2016 Congress on Atherosclerotic Cardiovascular Disease Prevention

Biomarkers: Tools for Heart Failure Management

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Duke University School of Medicine
After this presentation, participants will be able to

• Define biomarkers.

• Relate the varying roles of biomarkers to the diagnosis of heart failure and prognostic implications in managing heart failure.

• Cite literature in the emerging use of biomarkers to guide management of heart failure and in the prevention of heart failure.
Outline

I. Introduction – Biomarkers and their emerging utility in medicine.
II. Biomarkers in establishing the diagnosis of heart failure.
III. Biomarkers and predicting the clinical course of heart failure.
IV. Biomarkers and the prospective management of heart failure.
V. Biomarkers and the prevention of heart failure.
Biomarker Definition

“A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”

Uses of Biomarkers

• **Diagnosis**: Evaluating ambiguous symptoms
• **Screening**: Pursuit of disease in asymptomatic populations
• **Risk stratification**: Assessing prognosis for future course in both symptomatic and asymptomatic individuals
• **Guiding therapy**: Therapy selection and titration to goals
• **Surrogate end-points**: Aid in therapy development (clinical trials)
• **Fundamental research**: Insights into disease mechanisms

Adapted from Mark and Felker. *NEJM* 2004.
## BNP and NT-ProBNP

<table>
<thead>
<tr>
<th></th>
<th>BNP 1-32</th>
<th>NT-ProBNP 1-76</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mol. wt.</em></td>
<td>3.5 kD</td>
<td>8.5 kD</td>
</tr>
<tr>
<td>*In vitro stability:</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><em>½ life (min)</em></td>
<td>13-20</td>
<td>25-70</td>
</tr>
<tr>
<td><em>Activity:</em></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><em>Metabolism:</em></td>
<td>clearance receptors</td>
<td>renal neutral endopeptidases</td>
</tr>
</tbody>
</table>
BNP for Diagnosis in Patients with Acute Dyspnea

Optimal cut-off point determined @ 100 pg/mL

<table>
<thead>
<tr>
<th>BNP 100 pg/mL</th>
<th>Final Diagnosis</th>
<th>Final Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>Heart Failure</td>
<td>NOT Heart Failure</td>
</tr>
<tr>
<td>673</td>
<td>227</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BNP &lt;100 pg/mL</th>
<th>Final Diagnosis</th>
<th>Final Diagnosis</th>
</tr>
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<tbody>
<tr>
<td>Test negative</td>
<td>Heart Failure</td>
<td>NOT Heart Failure</td>
</tr>
<tr>
<td>71</td>
<td>615</td>
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</tr>
</tbody>
</table>

Sensitivity = 90%
Specificity = 73%
Positive predictive value = 75%
Negative predictive value = 90%

BNP Correlates with LV Filling Pressures

*Pulmonary artery wedge.

Kazanegra J, Cardiac Failure 2001
Causes for Elevated Natriuretic Peptide Levels

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Noncardiac</th>
</tr>
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<tbody>
<tr>
<td>• Heart failure, including RV syndromes</td>
<td>• Advancing age</td>
</tr>
<tr>
<td>• Acute coronary syndrome</td>
<td>• Anemia</td>
</tr>
<tr>
<td>• Heart muscle disease, including LVH</td>
<td>• Renal failure</td>
</tr>
<tr>
<td>• Valvular heart disease</td>
<td>• Pulmonary causes: obstructive sleep apnea, severe pneumonia, pulmonary hypertension</td>
</tr>
<tr>
<td>• Pericardial disease</td>
<td>• Critical illness</td>
</tr>
<tr>
<td>• Atrial fibrillation</td>
<td>• Bacterial sepsis</td>
</tr>
<tr>
<td>• Myocarditis</td>
<td>• Severe burns</td>
</tr>
<tr>
<td>• Cardiac surgery</td>
<td>• Toxic-metabolic insults, including cancer chemotherapy and envenomation</td>
</tr>
<tr>
<td>• Cardioversion</td>
<td></td>
</tr>
</tbody>
</table>
Natriuretic Peptides and Prognosis in Chronic HF: Data from Val-HeFT

Anand, I. et al, Circ 2003
In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty.

Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.
BNP- or NT-proBNP guided HF therapy can be useful to achieve optimal dosing of GDMT in select clinically euvolemic patients followed in a well-structured HF disease management program.

The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established.

Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF.
Hospitalized/Acute

Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis.

Measurement of BNP or NT-proBNP and/or cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF.
The usefulness of BNP- or NT-proBNP guided therapy for acutely decompensated HF is not well-established.

Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with acutely decompensated HF.
Predischarge BNP Is Strong Predictor of Post-Discharge Events

Logeart et al. JACC 2004;43:635-41
Change in NTproBNP and Outcomes

Masson, S. et al. JACC 2008;52:997-1003
High sensitivity troponins

- Contractile proteins intimately involved with cardiac and skeletal muscle contraction
- Leak from injured or dying myocytes, whatever the cause.
High sensitivity troponins

ST2 - What it is and what it does

- Inflammatory molecule (family of IL-33) with increased activity in many states of inflammation (RA, CTD, pulmonary fibrosis).
- Gene expressed when cardiomyocytes are stressed or with ventricular remodeling.
ST2 Predicts Response to Therapy in STEMI

- ST2 predicts which patients will benefit most from aldosterone blockade.

- Eplerenone attenuates remodeling more in patients with a higher baseline ST2.

- ST2 not only predicts outcomes but also predicts which patients will benefit most from intervention.
Galectin-3 What it is and what it does

- Lectin with role in promoting inflammation and fibrosis in many settings, including pulmonary and cardiac fibrosis and cardiac re-modeling.
Galectin-3 Biology

- Beta-galactoside binding lectin
- Secreted by macrophages
- Mechanistic role in fibrosis
- Anti-apoptotic
- The “switch” that turns quiescent fibroblasts into activated, matrix-secreting myofibroblasts
Galectin-3 and Treatment Effect in CORONA

Patients with low levels of galectin-3 derive an important mortality benefit while no benefit is observed when galectin-3 is elevated.

### AHA/ACC Recommendations for Biomarkers in HF (2013)

<table>
<thead>
<tr>
<th>Biomarker, Application</th>
<th>Setting</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
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<td>Diagnosis or exclusion of HF</td>
<td>Ambulatory, Acute</td>
<td>I</td>
<td>A</td>
<td>212, 217–223, 245–250</td>
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<td>A</td>
<td>222, 224–229, 248, 251–258</td>
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<td>Achieve GDMT</td>
<td>Ambulatory</td>
<td>IIa</td>
<td>B</td>
<td>230–237</td>
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<td>Acute</td>
<td>IIb</td>
<td>C</td>
<td>259, 260</td>
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COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; and LOE, Level of Evidence.

## Recommendations for Biomarkers in HF

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Evolving Concepts in Patient Management

• Standard of care driven by EBM from RCT dosing or highest dose tolerated by patient.
• Standard of care driven by quantitative measures of ongoing clinical variables.
Established Biomarker-Directed Patient Management

- HIV/hepatitis: viral load
- Diabetes mellitus: Hgb A1c
- Hypertension: BP
- Hyperlipidemia: LDL
- Anticoagulation: INR
- Polymyalgia rheumatica: ESR
Chronic HF Therapy Guided by BNP

Cardiovascular events

Heart failure or death

P = 0.034

P = 0.049

Time after randomisation (days)

NT-proBNP

Clinical

N = 69

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Troughton, R. Lancet 2000
Biomarker Guided Therapy and All-Cause Mortality: Meta-Analysis

Adjusted HR = 0.69 (0.55-0.86)

N = 1627

Felker GM. Am Heart J 2009
Some Potential Biomarker Candidates

• High sensitivity troponin
• Cistatin C
• MR-pro ANP
• Copeptin (C-terminal pro-ANP)
• Pro-calcitonin
Study Design

Patient with Class II-IV symptoms, EF ≤ 40%, recent HF event

Randomization echocardiogram

Standard of Care
- Minnesota Living With HF Questionnaire quarterly
- Therapy adjusted to achieve optimal drug targets
  - Visits q3 months
  - Extra visits as needed for treatment goals

