HIGH SENSITIVITY TROPONIN… COMING SOON TO A LAB NEAR YOU?

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Title: National Account Manager/Clinical Cardiac Specialist-Radiometer America.

Objectives

Upon completion the participant will be able to

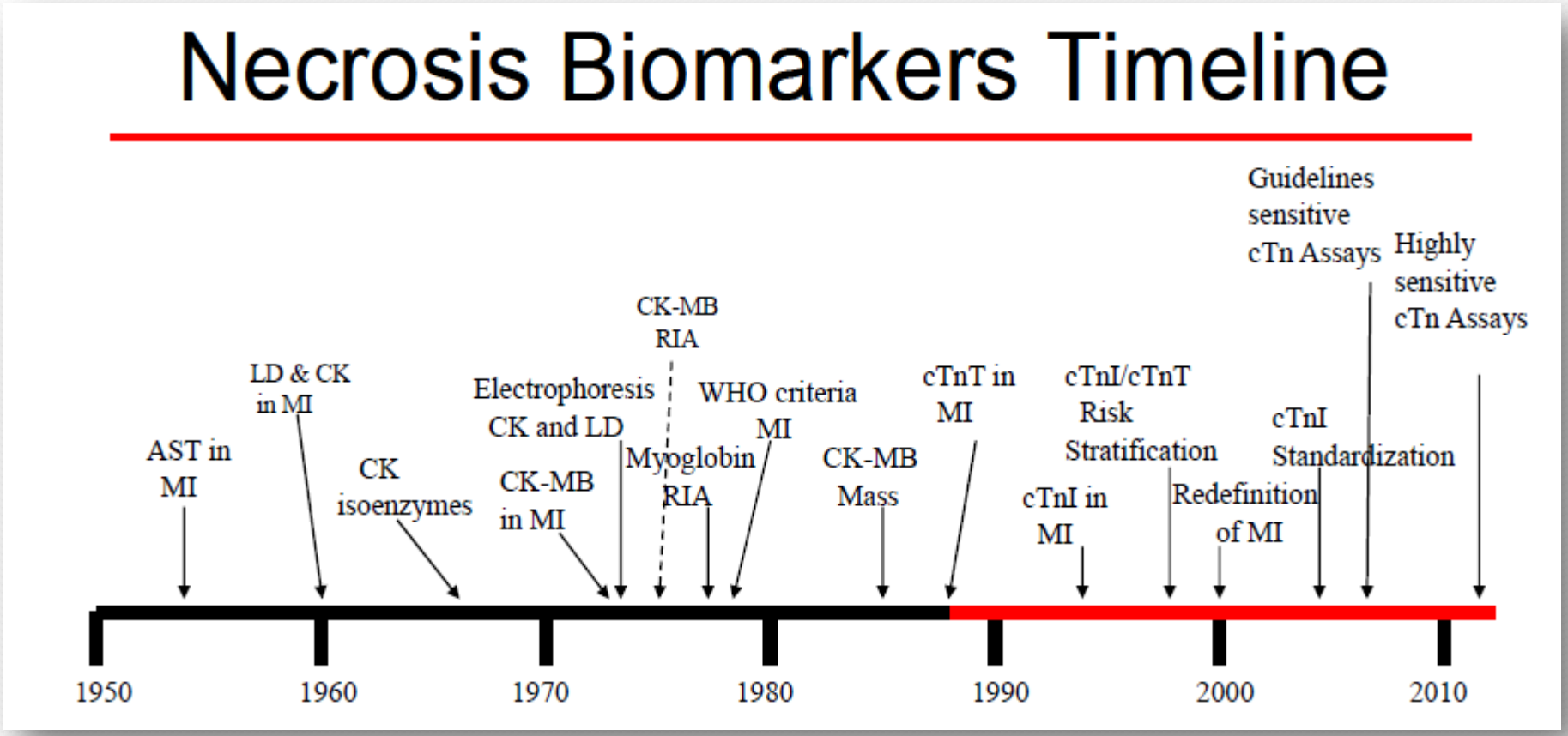
- Review current and evolving definitions of “High Sensitivity” troponin assays.
- Assess the analytical performance variables of these assays
- Describe how high sensitivity troponin assays have impacted patient care and the clinicians ordering this test.
- Recognize the best demonstrated practices of customers (OUS) that have integrated these assays into laboratory and clinical practice.
- Analyze the potential impact of these assays in the point-of-care setting.

Disclosures & Disclaimers

- All Material Contained In This Preseneation Have Been Carefully Reviewed To Ensure No Vendor Bias Has Been Included In This Presentation.
- Thoughts Expressed In This Presentation Do Not Necessarily Represent Those Of Radiometer America Or Its Affiliates.
- The majority of the presentation is **NOT** based upon U.S. based Consensus/Care Guidelines; the information presented represents international experience utilizing High Sensitivity Troponin Assays.

