State of the Art Lecture: Chest Pain in the Emergency Department

ACCA Masterclass 2017

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@highSTEACS @troponinpapers

WE ARE THE ESC

British Heart Foundation

Acute Cardiovascular Care Association ACCA
A Registered Branch of the ESC

EUROPEAN SOCIETY OF CARDIOLOGY®

Disclosures

Funding: High-STEACS clinical trial (PI) NCT01852123
British Heart Foundation Special Project Grant (SP/12/10/29922)
Abbott Diagnostics (reagent only)

Sponsors: University of Edinburgh
NHS Lothian

Interests: Consultancy and speaker fees (Roche, Abbott Diagnostics, Beckman & Coulter, Singulex, GlaxoSmithKline, Sanofi-Aventis); Research grants (Abbott Diagnostics)

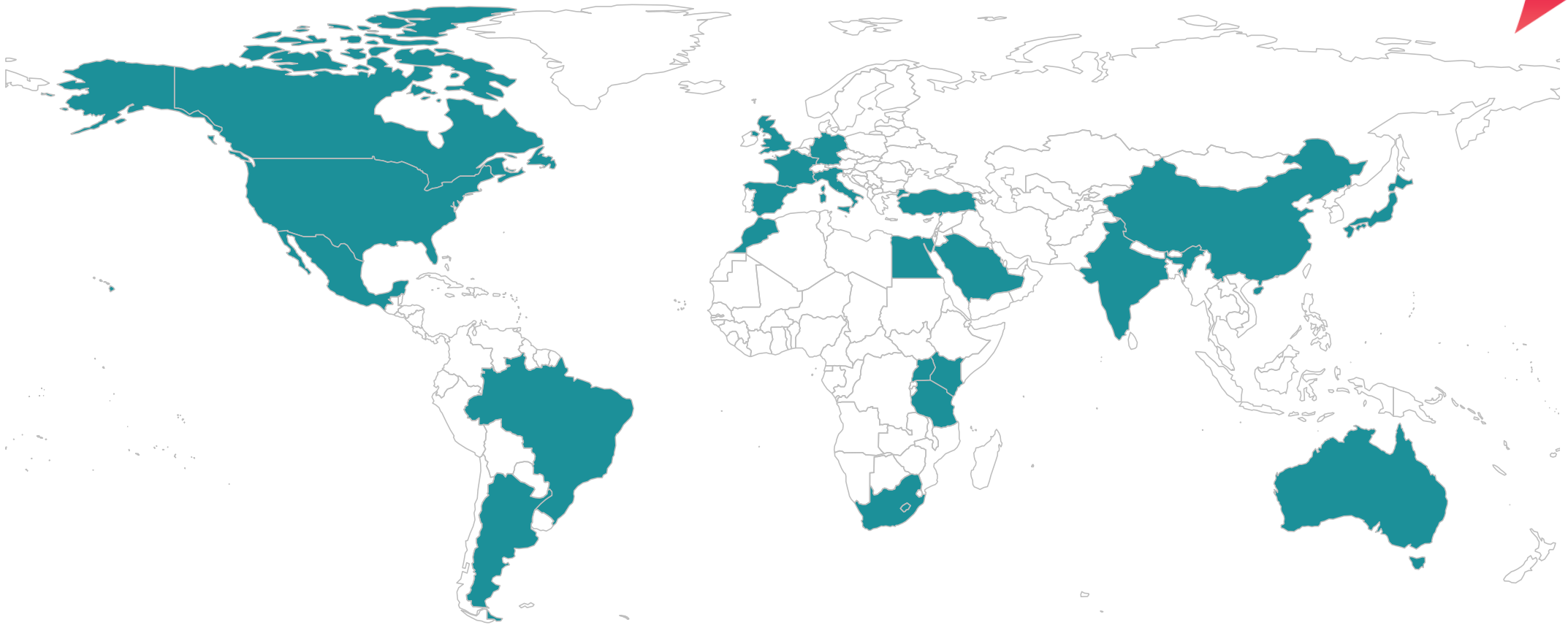
NICE Diagnostics Advisory Committee,
Scottish Inter-Collegiate Guideline Network

Universal definition of myocardial infarction

"A rise and/or fall of cardiac troponin with at least one value above the ***99th percentile*** upper reference limit (URL) from a healthy reference population"

JACC 2012;60(16):1581-98

Universal definition of myocardial infarction

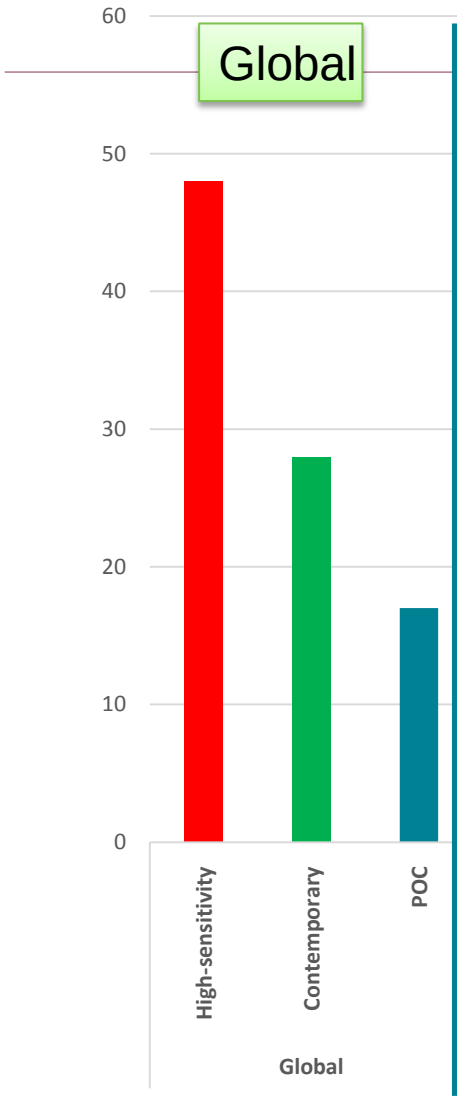


23 countries across high and low to middle income countries (1,902 hospitals)

North America 400; Europe 402; South America 400; Asia Pacific 400; Middle east 239; Africa 161

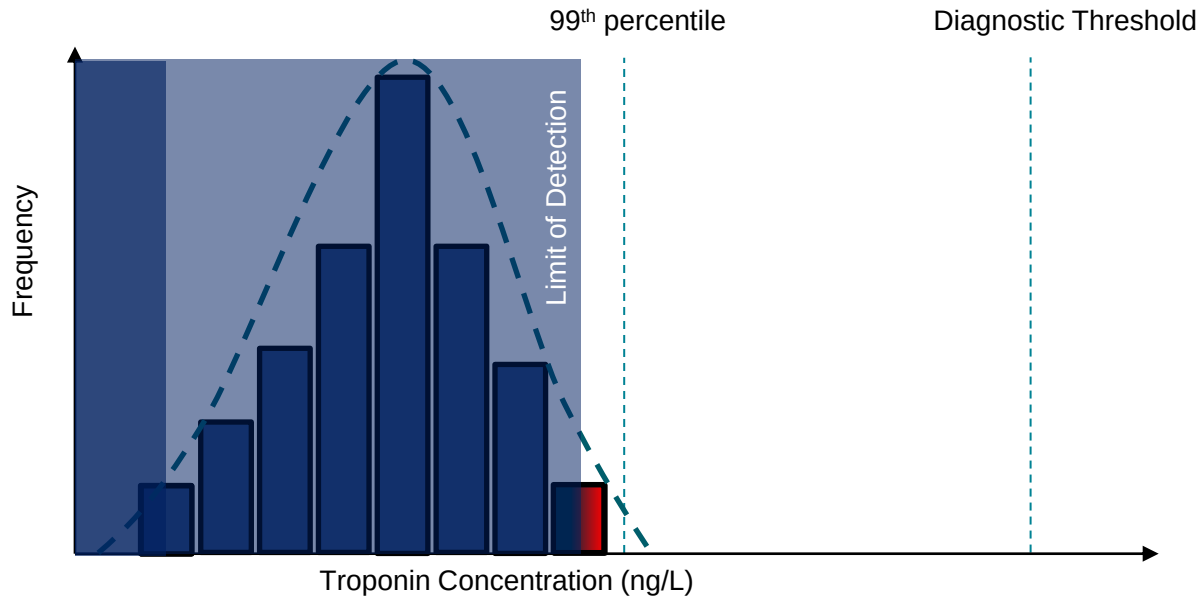
www.escardio.org/ACCA

Anand et al. 2016 (unpublished)



Anand et al. 2016 (unpublished)

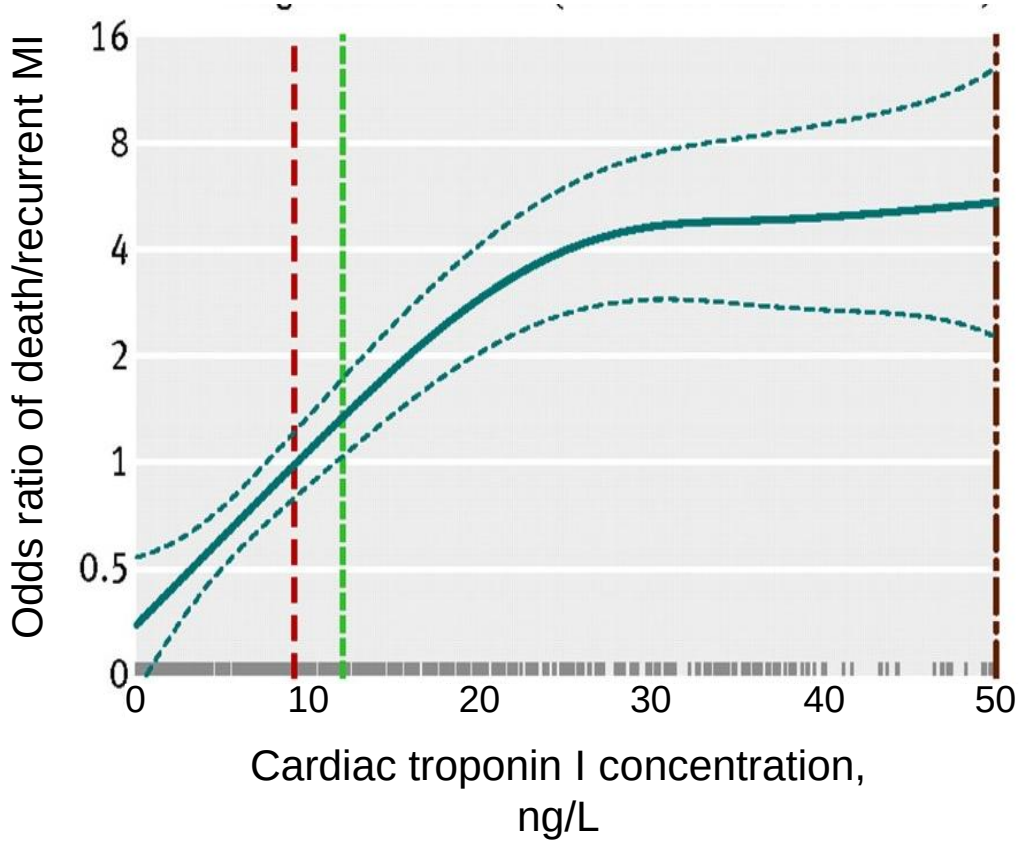
High-sensitivity cardiac troponin assays



- Greater analytical precision at very low concentrations (10-100 fold)
- Quantification of cardiac troponin concentrations in the majority of healthy persons
- **Permit development of accelerated diagnostic pathways**

Korley & Jaffe J Am Coll Cardiol. 2013;61(17):1753-8

Cardiac troponin concentrations within the reference range

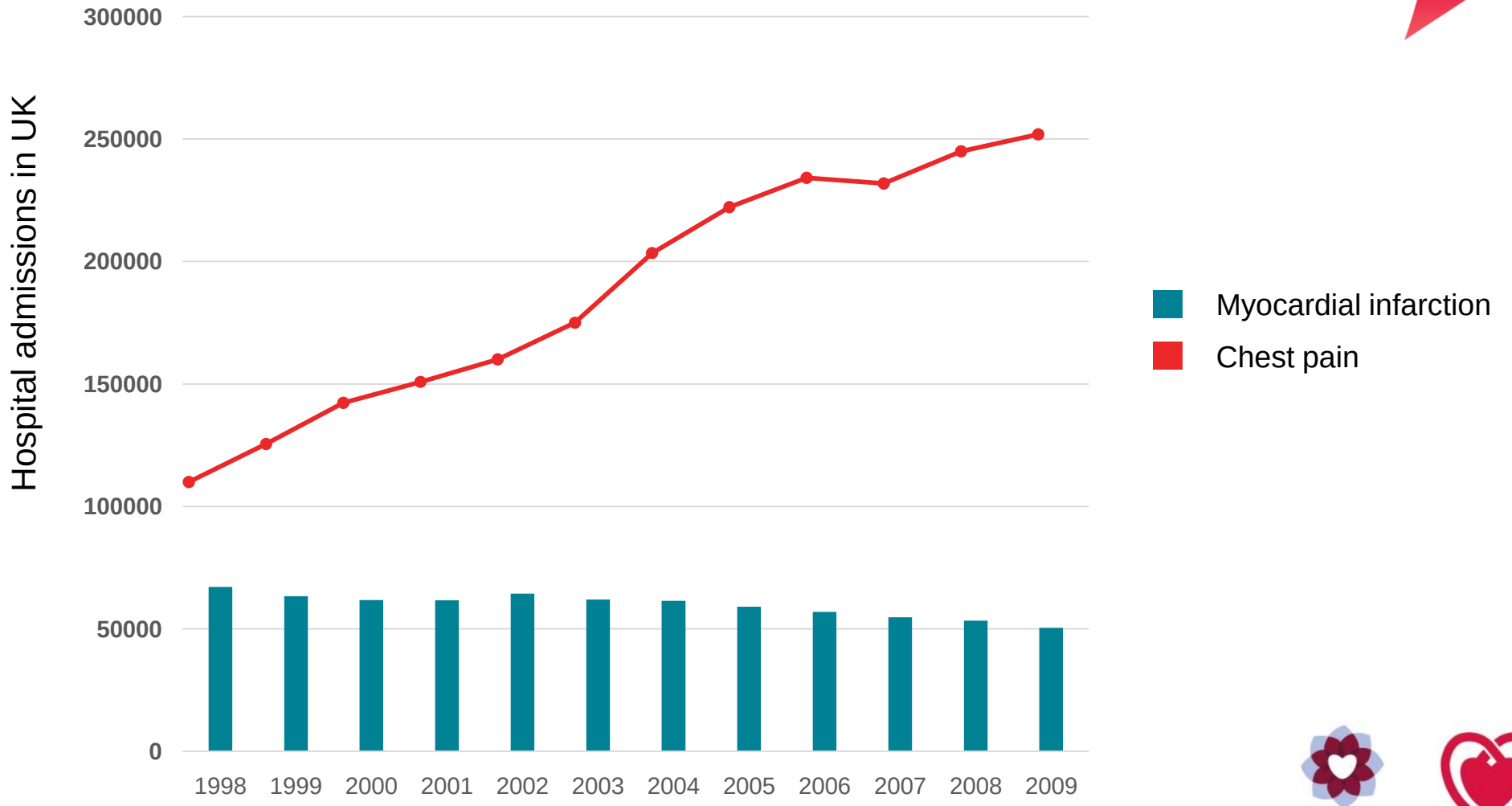


n = 2,092

Cardiac troponin concentrations in normal reference range associated with risk

Mills NL et al BMJ 2012;344:bmj.e1533;

Chest pain attendances in the Emergency Department



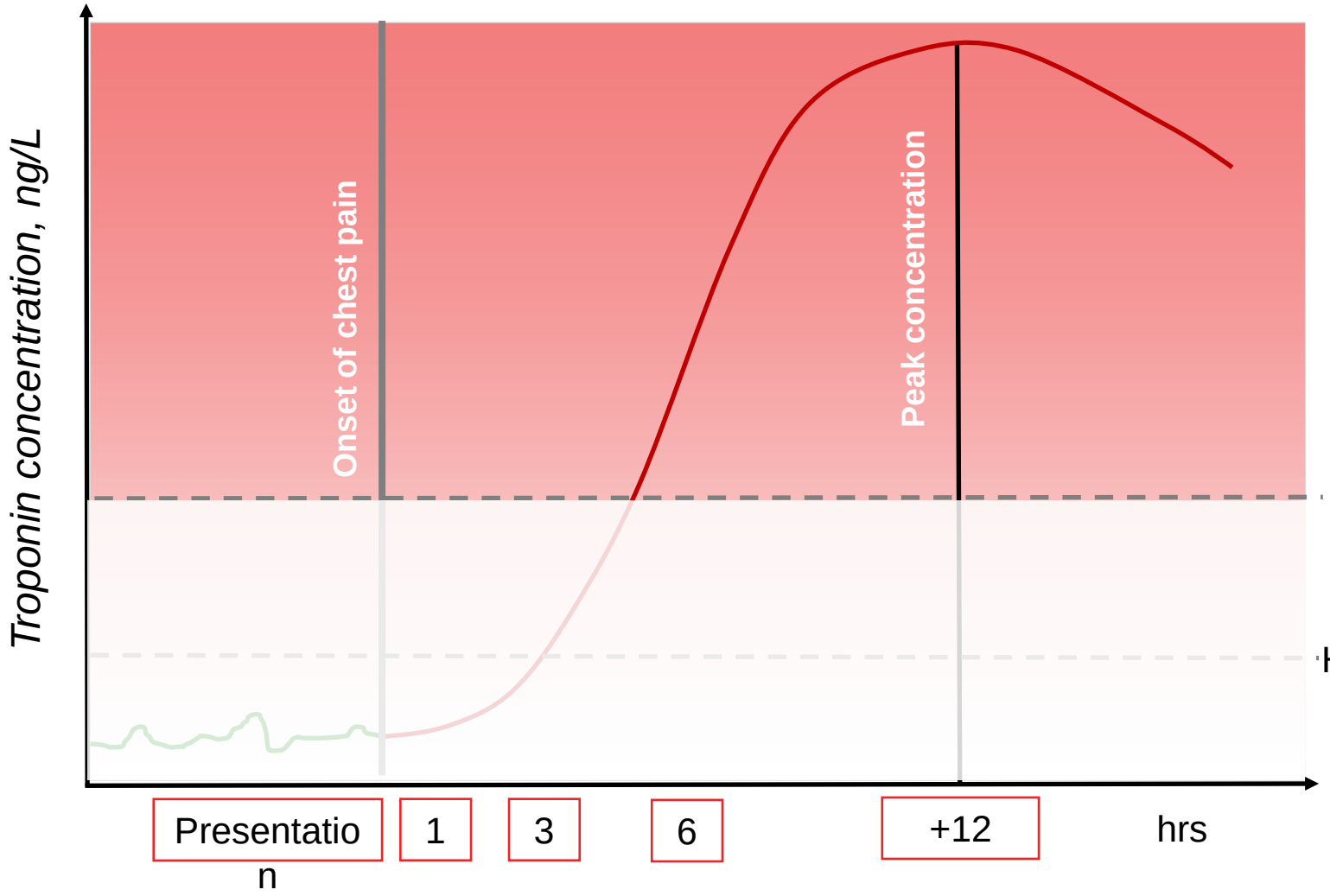
Goodacre et al. HTA 2013: 17 (1) 1-188

Can we rule out myocardial infarction safely in the Emergency Department?

