Future of Biomarkers

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The journey continues
Future of Biomarkers

• A historical perspective to reaching “Class I” guideline status
• New populations/New indications
• One is a lonely number
• Newer proteomic strategies
The 1990’s
Cardiac specific troponins enter clinical practice

Table 3. Major Cardiac Events during Hospitalization and Date of Occurrence. 33/84 USA patients +cTnT

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Creatine Kinase MB</th>
<th>Total MB</th>
<th>Cardiac Troponin T</th>
<th>Cardiac Events</th>
<th>Day after Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49/M</td>
<td>148</td>
<td>11</td>
<td>0.37</td>
<td>Infarction</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>58/M</td>
<td>117</td>
<td>4</td>
<td>&lt;0.20 f</td>
<td>Death after infarction</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>80/F</td>
<td>102</td>
<td>14</td>
<td>0.21</td>
<td>Death after infarction</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>73/M</td>
<td>36</td>
<td>0</td>
<td>1.1</td>
<td>Death after infarction</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>59/F</td>
<td>9</td>
<td>1</td>
<td>0.47</td>
<td>Death after bypass surgery and infarction</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>75/M</td>
<td>29</td>
<td>0</td>
<td>0.54</td>
<td>Death after bypass surgery and infarction</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>79/M</td>
<td>121</td>
<td>29</td>
<td>0.28</td>
<td>Infarction</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>72/M</td>
<td>45</td>
<td>3</td>
<td>0.81</td>
<td>Death after bypass surgery and infarction</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>68/M</td>
<td>41</td>
<td>5</td>
<td>1.07</td>
<td>Infarction</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>78/M</td>
<td>156</td>
<td>9</td>
<td>0.90</td>
<td>Infarction</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>66/M</td>
<td>94</td>
<td>16</td>
<td>0.30</td>
<td>Infarction</td>
<td>4</td>
</tr>
</tbody>
</table>

*Values of <25 U per liter for creatine kinase MB and <0.20 μg per liter for troponin T were considered normal. Infarction denotes acute myocardial infarction, and bypass surgery coronary artery bypass surgery.

This patient was classified as negative for troponin T.

The 2010’s
Cardiac troponin and ACS
Universal definitions and guidelines

• Third universal definition of myocardial infarction (2012) refines use of cardiac troponin for the diagnosis of myocardial infarction

• European Society of Cardiology 2015 guidelines

Diagnosis of NSTE-ACS

<table>
<thead>
<tr>
<th>It is recommended to measure cardiac troponins with sensitive or high-sensitivity assays and obtain the results within 60 min.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>A rapid rule-out protocol at 0 h and 3 h is recommended if high-sensitivity cardiac troponin tests are available.</th>
</tr>
</thead>
</table>

Risk criteria mandating invasive strategy in NSTE-ACS

- Rise or fall in cardiac troponin compatible with MI
- Dynamic ST- or T-wave changes (symptomatic or silent)
- GRACE score >140

Eur Heart J. 2016;37(3):267-315
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Community dwelling older adults
A high burden of cardiovascular disease


First acute heart failure annual event rates (ARIC:2005–2013)

Prevalence of heart failure stages

ARIC older adults

Biomarkers as a surrogate for early fibrosis
Frequency of LV scar by LGE cardiac MRI by hs-cTnT category in clinically CVD free adults

- LGE was identified in 113 (6.3%)
- LGE pattern distribution were classified as ischemia in 38 (33.6%)

The STOP-HF randomized trial

Outcomes

Admission for major adverse cardiovascular event

Ledwidge M JAMA 2013;310:66-74
HIV associated Cardiovascular disease
A Role of Chronic Inflammation during Antiretroviral Therapy

Excess pathogen burden (HIV, CMV, gut microbes)

Mucosal damage (microbial translation)

Immunodeficiency
Lymphoid fibrosis
Hematopoietic stem-cell dysfunction
Loss of immunoregulation
Thymic dysfunction

