Cardiac Troponin: Current Status and Future Promise

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Disclosures

- Honoraria: Siemens Healthcare, Roche Diagnostics, Mitsubushi, Abbott
- Consultant: Siemens Healthcare, Philips Healthcare, Roche Diagnostics
- Research Funding: BG Medicine, Roche Diagnostics, Siemens Healthcare, Beckman-Coulter, Mitsubushi, Abbott Diagnostics, Alere

Objectives

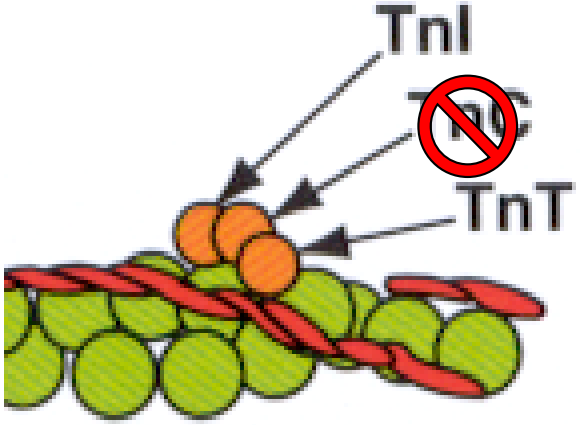
- List the biomarker criteria needed to establish the diagnosis of myocardial infarction
- List four characteristics that are critical to evaluate for determining an appropriate troponin
- Explain criteria and definition of early generation, contemporary and high sensitivity cardiac troponin assays
- Discuss four important criteria for a clinically appropriate point of care troponin system

Organization of Session

- Biomarker(s) used for MI diagnosis.
- Characteristics of assay(s).
  - Antibody configuration
  - Imprecision
  - Cutoffs, 99th %tile of a reference control population
- Focus on Turnaround Time
  - Point of Care vs. Central Laboratory Measurement
- Next Generation Assays

When troponin is increased think heart

Cardiac isoforms in blood



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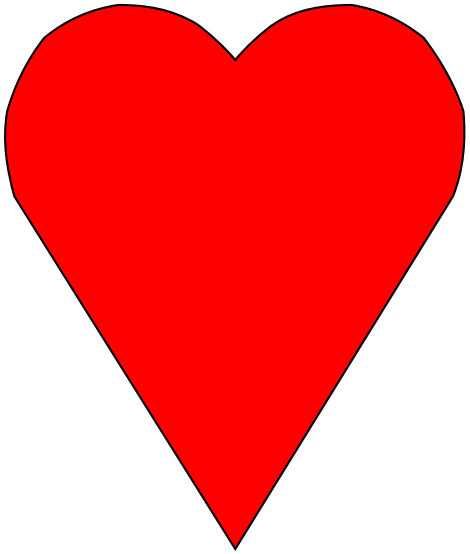
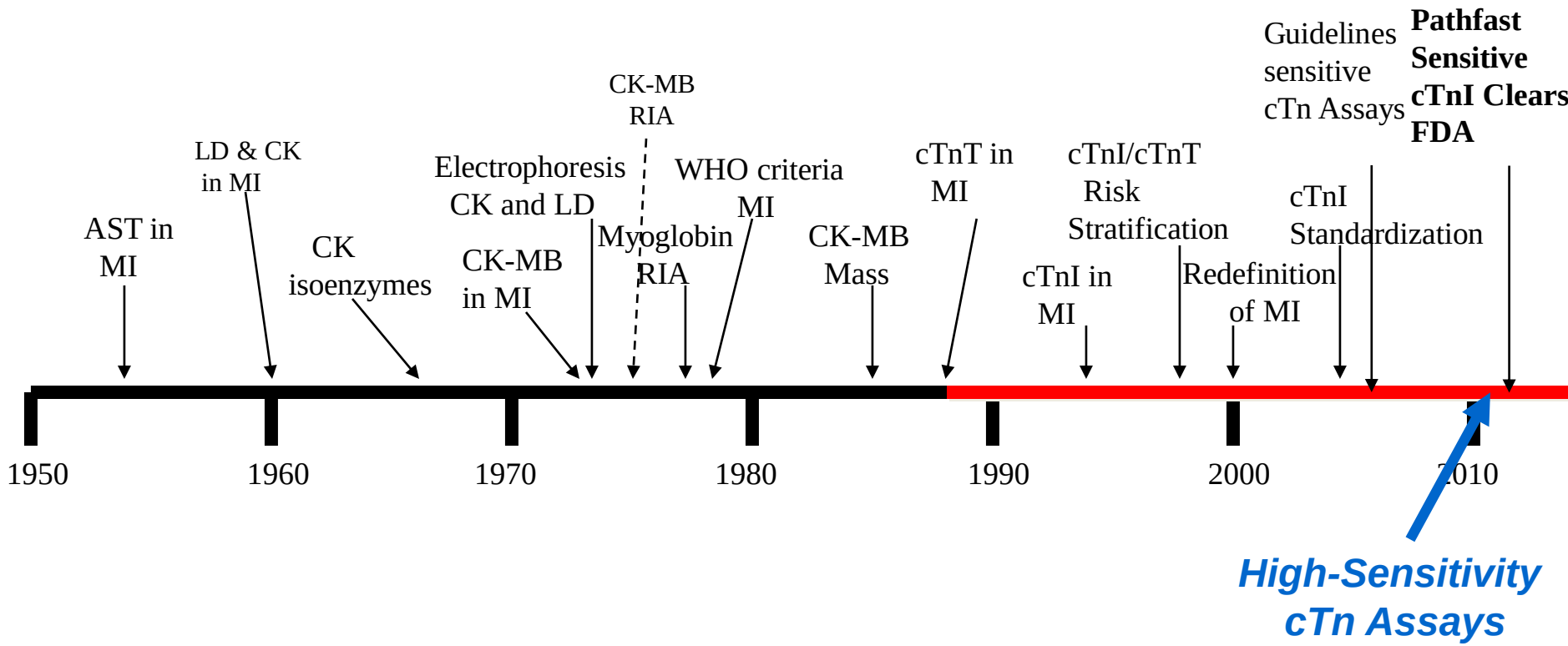
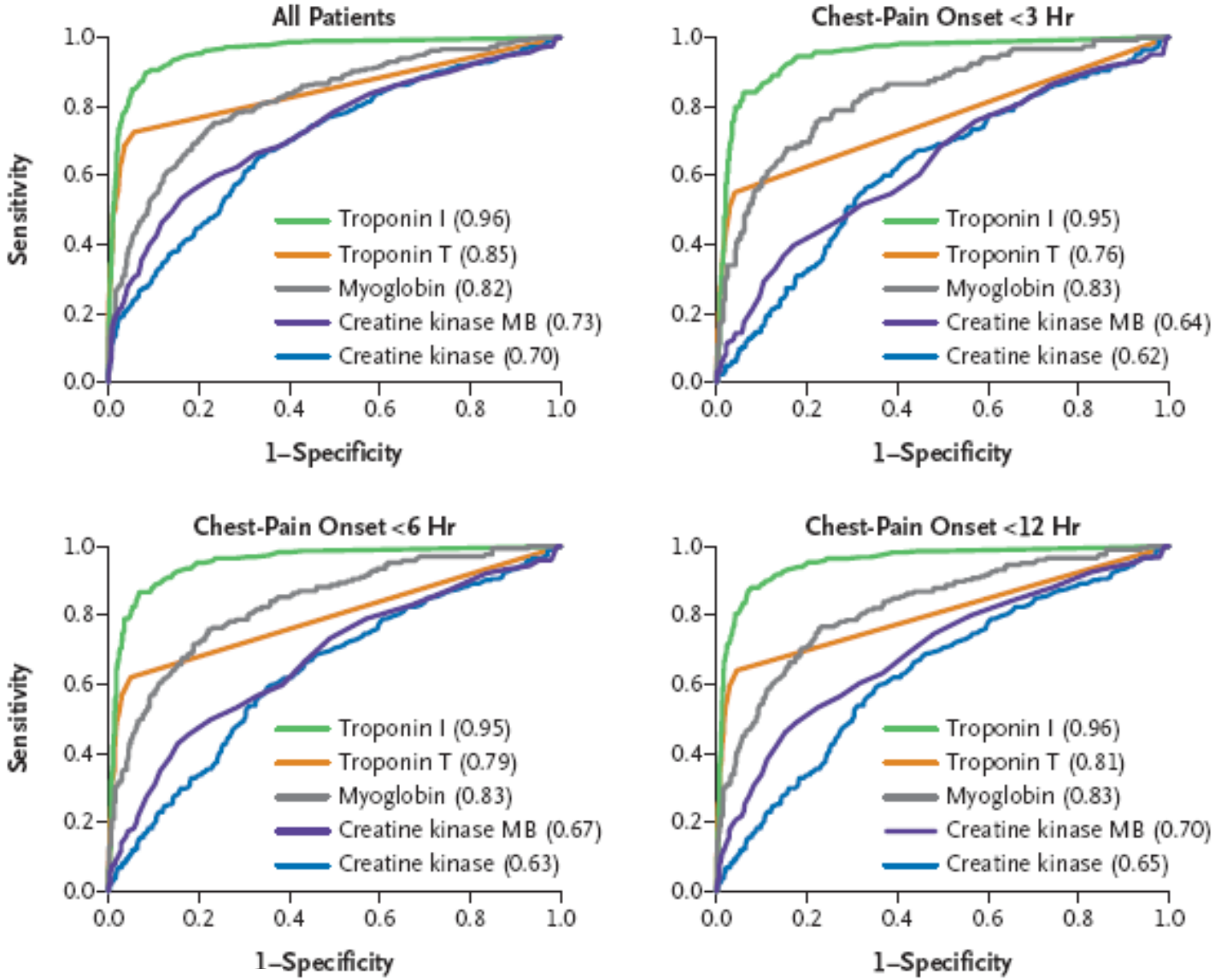


Necrosis Biomarkers Timeline



Single Biomarker Test for MI



N Engl J Med 2009;361:868-77.