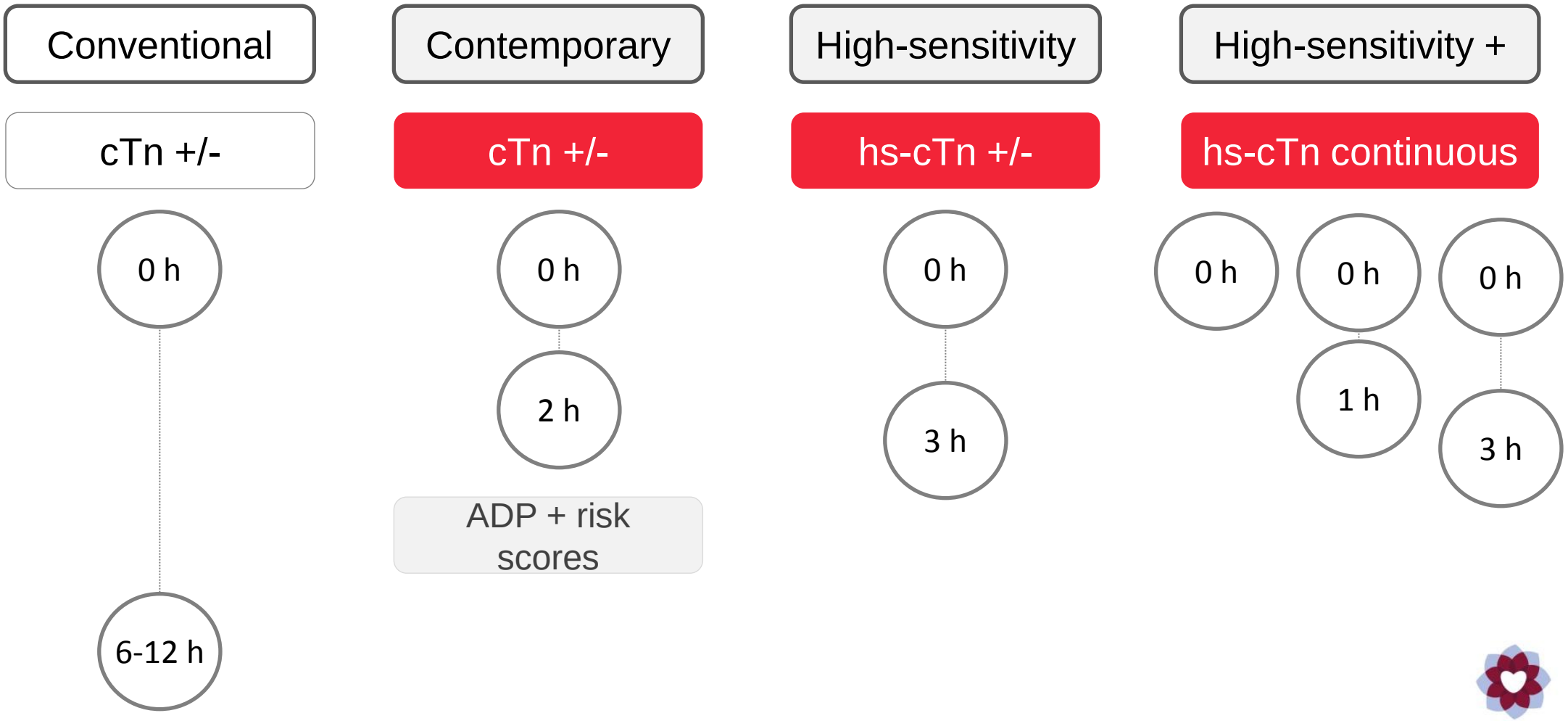
Royal Botanical Gardens, Edinburgh, Scotland

@HIGHSTEACS

Rapid rule out in the Emergency Department



Rapid rule out pathways for myocardial infarction



ADP = accelerated diagnostic pathway;
cTn = cardiac troponin; hs = high-sensitivity

Accelerated Diagnostic protocol to Assess Patients with chest Pain symptoms using contemporary Troponins (ADAPT)

0 h

2 h

TIMI Score = 0

AND

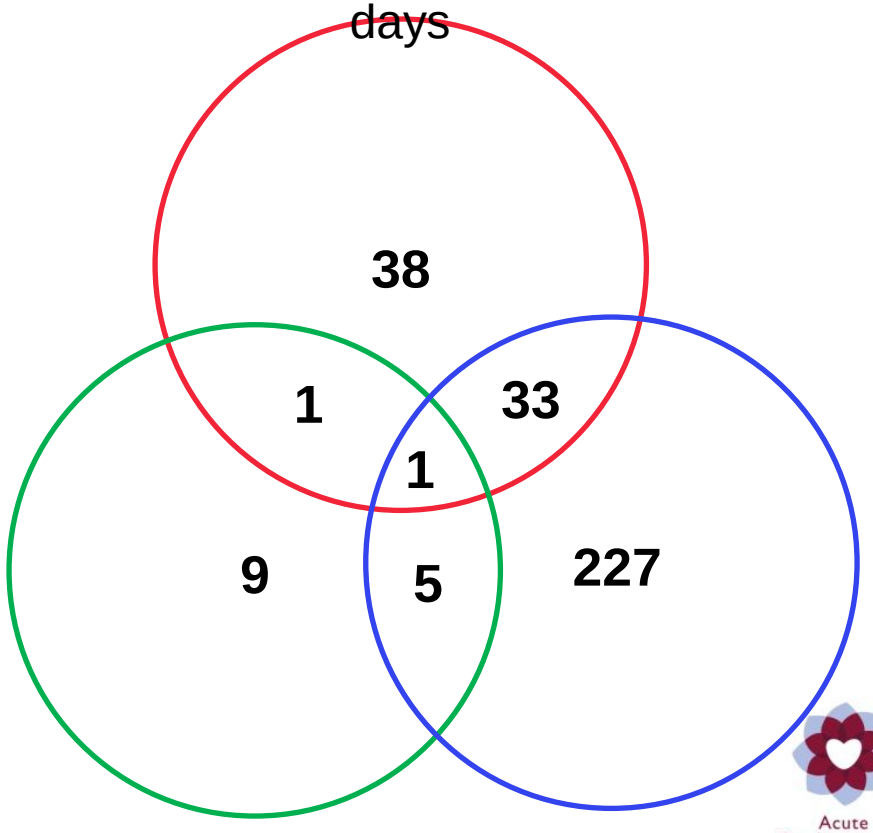
No ischemia on ECG

AND

Troponin <99th centile at 0 and 2 hrs

20% identified as low risk with MACE rate of 1:400 at 30 days (NPV 99.7%)

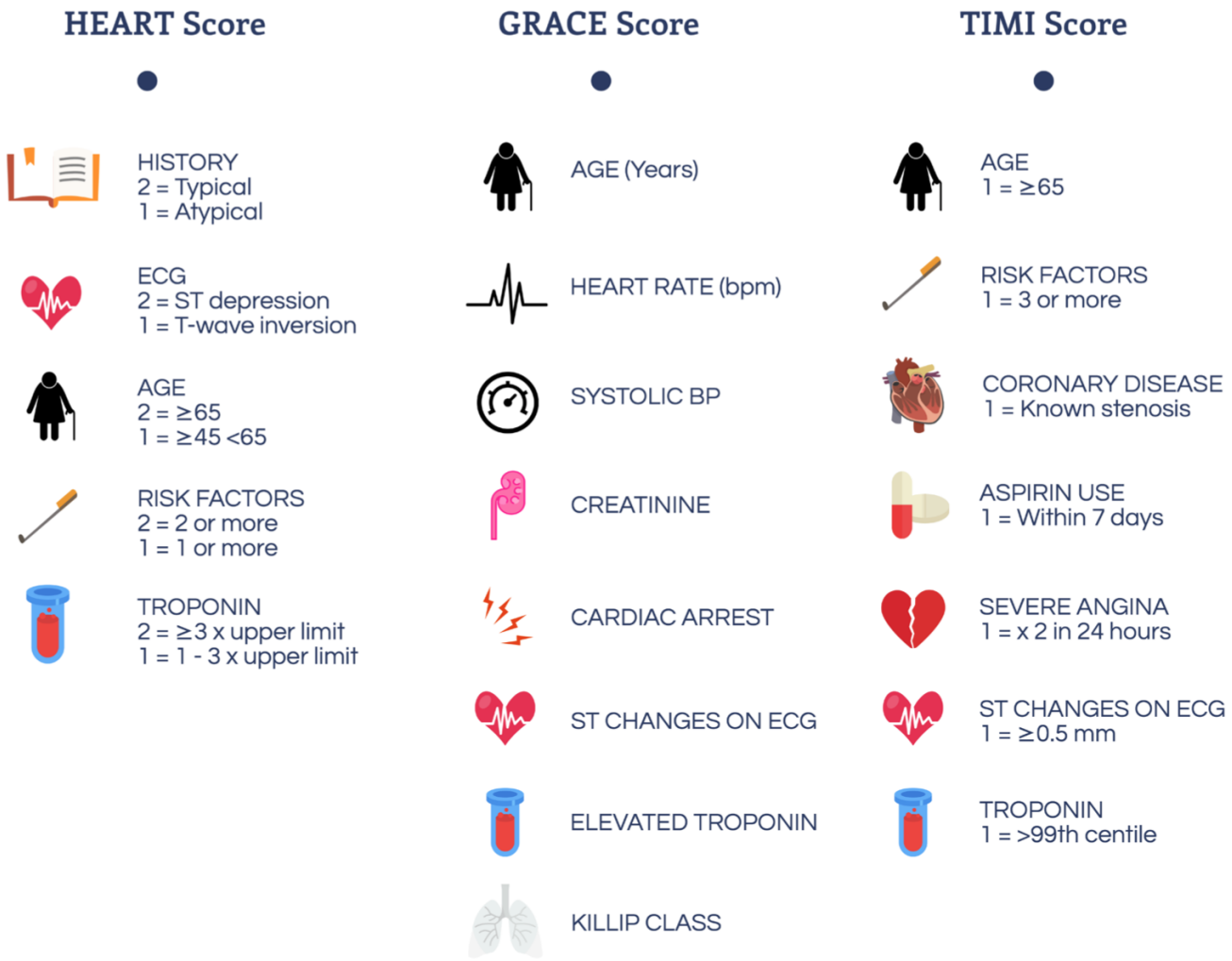
Patients with negative findings for each component of ADAPT who had MACE during up to 30-days



n=1,975

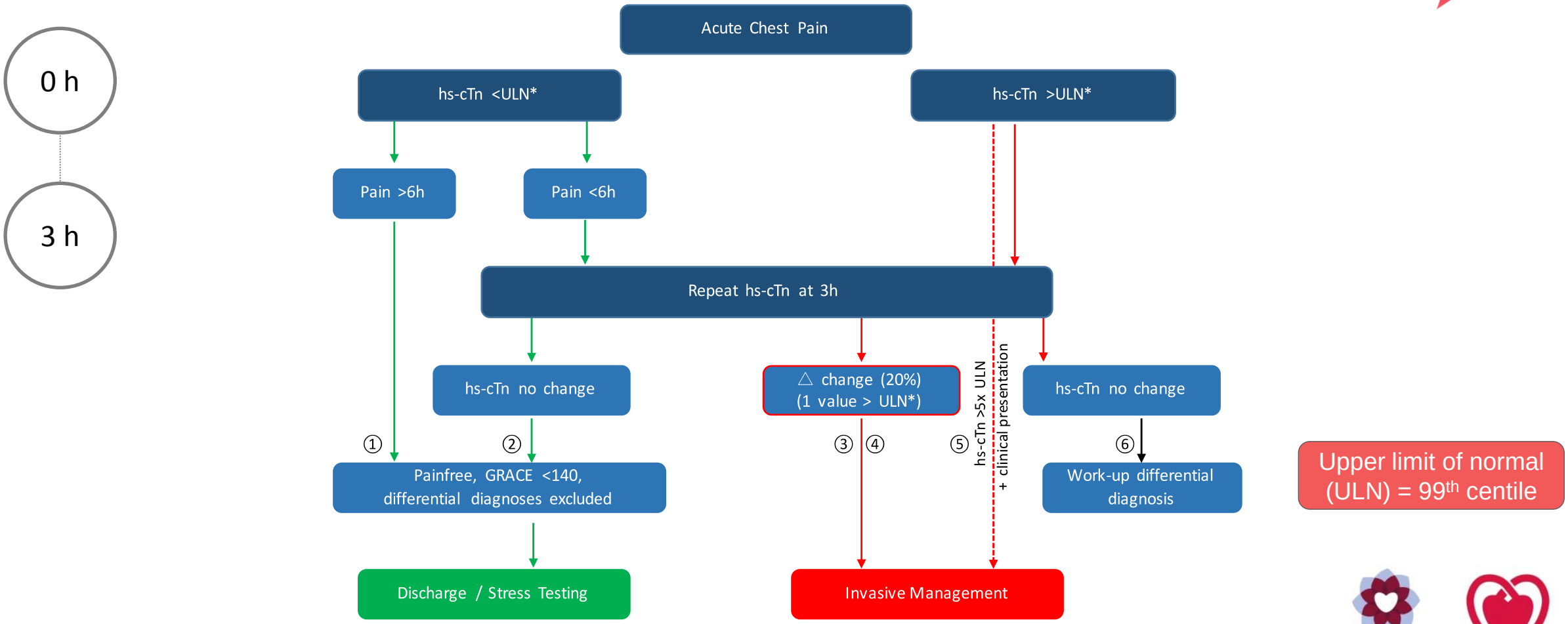
Cullen et al. J Am Coll Cardiol 2012;59:2091-2098

Risk scores in the era of contemporary troponin testing



JAMA. 2015 Nov 10;314(18):1955-65.

High-sensitivity cardiac troponin at 0 and 3 hours (European Society of Cardiology)



Upper limit of normal (ULN) = 99th centile

www.escardio.org/ACCA

Eur Heart J. 2016;37(3):267-315.