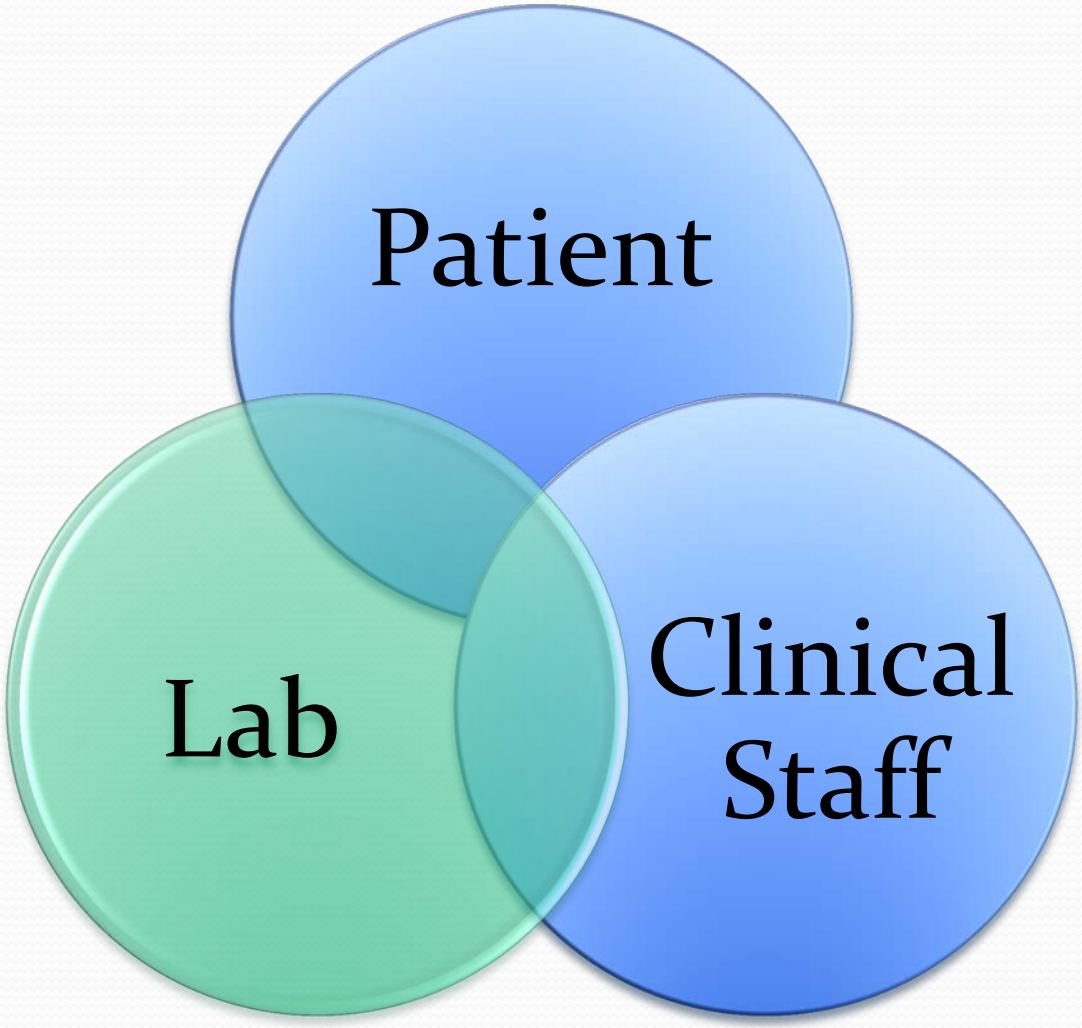
Many of the assays described are **not cleared for sale and distribution in the US, by the FDA.**

The Last 60+ Years…

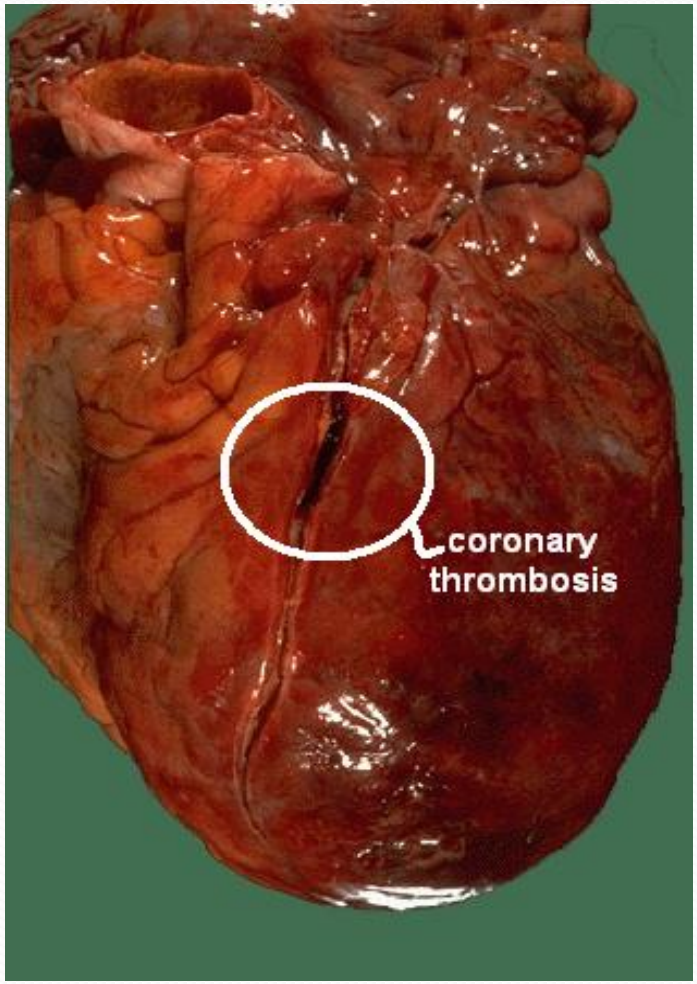


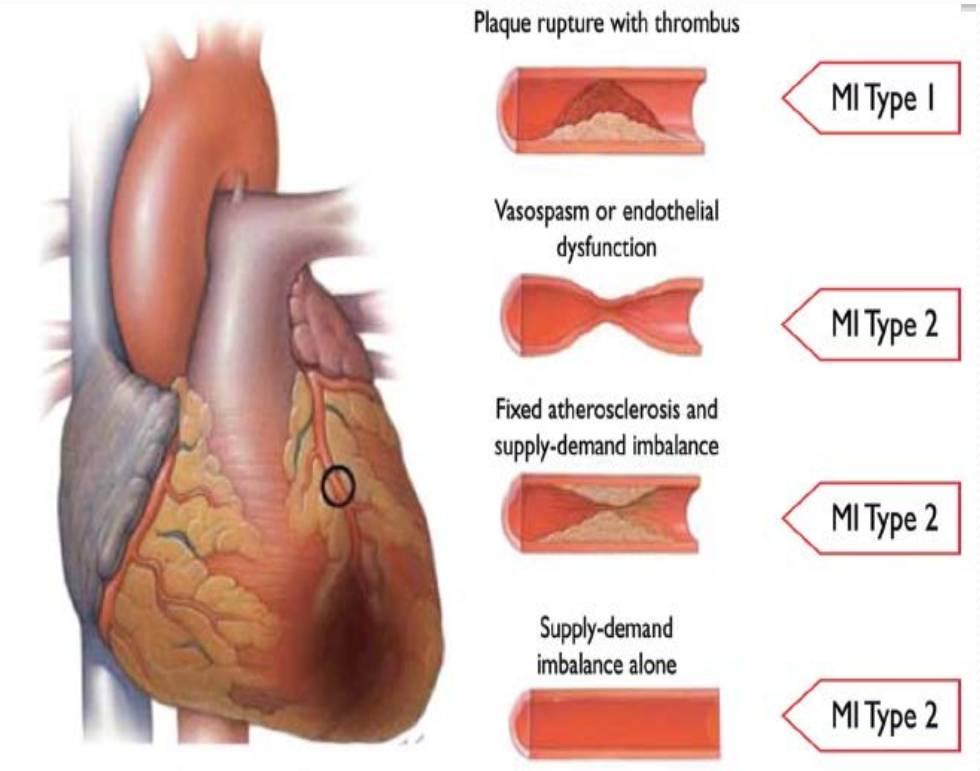
Slide Courtesy of R. Christenson University Of Maryland

Troponin Testing Beneficiaries



Chiefly Troponin Aids in MI (Myocardial Infarction)





Circulation 8-2012: Thygesen et al ESC/ACCF/AHA/WHF Third Universal Definition of MI

Photos courtesy of Boehringer Ingleheim International GmbH, by Lennart Nilsson.

