Novel Biomarkers in Heart Failure

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## Disclosure Statement of Financial Interest Relevant to the Presentation

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tr>
<td>Grant/Research Support</td>
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<tr>
<td>Other Financial Benefit</td>
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How Biomarkers Are Affected by the Government Shutdown

- Biomarker grants and trial submissions have halted
- Enrollment of patients and collection of biomarkers at the NIH Clinical Center has stopped
- The NIH GUIDE-IT Trial (Felker et al.) has limited project office support
- Research on novel biomarkers predicting government shutdown is needed
Always wanted to be like Mick
Personalized Medicine: Definition

“All personalized medicine will enable risk assessment, diagnosis, prevention, and therapy specifically tailored to the unique characteristics of the individual, thus enhancing the quality of life and public health.”

NHLBI Strategic Planning, Theme #10.
What Is a Biomarker?

“If it costs less than 20 bucks, it’s a lab test. If it costs more than 20 bucks, it’s a biomarker.”
Current Tools Used for Assessment of HF
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?
Biomarkers in Heart Failure
From Very Long List

• **Established for HF**
  – Natriuretic Peptides (NTproBNP, BNP)

• **Established for other conditions**
  – High sensitivity troponins

• **FDA approved but optimal use uncertain**
  – ST2
  – Galectin-3
Class I. Concentrations of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) should be measured in patients being evaluated for dyspnea in which the contribution of HF is not known. Final diagnosis requires interpreting these results in the context of all available clinical data and ought not to be considered a stand-alone test. (Level of Evidence: A)

Optimal cut-off point determined @ 100 pg/mL

- Sensitivity = 90%
- Specificity = 73%
- Positive predictive value = 75%
- Negative predictive value = 90%
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Sensitivity Training: Troponinology for the Non-Geek

- **Upper Reference Limit (URL):** 99th percentile value in “normal population”
- **Lower limit of detection (LLOD):** Value that can be reliably distinguished from 0
- **Discussion of troponin values as “positive” or “negative” increasingly irrelevant**
Troponin in Heart Failure


Cardiac troponins in congestive heart failure.
Del Carlo CH, O'Connor CM.
Duke Clinical Research Institute, Duke University Medical Center, Durham, NC 27710, USA.

Abstract
BACKGROUND: We sought to assess the release of cardiac troponins in congestive heart failure (CHF).

METHODS AND RESULTS: We performed a computer-assisted search of the English language literature (MEDLINE database) followed by a manual search of the reference list of pertinent articles retrieved. Studies evaluating the release of cardiac troponins (T and I) in patients with CHF were screened for review. Studies investigating cardiac troponins in patients with ischemic coronary syndromes that reported the rate of CHF were also selected. Available data on the release of cardiac troponins in ischemic and nonischemic CHF were summarized. Possible mechanisms of cell death in the progression to end-stage CHF were discussed.

CONCLUSIONS: Cardiac troponins were detected in patients with advanced CHF. These markers correlated with the severity of CHF and suggest an association with worse prognosis. Possible mechanisms for the release of cardiac troponins T and I in advanced CHF may include the following: ventricular remodeling, presence of coronary artery disease in CHF, abnormalities of coronary microcirculation, and reduced coronary reserve. Further studies will be necessary to elucidate the actual mechanism and determine the clinical significance of cardiac troponins in CHF.

PMID: 10502208 [PubMed - indexed for MEDLINE]
Causes of Tn Release in HF

- Proteolysis or turnover of myocardial contractile proteins
- Direct toxicity of circulating neurohormones, inflammation, infiltrative processes, etc.
- Supply-demand mismatch with subendocardial ischaemia
- Selected causes of reduced oxygen supply:
  - Anaemia
  - Hypotension
- Selected causes of increased myocardial oxygen demand:
  - Increased transmural wall stress
  - Dilated left ventricular chamber size
  - Elevated pressures in cardiac chambers
  - Left ventricular hypertrophy
  - Diastolic stiffening of the myocardium

Bar graph showing cTnI by etiology:
- Ischemic
- Non-Ischemic

P = 0.77

Januzzi et al. EHJ 2012
Felker, GM et al. EJHF 2012
Stages of Heart Failure

A. Risk Factors
- cTn 0.7-8%
- hsTnT 25-66%

B. Structural Abnormalities
- cTnT 10%
- hsTnT 92%

C. Symptoms
- cTn 6.2%
- hsTnI ~ 100%

D. % above 99th URL

Symptoms
Structural Abnormalities
Risk Factors
cTnI in AHF: Data from ASCEND-HF

Felker, GM et al. EJHF 2012
hs-cTnT & risk of death: GISSI HF

Hazard ratio (95% CI)

Masson, Circ 2012
Change in troponin and Day 60 cardiovascular (CV)/renal hospitalization or death.