2014 AHA/ACC* Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

Recommendations	COR	LOE
Diagnosis		
Measure cardiac-specific troponin (troponin I or T) at presentation and 3–6 h after symptom onset in all patients with suspected ACS to identify pattern of values	I	A
Obtain additional troponin levels beyond 6 h in patients with initial normal serial troponins with electrocardiographic changes and/or intermediate/high risk clinical features	I	A
Consider time of presentation the time of onset with ambiguous symptom onset for assessing troponin values	I	A
With contemporary troponin assays, CK-MB and myoglobin are not useful for diagnosis of ACS	III: No Benefit	A
Prognosis		
Troponin elevations are useful for short- and long-term prognosis	I	B
Remeasurement of troponin value once on d 3 or 4 in patients with MI may be reasonable as an index of infarct size and dynamics of necrosis	IIb	B
BNP may be reasonable for additional prognostic information	IIb	B

*American Heart Association/American College of Cardiology
Circulation. 2014 Dec 23;130(25):e344-426.

Cardiac Troponin

AHA/ACC Guideline

2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons

Endorsed by the American Association for Clinical Chemistry

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The National Academy of Clinical Biochemistry

Presents

LABORATORY MEDICINE PRACTICE GUIDELINES

BIOMARKERS OF ACUTE CORONARY SYNDROMES AND HEART FAILURE

EDITED BY
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European Heart Journal Advance Access published September 11, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv320

ESC GUIDELINES

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Marco Roffi* (Chairperson) (Switzerland), Carlo Patrono* (Co-Chairperson) (Italy), Jean-Philippe Collet† (France), Christian Mueller† (Switzerland), Marco Valgimigli† (The Netherlands), Felicita Andreotti (Italy), Jeroen J. Bax (The Netherlands), Michael A. Borger (Germany), Carlos Brotons (Spain), Derek P. Chew (Australia), Baris Gencer (Switzerland), Gerd Hasenfuss (Germany), Keld Kjeldsen (Denmark), Patrizio Lancellotti (Belgium), Ulf Landmesser (Germany), Julinda Mehilli (Germany), Debabrata Mukherjee (USA), Robert F. Storey (UK), and Stephan Windecker (Switzerland)

European Heart Journal (2012) **33**, 2551–2567
doi:10.1093/eurheartj/ehs184

EXPERT CONSENSUS DOCUMENT

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

Authors/Task Force Members Chairpersons: Kristian Thygesen (Denmark)*, Joseph S. Alpert, (USA)*, Harvey D. White, (New Zealand)*, Biomarker Subcommittee: Allan S. Jaffe (USA), Hugo A. Katus (Germany), Fred S. Apple (USA), Bertil Lindahl (Sweden), David A. Morrow (USA), ECG Subcommittee: Bernard R. Chaitman (USA), Peter M. Clemmensen (Denmark), Per Johanson (Sweden), Hanoch Hod (Israel), Imaging Subcommittee: Richard Underwood (UK), Jeroen J. Bax (The Netherlands), Robert O. Bonow (USA), Fausto Pinto (Portugal), Raymond J. Gibbons (USA), Classification Subcommittee: Keith A. Fox (UK), Dan Atar (Norway), L. Kristin Newby (USA), Marcello Galvani (Italy), Christian W. Hamm (Germany), Intervention Subcommittee: Barry F. Uretsky (USA), Ph. Gabriel Steg (France), William Wijns (Belgium), Jean-Pierre Bassand (France), Phillippe Menasché (France), Jan Ravkilde (Denmark), Trials & Registries Subcommittee: E. Magnus Ohman (USA), Elliott M. Antman (USA), Lars C. Wallentin (Sweden), Paul W. Armstrong (Canada), Maarten L. Simoons (The Netherlands), Heart Failure Subcommittee: James L. Januzzi (USA), Markku S. Nieminen (Finland), Mihai Gheorghiade (USA), Gerasimos Filippatos (Greece), Epidemiology Subcommittee: Russell V. Luepker (USA), Stephen P. Fortmann (USA), Wayne D. Rosamond (USA), Dan Levy (USA), David Wood (UK), Global Perspective Subcommittee: Sidney C. Smith (USA), Dayi Hu (China), José-Luis Lopez-Sendon (Spain), Rose Marie Robertson (USA), Douglas Weaver (USA), Michal Tendera (Poland), Alfred A. Bove (USA), Alexander N. Parkhomenko (Ukraine), Elena J. Vasilieva (Russia), Shanti Mendis (Switzerland).

Elevated Troponin in Patients without ACS or Heart Failure

Kelley et al. Clin. Chem. 2009 Dec;55(12):2098-112

- **Acute Disease**
- Cardiac and Vascular
- Acute Aortic dissection
- Cerebrovascular accident
- Ischemic Stroke
- Intracerebral Hemorrhage
- Subarachnoid Hemorrhage
- Medical ICU Patients

- **Chronic Disease**
- ESRD
- Cardiac infiltrative disorders
- Amyloidosis
- Sarcoidosis
- Hemochromatosis
- Scleroderma

Heart Specific

Disease Specific

- Birth Complications in Infants
- Extreme Low Birth Weight
- Preterm Delivery
- Acute Complications of
- Inherited Disorders
- Neurofibromatosis
- Duchenne Muscular Dystrophy
- Klippel-Feil syndrome
- Environmental Exposure
- Carbon Monoxide
- Hydrogen Sulfide
- Colchicine exposure

- Other Medications
- **Myocardial Injury**
- Blunt Chest Injury
- Endurance athletes
- Envenomation
- Snake
- Jellyfish
- Spider
- Centipede
- Scorpion

Are All Cardiac Troponin Assays Created Equal?

NO x 1000

National Academy of Clinical Biochemistry (NACB) Analytical Guidelines for ACS

2007 Clin Chem and Circulation

Class I (Level of Evidence C)

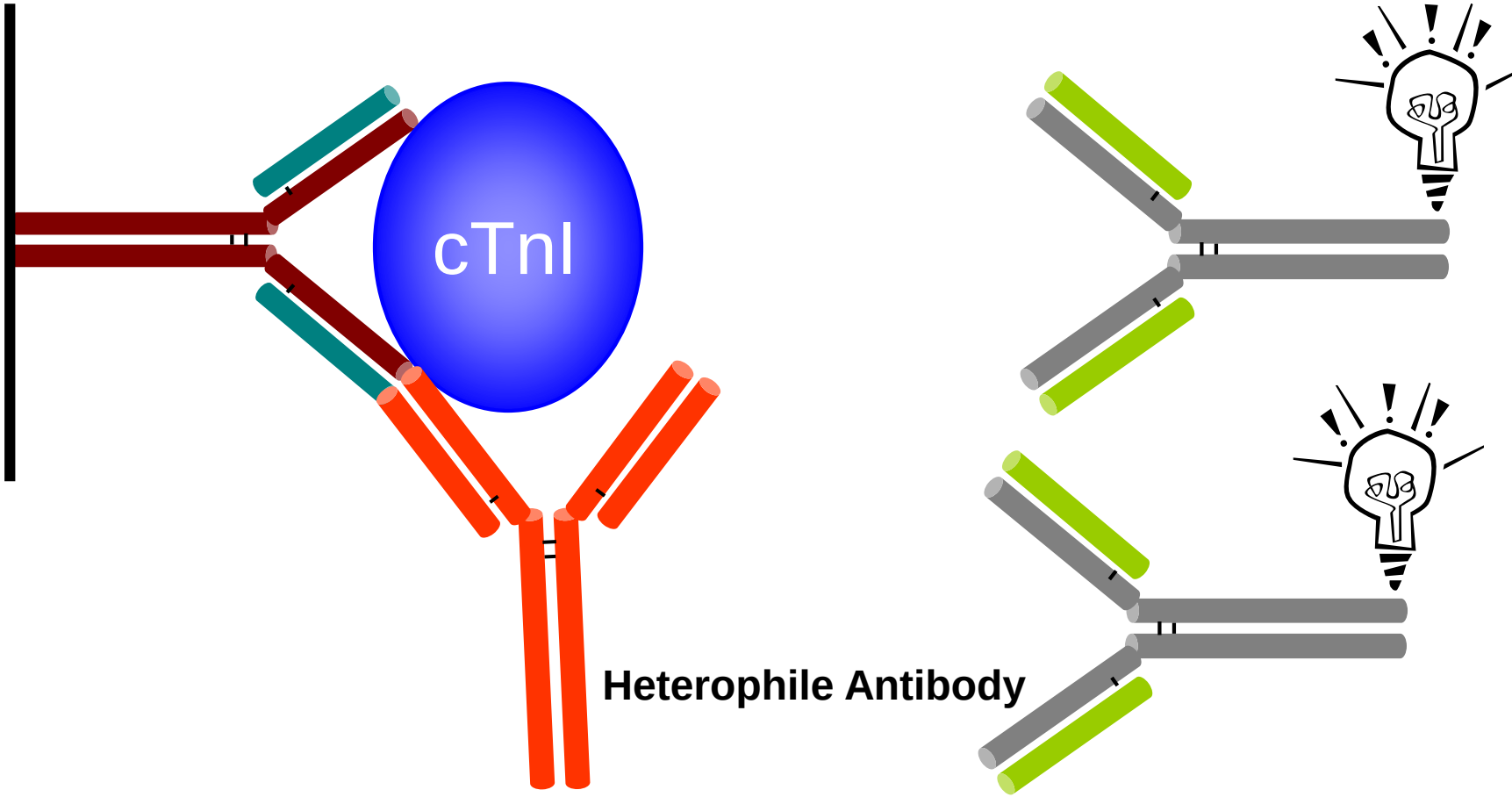
Cardiac biomarker assays must be characterized with respect to potential interferences, including rheumatoid factors, human anti-mouse antibodies, and heterophile antibodies.

Identification of antibody/epitope recognition sites for each biomarker.

Assays for cardiac biomarkers should strive for a total imprecision (%CV) of ≤10% at the 99th percentile reference limit.