The Third Universal Definition of MI…

MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. 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 ischemia.
- ECG changes…long list of criteria
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.
- Several other specific conditions associated with procedural MI conditions.

Assay Variability:

Epitopes, Antibodies and Instrumentation

Table 1. Analytical characteristics of contemporary sensitive and point-of-care cardiac troponin assays.

Company/platform/assay	Cardiac troponin concentration at: LoD,[a] μg/L	99th Percentile, μg/L (CV)[b]	10% CV concentration, μg/L	Amino acid residues of epitopes recognized by capture (C) and detection (D) MAbs
Abbott AxSYM ADV	0.02	0.04 (14%)	0.16	C: 87–91, 41–49; D: 24–40
Abbott ARCHITECT	0.009	0.028 (14%)	0.032	C: 87–91, 24–40; D: 41–49
Abbott i-STAT	0.02	0.08 (16.5%)	0.10	C: 41–49, 88–91; D: 28–39, 62–78
Alere Triage	0.05	<0.05 (NA)	NA	C: NA; D: 27–40
Alere Triage Cardio3[c]	0.01	0.02 (17%)	NA	C: 27–39; D: 83–93, 190–196
Beckman Access AccuTnI	0.01	0.04 (14%)	0.06	C: 41–49; D: 24–40
bioMérieux Vidas Ultra	0.01	0.01 (27.7%)	0.11	C: 41–49, 22–29; D: 87–91, MAb 7B9
Mitsubishi Pathfast	0.008	0.029 (5.0%)	0.014	C: 41–49; D: 71–116, 163–209
Ortho Vitros ECi ES	0.012	0.034 (10%)	0.034	C: 24–40, 41–49; D: 87–91
Radiometer AQT90 cTnI	0.009	0.023 (17.7%)	0.039	C: 41–49, 190–196; D: 137–149
Radiometer AQT90 cTnT	0.008	0.017 (15.2%)	0.026	C: 125–131; D: 136–147
Response RAMP	0.03	<0.01 (18.5% at 0.05)	0.21	C: 85–92; D: 26–38
Roche cobas h232 Cardiac T[c,d]	0.05	NA	NA	C: 125–131; D: 136–147
Roche Elecsys TnT Gen 4	0.01	<0.01	0.030	C: 136–147; D: 125–131
Roche Elecsys TnI	0.16	0.16 (10%)	0.30	C: 87–91, 190–196; D: 23–29, 27–43
Roche Cardiac Reader cTnT[e]	0.03	NA	NA	C: 125–131; D: 136–147
Siemens Centaur Ultra	0.006	0.04 (8.8%)	0.03	C: 41–49, 87–91; D: 27–40
Siemens Dimension RxL	0.04	0.07 (20%)	0.14	C: 27–32; D: 41–56
Siemens Immulite 2500	0.1	0.2 (NA)	0.42	C: 87–91; D: 27–40
Siemens Stratus CS	0.03	0.07 (10%)	0.06	C: 27–32; D: 41–56
Siemens Vista	0.015	0.045 (10%)	0.04	C: 27–32; D: 41–56
Tosoh AIA	0.06	<0.06 (NA)	0.09	C: 41–49; D: 87–91

[a] LoD, limit of detection; NA, not available; Gen 4, fourth-generation assay.
[b] CV at 99th percentile.
[c] Not cleared by the US Food and Drug Administration.
[d] Standardized against hs-cTnT assay.
[e] Standardized against Gen 4 cTnT assay.

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 among first generation assays were reported, and more recently, 2 to 5 fold amongst current assays.

Apple et al, High Sensitivity Cardiac Troponin Assays: *Clinical Chemistry, 58:1 (2012)*

High Sensitivity Troponin

What's Different?

High Sensitivity Troponin Defined?

1. First, The Total Imprecision (CV) At The 99th Percentile Value Should Be At 10%.

2. Second, Measurable Concentrations Below The 99th Percentile Should Be Attainable With An Assay At A Concentration Value Above The Assay's Limit Of Detection For At Least **50% (And Ideally 95%)** Of Healthy Individuals To Attain The Highest Level Of Scorecard Designation.

Presently <15% Of Cleared Assays Can Accurately Detect cTn Values In Healthy Individuals.

