Cardiac Bio-Marker Testing in Acute Coronary Syndromes

Dr. Zohair Alaseri, MD
FRCPc, Emergency Medicine
FRCPc, Critical Care Medicine
Intensivist and Emergency Medicine Consultant
Chairman, Department of Emergency Medicine
King Saud University Hospitals, Riyadh, KSA
Objectives

1. Describe current limitations of traditional cardiac biomarker testing.

2. Examine the utilization of a rapid algorithm to aid in ACS.

3. Discuss evidence based indications of use for Point-of-Care through review of current literature.
Challenges in Healthcare

Highest Quality of Care
Patient Satisfaction
Minimizing ED Overcrowding
Enhancing Operational Efficiency
Ideal Marker

• Found in high concentration in the heart

• Not found in other tissues

• Low molecular weight and thus released early in the course of AMI

• Remains elevated for several days

Currently, no single marker meets these ideal requirements
Professional Guidelines* Have Been Established for AMI Management

- Turn around Time (TAT) for cardiac markers should be 30 minutes
High Percentage of Hospitals Perform POC Testing

N = 584 hospitals

Enterprise Analysis Corporation Hospital point-of-care survey report 2001
## Turnaround Times for Common Laboratory Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Turn around time before POCT (min)</th>
<th>Turn around time during POC (min)</th>
<th>Change in Turnaround time after Initiating POCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis</td>
<td>40</td>
<td>4</td>
<td>90%</td>
</tr>
<tr>
<td>Pregnancy Testing</td>
<td>78</td>
<td>5</td>
<td>94%</td>
</tr>
<tr>
<td>Glucose testing</td>
<td>10</td>
<td>6</td>
<td>60%</td>
</tr>
<tr>
<td>Cardiac markers</td>
<td>110</td>
<td>17</td>
<td>84.5%</td>
</tr>
<tr>
<td>Average</td>
<td>59.5</td>
<td>8</td>
<td>86.6%</td>
</tr>
</tbody>
</table>

*IVD Technology June 2003 Study published; Archives of Pathology and Laboratory Medicine 2003 Study done at Massachusetts General Hospital (Boston)*
### Biomarkers of Choice

#### ADVANTAGES

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB</td>
<td>Cost-efficient, Prior Standard</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>High sensitivity, Useful in early detection of AMI, Useful in ruling out AMI (must use a more specific marker)</td>
</tr>
<tr>
<td>Troponins</td>
<td>Risk Stratification, Greater specificity than CK-MB, Detection of recent AMI up to 2 weeks after onset</td>
</tr>
</tbody>
</table>

ACC/AHA Pocket Guideline Update, 2002
Biomarkers of Choice

DISADVANTAGES

**CK-MB**
Lacks specificity with skeletal muscle disease/injury
- Low sensitivity during early AMI (<6h) or late (>36h) after symptom onset and for minor myocardial damage

**Myoglobin**
Very low specificity with skeletal muscle injury
- Rapid return to normal

**Troponins**
- Low sensitivity in early phase of AMI (<6 h after symptom onset)
- Limited ability to detect late minor reinfarction
Biomarker Release Kinetics Demonstrate “real time” Value

Maximal Benefit
Definite Benefit
No Clear Benefit

Multiple of Upper Reference Range

0 2 4 6 8 10
0 2 4 6 8 10
0 2 4 6 8 10
0 2 4 6 8 10

Hours After Onset of MI

Myoglobin
CKMB
TnI
For emergency department physicians, timely triage and risk stratification of chest pain patients remains a challenge.

Clinicians are seeking more effective ways to diagnose acute coronary syndromes rapidly and accurately.
Clinical algorithm based on these cardiac markers—myoglobin, cardiac troponin (cTnI), creatine kinase-MB, and B-type natriuretic peptide (BNP)—provides the sensitivity and specificity required for confirmatory diagnosis and rapid rule-out method.
Your door to treatment is too long,
Where Is the problem??????????

FIGURE 5. Reducing interval between chest pain onset and intervention (wire) “P2W.”
Your door to treatment is too long, Where Is the problem?????????

