INVESTIGATION OF POSSIBLE ACS IN THE ED

Martin P Than

DISCLOSURES

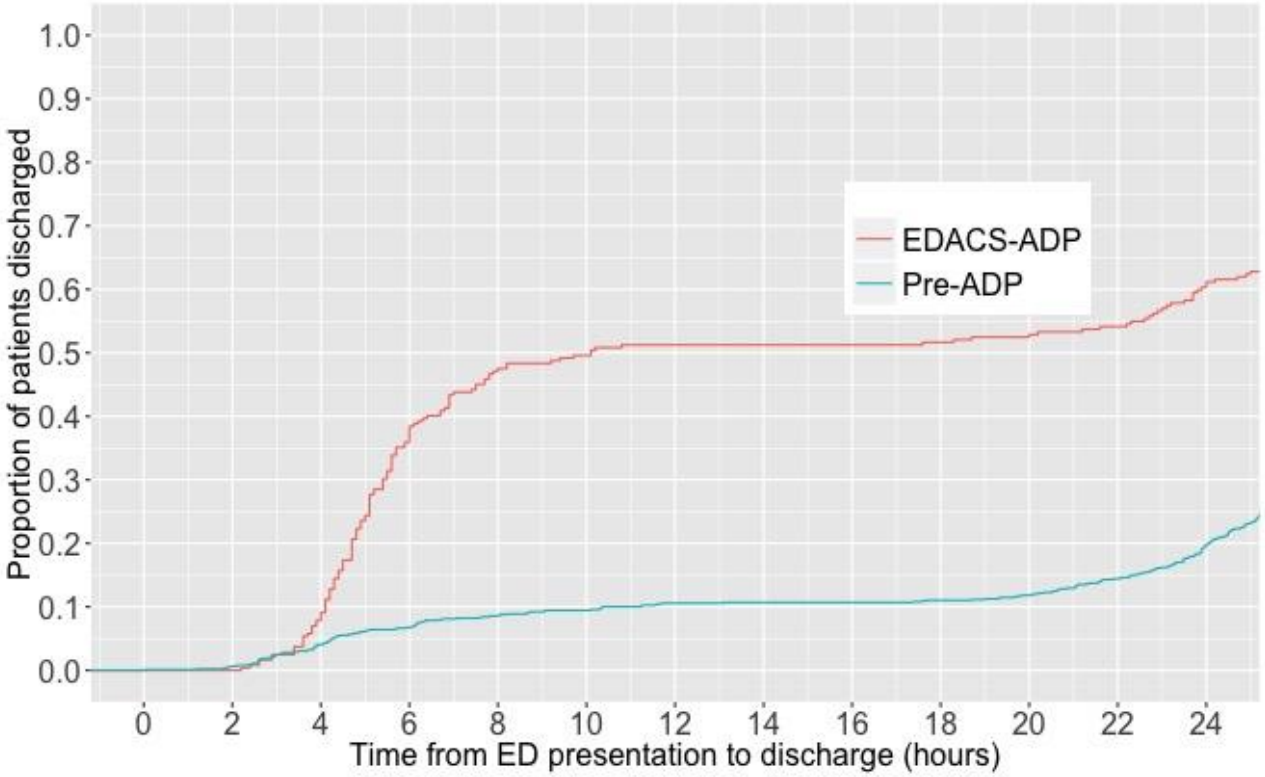
Have received grants and/or speakers fees from:

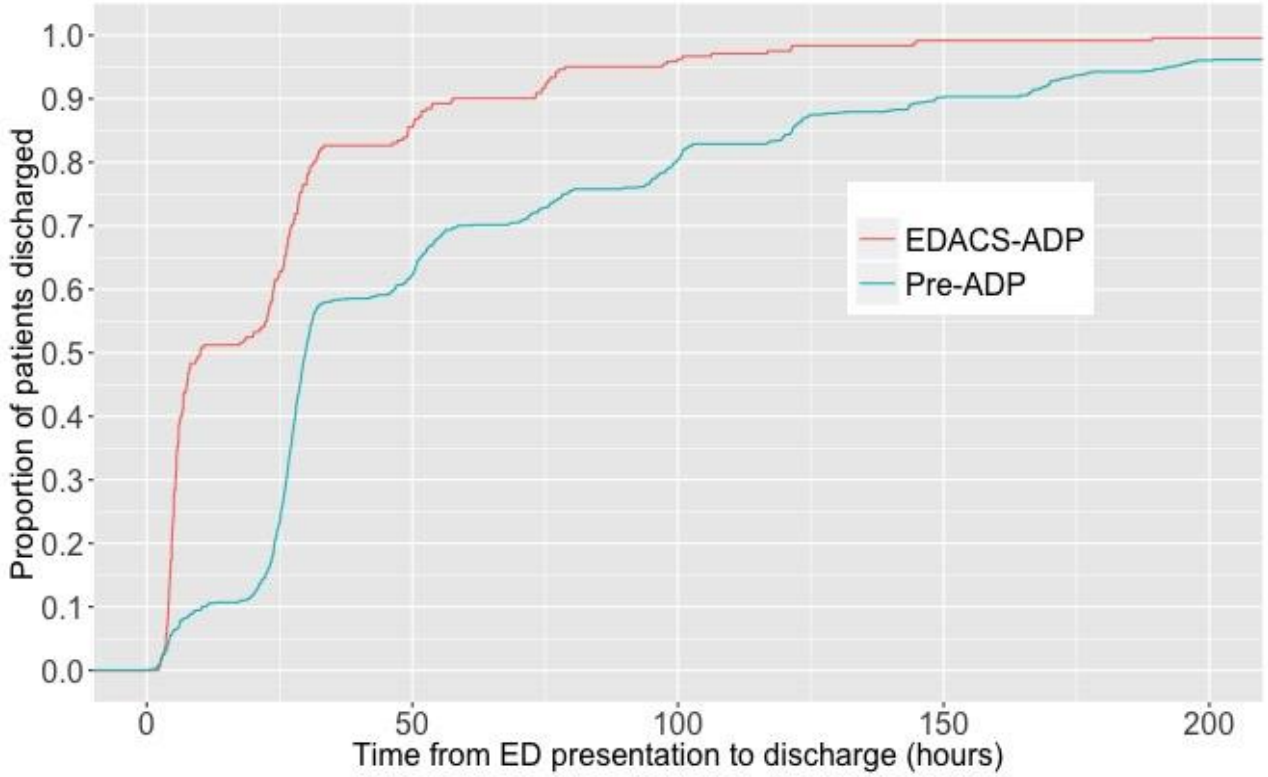
Abbott, Abbott Point of Care, Alere, Beckman and Roche

Have had research discussions with ET, Radiometer, Siemens

Also:

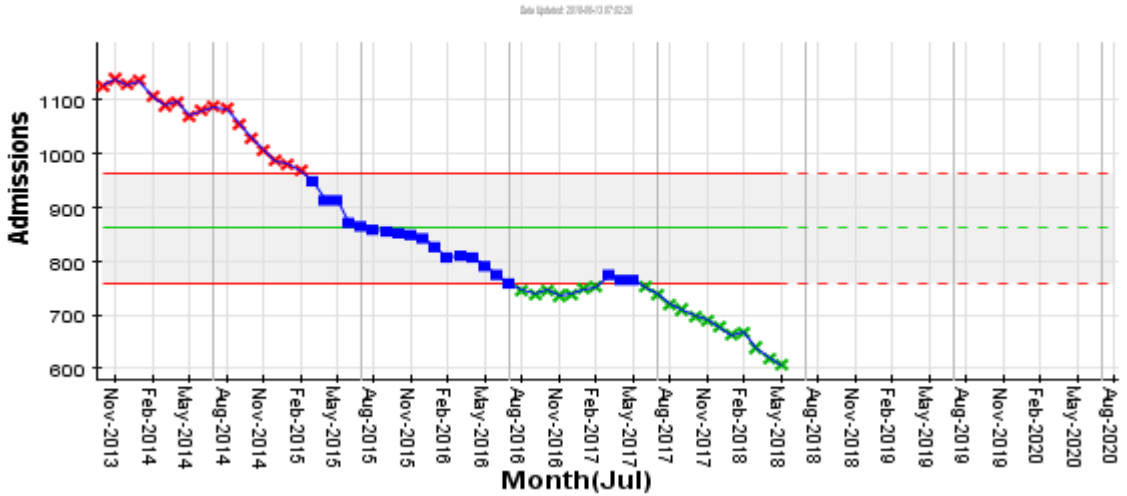
Health Research Council (NZ), Heart Foundation, Christchurch Heart Institute and many, many stakeholder partners


Proportion of patients discharged
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
EDACS-ADP
Pre-ADP
0
2
4
6
8
10
12
14
16
18
20
22
24
Time from ED presentation to discharge (hours)

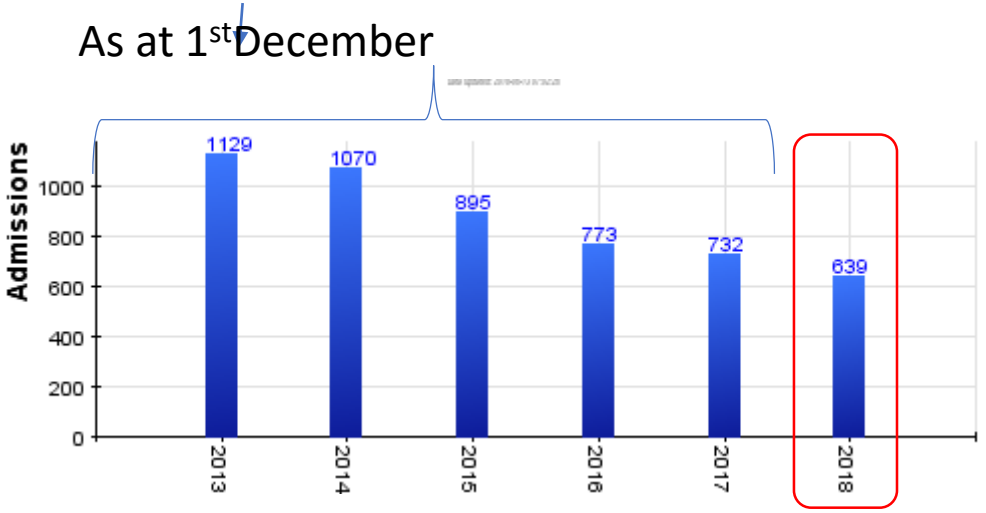

Proportion of patients discharged
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
EDACS-ADP
Pre-ADP
0
50
100
150
200
Time from ED presentation to discharge (hours)

ED Chest Pain ICD Primary Diag. R00-R09 Symptoms and signs involving the circulatory and respiratory systems
Cardiology admitted

Accumulative of the last 12 months as at 1st of month



As at 1st December



As at 1st June

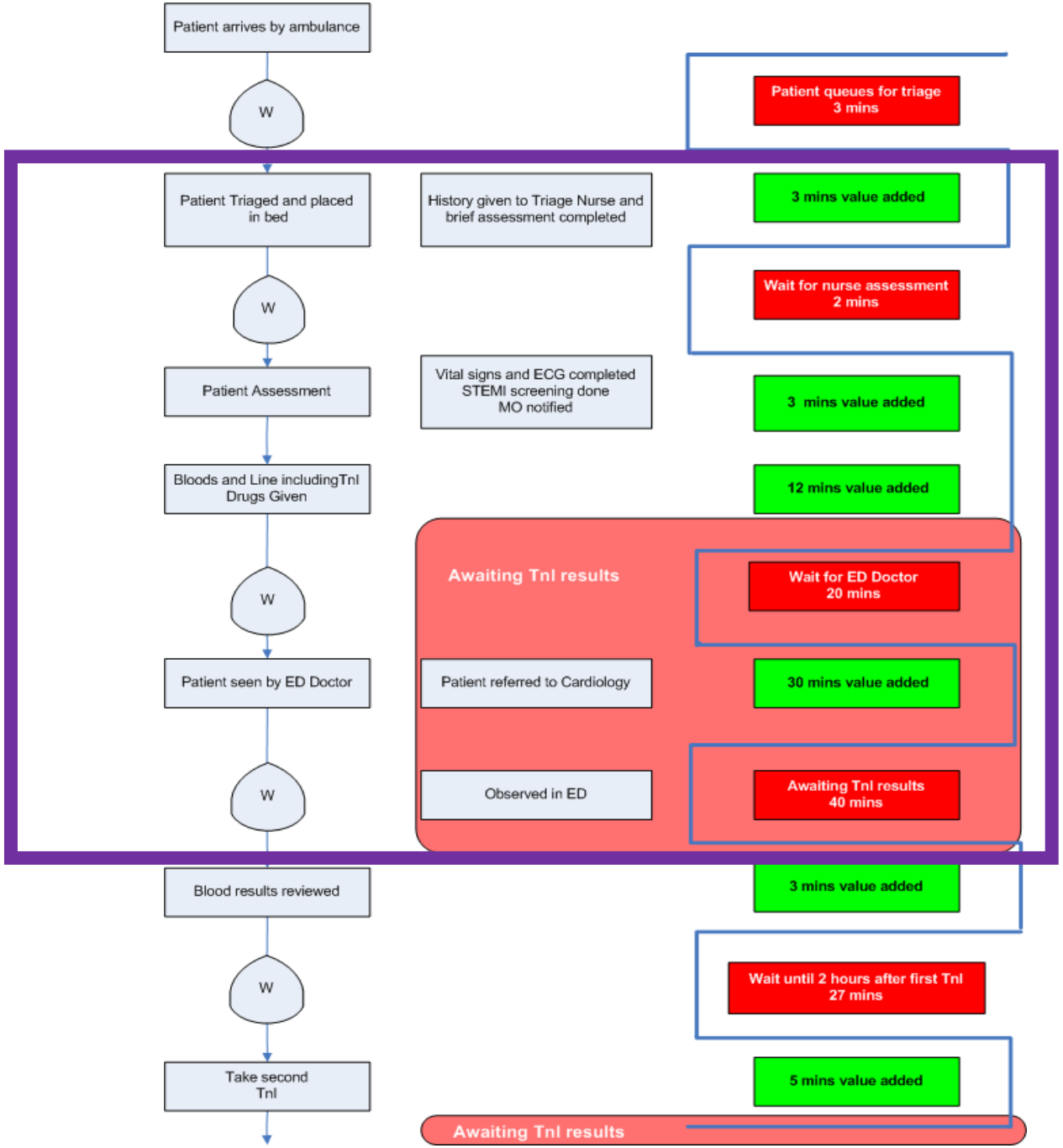
SUMMARY

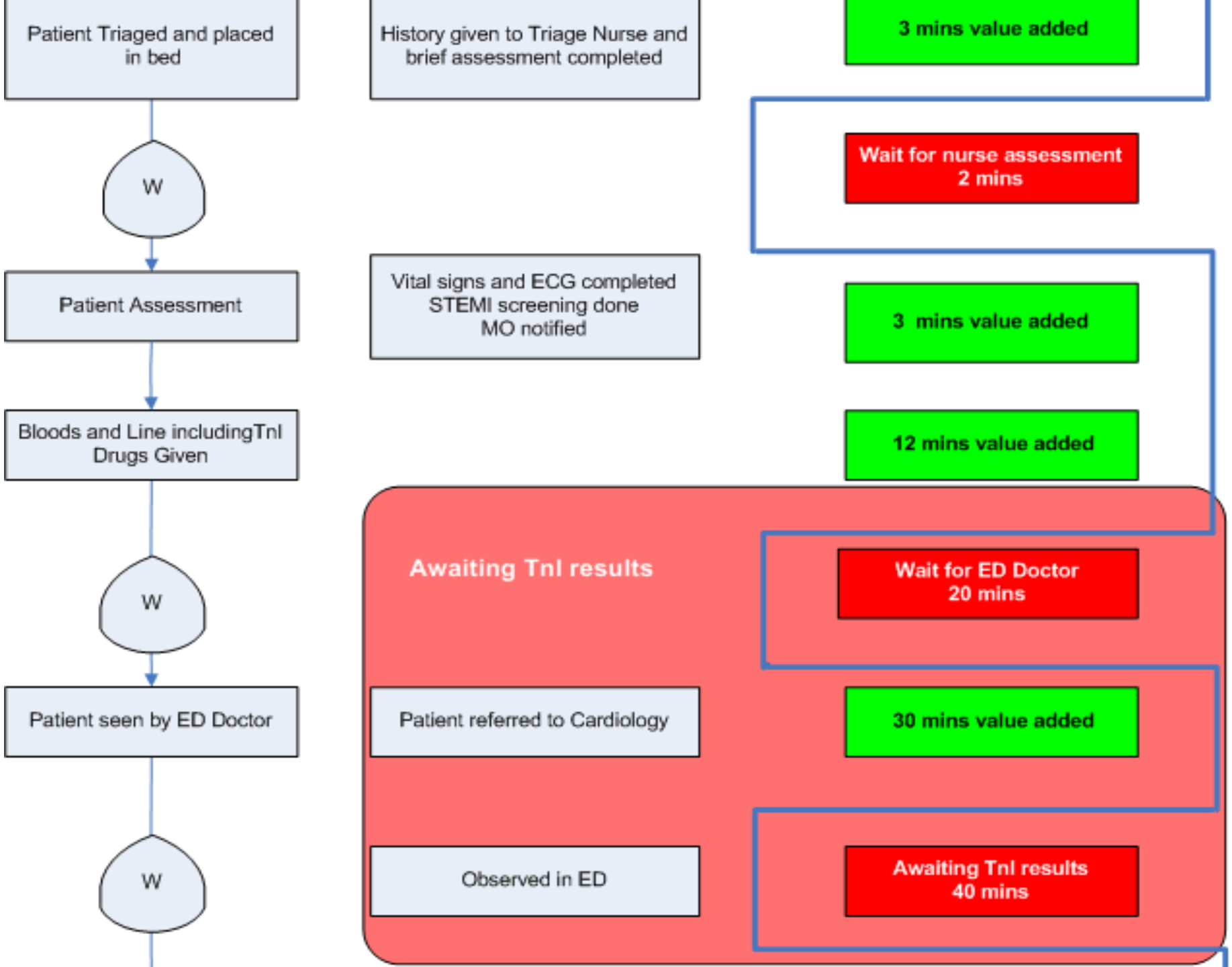
- Impact of working up patients for AMI on crowding and flow
- Troponin metrics and characteristics
- Historical use of x2 troponin measurements
- High precision assays make rule-out possible with single ‘baseline’ test
- Evidence is very strong with central lab. assays
- Evidence now emerging with new point-of-care (POC) assays

If there was faster turnaround of troponin results…..would it help?

