Current guidelines on cardiac markers
- how should they be introduced
and how should the implementation be evaluated

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Conflicts of interest

- Member NICE Diagnostics Advisory Committee
- National Clinical Lead National Laboratory Medicine Catalogue UK
- Advisory Boards for Siemens Healthcare Diagnostics and Phillips.
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Acknowledgements

- Everyone who participated in the CARMAGUE surveys
- And a reminder to those that haven’t (yet)
  - There is still time
  - Or the incoming president will make you an offer you can’t refuse
Assess

Analyse

Change

Evidence base

Primary research

Systematic review

Guidelines

Cost

Process

Outcome

Assess

Analyse

Audit cycle

Conclusions and recommendations

Primary research

Best practice

Current practice

Compare

Collinson PO in Evidence-Based Laboratory Medicine. AACC press, Washington DC. 2007
Current guidelines on cardiac markers - how should they be introduced and how should the implementation be evaluated

• What are the guidelines and where did they come from
• Guidelines and reality – how do we use cardiac biomarkers in Europe?
• Barriers to implementation
• Evaluation of implementation
• Conclusions
What are the guidelines and where did they come from

- How do we get guidelines?
Opinion leaders
Opinion leaders

• Opinion may be wrong even when widely held (and enforced)
  – The Sun rotates around the earth
  – The holy office had a short way with dissenters
Opinion may be wrong

• In 1843, Oliver Wendell Holmes published *The Contagiousness of Puerperal Fever.*

• He maintained:
  – Puerperal fever was frequently carried from patient to patient by physicians and nurses
  – Hand-washing, clean clothing, and avoidance of autopsies by those aiding birth would prevent the spread of puerperal fever
  – Holmes' conclusions were ridiculed by many contemporaries, including Charles Meigs, a well-known obstetrician, who stated "Doctors are gentlemen, and gentlemen's hands are clean."
    • Both statements are probably untrue (still) in the era of MRSA
Opinion may be wrong

• In 1844, Ignaz Semmelweis appointed to Allgemeines Krankenhaus in Vienna

• He noticed
  – His ward’s 16% mortality rate from fever was substantially higher than the 2% mortality rate in the Second Division, where midwifery students were trained.
  – That puerperal fever was rare in women who gave birth before arriving at the hospital.
  – The First Division performed autopsies each morning on women who had died the previous day but the midwives were not required or allowed to perform such autopsies.
  – A colleague, Jakob Kolletschka, died of septicaemia after accidentally cutting his hand while performing an autopsy.
Opinion may be wrong

• Instituted that all doctors and students working in the First Division wash their hands in chlorinated lime solution before starting ward work, and later before each vaginal examination.
  – The mortality rate from puerperal fever in the division fell from 18% in May 1847 to less than 3% in June–November of the same year.
  – He was treated with skepticism and ridicule. The combination of his abrasive personality and the hostility of the medical establishment in Vienna proved too much for him, and in 1851 he returned to Hungary as a professor of obstetrics in Budapest.
Opinion leaders

- Influenced by Industry?
SHOULD THE DRUG INDUSTRY USE KEY OPINION LEADERS?

PLUS Does vitamin A improve child survival?

The NHS at 60: does central funding still make sense?

Endovascular stenting for caval obstruction

JOBS, COURSES, CAREERS
Opinion leaders

- Opinion (consensus statements) is Class III level of evidence in the evidence based hierarchy
- And quite rightly so
Peers

- Peer opinion suffers from the same defects as opinion leaders
- But there are more of them
- So we can all be wrong together
Guideline development