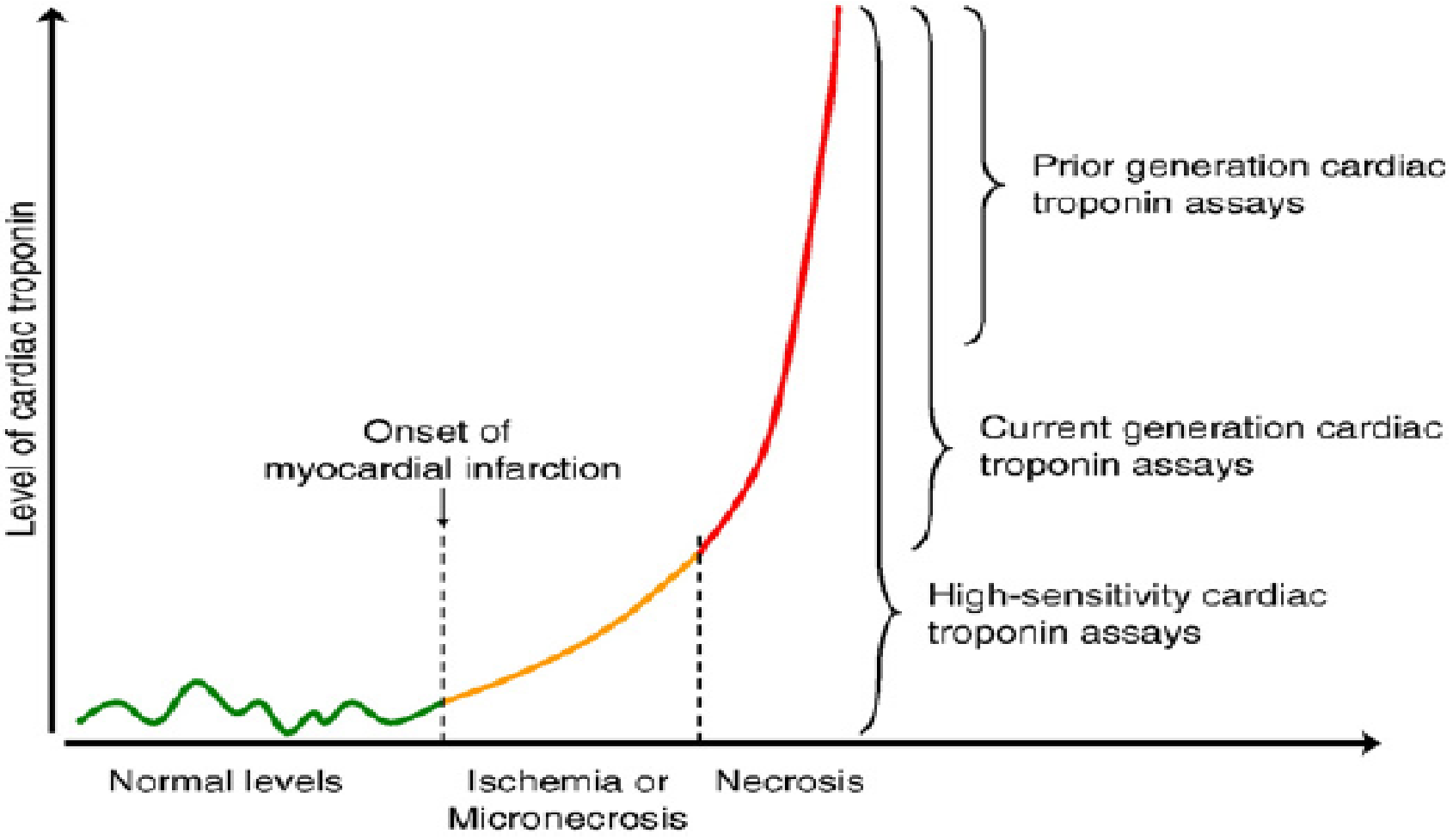
Table 1. Scorecard designations of cTn assays.

Acceptance designation	Total imprecision at the 99th percentile, CV%
Guideline acceptable	≤10
Clinically usable	>10 to ≤20
Not acceptable	>20
Assay designation	**Measurable normal values below the 99th percentile, %**
Level 4 (third generation, hs)	≥95
Level 3 (second generation, hs)	75 to <95
Level 2 (first generation, hs)	50 to <75
Level 1 (contemporary)	<50

Analytical Characteristics of High-Sensitivity Cardiac Troponin Assays: *Clin Chem* 58:1 54–61 (Sept. 2012): Apple F., et al.

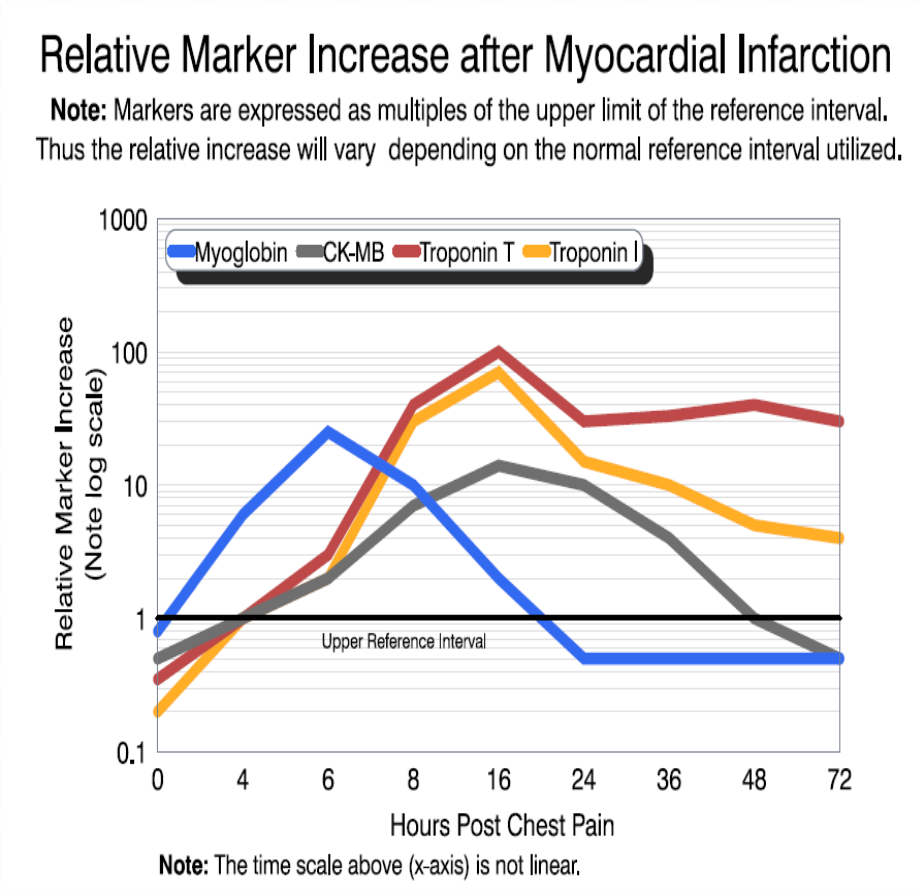
Apple, F.S. Opinion Clinical Chemistry 55:27 (2009)