Stability (over time and across temperature ranges) for each acceptable specimen type

Analytical False Positive



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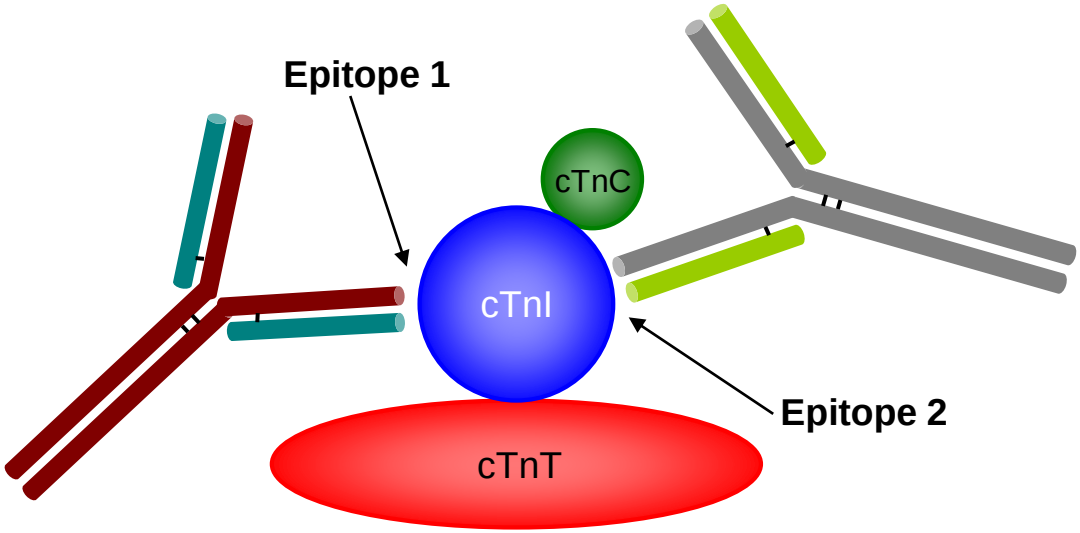
Assays for cardiac biomarkers should strive for a total imprecision (%CV) of ≤10% at the 99th percentile reference limit.

Stability (over time and across temperature ranges) for each acceptable specimen type

Six commercial (Hytest) mAbs evaluated for use in a 1 x 1 “reference “immunoassay



mAb M18 mAb 3C7 mAb 19C7

1 A D G S S D A A R E P R P A P A P I R R R S S N Y R A Y A T E P H A K K K S I S A S R K L Q L K T 50

mAb 560

51 L L L Q I A K Q E L E R E A E E R R G E K G R A L S T R C Q P L E L A G L G F A E L Q D L C R Q L H 100

101 A R V D K V D E E R Y D I E A K V T K N I T E I A D L T Q K I F D L R G K E K R P T L R R V R I S A 150

mAb 267 mAb MF4

151 D A M M Q A L L G A R A K E S L D L R A H L K Q V K K E D T E K E N R E V G D W R K N I D A L S G M 200

201 E G R K K K F E S 209

IFCC%20Troponin%20Tables%20ng_L%20DRAFT%20Update%20NOVEMBER%202014%20(1).pdf

Commercially available assays - Company/ platform(s)/ assay	LoB [a] (ng/L)	LoD [b] (ng/L)	99th % (ng/L)	%CV at 99th %	10% CV (ng/L)	Reference population N: age range (y)	Epitopes recognised by Antibodies	Detection Antibody Tag
Abbott AxSYM ADV	20		40	14.0	160		C 87-91, 41-49; D 24-40	ALP
Abbott Architect	<10		28	14.0	32	449: 18 – 63 (M: 224 18 - 63 F: 225 18 - 62)	C 87-91, 24-40; D: 41-49	Acridinium
Abbott Architect *STAT* hs-cTnI [e]	0.7 – 1.3	1.1 – 1.9	26.2 M: 34.2 F: 15.6	4.0 M: 3.5 F: 5.3	4.7	1531: 21 - 75 (M: 766 21 - 73 F: 765 21 - 75)	C: 24-40; D: 41-49	Acridinium
Abbott i-STAT	20		80	16.5	100		C: 41-49, 88-91; D: 28-39, 62-78	ALP
Alere Triage SOB	50		NAD	NA	NA		C: NA; D: 24-40	Fluorophor
Alere Triage Cardio 3	2	10	22	17.0	37		C: 27-29; D: 83-93, 190-196	Fluorophor
Beckman Coulter Access Accu	10		40	14.0	60		C: 41-49; D: 24-40	ALP
Beckman Coulter Access AccuTnI+3 / Access 2 and DxI	<10	10	40 20 (30 DxI (US))	10.0 20.0	40	1000: > 40 527: 18 - 94 (50% > 40 y)	C: 41-49; D: 24-40	ALP
bioMerieux Vidas Ultra	<10	<10	10	27.7	110	747: 20 - 81	C: 41-49, 22-29; D: 87-91, 7B9	ALP
Mitsubishi PATHFAST cTnI [e]		1	20	5.2	3.1	380	C: 41-49; D: 71-116, 163-209	ALP
Mitsubishi PATHFAST cTnI-II [f]	2	8	29	5.0	14	490: 18 - 78	C: 41-49; D: 71-116, 163-209	ALP
Ortho VITROS Troponin I ES	7	12	34	10.0	34		C: 24-40, 41-49; D: 87-91	HRP
Radiometer AQT90 FLEX TnI		9.5	23	12.3	27	231 (M:125; F:106)	C: 41-49, 190-196; D: 137-149	Europium
Response Biomedical RAMP	30		100	20.0	210	180: 18 - 80 (M: 84; F: 96)	C: 85-92; D: 26-38	Fluorophor
Siemens ADVIA Centaur® TnI-Ultra™	6		40	8.8	30	648: 17 - 91	C: 41-49, 87-91; D: 24-40	Acridinium
Siemens Dimension® RxL CTNI	40 [d]		70	15 - 22	140	342: 18 - 83	C: 27-32; D: 47-56	ALP
Siemens Dimension® EXL™ TNI	10	17	56	10.0	50	241	C: 27-32; D: 47-56	Chemiluminescence
Siemens Dimension VISTA® CTNI	15		45	10.0	40	199	C: 27-32; D: 47-56	Chemiluminescence
Siemens IMMULITE® 1000 Turbo [e]	150		300	14	590	300	C: 87-91; D: 24-40	ALP – Chemiluminescence
Siemens IMMULITE® 1000 [e]	100		190	11	220	300	C: 87-91; D: 24-40	ALP – Chemiluminescence
Siemens IMMULITE® 2000 XPi [e]	200		290	10.3	320	300	C: 87-91; D: 24-40	ALP – Chemiluminescence
Siemens IMMULITE®1000 Turbo [f]	150		NA	NA	640		C: 87-91; D: 24-40	ALP – Chemiluminescence
Siemens Stratus® CS cTnI	30 [d]		70	10.0	60	101	C: 27-32; D: 47-56	ALP
Tosoh ST AIA-PACK cTnI (2nd gen)	60		60 [c]	8.5	NA		C: 41-49; D: 87-91	ALP

IFCC%20Troponin%20Tables%20ng_L%20DRAFT%20Update%20NOVEMBER%202014%20(1).

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Alere Triage SOB	50		NAD	NA	NA		C: NA; D: [illegible]40	Fluorophor
Alere Triage Cardio 3	2	10	22	17.0	37		C: 27-[illegible]9; D: [illegible]3, 190-196	Fluorophor
Beckman Coulter Access Accu	10		40	14.0	60		C: [illegible]9; D: [illegible]40	ALP
Beckman Coulter Access AccuTnI+3 / Access 2 and DxI	<10	10	40 20 (30 DxI (US))	10.0 20.0	40	1000: > 40 527: 18 - 94 (50% > 40 y)	C: [illegible]49; D: [illegible]40	ALP
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Ortho VITROS Troponin I ES	7	12	34	10.0	34		C: 24-[illegible]49; D: 87[illegible]1	HRP
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Siemens IMMULITE®1000 Turbo [f]	150		NA	NA	640		C: 8[illegible]91; D: [illegible]40	ALP – Chemiluminescence
Siemens Stratus® CS cTnI	30 [d]		70	10.0	60	101	C: 27-32; D: [illegible]56	ALP
Tosoh ST AIA-PACK cTnI (2nd gen)	60		60 [c]	8.5	NA		C: 4[illegible]49; D: 8[illegible]91	ALP

Cardiac Biomarkers and the Definition of Acute Myocardial Infarction (AMI)

Cardiac biomarkers should be used in clinical settings consistent with acute cardiac ischemia

- Rise and/or fall of cardiac biomarker values
  - Preferably cardiac troponin (cTn)
- At least one value above the 99th percentile upper reference limit (URL)
- Precision (CV) of ≤10% at the 99 percentile URL

NACB Analytical Guidelines for ACS

2007 Clin Chem and Circulation

Class I (Level of Evidence C)

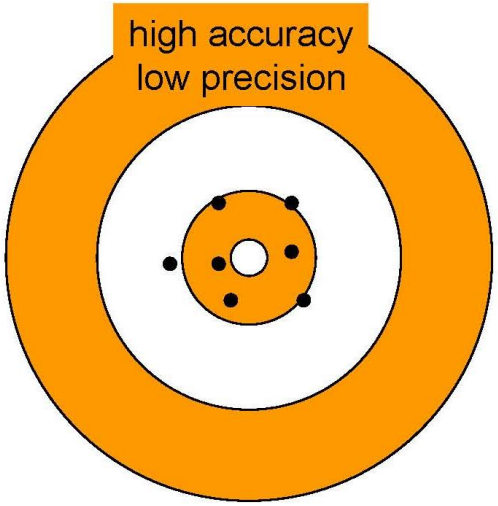
Identification of **antibody/epitope recognition sites** for each biomarker.

Assays for cardiac biomarkers should strive for a total imprecision (%CV) of ≤10% at the 99th percentile reference limit.

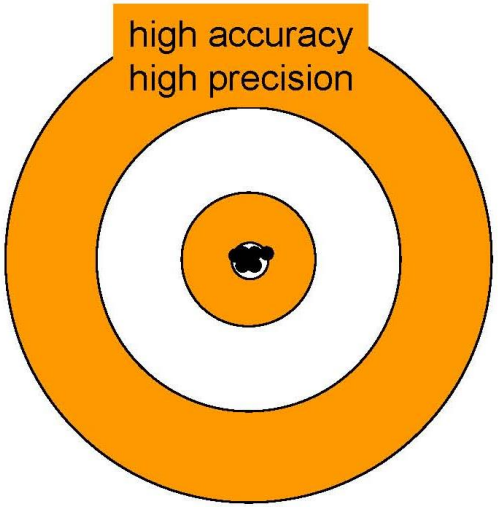
Cardiac biomarker assays must be characterized with respect to potential interferences, including **rheumatoid factors, human anti-mouse antibodies, and heterophile antibodies.**

Stability (over time and across temperature ranges) for each acceptable specimen type

High Accuracy, Different Precision



15% CV



5% CV

More Sensitive Troponin

Timing of sampling?
Evolution of Serial Blood Sample Timing

1. Rule-out
2. Rule-in

	0h	1h	2h	3h	4h	5h	6h	7h
	ECG							
NACB 2007	cTn						cTn →	
ESC 2011	hs-cTn			cTn				
ACC/AHA2014	cTn			←		cTn →		
High Sensitivity	cTnI cTnI							

Table. Analytical characteristics of commercial and research cardiac troponin I and T assays declared by the manufacturer.

