Accurate and Rapid Diagnosis of Myocardial Infarction Using a High-Sensitivity Troponin I 1-Hour Algorithm

Johannes Tobias Neumann1, Nils Arne Sörensen1, Tjark Schwemer1, Francisco Ojeda1, Rafael Bourry1, Vanessa Sciacca1, Sarina Schäfer1,2, Christoph Waldeyer1, Christoph Sinning1, Thomas Renné3, Martin Than5, Will Parsonage4, Karin Wildi6, Nataliya Makarova1,2, Renate B. Schnabel1,2, Ulf Landmesser7, Christian Mueller6, Louise Cullen4, Jaimi Greenslade4, Tanja Zeller1,2, Stefan Blankenberg1,2, Mahir Karakas1,2, Dirk Westermann1,2

1 Department of General and Interventional Cardiology, University Heart Center Hamburg Eppendorf, Hamburg, Germany
2 German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany
3 Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
4 Royal Brisbane and Women's Hospital, Department of Emergency Medicine, Brisbane 4006, Australia
5 Christchurch Hospital, Christchurch, New Zealand
6 Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, Switzerland
7 Department of Cardiology, Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany
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Dirk Westermann:

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Background

There is clinical need to rapidly and safely rule-in or rule-out acute myocardial infarction (AMI) in patients with acute chest pain in order to

1. initiate fast evidence based treatment for patients with AMI

2. limit overuse of scarce medical resources in the emergency room (ER) discharging patients without acute cardiac conditions.

Guidelines recommend measuring high sensitivity assayed troponins directly after admission and after 3 hours detecting elevated levels based on the 99th percentile of the specific assays together with an increase/decrease.

Recent studies (ADAPT (2-hour) and APACE (1-hour) cohort) challenge current guidelines with intervals shorter than 3 hours.

1 Hamm et al. EHJ 2011 and 2 Thygesen et al. EHJ 2012; 3 Than et al. JACC 2012; 4 Reichlin et al. CMAJ 2015
Aim of the study

To investigate the application of high sensitivity assayed troponin I (TnI) for

a) a rapid 1-hour rule-out and rule-in compared to a 3-hours approach

b) a lower and more sensitive cut-off value compared to the 99th percentile

in the Biomarkers in Acute Cardiovascular Care (BACC) cohort investigating 1,045 patients with acute chest pain.
Study design

BACC (n = 1,045) patients with acute chest pain suggestive of AMI:

Clinical routine troponin assay and clinical treatment based on ESC guidelines\(^1\):

0 hour hsTnT 3 hours hsTnT

+ clinical judgement, imaging and ECG to establish final diagnosis during the complete hospital stay (NSTEMI vs. no AMI)

(as recommended by ESC guidelines\(^1\))

hsTnT: troponin T assay (Elecsys® troponin T high sensitive, Roche Diagnostics)

1 Hamm et al. EHJ 2011
BACC (n = 1,045) patients with acute chest pain suggestive of AMI:

Clinical routine troponin assay and clinical treatment based on ESC guidelines¹:

hsTnT: troponin T assay (Elecsys® troponin T high sensitive, Roche Diagnostics)

hsTnl: troponin I assay (STAT high sensitive Troponin I, ARCHITECT i2000SR, Abbott Diagnostics, USA)

¹ Hamm et al. EHJ 2011
Study design

BACC (n = 1.045) patients with acute chest pain suggestive of AMI:

Clinical routine troponin assay and clinical treatment based on ESC guidelines¹:

- Calculate best performing cut-off and apply it
- Validate results in other cohorts
- Applicate cut-off in general population

+ clinical judgement, imaging and ECG to establish final diagnosis during the complete hospital stay

(NSTEMI vs. no AMI)

(as recommended by ESC guidelines¹)

+ without adding additional information

1 Hamm et al. EHJ 2011
Baseline characteristics are described by quartiles for continuous variables and by absolute and relative frequencies for categorical variables.

For the diagnostic algorithms considered negative and positive predictive values were computed (together with 95% confidence intervals).

Equality of predictive values was tested\(^1\).

