Cardiac Biomarkers in Asymptomatic Populations: Current Status, Future Promise

Biomarkers and Diagnostic Testing Translational Research Community

July 14, 2014

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Disclosures

• Honoraria: Siemens Healthcare, Critical Care Diagnostics, BG Medicine, Instrumentation Laboratories, Roche Diagnostics, Philips

• Advisory: BG Medicine, Instrumentation Laboratories, Siemens, Singulex, Nexus-Dx, Diadexus

• Grants: Critical Care Diagnostics, Radiometer, BG Medicine, Roche, Siemens, BRAHMS, Vital Diagnostics, Nanosphere, Beckman-Coulter, Becton Dickinson, Trinity Diagnostics, Mitsubushi
When troponin is increased think heart

Cardiac isoforms in blood
“Small heart attacks are so common; they are almost within normal range.”

Paul Dudley White, 1957
The Father of American Cardiology
Universal Definition of MI

- The preferred biomarker is cTn (I or T), which has high myocardial tissue specificity as well as high clinical sensitivity.
- An increased cTn concentration is defined as a value exceeding the 99th percentile of the upper reference limit.
- Detection of a rise and/or fall of the measurements is essential to the diagnosis of acute MI.

Thygesen K et al. JACC 2012;60:1581-98.
Elevated Troponin in Patients without ACS or Heart Failure

**Acute Disease**
- Cardiac and Vascular
  - Acute Aortic dissection
  - Cerebrovascular accident
  - Ischemic Stroke
  - Intracerebral Hemorrhage
  - Subarachnoid Hemorrhage
  - Medical ICU Patients
  - Gastrointestinal bleeding

**Chronic Disease**
- ESRD
- Cardiac infiltrative disorders
- Amyloidosis
- Sarcoidosis
- Hemochromatosis
- Scleroderma
- Hypertension

**Disease Specific**
- Inherited Disorders
  - Neurofibromatosis
  - Duchenne Muscular Dystrophy
  - Klippel-Feil syndrome
  - Environmental Exposure
  - Carbon Monoxide
  - Hydrogen Sulfide
  - Colchicine exposure

- Envenomation
  - Snake
  - Jellyfish
  - Spider
  - Centipede
  - Scorpion
Are All Cardiac Troponin Assays Created Equal?

No
“...when troponin was a lousy assay it was a great test, but now that it's becoming a great assay, it's getting to be a lousy test.”
The Next Generation

Current commercial TnI
Limit of detect ~ 0.005 ng/ml
10% CV = 0.02 - 0.04 ng/ml

Prior Gen commercial TnI
Limit of detect ~ 0.1 ng/ml
10% CV = 0.4 ng/ml

Next Gen Ultrasensitive
Limit of detect ~ 0.0001 ng/ml
10% CV < 0.001 ng/ml

From: Contemporary Cardiology: Cardiovascular Biomarkers: Pathophysiology and Disease Management
Edited by: David A. Morrow © Humana Press Inc., Totowa, NJ
Troponin Normal Reference Interval

LoD for hsTn assays

LoD for ssTn assays

LoD for Sensitive Assays

Current cTnT

99th
ROC Area and Time of Symptoms Onset

Implementation of a Sensitive Troponin I Assay and Risk of Recurrent Myocardial Infarction and Death in Patients With Suspected Acute Coronary Syndrome

A prudent question is ½ of wisdom-Francis Bacon

Does use of a more sensitive troponin assay improve patient outcomes?

Mills et al. JAMA. 2011;305(12):1210-1216
Total Error in Temporal Samples

Troponin (ng/L) vs Time (Admission, 1 Hr, 3 Hr, 8 Hr)
Tip of the Outcomes Iceberg

Sensitivity of Assay

Missed opportunity To treat patients Who might benefit From HF or other therapies?
Criteria of Congestive Heart Failure

Table 1. Criteria of CHF.*

<table>
<thead>
<tr>
<th>MAJOR CRITERIA</th>
<th>MINOR CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal nocturnal dyspnea or orthopnea</td>
<td>Ankle edema</td>
</tr>
<tr>
<td>Neck-vein distention</td>
<td>Night cough</td>
</tr>
<tr>
<td>Rales</td>
<td>Dyspnea on exertion</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>Pleural effusion</td>
</tr>
<tr>
<td>S₃ gallop</td>
<td>Vital capacity ↓ ½ from maximum</td>
</tr>
<tr>
<td>Increased venous pressure -&gt; 16 cm of water</td>
<td>Tachycardia (rate of ≥ 120/min)</td>
</tr>
<tr>
<td>Circulation time ≥ 25 sec</td>
<td>Major or Minor Criterion</td>
</tr>
<tr>
<td>Hepatofugal reflux</td>
<td>Weight loss ≥ 4.5 kg in 5 days in response to treatment</td>
</tr>
</tbody>
</table>

*For establishing a definite diagnosis of congestive heart failure in this study, 2 major or 1 major & 2 minor criteria had to be present concurrently.

