Biomarkers in Acute Cardiac Disease

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Multimarker Strategy in ACS

Myocyte Necrosis
Troponin

Inflammation
hs-CRP, CD40L

Hemodynamic Stress
BNP, NT-proBNP

HbA1c
Blood glucose

Accelerated Atherosclerosis

Vascular Damage

CrCl
Microalbuminuria

Ischemia Markers: Potential Candidates

- Ischemia Modified Albumin
- Natriuretic peptides
- Myeloperoxidase
- Matrix metalloproteinases
- Placental Growth Factor
- Whole blood choline
- Nourin-1
- Soluble CD40L
- D-Dimer
- CRP, IL-1, IL-6
- Free fatty acid
- Troponin (fragments)

- Pregnancy Associated Plasma Protein A (PAPP-A)
- Cell adhesion molecules
- Glutathione peroxidase 1
- Glycogen phosphorylase-BB
- Antiplatelet Factor 4/heparin antibodies
- Thrombus precursor protein
- Lipoprotein associated Phospholipase A2
- Ox-LDL/MDA-modified LDL
When troponin is increased think heart

Cardiac isoforms in blood

\[ \text{TnI} \quad \text{and} \quad \text{TnT} \]

=  

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<table>
<thead>
<tr>
<th>Table 1: Non-coronary conditions with troponin elevations</th>
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<tbody>
<tr>
<td>Severe congestive heart failure - acute and chronic</td>
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<tr>
<td>Aortic dissection, aortic valve disease or hypertrophic cardiomyopathy</td>
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<td>Cardiac contusion, ablation, pacing, cardioversion, or endomyocardial biopsy</td>
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<td>Inflammatory diseases, e.g., myocarditis, or myocardial extension of endo-/pericarditis</td>
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<td>Hypertensive crisis</td>
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<td>Tachy- or bradyarrhythmias</td>
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<td>Pulmonary embolism, severe pulmonary hypertension</td>
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<td>Hypothyroidism</td>
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<td>Apical ballooning syndrome</td>
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<tr>
<td>Chronic or acute renal dysfunction</td>
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<tr>
<td>Acute neurological disease, including stroke, or subarachnoid haemorrhage</td>
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<td>Infiltrative diseases, e.g., amyloidosis, haemochromatosis, sarcoidosis, scleroderma</td>
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<tr>
<td>Drug toxicity, e.g., adriamycin, 5-fluorouracil, herceptin, snake venoms</td>
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<td>Burns, if affecting &gt; 30% of body surface area</td>
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<td>Rhabdomyolysis</td>
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<td>Critically ill patients, especially with respiratory failure, or sepsis</td>
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Time course of the appearance of various markers in the blood after acute myocardial infarction (AMI)

Potentially outdated markers

- **CK-MB. Creatine kinase-MB**
  could be used to define infarct timing or after PCI.

- **Myoglobin and CK isoforms**
  have been used with the hope of shortening the time to a more definitive diagnosis in patients with chest pain.
  They have been relied on particularly for their negative predictive value.
  Myoglobin may identify additional patients at risk.
Sensitivity of cardiac troponin (cTn)I compared with myoglobin and creatine kinase (CK)-MB for the detection of myocardial injury

Cardiac events after emergency department discharge based on levels of cardiac troponin T

TIMI IIIB: Troponin I Levels Predict Mortality in UA/NSTEMI

Mortality at 42 Days (% of Patients)

Risk Ratio | Cardiac Troponin I (ng/ml)
--- | ---
1.0 | 0 to <0.4
1.8 | 0.4 to <1.0
3.5 | 1.0 to <2.0
3.9 | 2.0 to <5.0
6.2 | 5.0 to <9.0
7.8 | >9.0

831 | 174 | 148 | 134 | 50 | 67

Abnormal troponin levels are associated with an increased risk of death after adjustment for age and ST segment $\Delta$. The risk increases with progressively higher levels of troponin.

About 15% of patients with initially normal Tn T levels will show elevated values in subsequent samples, regardless of time since onset of symptoms.

