Clinical Use of Cardiac Markers

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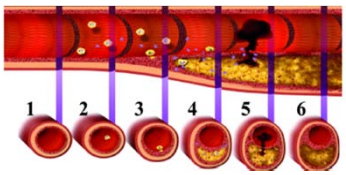


6/20/2014

Clinical Use of Cardiac Markers

OBJECTIVES:

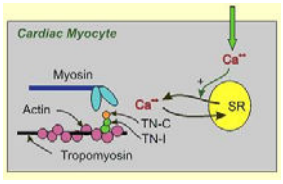
1) TROPONIN, CK-MB AND MYOGLOBIN IN TERMS OF:

- **biology**
- **role in diagnosis of MI**
- **limitations**

2) Risk assessment for ACS patients

3) Focus on Clinical Use

PART I : *Troponin Biology*



Troponin Biology

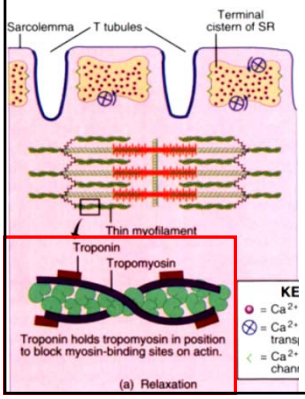
- Discovered in 1965 as "a new protein factor promoting aggregation of tropomyosin
- Purified troponin was separated into its three isoforms in 1971

Troponin T - tropomyosin binding

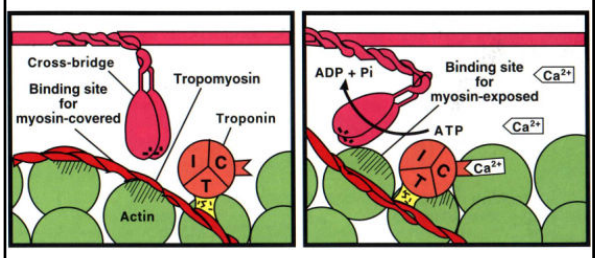
Troponin I - inhibitory

Troponin C - calcium binding

SKELETAL MUSCLE CONTRACTION



SKELETAL MUSCLE CONTRACTION (2)



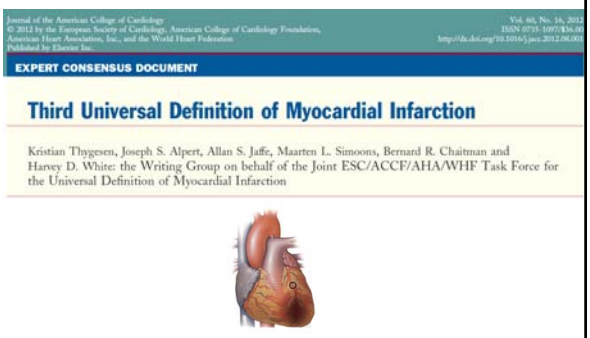
Troponin Biology

- Most cellular troponin is localized to myofibrils (~95%)
- The release of this troponin upon cellular necrosis is slow with troponin T being released slower than troponin I
- A small percentage is in the cytosol (~5%). As with other cytosolic biomarkers this fraction is is released quickly from necrotic cells

PART II: *Definitions*

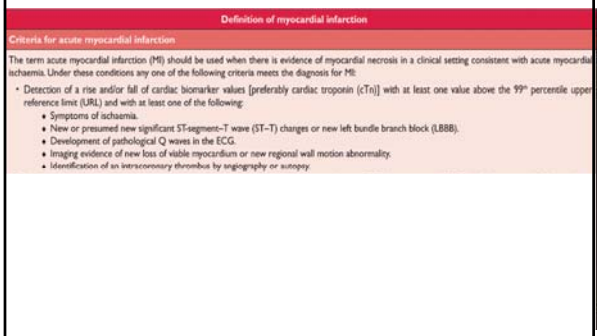
MI and ACS

MI: Current Definition



Thygesen K et al. Journal of the American College of Cardiology 60:1581–98, 2012

Current Recommendations



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.

Thygesen K et al. Journal of the American College of Cardiology 60:1581–98, 2012

How do you define a Reinfarction?