Heart Failure Statistics

- Nearly 5 million Americans living with heart failure (prevalent HF)
- Approximately 550,000 new cases are diagnosed each year. (incident HF)
- Half of HF is asymptomatic
- HF is responsible for 11 million physician visits each year, and more hospitalizations than all forms of cancer
- More than half of those who develop HF die within 5 years of diagnosis.
- CHF is the first-listed diagnosis in 875,000 hospitalizations, and the most common diagnosis in hospital patients age 65 years and older.
- In that age group, 20% of all hospitalizations have a primary or secondary diagnosis of HF.
- Heart failure contributes to approximately 287,000 deaths a year.
- HF costs in the United States exceed $30 billion
HF reduced EF

EF≤40%

Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HF/EF, and it is only in these patients that efficacious therapies have been demonstrated to date.

Circulation 2013;128:e240-e327; originally published online June 5, 2013
HF preserved EF

EF ≥ 50%

Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
Prevalence of Heart Failure
A disease of older adults

Circulation 2012;125:e12–30
BNP and NTproBNP Release

Ventricle Stretch

proBNP

Cleavage by enzyme corin

NT-proBNP

BNP

T_{1/2} 20 minutes
Active Hormone

T_{1/2} 1.5 to 2.0 hours
Inactive
Incidence of detectable troponin in acute and chronic HF

<table>
<thead>
<tr>
<th>First Author, Year (Ref. #)</th>
<th>n</th>
<th>Troponin</th>
<th>Cut-Off Values</th>
<th>HF Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peacock et al., 2008 (19)</td>
<td>67,924</td>
<td>Tnl and TnT</td>
<td>Tnl or TnT &gt; 0.1 µg/l</td>
<td>AHF</td>
</tr>
<tr>
<td>Gheorghiade et al., 2005 (10)</td>
<td>51</td>
<td>Tnl and TnT</td>
<td>Tnl &gt; 0.03 µg/l or TnT &gt; 0.01 µg/l</td>
<td>AHF</td>
</tr>
<tr>
<td>Del Carlo et al., 2004 (8)</td>
<td>62</td>
<td>TnT</td>
<td>TnT ≥ 0.01 µg/l</td>
<td>AHF</td>
</tr>
<tr>
<td>La Vecchia et al., 2000 (14)</td>
<td>34</td>
<td>Tnl</td>
<td>Tnl &gt; 0.3 ng/ml</td>
<td>AHF</td>
</tr>
<tr>
<td>Metra et al., 2007 (28)</td>
<td>116</td>
<td>TnT</td>
<td>TnT &gt; 0.01 ng/ml</td>
<td>AHF</td>
</tr>
<tr>
<td>Nizeki et al., 2007 (58)</td>
<td>126</td>
<td>TnT</td>
<td>TnT &gt; 0.01 ng/ml</td>
<td>AHF</td>
</tr>
<tr>
<td>Parenti et al., 2008 (18)</td>
<td>99</td>
<td>Tnl</td>
<td>Tnl &gt; 0.05 ng/ml</td>
<td>AHF</td>
</tr>
<tr>
<td>Perna et al., 2005 (21)</td>
<td>184</td>
<td>TnT</td>
<td>TnT &gt; 0.1 ng/ml</td>
<td>AHF</td>
</tr>
<tr>
<td>You et al., 2007 (41)</td>
<td>2,025</td>
<td>Tnl</td>
<td>Tnl &gt; 0.5 µg/l</td>
<td>AHF</td>
</tr>
<tr>
<td>Logeart et al., 2001 (16)</td>
<td>71</td>
<td>Tnl</td>
<td>Tnl &gt; 0.026 ng/ml</td>
<td>AHF and CHF</td>
</tr>
<tr>
<td>Horwich et al., 2003 (11)</td>
<td>238</td>
<td>Tnl</td>
<td>Tnl ≥ 0.04 ng/ml</td>
<td>CHF</td>
</tr>
<tr>
<td>Hudson et al., 2004 (12)</td>
<td>136</td>
<td>TnT</td>
<td>TnT ≥ 0.02 ng/ml</td>
<td>CHF</td>
</tr>
<tr>
<td>Latini et al., 2007 (15)</td>
<td>4,053</td>
<td>TnT and hsTnT</td>
<td>TnT ≥ 0.01 ng/ml or hsTnT ≥ 0.001 ng/ml</td>
<td>CHF</td>
</tr>
<tr>
<td>Miller et al., 2007 (17)</td>
<td>190</td>
<td>TnT</td>
<td>TnT ≥ 0.01 ng/ml</td>
<td>CHF</td>
</tr>
<tr>
<td>Missov et al., 1999 (27)</td>
<td>33</td>
<td>TnT</td>
<td>TnT &gt; 0.1 ng/ml</td>
<td>CHF</td>
</tr>
<tr>
<td>Perna et al., 2004 (20)</td>
<td>115</td>
<td>TnT</td>
<td>TnT ≥ 0.02 ng/ml</td>
<td>CHF</td>
</tr>
</tbody>
</table>