Retrospective validation of the ESC 0 and 3 hour pathway

Abbott ARCHITECT high-sensitivity troponin I assay >99th centile at presentation and 3 hours

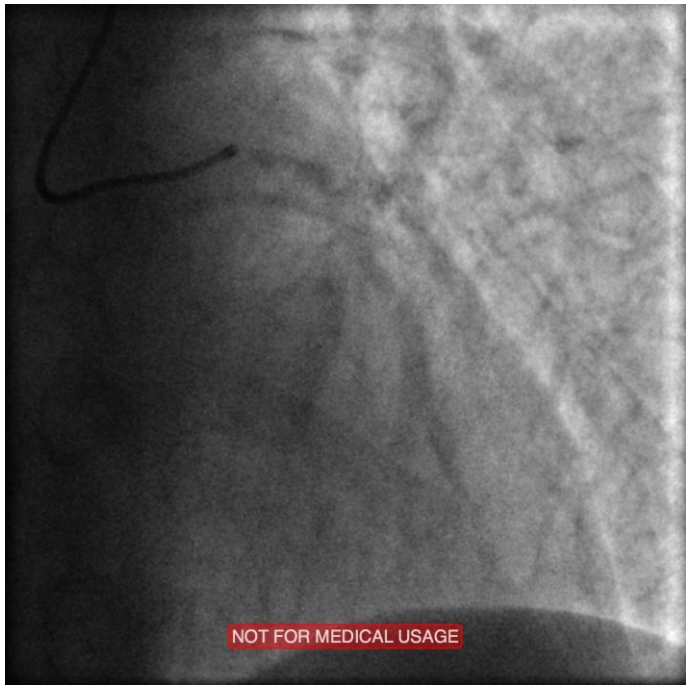
		AMI	Not AMI	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Brisbane ADAPT	Test positive	10	5	66.7 (38.3 to 88.2)	97.9 (95.1 to 99.3)	97.9 (95.1 to 99.3)	66.7 (38.4 to 88.2)
	Test negative	5	231				
Christchurch ADAPT	Test positive	47	7	60.3 (48.5 to 71.2)	97.9 (95.7 to 99.1)	91.3 (87.8 to 93.9)	87.0 (75.1 to 94.6)
	Test negative	31	324				
Christchurch ADAPT-ADP	Test positive	21	1	75.0 (55.1 to 89.3)	99.5 (97.4 to 100)	96.7 (93.4 to 98.7)	95.5 (77.2 to 99.9)
	Test negative	7	208				
Christchurch EDACS	Test positive	6	1	75.0 (34.9 to 96.8)	98.9 (94.1 to 100)	97.8 (92.4 to 99.7)	85.7 (42.1 to 99.6)
	Test negative	2	91				

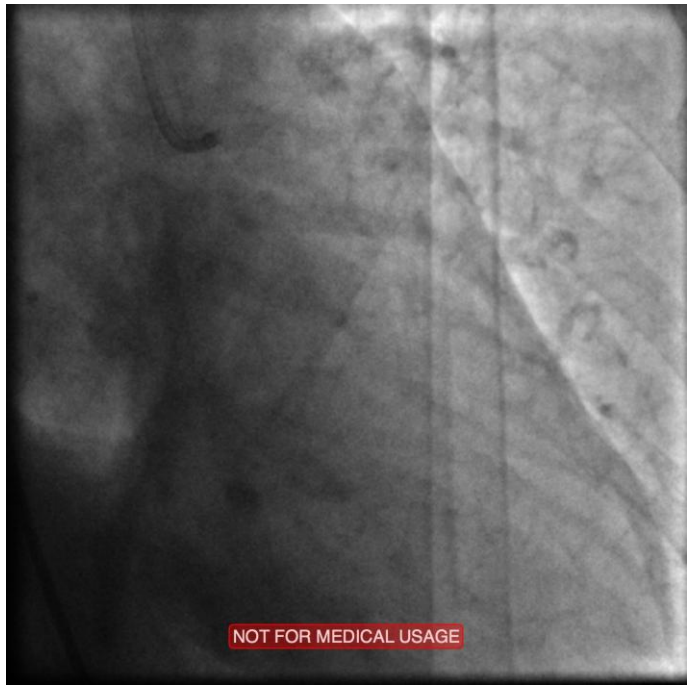
Parsonage et al. Heart 2016; Pickering et al. Heart 2016

Case 386

0 h

3 h





63 year old women with left sided chest pain 2 hours prior to arrival in the Emergency Department. Cigarette smoker with a family history of premature coronary artery disease. Examination normal. Initial 12-lead electrocardiogram was unremarkable

hs-cTnI concentrations were 10, 16 and 187 ng/L at presentation, and at 3 and 12 hours

Limitations of the 99th centile in 0 and 3 hour pathways

0 h

3 h

Age	Sex	0 hrs	3 hrs	Peak	Pain onset
82	F	11	15	26	150 mins
63	F	10	16	167	150 mins
74	M	5	8	57	180 mins
62	M	27	32	43	150 mins
87	M	5	16	691	150 mins
73	M	26	29	41	-
61	M	12	30	51	180 mins
75	M	23	25	39	150 mins

Age	Sex	0 hrs	3 hrs	Peak	Pain onset
58	M	26	33	46	180 mins
66	M	12	31	202	270 mins
60	M	2	6	2932	120 mins
56	M	8	14	307	-
77	M	21	26	56	270 mins
66	M	22	25	36	-
84	M	17	16	53	-
60	M	14	14	170	270 mins

n=330

hs-cTnI at presentation and at 3 hours missed 16/330 of patients with myocardial infarction identified at 12 hours

SHOULD WE USE DIFFERENT THRESHOLDS TO RULE IN AND RULE OUT MI?

Botanical Building, Balboa Park, San Diego, California

@HIGHSTEACS

Ruling out with high-sensitivity cardiac troponin T using the limit of detection (LOD) at presentation

0 h

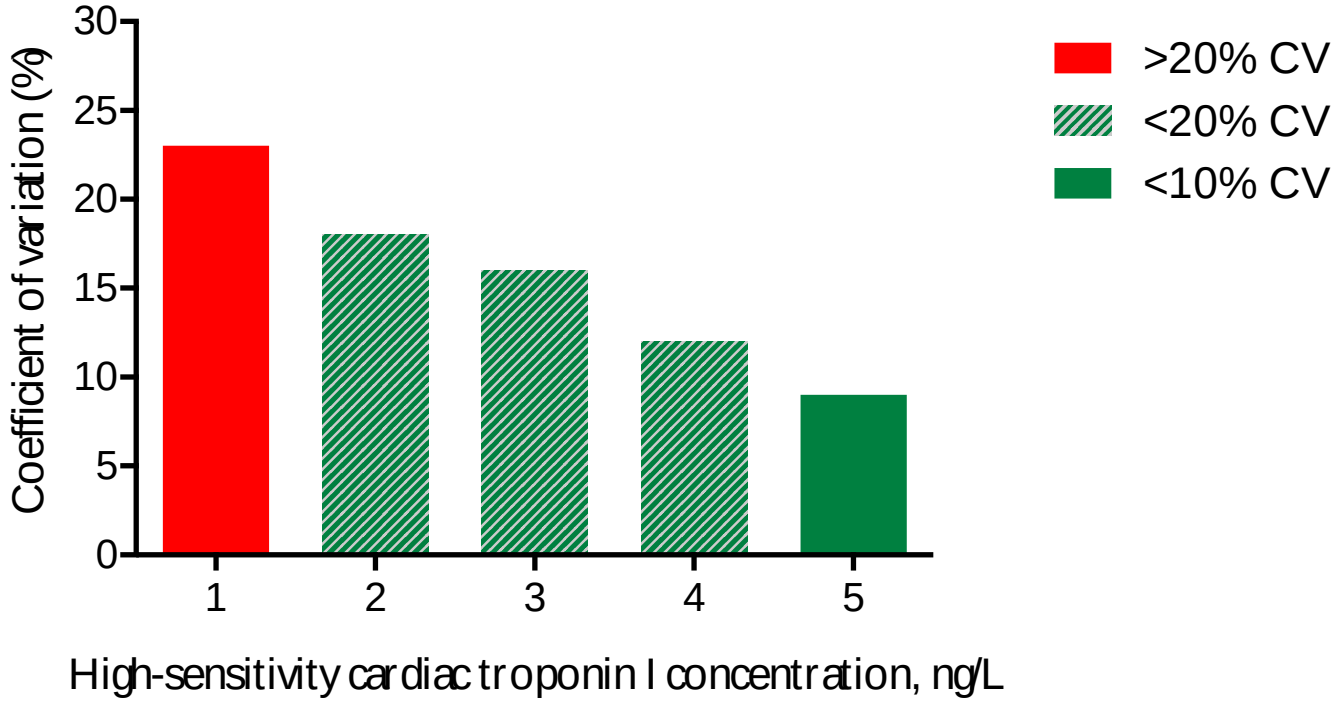
High-sensitivity cardiac troponin T<LOD (5 ng/L) at 0 h rules out myocardial infarction in 20-44% of patients with an NPV >98.6%

Cohort	Year	n	FN	TN	NPV	Proportion
Manchester (1)	2011	703	0	130	100.0%	27%
APACE (2)	2013	2,072	8	542	98.6%	26%
Manchester (3)	2015	463	1	95	99.0%	20%
France (4)	2016	413	1	176	99.5%	43%
TRAPID-AMI (5)	2016	1,283	4	556	99.3%	44%

(1) Body et al JACC. 2011;54:1332; (2) Rubini Gimenez et al. Int J Cardiol. 2013;168:3896-901; (3) Body et al. Clin Chem. 2015;61:983-9. (4) Chenevier-Gobeaux et al. Clin Biochem. 2016;49:1113-1117. (5) Body et al. Acad Emerg Med. 2016;23:1004-13.

Enhanced precision with high-sensitivity cardiac troponin I

Abbott ARCHITECT high-sensitivity cardiac troponin I (hs-cTnI) assay



Coefficient of variation 20% ~ **2 ng/L**

Shah AS et al Lancet 2015;386:2481-8

Optimal threshold to rule out at presentation with hs-cTnI

0 h

Aim: to define a threshold that identifies patients with suspected acute coronary syndrome at presentation as low risk of myocardial infarction for immediate discharge

Derivation: n=4,870 consecutive patients across hospitals in Scotland, UK

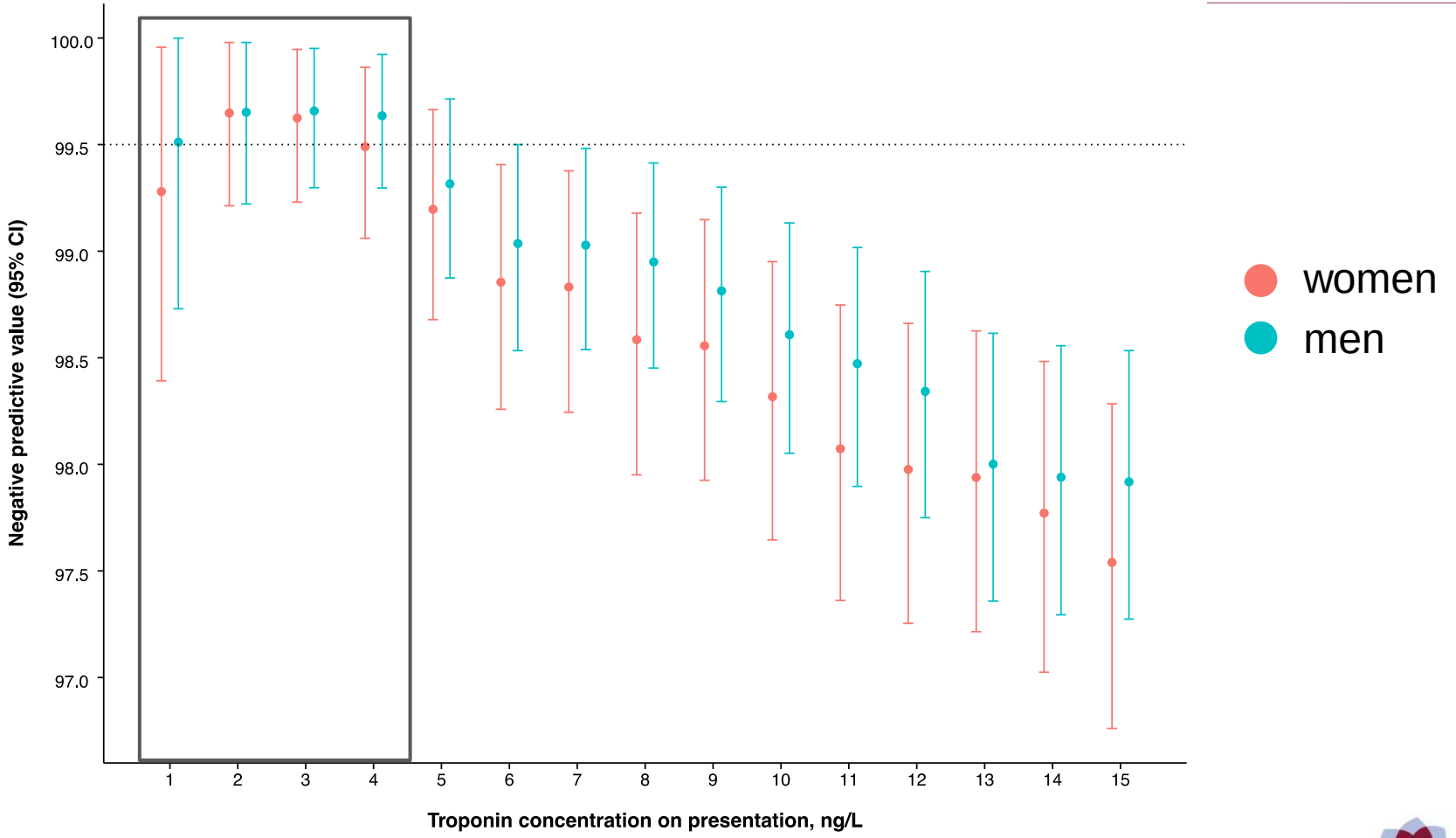
Validation: n=1,434 consecutive patients in Minneapolis, USA

Index myocardial infarction, subsequent myocardial infarction or cardiac death at 30 days