- Value stream mapping

Value stream mapping




Patient Triaged and placed in bed
History given to Triage Nurse and brief assessment completed
3 mins value added
W
Wait for nurse assessment 2 mins
Patient Assessment
Vital signs and ECG completed
STEMI screening done
MO notified
3 mins value added
Bloods and Line includingTnI
Drugs Given
12 mins value added
Awaiting TnI results
W
Wait for ED Doctor 20 mins
Patient seen by ED Doctor
Patient referred to Cardiology
30 mins value added
W
Observed in ED
Awaiting TnI results 40 mins

All troponin assays are different

- They use varying antibodies for signal creation

- **Understand yours**

- Additionally, point-of care assay do **NOT** meet accuracy of lab assays

Point of Care Cardiac Troponin I and T Assay Analytical Characteristics Designated by Manufacturer

IFCC Committee on Clinical Applications of Cardiac Bio-Markers (C-CB) v072618

Company/Platform/ Assay	LoB (µg/L)	LoD (µg/L)	% CV at 99th Percentile	Conc at 20% CV (µg/L)	Conc at 10% CV (µg/L)	Reference Population N, Ages, Sex	Specimen Type	99th Percentile (µg/L)	Percent Normals Measured ≥ LoD	Statistic Used to Calc 99th Percentile	Epitopes Recognized by Antibodies	Country of Package Insert: Version Date
Abbott i-STAT	0.02	NP	16.5%	0.07	0.1	Overall n = 162	Sodium and lithium heparinized whole blood and plasma	Overall: 0.08	NP	NP	NP	US: Rev. Date: 01-Jul-13
LSI Medience (formerly Mitsubishi) PATHFAST cTnI; commercial	NP	1	< 6%	2	3.1	Overall n =474 18-86y F: 236 M: 238	Overall: 15.48 M: 16.91 F: 11.46	Whole blood, plasma	Overall: 76.3%	Non-Parametric	C: 41-49, D: 71-116, 163-209	WW except US & Japan: Ver.6,2017.10
LSI Medience (former Mitsubishi) PATHFAST hs-cTnI /PATHFAST cTnI-II	1.23	2.33	6.1	4	15	Overall n=734 Age >18 F: 352 M: 382	Overall: 27.9 F: 20.3 M: 29.7	Whole blood, Plasma	Total: 66.3% F: 52.8% M: 78.8%	Non-Parametric	C:41-49, D: 71-116, 163-209	hs-cTnI : WW except US & Japan Ver.1, May 2018 cTnI-II: US, ver.4 Mar 2015
Philips Electronics Nederland BV /Minicare I-20/ Minicare cTnI	0.0085	0.018	18.6%	0.038	NP	Overall n =750 18-86y F: 377 M: 373	Li-heparin whole blood, capillary whole blood and plasma	Overall: 0.043	Overall: 5.1% for capillary	Non-Parametric	C: 41-49 D: 20-100 anti cTnC MAb	IFU cTnI EN Issue #5122300 12922*2017-03 Document version 3.0
Quidel/Alere Triage Cardiac Panel	NP	0.050	NP	16.3% at 0.120	NP	Overall n = 323 F: 168 M: 155	EDTA whole blood or plasma	NP	NP	NP	NP	USA, 2014, rev. D
Quidel/Alere Triage SOB	NP	0.050	NP	16.3% at 0.120	NP	Overall n = 323 F: 168 M: 155	EDTA whole blood or plasma	NP	NP	NP	NP	USA, 2014, rev. D
Quidel/Alere Triage Cardio	0.002	0.01	NP	0.020	0.040	Overall n = 989	EDTA whole blood or plasma	Overall: 0.020	Overall: 11.8%	Non-Parametric	NP	USA, 2014, rev. D
Radiometer AQT90 FLEX TnI	NP	0.009	12.3%	NP	0.027	Overall n = 231 F: 106 M: 128	EDTA and heparinized whole blood and plasma	Overall: 0.023	NP	Non-Parametric	C: 41-49, 190-196 D:137-149	990-872 InterNPtioNPI 201608X
Radiometer AQT90 FLEX TnT	NP	0.008	15.2%	NP	0.026	Overall n = 260 F: 132 M: 128	EDTA and heparinized whole blood and plasma	Overall: 0.017	NP	Non-Parametric	C:125-131 D:136-147	990-872 InterNPtioNPI 201608H
Response Biomedical RAMP Troponin I	NP	0.03	20.0%	0.10	0.21	Overall n =180	Only EDTA whole blood	Overall: <0.10	NP	NP	NP	Eu IFU 90012-1.2
Roche CARDIAC POC Troponin T – Roche cobas h 232	NP	0.04	NP	0.04 – 2.0	9.3% between 0.04 –0.2	Overall n = 302	Heparinized whole blood	NP	NP	NP	D: 125-131 C: 136-147	EU, 2016-05
Siemens Stratus CS Acute Care cTnI test pack	<0.03	NP	8.2%	0.03	0.06	Overall n=101 No age No sex	Whole blood (Li or NP heparin) or plasma Li or Na heparin	Overall: 0.07	NP	NP	C: 27-32 D: 41-56	CE, 2008-04

LoB, limit of blank; LoD, limit of detection, NP, not provided; C, capture antibody; D, detection antibody; M, male, F, female; Conc, concentration; WW worldwide. All data have been listed as provided by the manufacturer, except assays in blue were abstracted from package insert due to lack of correspondence from manufacturer.

How to find details about your assay

- IFCC troponin table
- IFCC = International Federation of Clinical Chemistry
- http://www.ifcc.org/ifcc-education-division/emd-committees/task-force-on-clinical-applications-of-cardiac-bio-markers-tf-cb/

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

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: 27-40	Fluorophor
Alere Triage Cardio 3	2	10	22	17.0	37		C: 27-39; D: 83-93, 190-196	Fluorophor
Beckman Coulter Access Accu	10		40	14.0	60		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	17.7	39		C: 41-49, 190-196; D: 137-149	Europium
Radiometer AQT90 FLEX TnT		8	17	15.2	26		C: 125-131; D: 136-147	Europium
Response Biomedical RAMP	30		100	20.0	210	180: 18 - 80 (M: 84; F: 96)	C: 85-92; D: 26-38	Fluorophor

Limit of Detection (LoD): is the lowest analyte concentration at which reliable detection is feasible

(though it may not be able to do this with consistent accuracy).

Siemens IMMULITE® 2000 XPi [f]	200		290	10.3	320	300	C: 87-91; D: 27-40	ALP – Chemiluminescence
Siemens IMMULITE®1000 Turbo [f]	150		NA	NA	640		C: 87-91; D: 27-40	ALP – Chemiluminescence
Siemens Stratus® CS cTnI	30 [d]		70	10.0	60	101	C: 27-32; D: 41-56	ALP
Tosoh ST AIA-PACK	60		60 [c]	8.5	NA		C: 41-49; D: 87-91	ALP

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

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 [c]	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: 27-40	Fluorophor
Alere Triage Cardio 3	2	10	22	17.0	37		C: 27-39; D: 83-93, 190-196	Fluorophor
Beckman Coulter Access Accu	10		40	14.0	60		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 [c]		1	20	5.2	3.1	380	C: 41-49; D: 71-116, 163-209	ALP
Mitsubishi PATHFAST cTnI-II [1]	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	17.7	39		C: 41-49, 190-196; D: 137-149	Europium
Radiometer AQT90 FLEX TnT		8	17	15.2	26		C: 125-131; D: 136-147	Europium
Response Biomedical RAMP	30		100	20.0	210	180: 18 - 80 (M: 84; F: 96)	C: 85-92; D: 26-38	Fluorophor

The 99th percentile (mean ± 3 standard deviations)
A cut-off below which 99% of the results occurred in a (apparently) healthy reference population.

Levels recorded above this are considered to be abnormal.

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

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
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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: 27-40	Fluorophor
Alere Triage Cardio 3	2	10	22	17.0	37		C: 27-39; D: 83-93, 190-196	Fluorophor
Beckman Coulter Access Accu	10		40	14.0	60		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	17.7	39		C: 41-49, 190-196; D: 137-149	Europium
Radiometer AQT90 FLEX TnT		8	17	15.2	26		C: 125-131; D: 136-147	Europium
Response Biomedical RAMP	30		100	20.0	210	180: 18 - 80 (M: 84; F: 96)	C: 85-92; D: 26-38	Fluorophor

The **coefficient of variation** (CV): a lab statistical term for assay consistency

It describes the reproducibility of a result at a given level if the same sample were to be tested over and over again.

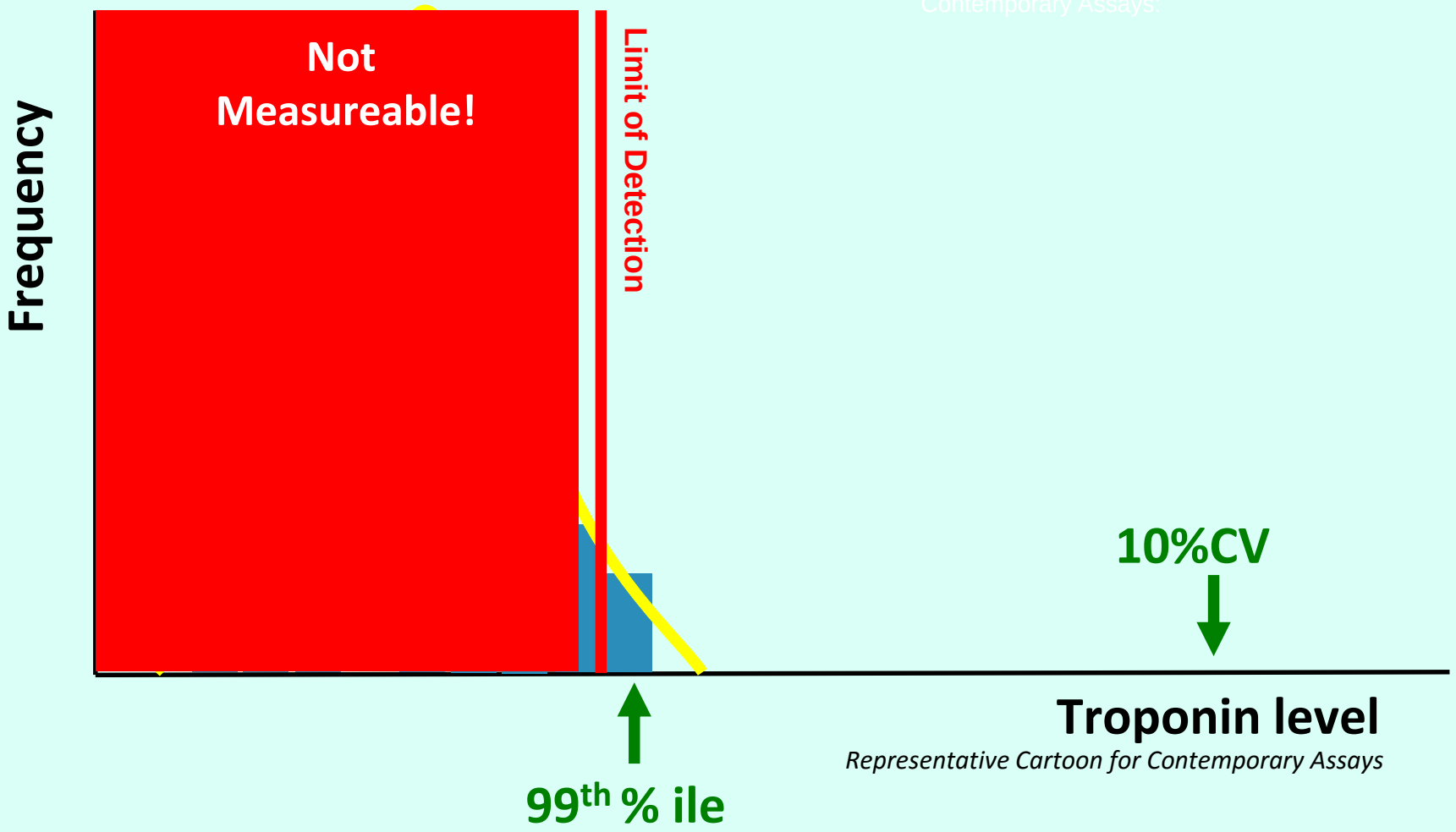
Commercially available assays - Company/ platform(s)/ assay	LoB [a] (ng/L)	LoD [b] (ng/L)	99th % (ng/L)	%CV at 99th %	10% CV (ng/L)	Reference population N: age range (y)	Epitopes recognised by Antibodies	Detection Antibody Tag
Abbott AxSYM ADV	20		40	14.0	160		C 87-91, 41-49; D 24-40	ALP
Abbott Architect	<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: 27-40	Fluorophor
Alere Triage Cardio 3	2	10	22	17.0	37		C: 27-39; D: 83-93, 190-196	Fluorophor
Beckman Coulter Access Accu	10		40	14.0	60		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	17.7	39		C: 41-49, 190-196; D: 137-149	Europium
Radiometer AQT90 FLEX TnT		8	17	15.2	26		C: 125-131; D: 136-147	Europium
Response Biomedical RAMP	30		100	20.0	210	180: 18 - 80 (M: 84; F: 96)	C: 85-92; D: 26-38	Fluorophor
Roche Cardiac Reader cTnT	30		NAD	NA	NA		C: 125-131; D:136-147	Gold particles
Roche cobas h 232 TnT	50		NAD	NA	NA		C: 125-131; D:136-147	Gold particles
Roche E 2010 /cobas e 411 / E 170 / cobas e 601 / 602 TnT (4th gen)	10		NAD	NA	30	533: 20 - 71 (M: 268; F: 265)	C: 125-131; D:136-147	Ruthenium
Roche E 2010/cobas e 411 / E 170 / cobas e 601 / 602 hs-TnT		5	14	10.0	13		C: 125-131; D: 136-147	Ruthenium
Roche E 2010/cobas e 411 / Roche E 170/cobas e 601 / 602 cTnI		160	160 [c]	NA	300		C: 87-91, 190-196; D: 23-29, 27-43	Ruthenium
Siemens ADVIA Centaur® TnI-Ultra™	6		40	8.8	30	648: 17 - 91	C: 41-49, 87-91; D: 27-40	Acridinium

The precision of an assay (represented by the CV) worsens at lower levels of detection.

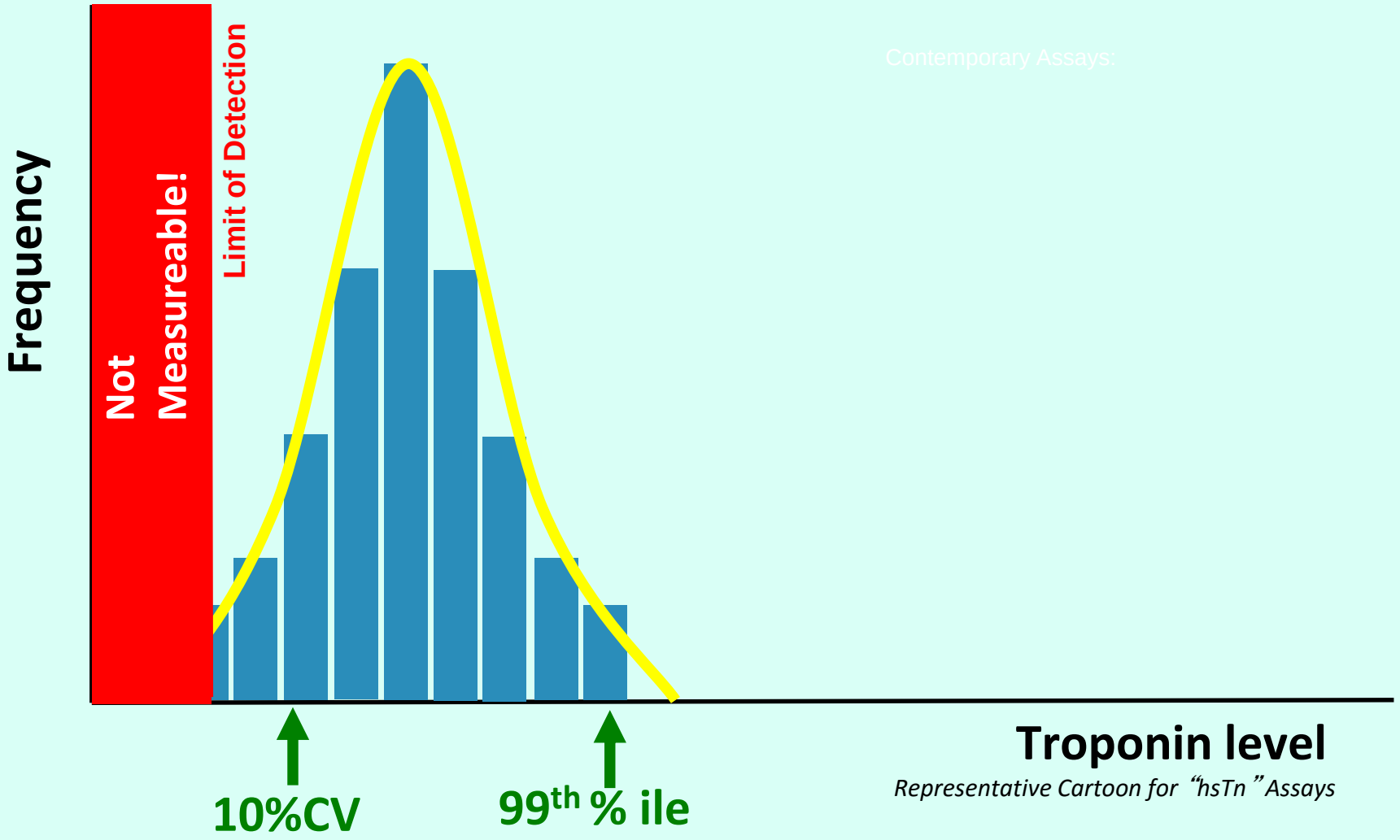
WHAT DOES THIS MEAN?

- Variation is low (that's good) at high concentrations
  - But that is not where we make rule-out decisions
- Variation increases (gets worse) at lower concentrations

What is meant by % Detection above the LoD?



What is meant by % Detection above the LoD?