Commercially available assays - Company/ platform(s)/ assay	%CV at 99th %
Abbott AxSYM ADV	14.0
Abbott Architect	14.0
Abbott i-STAT	16.5
Alere Triage SOB	NA
Alere Triage Cardio 3	17.0
Beckman Coulter Access Accu	14.0
bioMerieux Vidas Ultra	27.7
Mitsubishi Chemical PATHFAST	5.0
Ortho VITROS Troponin I ES	10.0
Radiometer AQT90 FLEX TnI	17.7
Radiometer AQT90 FLEX TnT	15.2
Response Biomedical RAMP	18.5 (at 0.05)
Roche Cardiac Reader cTnT	NA
Roche cobas h 232 TnT	NA

Commercially available assays - Company/ platform(s)/ assay	%CV at 99th%
Roche E 2010 /cobas e 411 / E 170 / cobas e 601 / 602 TnT (4th gen)	NA
Roche E 2010/cobas e 411 / E 170 / cobas e 601 / 602 hs-TnT	10.0
Roche E 2010/cobas e 411 / Roche E 170/cobas e 601 / 602 cTnI	NA
Siemens ADVIA Centaur® TnI-Ultra™	8.8
Siemens Dimension® EXL™ TNI	10.0
Siemens Dimension® RxL CTNI	15 - 22
Siemens Dimension VISTA® CTNI	10.0
Siemens IMMULITE® 1000 Turbo [e]	14
Siemens IMMULITE® 1000 [e]	11
Siemens IMMULITE® 2000 XPi [e]	10.3
Siemens IMMULITE® 2500 STAT [f]	NA
Siemens IMMULITE® 1000 Turbo [f]	NA
Siemens Stratus® CS cTnI	10.0
Tosoh ST AIA-PACK	8.5

Definition of Myocardial Infarction

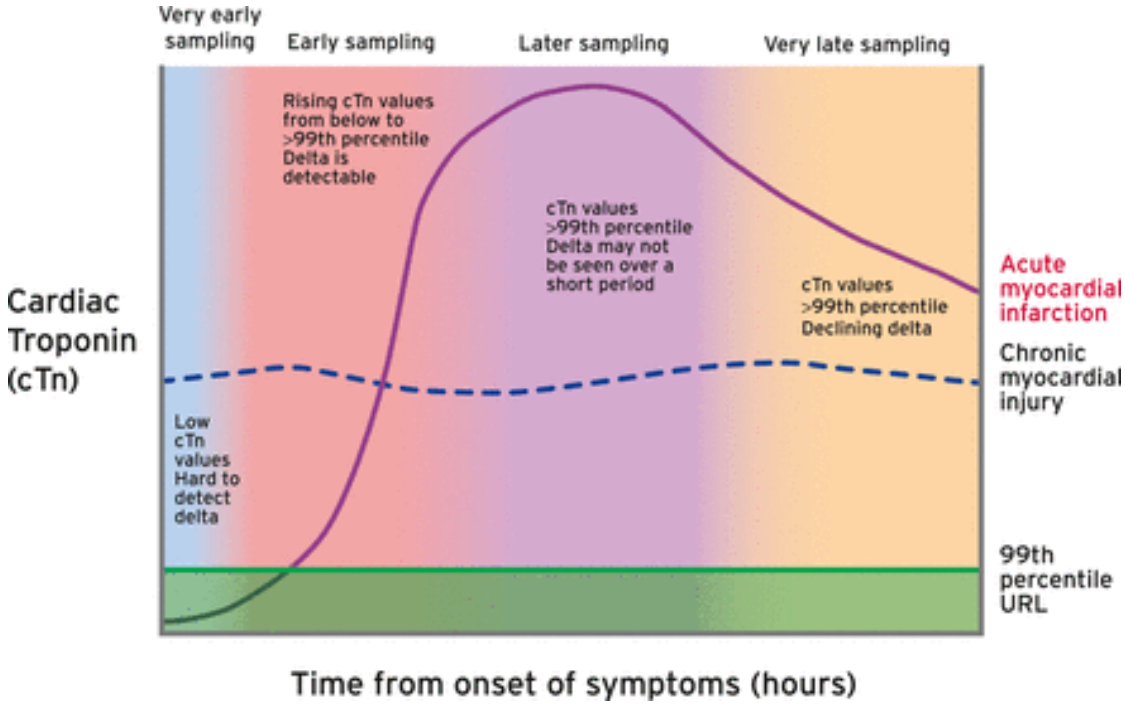
"Small heart attacks are so common; they are almost within normal range."

Paul Dudley White, 1957
The Father of American Cardiology

4th Universal Definition of Myocardial Infarction

Eur Heart J. **2019** Jan 14;40(3):237-269.

- cTnI and cTnT are the preferred biomarkers recommended to both rule in and rule out myocardial injury, and thus to define MI and each specific subtype of MI.
- Detection of a rise and/or fall of cTn values is essential, and a key early component along with other elements of the clinical evaluation to establish the diagnosis of acute MI

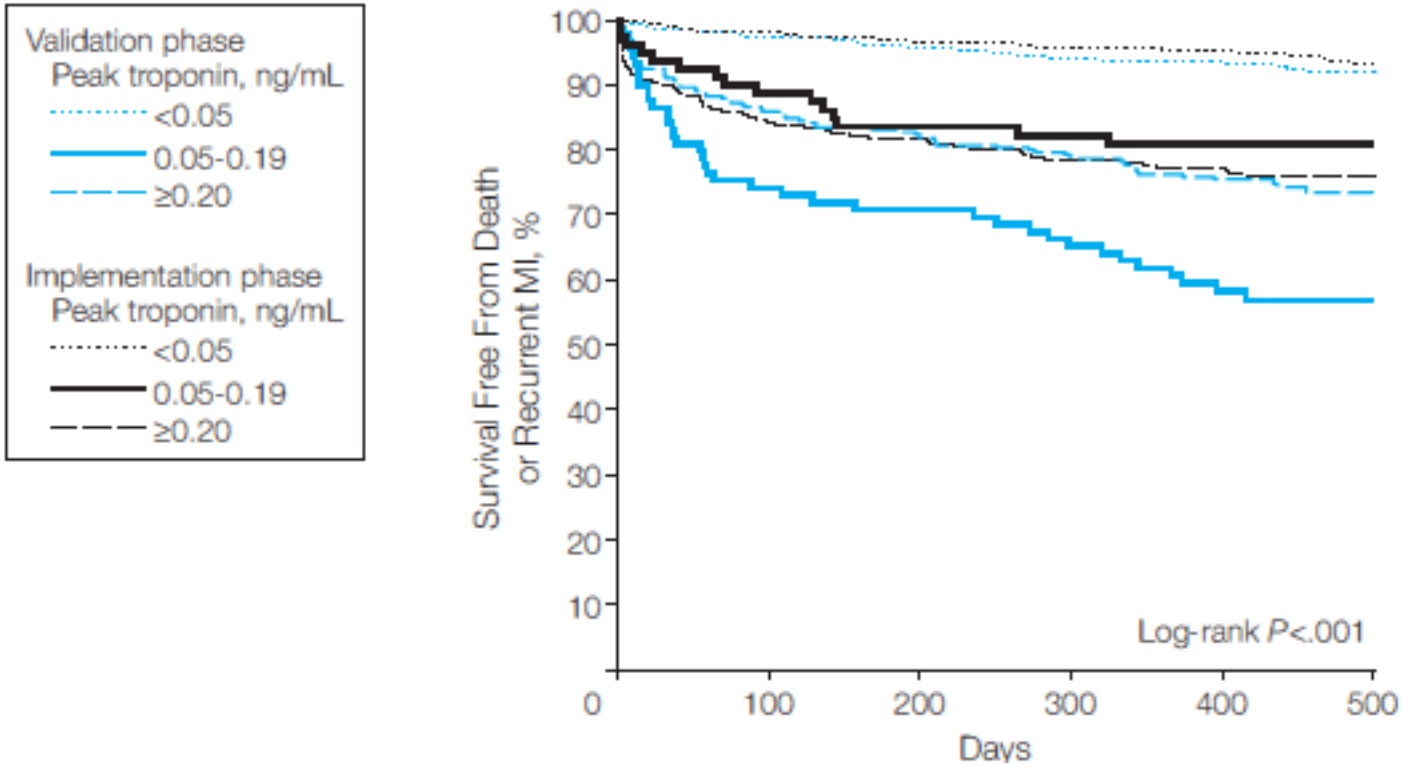


Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin] with at least one value above the 99th percentile upper reference limit …

- Less than 50% of institutions in the USA use the recommended 99th percentile cutpoint for diagnosis of myocardial infarction.
- Less that 50% of the institutions in the developed world use the 99th percentile cutpoint for diagnosis of myocardial infarction.

Does improved precision at 99th percentile result in better outcomes?