Shah AS et al Lancet 2015;386:2481-8

Optimal threshold to rule out at presentation with hs-cTnI

0 h



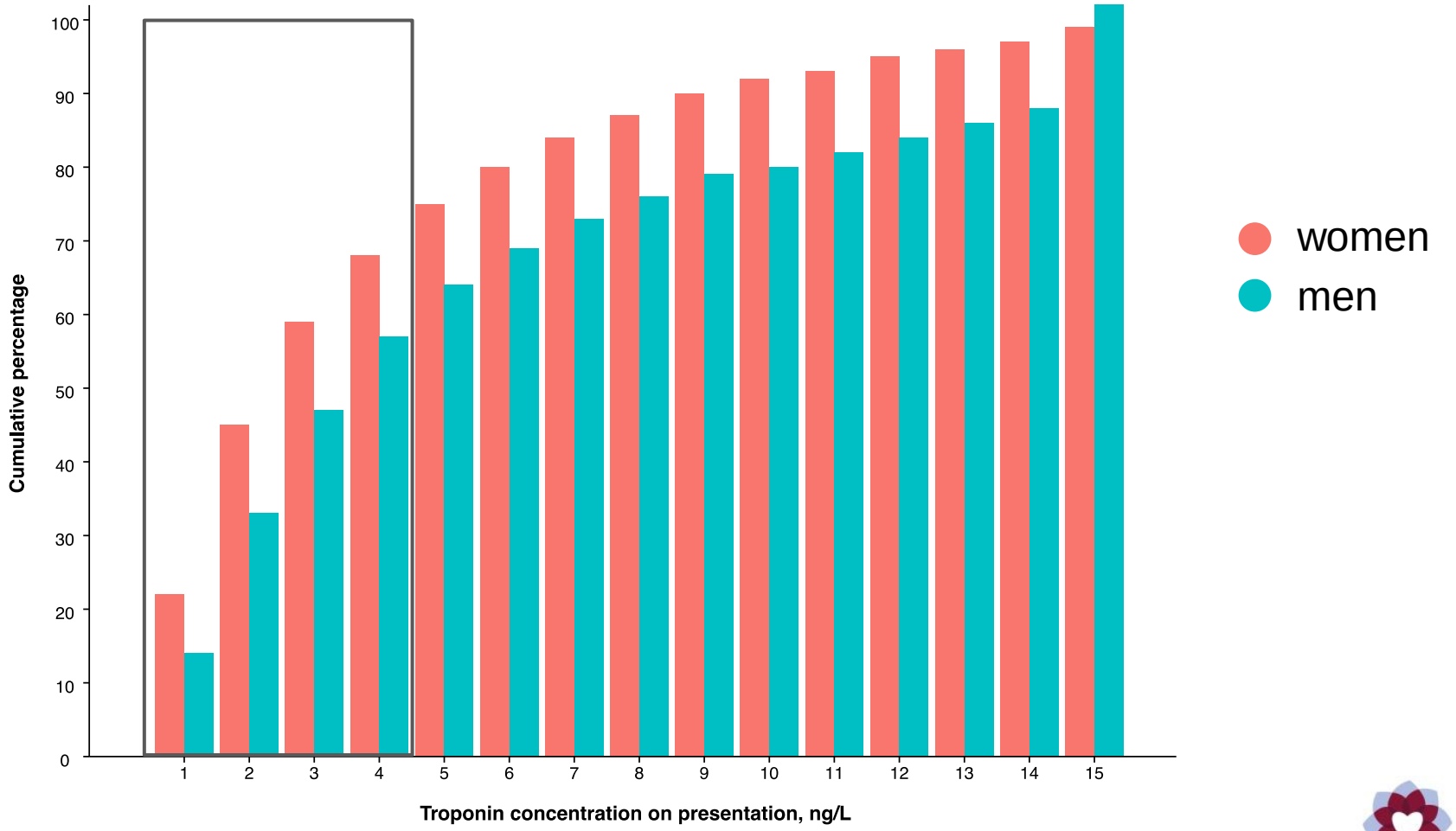
n=4,870

NPV is 99.6% (95% CI 99.3 to 99.8) at troponin concentrations <5 ng/L

Shah AS et al Lancet 2015;386:2481-8

Optimal threshold to rule out at presentation with hs-cTnI

0 h



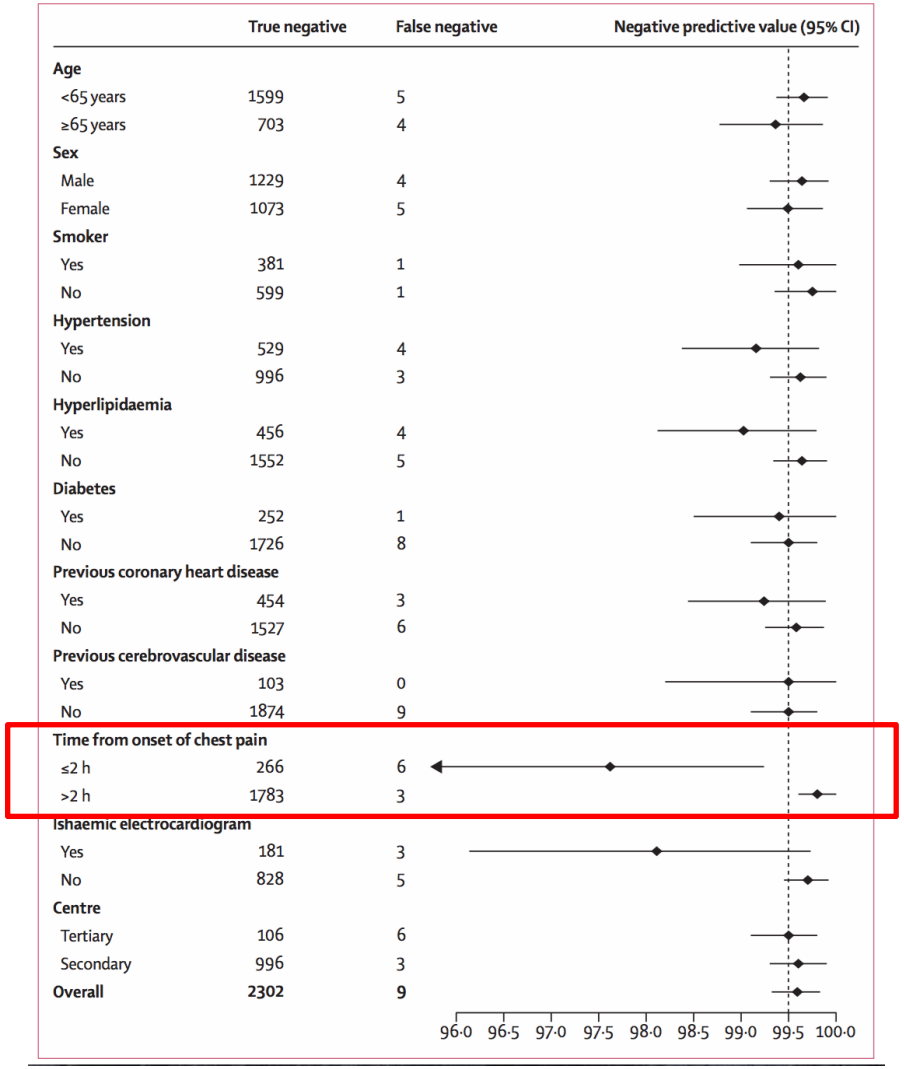
n=4,870

Derivation cohort : 68% of women and 59% of men <5 ng/L on presentation

Shah AS et al Lancet 2015;386:2481-8

Performance of <5 ng/L threshold in key subgroups

0 h

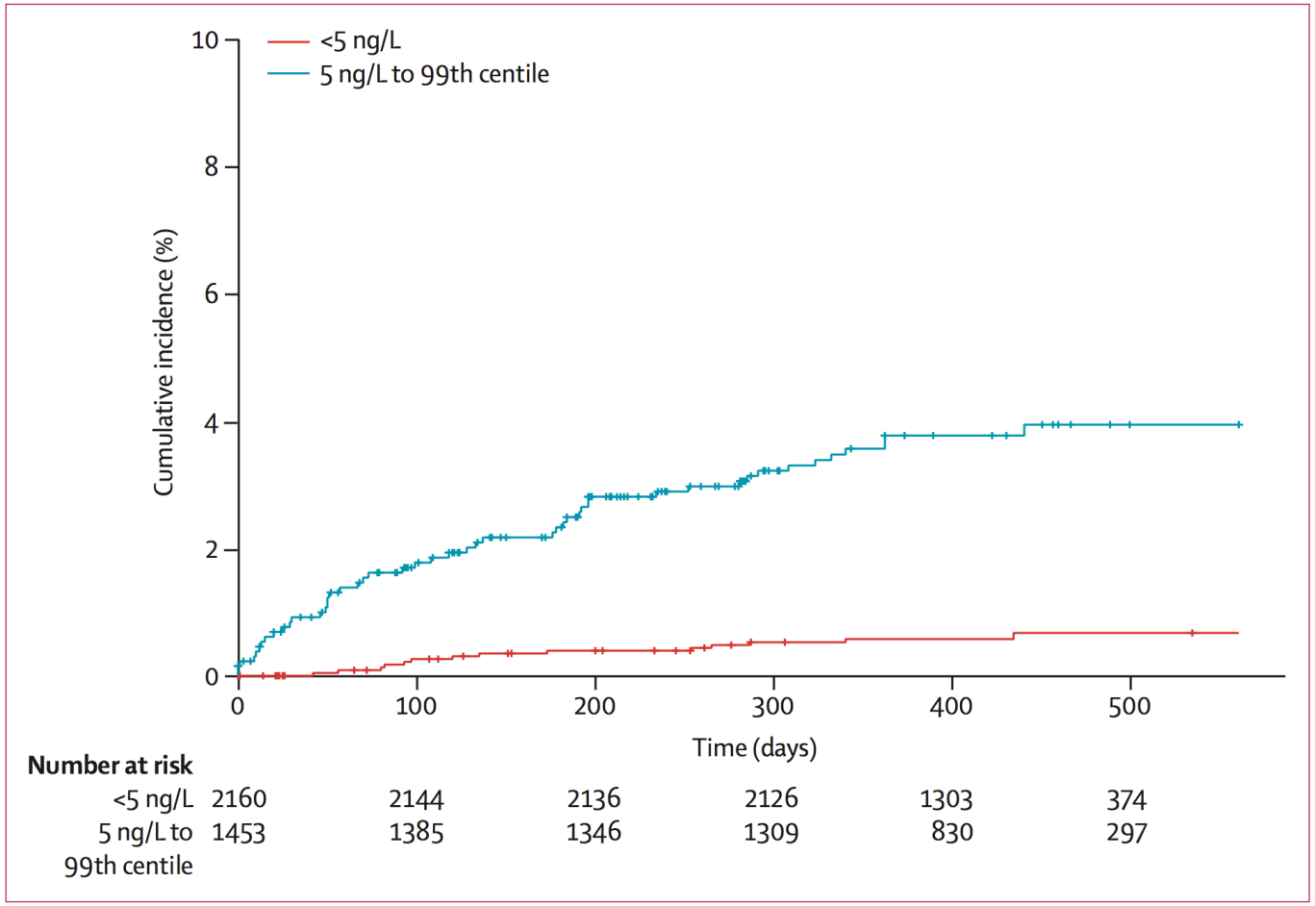


Negative predictive value

n=4,870

One year outcomes in patients without myocardial infarction

0 h



n=4,870

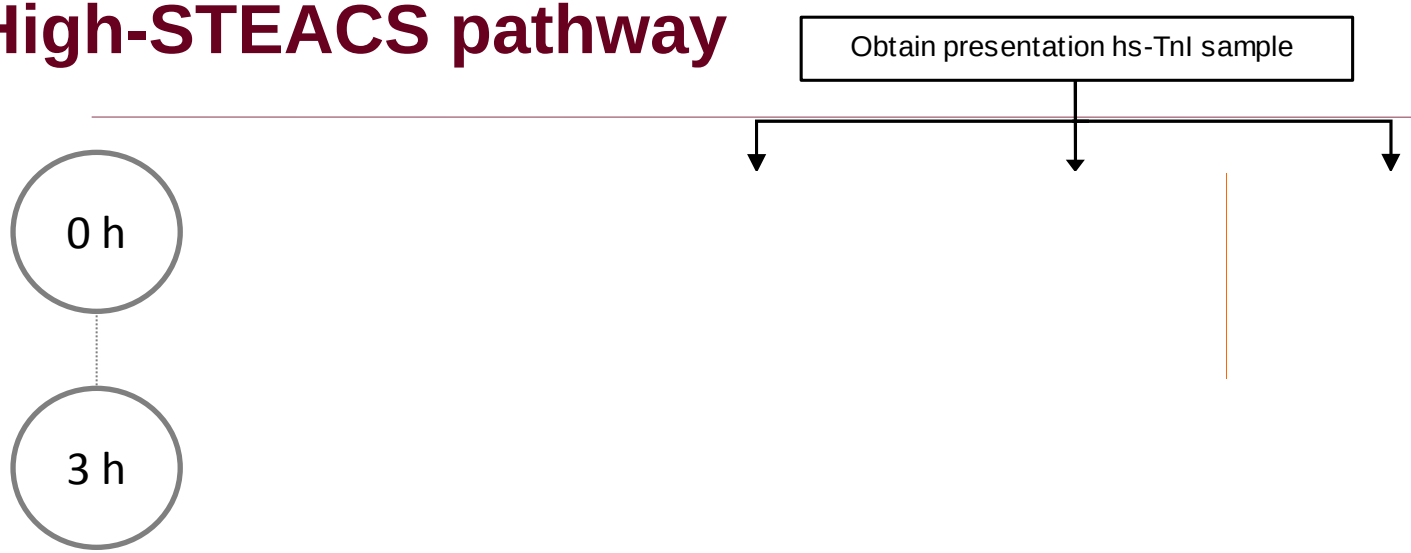
Risk stratification of patients without myocardial infarction

Shah AS et al Lancet 2015;386:2481-8

HOW TO INTEGRATE RISK STRATIFICATION THRESHOLDS INTO THE PATHWAY

Scottish wildflowers, Edinburgh

High-STEACS pathway

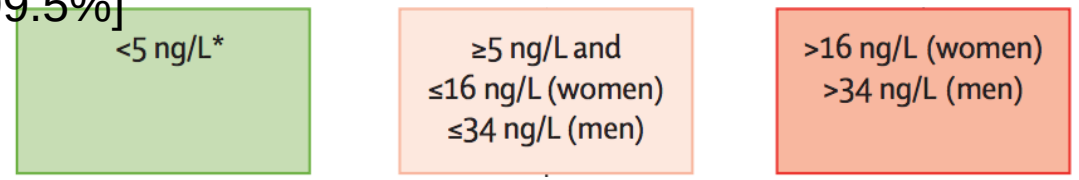


*patients <2 hours from symptom onset require serial testing

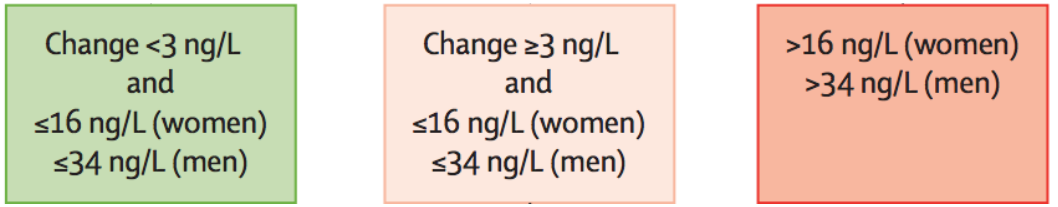
Shah et al. Lancet 2016;387:2289-91

Validation of risk stratification thresholds

<5 ng/L at presentation	**NPV [95%CI]**
Carlton et al (3,155 patients) JAMA Cardiology 2016	99.2% [98.8 - 99.5%]
Boeddinghaus et al (2,828 patients) Eur. Heart. J. 2016	99.1% [98.5 - 99.5%]



<3 ng/L at three hours	**NPV [95%CI]**
Internal Validation (310 patients) Circulation 2017	98.8% [97.4-99.9%]
External Validation (2,533 patients) Circulation 2017	99.9% [99.7-100%]



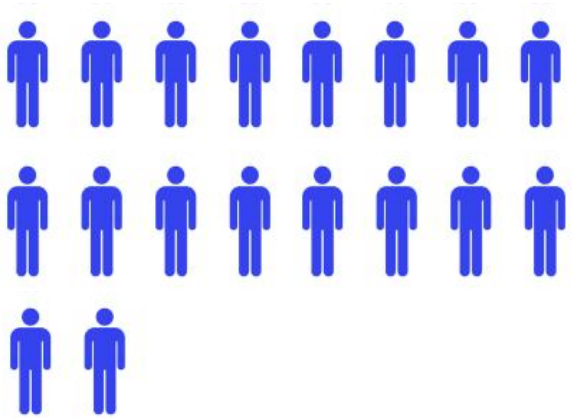
Carlton et al JAMA Cardiology 2016; Chapmen et al. Circulation 2017

How do the High-STEACS and ESC pathways compare?

0 h

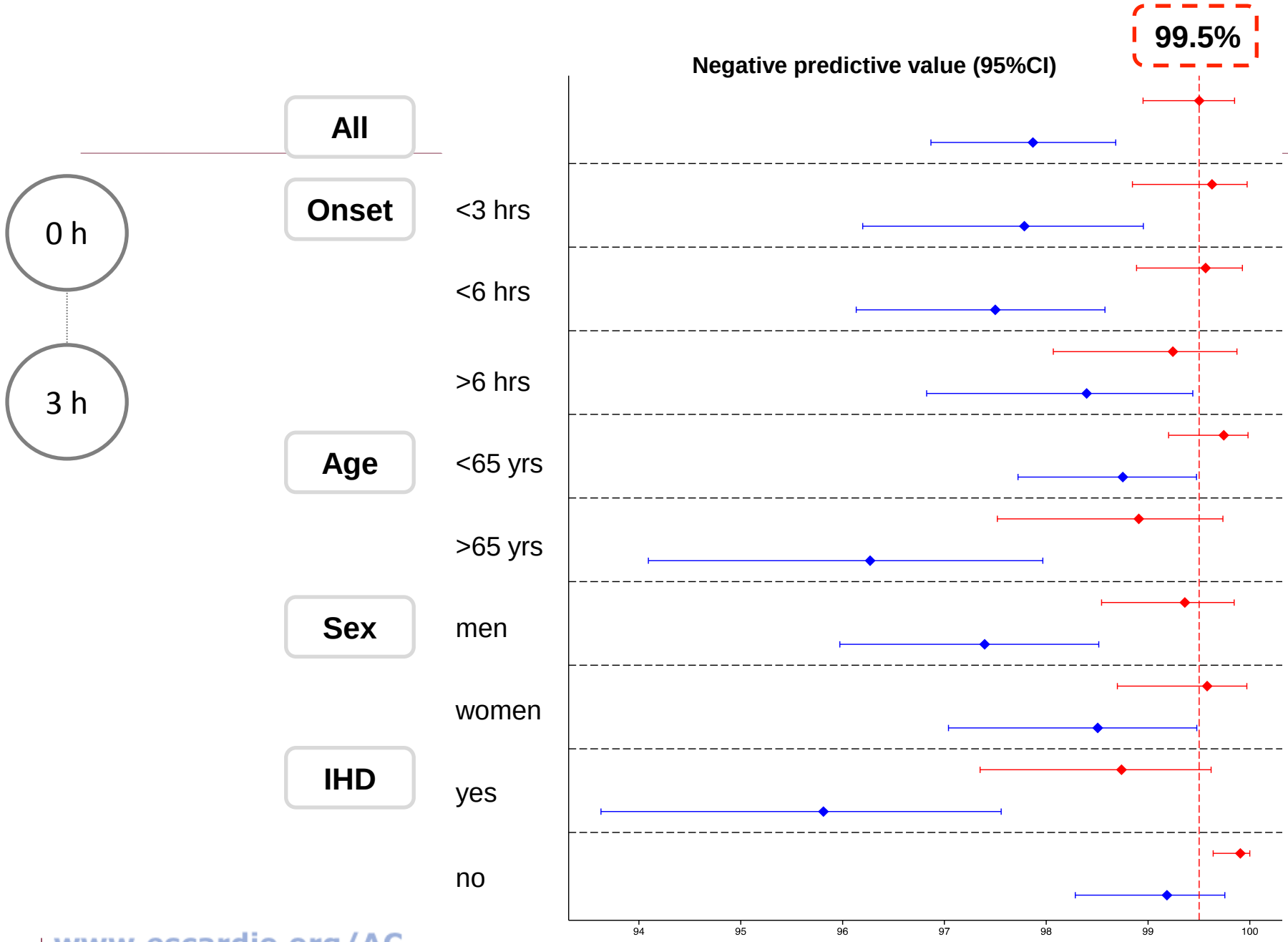
3 h

INDEX TYPE 1 MI

High-STEACS pathway	ESC 3 hour pathway
NPV 99.5% [99.0-99.9%]	**NPV 97.9% [96.9-98.7%]**
	
