Incremental Value of Copeptin for Rapid Rule out of Acute Myocardial Infarction


University Hospital Basel
Presenter Disclosure Information

Research grants

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University Hospital Basel, Switzerland
Brandenburg Ministry of Economics, Germany
European Regional Development Fund
Brahms, Roche, Abbott, Siemens
Background

- **Chest pain** ~ 10% of ED consultations

- **Current guidelines:**
  1. History (ACC/AHA 2007)
  2. ECG
  3. Cardiac troponins

- Troponin **retesting after 6 hours** recommended to rule out AMI due to delayed elevation

- **Early rule out** of AMI is an **unmet clinical need**
Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponin T

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>All patients (n = 415)</th>
<th></th>
<th>Patients admitted within 4 h from symptom onset (n = 156)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>c-Statistic</td>
<td>95% CI</td>
<td>P-value</td>
<td>c-Statistic</td>
</tr>
<tr>
<td>Initial cTnT (μg/L)</td>
<td>0.88</td>
<td>0.83–0.92</td>
<td>&lt;0.001</td>
<td>0.78</td>
</tr>
<tr>
<td>H-FABP (ng/mL)</td>
<td>0.74</td>
<td>0.69–0.80</td>
<td>&lt;0.001</td>
<td>0.77</td>
</tr>
<tr>
<td>GP-BB (ng/mL)</td>
<td>0.61</td>
<td>0.55–0.67</td>
<td>0.001</td>
<td>0.63</td>
</tr>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>0.68</td>
<td>0.62–0.74</td>
<td>&lt;0.001</td>
<td>0.57</td>
</tr>
<tr>
<td>D-dimer (μg/mL)</td>
<td>0.62</td>
<td>0.55–0.68</td>
<td>&lt;0.001</td>
<td>0.64</td>
</tr>
<tr>
<td>hsCRP (ng/L)</td>
<td>0.58</td>
<td>0.51–0.64</td>
<td>0.018</td>
<td>0.56</td>
</tr>
<tr>
<td>MPO (ng/mL)</td>
<td>0.55</td>
<td>0.49–0.61</td>
<td>0.118</td>
<td>0.52</td>
</tr>
<tr>
<td>MMP-9 (ng/mL)</td>
<td>0.56</td>
<td>0.50–0.62</td>
<td>0.060</td>
<td>0.57</td>
</tr>
<tr>
<td>PAPP-A (ng/mL)</td>
<td>0.56</td>
<td>0.50–0.62</td>
<td>0.072</td>
<td>0.60</td>
</tr>
<tr>
<td>sCD40L (pg/mL)</td>
<td>0.48</td>
<td>0.42–0.54</td>
<td>0.554</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Novel markers and strategies needed to **rule out** AMI **already at presentation**

McCann et Al., EHJ 2008;29:2843-50
Hypothesis

Combination of

Cardiac necrosis + Endogenous Stress
Troponin Copeptin

rapid and reliable rule out of AMI
• directly at initial presentation
• without the need to retest after 6 hours
Endocrine Stress System

1) Cortisol

2) Vasopressin
Copeptin

- C-terminal part of the vasopressin prohormone

- in healthy individuals: median 3.7 pmol/l

Struck et Al., Peptides 2005;26(12):2500-4
Morgenthaler et Al., Clin Chem 2006;52:112-9
Copeptin in AMI patients

LAMP – Study

Khan et Al., Circulation 2007;115:2103-10
Methods

- **Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE-Study)**

- **Design**
  - Ongoing prospective observational multicenter study

- **Inclusion Criteria**
  - Chest pain or other symptoms suggestive of AMI with an onset of symptoms or peak within the last 12 hours