- The second most common cause of treatment delay is delayed test results.
- TAT, the interval between ordering a test and the availability of a definitive report or interpretation.
According to the ACC/AHA guidelines, the suggested TAT for cardiac biomarkers is 60 minutes or less, with a preferred time of 30 minutes.
Assay Procedure

Step 1: Add whole blood to device

Step 2: Insert device into Meter

Step 3: Read Results
Sensitivity of Algorithm at 90 Minutes Following Patient Arrival

- cTnI: 86%
- CK-MB: 77%
- Myo: 29%
- cTnI & Myo: 94%
- cTnI & CK-MB: 94%
- CK-MB & Myo: 86%
- Myo CKMB Tnl: 100%

Ng SM et al. Am J Cardiol 2001; 88: 611-17
CHECKMATE The Chest pain Evaluation by Creatine Kinase-MB, Myoglobin and Troponin I Study

Purpose: Evaluate the ability of quantitative bedside markers to risk stratify patients with chest pain and non-diagnostic ECG

Newby, K. MD et al

Circulation

2001
Design / Methods

- 1,005 chest pain patients, non-diagnostic ECG
- Prospective, multi-center trial 6 CPUs in US
- Compared local lab (LL) testing with near patient multiple marker strategies (MMS).
  - MMS-1 = Myoglobin, CK-MB, TnI
  - MM-2 = CK-MB, TnI
- Testing frequency
  - Baseline, 3 hours and 6 hours
  - 9-12 hours and 16-24 hours if patient still under observation
CHECKMATE Trial: Median Time to Positivity

Newby, K. MD et al *Circulation* 2001
Conclusions

- Quantitative, multi-marker strategies identifies positive patients earlier and provides better risk stratification for mortality than a local laboratory single-marker approach.

- Myoglobin helped reduce time to positive result

- Myoglobin has excellent sensitivity and negative predictive value

Newby, K. MD et al Circulation 2001
Ninety-Minute Exclusion of Acute Myocardial Infarction By Use of Quantitative Point-of-Care Testing of Myoglobin and Troponin I

Purpose: Determine if a combination of a biomarker that rises early (Myo) with one that rises later (CK-MB or TnI) could exclude AMI in either 90 or 180 minutes

McCord, J. MD et al

Circulation

September 2001
Study Design / Methods

- Study looked at 817 patients with nondiagnostic ECGs

- Measurements of Myo, TnI, and CK-MB were obtained at baseline, 90 minutes, 3 hours and 9 hours.

- Triage decisions were made by ED physicians who were unaware of the point-of-care results.
Henry Ford Trial: Time to Laboratory Reporting

![Bar chart showing time (in minutes) for Central Lab and Point of Care Device. The Central Lab time is 71 minutes, and the Point of Care Device time is 24 minutes.]

Circulation, McCord, J. Vol. 104 no. 13 September 2001
Conclusions

• Myoglobin and Troponin I at 0 and 90 minutes is a rapid and effective strategy to exclude AMI in pts presenting to the Emergency Department

• More rapid turnaround time of cardiac marker results was achieved with POC technology

• This may lead to more rapid patient triage and treatment

Circulation, McCord, J. Vol. 104 no. 13 September 2001
Improving Care of ACS Patients

3- Marker Panel
Accelerated Algorithm

- **Risk Stratification**
  - More positives identified with 3 markers
  - Earlier and more accurate diagnosis allows for speedier, targeted use of medicines

- **Appropriate Disposition**
  - 100% Sensitivity within 90 minutes
  - NPV 99.7%
  - Decreased CCU admissions 40%

- **Rapid Rule-Out**
  - Effective in rule out of AMI
  - 99.6% NPV at 90 minutes
  - Reduce length of stay in ED

CHECKMATE, *Circulation* 2001

90 Minute Accelerated Pathway, *Am J Cardiol* 2001

90 Minute Rule-out, *Circulation* 2001
Triage Cardiac Panel Highlights

- Triage Cardiac is a fluorescence immunoassay used for the quantitative determination of Creatine Kinase MB, Myoglobin and Troponin I in whole blood or plasma
- No interference with typically prescribed heart related drugs

*Triage cardiac package insert. Data on File at Biosite Diagnostics Inc.*
Census Connectivity

**Lab**

Test results are automatically transferred from the Meter to Census

POCC’s can view, analyze, or edit results, and provide supervisor control of remote meters

**ER**

Hospital Network Connection

Results that meet user-defined criteria are transferred to the LIS for placement on the patient’s permanent medical record

**Chest Pain Unit**

Hospital Network Connection

Normally located in POCC office

RALS-ADT gathers demographic data to enable patient verification

Results are available from LIS at POC

**LIS**

**HIS**

**Hospital Network Connection**

**ER**

**Lab**

**Chest Pain Unit**

**Hospital Network Connection**
Impact of point-of-care testing in the emergency department evaluation and treatment of patients with suspected acute coronary syndromes.