TRIM, Lüscher et al, Circulation 1997

N= 510, median time to B sampling 12 h
Troponins in Unstable Angina: Metaanalysis

Hamm, 1992
Wu, 1995
Antman, 1996
Cin, 1996
Galvani, 1997
Solymoss, 1997
Luscher, 1997
Benamer, 1998
Olatidoye, 1998
Rebuzzi, 1998
Brisics, 1998
Hamm, 1999

Total

Low Risk
High Risk

9.39 (6.46, 1367)

Ottani et al. Am Heart J, 2000
Troponins and ECG

AMI free survival (%)  

n = 870 Pts.

Risk stratification in acute coronary syndromes: role of troponin

Abnormal troponin levels are associated with an increased risk of death after adjustment for age and ST segment Δ. The risk increases with progressively higher levels of troponin.

TIMI IIIIB, Antman et al, NEJM 1996
Emerging markers
C-reactive protein is an acute-phase reactant protein made in the liver.

Its most proximate stimulator is interleukin 6. Values above 10 mg/l are likely caused by acute disease.

Values >3 mg/l are associated with higher risk. Values <1 mg/l are associated with low risk. Values and 3 mg/l are considered intermediate.
Synergistic prognostic value of C-reactive protein (CRP) and low-density lipoprotein (LDL) in PROVE-IT study

Risk Stratification With CRP and Troponin T

Chi Square: $P=0.0007$

14-Day Mortality (%)

- RctTnT Neg AND CRP < 1.55
  - N=277
  - 0.4%

- RctTnT(early +) OR CRP ≥ 1.55
  - N=129
  - 4.7%

- RctTnT(early +) AND CRP ≥ 1.55
  - N=22
  - 9.1%

Predictive Value of Troponin T and hs-CRP for Mortality from ACS in FRISC Substudy

**CRP**

- CRP > 10 mg/l (n=309)
  - Cumulative Probability of Death (%)
  - Months
  - $P = .001$

- CRP 2-10 mg/l (n=294)
  - $P = .29$

- CRP < 2 mg/l (n=314)

**Troponin**

- Troponin T ≥ 0.60 µg/l (n=377)
  - Cumulative Probability of Death (%)
  - Months
  - $P = .007$

- Troponin T 0.60-0.59 µg/l (n=367)
  - $P = .001$

- Troponin T < 0.60 µg/l (n=173)

CRP, the Metabolic Syndrome, and Future CV Events (N=14,719)

CRP, C-reactive protein; CV, cardiovascular.

Relative Risk of Cardiovascular Events According to Several Biochemical Markers

Relative Risk of Future CV Events

Lipoprotein(a)
Homocysteine
TC
LDLC
Apolipoprotein B
TC:HDLC
hs-CRP
hs-CRP + TC:HDLC

CV, cardiovascular; TC, total cholesterol; LDLC, low-density lipoprotein cholesterol; HDL-C, high-density lipo-protein cholesterol; CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; TC, total cholesterol.
B-type natriuretic peptide

- Is a 32-amino-acid counterregulatory peptide released in response to cardiac stretch. It is synthesized as a pro peptide and then cleaved to the active moiety by a protease called corin.

- There is an immunoassay for NT-proBNP which detects the 76 amino acid carrier protein, which with the active 32 amino acid compound is called proBNP.
Use of the marker the BNP and/or NT-proBNP

- Detection of congestive heart failure in patients in whom one is unsure of the cause of dyspnea.

- For BNP, values <100 ng/l make heart failure unlikely with a negative predictive value of 90%.

- For NT-proBNP, levels >450 ng/l for patients <50 years of age and >900 ng/l for patients 50 years of age are sensitive and specific for heart failure.

- Patients with right-sided heart failure, sepsis, volume overload, stroke, and left ventricular hypertrophy also have higher values.
In ACS patients, BNP and NT-proBNP elevations

- **TACTICS-TIMI-18 study:**
  - Women with elevated BNP or CRP values seemed to benefit from early PCI even if they had normal cTn values.
  - Higher BNP values identify patients with ACS who are at higher risk.
  - Elevated values also predict an adverse outcome in stroke.
B-type Natriuretic Peptide (BNP) and Mortality in ACS Patients

**P < .001**

Days After Randomization

Mortality (%)

Quartile 1 (n=631)
Quartile 2 (n=632)
Quartile 3 (n=632)
Quartile 4 (n=630)

BNP and Risk of Death in ACS

- **ST ↑ MI**: Q1 = 5.5%, Q2 = 4.5%, Q3 = 3.5%, Q4 = 2.5%
  - \( P = .02 \)