Rules out 74% at 3 hrs	**Rules out 79% at 3 hrs**

n=1,218

Chapman et al. Circulation 2017



High-STEACS

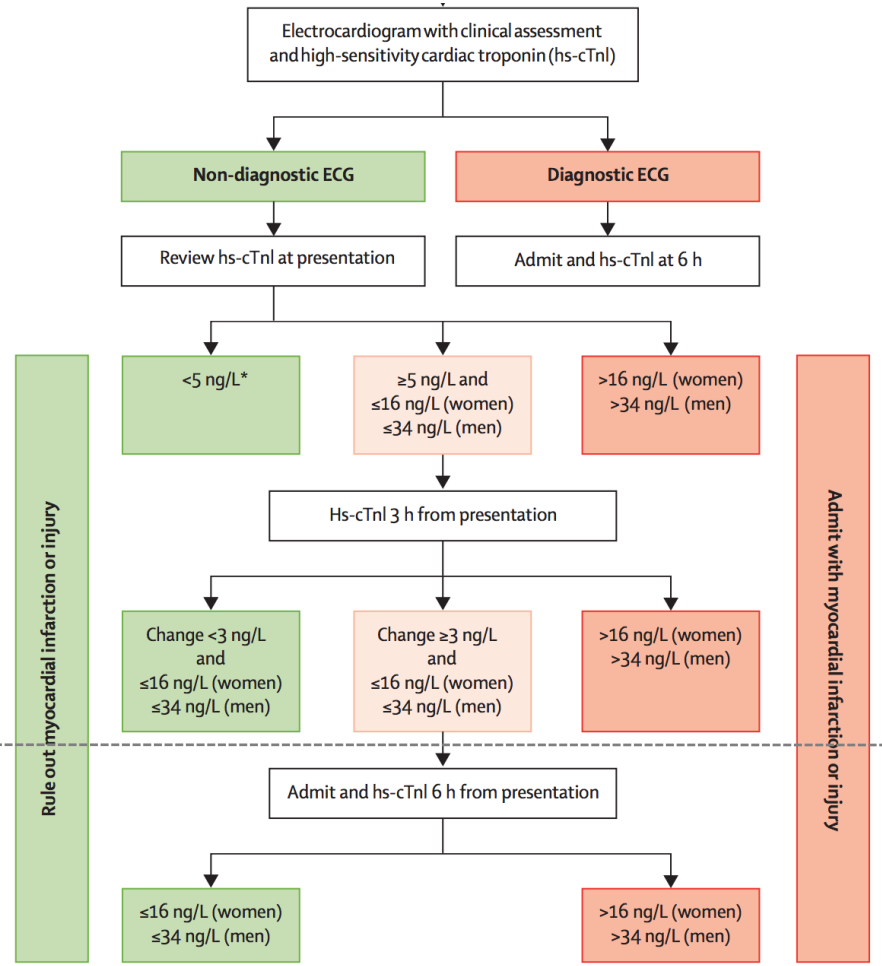
ESC Pathway

Chapman et al. Circulation 2017

Implementation of HighSTEACS pathway

EMERGENCY DEPARTMENT

HOSPITAL ADMISSION



* Retest at 3h if <2h from onset

Shah et al. Lancet 2016;387:2289-91

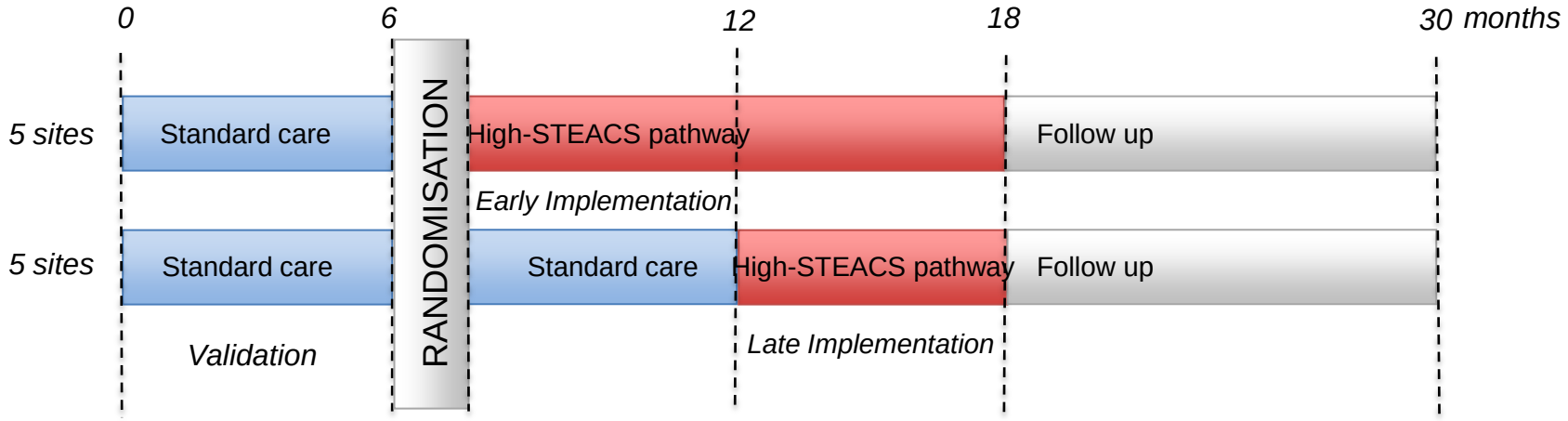
*Hi*gh-Sensitivity cardiac *T*roponin at presentation t*O* *R*ule out myocardial *I*nfar*C*tion: (HiSTORIC) a stepped wedge cluster randomised trial

WE ARE THE ESC

0 h

3 h

Stepped-wedge cluster randomised trial



Aim: to evaluate the efficacy and safety of implementation of High-STEACS pathway to rule out myocardial infarction in consecutive patients with suspected acute coronary syndrome

Abbott Diagnostics

British Heart Foundation

NHS SCOTLAND

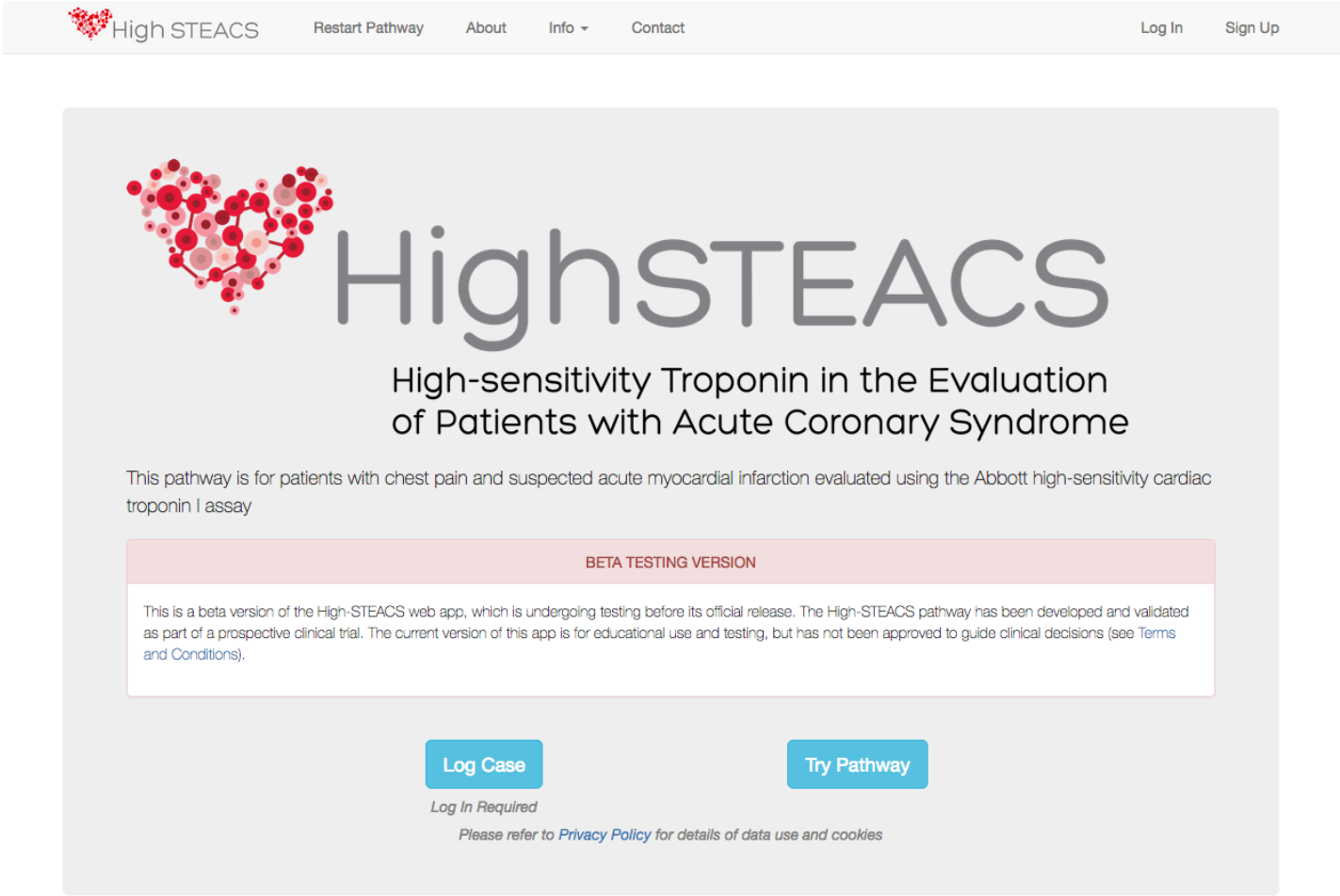
Acute Cardiovascular Care Association ACCA

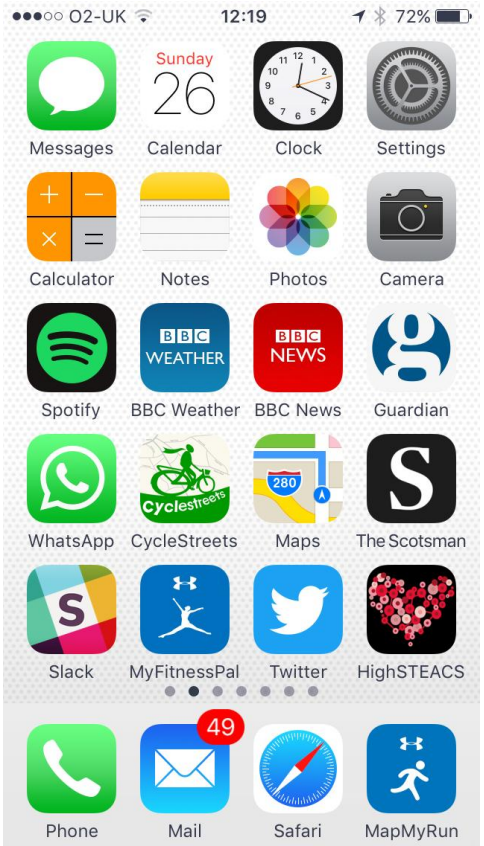
EUROPEAN SOCIETY OF CARDIOLOGY®

www.escardio.org/ACCA

www.clinicaltrials.gov number: NCT01852123

www.highsteacs.com





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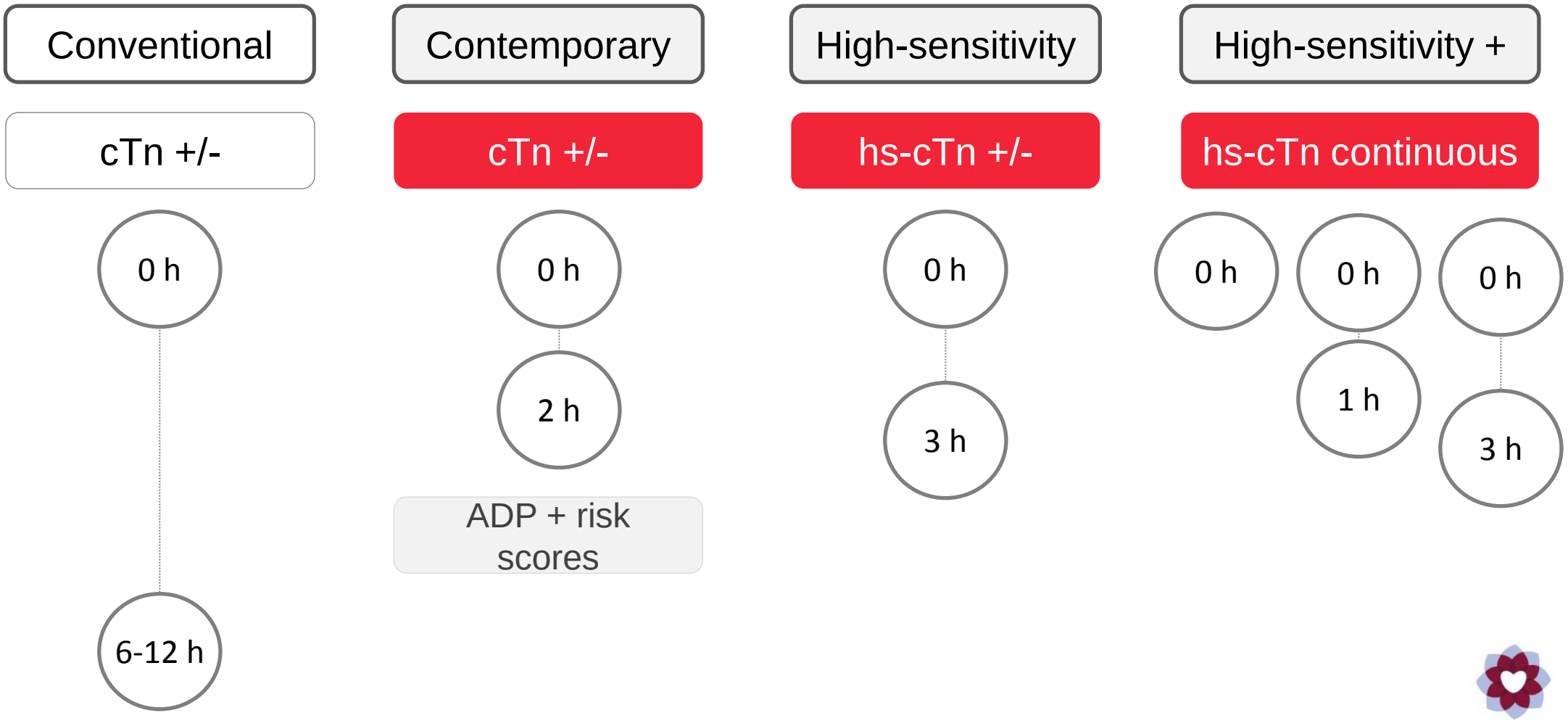
Rapid rule out pathways for myocardial infarction

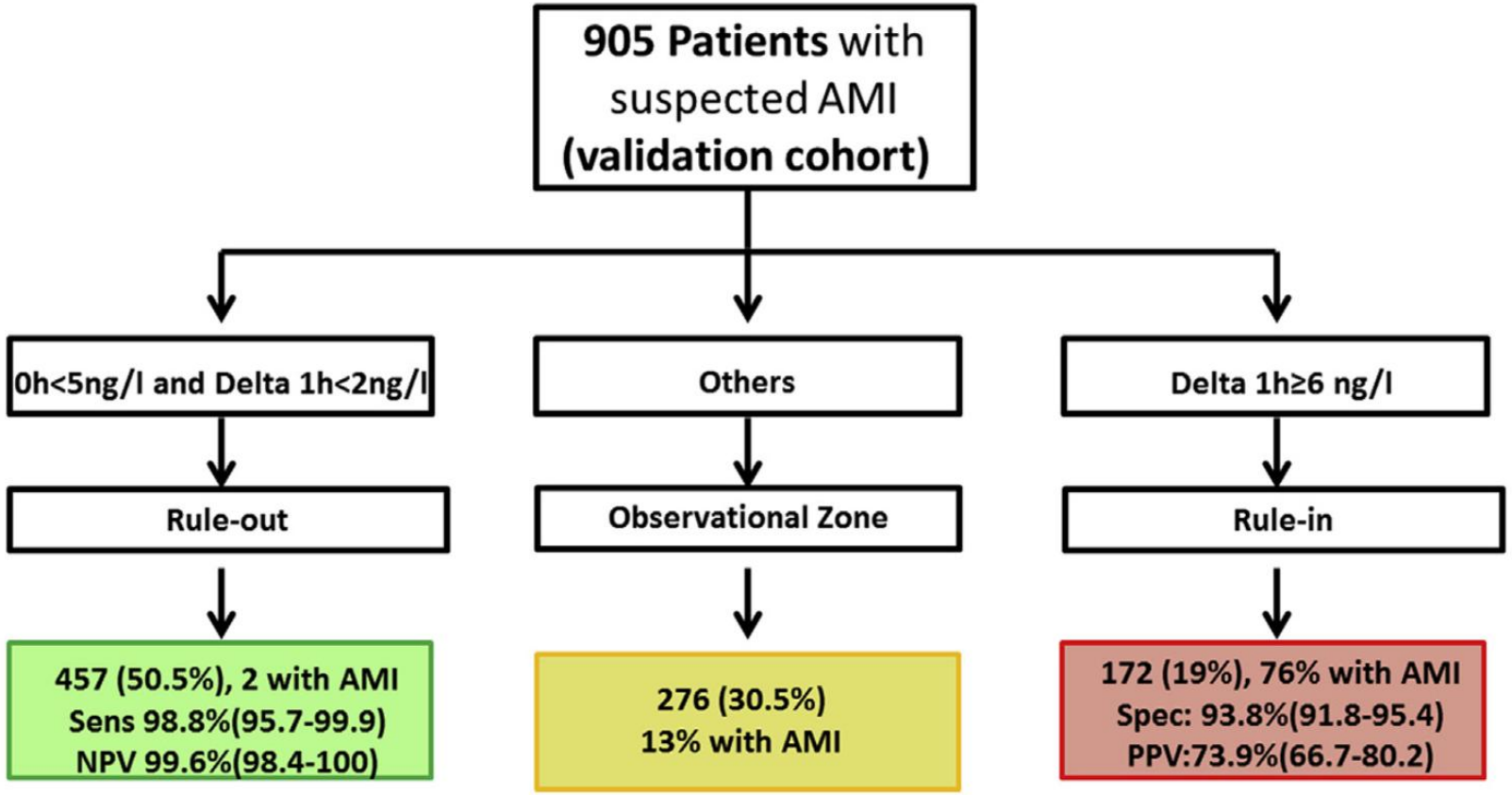


ADP = accelerated diagnostic pathway;
cTn = cardiac troponin; hs = high-sensitivity