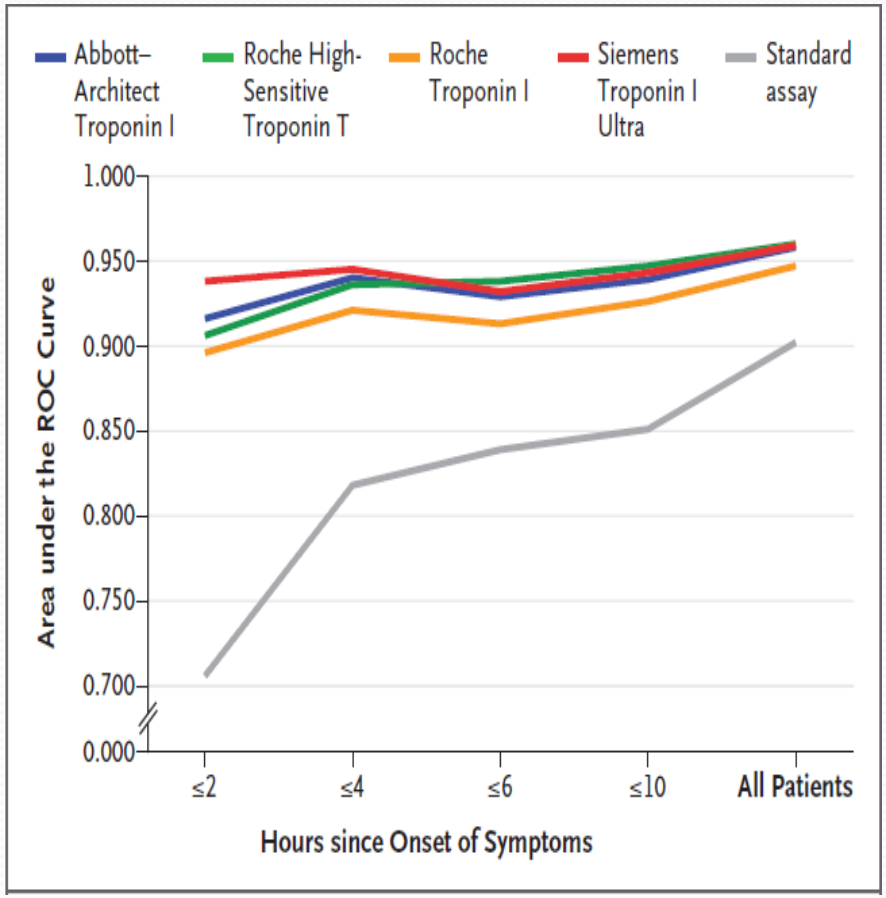
High Sensitivity Troponin…Change & Challenges



Am Heart J 2010;160:583-94.

Cardiac Marker Temporal Release Patterns Present & Future





NEJM: 2009 361: 858-67

Slide Courtesy R. Christensen-University of Maryland

South Africa's hsCtn Consensus Documents (2012)

Sensitivity and Specificity-a balancing act?

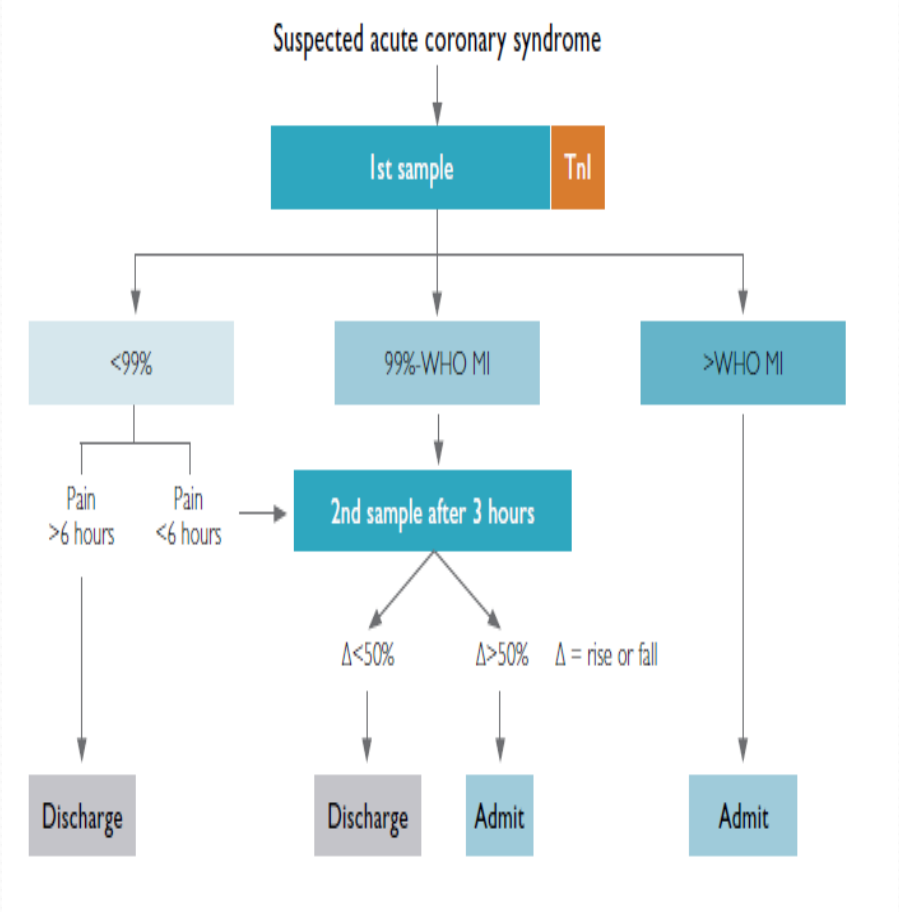
The increased sensitivity of high sensitivity cardiac troponin assays comes at a cost of **decreased specificity**, and "**false positive**" diagnosis of acute coronary syndromes has made clinicians wary of their use, fearing unnecessary hospitalizations, angiography and revascularization.

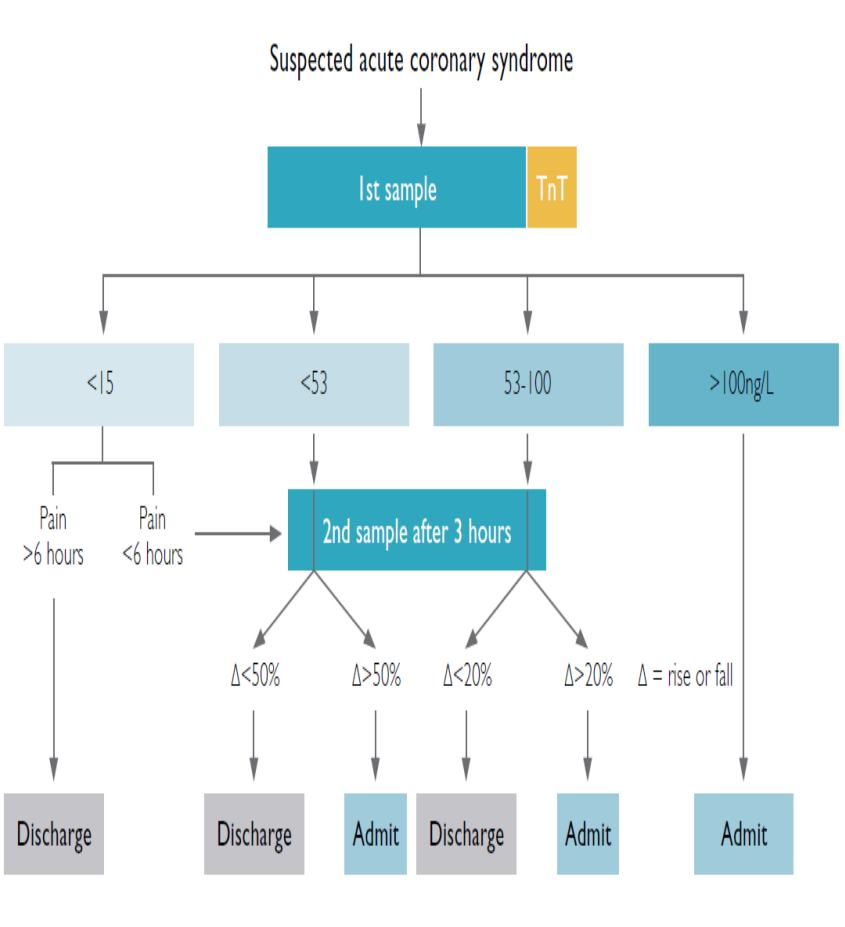
South African Heart Journal, Consensus Statement Winter 2012