1 Kosinski et al. Stat Med 2013
Baseline data

<table>
<thead>
<tr>
<th></th>
<th>All (N=1,045)</th>
<th>NSTEMI (N=184)</th>
<th>Non-AMI (N=793)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.0 (52.0, 75.0)</td>
<td>70.0 (60.4, 77.0)</td>
<td>64.0 (50.7, 74.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>678 (64.9)</td>
<td>124 (67.4)</td>
<td>505 (63.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0 (23.5, 29.4)</td>
<td>26.2 (23.7, 29.7)</td>
<td>26.0 (23.5, 29.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>731 (70.0)</td>
<td>147 (79.9)</td>
<td>541 (68.2)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Hyperlipoproteinemia (%)</td>
<td>459 (43.9)</td>
<td>103 (56.0)</td>
<td>327 (41.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>150 (14.5)</td>
<td>39 (21.3)</td>
<td>102 (12.9)</td>
<td>0.0051</td>
</tr>
<tr>
<td>Former smoker (%)</td>
<td>334 (32.0)</td>
<td>59 (32.1)</td>
<td>259 (32.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>241 (23.1)</td>
<td>41 (22.3)</td>
<td>169 (21.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>History of CAD/Bypass/PCI (%)</td>
<td>353 (33.8)</td>
<td>80 (43.5)</td>
<td>255 (32.2)</td>
<td>0.0044</td>
</tr>
<tr>
<td>History of AMI (%)</td>
<td>165 (15.8)</td>
<td>41 (22.4)</td>
<td>114 (14.4)</td>
<td>0.0097</td>
</tr>
</tbody>
</table>

STEMI (57) and SAP (11) patients were excluded from the non-AMI group
## Best performing cut-off

<table>
<thead>
<tr>
<th>Cut-off (ng/L)</th>
<th>NPV (95% CI)</th>
<th>False Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>100.0 (97.1-100.0)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>99.6 (98.0-100.0)</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>99.7 (98.3-100.0)</td>
<td>1</td>
</tr>
<tr>
<td>5,2 (10% coefficient of variation)</td>
<td>99.7 (98.4-100.0)</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>99.7 (98.6-100.0)</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>99.6 (98.4-99.9)</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>99.4 (98.3-99.9)</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>99.4 (98.4-99.9)</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>99.3 (98.2-99.8)</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>98.9 (97.8-99.6)</td>
<td>7</td>
</tr>
<tr>
<td>20</td>
<td>98.8 (97.7-99.5)</td>
<td>8</td>
</tr>
<tr>
<td>27 (99th percentile)</td>
<td>98.4 (97.2-99.2)</td>
<td>11</td>
</tr>
</tbody>
</table>
### Suggested 1-hour algorithm

**NSTEMI rule-out:**

\[ \text{hsTnI} \leq 6 \text{ ng/L} \text{ at } 0\text{h and } 1\text{h} \]

resulted in 402 out of 1,045 patients being discharged

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Time after admission</th>
<th>NPV NSTEMI 1 (95% CI)</th>
<th>Sensitivity NSTEMI 1 (95% CI)</th>
<th>NPV NSTEMI (95% CI)</th>
<th>Sensitivity NSTEMI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6ng/L</td>
<td>1-hour</td>
<td>99.7 (98.6-100.0)</td>
<td>99.1 (94.9-100.0)</td>
<td>99.0 (97.5-99.7)</td>
<td>97.6 (94.1-99.4)</td>
</tr>
<tr>
<td></td>
<td>3-hour</td>
<td>100.0 (98.5-100.0)</td>
<td>100.0 (94.9-100.0)</td>
<td>99.5 (98.1-99.9)</td>
<td>98.8 (95.8-99.9)</td>
</tr>
</tbody>
</table>

\( p = \text{n.s. vs. } 1\text{h} \)
Higher performance of 6 ng/L vs. 27 ng/L

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Time after admission</th>
<th>NPV NSTEMI 1 (95% CI)</th>
<th>Sensitivity NSTEMI 1 (95% CI)</th>
<th>NPV NSTEMI (95% CI)</th>
<th>Sensitivity NSTEMI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 ng/L</td>
<td>1-hour</td>
<td>99.7 (98.6-100.0)</td>
<td>99.1 (94.9-100.0)</td>
<td>99.0 (97.5-99.7)</td>
<td>97.6 (94.1-99.4)</td>
</tr>
<tr>
<td></td>
<td>3-hour</td>
<td>100.0 (98.5-100.0)</td>
<td>100.0 (94.9-100.0)</td>
<td>99.5 (98.1-99.9)</td>
<td>98.8 (95.8-99.9)</td>
</tr>
<tr>
<td>27 ng/L (99th percentile)</td>
<td>1-hour</td>
<td>98.4* (97.2-99.2)</td>
<td>89.6 (82.2-94.7)</td>
<td>94.8* (92.9-96.3)</td>
<td>77.5 (70.5-83.6)</td>
</tr>
<tr>
<td></td>
<td>3-hour</td>
<td>99.1# (98.1-99.7)</td>
<td>94.3 (88.1-97.9)</td>
<td>96.8# (95.3-98.0)</td>
<td>87.1 (81.2-91.8)</td>
</tr>
</tbody>
</table>

p < 0.05 for 6 ng/L at * 1h or # 3h

NPV: negative predictive value; NSTEMI 1: non STEMI type 1 in view of Thygesen K et al. EHJ 2012
**Best performing Rule-In Algorithm**