Development of a one hour pathway for myocardial infarction

0 h

1 h

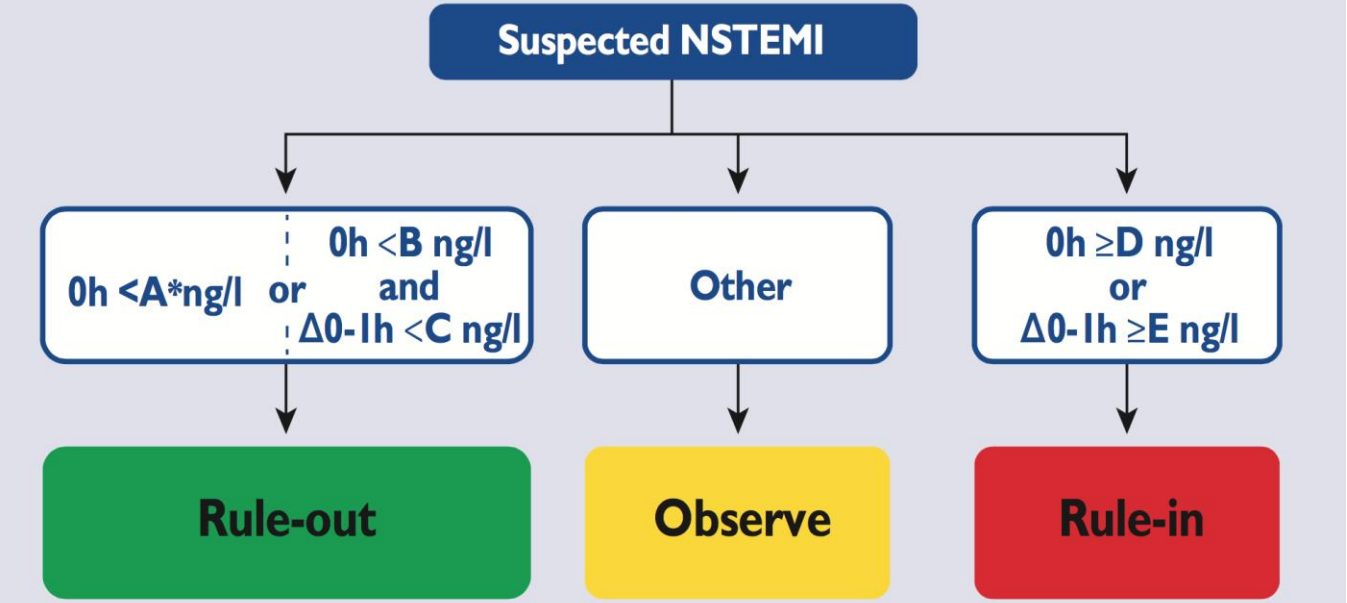


Rubini Gimenez et al. Am J Med. 2015; 128, 861-870

High-sensitivity cardiac troponin at 0 and 1 hours (European Society of Cardiology)

0 h

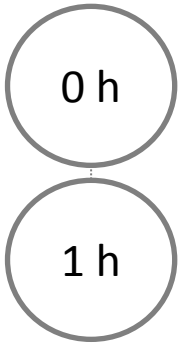
1 h



	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

Mueller C et al. Ann Emerg. Med. 2016;68:76-87;
Eur Heart J. 2016;37:267-315.

High-sensitivity cardiac troponin at 0 and 1 hours (European Society of Cardiology)



	Hs-cTnT algorithm		Hs-cTnI algorithm	
2x2	AMI	Not AMI	AMI	Not AMI
Algorithm did not rule-out	233	564	237	780
Algorithm ruled-out	7	1419	3	1202
Sensitivity (95%CI)	97.1 (94.0 to 98.8)		98.8 (96.4 to 99.7)	
NPV (95%CI)	99.5 (99.0 to 99.8)		99.8 (99.3 to 99.9)	
Proportion Rule-Out (%)	64.2		54.2	

Pickering J et al. Circulation. 2016

Is there a role for ‘scores’ if hs-cTnI is used to risk stratify?

HEART Score

- HISTORY
  2 = Typical
  1 = Atypical
- ECG
  2 = ST depression
  1 = T-wave inversion
- AGE
  2 = ≥65
  1 = ≥45 <65
- RISK FACTORS
  2 = 2 or more
  1 = 1 or more
- TROPONIN
  2 = ≥3 x upper limit
  1 = 1 - 3 x upper limit

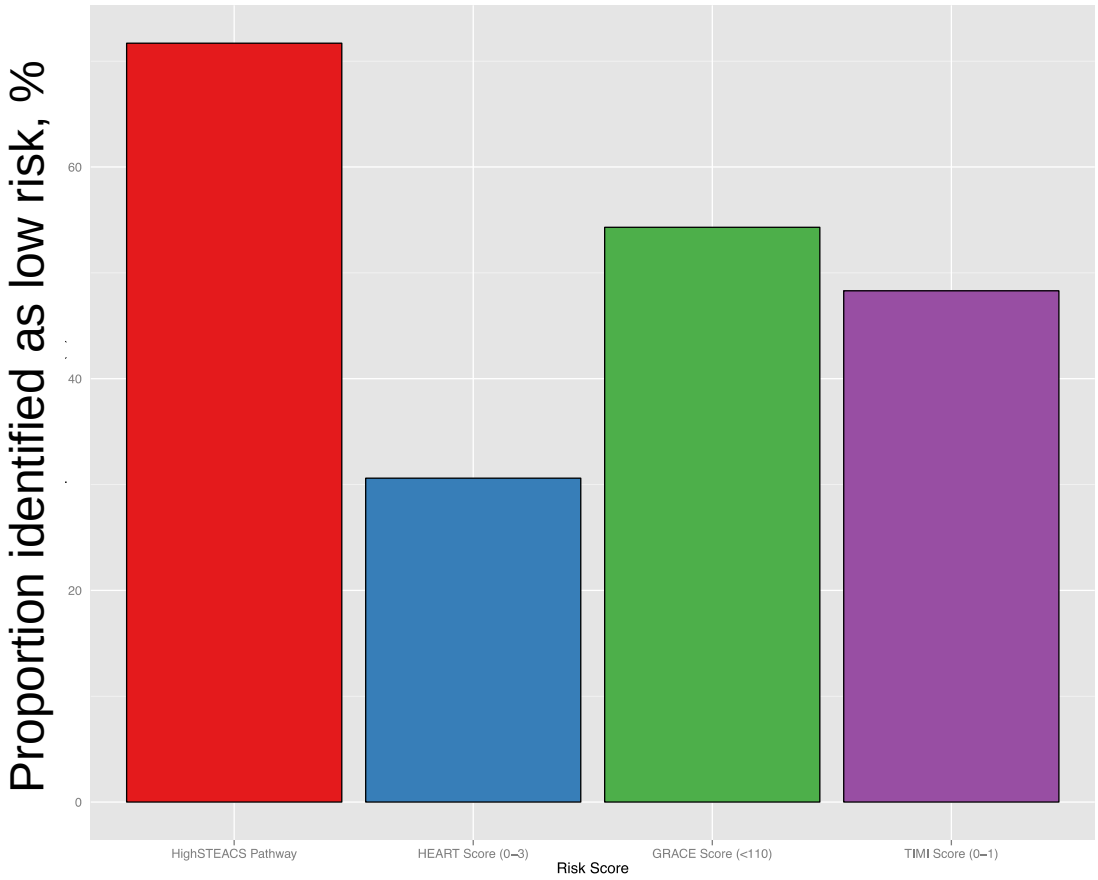
GRACE Score

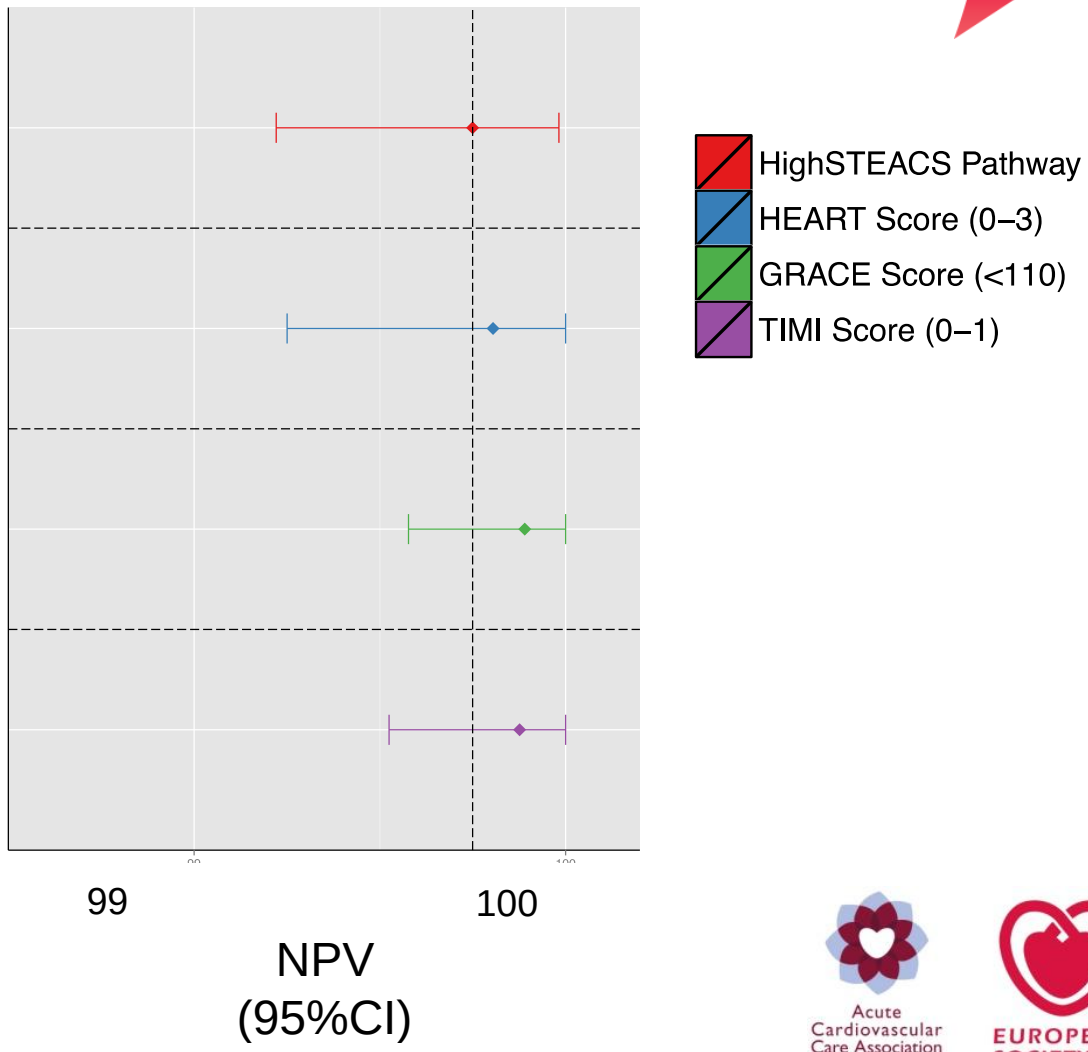
- AGE (Years)
- HEART RATE (bpm)
- SYSTOLIC BP
- CREATININE
- CARDIAC ARREST
- ST CHANGES ON ECG
- ELEVATED TROPONIN
- KILLIP CLASS

TIMI Score

- AGE
  1 = ≥65
- RISK FACTORS
  1 = 3 or more
- CORONARY DISEASE
  1 = Known stenosis
- ASPIRIN USE
  1 = Within 7 days
- SEVERE ANGINA
  1 = x 2 in 24 hours
- ST CHANGES ON ECG
  1 = ≥0.5 mm
- TROPONIN
  1 = >99th centile

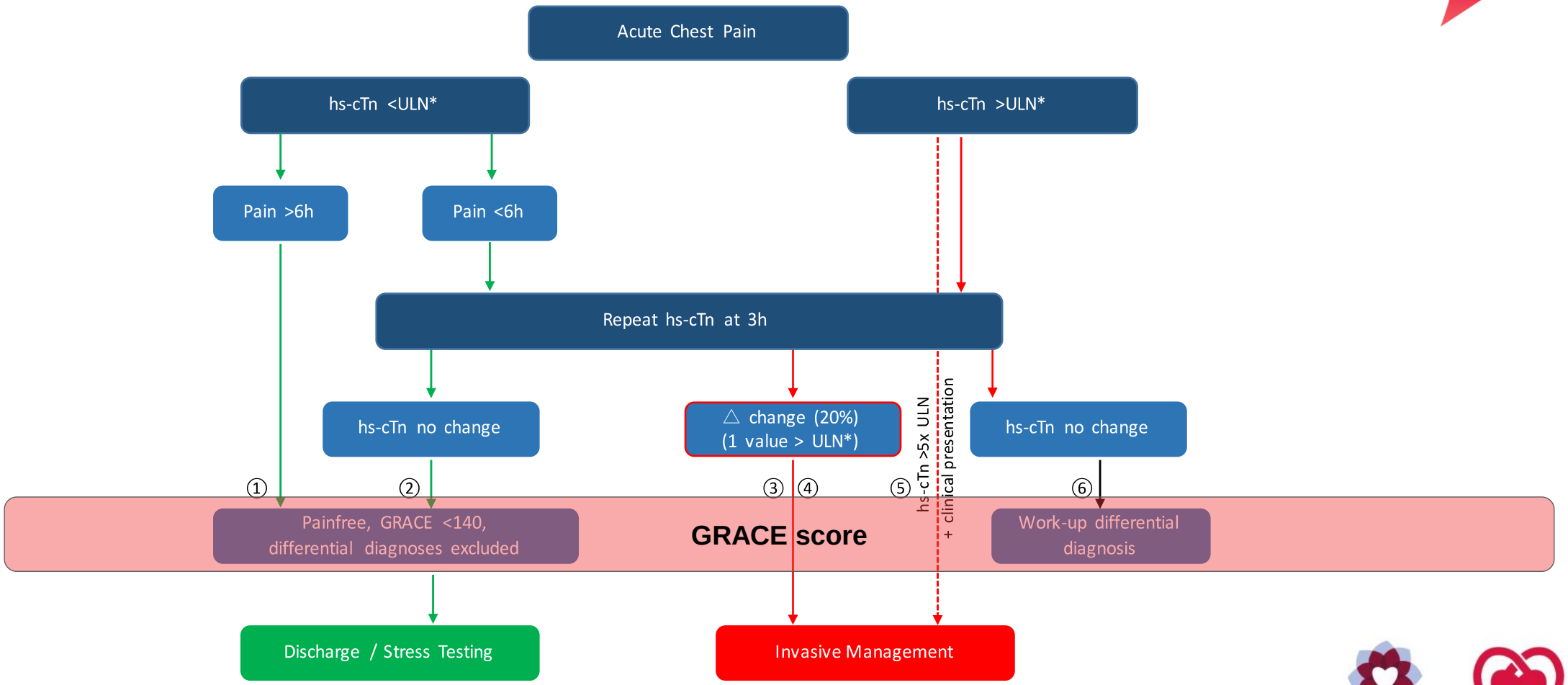
Is there a role for ‘scores’ if hs-cTnI is used to risk stratify?