- ***In patients in whom reinfarction is suspected from clinical signs or symptoms following the initial MI, an immediate measurement of cTn is recommended.***
- ***A second sample should be obtained 3–6 h later.***
- ***If the cTn concentration is elevated, but stable or decreasing at the time of suspected reinfarction, the diagnosis of reinfarction requires a 20% or greater increase of the cTn value in the second sample.***
- ***If the initial cTn concentration is normal, the criteria for new acute MI apply.***

Thygesen K et al. Journal of the American College of Cardiology 60:1581–98, 2012

KEY POINTS

- **Keeps the emphasis on biomarkers especially troponin as defining an MI**
- **Cutoff limit of Troponin defined to the upper 99% of reference range and any elevation of Troponin over this limit is considered a possible MI in the right clinical setting**
- **Defined precision of 10% at the medical decision Point (99th percentile)**

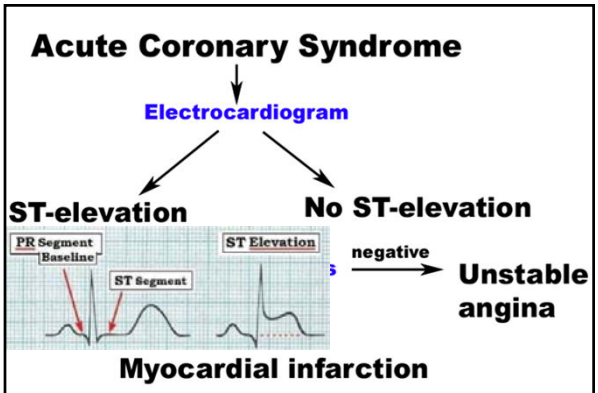
CONCERNS

- **Interpretation of a single Troponin value will be interpreted as an MI**

Acute Coronary Syndrome

Acute coronary syndrome or ACS is a set of signs and symptoms, usually including chest pain, that result from cardiac ischemia.

- Unstable Angina (+/- cardiac myocyte damage)
- Non-ST segment elevation MI
- ST segment elevation MI



PART III:
Clinical Use of Cardiac Biomarkers

WHY USE THE 99TH PERCENTILE TO DIAGNOSE MI?

Clinical Chemistry 52:11
2028–2035 (2006)

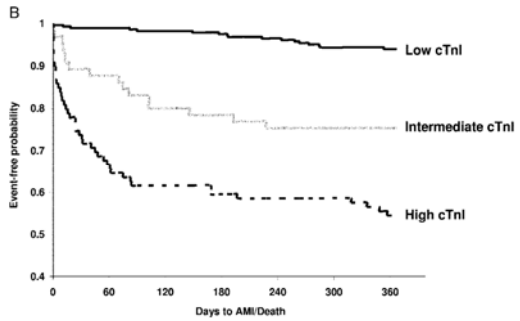
Evidence-Based
Laboratory Medicine
and Test Utilization

Health Outcomes Categorized by Current and Previous Definitions of Acute Myocardial Infarction in an Unselected Cohort of Troponin-Naïve Emergency Department Patients

Peter A. Kavsak,[1*] Andrew R. MacRae,[2] Glenn E. Palomaki,[3] Alice M. Newman,[4] Dennis T. Ko,[4] Viljam Lustig,[2] Jack V. Tu,[4] and Allan S. Jaffe[5]

- *448 patients who presented to the emergency department with symptoms suggestive of cardiac ischemia*
- *a low-cTnI group (i.e., cTnI <0.04 μg/L; also the manufacturer's indicated 99th percentile),*
- *an intermediate-cTnI group (cTnI 0.04–0.10 μg/L),*
- *and a high-cTnI group (cTnI >0.10 μg/L)*

WHY USE THE 99TH PERCENTILE TO DIAGNOSE MI?



Kaplan–Meier curve for mortality from all causes and/or subsequent AMI, among 448 patients stratified by AMI as determined by cTnI levels. Patients were stratified into 3 groups (low: peak cTnI 0.04 μg/L; intermediate: 0.04– 0.10 μg/L; high: 0.10 μg/L). *Kavsak PA et al. Clinical Chemistry 52:2028–2035 (2006)*

What is a high-sensitivity troponin (hsTn) assay?

