference
Acute Cardiac Care
June 16-18, 2013
Jerusalem, Israel
Second Announcement
CME Accredited

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Disclosures

- **Grants**: Roche Diagnostics, Siemens, Critical Diagnostics, Thermo Fisher, Singulex, BG Medicine, NHLBI

- **Consulting**: Roche Diagnostics, Critical Diagnostics, BG Medicine, Zensun, Amgen, Novartis
Age-adjusted hospitalization rates for heart failure

Acute/sub-acute HF outcomes

Ko, Arch Intern Med 2005
Assessment of Heart Failure

No gold standard for the evaluation of HF exists!

What about diagnostic testing?

History and Physical
### Table 1. Examples of candidate biomarkers in HF, divided into categories.

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Neurohormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Renin</td>
</tr>
<tr>
<td>TNF-like weak inducer of apoptosis</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>IL-1, −6, −10, and −18</td>
<td>Aldosterone</td>
</tr>
<tr>
<td>Lipoprotein-associated phospholipase A2</td>
<td>Arginine vasopressin, copeptin</td>
</tr>
<tr>
<td>soluble TNF receptors 1 and 2</td>
<td>Endothelin-1</td>
</tr>
<tr>
<td>YKL-40</td>
<td>Urocortin</td>
</tr>
<tr>
<td>IL-1 receptor antagonist</td>
<td>Chromogranin A and B</td>
</tr>
<tr>
<td>Midkine</td>
<td>MR-proADM</td>
</tr>
<tr>
<td>Leucine-rich 2-glycoprotein</td>
<td>Myocyte injury and apoptosis</td>
</tr>
<tr>
<td>PTX3</td>
<td>Troponins I and T</td>
</tr>
<tr>
<td>CA-125</td>
<td>Myosin light-chain kinase I</td>
</tr>
<tr>
<td>S100A8/A9 complex</td>
<td>Heart-type fatty-acid binding protein</td>
</tr>
<tr>
<td>Osteoprotegerin</td>
<td>Creatine kinase MB fraction</td>
</tr>
<tr>
<td>Serine protease PR3</td>
<td>Soluble apoptosis-stimulating fragment</td>
</tr>
<tr>
<td>Soluble endoglin</td>
<td>Heat shock protein 60</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Soluble TNF-related apoptosis-inducing ligand</td>
</tr>
<tr>
<td><strong>Oxidative stress</strong></td>
<td><strong>Myocyte stress</strong></td>
</tr>
<tr>
<td>Oxidized LDLs</td>
<td>BNP, NT-proBNP, MR-proANP</td>
</tr>
<tr>
<td>Myeloperoxidase</td>
<td>sST2</td>
</tr>
<tr>
<td>Urinary biopyrrins</td>
<td>GDF-15</td>
</tr>
<tr>
<td>Urinary and plasma isoprostanes</td>
<td>Extracardiac involvement</td>
</tr>
<tr>
<td>Urinary 8-hydroxy-2′-deoxyguanosine</td>
<td>RDW</td>
</tr>
<tr>
<td>Plasma malondialdehyde</td>
<td>Cystatin-C, β-trace protein</td>
</tr>
<tr>
<td>Extracellular-matrix remodeling</td>
<td>NGAL, N-acetyl-β-(D)-glucosaminidase, kidney injury molecule-1</td>
</tr>
<tr>
<td>MMPs (MMP2, MMP3, MMP9)</td>
<td>β2-microglobulin</td>
</tr>
<tr>
<td>TIMP1</td>
<td>Urinary albumin-to-creatine ratio</td>
</tr>
<tr>
<td>IL-6</td>
<td>Triiodothyronine</td>
</tr>
<tr>
<td>Collagen propeptides</td>
<td></td>
</tr>
<tr>
<td>N-terminal collagen type III peptide</td>
<td></td>
</tr>
<tr>
<td>Myostatin</td>
<td></td>
</tr>
<tr>
<td>Syndecan-4</td>
<td></td>
</tr>
<tr>
<td>Galectin-3</td>
<td></td>
</tr>
</tbody>
</table>
New recommendations for biomarkers in HF

the 2013 ACC/AHA guideline update

<table>
<thead>
<tr>
<th>Biomarker, Application</th>
<th>Setting</th>
<th>Rec</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natriuretic peptides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis or exclusion of HF*</td>
<td>Ambulatory, Acute</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Prognosis of HF</td>
<td>Ambulatory, Acute</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Guidance of Chronic HF</td>
<td>Ambulatory</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Guidance of ADHF</td>
<td>Acute</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td><strong>Troponin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive risk stratification</td>
<td>Acute, Ambulatory</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>Galectin-3, ST2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Ambulatory</td>
<td>Iib</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Acute</td>
<td>Iib</td>
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</tr>
</tbody>
</table>