AHF = acute heart failure; CHF = chronic heart failure; HF = heart failure; hsTnT = high-sensitivity troponin T; Tnl = troponin I; TnT = troponin T.
## Biomarker Recommendations for HF

<table>
<thead>
<tr>
<th>Biomarker, Application</th>
<th>Setting</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natriuretic peptides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis or exclusion of HF</td>
<td>Ambulatory, Acute</td>
<td>I A</td>
<td>A</td>
</tr>
<tr>
<td>Prognosis of HF</td>
<td>Ambulatory, Acute</td>
<td>I A</td>
<td>A</td>
</tr>
<tr>
<td>Achieve GDMT</td>
<td>Ambulatory</td>
<td>IIa B</td>
<td>B</td>
</tr>
<tr>
<td>Guidance for acutely decompensated HF therapy</td>
<td>Acute</td>
<td>IIb C</td>
<td>C</td>
</tr>
<tr>
<td>Biomarkers of myocardial injury</td>
<td></td>
<td>I A</td>
<td>A</td>
</tr>
<tr>
<td>Additive risk stratification</td>
<td>Acute, Ambulatory</td>
<td>I A</td>
<td>A</td>
</tr>
</tbody>
</table>

**COR, Class of Recommendation; GDMT, guideline-directed medical medical therapy; HF, Heart Failure; LOE, level of evidence**

Circulation 2013;128:e240-e327; originally published online June 5, 2013;
Biomarker levels represent a summation of the influence of acute and chronic comorbidities.
Population Focus

*Elderly Population with no incident Heart Failure presenting with no signs, symptoms*
Dynamic Cardiovascular Risk Assessment in Elderly People

The Role of Repeated N-Terminal Pro-B-Type Natriuretic Peptide Testing

Christopher R. deFilippi, MD,* Robert H. Christenson, PhD,† John S. Gottdiener, MD,* Willem J. Kop, PhD,* Stephen L. Seliger, MD, MS‡

Baltimore, Maryland
5,888 enrolled in CHS

275 prevalent HF at enrollment

5,613

1,301 (23.2%) no sample available

4,312 with NT-proBNP at baseline

180 incident HF
120 deceased
543 no in-person study visit*

3,469 with in-person study visit

492 no follow-up sample available

2,975 with available follow-up sample
Incident Rates for CV Outcomes Based on Change in NT-proBNP Level
Time to New Onset HF Diagnosis

A

Proportion free of heart failure

Quintiles of NT-proBNP (pg/ml)

- Q1 (<5-47.5)
- Q2 (47.5-86.8)
- Q3 (86.9-143.1)
- Q4 (143.2-267.5)
- Q5 (267.7-23,445)

Follow-up time (years)
Incident Rates for CV Outcomes Based on Change in NT-proBNP Level

- >25% Decline
- No Significant Change
- >25% Increase

**Initial NT-proBNP**

- <190 pg/mL
- ≥190 pg/mL

**Rate of incident HF (per 100 person years)**

- p<.001
- p=.004
- p=0.4
Incident Rates for CV Outcomes Based on Change in NT-proBNP

- > 25% Decline
- No Significant Change
- > 25% Increase

Rate of CV death (per 100 person years)

Initial NT-proBNP

- <190 pg/mL
- ≥190 pg/mL

- p<.001
- p=.01
- p=.6

p<.001
Association of Serial Measures of Cardiac Troponin T Using a Sensitive Assay With Incident Heart Failure and Cardiovascular Mortality in Older Adults

Christopher R. deFilippi, MD
James A. de Lemos, MD
Robert H. Christenson, PhD
John S. Gottdiener, MD
Willem J. Kop, PhD
Min Zhan, PhD
Stephen L. Seliger, MD, MS

JAMA. 2010;304(22):2494-2502
hsTnT and incident HF and Cardiovascular Death

- Community Dwelling Adults
- N=4221
- 65 years or older
- Without prior HF
- hs-TnT measurement at baseline
- Repeat hs-TnT measurement 2-3 years later