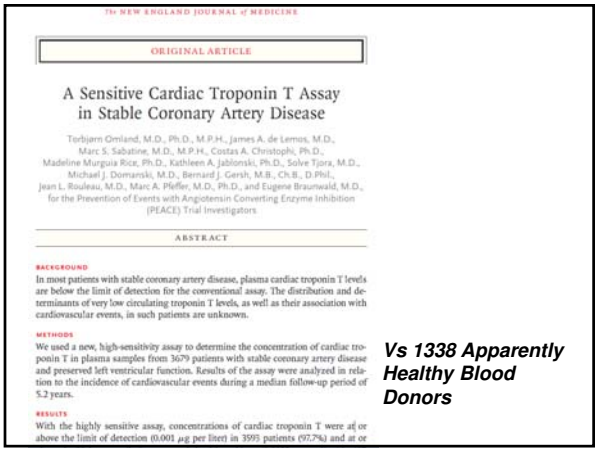
- **Hs-Tn assays have been defined as having less than or equal to 10% CV at the 99th percentile of a normal population and being able to detect concentrations of troponin in the measurable range of the assay for most normal individuals (*Apple FS, Collinson PO. Clinical Chemistry 58:54–61 2012*).**

Table 2. Analytical characteristics of hs cardiac troponin assays.

Company/ platform/assay	Cardiac troponin concentration at: LoD,[a] ng/L	99th Percentile, ng/L (CV)[b]	10% CV concentration, ng/L	Amino acid residues of epitopes recognized by capture (C) and detection (D) MAbs
hs-cTnI				
Abbott ARCHITECT[c]	1.2	16 (5.6%)	3.0	C: 24–40; D: 41–49
Beckman Access[c]	2–3	8.6 (10%)	8.6	C: 41–49; D: 24–40
Nanosphere MTP[c]	0.2	2.8 (9.5%)	0.5	C: 136–147; D: MAb PA1010
Singulex Erenna[c]	0.09	10.1 (9.0%)	0.88	C: 41–49; D: 27–41
Siemens Vista[c]	0.5	9 (5.0%)	3	C: 30–35; D: 41–56, 171–190
hs-cTnT				
Roche Elecsys[d]	5.0	14 (8%)	13	C: 136–147; D: 125–131

[a] LoD, limit of detection; MTP, microtiter plate.
[b] CV at the 99th percentile.
[c] Under development and not available for commercial use.
[d] Available for use worldwide but not cleared by the US Food and Drug Administration for use in the US.

Apple FS, Collinson PO. Clinical Chemistry 58:54–61 2012.


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease

Torbjørn Omland, M.D., Ph.D., M.P.H., James A. de Lemos, M.D., Marc S. Sabatine, M.D., M.P.H., Costas A. Christophi, Ph.D., Madeline Murguia Rice, Ph.D., Kathleen A. Jablonski, Ph.D., Solve Tjora, M.D., Michael J. Domanski, M.D., Bernard J. Gersh, M.B., Ch.B., D.Phil., Jean L. Rouleau, M.D., Marc A. Pfeffer, M.D., Ph.D., and Eugene Braunwald, M.D., for the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial Investigators

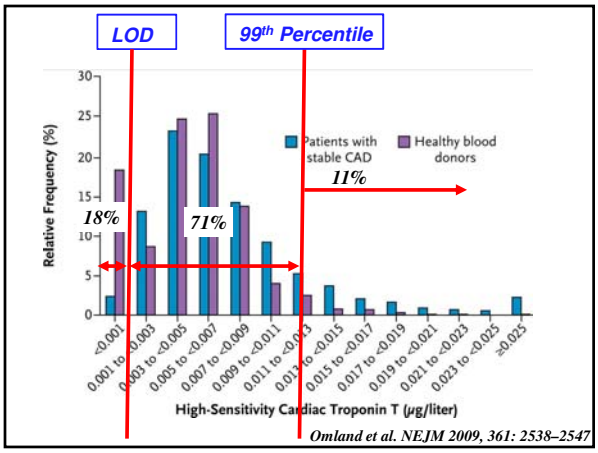
ABSTRACT

BACKGROUND
In most patients with stable coronary artery disease, plasma cardiac troponin T levels are below the limit of detection for the conventional assay. The distribution and determinants of very low circulating troponin T levels, as well as their association with cardiovascular events, in such patients are unknown.

METHODS
We used a new, high-sensitivity assay to determine the concentration of cardiac troponin T in plasma samples from 3679 patients with stable coronary artery disease and preserved left ventricular function. Results of the assay were analyzed in relation to the incidence of cardiovascular events during a median follow-up period of 5.2 years.

