British Heart Foundation

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

Professor Nicholas L Mills on behalf of the HiSTORIC Investigators
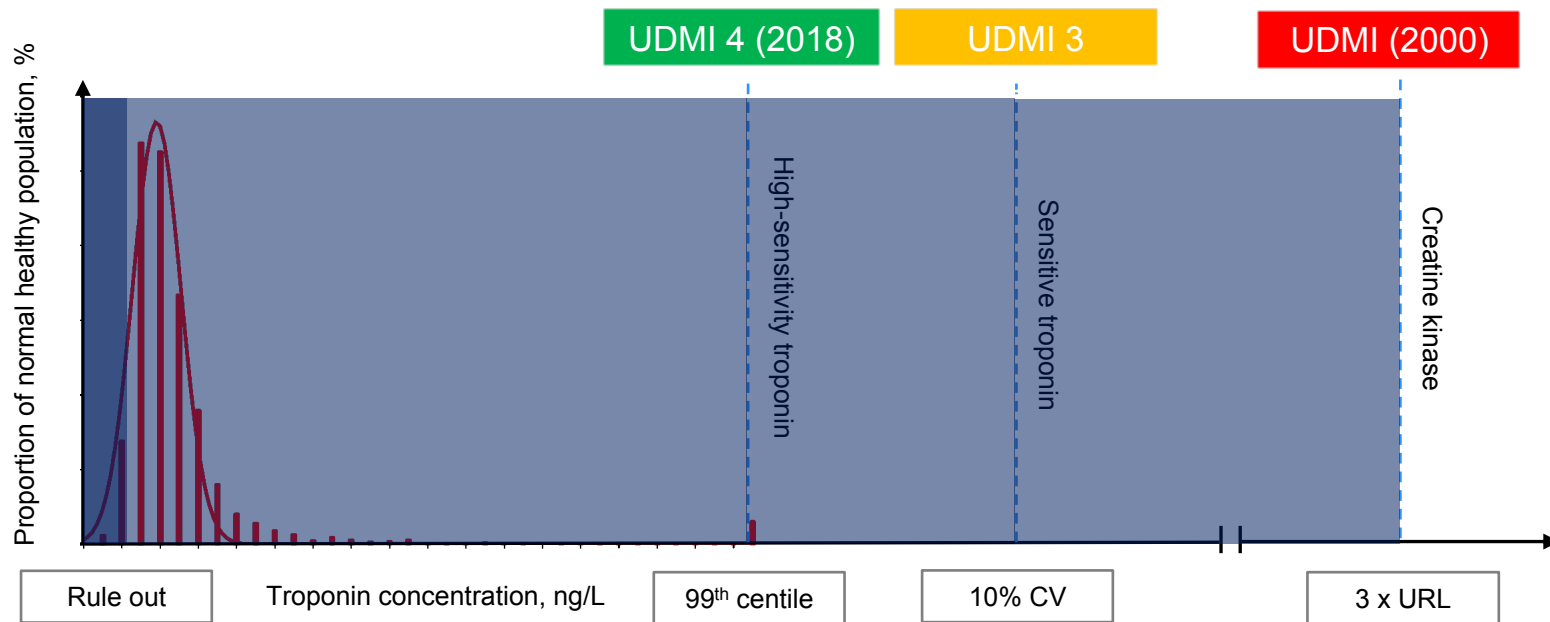
THE UNIVERSITY of EDINBURGH

NHS SCOTLAND

University of Glasgow

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Declaration of interest

- Research contracts (Abbott Diagnostics, Siemens Healthineers)

High-sensitivity cardiac troponins

- Cardiac troponin now measurable in majority of healthy men and women
- Development of novel approaches to **risk stratification** and **early rule-out pathways**

UDMI = Universal Definition of Myocardial Infarction; CV = coefficient of variation; URL = upper reference limit

Separate risk stratification and diagnostic thresholds

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Reference range studies
Expert consensus