Chapman et al. 2016 (unpublished)

High-sensitivity cardiac troponin at 0 and 3 hours (European Society of Cardiology)



IMPROVING PATIENT SELECTION FOR CARDIAC TROPONIN TESTING

Charles Jenks' Cells of Life, Jupiter Artland, Edinburgh, Scotland

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Universal definition of myocardial infarction

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1 TYPE 1 MYOCARDIAL INFARCTION

Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

2 TYPE 2 MYOCARDIAL INFARCTION

Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply

3 TYPE 3 MYOCARDIAL INFARCTION

Sudden unexpected cardiac death often with symptoms suggestive of myocardial ischaemia

4 TYPE 4 MYOCARDIAL INFARCTION

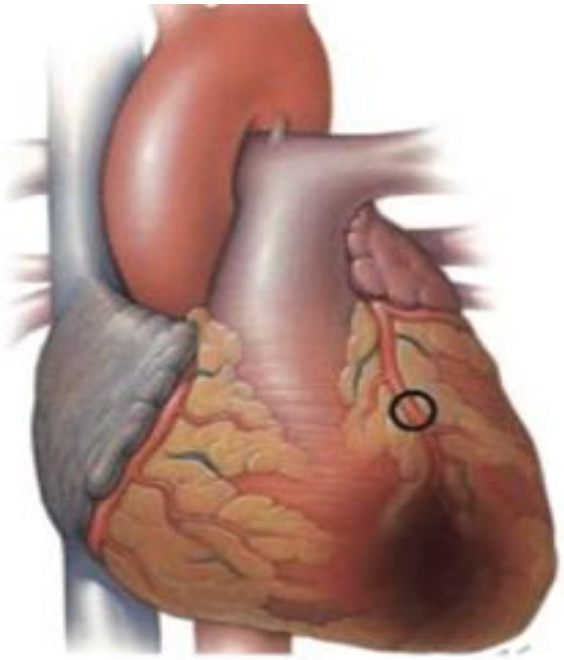
Myocardial infarction associated with percutaneous coronary intervention (4a) or stent thrombosis (4b)

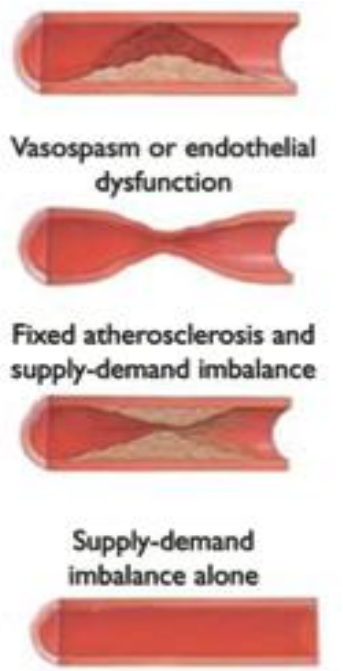
5 TYPE 5 MYOCARDIAL INFARCTION

Myocardial infarction associated with cardiac surgery

Injury MYOCARDIAL INJURY

Multifactorial aetiology; acute or chronic based on change in cardiac troponin concentrations with serial testing





1

2

2

Injury

www.escardio.org/ACCA

JACC 2012;60(16):1581-98

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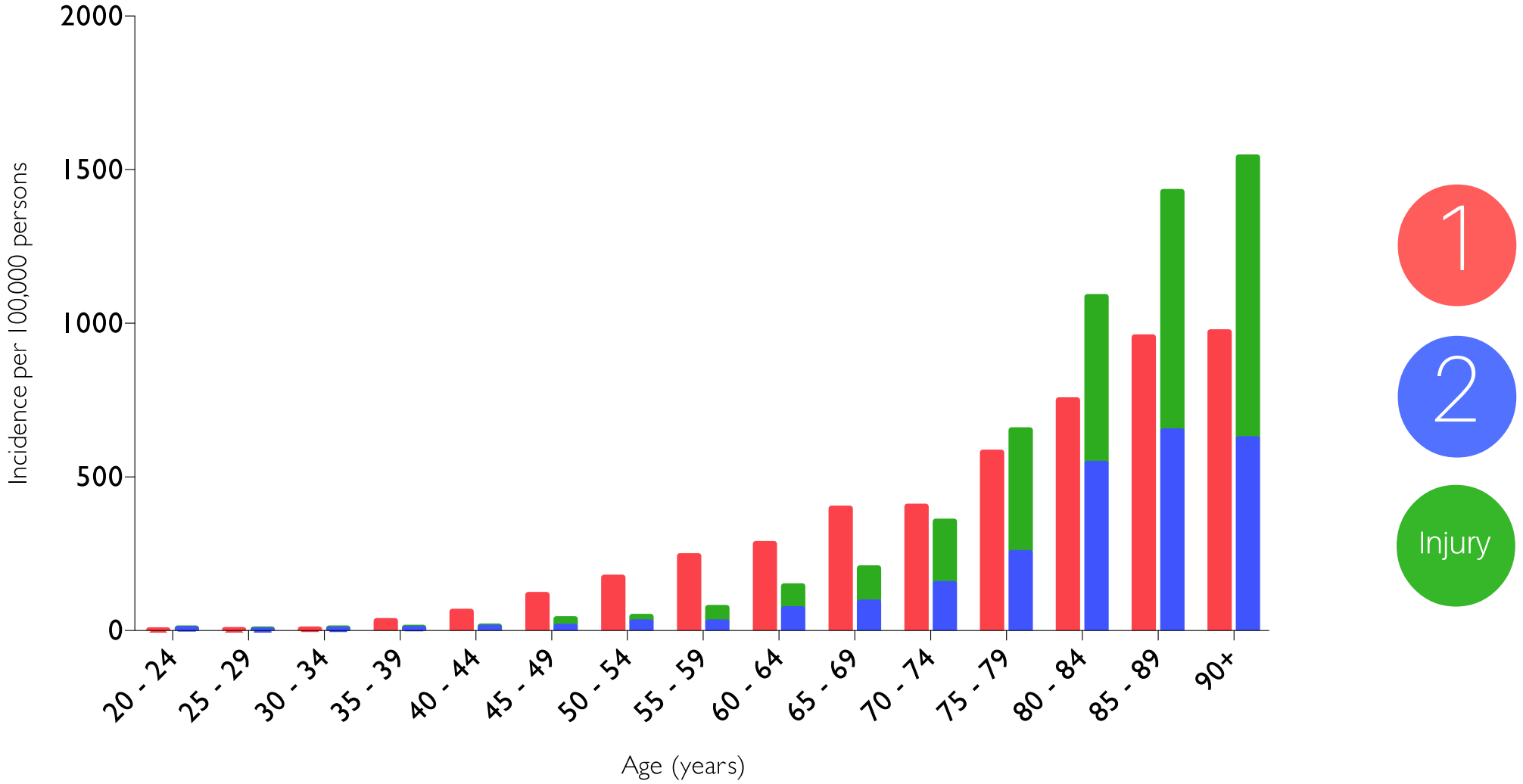
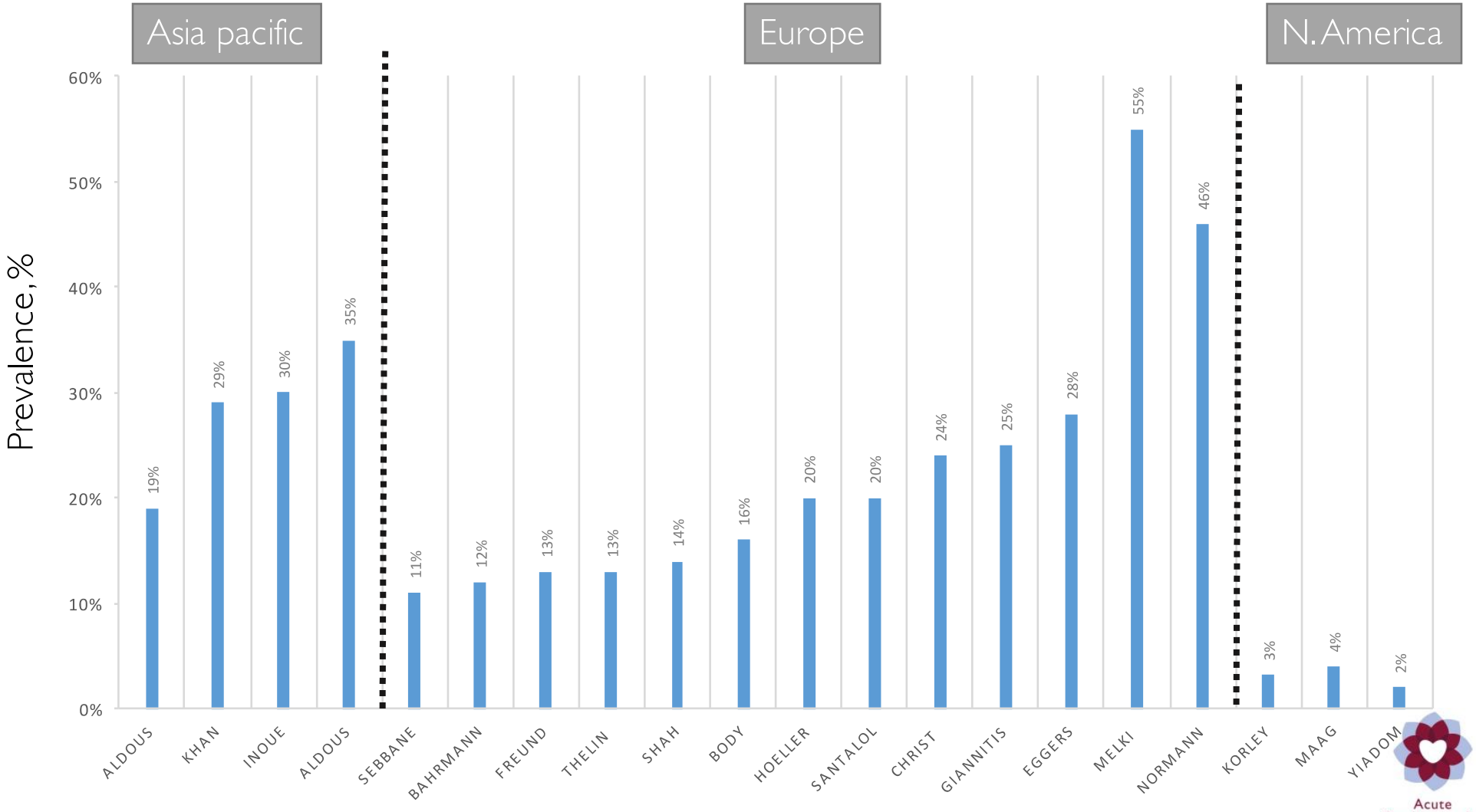
Type 2 myocardial infarction and myocardial injury is common



n = 2,929

Shah AS et al Am J Med. 2015;128:493-501.

Variation in the approach to cardiac troponin testing: impact on the prevalence of type 1 myocardial infarction



How does the approach to cardiac troponin testing effect performance?

Prospective cohort study across two independent consecutive patient cohorts presenting to the Emergency Department

Unselected testing (n=1,054)

Selected testing (n=5,815)

Primary outcome: diagnosis of type 1 myocardial infarction

Shah et al. 2016 (under review)

How does the approach to cardiac troponin testing effect performance?

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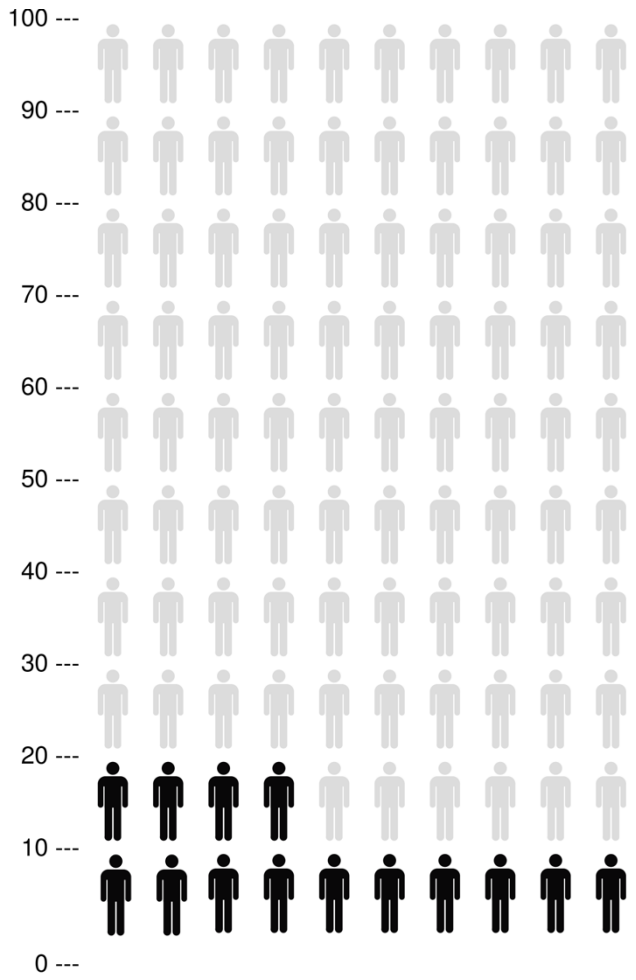
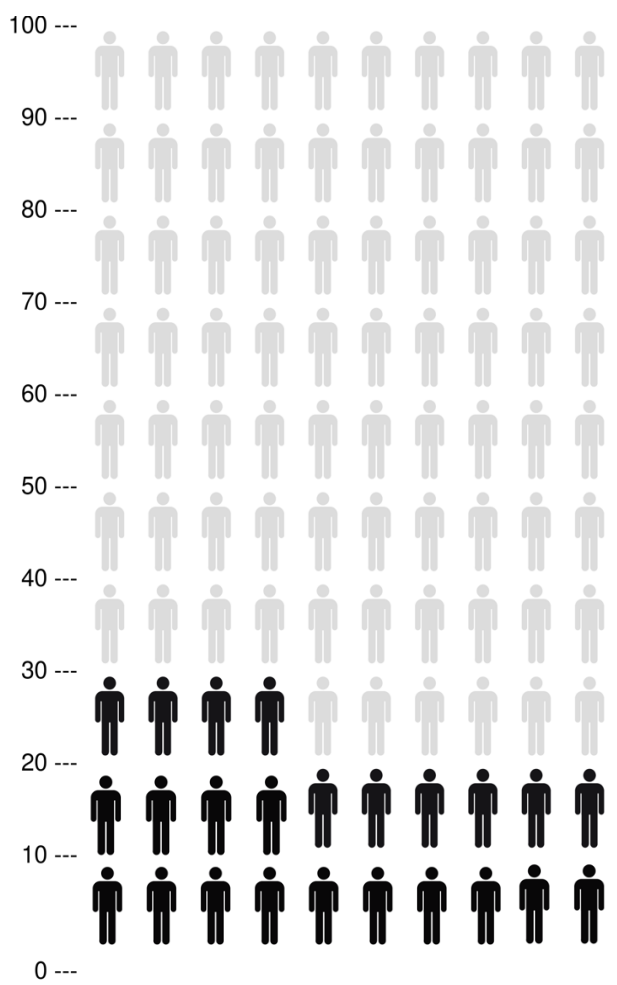
Unselected testing



Selected testing



●>99th centile

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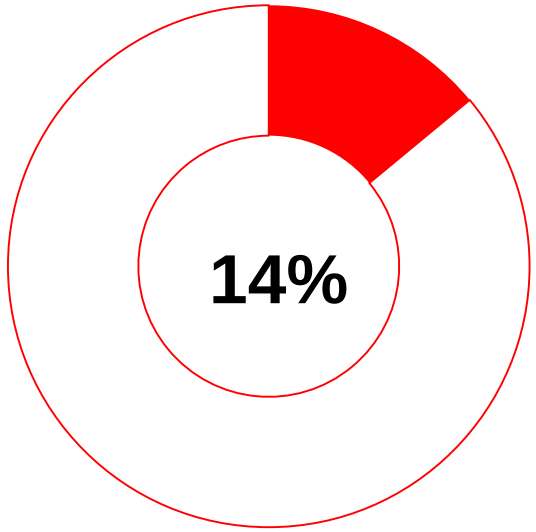
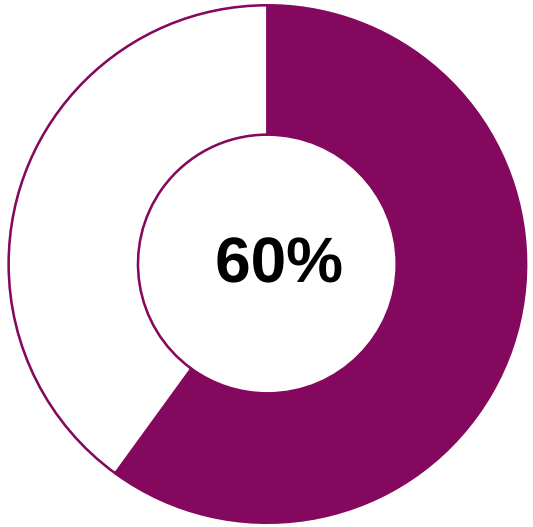
Shah et al. 2016 (under review)

How does the approach to cardiac troponin testing effect performance?