RESULTS
With the highly sensitive assay, concentrations of cardiac troponin T were at or above the limit of detection (0.001 μg per liter) in 3593 patients (97.7%) and at or

Vs 1338 Apparently Healthy Blood Donors



Omland et al. NEJM 2009, 361: 2538–2547

Nomenclature of troponin assays and clinical usage.

	Assay Criterion	Application Diagnosis Myocardial Infarction	Risk Stratification Secondary Prevention	Risk Stratification Primary Prevention
Conventional troponin		+	(+)	-
Contemporary sensitive troponin	10%CV ≤ 99th percentile	++	+	-
High sensitive troponin	Detectable in ≥ 50% of a general population	++	++	+
Super sensitive troponin	Detectable in ≥ 95% of a general population	?	?	?

Keller T et al. Circulation. 2011;123:1361-1363

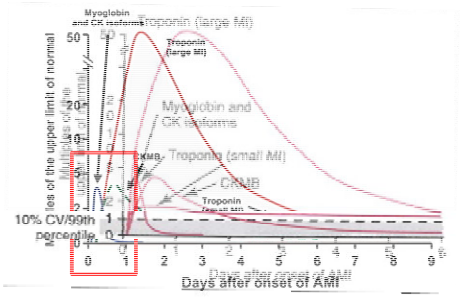
American Heart Association

When should cardiac markers be used?

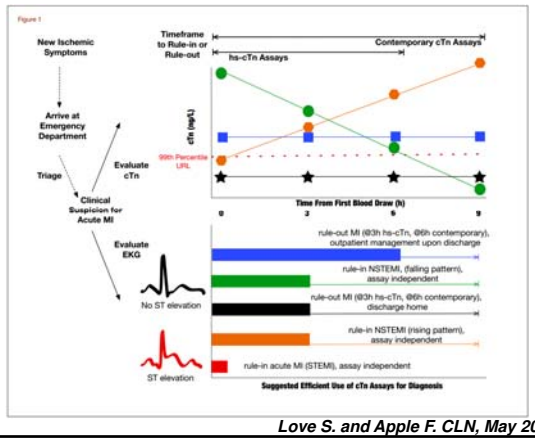
- **For detection of AMI by cardiac markers, in the absence of definitive ECGs, the following sampling frequency is recommended:**

Marker	Admission	2-4 h	6-9 h	12-24 h
Tn	X	X	X	optional

Temporal Changes in Cardiac Markers Post AMI



This is NOW!



Love S. and Apple F. CLN, May 2014

Can lowering the diagnostic threshold for MI improve clinical outcomes?

Implementation of a Sensitive Troponin I Assay and Risk of Recurrent Myocardial Infarction and Death in Patients With Suspected Acute Coronary Syndrome

Nicholas L. Mills, MD, PhD
Antonia M. D. Churchhouse, BSc, MD
Kuan Ken Lee
Atul Anand, BSc, MD
David Gamble, MD
Anoop S. V. Shah, MD
Elspeth Paterson, MD
Margaret MacLeod, BSc
Catriona Graham, MSc
Simon Walker, DM, FRCPath
Martin A. Denvir, PhD, FRCP
Keith A. A. Fox, FESC, FMedSci

Context Although troponin assays have become increasingly more sensitive, it is unclear whether further reductions in the threshold of detection for plasma troponin concentrations will improve clinical outcomes in patients with suspected acute coronary syndrome (ACS).

Objective To determine whether lowering the diagnostic threshold for myocardial infarction (MI) with a sensitive troponin assay could improve clinical outcomes.

Design, Setting, and Patients All consecutive patients admitted with suspected ACS to the Royal Infirmary of Edinburgh, Edinburgh, Scotland, before (n = 1038; February 1-July 31, 2008, during the validation phase) and after (n = 1054; February 1-July 31, 2009, during the implementation phase) lowering the threshold of detection for myocardial necrosis from 0.20 to 0.05 ng/mL with a sensitive troponin I assay were stratified into 3 groups (<0.05 ng/mL, 0.05-0.19 ng/mL, and ≥0.20 ng/mL). During the validation phase, only concentrations above the original diagnostic threshold of 0.20 ng/mL were reported to clinicians.

Main Outcome Measure Event-free survival (recurrent MI and death) at 1 year in patients grouped by plasma troponin concentrations.

JAMA. 2011;305(12):1210-1216

Methods

Study Phases: The study was divided into 2 phases (validation and implementation).