• OBJECTIVES: To assess the impact of point-of-care testing (POCT) for troponin I (cTnI) measurement on the time to anti-ischemic therapy (TAIT) for patients with suspected (NSTE-ACS) presenting to the emergency department (ED).

Impact of point-of-care testing in the emergency department evaluation and treatment of patients with suspected acute coronary syndromes.

- **METHODS:** This was an open-label, randomized, single-center trial conducted in a university-affiliated hospital.
- cTnI measurement of patients with suspicion of NSTE-ACS coming to the ED was randomly allocated to POCT or central hospital laboratory testing.
RESULTS:

• Of the 860 patients enrolled, 113 were high-risk NSTE-ACS patients, including 53 (46.9%) allocated to POCT and 60 (53.1%) to CHLT.

• POCT was associated with decreased time to anti-ischemic therapy of about three-quarters of an hour, which was due to a shorter time to physician notification of cTnI level, in both all and subgroup participants.
Impact of point-of-care testing in the emergency department evaluation and treatment of patients with suspected acute coronary syndromes.

CONCLUSIONS:

Point-of-care testing for cTnI measurement might be clinically relevant for ED patients with a suspicion of NSTE-ACS, particularly for high-risk patients with a low suspicion of ACS.
The Value of Bedside Cardiac Multibiomarker Assay in Rapid and Accurate Diagnosis of Acute Coronary Syndromes

Shahriar Dadkhah, MD, Korosh Sharain, BS, Roza Sharain, BS, Hamid Kiabayan, MD, Alberto Foschi, MD, Carolynn Zonia, DO, Brian Huettl, MD, Scott French, MD, Elizabeth Gray, BA, Sridhar Venkatachalam, MD, Housam Hegazy, MD, and Glenn Aldinger, MD

(Crit Pathways in Cardiol 2007;6: 76–84)
• SFH has focused on the critical steps that impact time to intervention, including
  • the reduction of patient delay time to the ED
  • improving the time to (ECG)
  • minimizing laboratory TAT.
they implemented a 4-hour rule-out protocol in the ED, testing cardiac multimarkers 0,2 and 4h

The rapid diagnostic protocol has enabled SFH to triage patients quickly and get them on the appropriate care pathway.
Myoglobin

- is the first biomarker to become elevated after an ischemic event, increasing at approximately 1 to 2 hours post-MI.
- has a low specificity
- it is an early ischemic marker
- a sensitivity and negative predictive value of 100% when considered 2 hours apart, at admission 2 hours post admission.