**Suggested 1-hour algorithm**

**NSTEMI rule-in:**

hsTnI after 1h > **6 ng/L** together with a delta of **12 ng/L** to 0h

<table>
<thead>
<tr>
<th>Criteria to diagnose patients as NSTEMI</th>
<th>PPV NSTEMI 1 (95% CI)</th>
<th>Specificity NSTEMI 1 (95% CI)</th>
<th>PPV NSTEMI (95% CI)</th>
<th>Specificity NSTEMI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1-hour rule-in</strong></td>
<td>82.8 (73.2-90.0)</td>
<td>98.0 (96.7-98.9)</td>
<td>87.1 (79.6-92.6)</td>
<td>98.0 (96.7-98.9)</td>
</tr>
<tr>
<td><strong>3-hour rule-in</strong></td>
<td>78.6 (69.8-85.8)</td>
<td>96.8 (95.2-97.9)</td>
<td>84.6 (78.0-89.9)</td>
<td>96.8 (95.2-97.9)</td>
</tr>
</tbody>
</table>

**p = n.s. vs. 1h**

**PPV:** positive predictive value; **NSTEMI 1:** non STEMI type 1 in view of Thygesen K et al. EHJ 2012
Validation in 2 independent cohorts

<table>
<thead>
<tr>
<th></th>
<th>ADAPT (2-hour)</th>
<th>APACE (1-hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-AMI</td>
<td>NSTEMI</td>
</tr>
<tr>
<td>Number of patients</td>
<td>1,499</td>
<td>249</td>
</tr>
<tr>
<td>Age, years, Median</td>
<td>59 (49-70)</td>
<td>71 (60-79)</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>868 (57.9)</td>
<td>163 (65.5)</td>
</tr>
</tbody>
</table>

**Rule used to diagnose all NSTEMI**

<table>
<thead>
<tr>
<th>Troponin I</th>
<th>APACE¹</th>
<th>ADAPT²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rule-out algorithm</strong>&lt;br&gt;(≤ 6 ng/L and after 1h ≤ 6 ng/L)</td>
<td>99.2 (98.4-99.6)</td>
<td>99.7 (99.2-99.9)</td>
</tr>
<tr>
<td><strong>Rule-in algorithm</strong>&lt;br&gt;(1h &gt; 6 ng/L and e 12 ng/L)</td>
<td>80.4 (75.1-84.9)</td>
<td>81.5 (75.8-86.3)</td>
</tr>
</tbody>
</table>

1 Reichlin et al. CMAJ 2015, 2 Than et al. JACC 2012
Follow-up mortality

Suggested 1-hour algorithm

**NSTEMI rule-out:** hsTnI ≤ 6 ng/L at 0h and 1h

**NSTEMI rule-in:** hsTnI after 1h > 6 ng/L and a delta of 12 ng/L to 0h

**Greyzone:** Patients not identified by both algorithms (elevated but stable TnI values)

3 of 1,045 patients lost to follow-up: median 183 days

6 months
### Follow-up mortality

<table>
<thead>
<tr>
<th>Rule-out</th>
<th>6 ng/L</th>
<th>27 ng/L (99th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months mortality</td>
<td>3 deaths (0.79%)</td>
<td>12 deaths (1.73%) *</td>
</tr>
</tbody>
</table>

- **Rule-out**: 6 ng/L
- **6 ng/L (99th percentile)**: 12 deaths (1.73%) *
- **27 ng/L**: 3 deaths (0.79%)

- **3 of 1,045 patients lost to follow-up: median 183 days * p>0.05 vs 6 ng/L**

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**Graph:***
- **Ruled-in**: (11.9%) patients
- **Grey zone**: (46.9%) patients

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**ESC Congress London 2015**

**Hot Line presentation**
Follow-up mortality in

74,738 individuals (aged 51.0 years (42-60)) of the general population without prevalent CVD with follow up for cardiovascular mortality.

Survival

1 year follow-up

P <0.001

32 events

70 events

1.000

0.9992

0.996

0.994

0.00

0.25

0.50

0.75

1.00

Troponin I ≤ 6ng/L

Troponin I ≤ 27ng/L

5 years follow-up

P <0.001

206 events

423 events

1.000

0.998

0.996

0.994

0.00

1

2

3

4

5

Troponin I ≤ 6ng/L

Troponin I ≤ 27ng/L
A 1-hour algorithm is safe to rule-out AMI.

A sensitive troponin I cut-off (6 ng/L) performed better compared to the 99th percentile (27 ng/L) in view of lower follow-up mortality.

Low troponin I values predict mortality in the general population.

Further studies are needed to test the best cut-off for each troponin assay and to validate a 1-hour algorithm prospectively.
Acknowledgement

- To the patients included in the BACC, ADAPT and APACE cohorts.

- To the individuals of the BiomarCaRE cohort.

- To the study teams involved in all cohorts and trials.