- **Non-ST ↑ MI**: Q1 = 10%, Q2 = 9%, Q3 = 8%, Q4 = 7%
  - \( P < .0001 \)

- **Unstable Angina**: Q1 = 5%, Q2 = 4%, Q3 = 3%, Q4 = 2%
  - \( P = .001 \)

Mortality at 10 mo (%)

-de Lemos JA, et al. *N Engl J Med*. 2001;345:1014-1021. (Copyright © 2001 Massachusetts Medical Society. All rights reserved)
Figure 2. Mortality at 1-year follow-up among strata of patients, according to deciles of NT-proBNP levels. Number of deaths in each decile is given at the bottom of the bars.
Multimarker Approach: Troponin I, CRP, and BNP to Predict 30-Day Mortality in ACS

OPUS-TIMI 16
- 0: 1
- 1: 1.8
- 2: 3.5
- 3: 6
- $P = 0.014$

TACTICS-TIMI 18
- 0: 1
- 1: 2.1
- 2: 5.7
- 3: 13
- $P = 0.001$

Developing markers
**sCD40 ligand**

- Is a signaling protein that reflects both inflammatory and platelet interactions with the plaque.

- Increased sCD40 ligand has been shown in patients with ACS. Moreover, articles have suggested that it has prognostic significance in these patients.
Inflammation, ACS, and CD-40L

Clinical Investigation Reports
Soluble CD40L
Risk Prediction After Acute Coronary Syndromes

*P<.01 compared to first quartile
†P<.03 compared to first quartile

<table>
<thead>
<tr>
<th>Hazard Ratios (HR)</th>
<th>Death</th>
<th>MI</th>
<th>DIMI</th>
<th>CHF</th>
<th>DIMI CHF</th>
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<td>Q1</td>
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<td>Q2</td>
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Soluble CD-40L in ACS

Association between soluble CD40 ligand levels and the rate of cardiac events (death or nonfatal myocardial infarction) at 24 hours, 72 hours, 30 days, and 6 months among 544 patients receiving placebo.

Myeloperoxidase

- A degranulation product, comes from white cells. Elevations occur even when values are obtained from the coronary effluent draining a nonculprit coronary vessel.
- Used to prognosticate in patients presenting to the emergency department with chest pain.
- **Ischemia-modified albumin**
  - Ischemia-modified albumin has been touted as a way to detect ischemia even if necrosis is not present.
  - The theory is that the metal binding site on the amino terminus of albumin is damaged by ischemia. It is marketed for its "negative predictive value.

- **Pregnancy-associated plasma protein-A**
  - is thought to be released when neovascularization occurs and thus may be a marker of incipient plaque rupture
  - identify patients at risk for subsequent events
- **Choline**
  - Choline is a biomarker that is released when phospholipids are cleaved, which suggests that perhaps it could be a marker of ischemia and/or necrosis.
  - Several studies suggest that the marker might improve prognostication in patients with ACS.

- **Placental growth factor**
  - Placental growth factor is a member of the vascular endothelial growth factor family that has been touted by some but not others to be prognostic in patients with ACS.
- **Cystatin C**
  - a low-molecular-weight basic protein (13 kDa) that is freely filtered and metabolized after tubular reabsorption.
  - It seems that it is less influenced by age, gender, and muscle mass than serum creatinine.
  - Some studies suggest that it is useful for prognostication in heart failure and ACS.

- **Fatty acid binding protein**
  - Fatty acid binding protein is rapidly released after infarction and thus has been touted as an alternative to myoglobin. It has been reported to perform better, but it still lacks cardiac specificity.
## Conclusion

- The present and future for cardiac biomarkers is exciting.

- In the near future, many of these biomarkers will provide important new insights into pathophysiology and aid in the diagnosis and management of cardiovascular patients.

- We are likely to be able to multiplex assays, personalizing biomarker strategies and providing large numbers of values quickly and cheaply.

- However, before we implement such a strategy, we must overcome poorly done yet enthusiastic limited reports.

- In the interim, to provide optimal clinical care, clinicians need to learn more about the biomarkers that they rely on in current clinical practice, i.e., cTn, natriuretic peptides, and CRP, both analytically and clinically.
Thank you