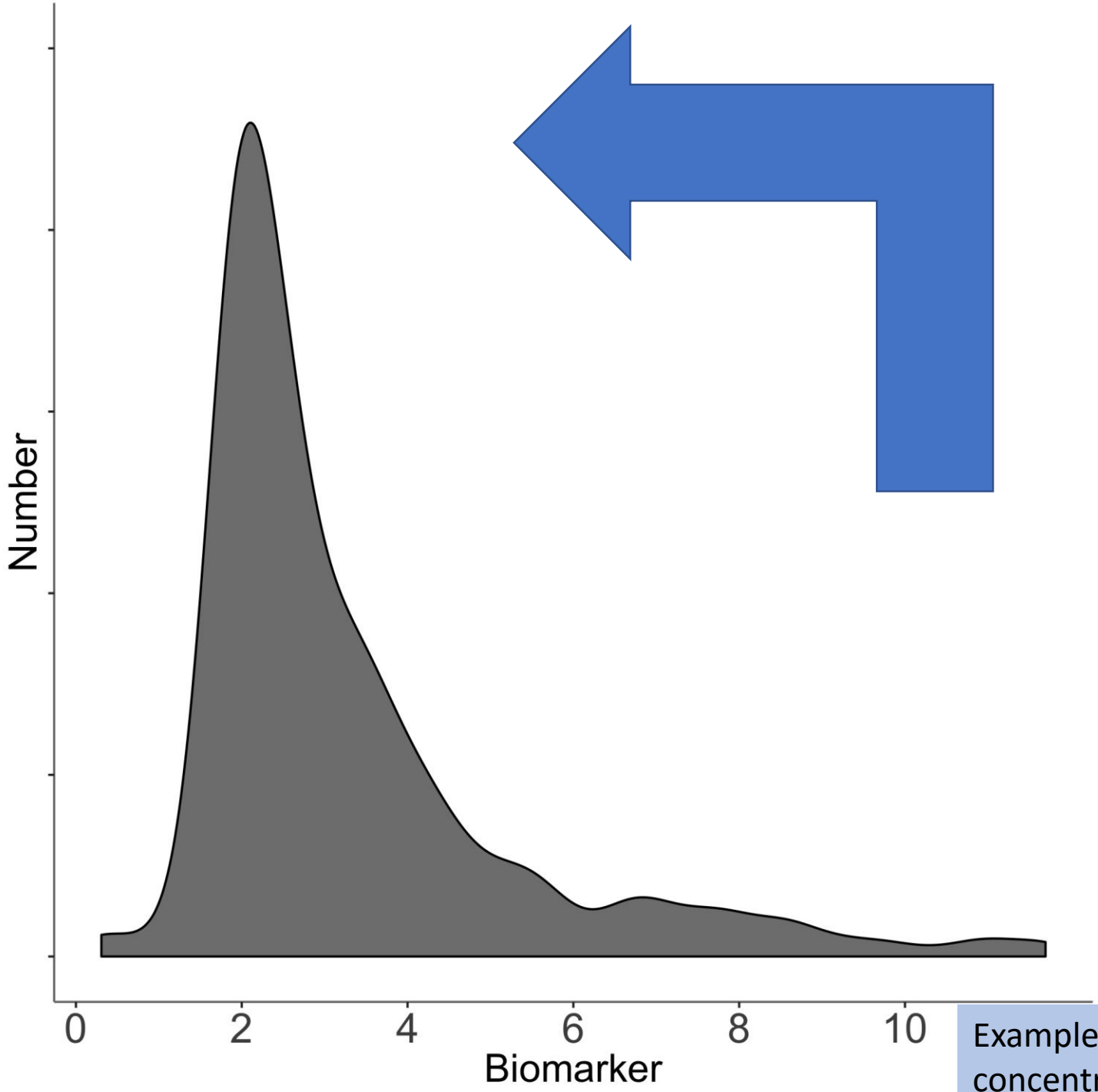


Diagnostic 2x2 table

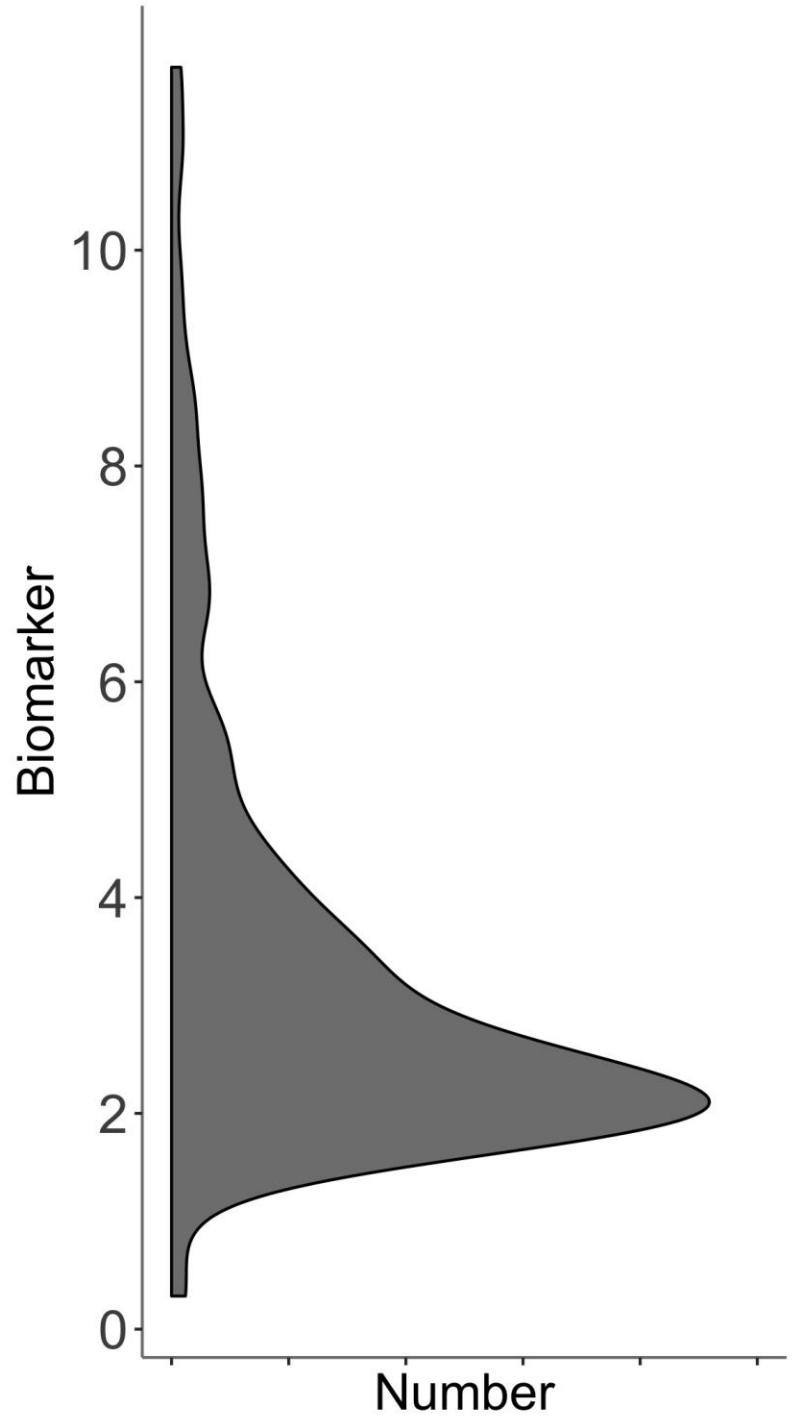
	Reference Standard Positive	Reference Standard Negative
Clinical Test Positive	**True positive result**	False positive result
Clinical Test Negative	False negative result	**True negative result**

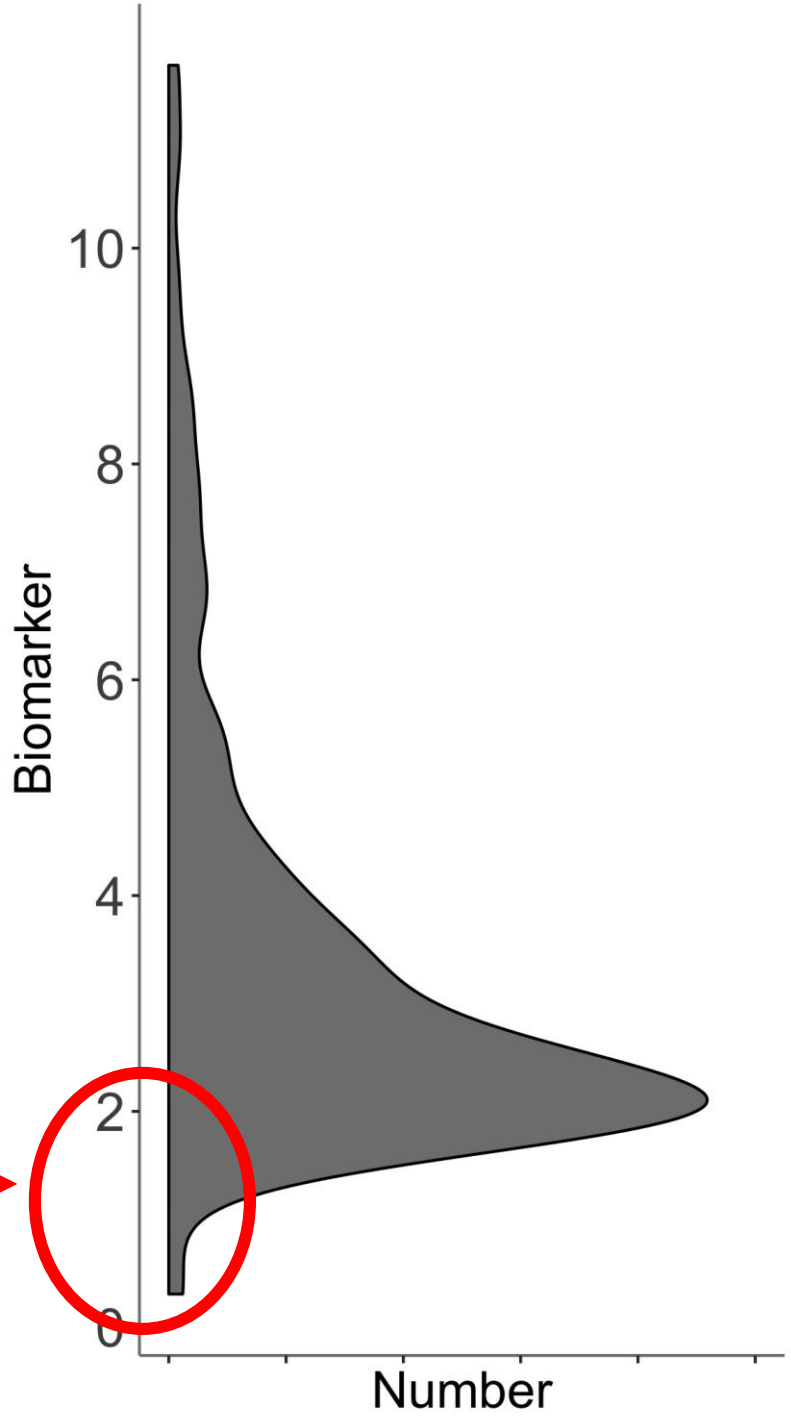
	AMI	No AMI
TROPONIN POSITIVE	True positive (TP)	False positive (FP)
TROPONIN NEGATIVE	False negative (FN)	True negative (TN)

Patient numbers

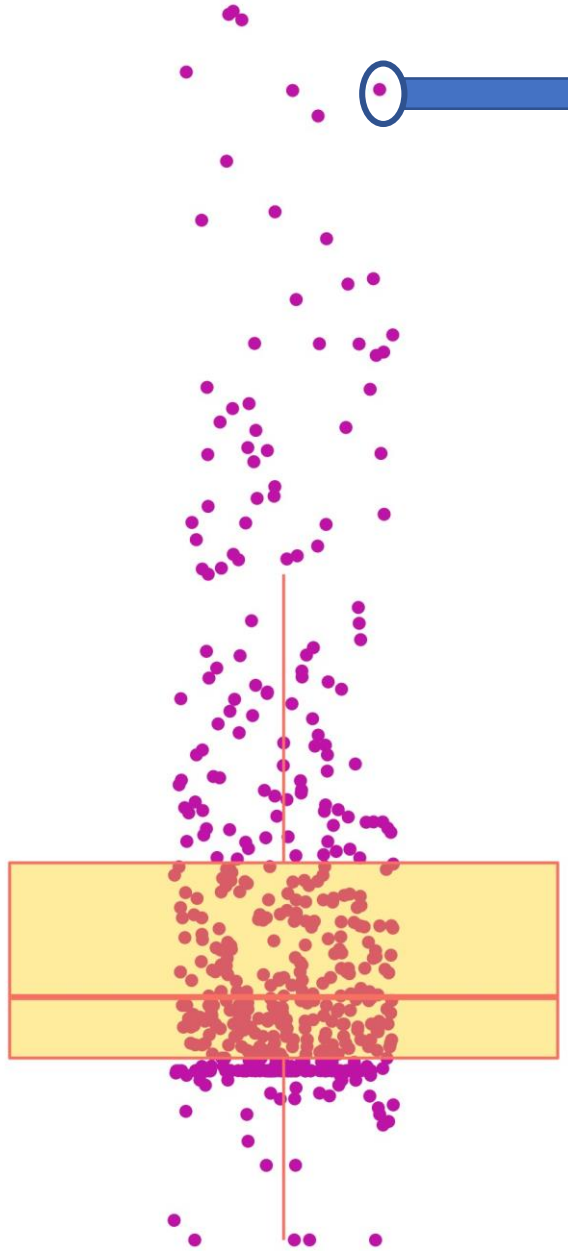


Example increasing troponin concentrations


Biomarker
10
8
6
4
2
0
Number

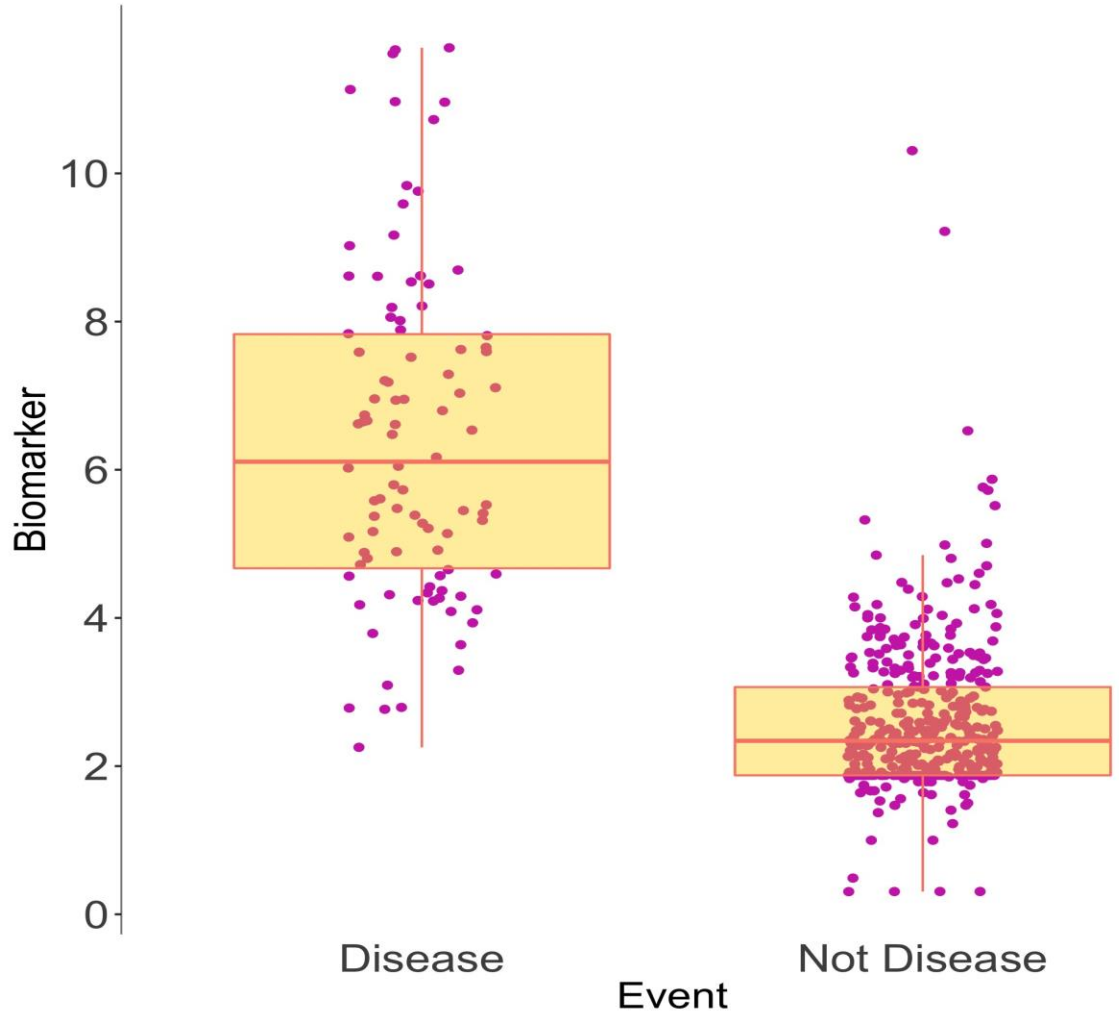


Troponin assays with high precision allow reliable measurement at low concentrations



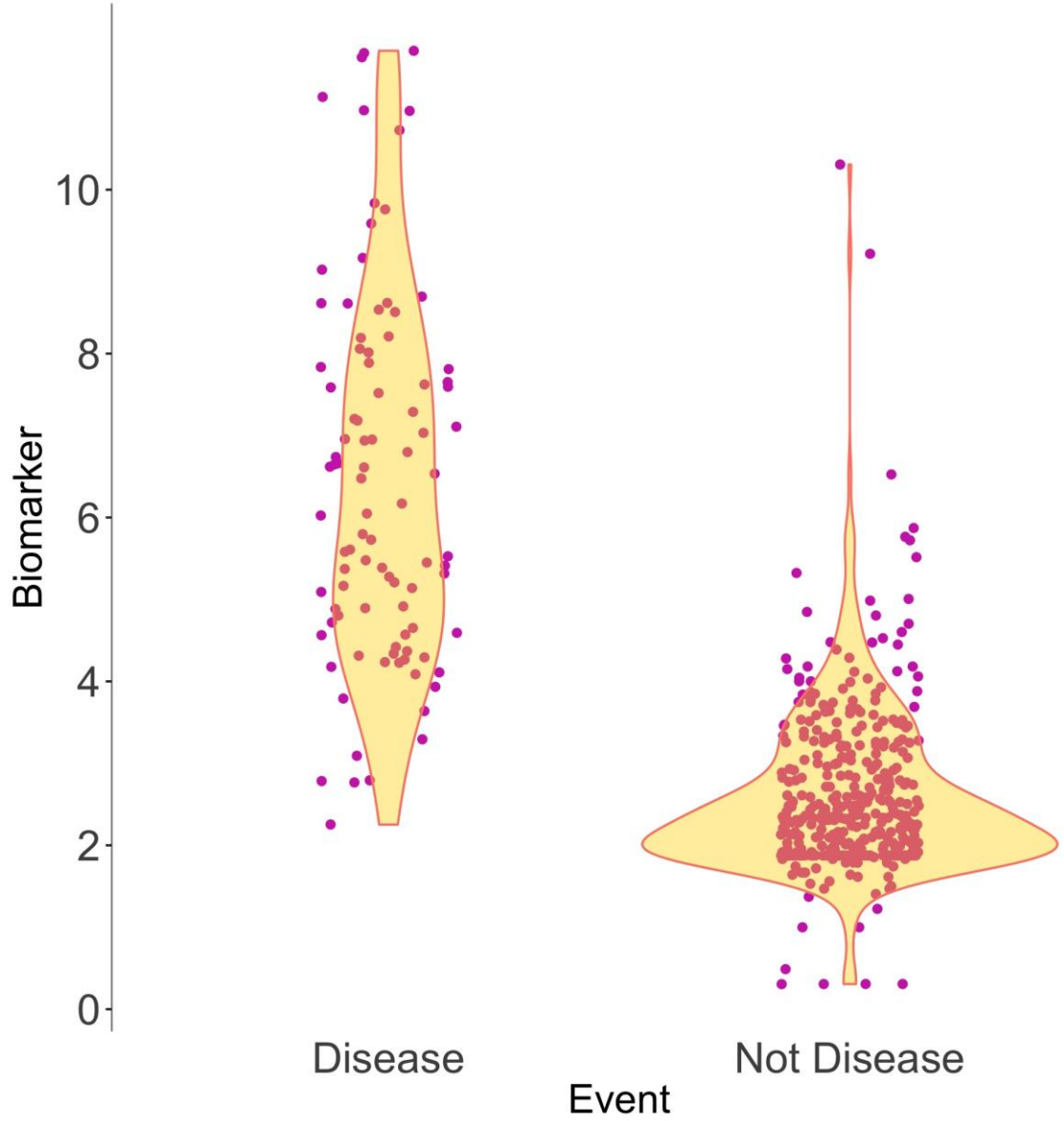
Individual patient

	AMI	No AMI

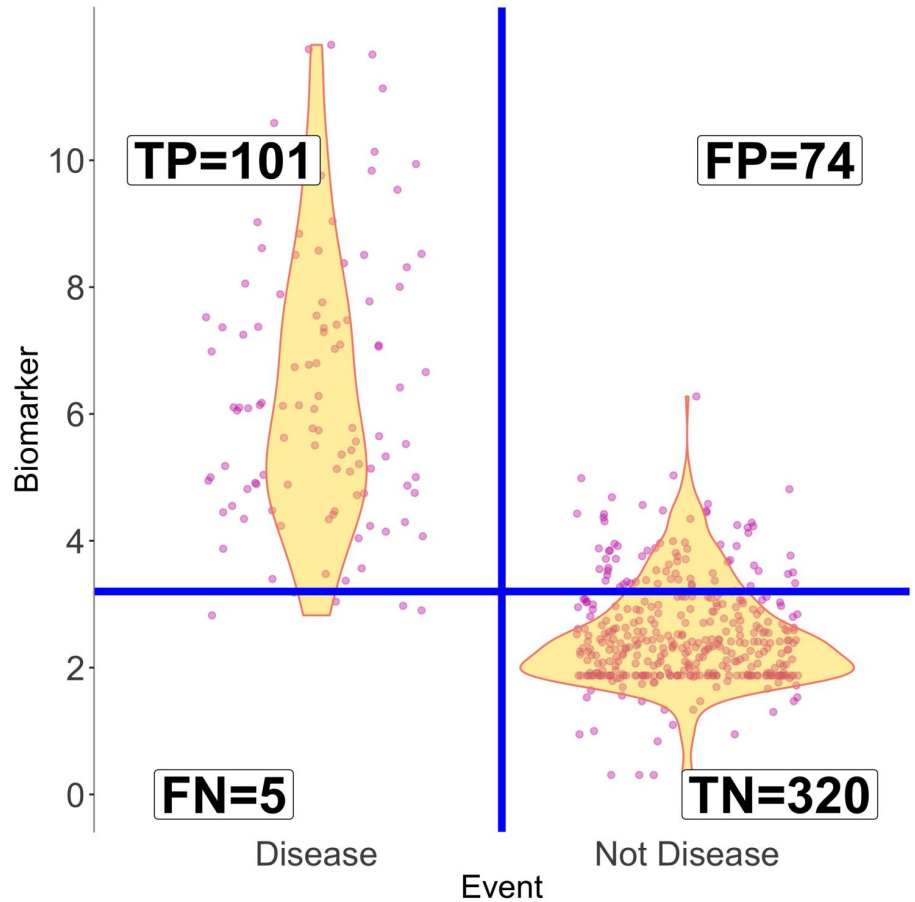


Event of interest is AMI

AMI	No AMI

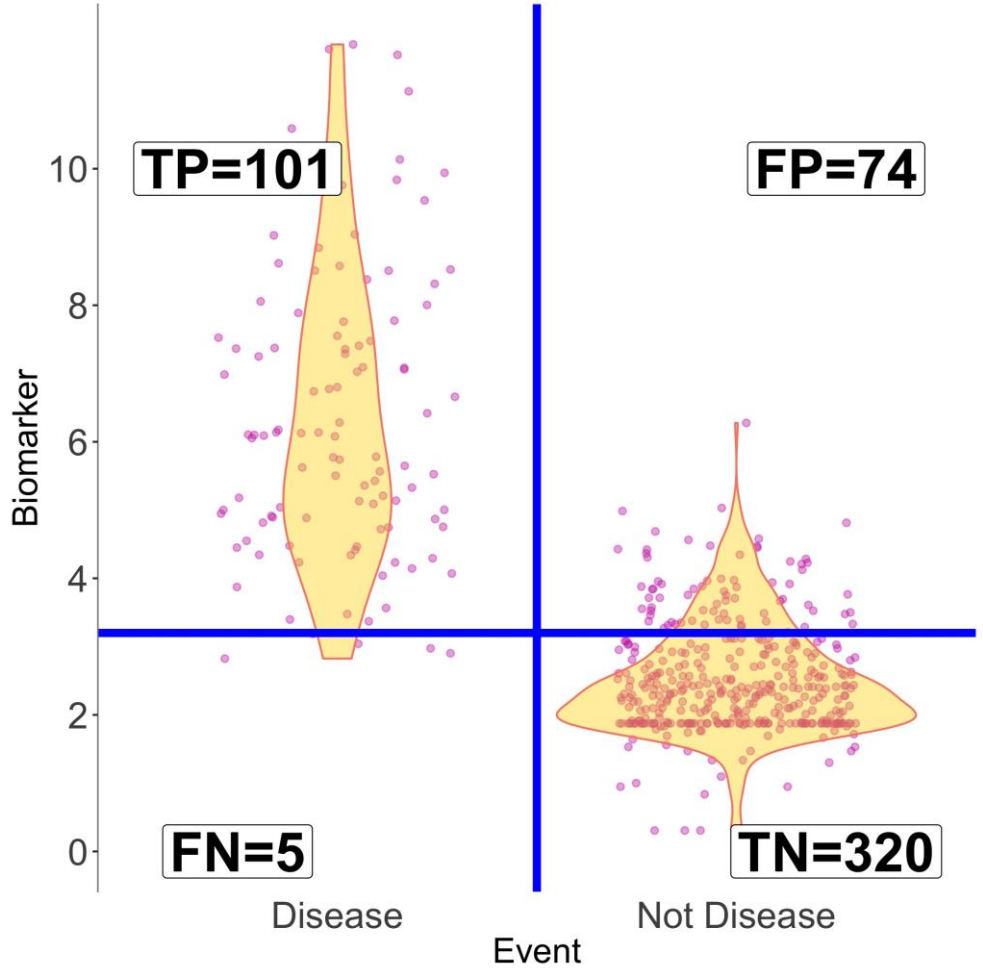


	AMI	No AMI
TROPONIN POSITIVE	True positive (TP)	False positive (FP)
TROPONIN NEGATIVE	False negative (FN)	True negative (TN)