Diagnostic threshold >99th centile

DIAGNOSIS

Risk stratification threshold

Diagnostic performance in large prospective cohort studies [1,2]
Meta-analysis of 22,457 from 22 cohorts across 9 countries [3,4]

(1) Lancet 2015;386:2481-8; (2) N Engl J Med. 2019;380:2529-40.
(3) JAMA. 2017;318:1913-24; (3) Ann Intern Med. 2017;166:715-24

Defining the optimal risk stratification threshold to rule out myocardial infarction at presentation

Safety

versus

Effectiveness
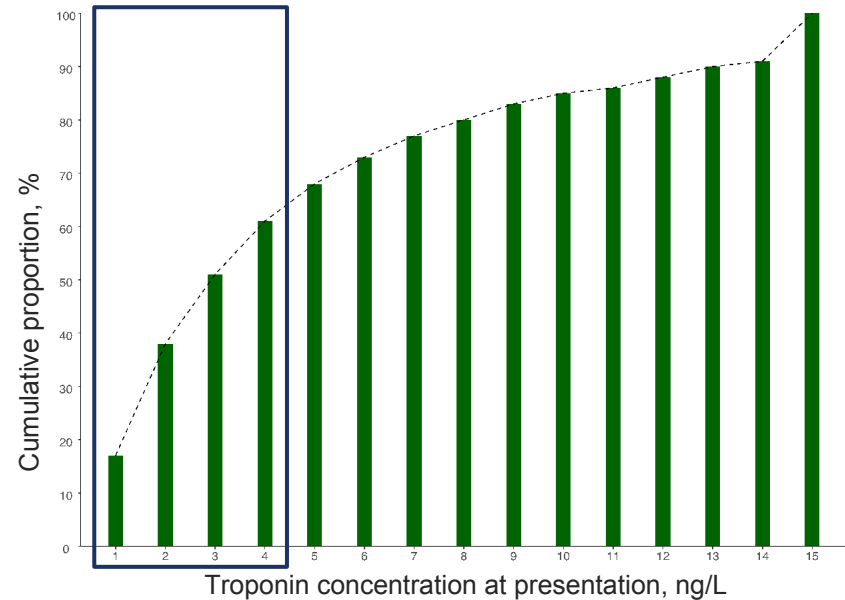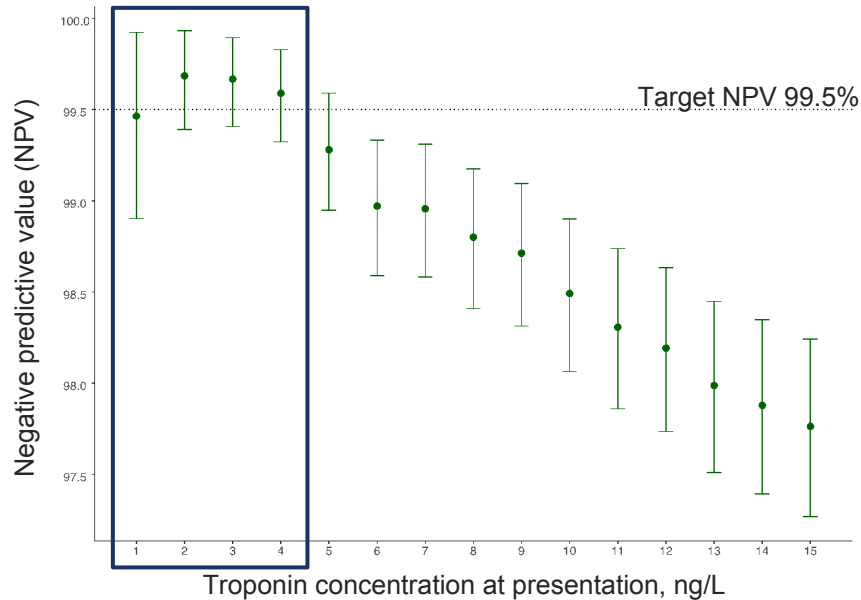
Risk stratification threshold	NPV of ≥99.5% for myocardial infarction or cardiac death at 30 days and Identifies the largest proportion of patients as low-risk

