Elecsys® Troponin T-high sensitive assay
New evidence
Topics of the presentation

1. Introduction
   - Troponin overview
   - Universal definition of AMI

2. Elecsys® cTnT-hs assay
   - Test design
   - Analytical evaluation

3. Clinical evidence
   - Algorithm
   - Indications of uses
   - Publication

4. Conclusion
History of markers for acute myocardial infarction

- 1958: 1st WHO criteria for AMI
- 1960: CK enzyme in AMI
- 1970: 2nd WHO criteria for AMI
- 1979: CK-MB enzyme inhibition activity
- 1980: WHO MONICA criteria for AMI
- 1990: CK-MB mass immunoassay
- 1990: cTnT
- 2000: Universal definition of MI
- 2000: Redefinition of AMI
- 2010: ESC guidelines - NSTEMI
- 2010: hs-TnT launched
- 2007: Universal definition of MI
- 1958: 1st WHO criteria for AMI
- 1960: CK enzyme in AMI
- 1970: 2nd WHO criteria for AMI
- 1979: WHO MONICA criteria for AMI
- 1990: CK-MB mass immunoassay
- 1990: cTnT
- 2000: Universal definition of MI
- 2000: Redefinition of AMI
- 2010: ESC guidelines - NSTEMI
- 2010: hs-TnT launched

AST enzyme in AMI, CK enzyme in AMI, CK-MB enzyme inhibition activity, Myoglobin RIA, cTnT, hs-TnT, pre-commercial
Third universal definition of myocardial infarction, 2012

Detection of a rise and/or fall of cardiac biomarkers values (preferably cardiac troponin (cTn)) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- 허혈의 증상
- 새로운 허혈을 나타내는 심전도의 변화- ST 분절 상승, LBBB 변화
- ECG 소견 상 병리적 Q파
- 새로운 기존의 생존 심근의 상실 혹은 국소적 심근벽운동의 이상-영상근거

• Troponin assay 의 조건
  CV 10% 를 충족하는 값이 99% 의 URL 보다 더 낮아야 함
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   • Publication

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# Troponin T Test Evolution

<table>
<thead>
<tr>
<th>Generation</th>
<th>Year</th>
<th>Test Name</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1989</td>
<td>ELISA Troponin T</td>
<td>1 cardio-specific monoclonal Ab</td>
</tr>
<tr>
<td>2nd</td>
<td>1993</td>
<td>Enzymun Troponin T, Elecsys Troponin T</td>
<td>2 cardio-specific monoclonal Ab (cal: bovine cTnT)</td>
</tr>
<tr>
<td>3rd</td>
<td>1996</td>
<td>Elecsys Troponin T</td>
<td>2 cardio-specific monoclonal Ab (cal: human recom. cTnT)</td>
</tr>
<tr>
<td>4th</td>
<td>2005</td>
<td>Elecsys Troponin T</td>
<td>No interferences with heparin</td>
</tr>
<tr>
<td>5th</td>
<td>2009</td>
<td>Elecsys Troponin T - high sensitive</td>
<td>Mini Det conc: 0.003 ng/ml, 99&lt;sup&gt;th&lt;/sup&gt; percentile: &lt; 0.014 ng/ml, 10&lt;sup&gt;th&lt;/sup&gt; CV: 0.013 ng/ml</td>
</tr>
</tbody>
</table>
Analytical evaluation of the cTnT-hs assay

Fig. 3 Bias plot in low troponin concentrations
Inset: Regression of Tn T methods at concentrations <50 ng/L

In low troponin concentrations, the bias plot shows a regression line with the equation $y = 0.10872x + 0.0161$ and a coefficient of determination $r^2 = 0.702$. The plot compares the percent difference between cTnT-hs and cTnT 4th Gen at concentrations below 50 ng/L.
Inter-laboratory comparison
Excellent comparability at low cTnT-hs levels

- Platform 과 병원간의 비교 성능 평가는 5개의 혈청을 가지고 평가
- Platforms 간에서는 cTnT-hs 간의 유의한 차이가 없었음.
- 각 Lab 에서 얻은 혈청 폐의 평균 농도는 평균 2SD 제한의 범위 내에서 유의하였음.
- 모든 검사실과 장비간에서는 낮은 농도로 평가한 결과 CV가 10% 이하로 보고됨. (mean of the means: 14.6 ng/L, overall CV: 6.5%)

Sample A (n=5 runs)