- **Troponin I was measured using the reformulated sensitive assay throughout both phases, only concentrations above the original diagnostic threshold (0.20 ng/mL) were reported in the validation phase**
- **Concentrations above the revised diagnostic threshold (0.05 ng/mL) were reported during the implementation phase**
- **Patients stratified into 3 groups based on peak plasma troponin I assay concentration (0.05 ng/mL, 0.05-0.19 ng/mL, and 0.20 ng/mL).**

JAMA. 2011;305(12):1210-1216

Lowering the diagnostic threshold of plasma troponin was associated with major reductions in morbidity and mortality

Table 3. Clinical Outcomes of Patients With Suspected Acute Coronary Syndrome Before (Validation Phase) and After (Implementation Phase) the Introduction of a Sensitive Troponin Assay[a]

	No. (%) of Patients					Post Hoc Analysis *P* Value		
		Stratified by Peak Troponin Concentration, ng/mL						
	All	<0.05	0.05-0.19	≥0.20	*P* Value	<0.05 vs 0.05-0.19	<0.05 vs ≥0.20	0.05-0.19 vs ≥0.20
Validation phase	(N = 1038)	(n = 657)	(n = 90)	(n = 291)				
3 mo								
Death	43 (4)	10 (2)	14 (16)	19 (7)	<.001	<.001	<.001	.02
MI	54 (5)	11 (2)	18 (20)	25 (9)	<.001	<.001	<.001	.007
Death or recurrent MI	82 (8)	18 (3)	24 (27)	40 (14)	<.001	<.001	<.001	.006
12 mo								
Death	75 (7)	23 (4)	19 (21)	33 (11)	<.001	<.001	<.001	.02
MI	104 (10)	30 (5)	26 (29)	48 (16)	<.001	<.001	<.001	.01
Death or recurrent MI	150 (14)	45 (7)	35 (39)	70 (24)	<.001	<.001	<.001	.007
Implementation phase	(N = 1054)	(n = 683)	(n = 80)	(n = 291)				
3 mo								
Death	47 (4)	6 (1)	4 (5)[b]	37 (13)[b]	<.001	.01	<.001	.07
MI	29 (3)[b]	9 (1)	5 (6)[b]	15 (5)	<.001	.01	.001	.78
Death or recurrent MI	70 (7)	14 (2)	9 (11)[b]	47 (16)	<.001	<.001	<.001	.38
12 mo								
Death	78 (7)	20 (3)	9 (11)	49 (17)	<.001	.002	<.001	.30
MI	56 (5)[c]	16 (2)[b]	9 (11)[b]	31 (11)	<.001	<.001	<.001	.84
Death or recurrent MI	119 (11)[b]	33 (5)	17 (21)[b]	69 (24)	<.001	<.001	<.001	.76

Abbreviation: MI, myocardial infarction.
[a] Variables analyzed using χ^2 test with post hoc Fisher exact testing between individual groups.
[b] $P < .05$ for validation phase vs implementation phase.
[c] $P < .001$ for validation phase vs implementation phase.

JAMA. 2011;305(12):1210-1216

Is there a down side to hsTn?

- **The advantages of the hs-troponin assays are that they detect AMI earlier than standard assays and provide improved risk stratification. In patients with suspected ACS hs-troponin testing improved morbidity and mortality.**
- **However the increased sensitivity of these assays comes with a reduction in the specificity. It is important to remember that troponin measures <u>myocardial cell injury/death</u> which can result from various causes including AMI.**

(Katus HA, Giannitsis E, Jaffe AS. Clin Chem. 2012;58:39-43)

Conditions that increase serum cardiac troponin

- ***myocarditis,***
- ***congestive heart failure,***
- ***Percutaneous Transluminal Coronary Angioplasty(PCTA),***
- ***Coronary Artery Bypass Graft (CABG),***
- ***aortic valve disease and hypertrophic obstructive cardiomyopathy with significant left ventricular,***
- ***hypotension often with arrhythmias,***
- ***drug toxicity (Adriamycin, 5FU, Herceptin, snake venoms),***
- ***hypothyroidism pulmonary embolism,***
- ***vital exhaustion,***
- ***rhabdomyolysis with cardiac injury,***
- ***cardiac contusion,***
- ***trauma,***
- ***sepsis,***
- ***renal failure/chronic dialysis,***
- ***stroke,***
- ***marathon running***