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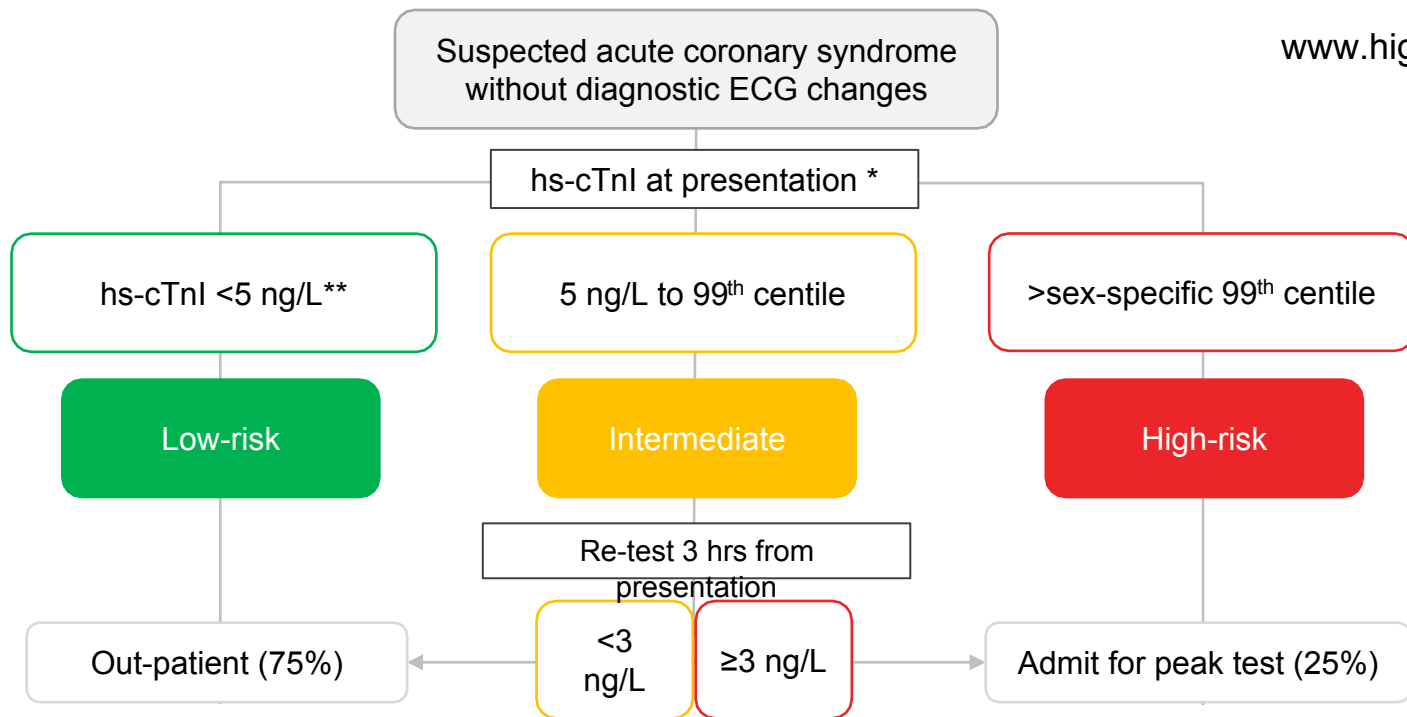# Defining the optimal risk stratification threshold to rule out myocardial infarction at presentation

Risk stratification threshold <5 ng/L

NPV of 99.6% (95% CI 99.3 to 99.8) for myocardial infarction or cardiac death at 30 days