C6000 / E170
TnT-hs 18 minutes

E2010 / e 411
STAT application

Laboratory / Instruments

Analytical evaluation of the cTnT-hs assay

Passing–Bablock regression of TnT methods and specimen types

A: Comparison of cTnT-hs with 4th Gen cTnT assay; \( y = 1.02x + 18.4 \) (Analytical range: 2.1–9953 ng/L; n=745); \( r = 0.99 \)

B: Comparison of cTnT-hs STAT (9 min) assay with the cTnT-hs routine (18 min) assay; \( y = 1.02x + 1.04 \) (Analytical range: 0.1–9953 ng/L; n=725); \( r = 0.99 \)

C: Comparison of lithium heparin plasma with serum cTnT-hs; \( y = 0.96x + 0.02 \) (Analytical range: 0.07–96 ng/L; n=140); \( r = 0.99 \)

D: Comparison of EDTA plasma with serum cTnT-hs; \( y = 0.99x + 0.13 \) (Analytical range: 0.3–99 ng/L; n=114); \( r = 0.99 \)

hsTnT assay classifications

The 2 criteria of Fred Apple’s scorecard

1 Guideline optimum

Imprecision:

The total imprecision (CV) at the 99th percentile value should be ≤ 10%.

2 High-sensitivity

At least 50% measurable normal values below the 99th percentile:
(and ideally 95% to attain the highest level of scorecard designation)

Reference population (2012)*


* In the original MCE, it was 57%. (Saenger et al., Clinica Chimica Acta 2011;412:748–754)
Analytical evaluation of the cTnT-hs assay  
Saenger AK. et al., Clin Chim Acta, Jan 8, 2011.

Fig 4. Determination of the 99th percentile in a healthy population

533 adults (268 males and 265 females; mean age: 37 years, range 20–71 years) were prospectively recruited at 7 sites. Health status was assessed using a standardised questionnaire. Individuals with heart disease, renal disease, diabetes, cancer, peripheral arterial vascular disease, inflammatory conditions, and thyroid disorders, pregnancy, prescribed medications indicative of chronic disease (inclusive of statin and antihypertensive therapies), hospitalisation(s) within the prior 3 months, or abnormal BMI (>35 or <18) were excluded. The 99th percentile upper reference limit was calculated using non-parametric estimation.

<table>
<thead>
<tr>
<th>Age (mean)</th>
<th>n</th>
<th>Mean cTnT-hs (ng/L)</th>
<th>99th percentile (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>533</td>
<td>4.0</td>
<td>14.2</td>
</tr>
<tr>
<td>20–29</td>
<td>106</td>
<td>2.9</td>
<td>8.9</td>
</tr>
<tr>
<td>30–39</td>
<td>52</td>
<td>2.6</td>
<td>8.0</td>
</tr>
<tr>
<td>40–49</td>
<td>61</td>
<td>2.9</td>
<td>9.1</td>
</tr>
<tr>
<td>50–59</td>
<td>40</td>
<td>3.5</td>
<td>8.2</td>
</tr>
<tr>
<td>60–69</td>
<td>6</td>
<td>3.8</td>
<td>4.5</td>
</tr>
<tr>
<td>70+</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trend (χ²)\(^a\) \(\chi^2=11.2; p=0.02\)

<table>
<thead>
<tr>
<th>Age (mean)</th>
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<th>Mean cTnT-hs (ng/L)</th>
<th>99th percentile (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>268</td>
<td>5.1</td>
<td>15.5</td>
</tr>
<tr>
<td>20–29</td>
<td>95</td>
<td>4.5</td>
<td>10.7</td>
</tr>
<tr>
<td>30–39</td>
<td>58</td>
<td>4.3</td>
<td>14.9</td>
</tr>
<tr>
<td>40–49</td>
<td>57</td>
<td>5.2</td>
<td>17.6</td>
</tr>
<tr>
<td>50–59</td>
<td>42</td>
<td>6.7</td>
<td>19.9</td>
</tr>
<tr>
<td>60–69</td>
<td>15</td>
<td>8.1</td>
<td>14.0</td>
</tr>
<tr>
<td>70+</td>
<td>1</td>
<td>7.2</td>
<td></td>
</tr>
</tbody>
</table>

Trend (χ²)\(^a\) \(\chi^2=32.4; p=<0.00001\)

\(^a\)Kruskall–Wallis test

533 adults (268 males and 265 females; mean age: 37 years, range 20–71 years) were prospectively recruited at 7 sites. Health status was assessed using a standardised questionnaire. Individuals with heart disease, renal disease, diabetes, cancer, peripheral arterial vascular disease, inflammatory conditions, and thyroid disorders, pregnancy, prescribed medications indicative of chronic disease (inclusive of statin and antihypertensive therapies), hospitalisation(s) within the prior 3 months, or abnormal BMI (>35 or <18) were excluded. The 99th percentile upper reference limit was calculated using non-parametric estimation.
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3. Clinical evidence
   - Algorithm
   - New publication

