B-type Natriuretic Peptide in the Prognosis and Management of Acute Coronary Syndromes

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Figure 2. Acute myocardial infarction (AMI) with disruption of cellular elements and the release of classic markers of myocardial necrosis used in the diagnosis of acute coronary syndromes. AMPK, adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; Ca, calcium; CK-MB, creatine kinase-myocardial band; LAMP2, lysosomal-associated membrane protein 2; MI, myocardial infarction; SERCA, Sarco/endoplasmic reticulum Ca^{2+}-ATPase.
Contemporary Prospective Studies Using Multiple Markers in Suspected ACS

ASPECT Study, N=3582, positive (↓major adverse cardiac events)

RATPAC Trial, N=2263, positive (↑successful discharge home, ↓LOS)


Case 1

58 year old male

Sudden onset severe substernal chest pain walking out of the house to his car on the way to work

No prior history

Wife calls 911

30 minutes from onset of pain to ECG and blood draw
Case 1 (cont)

- Acute inferior ST segment elevation myocardial infarction
- "Rainbow of tubes" drawn in field
- Taken directly to catheterization laboratory
Urgent PCI for ACS
Case 1 (cont)

- Troponin I: 0.05 ng/ml
- CK-MB: 4 ng/ml
- Myoglobin: 80 ng/ml
- BNP: 180 pg/ml

<table>
<thead>
<tr>
<th>Analyte</th>
<th>95th Percentile</th>
<th>97.5th Percentile</th>
<th>99th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin I</td>
<td>&lt; 0.05 ng/mL</td>
<td>&lt; 0.05 ng/mL</td>
<td>&lt; 0.05 ng/mL</td>
</tr>
</tbody>
</table>

Figure 3 (A). Left anterior oblique projection showing distal right coronary artery (RCA) with atherosclerotic plaque (arrow). (B) Left anterior oblique projection showing total occlusion of distal RCA. (C) Left anterior oblique projection showing TIMI-3 flow in RCA post stent placement.
Case 1 (cont)

Admitted to CCU after PCI

Elevated BNP major signal of complicated early course

Held and not allowed early discharge

Day 3, has syncope and monitor reveals sustained ventricular tachycardia requiring cardioversion

Day 4, has ICD implanted
Probability of Death Through 30 Days Stratified by B-Type Natriuretic Peptide (BNP)

- **BNP >80 pg/ml**
  - 30 Days: 15.2% vs. 1.3%, *P* < 0.0001

- **BNP ≤80 pg/ml**
  - 48 Hours: 8.7% vs. 1.3%, *P* = 0.001

Serum BNP, hs-C-reactive protein, procollagen to assess the risk of ventricular tachycardia in ICD recipients after myocardial infarction

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Table 2  Significant adjusted relative risks for ventricular tachycardia occurrence according to baseline clinical characteristics and to serum markers levels

<table>
<thead>
<tr>
<th></th>
<th>OR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP &gt; median (64 ng/L)</td>
<td>3.75 (1.46–9.67)</td>
<td>0.014</td>
</tr>
<tr>
<td>hs-C-reactive protein &gt;</td>
<td>3.20 (1.26–8.10)</td>
<td>0.006</td>
</tr>
<tr>
<td>median (0.32 mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PINP &gt; median (36.5 μg/L)</td>
<td>3.71 (1.40–9.88)</td>
<td>0.009</td>
</tr>
<tr>
<td>PIIINP &gt; median (4.3 μg/L)</td>
<td>0.21 (0.08–0.59)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Figure 1  Ventricular tachycardia episodes in the 121 patients included in the study.
Multiple Biomarkers at Admission Significantly Improve the Prediction of Mortality in Patients Undergoing Primary Percutaneous Coronary Intervention for Acute ST-Segment Elevation Myocardial Infarction

Peter Damman, MD, Marcel A. M. Beijk, MD, Wichert J. Kuijt, MD, Niels J. W. Verouden, MD, Nan van Geloven, MSc, José P. S. Henriques, MD, PhD, Jan Baan, MD, PhD, Marije M. Vis, MD, Martijn Meuwissen, MD, PhD, Jan P. van Straalen, Johan Fischer, PhD, Karel T. Koch, MD, PhD, Jan J. Piek, MD, PhD, Jan G. P. Tijssen, PhD, Robbert J. de Winter, MD, PhD

Amsterdam, the Netherlands

Objectives
We investigated whether multiple biomarkers improve prognostication in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention.