TP=101
FP=74
FN=5
TN=320
Biomarker
10
8
6
4
2
0
Disease
Not Disease
Event

Prevalence = (TP+FN)/n

21%



Positive Predictive Value
= TP/(TP+FP)

55%

Negative Predictive Value
= TN/(TN+FN)

98%

Sensitivity = TP/(TP+FN)

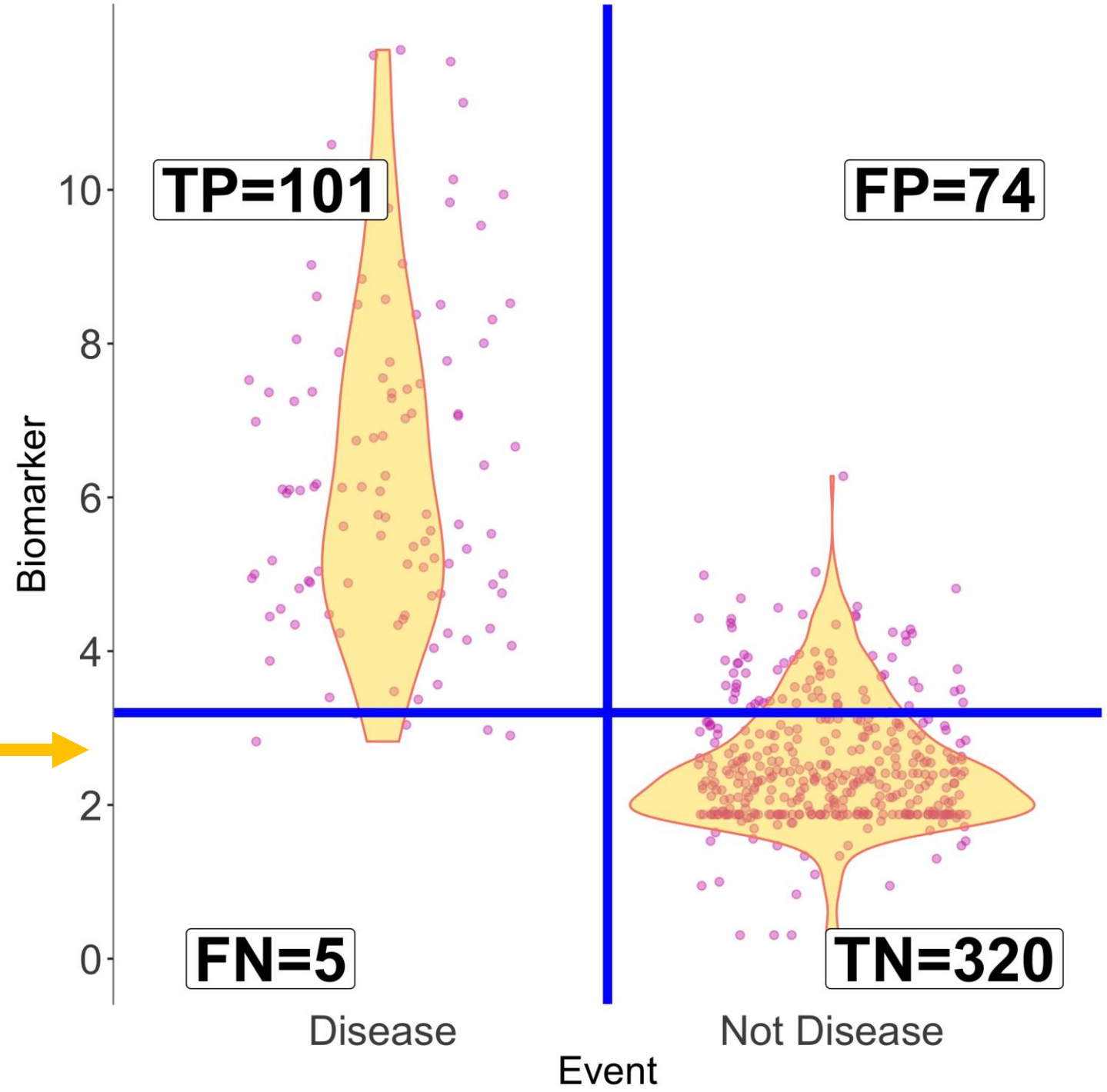
95%

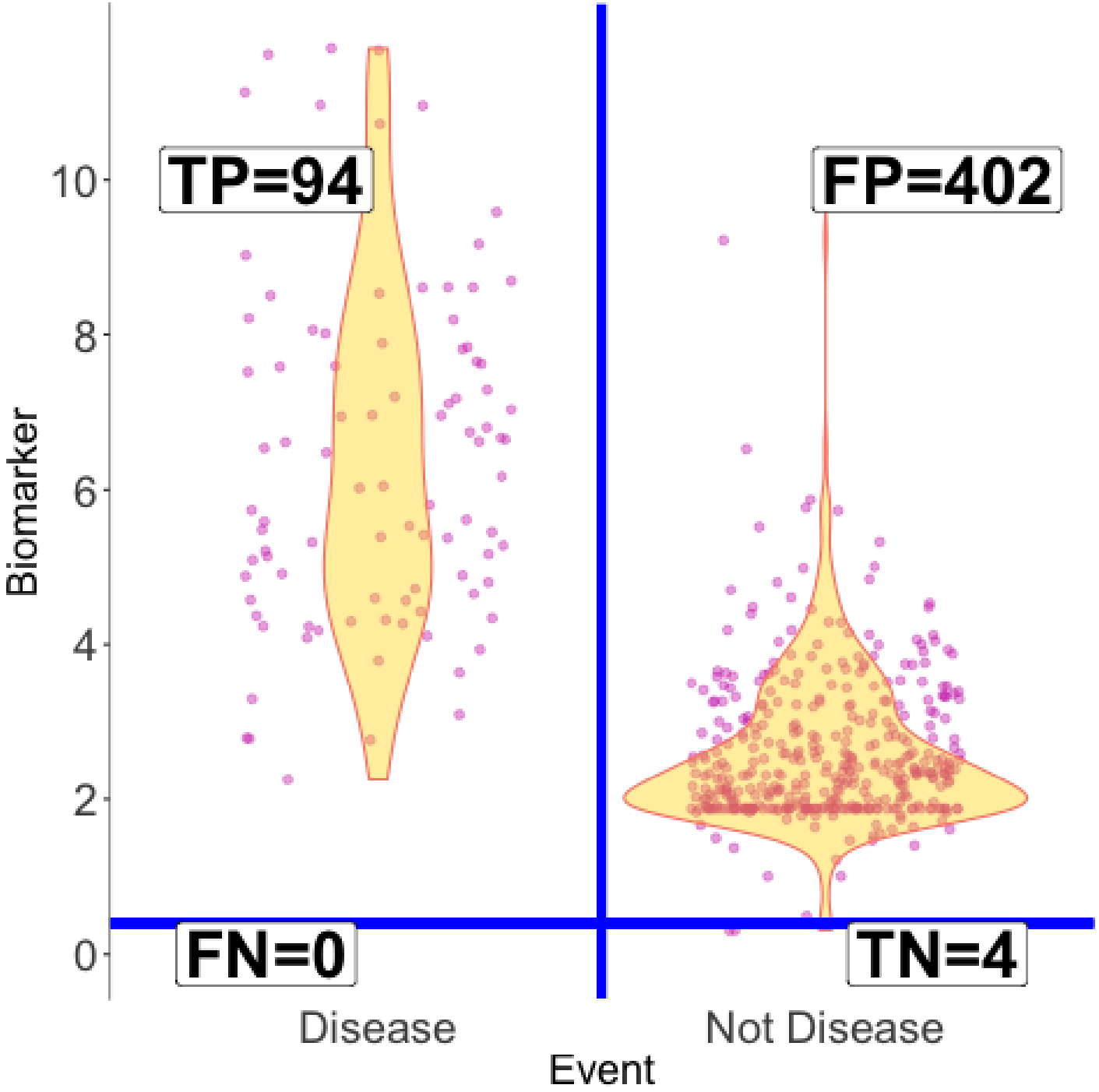
Specificity = TN/(TN+FP)

81%

There is a threshold below which there are 0 false negatives

Not previously reliable with old assays




TP=94
FP=402
FN=0
TN=4
Biomarker
10
8
6
4
2
0
Disease
Not Disease
Event

High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome

WITH PERMISSION OF:
Dr Andrew Chapman
BHF Clinical Research Fellow

THE UNIVERSITY of EDINBURGH
British Heart Foundation

Defining a risk stratification threshold at presentation

High-sensitivity cardiac troponin I assay

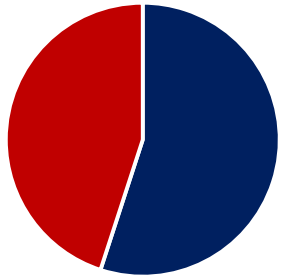
In 4,739 consecutive patients with suspected ACS[1]

A risk stratification threshold of <5 ng/L at presentation:

NPV 99.6%
(95%CI 99.3 – 99.8)

for myocardial infarction or cardiac death at 30 days

>50% of patients



1. Shah AS et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome. *Lancet*. 2015

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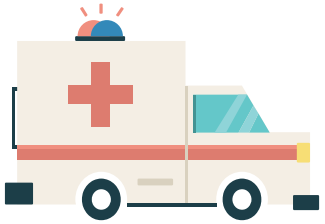
What is the optimal threshold to rule out myocardial infarction?

Systematic review and individual patient-level data meta-analysis



Prospective studies of patients with suspected acute coronary syndrome

High-sensitivity cardiac troponin I measured at presentation

22,457 patients

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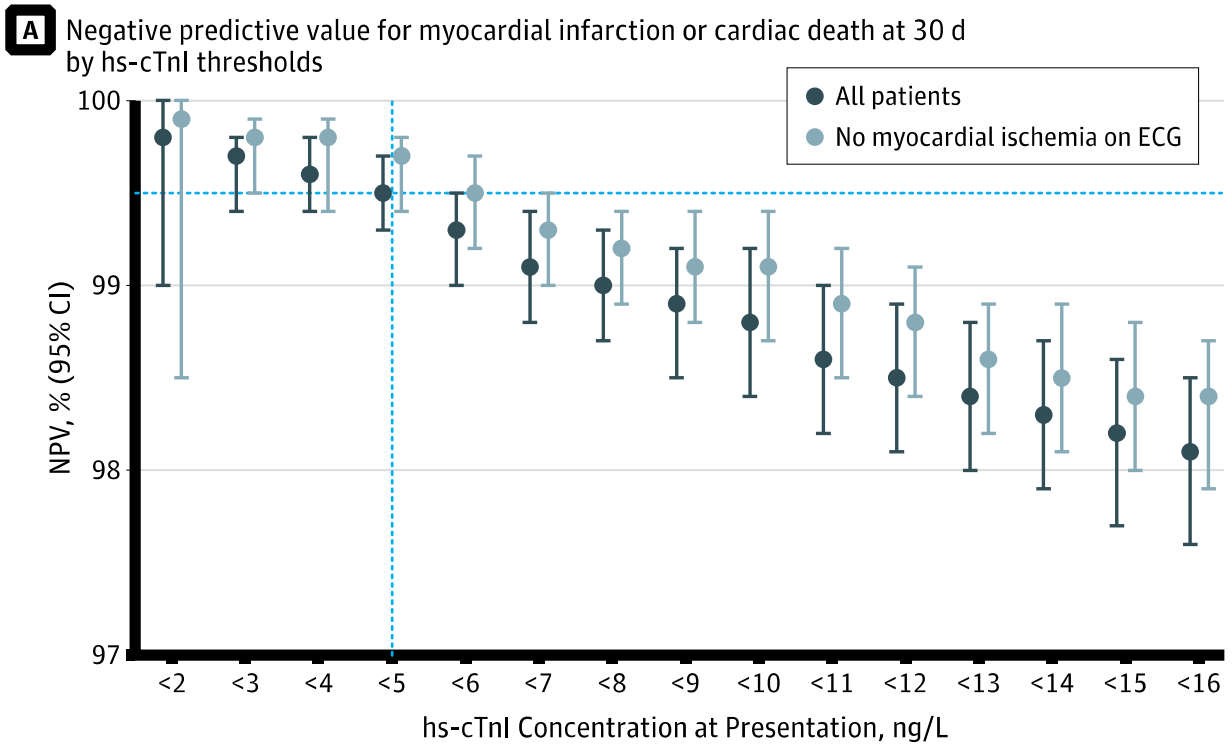
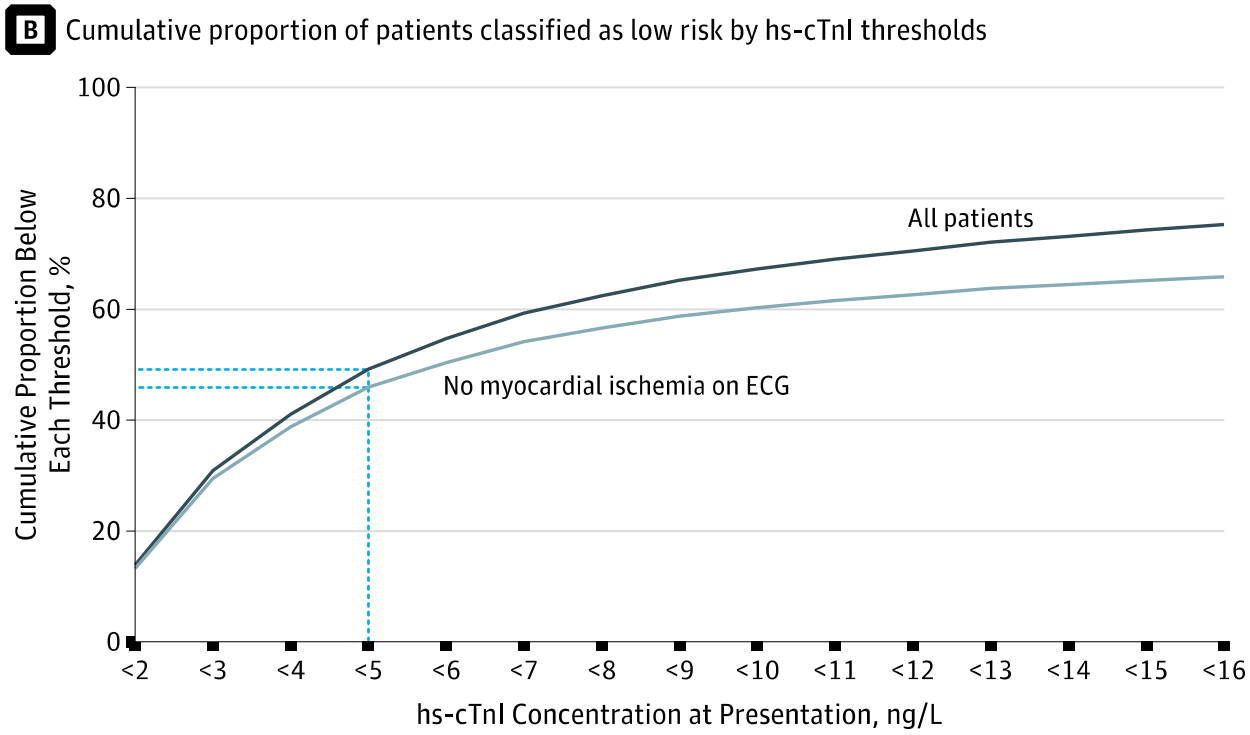
Secondary analysis of different thresholds





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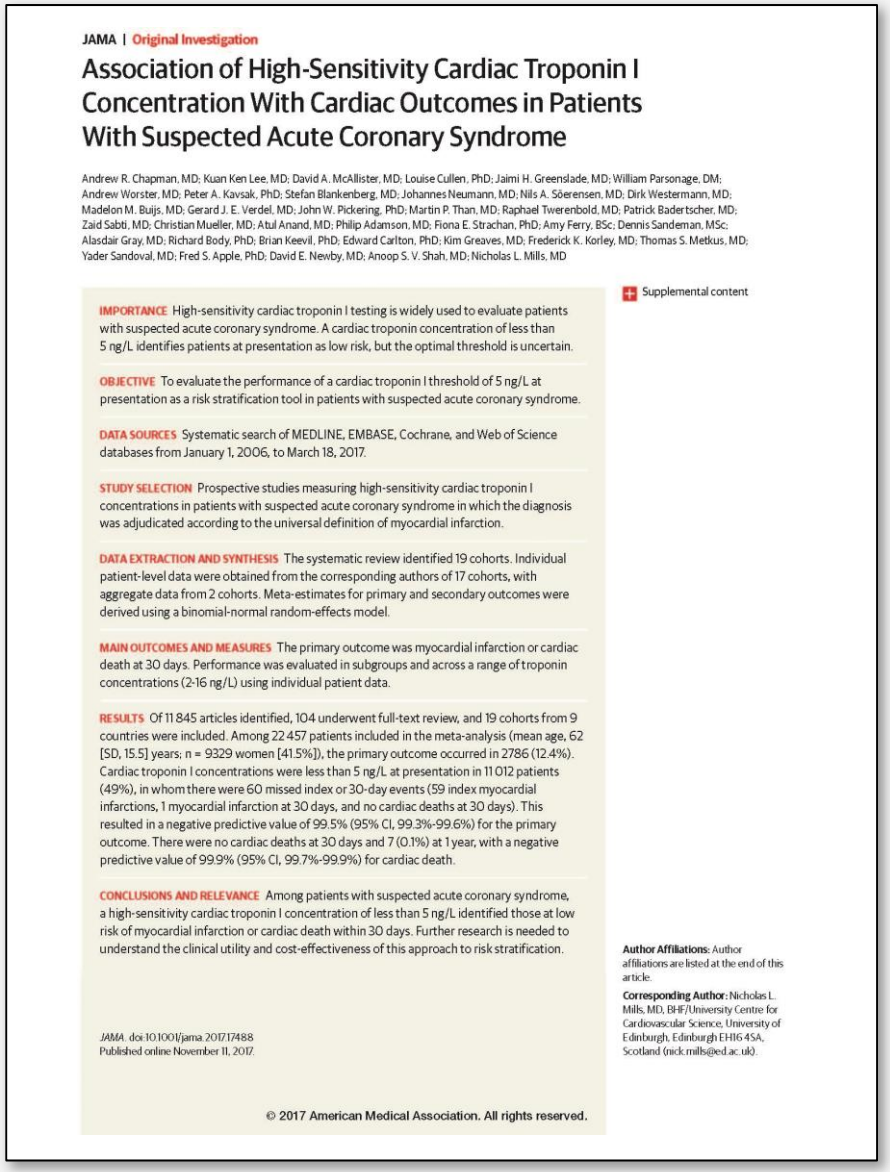

JAMA | Original Investigation

Association of High-Sensitivity Cardiac Troponin I Concentration With Cardiac Outcomes in Patients With Suspected Acute Coronary Syndrome

Andrew R. Chapman, MD; Kuan Ken Lee, MD; David A. McAllister, MD; Louise Cullen, PhD; Jaimi H. Greenslade, MD; William Parsonage, DM; Andrew Worster, MD; Peter A. Kavsak, PhD; Stefan Blankenberg, MD; Johannes Neumann, MD; Nils A. Söerensen, MD; Dirk Westermann, MD; Madelon M. Buijs, MD; Gerard J. E. Verdel, MD; John W. Pickering, PhD; Martin P. Than, MD; Raphael Twerenbold, MD; Patrick Badertscher, MD; Zaid Sabti, MD; Christian Mueller, MD; Atul Anand, MD; Philip Adamson, MD; Fiona E. Strachan, PhD; Amy Ferry, BSc; Dennis Sandeman, MSc; Alasdair Gray, MD; Richard Body, PhD; Brian Keevil, PhD; Edward Carlton, PhD; Kim Greaves, MD; Frederick K. Korley, MD; Thomas S. Metkus, MD; Yader Sandoval, MD; Fred S. Apple, PhD; David E. Newby, MD; Anoop S. V. Shah, MD; Nicholas L. Mills, MD

Supplemental content

IMPORTANCE High-sensitivity cardiac troponin I testing is widely used to evaluate patients with suspected acute coronary syndrome. A cardiac troponin concentration of less than 5 ng/L identifies patients at presentation as low risk, but the optimal threshold is uncertain.

