“CARDIAC MARKERS”—WHY ALL THE CONFUSION?

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Disclosures

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Objectives

Upon completion of this session the participant will be able to:

1. Describe the challenges associated with cardiac patient testing to both the laboratory and clinical staff.
2. Discuss the role the lab must play as educator to the clinical staff.
3. Delineate the differences between analytical and clinical performance of cardiac marker testing.
How Laboratorians Rated The Importance of Cardiac Testing

![Pie charts showing top tests of the past decade by volume and tests with the most clinical significance of the past decade.](chart.png)

Respondents were asked to choose the top three tests.
“U.S. spends an estimated $8 billion to $13 billion per year in managing chest pain patients in the ED. “And approximately up to 80 percent of these patients don’t have ACS.”

Dr. Luis LeSaliva CAP Today Feb. 2009
2 Types of Myocardial Infarction

**STEMI (EKG Diagnosed)**
400k Cases Annually in the United States
EKG Diagnosed
50% Sensitivity?

**NSTEMI (Biomarker Confirmed)**
1.4m Cases Annually in the United States
Biomarker Diagnosed
Sensitivity and Specificity Variable

Photos courtesy of Boehringer Ingeheim International GmbH, by Lennart Nilsson.
CARDIAC MARKERS—HISTORICAL OVERVIEW
## The 3 Main Markers of Necrosis

### TABLE 1. PROPERTIES OF BIOMARKERS OF MYOCARDIAL NECROSIS.

<table>
<thead>
<tr>
<th>Biochemical marker</th>
<th>Molecular weight, g/mole</th>
<th>Cardiac specific?</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Duration of elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoglobin</td>
<td>18 000</td>
<td>No</td>
<td>High sensitivity and negative predictive value. Useful for early detection of MI and reperfusion.</td>
<td>Low specificity in presence of skeletal muscle injury and renal insufficiency. Rapid clearance after necrosis.</td>
<td>12–24 h</td>
</tr>
<tr>
<td>h-FABP</td>
<td>15 000</td>
<td>+</td>
<td>Early detection of MI</td>
<td>Low specificity in presence of skeletal muscle injury and renal insufficiency.</td>
<td>18–30 h</td>
</tr>
<tr>
<td>CK-MB, mass assays</td>
<td>85 000</td>
<td>+++</td>
<td>Ability to detect reinfarction. Large clinical experience. Previous gold standard for myocardial necrosis</td>
<td>Lowered specificity in skeletal muscle injury.</td>
<td>24–36 h</td>
</tr>
<tr>
<td>CK-MB isoforms</td>
<td>85 000</td>
<td>+++</td>
<td>Early detection of MI</td>
<td>Lack of availability/experience</td>
<td>18–30 h</td>
</tr>
<tr>
<td>cTnT</td>
<td>37 000</td>
<td>++++</td>
<td>Tool for risk stratification. Detection of MI up to 2 weeks. High specificity for cardiac tissue</td>
<td>Not an early marker of myocardial necrosis. Serial testing needed to discriminate early reinfarction.</td>
<td>10–14 days</td>
</tr>
<tr>
<td>cTnI</td>
<td>23 500</td>
<td>++++</td>
<td>Tool for risk stratification. Detection of MI up to 7 days. High specificity for cardiac tissue</td>
<td>Not an early marker of myocardial necrosis. Serial testing needed to discriminate early reinfarction. No analytical reference standards.</td>
<td>4–7 days</td>
</tr>
</tbody>
</table>

Time of first increase for the markers are 1–3 h for myoglobin, 3–4 h for CK-MB mass, 3–4 h for cTnT, and 4–6 h for cTnl. h-FABP, heart fatty acid–binding protein.


1970-80’s A giant leap forward

To clinicians, CK-MB values augmented a thorough history, physical, and ECG findings, and elevations rapidly became the gold standard for identifying cardiac injury.

- CK-MB allowed earlier diagnosis of acute myocardial infarction (AMI), and detection of reinfarction, and measurements could be used to provide a facile clinical estimate of infarct size.

- CK-MB assays initially relied on the measurement of enzyme activity, but over time, improved accuracy and ease of use were established by the use of mass assays.