*JAMA. 2010;304(22):2494-2502*
Cardiovascular death

Categories
1. <3.00  2. 3.00 - 5.44  3. 5.44 - 8.16  4. 8.17 – 12.94  5. >12.94

Log-rank P < .001

Follow-up Time, y

Proportion Without Cardiovascular Death

JAMA. 2010;304(22):2494-2502
hs cTnT in the General Population

Study Designs

**Dallas Heart Study**
- N=3546
- Ages 30-65
- f/u 6.4 years
- cTnT measured by std and hs-cTnT assay
- Cardiac MRI (n=2501)
- EBCT (n=2770)
- Endpoints: Cardiac Phenotypes Mortality

**Cardiovascular Health Study**
- N=4221
- Age ≥ 65
- No prior heart failure
- Avg f/u 11.8 years
- cTnT by hs assay
- Repeat measurement of cTnT at 2-3 yrs (n=2918)
- Endpoints: CVD death New Heart Failure

**Atherosclerosis Risk in Communities**
- N=9698
- Ages 54-74
- Avg f/u 9.9 years
- cTnT measured by hs assay
- Endpoints: Coronary heart disease All-cause mortality HF Hospitalization
Heart failure

![Graph showing incidence rate per 100 person-years for different baseline cTnT levels, with categories for >50% decrease, change ≤50%, and >50% increase.]

Incidence Rate, per 100 Person-Years

Baseline cTnT, pg/mL

JAMA. 2010;304(22):2494-2502
Conclusions:

In older adults without known HF, baseline cTnT levels and changes in hs-TnT levels over 2-3 years were significantly associated with incident HF and cardiovascular death.

JAMA. 2010;304(22):2494-2502
Dose Response Between Physical Activity and Risk of Coronary Heart Disease: A Meta-Analysis

Jacob Sattelmair, Jeremy Pertman, Eric L. Ding, Harold W. Kohl III, William Haskell and I-Min Lee

*Circulation*. 2011;124:789-795; originally published online August 1, 2011; doi: 10.1161/CIRCULATIONAHA.110.010710
Methods

• Meta-analysis of epidemiological studies investigating physical activity and primary prevention of CHD. We included prospective cohort studies published in English since 1995.

• Reviewing 3194 abstracts, included 33 studies. leisure-time physical activity. Individuals who engaged in the equivalent of 150 min/wk of moderate-intensity
Individuals who met the basic guideline had a 14% lower risk of CHD than those who engaged in no LTPA.
Plot with spline (smoothed fit) and 95% confidence intervals (CIs) of relative risks of coronary heart disease by kilocalories per week of leisure-time physical activity (LTPA).

Those who met advanced guideline had a 20% lower risk of CHD than those who engaged in no LTPA.

Generalized least squares (GLST) regression spline (smoothed fit) models with 95% confidence intervals (CIs).

Leisure-time physical activity 150 min/wk had 14% lower CHD relative risk, 0.86; 95% confidence interval, 0.77 to 0.96, compared with no leisure-time physical activity.

Engaging in the equivalent of 300 min/wk of moderate-intensity physical activity had a 20% lower CHD relative risk, 0.80; 95% confidence interval, 0.74 to 0.88.

Higher physical activity levels associated with modestly lower relative risk.

Physically activity at lower levels also had significantly lower CHD.

There was a significant interaction by sex (P<0.03); the association was stronger among women than men.

**Conclusions**—These findings provide quantitative data supporting US physical activity guidelines that stipulate that “some physical activity is better than none” and “additional benefits occur with more physical activity.”
Composite physical activity score:
Summed leisure time activity quartiles (range, 1 to 4) and walking pace (range, 1 to 3) to generate a combined with a possible range of 2 to 7.

- 2 as low activity
- 3 to 6 as moderate activity
- 7 as high activity
Proportion of patients with a significant Biomarker Increase vs Physical Activity

J Am Coll Cardiol 2012;60:2539–47
Rate of Incident HF

J Am Coll Cardiol 2012;60:2539–47
These findings suggest that moderate physical activity has protective effects on early heart failure phenotypes, preventing cardiac injury and neurohormonal activation.

J Am Coll Cardiol 2012;60:2539–47
Randomized Design

Individuals With Elevated Biomarker Enrolled

Randomize

Exercise Regimen

Usual Care

Data collection

Outcomes hsTn, NT-proBNP

Outcomes hsTn, NT-proBNP
LIFE-P study

• Adults age 70-85 years enrolled
• Feasibility study of 400 sedentary community dwelling adults without walking disabilities
• at baseline all performed <20 min per week of moderate physical activity, but could complete a 400m walk in ≤ 15 minutes without sitting or using assist devices.
Change in (hs cTnT) from baseline to 12 months

![Bar graph showing absolute change in hs cTnT level (pg/mL) between physical activity and sedentary control groups. The graph indicates a significant difference (p=0.02) between the two groups.](image)
Thank You!
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