On the Relative Value of an Assay Versus That of a Test

A History of Troponin for the Diagnosis of Myocardial Infarction*

Robert L. Jesse, MD, PhD
Richmond, Virginia

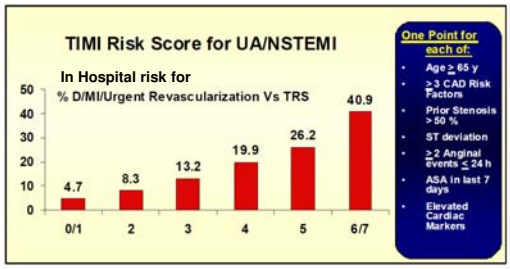
- *"…we have done little to resolve the confusion around non-ischemic Tn elevations. These are frequently referred to as "false positive troponins"— or by some as "'expletive' false positive troponins."*
- *"A major consequence of the increasingly sensitive and specific Tn ….. has been the erosion of the importance of the clinical findings, a diminished value of the ECG, and most importantly a marginalization of the value of serial biomarker measurements."*
- *"As the Tn assays become more and more sensitive, and analytical performance improves, the clinical context in which results are interpreted will be increasingly important."*

JACC Vol. 55, 2010:2125–8

Clinical Risk Scores

TIMI Risk Score for UA/NSTEMI – Establishment of a simple risk score derived from baseline clinical information as a powerful predictor of clinical outcomes in patients with UA/NSTEMI ***~ 84,000 patients NRMI***

TIMI 11B

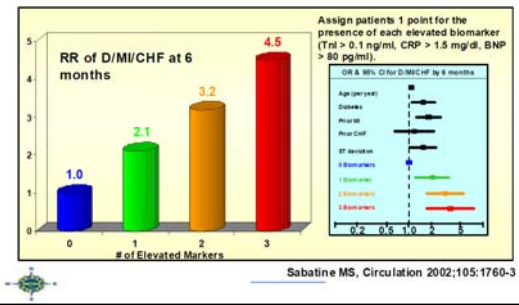


Antman EM, JAMA 2000;284:835-842

Clinical Risk Scores

Multimarker Strategy in ACS - Demonstration that with a multimarker approach, troponin, hs-CRP, and BNP provide independent and complementary prognostic information in patients with non-ST elevation ACS

TACTICS-TIMI 18 ***1635 patients***



Sabatine MS, Circulation 2002;105:1760-3

Using the change of cTnI rise or delta improves diagnosis of AMI

Table 2. Stratification for AMI by initial cTnI and delta criterion.

cTnI, μg/L	Patients with AMI
Initial <0.034	
Increase <20%	2 of 226 (0.9%)
Increase >20%	14 of 45 (31%)
Initial >0.034	
Increase <20%	11 of 72 (15%)
Increase >20%	25 of 38 (66%)
Initial <0.034	
Increase <30%	2 of 223 (0.9%)
Increase >30%	14 of 38 (37%)
Initial >0.034	
Increase <30%	11 of 78 (14%)
Increase >30%	25 of 32 (78%)

cTnI was measured on admission and approximately 6 h postadmission in 381 patients. The 99th percentile cTnI concentration = (0.034 μg/L)

Note improved sensitivity at each cTnI concentration

Apple et al. Clin Chem 55:930-937, 2009

What about POCT for MI?

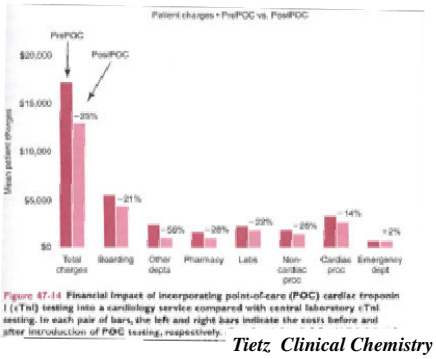


Figure 47-14 Financial impact of incorporating point-of-care (POC) cardiac troponin I (cTnI) testing into a cardiology service compared with central laboratory cTnI testing. In each pair of bars, the left and right bars indicate the costs before and after introduction of POC testing, respectively.