- Mass assays allowed earlier detection of abnormal values and improved both clinical sensitivity and specificity.
  - However, mass assays unmasked an increased frequency of CK-MB elevations due primarily to skeletal muscle injury due to increased sensitivity.

- Clinical use of the percent relative index (CKMB Index) was then initiated.
  - This approach improved specificity of elevations for cardiac muscle injury.

  - Lacked sensitivity when concurrent cardiac injury and skeletal muscle injury were present because elevations from skeletal muscle often are of a large magnitude.
The Issues

A large amount of analytical confounders such as macrokinases and interfering substances also were substantial problems with these assays.

Attempts to standardize assays have been partially successful, but differences still exist between manufacturers and even between the same testing antibodies used on different analytical platforms.

A frequency of up to 20% “false positive” levels, thought to be due to skeletal muscle injury, was reported in patients with renal failure.

Many other conditions also influence results:
- noncardiac surgery, chest trauma, asthma, pulmonary embolism, chronic and acute muscle disease, head trauma, hyperventilation, and hypothyroidism in which CK-MB was elevated in the absence of cardiac injury.

The lack of cardiac specificity provided clinicians with more flexibility in their decision-making processes.

Enough reasons not related to cardiac injury were available that elevations of CK-MB in any given patient could be considered false positives if the physician did not believe the assay results fit the clinical presentation.
The Future Of CKMB- Not A Bright One!

Cost vs. Clinical Benefit
- Does CKMB provide incremental information that other markers can’t?

Quality control of CK-MB assays
- There has been increasing difficulty in controlling the quality of current CK-MB assays, and there often is considerable machine-to-machine variability.

How much is the diagnostic industry investing to enhance CKMB performance?
- It is clear that the level of commitment by industry to enhance CK-MB has decreased significantly, it is becoming clear that its use probably will be coming to a close in the near future.

Correct Utilization
- In many places, CK-MB is not being used correctly.
  - Recent data have reiterated the need for gender-specific reference ranges and cutoffs if CK-MB is to be used. Very few studies published today include this consideration.

Confusion & Resistance to Change.
- Some clinicians continue to use CK-MB which keeps staff from learning how to use Troponin properly and effectively
  - Learning new paradigms takes time and effort— who should be providing this education—LAB!

Eventually, however, clinicians need to learn how to use Troponin properly. Others have never learned how to use CK-MB properly because they have relied on Troponin and are thus confused when elevations occur in the absence of Troponin increases. This can negatively affect patient care.  

A. Jaffe-Mayo Clinic
CKMB—My Final Thoughts...

- The most current guidelines do not exclude CKMB:
  - Emerging countries may not have the availability of Troponin Testing

- Prognostic determinants for CKMB versus cTn are not very compelling...

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**Fig. 2.** Risk of death and recurrent ischemic events among patients with NSTEACS and normal serial CK-MB with and without increase baseline concentration of cardiac troponin I (Dimension RxL, Dade Behring). As discussed in section II-B1.c, the cut point applied in this study is specific to the assay used. Data from Morrow et al. The cut point applied in this study is specific to the assay used. Data from Morrow et al.67. UR, urgent revascularization prompted by recurrent ischemia.

What About Myoglobin?

Myoglobin is a low-molecular-weight protein that is present in both cardiac and skeletal muscle.

- It can be detected in the serum as early as 1-2 hours after myocardial necrosis begins.

- Myoglobin has low cardiac specificity but high sensitivity, which makes it most useful for ruling out myocardial infarction if the level is normal in the first four to eight hours after the onset of symptoms.

- Time changes in the myoglobin value also can be extremely helpful. Combining a doubling of the baseline myoglobin level at two hours after symptom onset with an abnormal myoglobin test at six hours after symptom onset increases the sensitivity to 95% at six hours.

- Myoglobin should be used in conjunction with other serum markers, because its level peaks and falls rapidly in patients with ischemia.
Multi-marker strategies that include myoglobin have been shown to identify patients with MI more rapidly than laboratory-based determination of a single marker.