## Myoglobin & Troponin

<table>
<thead>
<tr>
<th>Point of Care</th>
<th>Time 0</th>
<th>0, 90 min</th>
<th>0, 90 min, 3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Myo</td>
<td>70.8 (58–81)</td>
<td>75.6 (72–79)</td>
<td>84.6 (74–92)</td>
</tr>
<tr>
<td>CK-MB</td>
<td>75.4 (63–85)</td>
<td>84.7 (82–87)</td>
<td>83.1 (72–91)</td>
</tr>
<tr>
<td>cTnl</td>
<td>64.6 (52–76)</td>
<td>87.6 (85–90)</td>
<td>76.9 (65–86)</td>
</tr>
<tr>
<td>Myo, CK-MB</td>
<td>83.1 (72–91)</td>
<td>70.2 (67–73)</td>
<td>92.3 (83–98)</td>
</tr>
<tr>
<td>Myo, cTnl</td>
<td>84.6 (74–92)</td>
<td>66.8 (63–70)</td>
<td>96.9 (89–100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myo</td>
<td>96.8 (95–98)</td>
<td>20.1 (15–26)</td>
<td>98.2 (97–99)</td>
<td>21.4 (16–27)</td>
<td>98.3 (97–99)</td>
<td>20.4 (16–26)</td>
</tr>
<tr>
<td>CK-MB</td>
<td>97.5 (96–99)</td>
<td>29.9 (23–38)</td>
<td>98.3 (97–99)</td>
<td>29.8 (23–37)</td>
<td>98.9 (98–100)</td>
<td>29.9 (24–38)</td>
</tr>
<tr>
<td>cTnl</td>
<td>96.6 (95–98)</td>
<td>31.1 (23–40)</td>
<td>97.5 (96–99)</td>
<td>24.2 (18–31)</td>
<td>98.5 (97–99)</td>
<td>20.2 (16–25)</td>
</tr>
<tr>
<td>Myo, CK-MB</td>
<td>98.0 (96–99)</td>
<td>19.4 (15–25)</td>
<td>99.0 (98–100)</td>
<td>19.7 (15–25)</td>
<td>99.0 (98–100)</td>
<td>19.0 (15–24)</td>
</tr>
<tr>
<td>Myo, cTnl</td>
<td>98.0 (96–99)</td>
<td>18.1 (14–23)</td>
<td>99.6 (98–100)</td>
<td>17.3 (14–22)</td>
<td><strong>99.5 (98–100)</strong></td>
<td>15.2 (12–19)</td>
</tr>
</tbody>
</table>

Myo indicates myoglobin. Values are all % (95% CI). If any value of a combination of markers was positive, the combination was considered positive. All values had to be negative for the combination to be considered negative.
<table>
<thead>
<tr>
<th>Reference</th>
<th>POCT</th>
<th>Central Laboratory</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caragher et al</td>
<td>38</td>
<td>87</td>
<td>76</td>
</tr>
<tr>
<td>Lee-Lewandrowski et al</td>
<td>17</td>
<td>110</td>
<td>87</td>
</tr>
<tr>
<td>Collinson et al</td>
<td>20</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td>McCord et al</td>
<td>24</td>
<td>71</td>
<td>75</td>
</tr>
<tr>
<td>Singer et al</td>
<td>15</td>
<td>83</td>
<td>85</td>
</tr>
<tr>
<td>Mean</td>
<td>23</td>
<td>89</td>
<td>79</td>
</tr>
</tbody>
</table>

Adapted from Wu."
• Bedside testing implementation for cardiac biomarkers reduced TATs by approximately 79% over central laboratory methods.

in a historically controlled study of 4 hospitals

- mortality rate of 8.9% for ACS patients (n = 1092) for central lab
- and only 6.7% (n = 1156) ($P = 0.049$) when cardiac markers were measured by a point-of-care device

In 773 consecutive patients who had had acute chest pain for less than 12 hours without ST-segment elevation on their ECGs, troponin T and troponin I status (positive or negative)
• Troponin T and troponin I proved to be strong, independent predictors of cardiac events.

• The event rates in patients with negative tests were only 1.1 percent for troponin T and 0.3 percent for troponin I.

Emergency Room Triage of Patients with Acute Chest Pain by Means of Rapid Testing for Cardiac Troponin T or Troponin I.
• 151 patients
• There was no difference in diagnostic performance
• For exclusion of damage, the two tests have similar and reliable diagnostic capacities 12 hours after the onset of symptoms.

• The bedside diagnosis or exclusion of acute myocardial infarction was carried out rapidly (within 20 minutes) and reliably by the CCU nurses.

Excellent reliability of nurse-based bedside diagnosis of acute myocardial infarction by rapid dry-strip creatine kinase MB, myoglobin, and troponin T. Sylven, Christer, MD, PhD, FACC, FESC, Lindahl, Susanne, Hellkvist, Karin, Nyquist, Olof, MD, PhD, Rasmanis, Gundars, MD, PhDAmerican Heart Journal. 135(4):677-683, April 1998.
The Benefits of Bedside Testing

- do not require centrifugation or anticoagulation
- do not require laboratory personnel to conduct testing.
- nurses and patient care technicians can easily be trained to perform
• This allows nurses to be more involved with their patient’s condition, because they are the medium between blood draw and test analysis.
Thank you

??????