TABLE 2: Causes of cardiac troponin elevation (other than acute coronary syndromes).

Acute	Acute
Ischaemic mechanism	**Other mechanisms**
Acute heart failure	Cardiac contusion
Pulmonary embolism	Procedural trauma:
Tachy-arrhythmias	Cardiac surgery
Brady-arrhythmias	Uncomplicated PCI
Accelerated hypertension	ASD closure
Hypotension / shock	Endomyocardial biopsy
Sepsis	Pacing
ARDS	ICD shocks
Aortic dissection	RF/cryo ablation
Carbon monoxide poisoning	External cardiac massage
	External cardioversion / defibrillation
Chronic	Myo-pericarditis
Stable atherosclerotic coronary artery disease	Endocarditis
Other coronary disease e.g. SLE, scleroderma, Kawasaki's disease, transplant vasculopathy	Stroke
Atrial fibrillation	Tako-tsubo cardiomyopathy
Chronic heart failure	Rhabdomyolysis
Chronic renal failure	COPD exacerbation
Hypertension/ LV hypertrophy	Acute renal failure
Pulmonary arterial hypertension	Burns >30%
Aortic valve disease	Snake venoms
Hypertrophic cardiomyopathy	Chemotherapy: Adriamycin, 5-fluoro-uracil, herceptin
Infiltration: amyloidosis, haemochromatosis, sarcoidosis	Sympathomimetic drugs
Peri-partum cardiomyopathy	Strenuous exertion
Hypothyroidism	After non-cardiac surgery
Diabetes	

Relative & Absolute Changes in Values





South African Heart Journal, Consensus Statement Winter 2012

European Guidelines

Compared with standard cardiac troponin assays, high-sensitivity assays:

- Have higher negative predictive value for acute MI.
- Reduce the "troponin-blind" interval leading to earlier detection of acute MI.
- Result in a ~4% absolute and ~20% relative increase in the detection of type 1 MI and a corresponding decrease in the diagnosis of unstable angina.
- Are associated with a 2-fold increase in the detection of type 2 MI.

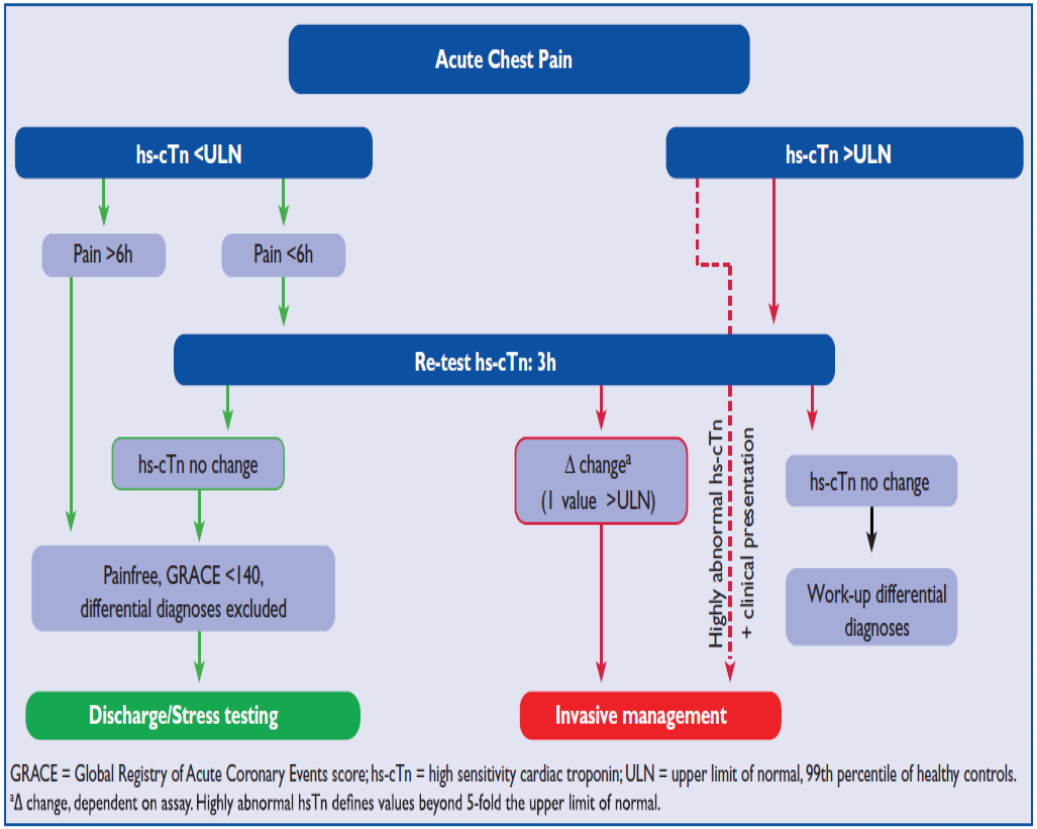
Rising and/or falling cardiac troponin levels differentiate acute from chronic cardiomyocyte damage (the more pronounced the change, the higher the likelihood of acute MI).