1. Better as a **rule out** marker-negative predictive value

2. **Never** as a single marker—one time

3. Can enhance sensitivity and specificity when associated with early generation (less sensitive) Troponins.

However, this potential advantage of myoglobin will probably diminish with use of contemporary decision-limits and the enhanced sensitivity of newer Troponin assays.
Troponin
3 Types of Troponin

Cardiac Implications

- Troponin C
- Troponin I
- Troponin T

Presently the belief is that Troponin I & T reside only in myocardial cells = great cardiac specificity

- Troponin C is found in other muscle fibers in addition to the heart.

Present cardiac guidelines state that either Troponin I (cTnI) or Troponin T (cTnT) will yield clinically similar information.

Illustration: Chaikhouni A, M.D.; Al-Zaim H, M.D.; Department of Cardiothoracic Surgery, Al-Salam Hospital, Aleppo, Syria.
Current Utilization for Troponin Testing

Diagnostic Utilization

1. Detect elevations caused by impaired blood flow to the myocardium:
   - Acute Coronary Syndromes
     - NSTEMI
     - STEMI

2. Risk Stratification
   - To assess the probability that the patient’s symptoms are related to acute coronary ischemia;
   - To assess the patient’s risk of recurrent cardiac events, including death and recurrent ischemia.

Prognostic Utilization

- Predicting morbidity and mortality
- Predicting future ACS events
- Prognosis in Heart Failure outcomes...to name a few

“These abnormal concentrations have been significant predictors of an adverse short and/or long-term prognosis in nearly every available study.”

AHA/ACC/NACB Guidelines; Circulation 2007
cTn History—A Moving Target

In early studies, first-generation assays did not consistently outperform the then-gold standard CK-MB in sensitivity or analytical precision. NACB guidelines for cardiac biomarkers, published in 1999:

- Two cutpoints,
  - ROC curve used to establish acute MI decision limits.
  - They “Gray Zone” was born
  - Elevations below AMI curve were mainly labeled as false positives or ignored.
  - Risk Stratification was a concept few were believing in at this point.

“That set the stage for using whatever cutoff you want, and the field has never recovered from it,”

Jaffe et al, Clinical Chemistry 2008

- 2005
  - Introduced the concept of elevations greater than the 99%tile (of a well patient population) with a Coefficient of variation [CV] of 10% or <.
    - Only one or two assays could meet this requirement at that time.
  - It did however force the diagnostic industry to a goal of assay performance (moving closer to standardization [harmonization?])

NACB Guidelines Published In 2007

- Represented the first attempt to get all cardiac testing standardized.
3 Things to Remember About Troponin and It’s All Bad!

- Troponin rising is bad!
- Troponin falling is bad!
- Troponin remaining elevated is bad!
WHY ALL THE CONFUSION?
Sources of Confusion

Clinical Confounders
- Diagnostic Dilemmas
- Prognostic Dilemmas
- Clinical vs. Analytical Variables

Guideline Perspectives
- Numerous organizations with differing standards
- Constantly evolving criteria for best demonstrated practices.

Laboratory Confounders
- Assay Performance Variables
- Analyzer Performance Variable

Industry Confounders
- Continuous enhancement of assay performance
- Next generation assays and expanded clinical utility?
- New analyzer platforms with decreased Turn Around Time (TAT)
Clinical Confusion, why after all these years?

“It’s almost being drawn for all emergency patients and people are using the assay in a way that wasn’t intended. The confusion about how to use and interpret cTn results is so significant that the assay is being misused.”

Kristin Newby, MD, MHS, Duke University Medical Center

There are a lot of places where doctors admit every single person with troponin elevations, and the admitting physicians are reflexively consulting cardiologists.

- When the cardiologists see these patients, they ask, ‘why am I being consulted’? because this patient clearly doesn’t have cardiac ischemia”

Francis Fesmire, MD, FACEP, director of the department of emergency medicine, University of Tennessee-Chattanooga

A cardinal misuse of the assay is that it is ordered often in patients with an extremely low pre-test likelihood of ACS, “If the doctor thinks the patient has extremely low odds of having ACS, then he/she shouldn’t order the test. That’s what gets you in trouble, particularly in terms of false positive results,”.