4. Conclusion
Absolute and relative changes in cardiac troponin

**Prediction of non-STEMI in the entire study population**

A

- Absolute change (AUC=0.898)*
- Relative change (AUC=0.752)
- Baseline cTnT-hs (AUC=0.731)
- Peak cTnT-hs (AUC=0.830)

**Prediction of non-STEMI in ACS patients**

B

- Absolute change (AUC=0.941)*
- Relative change (AUC=0.741)
- Baseline cTnT-hs (AUC=0.836)
- Peak cTnT-hs (AUC=0.894)

** ROC-optimised absolute delta change:** 9.2 ng/L  
** ROC-optimised absolute delta change:** 6.9 ng/L

**Absolute cTnT-hs changes** had the **highest AUC** for the prediction of non-STEMI
hsTnT algorithm
신속한 MI 의 진단

ESC 가이드라인에서 제언된 알고리듬에 따르면 “각각의 hs-cTn assay” 에 따라 최적의 변화값으로 MI (심근경색) 을 진단할 수 있음

입원
- Initial hs-cTn value ≤URL
- hs-cTn value at 3 hrs >URL + increase >50% of URL
- hs-cTn value at 6 hrs >URL + increase >50% of URL

3시간 후

6시간 후

급성 흉통

심근 곰사

허혈 증상

심근 경색

* Symptoms and/or new electrocardiogram changes and/or new imaging corroboration
AMI, acute myocardial infarction; URL, 99th percentile upper reference limit

Adapted from Thygesen K. et al, Eur Heart J 2012; 33: 2282-7
## Indication of uses

**Cardiac TnT**

<table>
<thead>
<tr>
<th>Indication</th>
<th>TnT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aid in the differential diagnosis of acute coronary syndrome (ACS) to identify necrosis acute myocardial infarction (AMI)</td>
<td></td>
</tr>
<tr>
<td>Risk stratification of patients presenting with unstable Angina (UA) or non-ST segment elevation acute coronary syndrome (NSTEMI)</td>
<td></td>
</tr>
<tr>
<td>Cardiac risk stratification in patients with chronic renal failure (CRF)</td>
<td></td>
</tr>
<tr>
<td>Helpful for the selection of more intensive therapy (eg. GPIIb3A) and intervention in patients with elevated levels of cardiac Tn</td>
<td></td>
</tr>
</tbody>
</table>

Source: Package inserts
## Number of peer reviews publications*

<table>
<thead>
<tr>
<th>Category</th>
<th>Publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS - Early diagnosis</td>
<td>40</td>
</tr>
<tr>
<td>ACS - Risk stratification &amp; prognostic value</td>
<td>42</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>7</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10</td>
</tr>
<tr>
<td>Stable coronary artery diseases</td>
<td>13</td>
</tr>
<tr>
<td>Heart failure and cardiomyopathy</td>
<td>42</td>
</tr>
<tr>
<td>Non-cardiac surgery</td>
<td>24</td>
</tr>
<tr>
<td>Renal diseases</td>
<td>19</td>
</tr>
<tr>
<td>Other pathologies</td>
<td>58</td>
</tr>
<tr>
<td>In the community</td>
<td>21</td>
</tr>
<tr>
<td>Exercise &amp; marathon runners</td>
<td>26</td>
</tr>
<tr>
<td>Analytical performances</td>
<td>21</td>
</tr>
<tr>
<td>Guidelines &amp; utilization in clinical practice</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>332</strong></td>
</tr>
</tbody>
</table>

Roche cTnT-hs

Roche cTnT-hs assay: validated by > 330 publications & 3 year clinical experience

* As by Jan 2014

TnT-hs performance is documented in >330 articles

TnT-hs has been investigated in multiple situations and populations.
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Conclusions

- The cTnT-hs assay meets the $\leq 10\%$ CV criterion at the 99th percentile URL

- The improved sensitivity leads to an earlier diagnosis of AMI: Sensitive troponin assays detect patients with AMI already at 2 hours after onset of symptoms

- The new cTnT-hs assay helps for risk stratification of ACS

- The cTnT-hs assay identifies patients at risk of future cardiovascular events

- As recommended by the guidelines, cTn results have to interpreted with the clinical presentation of the patient; and acute changes in serial samples are required to differentiate acute from chronic myocardial damage
Thank you for your attention!

Roche Diagnostics Ltd.
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Switzerland

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