OBJECTIVE To evaluate the performance of a cardiac troponin I threshold of 5 ng/L at presentation as a risk stratification tool in patients with suspected acute coronary syndrome.

DATA SOURCES Systematic search of MEDLINE, EMBASE, Cochrane, and Web of Science databases from January 1, 2006, to March 18, 2017.

STUDY SELECTION Prospective studies measuring high-sensitivity cardiac troponin I concentrations in patients with suspected acute coronary syndrome in which the diagnosis was adjudicated according to the universal definition of myocardial infarction.

DATA EXTRACTION AND SYNTHESIS The systematic review identified 19 cohorts. Individual patient-level data were obtained from the corresponding authors of 17 cohorts, with aggregate data from 2 cohorts. Meta-estimates for primary and secondary outcomes were derived using a binomial-normal random-effects model.

MAIN OUTCOMES AND MEASURES The primary outcome was myocardial infarction or cardiac death at 30 days. Performance was evaluated in subgroups and across a range of troponin concentrations (2-16 ng/L) using individual patient data.

RESULTS Of 11 845 articles identified, 104 underwent full-text review, and 19 cohorts from 9 countries were included. Among 22 457 patients included in the meta-analysis (mean age, 62 [SD, 15.5] years; n = 9329 women [41.5%]), the primary outcome occurred in 2786 (12.4%). Cardiac troponin I concentrations were less than 5 ng/L at presentation in 11 012 patients (49%), in whom there were 60 missed index or 30-day events (59 index myocardial infarctions, 1 myocardial infarction at 30 days, and no cardiac deaths at 30 days). This resulted in a negative predictive value of 99.5% (95% CI, 99.3%-99.6%) for the primary outcome. There were no cardiac deaths at 30 days and 7 (0.1%) at 1 year, with a negative predictive value of 99.9% (95% CI, 99.7%-99.9%) for cardiac death.

CONCLUSIONS AND RELEVANCE Among patients with suspected acute coronary syndrome, a high-sensitivity cardiac troponin I concentration of less than 5 ng/L identified those at low risk of myocardial infarction or cardiac death within 30 days. Further research is needed to understand the clinical utility and cost-effectiveness of this approach to risk stratification.

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Chapman AR and coauthors

Association of High-Sensitivity Cardiac Troponin I Concentration With Cardiac Outcomes in Patients With Suspected Acute Coronary Syndrome

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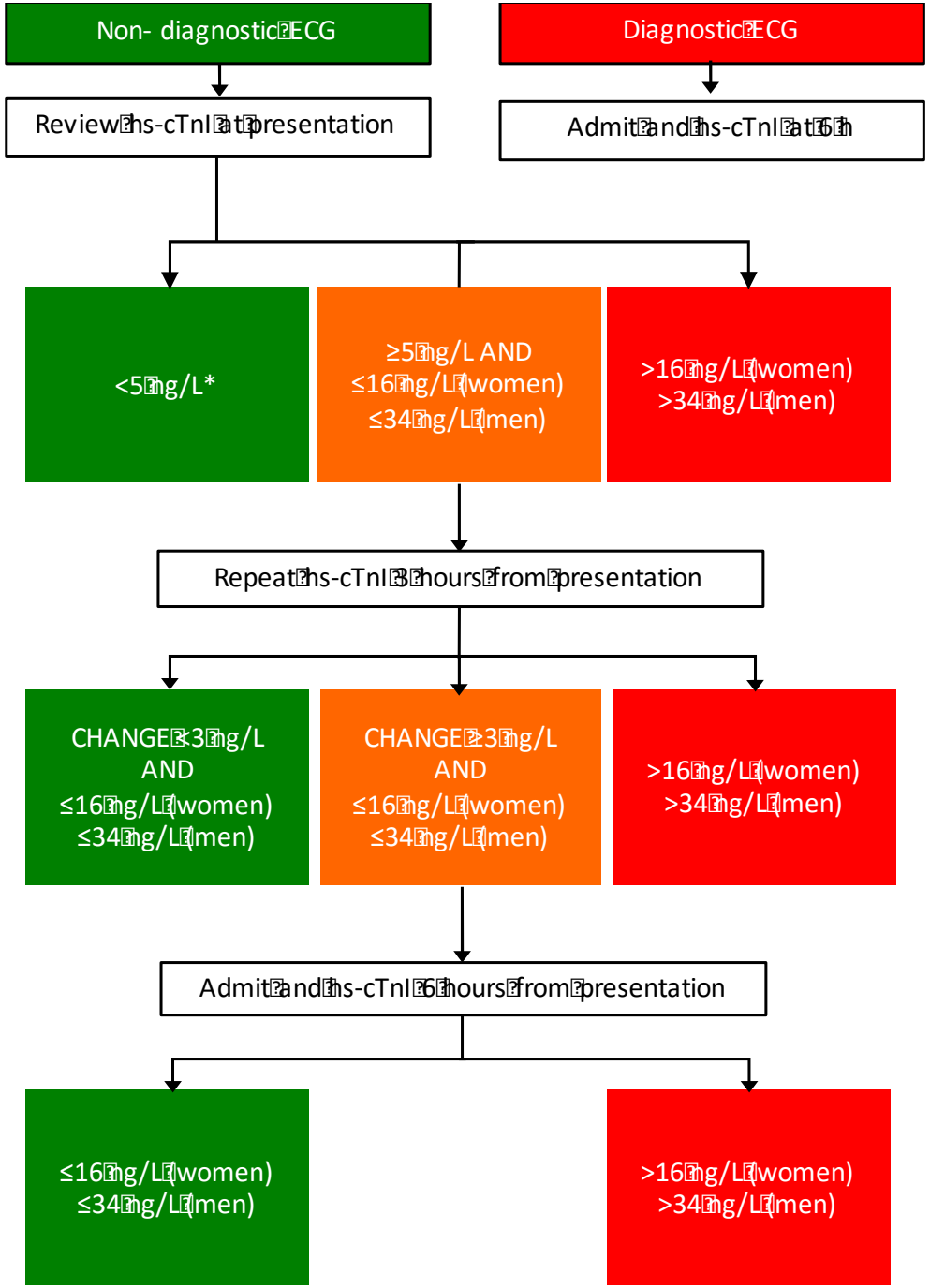
The JAMA Network


Non- diagnostic ECG
Diagnostic ECG
Review hs-cTnI at presentation
Admit and hs-cTnI at 6 h
<5 ng/L*
≥5 ng/L AND ≤16 ng/L (women) ≤34 ng/L (men)
>16 ng/L (women) >34 ng/L (men)
Repeat hs-cTnI 3 hours from presentation
CHANGE <3 ng/L AND ≤16 ng/L (women) ≤34 ng/L (men)
CHANGE ≥3 ng/L AND ≤16 ng/L (women) ≤34 ng/L (men)
>16 ng/L (women) >34 ng/L (men)
Admit and hs-cTnI 6 hours from presentation
≤16 ng/L (women) ≤34 ng/L (men)
>16 ng/L (women) >34 ng/L (men)

Single test rule-out of acute myocardial infarction with a novel point-of-care troponin assay: an early report of a prospective observational study

John W Pickering, Joanna M Young, Peter M George, Antony S Watson, Sally J Aldous, Richard W Troughton, Christopher J Pemberton, A Mark Richards, Louise A Cullen, Martin P Than

Christchurch Hospital, University of Otago Christchurch, Assure Health, National University of Singapore, Royal Brisbane and Women's Hospital, Brisbane

JAMA Cardiology Oct 2018

Setting

- single, regional, general and tertiary metropolitan ED

PARTICIPANTS

- Adults (≥18yrs)
- Acute presentation from community
- Symptoms suggestive of AMI
- Clinician intention to investigate for AMI with troponins

Exclusions

STEMI

Clear non-cardiac cause

transfers

TnI-Nx

Does TnI-Nx have same accuracy for AMI as hs-TnI?

- Compared TnI-Nx and hs-cTnI concentrations in 2629 blood samples.

- There was a very high agreement between the two assays, and on presentation
- no difference observed in discrimination ability for AMI

  (TnI-Nx AUC 0.975 cf hs-cTn AUC 0.970; p=0.46).

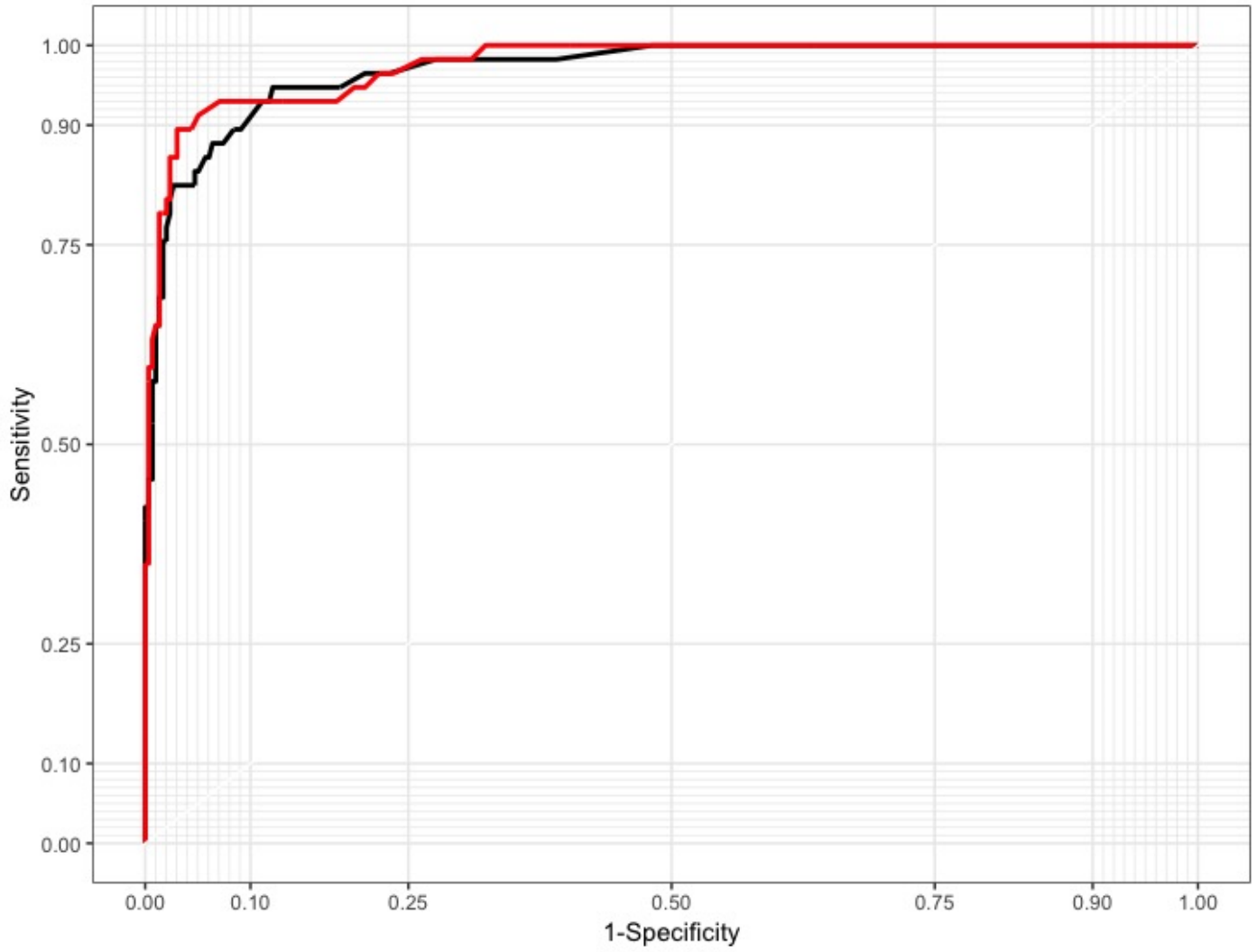
Comparison of ROC curves

TnI-Nx (red)

AUC = 0.975
(95%CI: 0.958 to 0.993)

hs-cTnI (black)

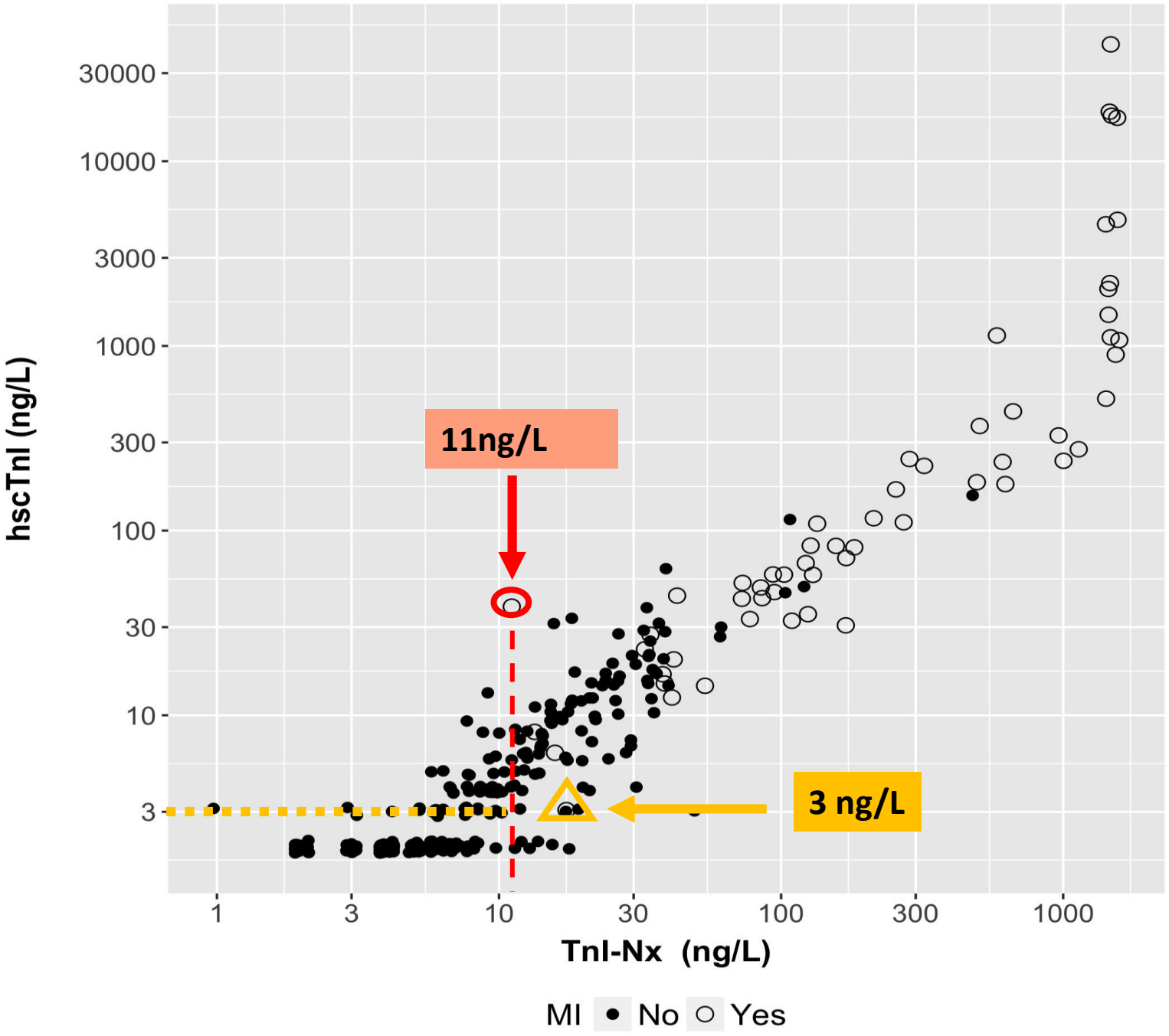
AUC = 0.970
(95%CI: 0.949 to 0.990)



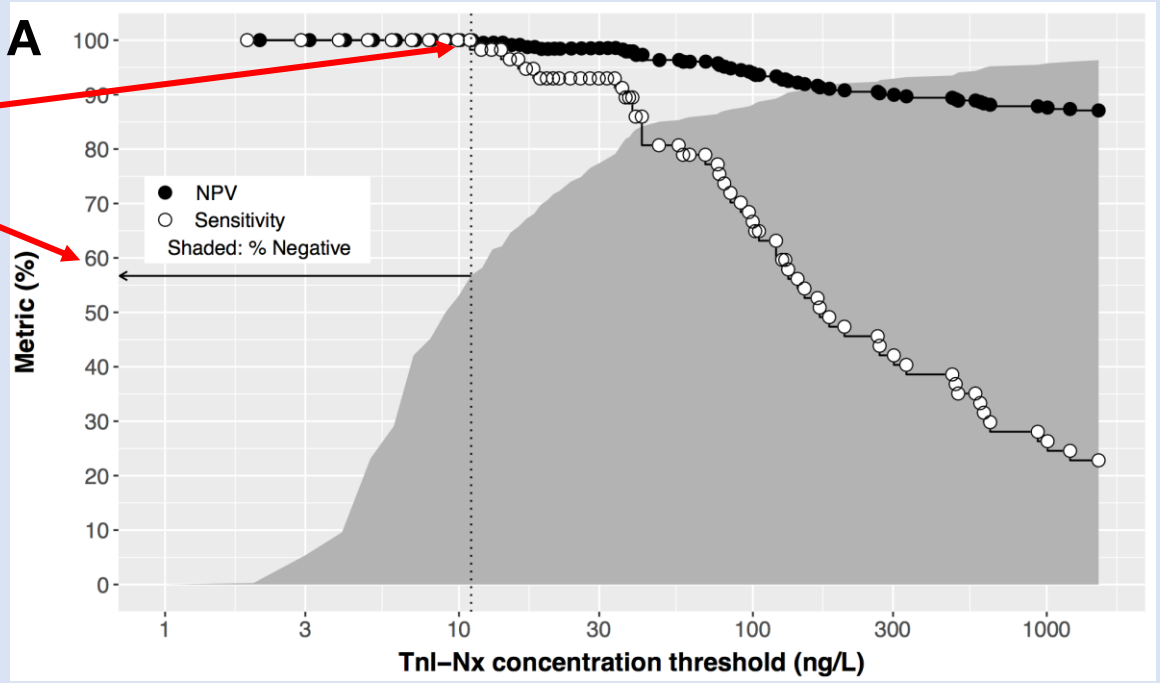
Can TnI-Nx give safe baseline rule-out?