- Systematic evaluation of published material with an evidence hierarchy
- Limitations
  - Publication bias
    - negative studies tend not to be published
    - It has been estimated that 65% of publications supporting guidelines are industry sponsored
  - Appropriateness of study populations
    - Clinical trial populations are selected and co-morbidities excluded. They are not all comers real world studies
    - Clinical study populations may include inappropriate patient groups
      - Population selection including ST segment elevation MI
    - Trial design factors
<table>
<thead>
<tr>
<th>Variable</th>
<th>Noncoronary Chest Pain</th>
<th>Unstable Angina Pectoris</th>
<th>Acute Myocardial Infarction</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine kinase — U/liter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>97</td>
<td>94</td>
<td>148</td>
<td>105</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>69–146</td>
<td>65–132</td>
<td>101–259</td>
<td>72–164</td>
</tr>
<tr>
<td>Creatine kinase MB — U/liter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
<td>15</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>12–19</td>
<td>11–19</td>
<td>15–37</td>
<td>12–21</td>
</tr>
<tr>
<td>C-reactive protein — mg/liter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.3</td>
<td>2.3</td>
<td>3.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1.1–5.4</td>
<td>1.3–4.5</td>
<td>1.7–8.8</td>
<td>1.3–5.8</td>
</tr>
<tr>
<td>Creatinine — mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.94</td>
<td>0.93</td>
<td>0.99</td>
<td>0.95</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.82–1.08</td>
<td>0.82–1.06</td>
<td>0.88–1.16</td>
<td>0.83–1.10</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate — ml/min/1.73 m² of body-surface area</td>
<td>80.1±21.1</td>
<td>79.8±21.1</td>
<td>75.5±22.3</td>
<td>79±21.4</td>
</tr>
<tr>
<td>Electrocardiographic results on admission — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment elevation</td>
<td>27/1153 (2.3)</td>
<td>6/239 (2.5)</td>
<td>56/397 (14.1)</td>
<td>89/1789 (5.0)</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>69/1153 (6.0)</td>
<td>27/239 (11.3)</td>
<td>109/397 (27.5)</td>
<td>205/1789 (11.5)</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>295/1153 (25.6)</td>
<td>77/239 (32.2)</td>
<td>174/397 (43.8)</td>
<td>546/1789 (30.5)</td>
</tr>
<tr>
<td>Left or right bundle-branch block</td>
<td>149/1153 (12.9)</td>
<td>35/239 (14.6)</td>
<td>61/397 (15.4)</td>
<td>245/1789 (13.7)</td>
</tr>
</tbody>
</table>
Potentially eligible people entered a prerandomisation “run-in” phase, which was intended chiefly to limit subsequent randomisation to those likely to take the randomly allocated study treatment for at least 5 years.26 Run-in treatment involved 4 weeks of placebo (to allow review of liver enzymes, creatinine, and creatine kinase by the central laboratory before starting any simvastatin) followed by 4–6 weeks of a fixed dose of 40 mg simvastatin daily (to allow a prerandomisation assessment of the LDL-lowering “responsiveness” of each individual:
63,603 attended screening

31,458 not eligible or refused

32,145 started prerandomisation “run-in”

11,609 not eligible or withdrew

20,536 randomised

10,269 allocated 40 mg simvastatin daily

Lost to follow-up for:
mortality 3 (0.03%)
morbidity 34 (0.33%)

10,232 (99.6%) with complete follow-up for average of 5 years

10,267 allocated matching placebo

Lost to follow-up for:
mortality 4 (0.04%)
morbidity 26 (0.25%)

10,237 (99.7%) with complete follow-up for average of 5 years
The guidelines
Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature

Circulation 1979;59:607-609

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C. Serum Enzymes. a) *Unequivocal change* consists of serial change, or initial rise and subsequent fall of the serum level. The change must be properly related to the particular enzyme and to the delay time between onset of symptoms and blood sampling. Elevation of cardiospecific isoenzymes is also considered unequivocal change.

b) *Equivocal change* consists of an enzyme pattern where an initially elevated level is not accompanied by a subsequent fall — the curve of enzyme activity is not obtained.
National Academy of Clinical Biochemistry Standards of Laboratory Practice: Recommendations for the Use of Cardiac Markers in Coronary Artery Diseases

Alan H.B. Wu,1* Fred S. Apple,2 W. Brian Gibler,3 Robert L. Jesse,4 Myron M. Warshaw,5 and Roland Valdes, Jr.6
Consensus Document

Myocardial infarction redefined — A consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction

The Joint European Society of Cardiology/American College of Cardiology Committee**
Universal definition of myocardial infarction

Kristian Thygesen, Joseph S. Alpert and Harvey D. White on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction

Third universal definition of myocardial infarction

Kristian Thygesen, Joseph S. Alpert, Allan S. Jaffe, Maarten L. Simoons, Bernard R. Chaitman and Harvey D. White: the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction
Definition of myocardial infarction

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker 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:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.

- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
Evolution of Diagnostic Criteria for AMI using cTn

- **WHO**
  - Unstable Angina
  - Myocardial infarction

- **NACB**
  - Unstable Angina
  - MMD
  - Myocardial infarction
  - Diagnostic limit for CK-MB
  - 97.5 centile or LLD

- **AHA/ESC**
  - Unstable Angina
  - Myocardial infarction
  - AMI Limit based on CK-MB (ROC equivalent)
  - 99th centile
Evidence base?

- For the shift to troponin
- For the 99th percentile
For the shift to troponin
## Table 3. Major Cardiac Events during Hospitalization and Date of Occurrence.*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Creatine Kinase</th>
<th>Troponin T</th>
<th>Cardiac Events</th>
<th>Day after Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>U/liter</td>
<td>µg/liter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>49/M</td>
<td>148</td>
<td>11</td>
<td>0.37</td>
<td>Infarction</td>
</tr>
<tr>
<td>2</td>
<td>58/M</td>
<td>117</td>
<td>4</td>
<td>&lt;0.20†</td>
<td>Death after infarction</td>
</tr>
<tr>
<td>3</td>
<td>80/F</td>
<td>102</td>
<td>13</td>
<td>0.21</td>
<td>Death after infarction</td>
</tr>
<tr>
<td>4</td>
<td>73/M</td>
<td>36</td>
<td>0</td>
<td>1.10</td>
<td>Death after infarction</td>
</tr>
<tr>
<td>5</td>
<td>59/F</td>
<td>9</td>
<td>1</td>
<td>0.47</td>
<td>Death after bypass surgery and infarction</td>
</tr>
<tr>
<td>6</td>
<td>75/M</td>
<td>29</td>
<td>0</td>
<td>0.54</td>
<td>Death after bypass surgery and infarction</td>
</tr>
<tr>
<td>7</td>
<td>79/M</td>
<td>121</td>
<td>29</td>
<td>0.28</td>
<td>Infarction</td>
</tr>
<tr>
<td>8</td>
<td>72/M</td>
<td>45</td>
<td>3</td>
<td>0.81</td>
<td>Death after bypass surgery and infarction</td>
</tr>
<tr>
<td>9</td>
<td>68/M</td>
<td>41</td>
<td>5</td>
<td>1.07</td>
<td>Infarction</td>
</tr>
<tr>
<td>10</td>
<td>78/M</td>
<td>156</td>
<td>9</td>
<td>0.90</td>
<td>Infarction</td>
</tr>
<tr>
<td>11</td>
<td>66/M</td>
<td>94</td>
<td>16</td>
<td>0.30</td>
<td>Infarction</td>
</tr>
</tbody>
</table>

*Values of <25 U per liter for creatine kinase MB and <0.20 µg per liter for troponin T were considered normal. Infarction denotes acute myocardial infarction, and bypass surgery coronary artery bypass surgery.

†This patient was classified as negative for troponin T.
Kaplan-Meier cumulative hazard function curves for unstable angina according to troponin T status and end points. +Mantel-Haenszel statistic. ++Log rank statistic.

Cardiac death as first event

- Troponin T positive 19% (12/62)
- Troponin T negative 12% (14/121)

P=0.035†

Cardiac death or coronary revascularisation as first event

- Troponin T positive 53% (33/62)
- Troponin T negative 33% (40/121)

P=0.004†

Need for coronary revascularisation as first event

- Troponin T positive 35% (22/62)
- Troponin T negative 21% (26/121)

P=0.03†

Cardiac death or non-fatal myocardial infarction as first event

- Troponin T positive 29% (18/62)
- Troponin T negative 17% (21/121)