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



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

Management of patients with suspected acute coronary syndrome before (validation phase) and after (implementation phase) the introduction of a sensitive Troponin Assay

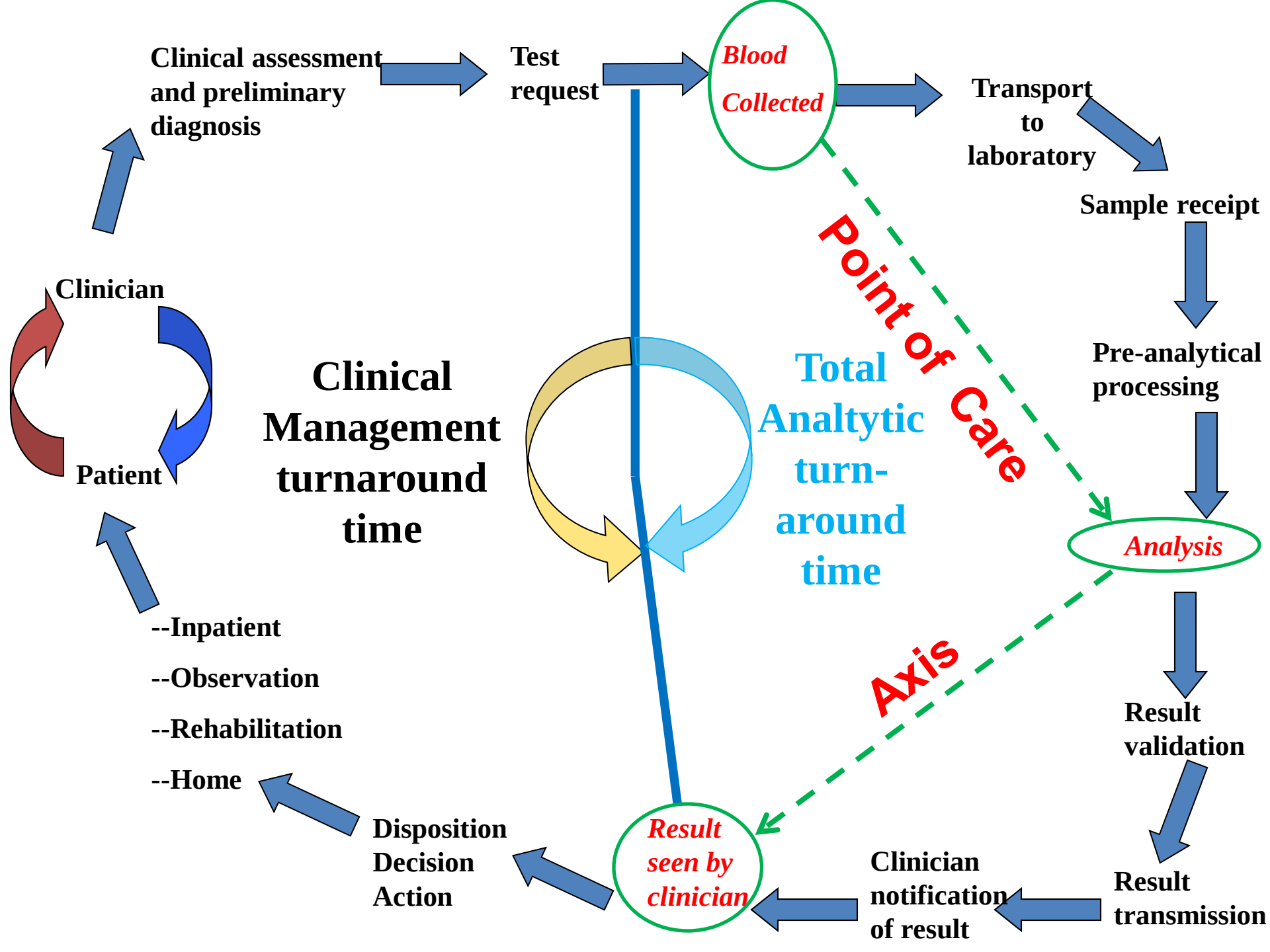
	No. (%) of Patients				
		Stratified by Peak Troponin Concentration, ng/mL			
	All	<0.05	0.05-0.19	≥0.20	*P* Value
Validation phase	(N = 1038)	(n = 657)	(n = 90)	(n = 291)	
Cardiology referral	508 (49)	197 (30)	40 (44)	271 (93)	<.001
Coronary angiography	257 (25)	39 (6)	18 (20)	200 (69)	<.001
PCI	187 (18)	13 (2)	14 (16)	160 (55)	<.001
CABG surgery	16 (2)	3 (0)	1 (1)	12 (4)	<.001
Medication on discharge					
Aspirin	712 (69)	376 (57)	67 (75)	269 (92)	<.001
Clopidogrel	393 (38)	118 (18)	28 (31)	247 (85)	<.001
Dual-antiplatelet therapy	336 (32)	79 (12)	24 (27)	233 (80)	<.001
β-Blockers	473 (46)	239 (36)	42 (47)	192 (66)	<.001
ACE inhibitors	477 (46)	217 (33)	39 (43)	221 (76)	<.001
Statins	685 (66)	374 (57)	52 (58)	259 (89)	<.001
Implementation phase	(N = 1054)	n = (683)	n = (80)	n = (291)	
Cardiology referral	573 (54)[b]	242 (35)	59 (74)[c]	272 (93)	<.001
Coronary angiography	302 (29)[b]	44 (6)	37 (46)[c]	221 (76)	<.001
PCI	212 (20)	23 (3)	16 (20)	173 (59)	<.001
CABG surgery	21 (2)	3 (0)	3 (4)	15 (5)	<.001
Medication on discharge					
Aspirin	707 (67)	376 (55)	66 (83)	265 (91)	<.001
Clopidogrel	403 (38)	89 (13)[b]	49 (61)[c]	265 (91)[b]	<.001
Dual-antiplatelet therapy	348 (33)	55 (8)[b]	46 (58)[c]	247 (85)	<.001
β-Blockers	468 (44)	232 (34)	50 (62)	186 (64)	<.001
ACE inhibitors	514 (49)	246 (36)	47 (59)	221 (76)	<.001
Statins	695 (66)	369 (54)	64 (80)[b]	262 (90)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; PCI, percutaneous coronary interven
[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.

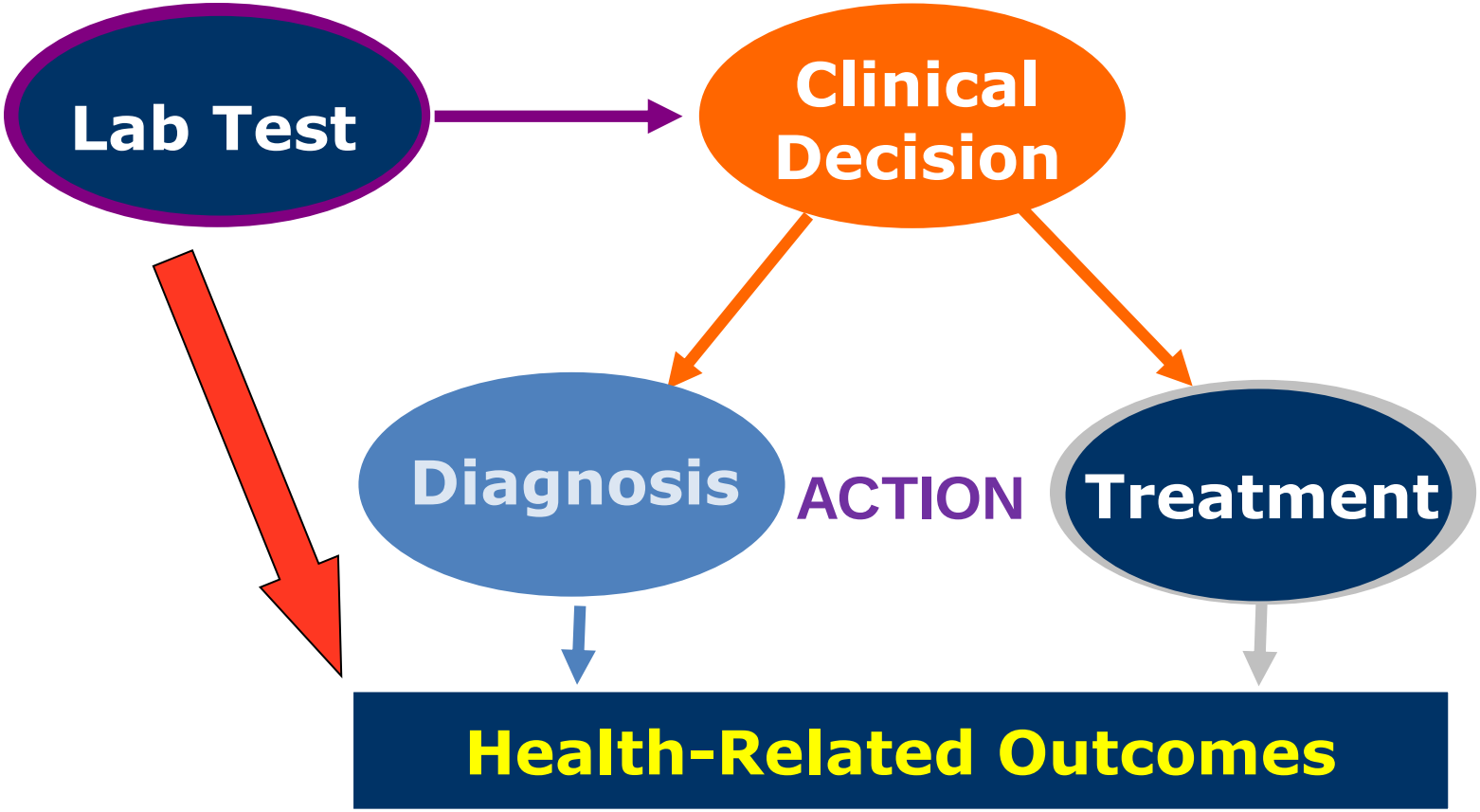
Mills, N. L. et al. JAMA 2011;305:1210-1216

Major Focus on Troponin TAT

- Society of Cardiovascular Patient Care (SCPC): Requiring POCT 60 minutes or less TAT (90%) for accreditation
- CAP: Established Q-Monitor that measures TAT
- National Academy of Clinical Biochemistry and International Federation of Clinical Chemistry: Recommend 60 minutes or less TAT
- American College of Cardiology & American Heart Assoc.: Recommends 60 minute TAT with preference at 30 minutes
- **Time is Critical (but Not <u>Everything</u>)**


Clinical assessment and preliminary diagnosis
Test request
Blood Collected
Transport to laboratory
Sample receipt
Pre-analytical processing
Analysis
Result validation
Result transmission
Clinician notification of result
Result seen by clinician
Disposition Decision Action
--Inpatient
--Observation
--Rehabilitation
--Home
Patient
Clinician
Clinical Management turnaround time
Total Analtytic turn-around time
Point of Care
Axis

Challenge: Connecting Laboratory Testing to Outcomes



Demonstrating the value of lab tests on health outcomes is reliant on linking the test with processes that directly impact outcomes.

Philips Minicare

Roche Cardiac Reader

Abbott iSTAT

Response Biomedical

Siemens Stratus CS

Mitsubushi Pathfast

Alere Triage

Point of Care Troponin Assays do **NOT** get a Pass on Quality!

POINT OF CARE TESTING DOES NOT GET A PASS ON ASSAY QUALITY!

High Sensitivity or Specificity for Screening?