Background
Few data exist on the prognostic value of combined biomarkers.
### Discrimination

<table>
<thead>
<tr>
<th>Risk Factors and Biomarkers</th>
<th>Harrell’s C Index</th>
<th>Net Reclassification Improvement</th>
<th>p Value</th>
<th>Integrated Discrimination Improvement</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established risk factors</td>
<td>0.77</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Established risk factors plus troponin T</td>
<td>0.78</td>
<td>0.388</td>
<td>&lt;0.01</td>
<td>0.0001</td>
<td>0.96</td>
</tr>
<tr>
<td>Established risk factors plus glucose</td>
<td>0.79</td>
<td>0.484</td>
<td>&lt;0.001</td>
<td>0.0057</td>
<td>0.25</td>
</tr>
<tr>
<td>Established risk factors plus NT-proBNP</td>
<td>0.78</td>
<td>0.554</td>
<td>&lt;0.001</td>
<td>0.0111</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Established risk factors plus eGFR</td>
<td>0.78</td>
<td>0.345</td>
<td>&lt;0.01</td>
<td>0.0193</td>
<td>0.04</td>
</tr>
<tr>
<td>Established risk factors plus CRP</td>
<td>0.77</td>
<td>0.375</td>
<td>&lt;0.01</td>
<td>0.0047</td>
<td>0.09</td>
</tr>
<tr>
<td>Established risk factors plus glucose, NT-proBNP, eGFR</td>
<td>0.81</td>
<td>0.494</td>
<td>&lt;0.001</td>
<td>0.0295</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The NRI was defined as \((\text{P}_{\text{new}}^{\text{predicted among deceased}} + \text{P}_{\text{new}}^{\text{predicted among alive}}) - (\text{P}_{\text{old}}^{\text{predicted among deceased}} + \text{P}_{\text{old}}^{\text{predicted among alive}})\), where \(p\) = proportion of patients. The IDI was defined as \((\sum_{\text{deaths}} (\text{P}_{\text{new}}(l) - \text{P}_{\text{old}}(l))/n(\text{deceased})) - (\sum_{\text{alive}} (\text{P}_{\text{new}}(l) - \text{P}_{\text{old}}(l))/n(\text{alive}))\), where \(p\) = predicted probability of mortality.

### Biomarker Score

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Add to Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/l)</td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>0</td>
</tr>
<tr>
<td>8-9</td>
<td>+2</td>
</tr>
<tr>
<td>≥10</td>
<td>+3</td>
</tr>
<tr>
<td>NT-proBNP (ng/l)</td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>0</td>
</tr>
<tr>
<td>150-599</td>
<td>+2</td>
</tr>
<tr>
<td>≥600</td>
<td>+3</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>0</td>
</tr>
<tr>
<td>60-89</td>
<td>+2</td>
</tr>
<tr>
<td>&lt;60</td>
<td>+4</td>
</tr>
</tbody>
</table>

**Total score**

<table>
<thead>
<tr>
<th>Total score</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4</td>
<td>Low risk</td>
</tr>
<tr>
<td>5-6</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>&gt;6</td>
<td>High risk</td>
</tr>
</tbody>
</table>

![Cumulative mortality graph](image)

- **High-risk group**
  - No. at risk: 178
  - Time since index procedure (years): 34
  - Cumulative mortality: 42.0%
- **Intermediate-risk group**
  - No. at risk: 196
  - Time since index procedure (years): 51
  - Cumulative mortality: 17.4%
- **Low-risk group**
  - No. at risk: 660
  - Time since index procedure (years): 220
  - Cumulative mortality: 5.8%

P < 0.001
Case 2

68 year old male

Hx CAD prior PCI

Collapse at home in the evening

Daughter calls 911

Police do CPR for 15 minutes
### Case 2 (cont)

<table>
<thead>
<tr>
<th>Test</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
<th>Value 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin I</td>
<td>0.05</td>
<td>1.2</td>
<td>3.4</td>
<td>2.2</td>
</tr>
<tr>
<td>CK-MB</td>
<td>3.8</td>
<td>3.0</td>
<td>7.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>180</td>
<td>230</td>
<td>341</td>
<td>240</td>
</tr>
<tr>
<td>BNP</td>
<td>684</td>
<td>1527</td>
<td>3644</td>
<td>4589</td>
</tr>
</tbody>
</table>

#### Measurable Ranges

- **Troponin I:** 0.05 - 30 ng/mL
- **CK-MB:** 1.0 - 80 ng/mL
- **Myoglobin:** 5 - 500 ng/mL
- **BNP:** 5 - 5,000 pg/mL
Admitted to the CCU

Remains intubated, initially stable

Systemically cooled for anoxic encephalopathy

BNP predicts very high risk of death, doctor counsels family appropriately

Day 2 develops cardiogenic shock

Balloon pump inserted at bedside

Expires on day 3
Sudden cardiac death was more frequent in patients with raised BNP (RR 3.68; 95% CI 1.90, 7.14)
BNP and Troponin
In the Prediction of In-hospital Mortality

Figure 3. The interaction among troponin, BNP, and in-hospital mortality. BNP, B-type natriuretic peptide.
Markedly Elevated BNP in ACS and Mortality

BNP (pg/ml) level and mortality, p=0.004 for trend.