P=0.042†

Meta-analysis data for cTnT (left) and cTnI (right) adapted from Heidenreich PA et al *J.Am.Coll.Cardiol.* 2001;38:478-85
For the 99th percentile
Figure. Survival Free From Death or Recurrent MI in Patients With Suspected Acute Coronary Syndrome Before (Validation Phase) and After (Implementation Phase) the Introduction of a Sensitive Troponin Assay

Validation phase
Peak troponin, ng/mL
- <0.05
- 0.05-0.19
- ≥0.20

Implementation phase
Peak troponin, ng/mL
- <0.05
- 0.05-0.19
- ≥0.20

Survival Free From Death or Recurrent MI, %

Days

Log-rank P<.001
Biomarkers of myocardial necrosis

- What is the audit standard
Universal definition of myocardial infarction

Kristian Thygesen, Joseph S. Alpert and Harvey D. White on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction

Third universal definition of myocardial infarction

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Class III

1. Total CK, CK-MB activity, aspartate aminotransferase (AST, SGOT), β-hydroxybutyric dehydrogenase, and/or lactate dehydrogenase should not be used as biomarkers for the diagnosis of MI (Level of Evidence: C).

2. For patients with diagnostic ECG abnormalities on presentation (e.g., new ST-segment elevation), diagnosis and treatment should not be delayed while awaiting biomarker results (Level of Evidence: C).
National Academy of Clinical Biochemistry Standards of Laboratory Practice: Recommendations for the Use of Cardiac Markers in Coronary Artery Diseases

Alan H.B. Wu,¹ Fred S. Apple,² W. Brian Gibler,³ Robert L. Jesse,⁴ Myron M. Warshaw,⁵ and Roland Valdes, Jr.⁶
Recommendation: Members of emergency departments, divisions of cardiology, hospital administrations, and clinical laboratories should work collectively to develop an accelerated protocol for the use of biochemical markers in the evaluation of patients with possible acute coronary syndromes.

Strength/consensus of recommendation: Class I.\(^8\)

For simplicity, this protocol should apply to either the facilitated diagnosis or the rule-out of AMI in the ED or to routine diagnosis from other areas of the hospital, should a patient develop symptoms consistent with acute coronary syndromes while hospitalized.

Strength/consensus of recommendation: Class II.
Biomarkers of myocardial necrosis

- Audit and reality – how do we use cardiac biomarkers in Europe?
Breadth of survey

![Bar chart showing the breadth of survey over years 2006, 2010, and 2013 (prelim). The chart indicates an increase in the total and university contributions across the years.]
What markers are used for the primary diagnosis of AMI?

![Bar chart showing the percentage of cTn and Other markers used for AMI diagnosis from 2006 to 2013. The percentages are as follows: 94% in 2006, 95% in 2010, and 96.8% in 2013.]
What other markers are used for the diagnosis of AMI (expressed as percentages)?
Units

- mg/L (cTnT)
- ng/L (cTnT)
- mg/L (cTnI)
- ng/L (cTnI)
Where do laboratories get their information – decision limits for AMI

- Locally derived
- Peer-reviewed literature
- National/International
- Data sheet
What decision limits for AMI are used (percentages)

- Do not know: 8.2%
- Other: 5.3%
- Guidelines: 16.4%
- Locally derived: 9.4%
- 99th percentile: 39.3%
- 20% CV: 3.4%
- 10% CV: 17.9%
Interpretation

- 99\textsuperscript{th} percentile or decision limits?
  - 33\% used a “grey zone”
Origin of protocol

- Written agreement
- Verbal agreement
- Informal consensus
- Other
Serial testing

- Yes – 62.7%
- Sometimes - 25.2%
- No – 6.5%

- 34% use a delta
  - Absolute 26.9%
  - Relative 53.9%
  - Both 17.9%
Conclusions

- Troponin IS the biomarker for AMI
- Encouraging trends in working with clinician colleagues
- Time for a biomarker update for recommended standards of practice
- There is a clear need for education in
  - Use of the 99th percentile
  - Use of delta values
Barriers to implementation

- Evidence base – lack of understanding of (hs) troponin
- Lack of clinician-laboratory dialogue
References


Remember

- [http://carmague.fi/2013](http://carmague.fi/2013)
- It is not yet too late