*Particularly when indecision for diagnosis is present

Yancy, et al, 2013
Accepted applications of BNP or NT-proBNP in HF

✓ Diagnosis
✓ Estimation of HF severity
✓ Prognostication

? Management
Diagnostic Uncertainty is Common in Dyspnea Evaluation

Following full evaluation, managing physician asked to provide an estimate from 0% to 100% for the likelihood for heart failure as the cause of dyspnea. 

“Uncertainty zone”
31% of subjects

Green et al, Arch Int Medicine, 2008;168:741
Diagnostic Uncertainty is Associated with Poor Prognosis in Acute Dyspnea

31% of subjects in PRIDE were judged uncertainly by the managing physician. Their prognosis was significantly worse, with higher rates of death and re-hospitalization and longer lengths of stay!

Green et al, Arch Int Medicine, 2008;168:741
Results: NT-proBNP Levels

P<.001

Januzzi et al, AJC 2005
All subjects had an NT-proBNP > age-adjusted URL.

Un-blinded NT-proBNP results led to considerable increase in the correct diagnosis of ADHF.

Meisel, et al, 2012
Where does NT-proBNP help most?

Data from the Canadian IMPROVE-CHF Study

Although NT-proBNP added incremental information at both ends of the spectrum of heart failure likelihood…

<table>
<thead>
<tr>
<th>Clinician impression</th>
<th>Model impression</th>
<th>Not HF</th>
<th>HF</th>
<th>% Appropriately Reclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low prob (n=343)</td>
<td>LP (n=282)</td>
<td>276</td>
<td>6</td>
<td>(2.1)*</td>
</tr>
<tr>
<td></td>
<td>IP (n=58)</td>
<td>30</td>
<td>28</td>
<td>48.3</td>
</tr>
<tr>
<td></td>
<td>HP (n=3)</td>
<td>0</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>(Accuracy = 89%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Int prob (n=139)</td>
<td>LP (n=38)</td>
<td>37</td>
<td>1</td>
<td>97.3</td>
</tr>
<tr>
<td></td>
<td>IP (n=77)</td>
<td>25</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HP (n=24)</td>
<td>0</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>High prob (n=91)</td>
<td>LP (n=0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>IP (n=18)</td>
<td>4</td>
<td>14</td>
<td>22.2</td>
</tr>
<tr>
<td></td>
<td>HP (n=73)</td>
<td>1</td>
<td>72</td>
<td>(1.4)*</td>
</tr>
<tr>
<td>(Accuracy = 95%)</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**Where does NT-proBNP help most?**

*Data from the Canadian IMPROVE-CHF Study*

*Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analyses suggested the biggest benefit was in the indecision zone…*

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<td>1</td>
<td>72</td>
<td>(1.4)*</td>
</tr>
</tbody>
</table>

MR-proANP as a biomarker of heart failure

ANP is unstable \textit{in vivo} and \textit{in vitro}, therefore not suitable for clinical diagnosis.
Mid-regional pro-atrial natriuretic peptide and pro-adrenomedullin testing for the diagnostic and prognostic evaluation of patients with acute dyspnoea

Ravi V. Shah¹, Quynh A. Truong¹, Hanna K. Gaggin¹, Jens Pfannkuche², Oliver Hartmann², and James L. Januzzi Jr¹*