- **Adjudicated Final Diagnosis:**
  - Adjudicated by two independent cardiologists
  - Review of all available medical records and test results pertaining to the patient
## Baseline Characteristics (n=756)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=756)</th>
<th>Acute myocardial infarction</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=131)</td>
<td>(n=625)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>62 ± 16</td>
<td>69 ± 14</td>
<td>61 ± 16</td>
</tr>
<tr>
<td>Male gender – no. (%)</td>
<td>496 (66)</td>
<td>93 (71)</td>
<td>403 (65)</td>
</tr>
<tr>
<td>Risk factors – no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>458 (61)</td>
<td>92 (70)</td>
<td>366 (59)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>327 (43)</td>
<td>66 (50)</td>
<td>261 (42)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>123 (16)</td>
<td>27 (21)</td>
<td>96 (15)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>186 (25)</td>
<td>38 (29)</td>
<td>148 (24)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>249 (33)</td>
<td>38 (29)</td>
<td>211 (34)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>264 (35)</td>
<td>46 (35)</td>
<td>218 (35)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>193 (26)</td>
<td>35 (27)</td>
<td>158 (25)</td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>213 (28)</td>
<td>31 (24)</td>
<td>182 (29)</td>
</tr>
</tbody>
</table>
Adjudicated Final Diagnoses

- Chest pain of unknown origin (9%)
- Myocardial Infarction (17%)
  - -> STEMI (37%)
  - -> NSTEMI (63%)
- Unstable Angina (16%)
- Non-cardiac chest pain (46%)
- Non-coronary cardiac chest pain (13%)
Copeptin at Presentation (t₀)

AMI
Unstable Angina
Cardiac but not CAD
Non-cardiac
unknown

Copeptin (pmol/l)

p<0.001
Copeptin at Presentation \((t_0)\)

- **Copeptin at admission (pmol/l)**
  - 200
  - 150
  - 100
  - 50
  - 0

- **Unstable Angina**
- **NSTEMI**
- **STEMI**

- **p < 0.001**

- **AMI**
- **Non-cardiac**
- **Cardiac but not CAD**
- **Unknown**

- **AMI**
- **Unstable Angina**
- **Cardiac but not CAD**
- **Non-cardiac**
- **Unknown**

- **Copeptin (pmol/l)**
  - **STEMI**
  - **NSTEMI**
  - **Unstable Angina**

- **p < 0.001**
Copeptin and Troponin (t₀) in AMI patients vs. Time since onset of symptoms

- **Copeptin (pmol/l)**
  - >10 hours
  - 0 - 4 hours
  - 5 - 10 hours

- **Troponin T (μg/l)**
  - >10 hours
  - 0 - 4 hours
  - 5 - 10 hours

**Time since onset of symptoms**
- 0-4 hours
- 5-10 hours
- >10 hours
Diagnostic Performance of the Combination Copeptin/Troponin T at presentation ($t_0$)

AUC 0.96 for Combination
### Diagnostic Performance of the Combination Copeptin/Troponin (t₀)

<table>
<thead>
<tr>
<th>Copeptin cutoff level</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 pmol/l</td>
<td>98.5</td>
<td>63.7</td>
<td>36.2</td>
<td>99.5</td>
</tr>
<tr>
<td>14 pmol/l</td>
<td>97.7</td>
<td>76.3</td>
<td>46.4</td>
<td>99.4</td>
</tr>
<tr>
<td>18 pmol/l</td>
<td>97.0</td>
<td>81.6</td>
<td>52.5</td>
<td>99.2</td>
</tr>
<tr>
<td>24 pmol/l</td>
<td>96.2</td>
<td>85.3</td>
<td>57.8</td>
<td>99.1</td>
</tr>
</tbody>
</table>

756 Patients

- 477 = 63% (TropT and Copeptin negative)
- 279 = 37% (TropT and/or Copeptin positive)
Limitations

• 131 AMI patients is a small number to definitively support a rule out claim, confirmation is needed

• Long-term follow-up information will be valuable

• Interventional studies are needed to exactly quantify the benefits regarding allocation of resources and treatment costs
Conclusions

1. Copeptin significantly improves the early diagnosis of AMI (AUC for combination with Troponin T 0.96)

2. The combination of Copeptin and Troponin T allows a rule out of AMI at presentation with a sensitivity of 97.7% and a NPV of 99.4%

3. The use of copeptin in conjunction with Troponin T, ECG and clinical findings may obviate the need for prolonged stay in the ED and troponin retesting after 6 to 8 hours in two-thirds of patients. This change in clinical practice might result in significant medical and economic benefits