Tietz Clinical Chemistry 2012

POCT for AMI

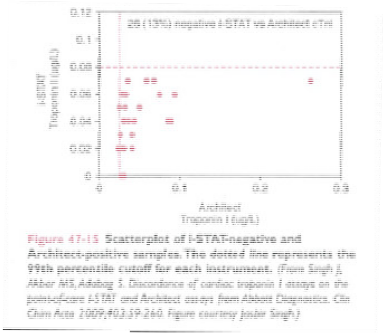


Figure 47-15 Scatterplot of i-STAT-negative and Architect-positive samples. The dotted line represents the 99th percentile cutoff for each instrument. (From Singh J, Abbor AS, Adabag S. Discordance of cardiac troponin I assays on the point-of-care i-STAT and Architect assays from Abbott Diagnostics. Clin Chim Acta 2009;403:39-260. Figure courtesy Jasbir Singh.)

Presently Siemens Stratus CS has adequate sensitivity

What do the results mean?

- Hs-troponin assays are able to diagnose MI earlier when the 99th percentile of the reference range is used as the cutoff reducing mortality and morbidity
- Hs-troponin assays will mean more abnormal troponins that are not necessarily MI's (reduces specificity for MI)
- We can actually measure values in the normal range although that remains to be seen
- Two reference ranges for males and females (eventually)

LIMITATIONS

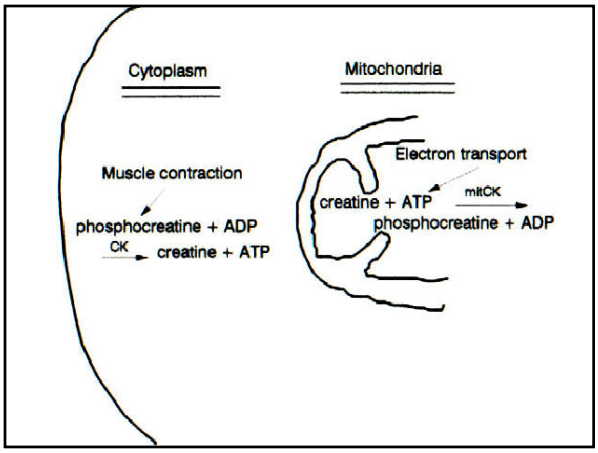
- Indicates cardiac myocyte death
- Must be interpreted with respect to time from onset of pain

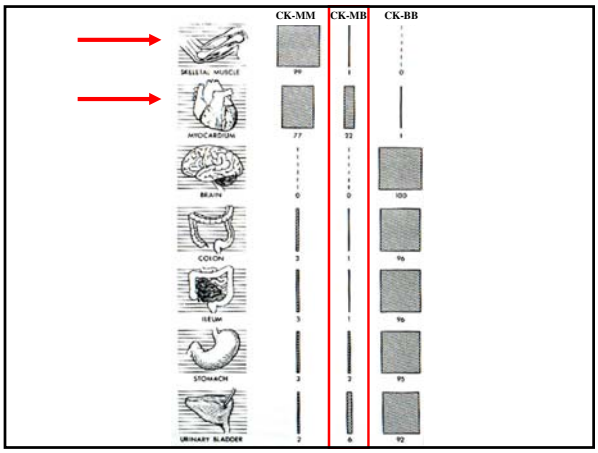
PART I V:

CKMB and Myoglobin

CREATINE KINASE

- 86-89 kDa cytoplasmic and mitochondrial enzyme involved in high energy phosphate production and utilization within contractile tissues
- CK exists as a dimer and use of isoenzymes has proved extremely useful in diagnosis of AMI
- former “gold standard” for biomarker detection of AMI





LIMITATIONS

Major limitation is lack of specificity, however this can be overcome to a large extent by using the *CK-MB/CK ratio*

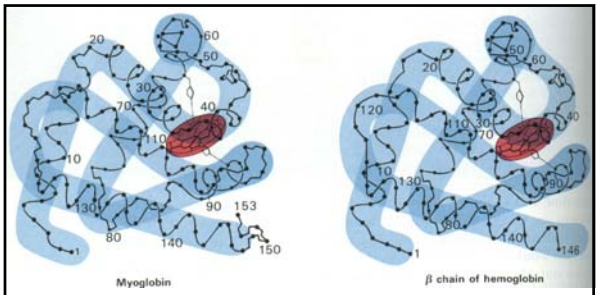
Shorter time window for elevation compared to troponins

May be useful in:

- **detecting reinfarction**
- **confirming Troponin elevations**

MYOGLOBIN

- **17.8 kDa OXYGEN BINDING PROTEIN PRESENT IN BOTH CARDIAC AND SKELETAL MUSCLE**
- **CYTOPLASMIC AND COMPRISES ~2% OF MUSCLE PROTEIN**
- **BECOMES ABNORMAL BETWEEN 2-4 HOURS POST AMI PEAKS AT 6-9 HOURS AND RETURNS TO NORMAL IN 24-26 HOURS**
- **EARLY RISE IN MYOGLOBIN POST AMI IS ATTRIBUTED TO ITS SMALL MOLECULAR SIZE AND CYTOPLASMIC LOCATION**



- No cardiac specific isoform
- Can be elevated in muscle injury and renal failure
- May be useful as a marker of reperfusion?