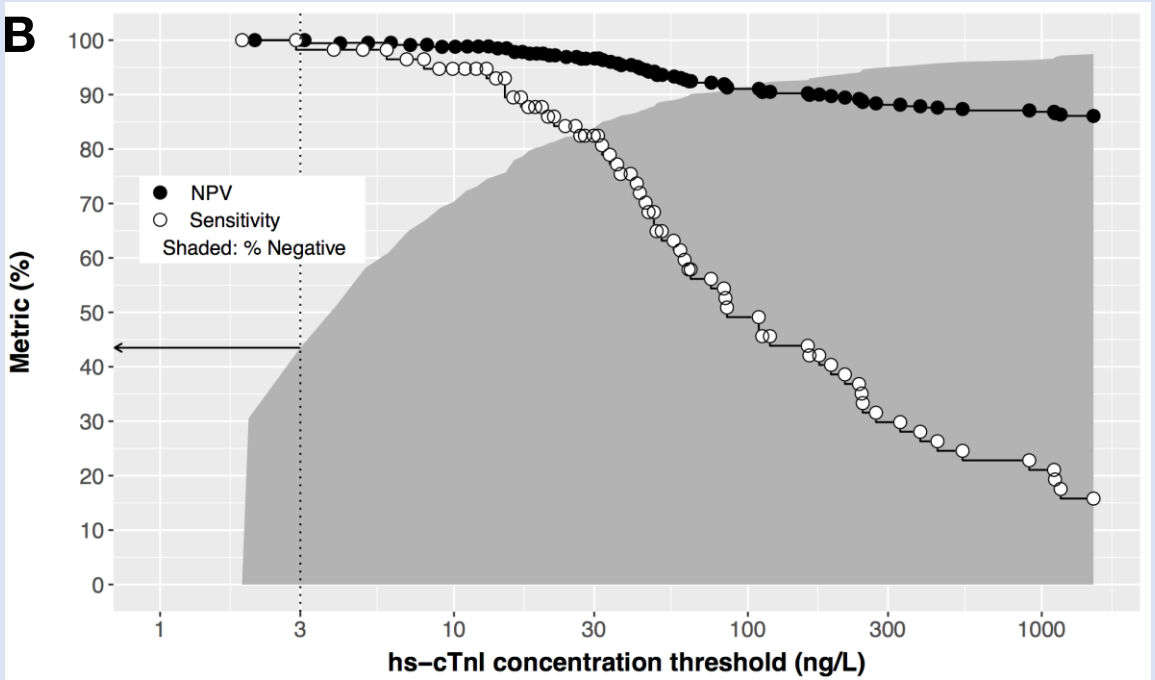
- If so
  - In what proportion of patients?

Variable	Entire cohort (n=354)
Male (%)	255 (72.0 %)
Age, mean (SD)	62 +/- 12
Smoking, No. (%)	46 (13.2 %)
Blood Pressure, mean (SD), mm Hg	
Systolic	148 +/- 27
Diastolic	83 +/- 14
Diabetes, No. (%)	46 (13.0%)
Dyslipidemia, No. (%)	234 (66.0%)
Hypertension, No. (%)	189 (53.3%)
Previous Heart Failure, No. (%)	19 (5.4%)
Previous Myocardial Infarction, No. (%)	100 (28.2%)
Peripheral Vascular disease, No. (%)	21 (5.9%)
Previous Angina, No. (%)	159 (44.9%)
Previous CABG, No. (%)	21 (5.9%)
Previous PTCA, No. (%)	106 (29.9%)
Previous TIA, No. (%)	12 (3.4%)
Time from symptom onset	
Median (IQR), h	4.5 (3-8.1)
< 2h, No. (%)	28 (7.9%)
2 to <3h, No. (%)	57 (16.1%)
3 to 24h, No. (%)	269 (76.0%)


30000
10000
3000
1000
300
100
30
10
3
hscTnI (ng/L)
11ng/L
3 ng/L
1
3
10
30
100
300
1000
TnI-Nx (ng/L)
MI
No
Yes

Below 11ng/L
NO FNs
=57% of patients





TnI Nx

Test	Disease	Not Disease
>= 11 ng/L	57	96
< 11 ng/L	0	201

Sensitivity: 100% (93.7% to 100%)

NPV: 100% (98.2% to 100%)

Negative: 57%

hscTnI

Test	Disease	Not Disease
>= 3 ng/L	57	143
< 3 ng/L	0	154

Sensitivity: 100% (93.7% to 100%)

NPV: 100% (97.6% to 100%)

Negative: 44%

CONCLUSION

- New generation of troponins allow accurate use of very thresholds for rule-out of AMI
- Rule-out of AMI using a single (baseline) lab. test now proven
- In near future
  - Single test rule-out using point of care (15-minute turnaround)

THANK YOU

Question to the Audience

If you were a patient and your doctor told you that an important test result was ‘negative’ would you be satisfied and reassured?

1. Yes
2. No

Question to the Audience

If you were a patient and your doctor told you that the result of an important test suggested that you had a 1 in 7 chance of death in the next 3-4 years would you be satisfied and reassured?

1. Yes
2. No

Question to the Audience

What is the significance to the patient of being diagnosed with NSTEMI?

1. Recognised increase in ongoing risk
2. Thorough further investigations
3. Secondary prevention Rx
4. Insurance

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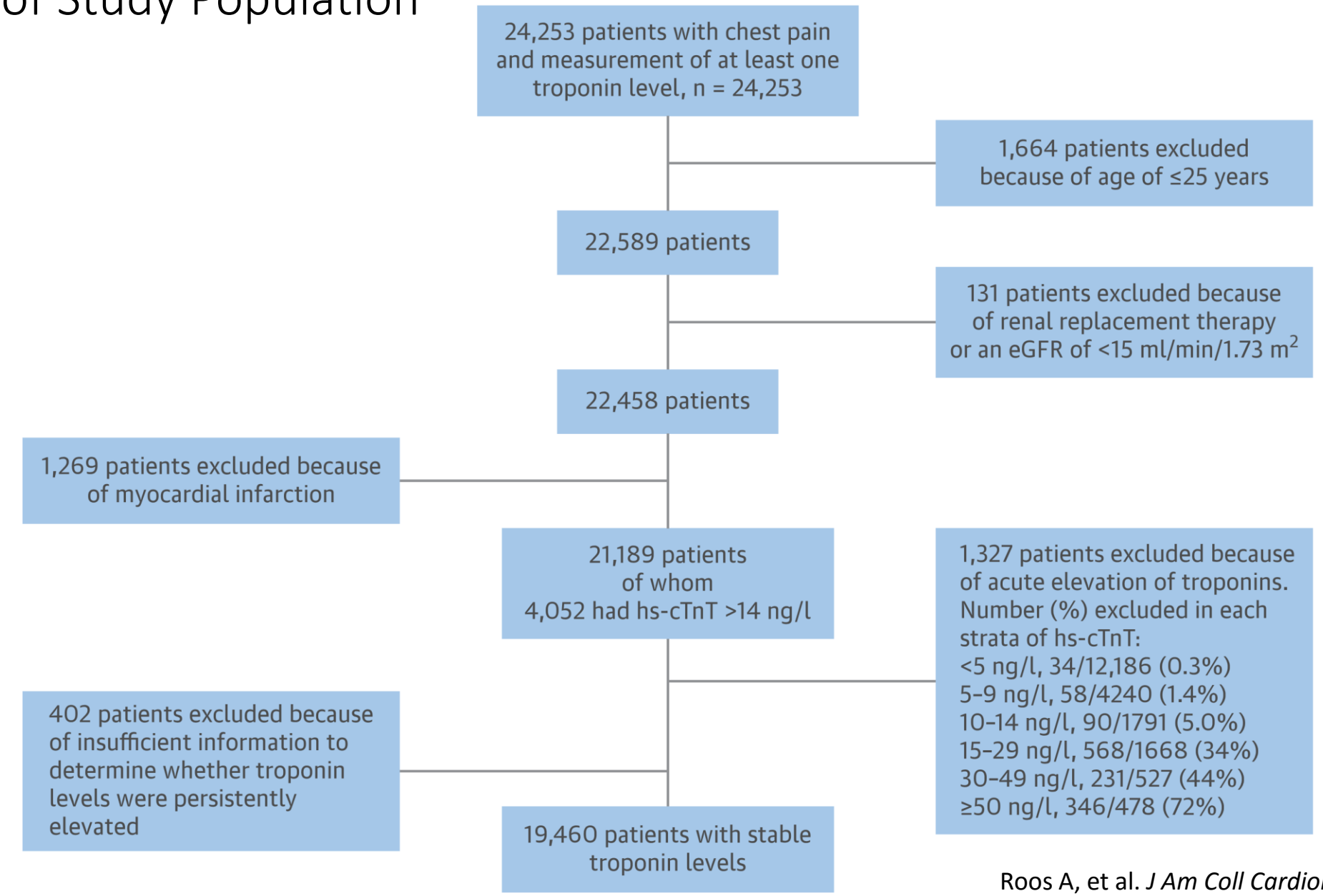
Stable High-Sensitivity Cardiac Troponin T Levels and Outcomes in Patients With Chest Pain

Andreas Roos, MD,[a,b] Nadia Bandstein, MD, PhD,[a,b] Magnus Lundbäck, MD, PhD,[c,d] Ola Hammarsten, MD, PhD,[e] Rickard Ljung, MD, PhD,[f] Martin J. Holzmann, MD, PhD[a,b]

Stable H-S Cardiac Troponin T Levels and Outcomes in Patients With Chest Pain: Selection of Study Population



Roos A, et al. *J Am Coll Cardiol*. 2017;70:2226-2236.

Stable H-S Cardiac Troponin T Levels and Outcomes in Patients with Chest Pain: Patient Characteristics

		High-Sensitivity Cardiac Troponin T Levels					
	All Patients	**<5 ng/l**	**5-9 ng/l**	**10-14 ng/l**	**15-29 ng/l**	**30-49 ng/l**	**≥50 ng/l**
Number of patients	19,460 (100)	12,152 (62)	4,097 (21)	1,683 (8.6)	1,100 (5.7)	296 (1.5)	132 (0.7)
Age, yrs	54 ± 16	48 ± 13	59 ± 14	69 ± 14	77 ± 12	79 ± 11	80 ± 13
Female	9,696 (50)	6,757 (56)	1,561 (38)	726 (43)	498 (45)	105 (35)	49 (37)
eGFR, ml/min/1.73 m^2							
>60	17,618 (91)	11,896 (98)	3,723 (91)	1,276 (76)	595 (54)	90 (30)	38 (29)
45-60	1,171 (6.0)	219 (1.8)	293 (7.2)	288 (17)	278 (25)	69 (23)	24 (18)
30-44	513 (2.6)	33 (0.3)	77 (1.9)	103 (6.1)	171 (15)	89 (30)	40 (30)
15-29	158 (0.8)	4 (0.03)	4 (0.1)	16 (1.0)	56 (5.1)	48 (16)	30 (23)
Comorbidities							
Myocardial infarction	1,283 (6.6)	348 (2.9)	344 (8.4)	225 (13)	239 (22)	88 (30)	39 (30)
Heart failure	831 (4.3)	116 (1.0)	148 (3.6)	147 (8.7)	244 (22)	123 (42)	53 (40)
Stroke	673 (3.5)	181 (1.5)	153 (3.7)	116 (6.9)	144 (13)	58 (20)	21 (16)
Prior revascularization	1,405 (7.2)	403 (3.3)	405 (9.9)	276 (16)	223 (20)	68 (23)	30 (23)
Atrial fibrillation	1,770 (9.1)	465 (3.8)	440 (11)	305 (18)	358 (33)	136 (46)	66 (50)
Diabetes	1,588 (8.2)	513 (4.2)	426 (10)	284 (17)	238 (22)	88 (30)	39 (30)
Hypertension	4,350 (22)	1,411 (12)	1,184 (29)	782 (46)	680 (62)	208 (70)	85 (64)
Medication							
Platelet inhibitors	3,147 (16)	971 (8.0)	878 (21)	578 (34)	500 (45)	160 (54)	60 (45)
Beta-blockers	4,141 (21)	1,432 (12)	1,120 (27)	705 (42)	615 (56)	186 (63)	83 (63)
ACE inhibitor/ARB	4,186 (22)	1,436 (12)	1,182 (29)	725 (43)	581 (53)	182 (61)	80 (61)
Statins	3,247 (17)	1,140 (9.4)	954 (23)	545 (32)	435 (40)	124 (42)	49 (37)

Roos A, et al. *J Am Coll Cardiol*. 2017;70:2226-2236.

Hazard Ratios for All-Cause Mortality, MI, and Heart Failure Related to hs-cTnT Levels in 19,460 Patients Without MI

	High-Sensitivity Cardiac Troponin T Levels					
	<5 ng/l	5–9 ng/l	10–14 ng/l	15–29 ng/l	30–49 ng/l	≥50 ng/l
Number of patients	12,152 (62)	4,097 (21)	1,683 (8.6)	1,100 (5.7)	296 (1.5)	132 (0.7)
All-cause mortality*						
Number of deaths	224 (1.8)	263 (6.4)	251 (15)	360 (33)	160 (54)	91 (69)
Rate per yr	0.5 (0.5–0.6)	2.1 (1.9–2.4)	5.1 (4.5–5.7)	12 (10–13)	23 (20–27)	33 (27–40)
30-day event rate	2 (0.02)	8 (0.2)	8 (0.5)	16 (1.4)	7 (2.4)	9 (6.8)
Hazard ratio (95% CI)						
Unadjusted	Reference	4.17 (3.49–4.99)	9.97 (8.32–11.9)	22.6 (19.2–26.8)	44.4 (36.3–54.5)	64.1 (50.2–81.9)
Multivariable adjusted†	Reference	2.00 (1.66–2.42)	2.92 (2.38–3.59)	4.07 (3.28–5.05)	6.77 (5.22–8.78)	9.68 (7.18–13.0)
Cardiovascular mortality‡						
Number of deaths	15 (0.1)	37 (0.9)	57 (3.4)	90 (8.2)	53 (18)	36 (27)
Rate per yr	0.05 (0.03–0.08)	0.5 (0.3–0.6)	1.8 (1.4–2.3)	4.3 (3.4–5.2)	11 (7.8–13)	17 (12–23)
30-day event rate	0	1 (0.02)	3 (0.2)	3 (0.3)	4 (1.3)	4 (3.0)
Hazard ratio (95% CI)						
Unadjusted	Reference	9.60 (5.26–17.5)	35.9 (20.3–63.4)	82.7 (47.8–142.8)	203.0 (114.4–360.3)	331.4 (181.3–605.7)
Multivariable adjusted†	Reference	3.59 (1.93–6.66)	7.32 (3.96–13.5)	9.12 (4.87–17.1)	17.5 (8.86–34.5)	27.0 (13.2–55.4)
Noncardiovascular mortality‡						
Number of deaths	147 (1.2)	129 (3.1)	108 (6.4)	145 (13)	65 (22)	36 (27)
Rate per yr	0.5 (0.4–0.6)	1.7 (1.4–2.0)	3.5 (2.8–4.2)	6.9 (5.8–8.0)	13 (9.9–16)	17 (12–23)
30-day event rate	2 (0.02)	7 (0.2)	5 (0.3)	13 (1.2)	3 (1.0)	5 (3.8)
Hazard ratio (95% CI)						
Unadjusted	Reference	3.23 (2.55–4.10)	6.61 (5.16–8.49)	13.1 (10.4–16.5)	24.5 (18.3–32.8)	32.3 (22.4–46.5)
Multivariable adjusted†	Reference	1.80 (1.40–2.33)	2.52 (1.89–3.36)	3.49 (2.58–4.71)	5.95 (4.09–8.66)	7.78 (5.02–12.1)
Myocardial infarction‡						
Number of MIs	90 (0.7)	60 (1.5)	66 (3.9)	56 (5.1)	23 (7.8)	9 (6.8)
Rate per yr	0.3 (0.3–0.4)	0.8 (0.6–1.0)	2.2 (1.7–2.7)	2.8 (2.1–3.5)	4.9 (2.9–6.9)	4.5 (1.6–7.4)
30-day event rate	2 (0.02)	2 (0.05)	12 (0.7)	4 (0.4)	3 (1.0)	2 (1.5)
Hazard ratio (95% CI)						
Unadjusted	Reference	2.44 (1.75–3.38)	6.68 (4.86–9.19)	8.45 (6.05–11.8)	14.7 (9.29–23.2)	13.4 (6.78–26.7)
Multivariable adjusted‡	Reference	1.18 (0.83–1.67)	2.06 (1.42–3.00)	1.83 (1.20–2.80)	2.66 (1.51–4.68)	2.77 (1.27–6.01)
Heart failure‡						
Number of cases	41 (0.3)	78 (1.9)	84 (5.0)	175 (16)	75 (25)	35 (27)
Rate per yr	0.1 (0.1–0.2)	1.0 (0.8–1.3)	2.8 (2.2–3.4)	9.3 (7.9–11)	18 (14–23)	20 (13–27)
30-day event rate	3 (0.02)	8 (0.2)	11 (0.6)	30 (2.7)	13 (4.4)	5 (3.8)
Hazard ratio (95% CI)						
Unadjusted	Reference	6.97 (4.77–10.2)	18.7 (12.8–27.1)	61.1 (43.5–86.0)	116 (79.0–169)	125 (79.6–196)
Multivariable adjusted‡	Reference	3.66 (2.46–5.45)	6.04 (3.97–9.19)	10.7 (7.00–16.3)	13.1 (8.03–21.3)	13.3 (7.69–23.1)

Values are n (%) or % (95% CI) unless otherwise indicated. *End of follow-up for all-cause mortality was March 28, 2016. † Multivariable adjustment was made for age, sex, eGFR, prior MI, heart failure, stroke, chronic obstructive pulmonary disease, atrial fibrillation, diabetes, hypertension, and treatment with aspirin, beta-blockers, ACE inhibitor/ARBs, and statins. ‡ End of follow-up for cardiovascular mortality, non-cardiovascular mortality, MI, and heart failure was December 31, 2014. Cases of cardiovascular mortality and noncardiovascular mortality do not add up to cases of all-cause mortality because of the different follow-up times for all-cause and cause-specific mortality. Rate per year means number of events per 100 person-years.

Roos A, et al. *J Am Coll Cardiol*. 2017;70:2226-2236.