Robert Christenson, PhD, professor of pathology University of Maryland School of Medicine in Baltimore
Rule #1  **KNOW YOUR ASSAY**

Why--Analytical Performance Variability

- Wide variations in detection, reference and cut-points limits and overall assay imprecision (coefficient of variation)
  - Specimen matrices (i.e., serum vs. plasma samples).
  - The presence of a large number of manufacturers of troponin assays in the U.S. makes standardization more difficult.
Epitopes-Antibody Variability, Instrumentation & Sample Management Issues

Differences in cTnI results between methods have been documented as due to a lack of calibrator standardization. Variation from 20- to 40-fold up to as much as a 100-fold amongst first generation assays has been reported, and more recently, 2-to 5-fold amongst current assays.

Source: IFCC 12-2010

Reference decision-limits should be established for each cardiac biomarker based on a population of normal, healthy individuals without a known history of heart disease (reference population).

*120 Patients Minimum!*
Rule #2 Know and Follow Manufacturers Instructions

For troponin testing, it is critical that patient specimens be collected and processed according to the manufacturers’ recommendations included in the device product insert. Improper collection, handling, and preparation of specimens can impact the accuracy of results.

- **Store** unused collection tubes and blood specimens according to the manufacturers’ recommendations.
- Follow manufacturers’ instructions for using collection tubes with anticoagulants. Some may contain insufficient anticoagulant and lead to elevated or decreased results.
- **Mix the content of tubes properly** at the time of blood collection to prevent incomplete clot formation (serum) and platelet clumping or clotting (plasma).
- **Process specimens according to the tube manufacturer’s recommendations.** Different types of tubes may have different requirements.
- Use a refrigerated, horizontal centrifuge head for best results. **Use the centrifuge settings recommended by the tube manufacturer.**
- **Inspect samples for clots, fibrin, particulate matter,** and other debris prior to processing them on an analyzer. Cellular debris from grossly hemolyzed samples may elevate test results.
- Follow manufacturer’s recommendation for running proper quality control samples. **At least one control should be run at the cutoff level.** If the risk stratification and acute myocardial infarction cutoff are different, separate controls should be considered at those levels.
- Follow the manufacturers’ recommended calibration and/or maintenance schedules.
  - Analyzer malfunction is one of the common assay interfering factors that leads to inaccurate results. Laboratories reporting troponin results should perform thorough and regular system maintenance to ensure peak performance of their analyzers and to reduce the possibility of inaccurate results.
Laboratorians should suspect the occurrence of **interfering antibodies in a troponin assay** when the test result:

- Does not agree with the patient’s clinical information for an acute myocardial infarction.
- May **not be reproducible** on the same or different assay system.
- Is not **linear after serial dilutions**.

**Digging Deeper…**

- Heterophile antibodies, human anti-animal antibodies, rheumatoid factor, and autoantibodies.
- Interference from other endogenous components in the blood such as bilirubin and hemoglobin.
- Immunocomplex formation.
- Microparticles in specimen.
- High concentration of alkaline phosphatase.
- Analyzer malfunction.
Rule #4 Understand What An Elevated Troponin Is Telling You!

Remember cTn elevation=myocyte death-think cardiac, but remember the etiology may not be ACS specific!