O'Connor C M et al. Circ Heart Fail 2011;4:724-732
Troponin in Heart Failure

- Greater sensitivity leading to many/most HF patients having elevated levels
- Know your assay
- Very sensitive assays may be most helpful in at risk individuals (stage A and B) as compared to those w advanced disease (stage C and D)
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  – Galectin-3
ST2 Background

- ST2 is a member of the interleukin-1 receptor family
- ST2 protein is found both as a trans-membrane form as well as a soluble form in serum
- The ligand for ST2 was recently identified to be IL-33
- Links inflammation, hemodynamic stress, and remodeling
ST2 and Mortality

**Chronic HF**

**Acute HF**
Multi-Marker Score for Predicting Outcomes

ST2, GDF15, hsTrop I, BNP

A

Cumulative incidence, %

Time to event, years

No. at risk  
1st quartile 821  
2nd quartile 818  
3rd quartile 814  
4th quartile 799  

Deaths

B

Cumulative incidence, %

Time to event, years

No. at risk  
1st quartile 808  
2nd quartile 813  
3rd quartile 803  
4th quartile 788  

Incident HF

Wang, Circulation 2012
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 NTproBNP in Chronic HF

Felker et al. Circ HF 2010
Galectin-3 and Incident HF: Framingham

<table>
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<tr>
<th>Outcome</th>
<th>Model</th>
<th>HR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Heart Failure</td>
<td>Age- and sex-adjusted</td>
<td>1.39 (1.17-1.65)</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>Multivariable-adjusted*</td>
<td>1.27 (1.06-1.52)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Multivariable + BNP</td>
<td>1.23 (1.04-1.47)</td>
<td>0.02</td>
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Ho, J. JACC 2012
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?

Lambert JM, et al. *Int J Cardiol* 2008
Significance of Estimating Prognosis for the Individual Patient is Limited

Great news!
I can predict you will live 4.5 months with a p value of 0.03
What are the Unmet Needs in Heart Failure?

• **Diagnostic markers?**
  – Natriuretic peptides are already extremely good for diagnosis of ADHF

• **Prognostic markers?**
  – >150 prognostic markers have already been identified in heart failure, very few of which are employed by clinicians

• **Markers that tell us what we should do (ie, what is likely to work) or what we shouldn’t do (ie, what is unlikely to work) for an individual patient**

• **Markers that may lead to new therapeutic targets**
Biomarker Targeted Therapy

All patients with same diagnosis

1. Marker not elevated
   - Remove non-responders and toxic responders

2. Marker elevated
   - Treat Responders and Patients Not Predisposed to Toxicity

ST2 Predicts Response to Aldosterone Blockade 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 predict which patients will benefit most from intervention.

Survival by ST2 Categories and Exercise Training

Product-Limit Survival Estimates

Days from randomization to death or LKDA

Survival Probability

- st2_cat=<= 35 ng/ml trt_ex=Exercise Training
- st2_cat=> 35 ng/ml trt_ex=Exercise Training
- st2_cat=<= 35 ng/ml trt_ex=Usual Care
- st2_cat=> 35 ng/ml trt_ex=Usual Care

+Censored
Galectin-3 and Drug Effect: CORONA

Gullestad, EHJ 2012
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
Rationale for Natriuretic Peptide Guided Therapy

- Decreases in NP levels over time associated with favorable outcomes
- Proven effective HF therapies decrease NP levels
  - Will a strategy of titrating therapy to specific NP targets improve outcomes?
### Therapies with Effects on NP Levels in HF

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<tr>
<th>Therapy</th>
<th>Effect on BNP/NT-proBNP</th>
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<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>May transiently ↑, then ↓</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>BNP infusions</td>
<td>↓ N-BNP, ↑ BNP then ↓</td>
</tr>
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Examples from other Areas of Medicine

- HIV/Hepatitis  Viral load
- Diabetes mellitus  HbA1C
- Hypertension  Blood pressure
- Hyperlipidemia  LDL
- Anticoagulation  INR

- Heart failure  ?
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.
Hospitalization for heart failure
LVEF ≤ 40 within 12 months
NTproBNP > 2000 pg/mL during index hospitalization

Randomized at hospital discharge (+ 2 weeks)

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
The Future

“It’s tough to make predictions, especially about the future.”

“The future ain’t what it used to be.”

Yogi Berra