Hazard Ratios for All-Cause Mortality, MI, and Heart Failure Related to hs-cTnT Levels in 19,460 Patients Without MI

	High-Sensitivity Cardiac Troponin T Levels					
	<5 ng/l	5-9 ng/l	10-14 ng/l	15-29 ng/l	30-49 ng/l	≥50 ng/l
Number of patients	12,152 (62)	4,097 (21)	1,683 (8.6)	1,100 (5.7)	296 (1.5)	132 (0.7)
All-cause mortality*						
Number of deaths	224 (1.8)	263 (6.4)	251 (15)	360 (33)	160 (54)	91 (69)
Rate per yr	0.5 (0.5-0.6)	2.1 (1.9-2.4)	5.1 (4.5-5.7)	12 (10-13)	23 (20-27)	33 (27-40)
30-day event rate	2 (0.02)	8 (0.2)	8 (0.5)	16 (1.4)	7 (2.4)	9 (6.8)
Hazard ratio (95% CI)						
Unadjusted	Reference	4.17 (3.49-4.99)	9.97 (8.32-11.9)	22.6 (19.2-26.8)	44.4 (36.3-54.5)	64.1 (50.2-81.9)
Multivariable adjusted†	Reference	2.00 (1.66-2.42)	2.92 (2.38-3.59)	4.07 (3.28-5.05)	6.77 (5.22-8.78)	9.68 (7.18-13.0)
Cardiovascular mortality‡						
Number of deaths	15 (0.1)	37 (0.9)	5 (3.4)	90 (8.2)	53 (18)	36 (27)
Rate per yr	0.05 (0.03-0.08)	0.5 (0.3-0.6)	1.8 (1.4-2.3)	4.3 (3.4-5.2)	11 (7.8-13)	17 (12-23)
30-day event rate	0	1 (0.02)	(0.2)	3 (0.3)	4 (1.3)	4 (3.0)
Hazard ratio (95% CI)						
Unadjusted	Reference	9.60 (5.26-17.5)	35.9 (20.3-63.4)	82.7 (47.8-142.8)	203.0 (114.4-360.3)	331.4 (181.3-605.7)
Multivariable adjusted†	Reference	3.59 (1.93-6.66)	7.32 (3.96-13.5)	9.12 (4.87-17.1)	17.5 (8.86-34.5)	27.0 (13.2-55.4)
Noncardiovascular mortality‡						
Number of deaths	147 (1.2)	129 (3.1)	1 (6.4)	145 (13)	65 (22)	36 (27)
Rate per yr	0.5 (0.4-0.6)	1.7 (1.4-2.0)	3.5 (2.8-4.2)	6.9 (5.8-8.0)	13 (9.9-16)	17 (12-23)
30-day event rate	2 (0.02)	7 (0.2)	(0.3)	13 (1.2)	3 (1.0)	5 (3.8)

	High-Sensitivity Cardiac Troponin T Levels					
	<5 ng/l	5-9 ng/l	10-14 ng/l	15-29 ng/l	30-49 ng/l	≥50 ng/l
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Rate per yr	0.5 (0.5-0.6)	2.1 (1.9-2.4)	5.1 (4.5-5.7)	12 (10-13)	23 (20-27)	33 (27-40)
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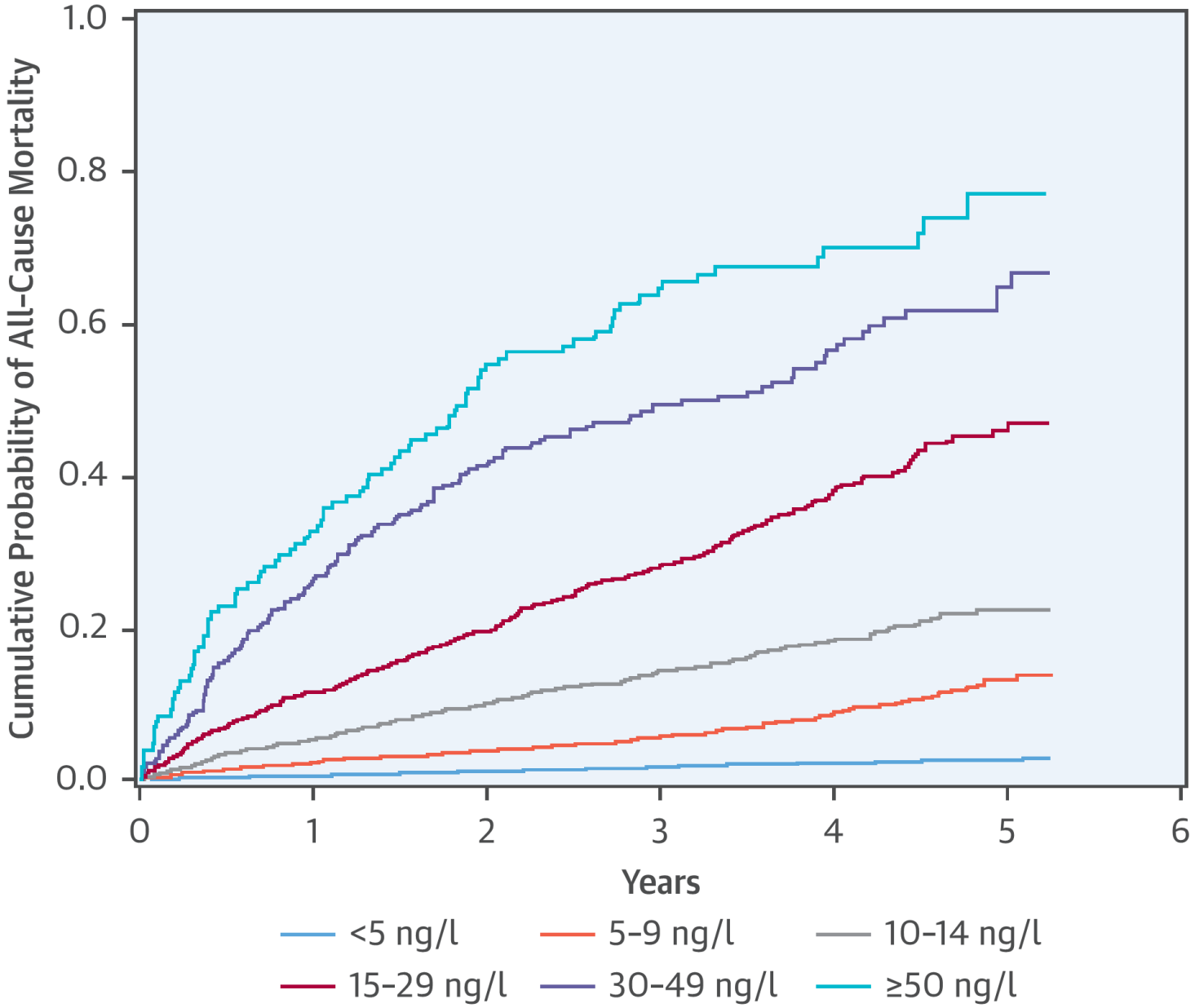
Roos A, et al. *J Am Coll Cardiol*. 2017;70:2226-2236.

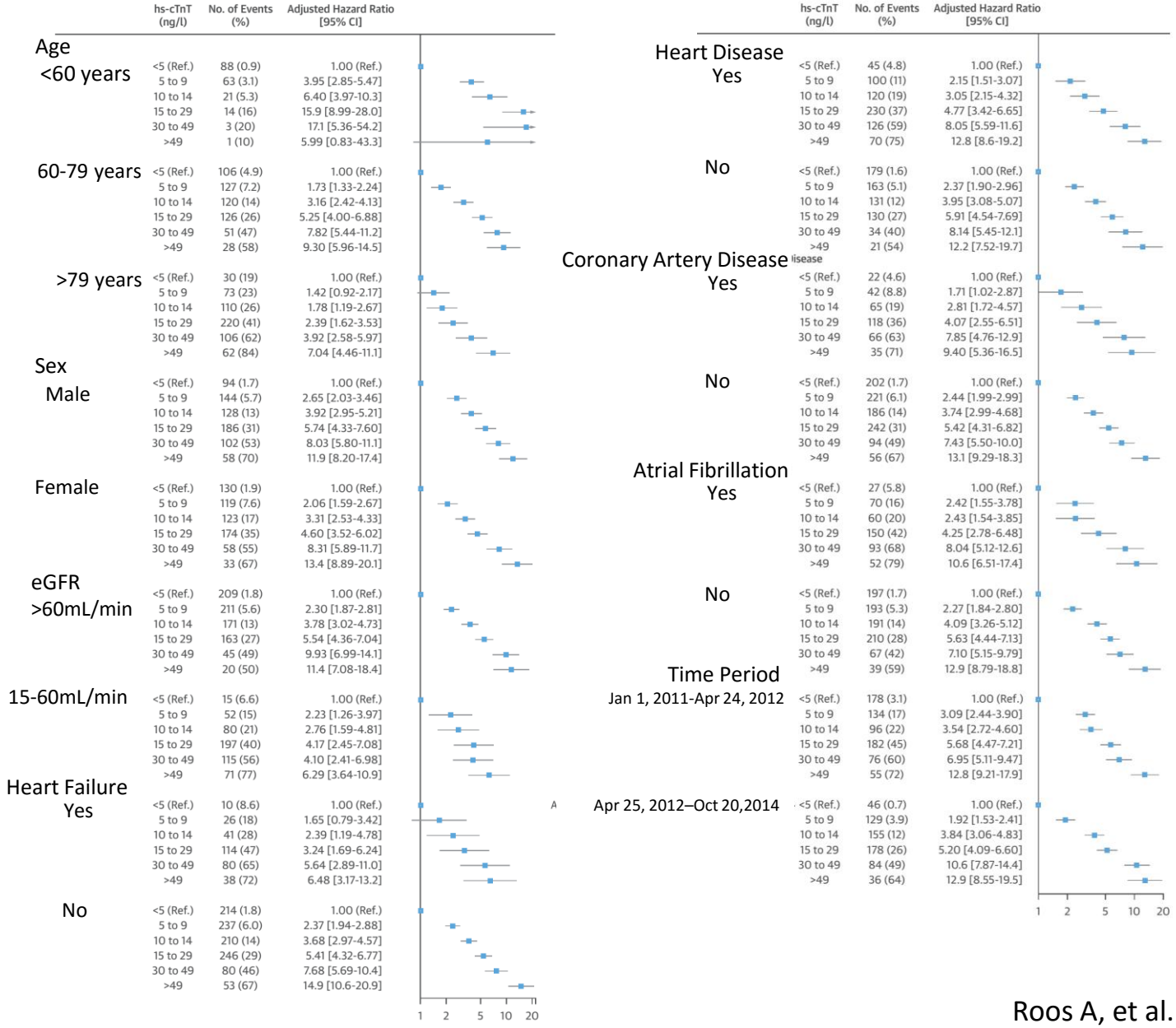
Elevated Troponin Levels and Outcomes: Cumulative Mortality in Patients With Chest Pain



Cumulative mortality in relation to different levels of high-sensitivity cardiac troponin T.

Roos A, et al. *J Am Coll Cardiol*. 2017;70:2226-2236.

Hazard Ratios (95% CIs) for the Association Between Different Levels of hs-cTnT and All-Cause Mortality in Different Subgroups of Patients



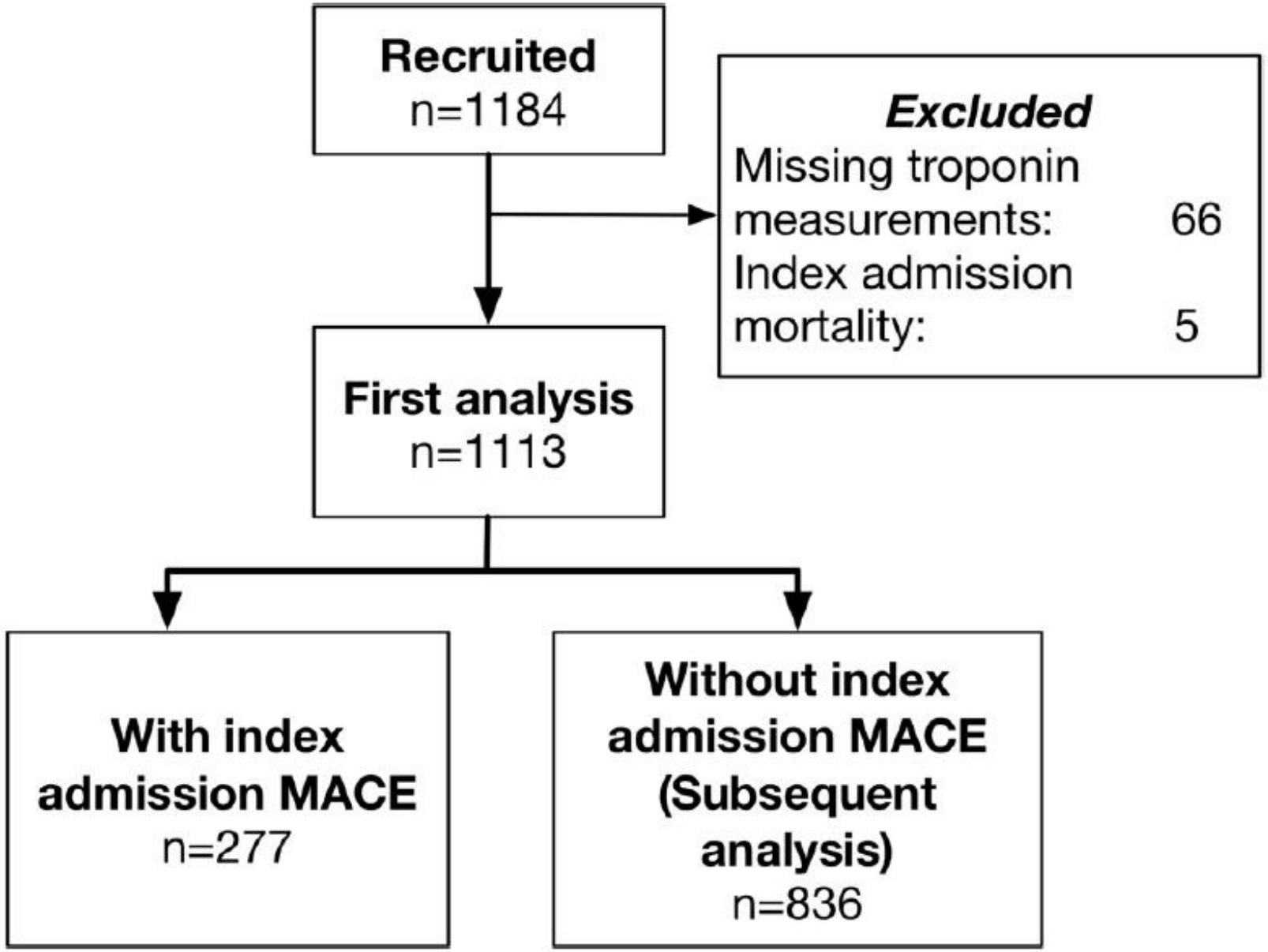
Roos A, et al. *J Am Coll Cardiol*. 2017;70:2226-2236.

Clinical Chemistry 64:7
1044–1053 (2018)

Detectable High-Sensitivity Cardiac Troponin within the Population Reference Interval Conveys High 5-Year Cardiovascular Risk: An Observational Study

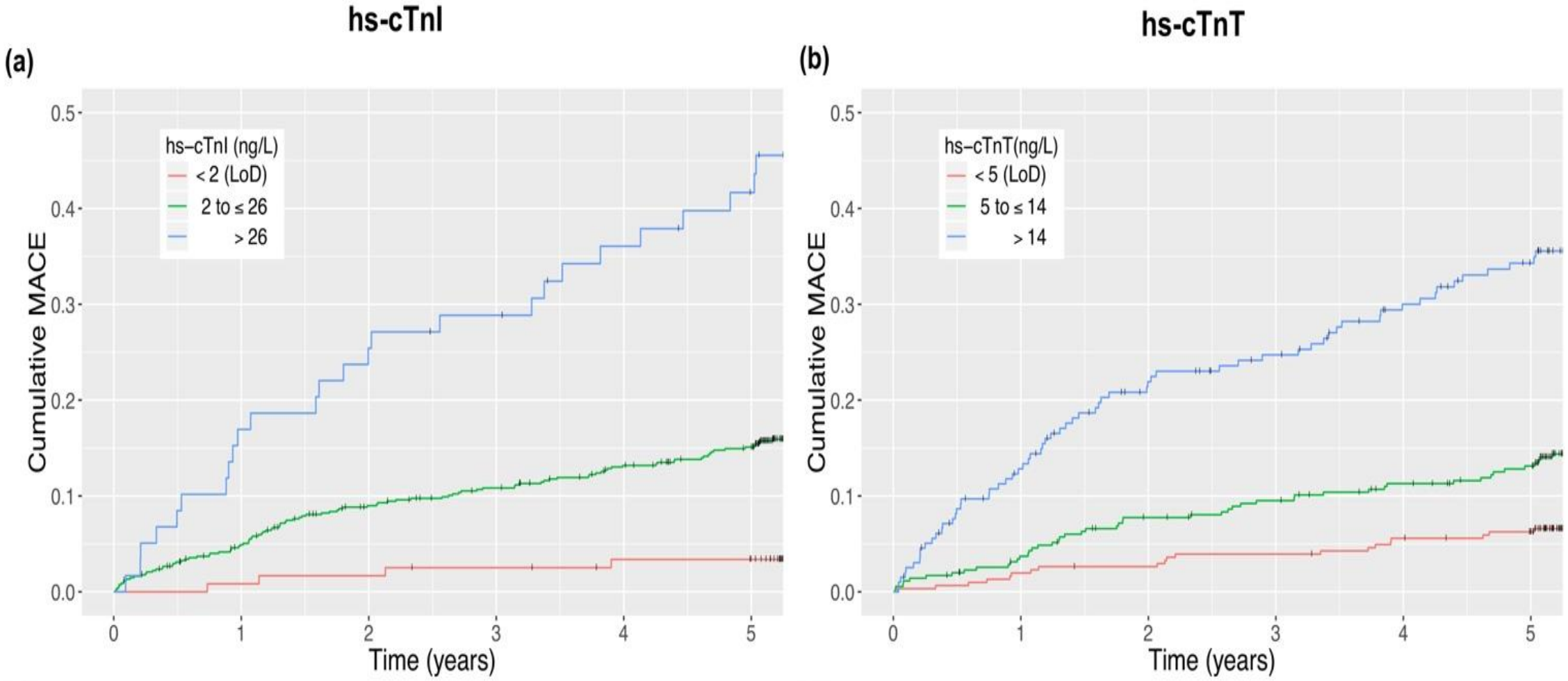
Martin P. Than,[1] Sally J. Aldous,[1] Richard W. Troughton,[1,2] Christopher J. Pemberton,[2] A. Mark Richards,[2,3] Christopher M.A. Frampton,[2] Christopher M. Florkowski,[1] Peter M. George,[1] Samantha Bailey,[1] Joanna M. Young,[1] Louise Cullen,[4,5,6] Jaimi H. Greenslade,[4,6] William A. Parsonage,[4] Brendan M. Everett,[7] W. Frank Peacock,[8] Allan S. Jaffe,[9] and John W. Pickering[1,2*]

Observational Study of Patients Recruited in the Emergency Department With Possible ACS: Flow Chart of Data Available for Analysis