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated age-adjusted MR-proANP³</td>
<td>4.34</td>
<td>2.11–8.92</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Elevated age-adjusted NT-proBNP⁴</td>
<td>9.73</td>
<td>4.63–20.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Radiographic pulmonary oedema</td>
<td>7.28</td>
<td>3.11–17.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Orthopnoea</td>
<td>6.60</td>
<td>2.87–15.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of loop diuretic on presentation</td>
<td>2.87</td>
<td>1.50–5.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presence of rales on exam</td>
<td>2.26</td>
<td>1.11–4.60</td>
<td>0.03</td>
</tr>
<tr>
<td>Age (by decade)</td>
<td>1.74</td>
<td>1.37–2.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cough</td>
<td>0.47</td>
<td>0.24–0.91</td>
<td>0.03</td>
</tr>
<tr>
<td>Fever</td>
<td>0.13</td>
<td>0.04–0.40</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Shah, Eur Heart J, 2012
Accepted applications of BNP or NT-proBNP in HF

- Diagnosis
- Estimation of HF severity
- Prognostication

? Management
Prognostic importance of baseline NT-proBNP in ADHF

Meisel et al, ESC Acute Card Care, 2012
Interpreting Unexpectedly Elevated B-type Natriuretic Peptide Levels: Know the Differential Diagnosis

- Unrecognized HF
- Prior HF
- LVH
- Valvular heart disease
- Atrial fibrillation
- Advancing age
- Myocarditis
- ACS
- Pulmonary hypertension
- Anemia
- Pulmonary embolism
- Cardiac surgery
- Sleep apnea
- Critical illness
- Sepsis
- Burns
- Renal failure
- Toxic-metabolic insults

Baggish, et al, Crit Path Cardiol, 2004
Relationships between discharge BNP and outcomes are curvilinear.

Hernandez et al, Circ Heart Fail, 2012
Accepted applications of BNP or NT-proBNP in HF

✓ Diagnosis
✓ Estimation of HF severity
✓ Prognostication

? Management
Why might natriuretic peptide testing assist with heart failure management?

- Earlier diagnosis
- Better triage

• As a target of therapy?
Effect of Selective NT-proBNP Testing On Costs/Outcomes:

Results of the Randomized IMPROVE-CHF Trial

Effect of Selective NT-proBNP Testing on Utilization/Costs

Effect of Selective NT-proBNP Testing on Outcomes

Why might natriuretic peptide testing assist with heart failure management?

- Earlier diagnosis
- As a target of therapy?
# Therapies with Effects on B-Type Natriuretic Peptide Levels

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effect on BNP/NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis</td>
<td>↓</td>
</tr>
<tr>
<td>ACE-I</td>
<td>↓</td>
</tr>
<tr>
<td>ARB</td>
<td>↓</td>
</tr>
<tr>
<td>β-blockers</td>
<td>↓</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>↓</td>
</tr>
<tr>
<td>BiV pacing</td>
<td>↓</td>
</tr>
<tr>
<td>Exercise</td>
<td>↓</td>
</tr>
<tr>
<td>Rate control of AF</td>
<td>↓</td>
</tr>
<tr>
<td>ANP/BNP infusions</td>
<td>↓</td>
</tr>
</tbody>
</table>
Natriuretic peptide treatment response:

*Absolute target and % change*

Data courtesy of Yigal Pinto, MD
Guided therapy combined analyses

Meta analysis of publication data

Pooled patient data from all available trials

Felker et al, Am Heart Journal, 2009

Troughton et al, ESC 2011
Beyond the natriuretic peptides

- **“Fibrosis”/remodeling markers**
  - ST2
  - Galectin 3
  - GDF-15
  - hs Troponin

- **Inflammatory markers**
  - Take your pick...

- **Salt and water derangement**
  - Copeptin

- **Co-morbidity markers**
  - Hemoglobin
  - RDW
  - Renal markers
  - ET-1
  - Adipokines

- **Hemodynamic stress**
  - MR-proADM

- **Genetic markers**
  - Pharmacogenomics
Biologic role of adrenomedullin

CNS and endocrine glands
- ↓ Thirst
- ↓ Salt Appetite
- ↓ Vasopressin secretion
- ↓ ACTH secretion
- ↓ Insulin secretion

Reproductive System
- Stimulatory Effect on FSH

Vascular System
- Vasodilation
  - ↓ blood pressure

Lung
- ↓ pulmonary hypertension
- ↓ synthesis of ET-1 and NO
- vasoprotective

Kidney
- → Sodium excretion
- → Urine volume
- → Renal blood flow
  - ↓ Aldosterone

Heart
- → Contractility
  - ↓ ANP

MR-proADM is prognostic for death in HF (particularly early events).