LIMITATIONS

- Poor specificity limits the usefulness of myoglobin in diagnosis of AMI
- Time period of usefulness is 2-4 hours post AMI and main value is rule out (eclipsed by hsTn)
- Not all studies demonstrate improved sensitivity at early time points
- May improve diagnostic sensitivity when used in combination with other markers

Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays

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BACKGROUND
The rapid and reliable diagnosis of acute myocardial infarction is a major unmet clinical need.

METHODS
We conducted a multicenter study to examine the diagnostic accuracy of new, sensitive cardiac troponin assays performed on blood samples obtained in the emergency department from 718 consecutive patients who presented with symptoms suggestive of acute myocardial infarction. Cardiac troponin levels were determined in a blinded fashion with the use of four sensitive assays (Abbott-Architect Troponin I, Roche High-Sensitive Troponin T, Roche Troponin I, and Siemens Troponin I Ultra) and a standard assay (Roche Troponin T). The final diagnosis was adjudicated by two independent cardiologists.

RESULTS
Acute myocardial infarction was the adjudicated final diagnosis in 123 patients (17%). The diagnostic accuracy of measurements obtained at presentation, as quantified by the area under the receiver-operating-characteristic curve (AUC), was significantly higher with the four sensitive cardiac troponin assays than with the standard assay (AUC for Abbott-Architect Troponin I, 0.96; 95% confidence interval [CI], 0.94 to 0.98; for Roche High-Sensitive Troponin T, 0.96; 95% CI, 0.94 to 0.98; for Roche Troponin I, 0.95; 95% CI, 0.92 to 0.97; and for Siemens Troponin I Ultra, 0.96; 95% CI, 0.94 to 0.98; vs. AUC for the standard assay, 0.90; 95% CI, 0.86 to 0.94). Among patients who presented within 3 hours after the onset of chest pain, the AUCs were 0.93 (95% CI, 0.88 to 0.99), 0.92 (95% CI, 0.87 to 0.97), 0.92 (95% CI, 0.86 to 0.99), and 0.94 (95% CI, 0.90 to 0.98) for the sensitive assays, respectively, and 0.76 (95% CI, 0.64 to 0.88) for the standard assay. We did not assess the effect of the sensitive troponin assays on clinical management.

CONCLUSIONS
The diagnostic performance of sensitive cardiac troponin assays is excellent, and these assays can substantially improve the early diagnosis of acute myocardial infarction, particularly in patients with a recent onset of chest pain. (ClinicalTrials.

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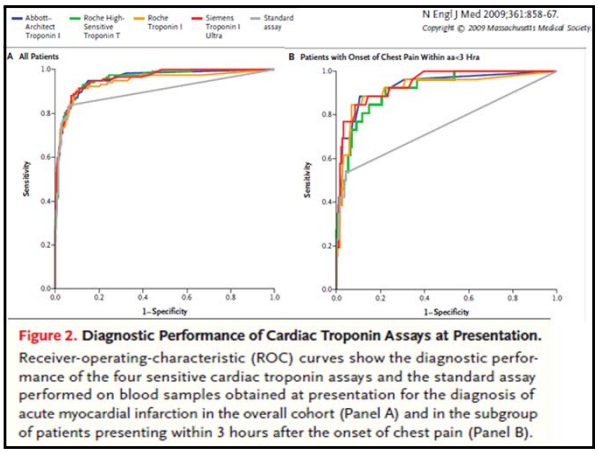

Figure 2. Diagnostic Performance of Cardiac Troponin Assays at Presentation.

Receiver-operating-characteristic (ROC) curves show the diagnostic performance of the four sensitive cardiac troponin assays and the standard assay performed on blood samples obtained at presentation for the diagnosis of acute myocardial infarction in the overall cohort (Panel A) and in the subgroup of patients presenting within 3 hours after the onset of chest pain (Panel B).