<table>
<thead>
<tr>
<th>Table 1. Differential diagnosis of increased cTn in patients without ACS or heart failure.</th>
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</thead>
<tbody>
<tr>
<td><strong>Acute disease</strong></td>
</tr>
<tr>
<td>- Cardiac and vascular</td>
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<tr>
<td>- Acute aortic dissection</td>
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<tr>
<td>- Cerebrovascular accident</td>
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<tr>
<td>- Ischemic stroke</td>
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<tr>
<td>- Intracerebral hemorrhage</td>
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<tr>
<td>- Subarachnoid hemorrhage</td>
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<tr>
<td>- Medical ICU patients</td>
</tr>
<tr>
<td>- Gastrointestinal bleeding</td>
</tr>
<tr>
<td>- Acute PE</td>
</tr>
<tr>
<td>- ARDS</td>
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<tr>
<td>- Cardiac inflammation</td>
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<tr>
<td>- Endocarditis</td>
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<tr>
<td>- Myocarditis</td>
</tr>
<tr>
<td>- Pericarditis</td>
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<tr>
<td>- Muscular damage</td>
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<tr>
<td>- Infectious</td>
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<tr>
<td>- Sepsis</td>
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<tr>
<td>- Viral illness</td>
</tr>
<tr>
<td>- Other acute causes of cTn increase</td>
</tr>
<tr>
<td>- Kawasaki disease</td>
</tr>
<tr>
<td>- Apical ballooning syndrome</td>
</tr>
<tr>
<td>- Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>- Rhabdomyolysis</td>
</tr>
<tr>
<td>- Birth complications in infants</td>
</tr>
<tr>
<td>- Preterm delivery</td>
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<tr>
<td>- Acute complications of inherited</td>
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<tr>
<td>disorders</td>
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<tr>
<td>- Neurofibromatosis</td>
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<tr>
<td>- Duchenne muscular dystrophy</td>
</tr>
<tr>
<td>- Klippel-Feil syndrome</td>
</tr>
<tr>
<td>- Environmental exposure</td>
</tr>
<tr>
<td>- Carbon monoxide</td>
</tr>
<tr>
<td>- Hydrogen sulfide</td>
</tr>
<tr>
<td>- Colchicine</td>
</tr>
</tbody>
</table>

ED Calling...They Say Our Results Are **WRONG**!

If a Troponin Test Result Does Not Match the Patient’s Clinical Picture for Acute Myocardial Infarction, **What Should Physicians Consider Doing?**

The physician must:

- Consider the possibility that some other clinical condition may be causing an elevated troponin level in the absence of acute myocardial infarction.

- **Communicate with the laboratory** about the test result and ask the laboratory to rule out technical errors, analytical interfering factors, and analyzer malfunction.

- **Consider repeating** the blood draw and retesting.

- Review the clinical presentation and consider additional diagnostic testing (e.g. reconsider the nature of chest pain, repeat ECG, etc.); bear in mind that the troponin test result is only one piece of the diagnostic puzzle.

FDA Website Document--Guidance Document, 7/2009 What Laboratorians Should Know to Manage Elevated Results
The Future
NEXT EXIT
It’s Going To Get Easier With Newer-Better Assay’s Right?

**Improving Performance**
- In contrast, the high sensitivity assays under investigation have reported that precision does not deteriorate as your lower limit of detection drops.

**Detecting disease in the asymptomatic stages**
- Prevention (Routine Screening)
- Detect cardiac remodeling occurring long before anatomical changes (cellular level)?
- Has our marker for Ischemia been under our noses all this time?
- Enhanced prognosis and earlier diagnosis

“Those of us invested in biomarkers can’t run so fast with [the next generation of Troponin testing] that we outstrip the ability of the clinical community to use that data.”

Apple et al. CAP Today, 2-2009
High Sensitivity Troponin
Preparing For Change

Am Heart J 2010;160:583-94.
NEJM 2009; 361: 858-67
How Low Can They Go?

How does LLD impact sensitivity and specificity?

- Are we ready to move from Nanograms to Picograms?
  
  \[0.01 \text{ng} = 10(\text{pg})\]

Source: IFCC 12-2010

Clinical studies emerging hint potential benefits in prognostic, diagnostic, and possibly therapeutic patient management strategies?
Opportunities Abound for Acute Cardiac Testing and Beyond!

Clinicians want Troponin to be a “yes” or “no” answer to Acute Coronary Syndrome (ACS) detection.

- Not in the cards for the immediate future at least.
- Research is ongoing--what % of increase (serial sampling)=ACS

Being able to measure reliably below the 99%tile will create more confusion—Yes

- The impact may be more patients diagnosed with ACS, that may have been diagnosed differently before hs-TN was available.

What impact will this have on existing cardiac POC testing?

- Lots of opinions, no one is really sure. Highly dependant on future studies and instrumentation advances!

Will guidelines be changing based off the enhanced performance characteristics?