Standard of Care + NT-proBNP
- Minnesota Living With HF Questionnaire quarterly
- Therapy adjusted to achieve optimal drug targets PLUS NT-proBNP ≤ 1000 pg/mL
  - Visits q3 months
  - Extra visits as needed for treatment goals

Close-out echocardiogram
- Total cardiovascular events assessed
Primary Endpoint

100 events

58 events

*Logistic Odds_{NT-proBNP} = 0.44 (95% CI = .22-.84; P = .019)

*Adjusted for age, LVEF, NYHA Class, and eGFR

Januzzi et al. JACC 2011
Equipoise?

BGT might work |
TIME-CHF
BATTLESCARRED

BGT works
PROTECT
STARS-BNP
Troughton pilot
Berger

BGT doesn’t work
PRIMA
Northstar
STARBRITE
Estimated Direct and Indirect Costs of HF in US

Total Cost $39.2 billion

Hospitalization $20.9 53.3%
Nursing Home $4.7 11.9%
Lost Productivity/ Mortality* $4.1 10.5%
Physicians/Other Professionals $2.5 6.4%
Home Healthcare $3.8 9.7%
Drugs/Other Medical Durables $3.2 8.2%

* Includes non-medical costs associated with missed work and lost productivity due to death


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GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment GUIDE-IT
Hospitalization for heart failure
LVEF ≤ 40 within 12 months
NTproBNP > 2000 pg/mL or BNP > 400 pg/mL during index hospitalization

Randomized within 2 weeks of hospital discharge

- Usual Care
  N= 550

- Biomarker Guided
  NTproBNP < 1000 pg/mL
  N=550

Follow up: 2 wks, 6 wks, 3 months, then Q3 month for 12-24 mos

Additional 2 week follow up after changes in therapy

Primary endpoint: Time to CV death or first HF hospitalization

Secondary Endpoints: All-cause mortality
  Total days alive and out of hospital during follow-up
  CV mortality or CV hospitalization
  Safety
  Health related quality of life
  Resource utilization, costs, cost-effectiveness
BNP and Prognosis in Asymptomatic Adults: Framingham Heart Study

Death

Heart Failure

Wang, TJ. NEJM 2004
STOP-HF TRIAL

Participant invited by primary care physician (PCP)

Central study centre contacted for randomization

Control
Blinded BNP annually

n=677

Routine PCP care

Lost to follow up n=69
Withdrawn consent n=132
Death n=37

Intervention
Unblinded BNP annually

n=697

NP-directed care

Lost to follow up n=70
Withdrawn consent n=92
Death n=35

END OF STUDY ASSESSMENT
- Doppler echocardiography
- BNP
- Blinded MACE Assessment

Intention to treat analysis

STOP-HF Intervention

Ledwidge, M. et al. JAMA 2013; 310;:66-74

**Routine PCP care**
- Annual BNP not available to clinicians
- At least annual review by PCP
- Cardiology review only if requested by PCP

**NP-directed care**
In addition to routine PCP care
- Annual BNP in all

*If BNP >50pg/ml at any time*
- Shared-care
  - Cardiology review
  - Echo-Doppler
  - Other CV investigations
  - CV nurse coaching
  - Regular Cardiology follow-up
Endpoint – MACE Event Rate


Event Rate OR 0.54 p=0.001 vs. Control

Number of events per 1,000 patient

<table>
<thead>
<tr>
<th></th>
<th>Control N=71 (10.5%)</th>
<th>Intervention N=51 (7.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TIA</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>PE/DVT</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>9.9</td>
<td></td>
</tr>
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</table>

Event Rate: OR 0.54, p=0.001 vs. Control.
Conclusion – Biomarkers and heart failure

- Biomarkers are a diverse family of unique characteristics identified in many illnesses, including heart failure.
- Biomarkers are very helpful for diagnosing heart failure, especially when the diagnosis is confounded by other factors.
- Biomarkers have important prognostic utility in heart failure.
- Biomarker-guided patient management may be coming soon.
- Biomarkers have properties useful in screening for subclinical illness, prompting early and beneficial preventive measures.