<u>SnOut:</u>

- Sensitivity (TP/TP+FN) describes the ability of a test to identify true disease
  - A high *sensitivity* test has few **false negatives** and is effective at ruling conditions "out" (SnOut)

<u>SpIn:</u>

- Specificity (TN/TN+FP) describes the ability of an IVD test to correctly identify the absence of disease
  - A high *specificity* test has few **false positives** and is effective at ruling conditions "in" (SpIn).

2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

Recommendations	COR	LOE
Diagnosis		
Measure cardiac-specific troponin (troponin I or T) at presentation and 3–6 h after symptom onset in all patients with suspected ACS to identify pattern of values	I	A
Obtain additional troponin levels beyond 6 h in patients with initial normal serial troponins with electrocardiographic changes and/or intermediate/high risk clinical features	I	A
Consider time of presentation the time of onset with ambiguous symptom onset for assessing troponin values	I	A
With contemporary troponin assays, CK-MB and myoglobin are not useful for diagnosis of ACS	III: No Benefit	A

Point-of-care troponin values may provide initial diagnostic information, although their sensitivity is substantially below that of central laboratory methods (refs). In addition, the rigorous quantitative assay standardization needed for routine diagnosis favors central laboratory testing.

Accrediting Organizations will likely state something akin:

Laboratory Based Assays* and the 99th% URL."

***PATHFAST, Stratus CS and …. Cardiac Biomarker Analyzers are equivalent.**

Circulation. 2014 Dec 23;130(25):e344-426.

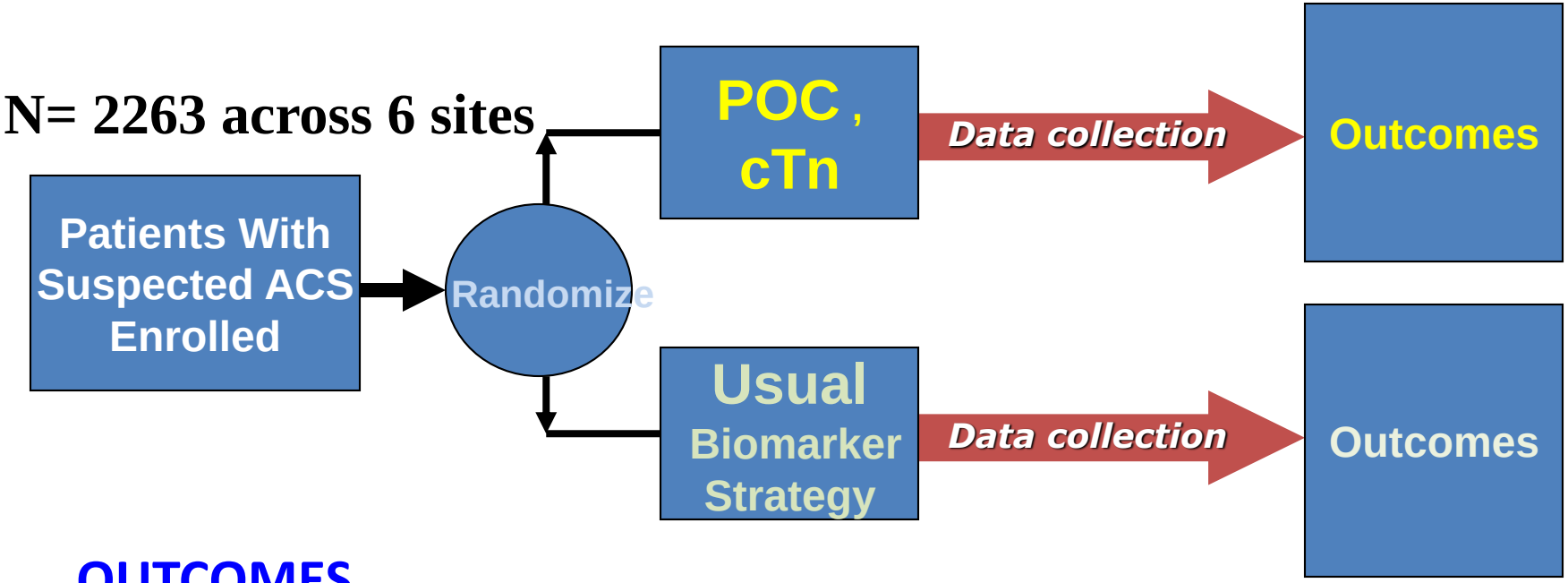
The RATPAC Trial

Heart. 2012 Feb;98(4):312-8.

Randomised **A**ssessment of **T**reatment using **P**anel **A**ssay of **C**ardiac markers: A randomised controlled trial of point-of-care cardiac markers in the emergency department

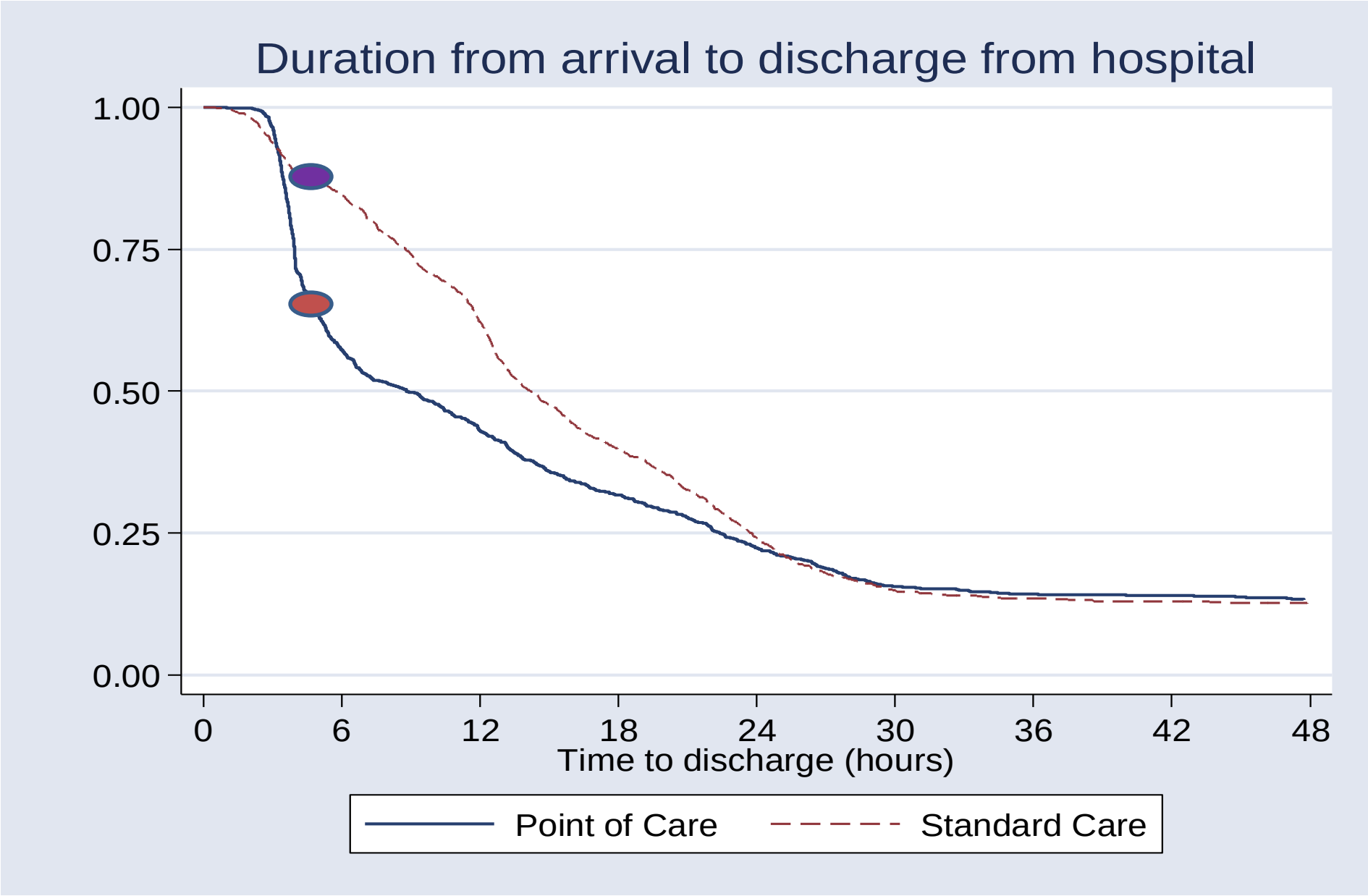
P. O. Collinson[1],Steve Goodacr[2], Mike Bradburn[2], Patrick Fitzgerald[2] , Liz Cross[2], Alasdair Gray[3], Alistair Hall[4] on behalf of the RATPAC investigators.

Randomized Design



OUTCOMES

- **Proportion of patients successfully discharged home or to in-patient ward after ED assessment by 4 hours.**
- **Discharge with no adverse event during the subsequent three months = Success.**


Duration from arrival to discharge from hospital
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
42
48
Time to discharge (hours)
Point of Care
Standard Care