Case 3

- 38 year old male
- No prior history
- 4 hours of burning chest pain
- Father drives him to ED
- Admitted to chest pain unit
Case 3 (cont)

- Troponin I  0.05 ng/ml
- CK-MB  3 ng/ml
- Myoglobin  41 ng/ml
- BNP  132 pg/ml

<table>
<thead>
<tr>
<th>Time</th>
<th>Cardiac Troponin I Sensitivity</th>
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<tbody>
<tr>
<td># of samples</td>
<td>0-6 hrs.</td>
</tr>
<tr>
<td></td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>65.0%</td>
</tr>
</tbody>
</table>
Case 3 (cont)

- Elevated BNP triggers prolonged observation and chest-x-ray
- While out of the ED and in radiology department
- Becomes unresponsive
- BP 70/30 and develops cardiogenic shock
- Rushed to the cath lab
- Plavix held until first diagnostic images
- Emergency angiography and PCI of a proximal LAD lesion
Elevated BNP in ACS

- Large zones of ischemia
  - Left main lesions
  - Severe 3-vessel disease
- Large infarctions
- Pre-existing LV impairment
  - Systolic
  - Diastolic
- Renal dysfunction

Class IIb: Measurement of B-type natriuretic peptide (BNP) or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS. *(Level of Evidence: B)*
NACB Guidelines

- **Class IIA recommendation for use of biomarkers in risk stratification for ACS**
  - Measurement of BNP or NT pro BNP may be useful in addition to a cardiac troponin for risk assessment in patients with a clinical syndrome consistent with ACS.

- **Class IIB recommendation for use of biomarkers in risk stratification for ACS**
  - A multimarker strategy that includes measurement of 2 or more pathobiologically diverse biomarkers in addition to a cardiac troponin may aid in enhancing risk stratification in patients with a clinical syndrome consistent with ACS.
32 prospective studies with > 100 subjects with ACS measuring BNP or NT-proBNP... all showed that the baseline natriuretic peptide level was an independent predictor for the development of heart failure, rehospitalization, or death.
Evidence-based algorithm for the measurement and clinical use of **Natriuretic Peptides** in NSTE-ACS

**Chest Pain or Shortness of Breath: Acute Coronary Syndromes (ACS) Considered**

- **12-Lead Electrocardiogram**
  - Normal or No Ischemic Changes
  - ST-Segment Depression Ischemic T-Wave Changes
  - ST-Segment Elevation

- **Troponin, CK-MB (-), AMI Ruled Out**
- **Troponin, CK-MB (+), AMI Confirmed**

- **No ACS**
  - Computed tomographic angiography or Stress imaging
  - Outpatient risk factor modification

- **Moderate Risk**
  - Usual unstable angina/non-ST-elevation AMI/ST-elevation AMI care
  - Expect favorable outcome

- **High Risk**
  - Higher TIMI/GRACE risk score
  - Proximal LAD culprit
  - Plaque rupture
  - Older
  - Preexisting LV dysfunction
  - Late HF or death
  - Chronic kidney disease
  - \( BNP \) in 6-12 wk, 6-12 mo

- **Very High Risk**
  - Features as listed for High Risk
  - Left main or 3-vessel disease
  - Large ischemic zone
  - Anticipate complicated PCI
  - No reflow
  - Shock
  - New LV dysfunction
  - Late HF or death
  - In-hospital death
  - \( BNP \) in 6-12 wk, 6-12 mo

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Adapted with permission.
Cumulative Incidence of Subsequent Death or New or Worsening CHF

B-Type Natriuretic Peptide Levels
Baseline-Month 4

- **High-High**
- **Low-High**
- **High-Low**
- **Low-Low**

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>120</th>
<th>240</th>
<th>360</th>
<th>480</th>
<th>600</th>
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<tbody>
<tr>
<td>High-High</td>
<td>137</td>
<td>128</td>
<td>121</td>
<td>91</td>
<td>59</td>
</tr>
<tr>
<td>Low-High</td>
<td>77</td>
<td>77</td>
<td>70</td>
<td>65</td>
<td>43</td>
</tr>
<tr>
<td>High-Low</td>
<td>330</td>
<td>322</td>
<td>292</td>
<td>225</td>
<td>161</td>
</tr>
<tr>
<td>Low-Low</td>
<td>2929</td>
<td>2877</td>
<td>2777</td>
<td>2539</td>
<td>2232</td>
</tr>
</tbody>
</table>

Figure 8. Meta-analysis of trials comparing BNP- or NT-proBNP-guided therapy versus usual care in patients with heart failure. Shown is a forest plot for all-cause mortality. BATTLESCARRED, NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PRIMA, Can Pro-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?; STARBRITE, Pilot Trial of BNP-Guided Therapy in Patients With Advanced Heart Failure; STARS-BNP, Systolic Heart Failure Treatment Supported by BNP; TIME-CHF, Trial of Intensified (BNP-guided) versus standard (symptom-guided) Medical therapy in Elderly patients with Congestive Heart Failure. Adapted with permission from Felker GM et al.43
Integration of the Clinical Laboratory in Cardiovascular Medicine

Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA

Figure 1. Four major domains of activity in the use of the clinical laboratory.

- **Screening**: Screen population to identify occult disease
- **Diagnosis**: Aid in diagnosis
- **Prognosis**: Aid in predicting risk of an adverse event or anticipate course of disease
- **Management**: Monitor progression of disease and alter clinical management