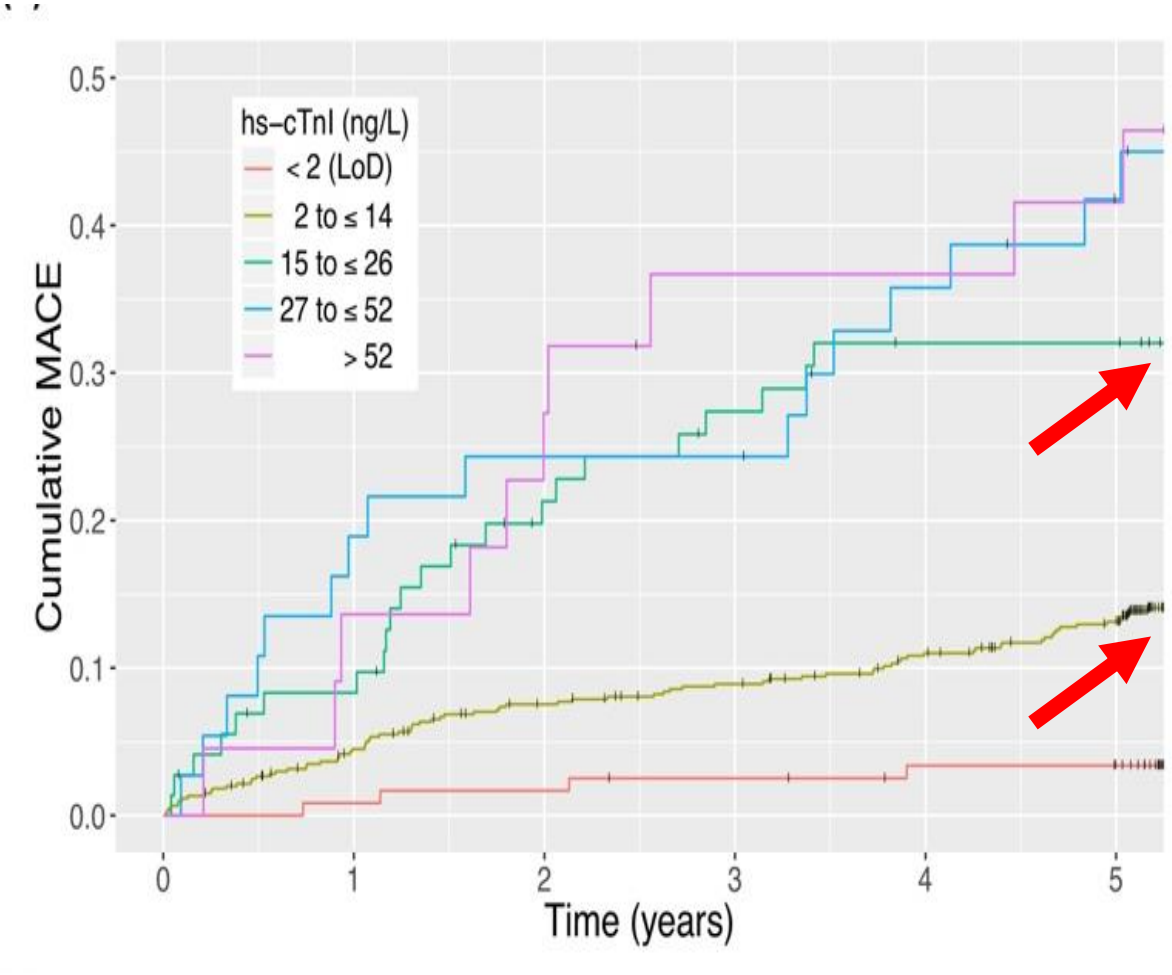


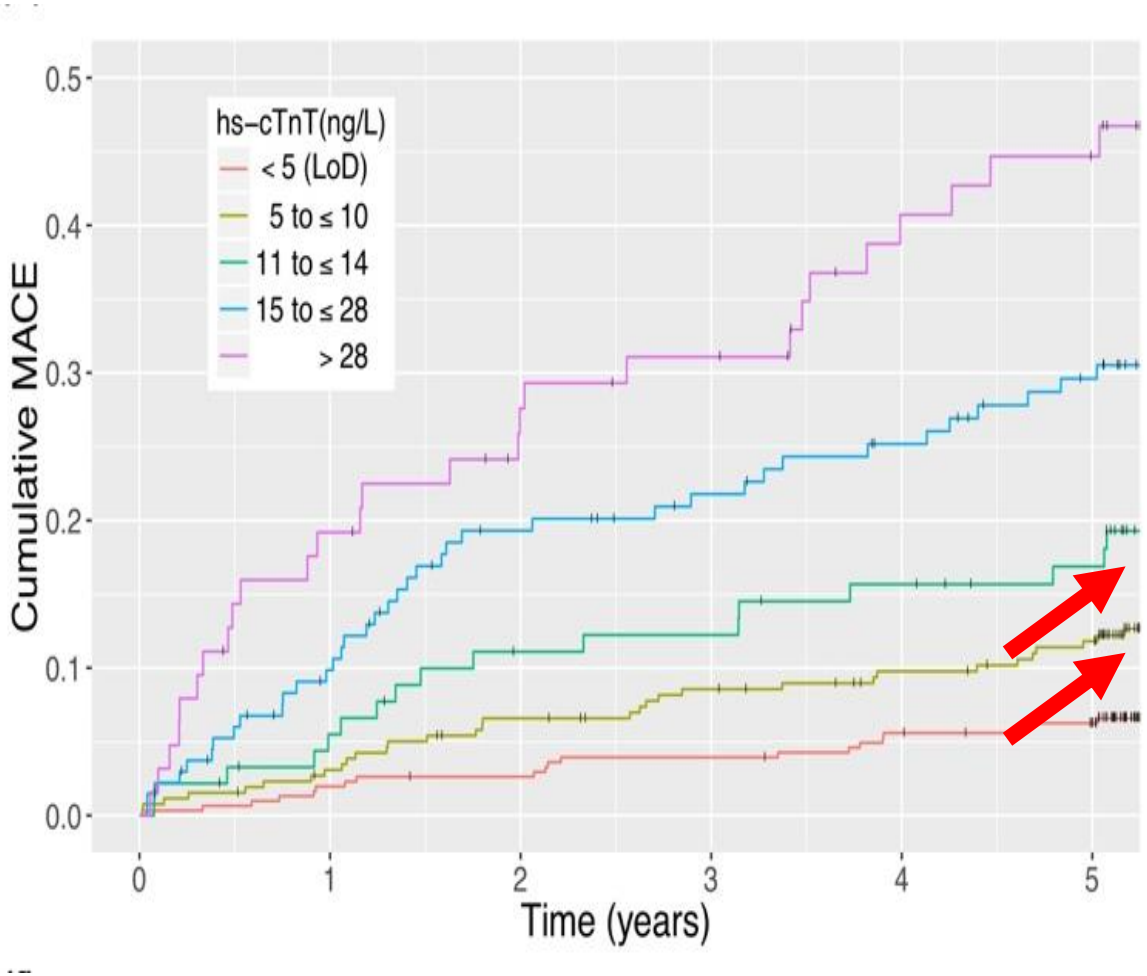
MACE = major adverse cardiovascular event

Than M, et al. *Clin Chem*. 2018;64:1044-1053.

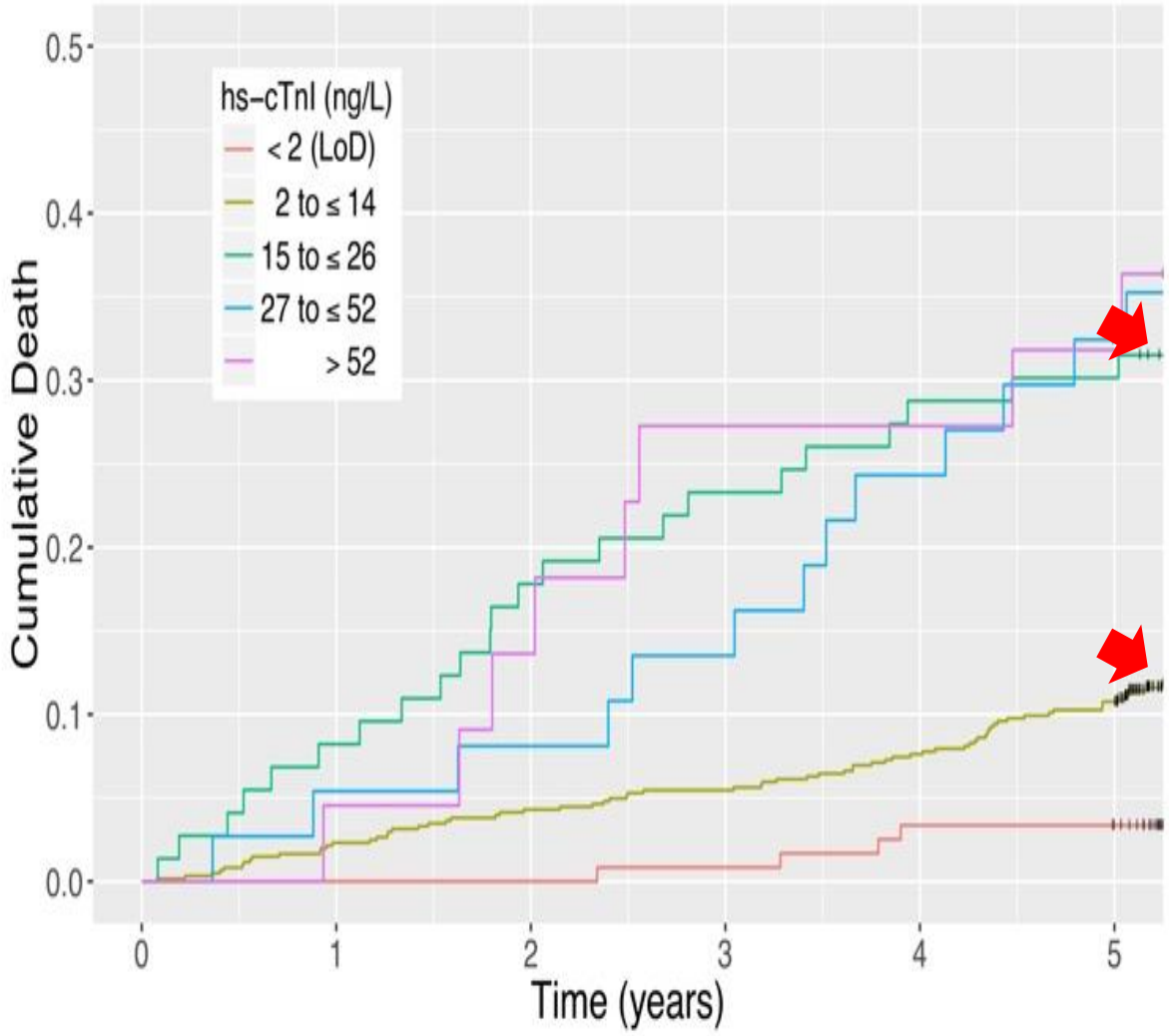


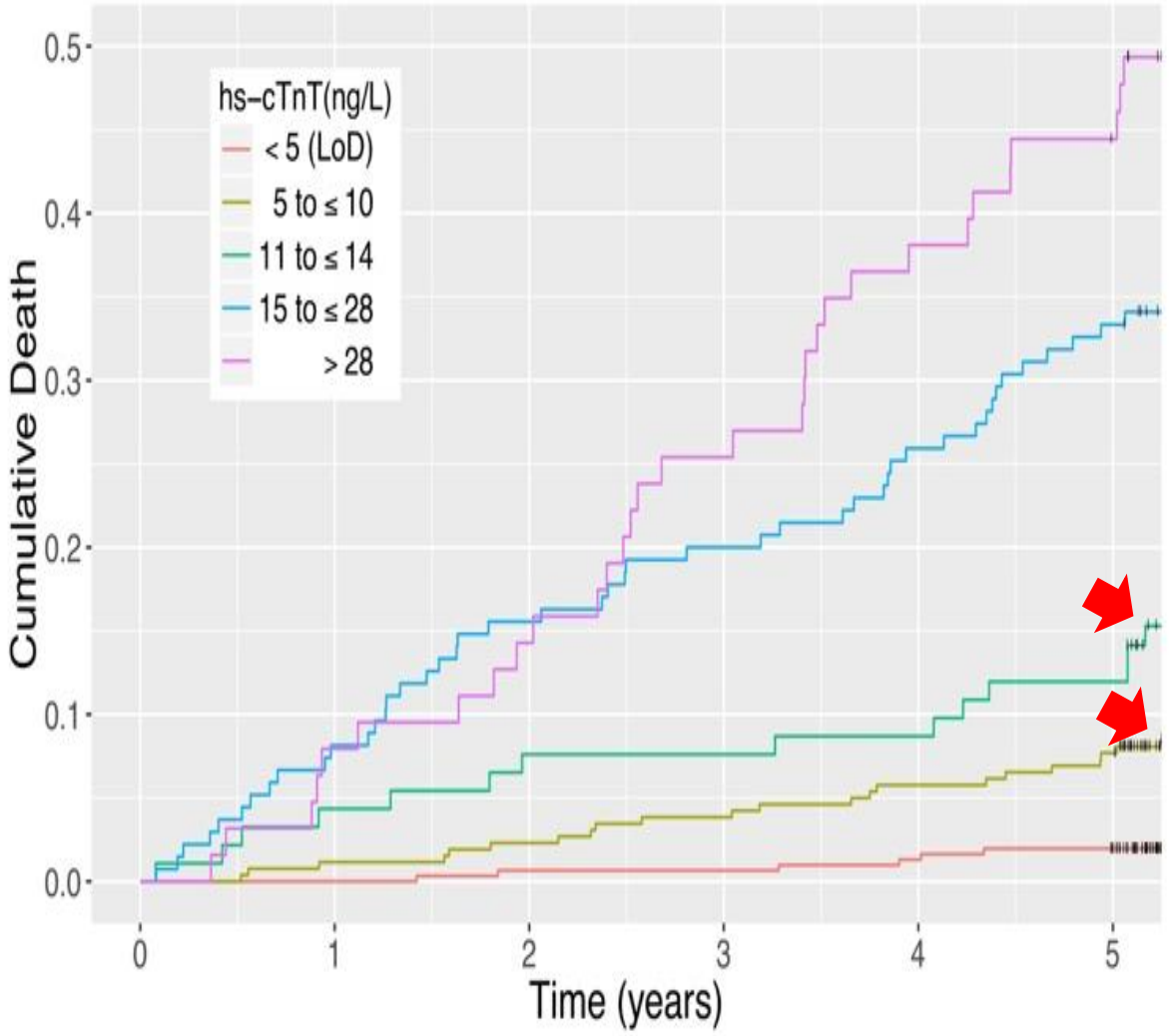
Kaplan-Meier plots of cumulative MACE





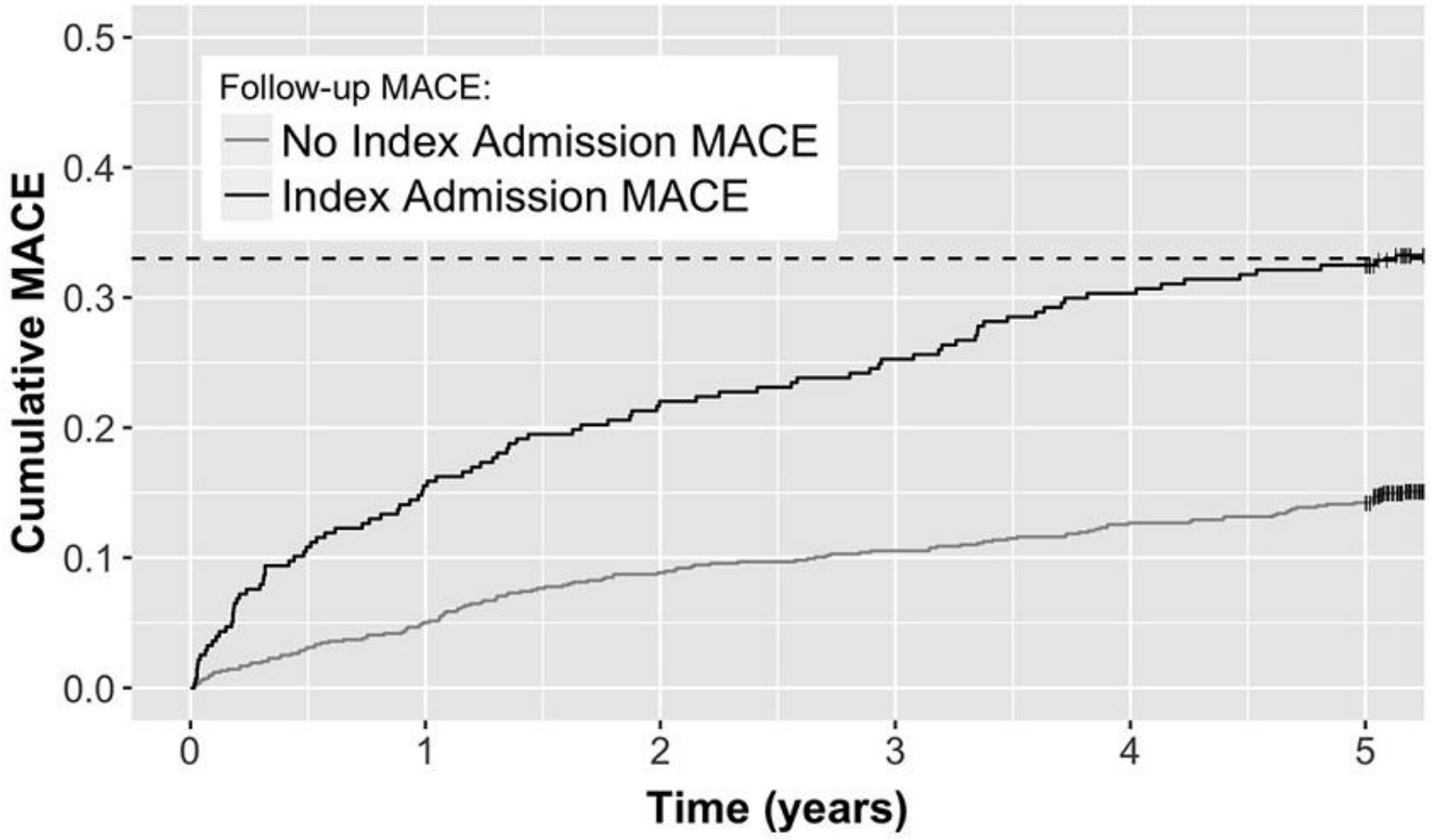
Kaplan-Meier plots of cumulative MACE





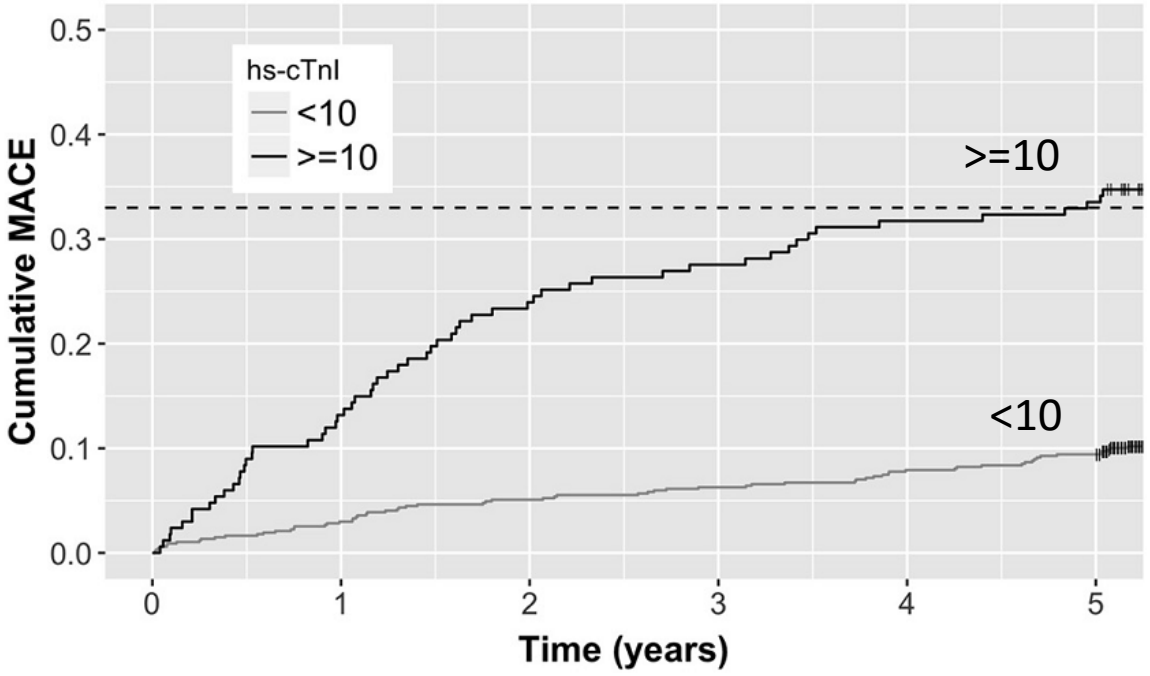
Kaplan-Meier plots of cumulative death

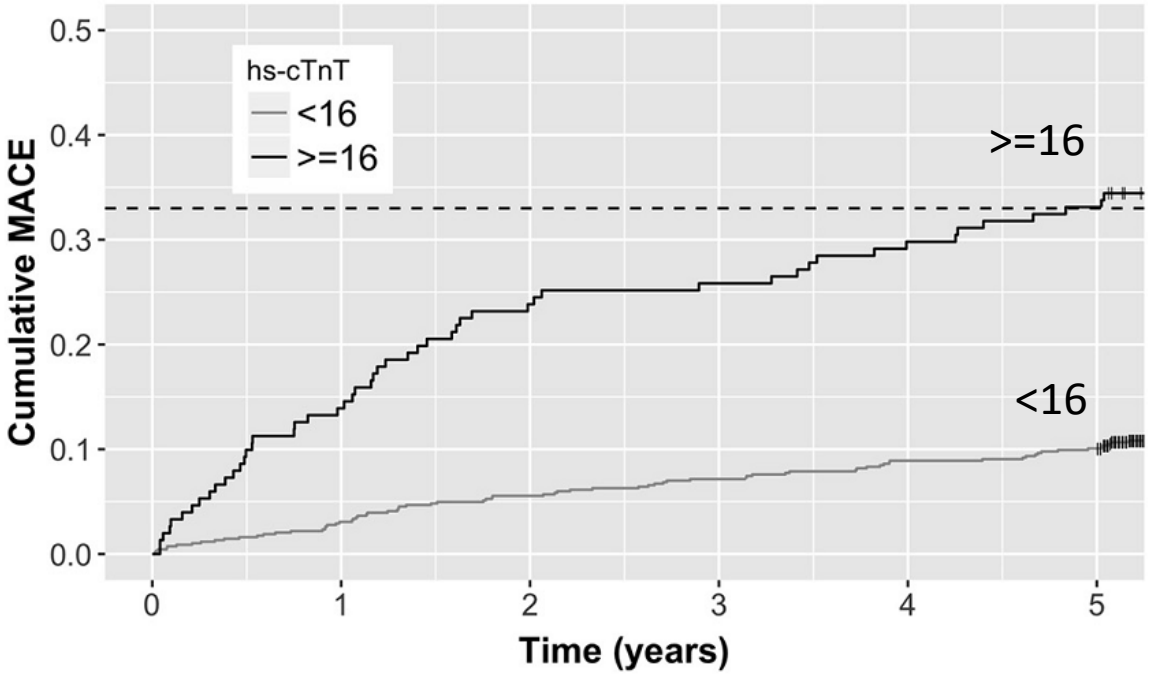
Cumulative MACE for Patients With and Without Index Admission MACE



Than M, et al. *Clin Chem*. 2018;64:1044-1053.

Cumulative MACE for Patients Split According to hs-cTnI (B) and hs-cTnT (C) Thresholds: Inpatients Without Index Admission MACE





The hs-cTn thresholds in (B) and (C) are chosen to give at least an equivalent 5-year cumulative MACE as for patients with index admission MACE of 0.33 (33%).

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Question to the Audience

The use of terms such as “troponitis”, “troponin leak” and “troponinemia” in clinical practice is OK

1. Agree
2. Disagree

Messages

- Detectable troponin at concentrations < 99th percentile increase CV risk
- Hs-cTnT additionally has prediction for mortality
- We need to develop strategies/guidance for clinicians