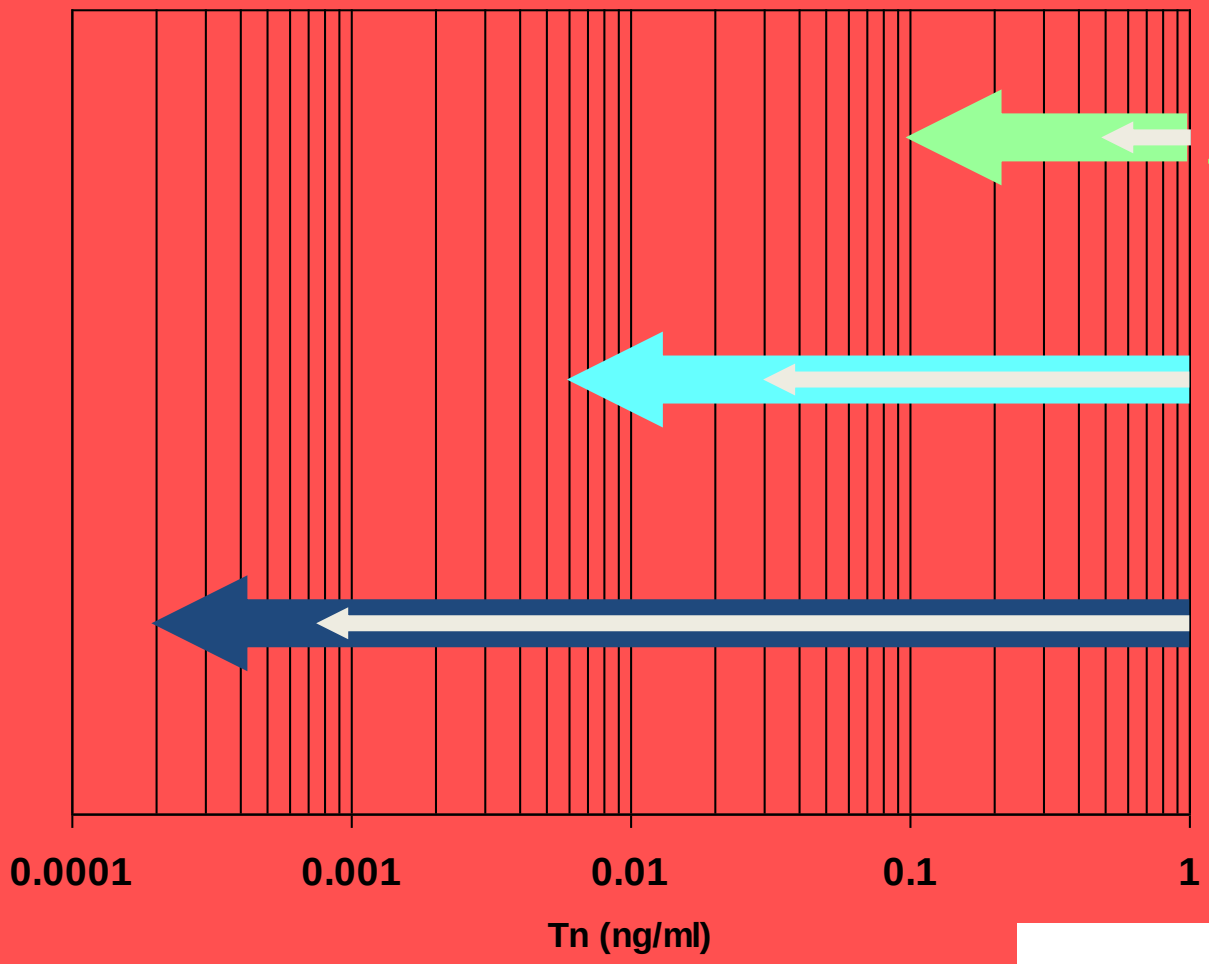
Successful discharge at 4 hrs?

	Point of care	Standard Care
Yes	358 (32%)	146 (13%)
Discharged but re-admitted	4 (<1%)	1 (<1%)
In hospital at 4 hours, decision to discharge	43 (4%)	13 (1%)

Major adverse events within 90 days

	Point of care	Standard Care	OR (95% CI)	P-value
Death	6 (1%)	2 (<1%)	3.4 (0.7 to 17.3)	0.142
Non-fatal AMI	5 (<1%)	5 (<1%)	0.9 (0.3 to 3.2)	0.903
Hospitalisation for ACS	18 (2%)	9 (1%)	1.8 (0.8 to 4.1)	0.149
Life threatening arrhythmia	6 (1%)	2 (<1%)	3.2 (0.6 to 15.9)	0.160
Emergency revascularisation	10 (1%)	14 (1%)	0.7 (0.3 to 1.5)	0.324

The Next Generation



Prior Gen commercial TnI
Limit of detect ~ 0.1ng/ml
10% CV = 0.4 ng/ml

Current commercial TnI
Limit of detect ~ 0.005 ng/ml
10% CV = 0.02 - 0.04 ng/ml

Next Gen Ultrasensitive
Limit of detect ~ 0.0001 ng/ml
10% CV <0.001 ng/ml

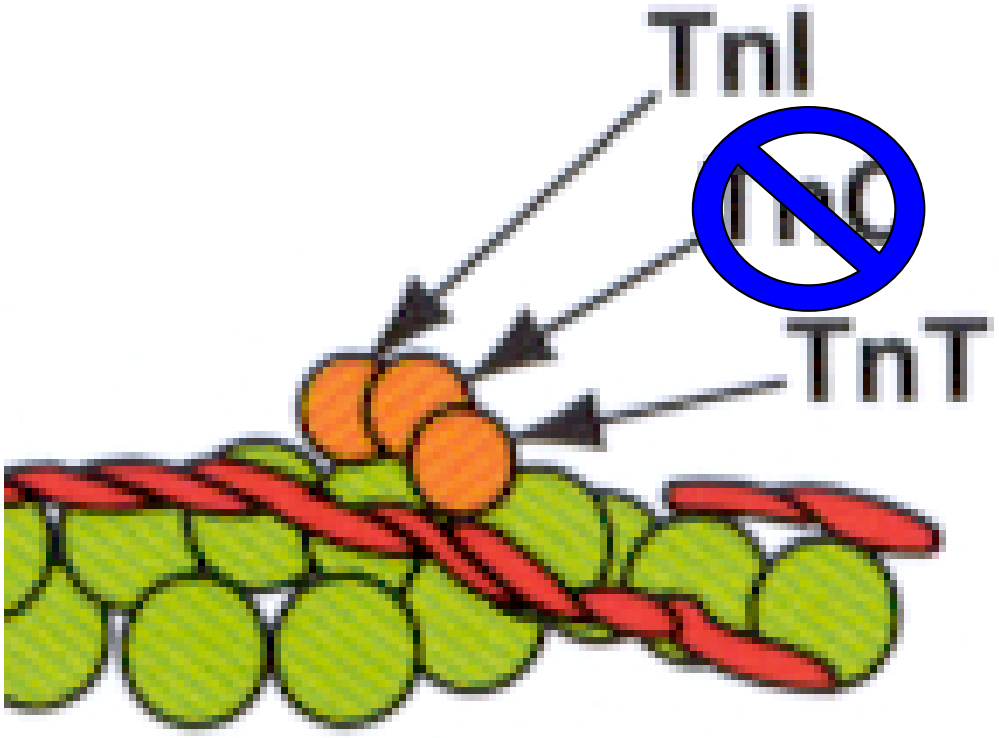
From: *Contemporary Cardiology: Cardiovascular Biomarkers: Pathophysiology and Disease Management*
Edited by: David A. Morrow © Humana Press Inc., Totowa, NJ

Dr. Robert Jesse, Cardiologist

"…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."

High Sensitivity?

Sensitive?



Hypersensitive?

Guideline compliant?

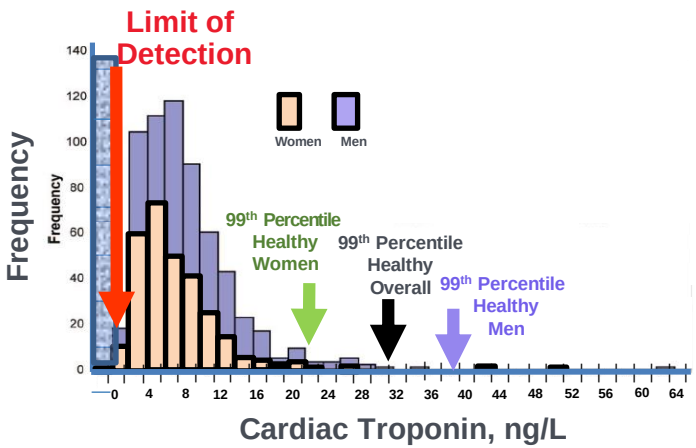
Contemporary?

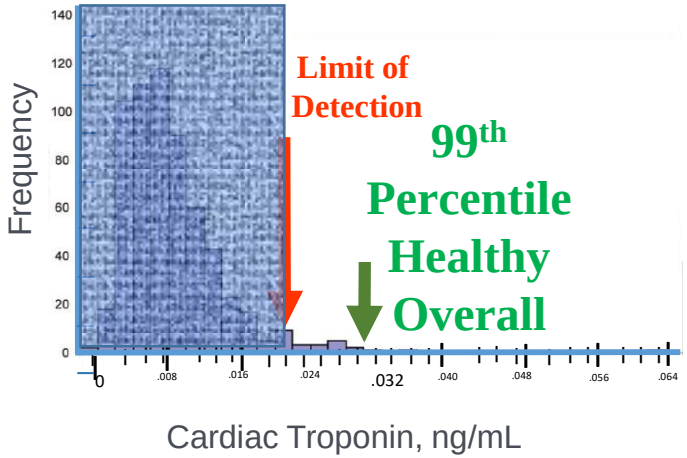
Next Generation?

State of the art?

High-sensitivity Cardiac Troponin Assays

Definition is Analytical, Benefit is Clinical





- **High-Sensitivity' is an analytical term**
  - **hsTn assays <u>DO NOT</u> measure a different analyte**

Clinical Chemistry 64:4
645–655 (2018)

Special Report

Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine

Alan H.B. Wu,[1*] Robert H. Christenson,[2] Dina N. Greene,[3] Allan S. Jaffe,[4] Peter A. Kavsak,[5] Jordi Ordonez-Llanos,[6] and Fred S. Apple[7]

What is High-Sensitivity Cardiac Troponin?

Clinical Chemistry 64:4;645–655 (2018)

AACC Academy and IFCC Task Force defines a high-sensitivity cTn as:

- an assay that can measure ≥ 50 % of healthy men and healthy women, i.e. values above the Limit of Detection.
- Also, hs-cTn assays are precise, i.e. day-to-day Total CV ≤ 10%.

AACC: American Association for Clinical Chemistry
IFCC: International Federation for Clinical Chemistry

Clinical Chemistry 64:4;645–655 (2018)

Recommendation 5: We recommend that assays unable to detect cTn at concentrations at or above the LoD in at least 50% of healthy men and women be labeled as contemporary cTn assays.

AACC Universal Sample Bank

Demographic and Clinical Laboratory Data For Enrolled Healthy Individuals

	Males	Females	Caucasian	African-American	Asian	Other
N	406	402	481	212	91	24
Age, years	39 (13)[a]	39 (13)	41 (13)	36 (13)	37 (11)	38 (13)
Hb A_{1c}, %	5.5 (0.33)	5.5 (0.30)	5.4 (0.28)	5.6 (0.37)	5.6 (0.30)	5.7 (0.25)
NT-proBNP, ng/L	27 (39)	56 (52)	49 (52)	31 (53)	26 (26)	40 (48)
eGFR, mL/min/1.73 m^2	89 (17)	89 (18)	86 (16)	90 (12)	90 (11)	85 (12)

[a] Data in parentheses are SD.