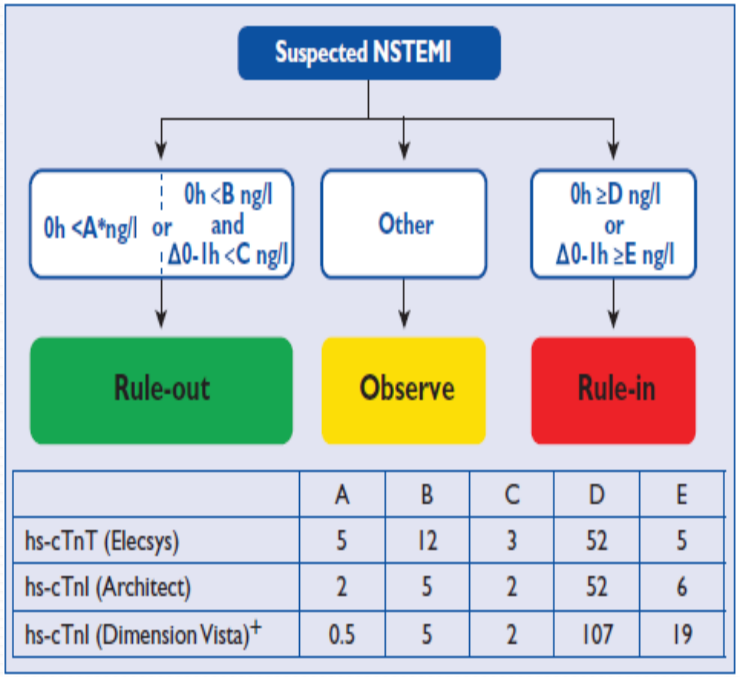
European Heart Journal (2016) 37, 267–315 doi:10.1093/eurheartj/ehv320

EUROPEAN SOCIETY OF CARDIOLOGY

2016 Guidelines

Serial Draw Protocols





	A	B	C	D	E
hs-cTnT (Elecsys)	5	12	3	52	5
hs-cTnI (Architect)	2	5	2	52	6
hs-cTnI (Dimension Vista)+	0.5	5	2	107	19

European Heart Journal (2016) 37, 267–315 doi:10.1093/eurheartj/ehv320

Patient Variables=Operational Challenges

Table 6 Differential diagnoses of acute coronary syndromes in the setting of acute chest pain

Cardiac	Pulmonary	Vascular	Gastro-intestinal	Orthopaedic	Other
Myopericarditis Cardiomyopathies[a]	Pulmonary embolism	Aortic dissection	Oesophagitis, reflus or spasm	Musculoskeletal disorders	Anxiety disorders
Tachyarrhythmias	(Tension)-Pneumothorax	Symptomatic aortic aneurysm	Peptic ulcer, gastritis	Chest trauma	Herpes zoster
Acute heart failure	Bronchitis, pneumonia	Stroke	Pancreatitis	Muscle injury/ inflammation	Anaemia
Hypertensive emergencies	Pleuritis		Cholecystitis	Costochondritis	
Aortic valve stenosis				Cervical spine pathologies	
Tako-Tsubo cardiomyopathy					
Coronary spasm					
Cardiac trauma					

Bold = common and/or important differential diagnoses.

[a]Dilated, hypertrophic and restrictive cardiomyopathies may cause angina or chest discomfort.

European Heart Journal (2016) 37, 267–315 doi:10.1093/eurheartj/ehv320

High Sensitivity Troponin & POC Testing?

Will The Need For Speed In The ED Trump The Need For A High-sensitive Assay with prolonged TAT from the lab?

"*It throws down the gauntlet to have point-of-care assays demonstrate the same characteristics as the quantitative tests we offer in the lab. There are a couple that have met that challenge. Otherwise, if the test is not as sensitive as troponin analyzed in the lab...* R. Christenson **February 2013 Clinical Laboratory News: Volume 39, Number 2**

- Will High Sensitivity Troponin And Contemporary Troponins Be Able To Coexist?
  - Dual Reference Ranges for ED and Lab? Not impossible but challenging, hospitals will have to carefully consider their serial draw protocols.

Best Demonstrated Practices-A Canadian Experience

ISSUE 04 JANUARY 2012

LABLink

Calgary Laboratory Services Pathology & Laboratory Medicine Newsletter

this issue

High Sensitivity Troponin Implementation P.1
C-Reactive Protein P.4
Urinalysis Automation P.5
Discontinuation of STAT Electrocardiograms P.5
New CLS Community General Requisition Format P.6

Cardiac Biomarker NEWS: High Sensitivity-Troponin T.

Plans for the Calgary Zone Hospitals and Community Practices

Dr. Andrew Lyon – Calgary Lab Services/ Department of Pathology and Laboratory Medicine andrew.lyon@cls.ab.ca
Dr. Steve Clark – Department of Emergency Medicine steve.clark@albertahealthservices.ca
Dr. James McMeekin – Department of Cardiology James.McMeekin@albertahealthservices.ca

Alberta Health Services and Calgary Laboratory Services will implement a new highly-sensitive Troponin T assay (TNT-HS) in the Calgary Zone adult hospitals and community testing in mid-January. This new assay is approximately fifteen fold more sensitive than the current Troponin T assay and will be reported in different units of measurement.

During the introduction phase, two versions of Troponin T test results will be charted. The Troponin T: high sensitivity test will be reported in ng/L units and a derived version of the current 4th generation assay results will be calculated and reported as Troponin-T: calculated (TNT-CALC) in familiar units of µg/L. By providing both the new and old versions of the results, we encourage the ongoing test interpretation based on current practice threshold values for "borderline elevation" and "elevation consistent with myocardial damage or infarction", to enable ongoing treatment of patients with the existing standard of care, Figure 1. An algorithm for management of patients presenting to emergency departments with possible acute coronary syndromes was developed to summarize current practice with both TNT-HS and the current troponin results, Figure 2.