Unselected testing		Selected testing	
Type 1 MI	2%	Type 1 MI	14%
Type 2 MI	1%	Type 2 MI	4%
Myocardial injury	11%	Myocardial injury	6%

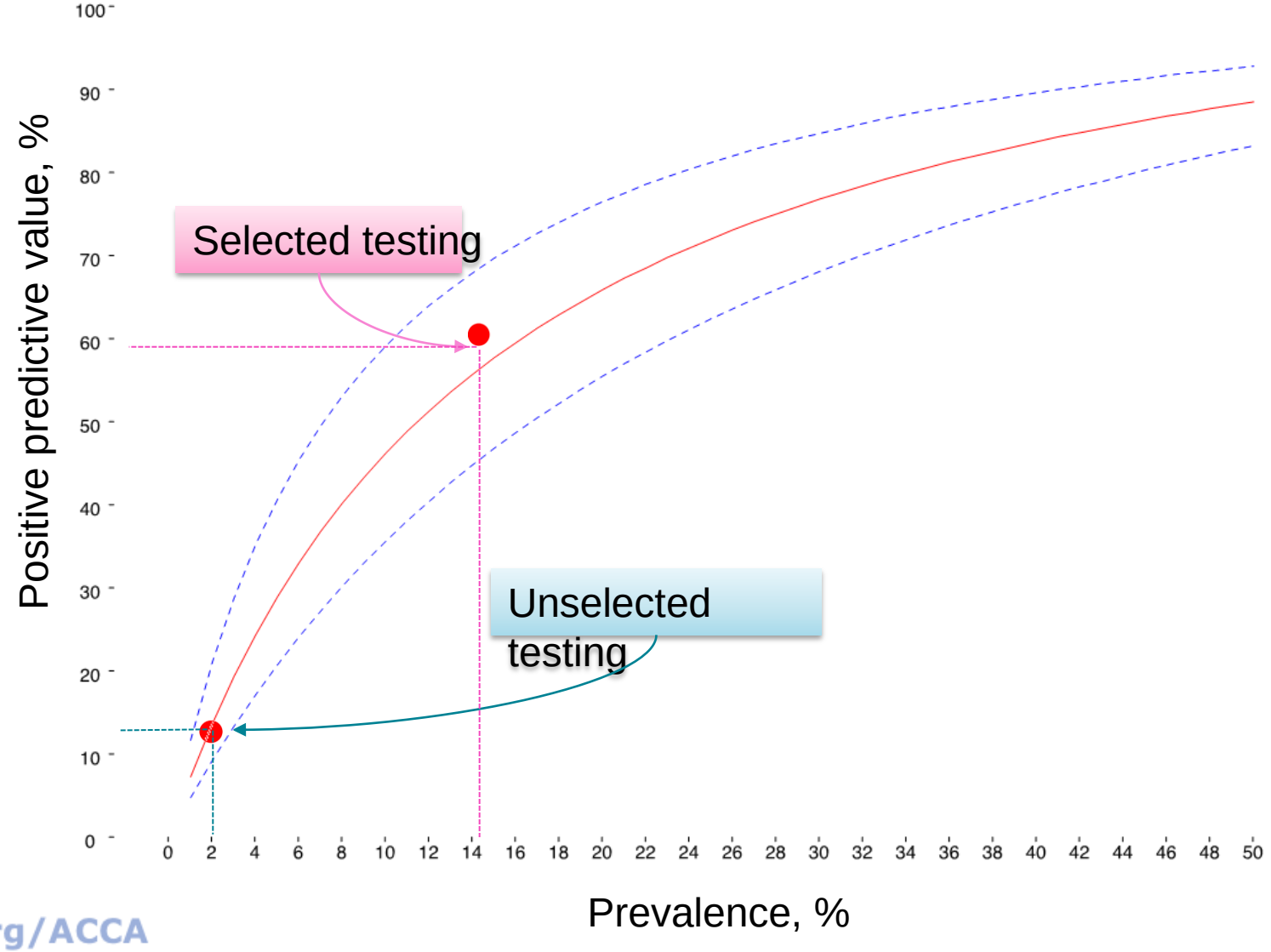
Positive predictive value



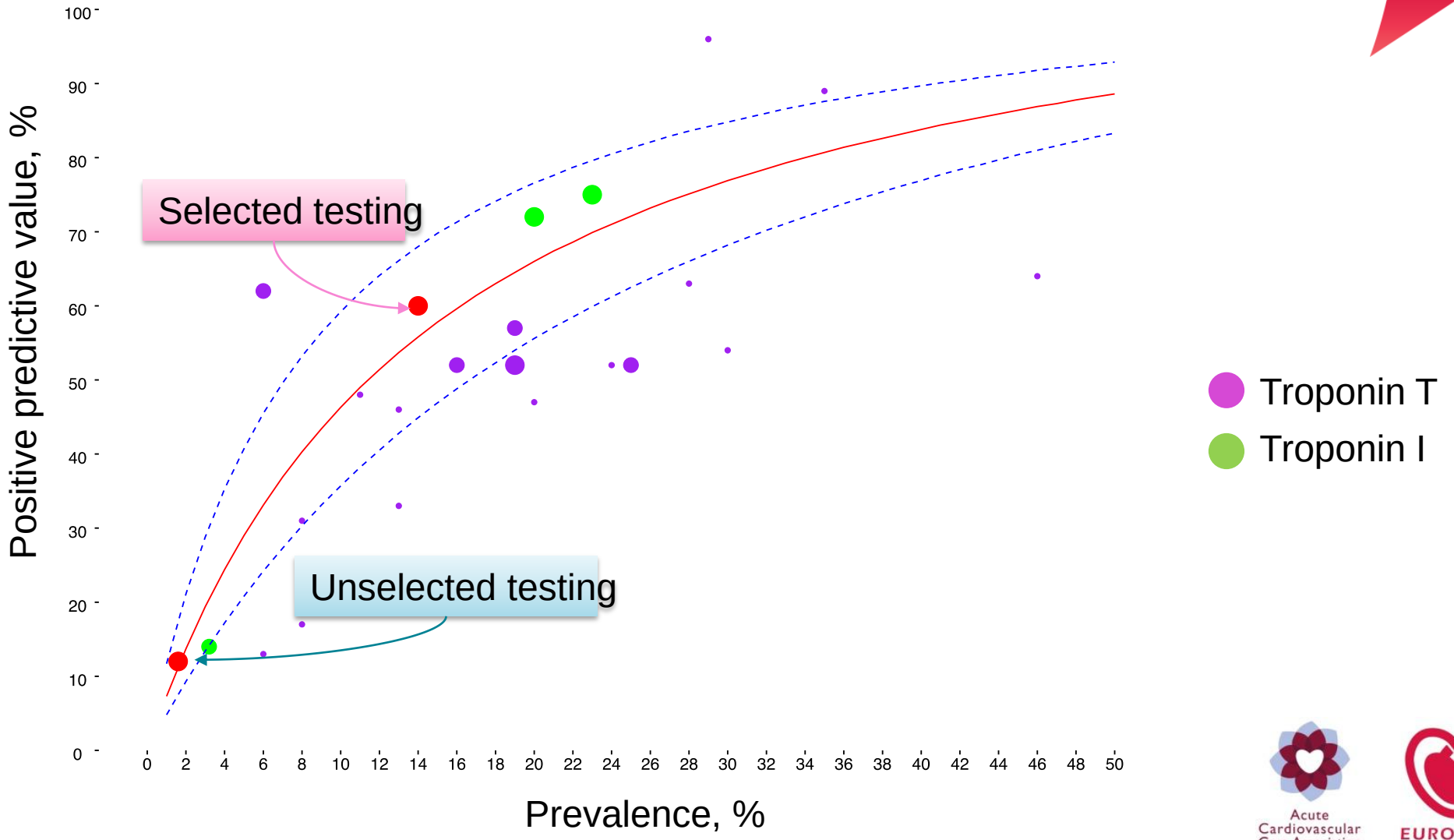


Shah et al. 2016 (under review)

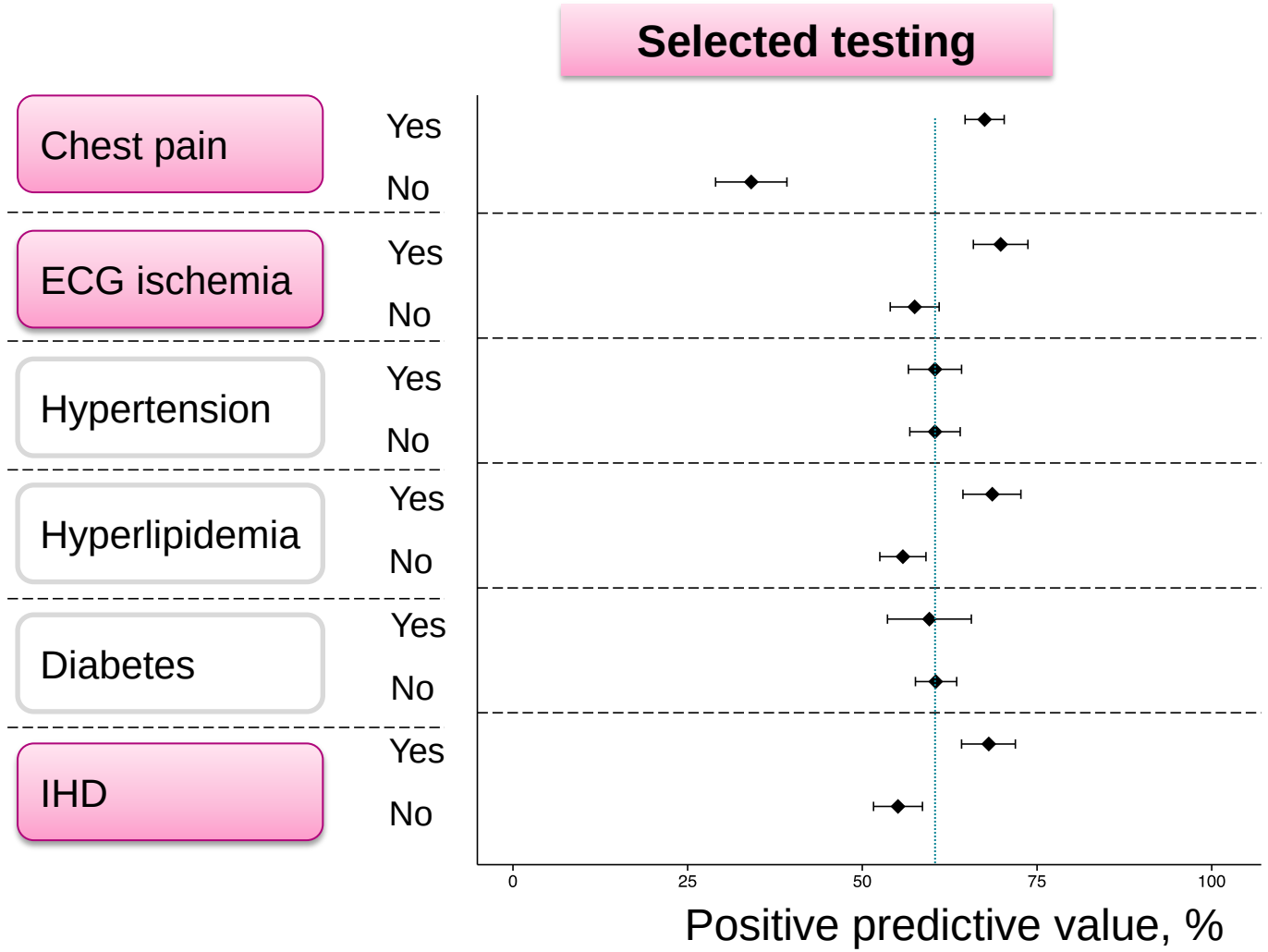
Impact of troponin testing on diagnosis of type 1 myocardial infarction



Impact of troponin testing on diagnosis of type 1 myocardial infarction



How can we improve the positive predictive value of troponin testing?



Shah et al. 2016 (under review)

Conclusions and summary

- High-sensitivity cardiac troponin I assays are changing the way we risk assess and diagnose patients with suspected myocardial infarction
- Patients with very low cardiac troponin concentrations are at low risk and may not require hospital admission or further investigation
- Integration of risk stratification thresholds into early rule out pathways appears to improve safety and permits myocardial infarction to be ruled in or out by 3 hours in ~95% of patients
- The true safety and efficacy of these pathways needs to be confirmed in trials evaluating their implementation in clinical practice

Acknowledgments

British Heart Foundation Special Project Grant (SP/12/10/29922) and Butler Senior Clinical Research Fellowship (FS/16/04/32023)

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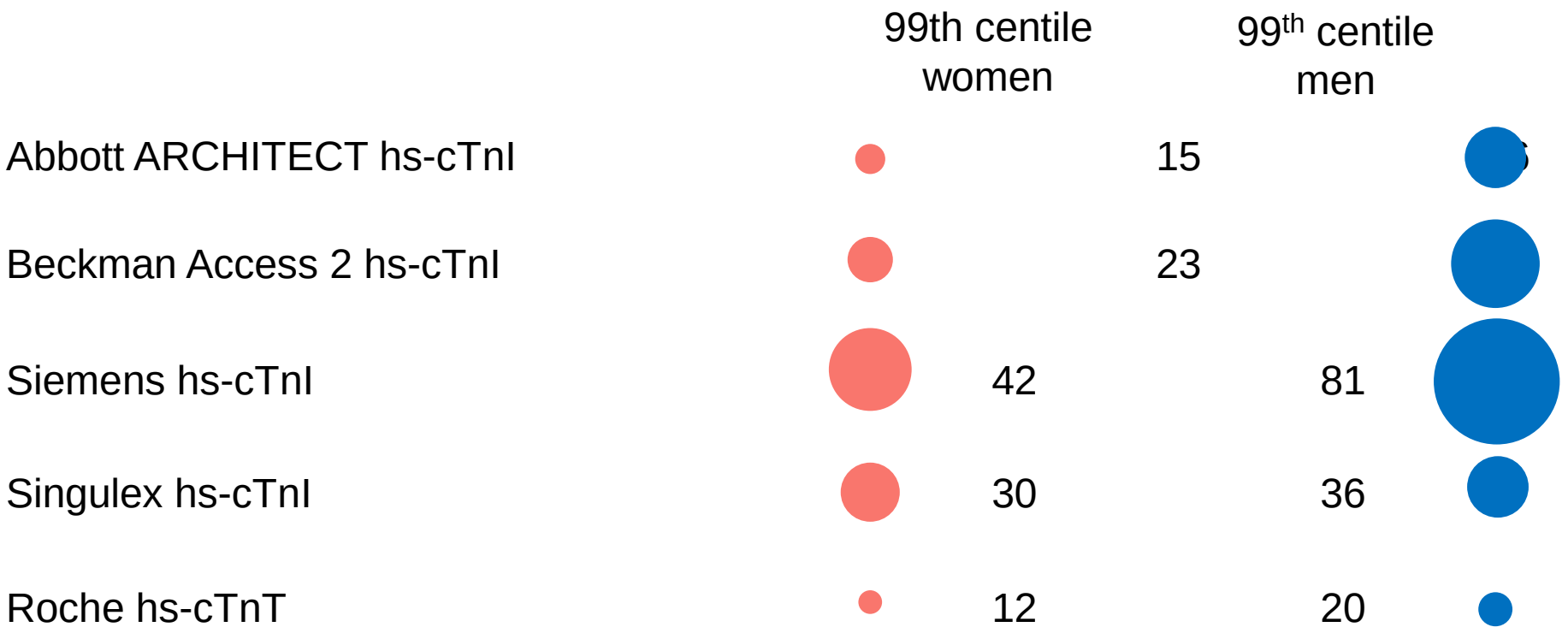
Sex-differences in the 99th centile upper reference limit

Definitive normal range (DNR) study



Reference range of high-sensitivity cardiac troponin assays

Apple FS et al. Clin Chem 2012

THE UNIVERSITY of EDINBURGH

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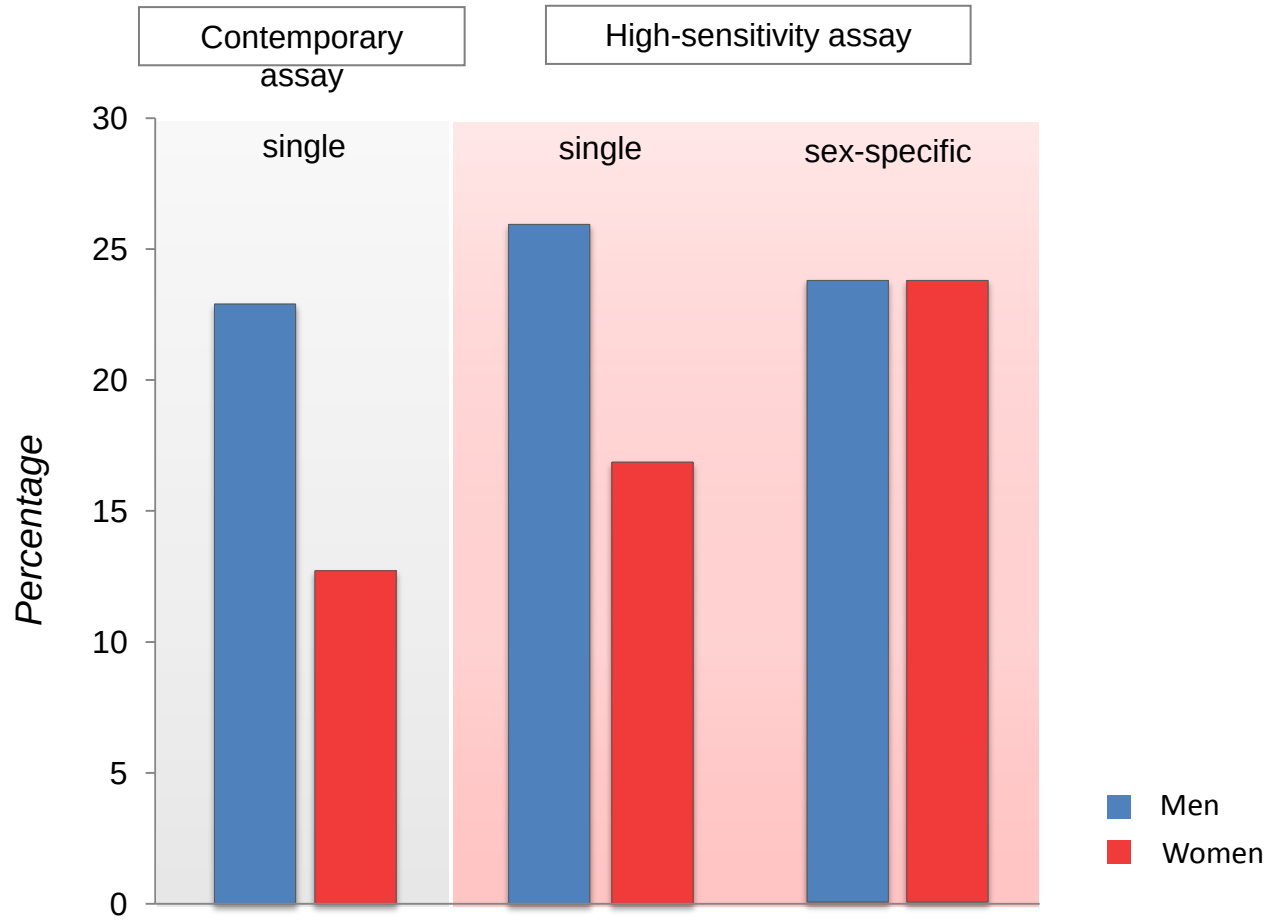
Diagnosis of type 1 myocardial infarction



	Contemporary assay	High-sensitivity assay	
	single	single	sex-specific
Men	77 (69 - 83)	87 (80 - 92)	86 (80 - 91)
Women	47 (38 - 56)	68 (59 - 77)	95 (89 - 98)

SENSITIVITY

Shah AS et al BMJ 2015: 350:h1295.