JALM 2017;1; 711–719 May 2017

First High-Sensitivity Cardiac Troponin I Assay Cleared by the United States Food and Drug Administration: Validation and Implications

PATHFAST cTnI-II cardiac biomarker assay (LSI Medience Corp, Tokyo, Japan)

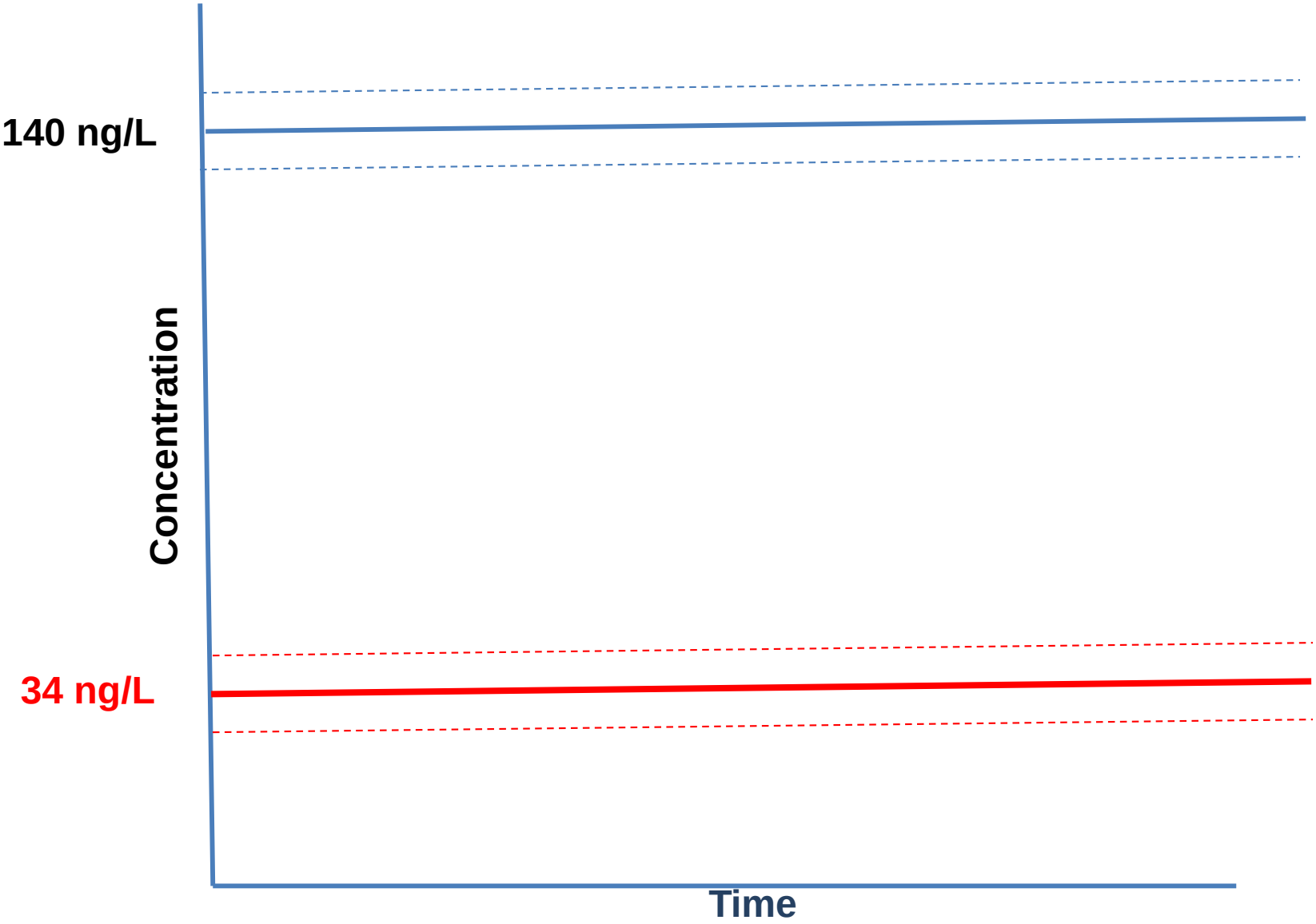
Population and Statistical Modeling Method	Overall cohort	Females	Males
Section IV. Healthy Population after exclusion for <60 eGFR<60 mL/min/1.73 m^2 AND HbA1c ≥ 6.5% AND NT-proBNP: >125 ng/L if <75 years; NT-proBNP: >450 ng/L if ≥75 years			
Healthy populations after eGFR AND Hb A_{1c} AND NT-proBNP exclusion	734	352	382
Number of subjects (% of specific cohort exceeding the Limit of Detection)	487 (66.3%)	186 (52.8%)	301 (78.8%)
Non-parametric percentile method (CLSI C28-A3)			
99th percentile decision point	27.9 ng/L	20.3 ng/L	29.7 ng/L
90% Confidence Interval	90% CI: 20.1 – 29.7	90% CI: 12.8 – 29.7	90% CI: 21.2 – 36.9
Robust method (CLSI C28-A3)*			
99th percentile decision point	14.0 ng/L	10.5 ng/L	16.4 ng/L
90% Confidence Interval	90% CI: 12.7 - 15.3	90% CI: 8.6 - 12.3	90% CI: 14.5 - 18.2
Harrell-Davis method			
99th percentile decision point	26.1 ng/L	21.0 ng/L	28.6 ng/L
90% Confidence Interval	90% CI: 20.7–31.5	90% CI: 13.9 - 28.0	90% CI: 23.9 – 33.3

Cardiac Troponin Units of Measure

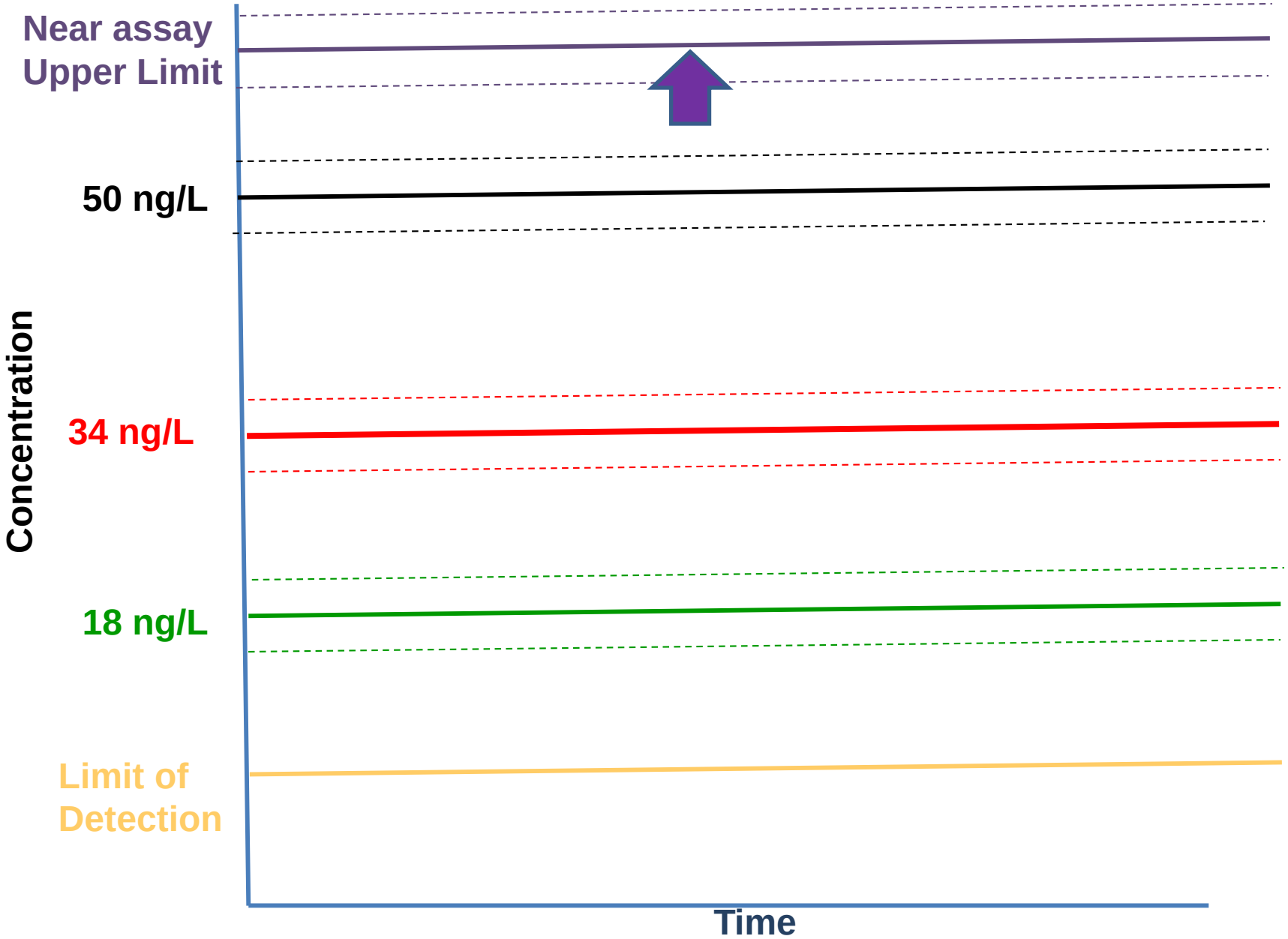
ng/mL, Contemporary versus ng/L, High-sensitivity

- **High-sensitivity** • 19 ng/L
- **Contemporary** • 0.03 **ng/mL** **or 30 ng/L**
- **High-sensitivity** • 22**ng/L**
- **Contemporary** • 0.003**ng/mL** **or 3 ng/L**
- **Contemporary** • 0.30 **ng/mL** **or 300 ng/L**
- **High-sensitivity** • 14**ng/L**
- **High-sensitivity** • 6 **ng/L**

Effective Quality Monitoring



Effective Quality Monitoring



Summary and Conclusions

- Cardiac Troponin is the biomarker for MI
  - Use 99th percentile as cutoff
  - CV at 99th percentile cutoff
  - Rise and/or fall in cTn
- Target appropriate epitopes, avoid interferences
- No 'Pass' for POC. Characteristics for POC must be the same as central lab assays.
  - There are attractive POC technologies, but caution is advised.
- Several generations of assays developed
- Higher Sensitivity Assays have advantages

Thank You!

rchristenson@umm.edu