Community Practice: Troponin results for specimens collected from out-patients will be reported in a similar manner to results from patients at hospitals. In accordance with a recent provincial laboratory guideline for community ordering of cardiac biomarkers, should Troponin-HS results exceed 110 ng/L, (similar to 0.1 µg/L of the current assay), the result will be phoned to the ordering physician as a critical result. The comments attached to Troponin –HS results will include a phrase to indicate that the interpretation of results from ambulatory out-patients is highly dependent on clinical presentation and that cardiac risk assessment by the ordering physician or "urgent-access" cardiology clinic (or emergency department) may be indicated. A series

Alberta Health Services

Calgary Laboratory Services

Notifications:

The 2010 CLS Report to the Community is available. If you would like a hard copy, please contact the CLS Communications Department:

communications@cls.ab.ca

It is also available on on our website:

http://www.calgarylabservices.com/who-we-are/company-profile/

Editor:
Dr. Alex C. Chin, Ph.D. DABCC FACB

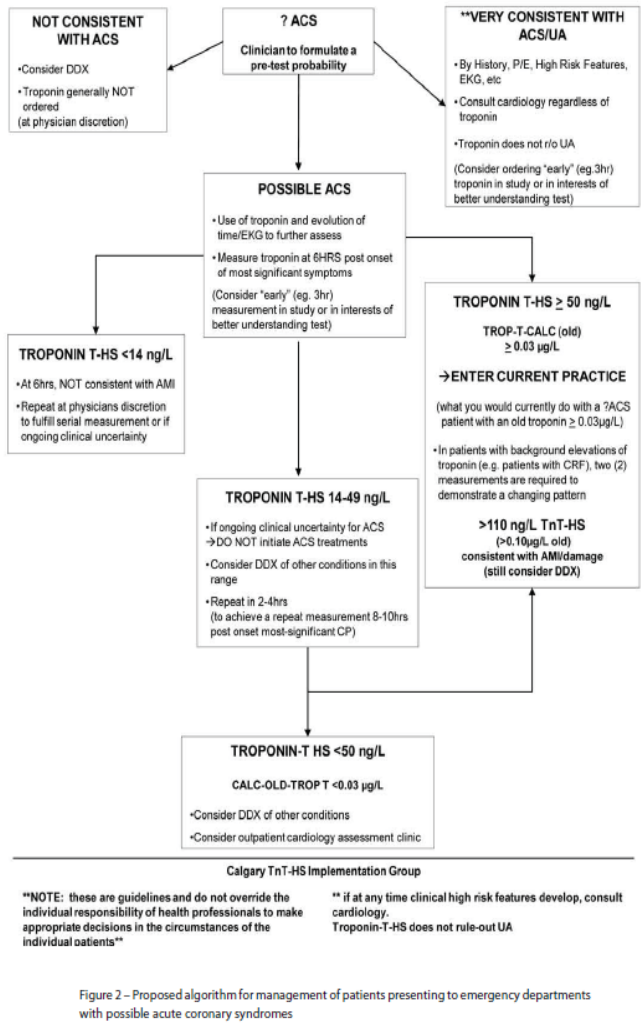
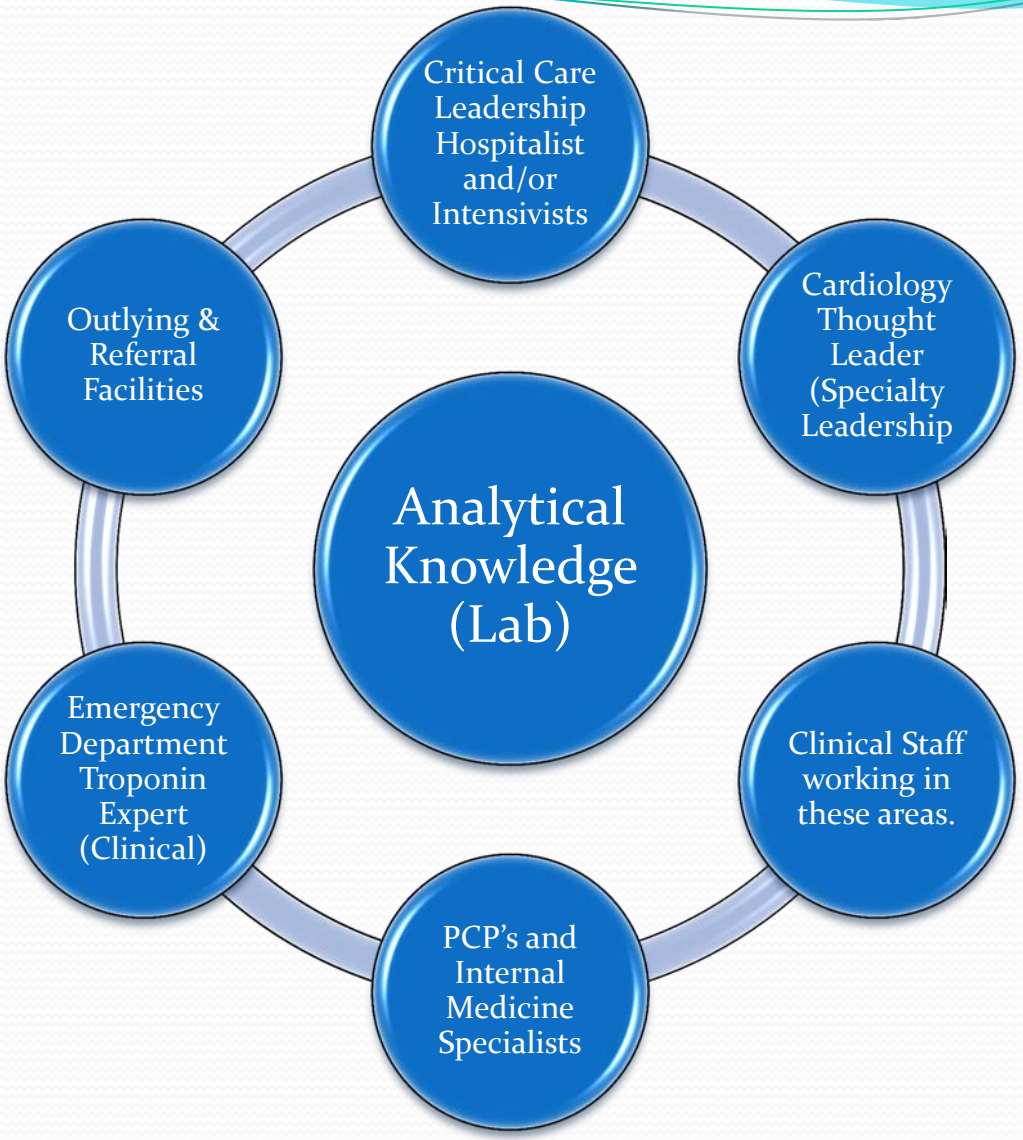


Figure 2 – Proposed algorithm for management of patients presenting to emergency departments with possible acute coronary syndromes



Best Demonstrated Implementation Practices

In Conclusion…

"when troponin was a lousy assay it was a great test, but now that it's becoming a great assay, it's getting to be a lousy test."

Jesse RL. On the relative value of an assay versus that of a test: a history of troponin for the diagnosis of myocardial infarction. J Am Coll Cardiol. 2010;55:2125–2128.