Open questions about MR-proADM:
- What exactly do I do with the result?
- Do I measure serially?
- Can I reduce the risk?
Copeptin (CT-proAVP) and outcomes in ADHF

Results from the BACH Study

Concentrations of copeptin were prognostic in all HF subjects...

And seemingly unrelated to serum sodium concentrations...

Xue et al, Circ Heart Fail, 2011
Copeptin and outcomes in ADHF

Results from the BACH Study

However, considered as a function of low sodium and high copeptin, more refined ability to risk stratify emerged...

The ACTIVATE study will examine the importance of copeptin to identify benefit from tolvaptan in hyponatremic subjects

Xue et al, Circ Heart Fail, 2011
Hypothesized links between troponin and incident HF

Troponin elevation in HF is:

• Common
• Not always related to CAD
• Caused by many mechanisms
• Prognostic!

Januzzi, Filippatos, Niemenen and Gheorghiade for the UDMI, European Heart Journal, 2012
99th Percentile for Troponin T

99th percentile = 13 pg/mL (imprecision 10%)

Old URL = 0.03 ng/mL (imprecision 10%)

Blood donors (n=1251)
Apparenty healthy individuals (n=500)
High sensitivity troponin in acutely decompensated heart failure

Serial measures

Xue et al, Eur Jour Heart Fail 2011
Galectin-3 in HF

Scientific Discovery

- In animal models of heart failure, Galectin-3 highly expressed in failing versus functionally compensated hearts

Galectin-3 Promotes Remodeling

Intrapericardial administration of galectin-3 significantly increases LV collagen content and reduces LV ejection fraction.

**Collagen Increase**

![Collagen Increase Graph]

**Reduced Ejection Fraction**

![Reduced Ejection Fraction Graph]


P<.05

P<.05
Galectin-3 and long term outcomes in ADHF

Open questions about galectin-3:

- What exactly do I do with the result?
- Do I measure serially?
- Can I reduce the risk?

P < .001

Shah, Eur J Heart Fail, 2011
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
Multiple biomarkers in ADHF: the GREAT Network Analysis

365 day risk

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>NRI [95% CI]</th>
<th>IDI [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>sST2</td>
<td>10.3 [1.9 ; 18.7]</td>
<td>0.048 [0.028 ; 0.067]</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>9.1 [4.0 ; 14.1]</td>
<td>0.025 [0.016 ; 0.034]</td>
</tr>
<tr>
<td>MR-proADM</td>
<td>9.1 [2.4 ; 15.8]</td>
<td>0.042 [0.028 ; 0.057]</td>
</tr>
<tr>
<td>MR-proANP</td>
<td>7.4 [1.6 ; 13.2]</td>
<td>0.028 [0.014 ; 0.041]</td>
</tr>
<tr>
<td>BNP</td>
<td>5.5 [1.5 ; 9.4]</td>
<td>0.020 [0.012 ; 0.027]</td>
</tr>
<tr>
<td>CRP</td>
<td>5.3 [1.9 ; 8.8]</td>
<td>0.011 [0.005 ; 0.016]</td>
</tr>
<tr>
<td>Troponin T</td>
<td>0.0 [-0.9 ; 1.0]</td>
<td>0.000 [-0.001 ; 0.002]</td>
</tr>
<tr>
<td>Troponin I</td>
<td>-0.2 [-1.8 ; 1.5]</td>
<td>0.000 [-0.001 ; 0.002]</td>
</tr>
</tbody>
</table>

Additive value of ST2 to NT-proBNP in long term prognosis

![Graph showing cumulative hazard over days from enrollment]

- Red line: Both sST2 and NT-proBNP elevated (n=276)
- Green line: Only sST2 elevated (n=95)
- Blue line: Only NT-proBNP elevated (n=54)
- Turquoise line: Neither elevated (n=168)

Cumulative hazard

Days from enrollment

P < .001
ST2 Trends as a Function of Mortality

NT-proBNP, hsTnT, and sST2 in ADHF: Multi-marker profiling

All 3 markers measured on admission in patients with ADHF
All 3 selected in bootstrapping models
All 3 reclassified significantly in NRI and IDI analyses

Pascual-Figal, Eur J Heart Fail 2011
Biomarkers of Heart Failure

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