Inflammation
Increase in endothelium adhesion
Increase in monocyte activation
Increase in T-cell activation
Dyslipidemia
Insulin resistance

Hypercoagulability (e.g., high D-dimer levels)

Endothelial dysfunction
Plaque formation
Acute thrombus

Figure: Schematic representation of the relationship between HIV and cardiovascular disease, highlighting the role of chronic inflammation during antiretroviral therapy.
HIV associated Cardiovascular disease
A Role of Chronic Inflammation during Antiretroviral Therapy

23/28 (82.1\%) HIV+ patients had LGE on CMR
HIV associated Cardiovascular disease
Prognosis: A role for soluble biomarkers

Secemsky et al. JACC Heart Fail. 2015;3:591-9
HIV associated Cardiovascular disease
Association with CVD: A role for soluble biomarkers

<table>
<thead>
<tr>
<th>Presence of plaque</th>
<th>Presence of noncalcified plaque</th>
<th>Presence of mixed plaque</th>
<th>Presence of calcified plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>hs-cTnT (ng/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.0 (3.0, 3.8)</td>
<td>3.2 (3.0, 5.0)</td>
<td>3.0 (3.0, 3.8)</td>
<td>3.5 (3.0, 5.1)</td>
</tr>
<tr>
<td>3.0 (3.0, 3.8)</td>
<td>3.2 (3.0, 5.0)</td>
<td>3.0 (3.0, 3.8)</td>
<td>3.5 (3.0, 5.1)</td>
</tr>
</tbody>
</table>

Fitch K et al. AIDS. 2016;30:2205-2214
HIV associated Cardiovascular disease
Biomarkers modifiable by treatment

Change in sST2 in placebo group vs. atorvastatin group

p=0.04

n=21
n=19

Sponsored by:
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Prevention of Events with Angiotensin Converting Enzyme (PEACE) trial
A role for a multi-marker strategy?

* Upper quartile of MR-proADM, MR-proANP and CT-proET-1

Pathogenesis of heart failure

Triggering myocardial injury → Compensatory mechanisms * → Cardiomyocyte hypertrophy

Deterioration of LV morphology and function → Clinical cardiac decompensation

Myocardial fibrosis → Cardiomyocyte death

Myocardial inflammation

Gonzalez A. J Am Coll Cardiol 2011;58:1833–43
“Malignant” Left Ventricular Hypertrophy
Cumulative risk of HFrEF and HFpEF by LVH-biomarker group

* Elevated hs-cTnT or NT-proBNP defined as upper tertile per decade of age

- No LVH, no biomarker elevated N=2206
- No LVH, ≥1 biomarker elevated N=2275
- LVH, no biomarker elevated N=153
- LVH, ≥1 biomarker elevated N=351

Peters M. et al. Submitted for publication
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Newer proteomic strategies
Targeted Proteomics

• The Proximity Extension Assay technology uses antibodies that recognize target proteins of interest labeled with short oligonucleotides

• The SOMAmer affinity assay uses DNA aptamers, which are short oligonucleotides that can bind their protein targets with high affinity
Proximity Extension Assay technology
Principle of multiplex SOMAmer affinity assay

Discovery protein-based risk score among patients with stable CHD

- 9-protein model from 1054 candidate proteins measured with aptamers
- 938 derivation patients and external 971 validation patients

AUC for refit Framingham 0.64 vs. 0.70 for 9-protein model
Future of Biomarkers

Conclusions

• Asymptomatic “at-risk” populations have potential to benefit from risk stratification and therapy guidance from protein based biomarkers.

• Combinations of biomarkers with or without other modalities, such as imaging, may offer greater specificity for targeting preventive therapies.

• New technologies offer biomarker investigators opportunities to understand new pathophysiologic mechanism and potentially improve risk-stratification/treatment algorithms with the measure of hundreds to thousands of proteins.