- Yes—some issues emerging in the early data suggest:
  - Age related cutoff’s may be warranted
  - Gender related cutoff’s may be considered.
  - Intra-patient variability will require further study and clinical guidance.
  - Serial sampling time intervals may be altered.

Will the demand for hs-cTn testing increase?

- Yes—as more practitioners understand the prognostic benefits of monitoring hs-TN it will expand beyond cardiology and ED. Provided studies and guidelines support this evolution.
The Future—A Complex Picture-filled with ?’s

<table>
<thead>
<tr>
<th></th>
<th>Prognostic impact</th>
<th>Diagnostic impact</th>
<th>Therapeutic impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Markers of necrosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine phosphokinase MB</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Troponin</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Markers of myocardial dysfunction or stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial natriuretic peptides</td>
<td>+++</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Brain natriuretic peptides</td>
<td>+++</td>
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<td>+++</td>
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<tr>
<td>Copeptin</td>
<td>++</td>
<td>+</td>
<td>?</td>
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<tr>
<td>Proadrenomedullin</td>
<td>+</td>
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<td><strong>Markers of inflammation</strong></td>
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<td>Adiponectin</td>
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<td>C-reactive protein</td>
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<td>Growth differentiation factor 5</td>
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<tr>
<td>Interleukin 6</td>
<td>+++</td>
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<tr>
<td><strong>Soluble ST2</strong></td>
<td>+</td>
<td>?</td>
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<td>Tumor necrosis factor α</td>
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<td>Myeloid-related protein 8/14</td>
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<td><strong>Markers of ischemia</strong></td>
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<tr>
<td>Choline</td>
<td>++</td>
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<td>Heart-type fatty acid-binding protein</td>
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<tr>
<td>Ischemia modified albumin</td>
<td>+</td>
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<tr>
<td><strong>Markers of plaque destabilization/rupture</strong></td>
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<tr>
<td>Lipoprotein-associated phospholipase A2</td>
<td>+++</td>
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<td>Matrix metalloproteinase-9</td>
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<tr>
<td>Myeloperoxidase</td>
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<td>Placental growth factor</td>
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<td>Pregnancy-associated plasma protein A</td>
<td>+++</td>
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<td>Secretory phospholipase A2</td>
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<td>Soluble fms-like tyrosine kinase 1</td>
<td>+</td>
<td>+</td>
<td>?</td>
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<tr>
<td>Soluble intercellular adhesion molecule 1</td>
<td>+++</td>
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<td>?</td>
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<tr>
<td><strong>Markers of platelet activation</strong></td>
<td></td>
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<tr>
<td>Soluble CD40 ligand</td>
<td>++/?</td>
<td>?</td>
<td>?</td>
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<tr>
<td>Soluble P-selectin</td>
<td>++</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

* Some evidence by small studies; ++, intermediate evidence from several studies or one large study or trial; ++++, good evidence from several large studies or trials; ++++, excellent evidence; 9, conflicting results or no results available or not applicable.

* This table only gives an overview of the evidence published for the various markers. It does not indicate the clinical utility of different markers (e.g., a marker might be very useful for risk stratification, but not feasible for the clinical setting due to limitations in detection or because it is also elevated at important differential diagnoses).

* For stratification of patients with heart failure.
In the Meantime...

As Laboratorians, we need to prepare now to implement this new generation of hs-cTn assays by initiating discussions with our clinical colleagues. When the assays are introduced to the market, it will be our job to ensure the highest level of quality and to help clinicians interpret the results. Together, we can improve care of ACS patients.

Fred S. Apple, PhD
Medical Director of clinical laboratories,
Hennepin County Medical Center
Minneapolis, Minn.

Clinical Laboratory News September 2009
Suggested Reading

Troponin and MI-related Guidelines

Key professional organizations have published guidelines on the use and interpretation of cardiac biomarkers in ACS, including:


- http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/TipsandArticlesonDeviceSafety/ucm109362.htm

- http://www.ifcc.org/index.asp?cat=Scientific_Activities&scat=Troponin_Assay_Analytical_Characteristics&rif=4&dove=1
Questions

Email: rheitsman@radiometeramerica.com