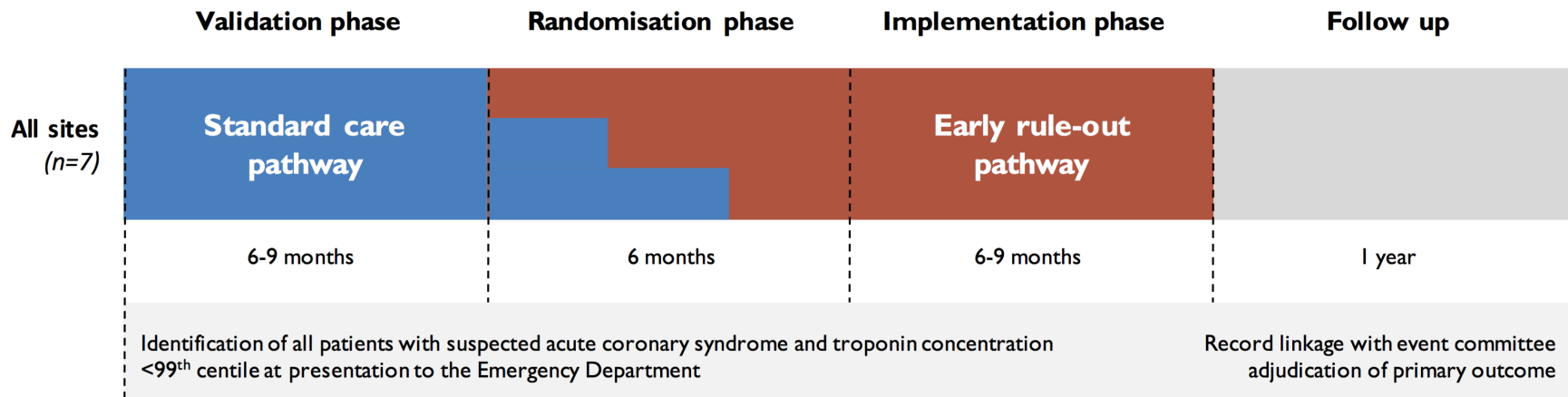Identifies two-thirds of patients as low-risk using single test at presentation

Lancet 2015;386:2481-8

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The High-STEACS early rule-out pathway

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Suspected acute coronary syndrome without diagnostic ECG changes

hs-cTnI at presentation *

hs-cTnI <5 ng/L**	5 ng/L to 99th centile	>sex-specific 99th centile
Low-risk	Intermediate	High-risk

Re-test 3 hrs from presentation

Out-patient (75%) ← <3 ng/L | ≥3 ng/L → Admit for peak test (25%)

*Abbott Diagnostics ARCHITECT$_{STAT}$ high-sensitive cardiac troponin I (16 ng/L women and 34 ng/L men); **Retest if ≤2h from symptoms onset

Screening, enrollment and outcomes via DataLoch™

Screening by electronic order for cardiac troponin
- Suspected acute coronary syndrome
- Presenting symptom
- Time of onset of presenting symptom
- Location of patient
  - Emergency Department
  - Primary Assessment Area
- Date and time of order

CHI number
- Linkage in NHS Safe Haven
  - Unique study ID allocated
  - Anonymised data transferred to analysis platform

Assay platform
- hs-cTnI concentration

Electronic patient record
- Patient demographics
  - Age
  - Sex
  - Ethnicity
  - Deprivation (SIMD)

Investigations
- Haematology (SCI store)
- Clinical chemistry (SCI store)
- Electrocardiography (MUSE)
- Coronary angiography (TOMCAT)

Treatments
- Discharge prescriptions (TrakCare)
- Community prescriptions and dispensing (PIS)

Adjudication of trial outcomes
- Hospitalisations - Scottish Morbidity Record (ICD-10)
- Deaths - National Health Services Central Register (NHSCR)

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Primary and secondary endpoints

Sequential hypothesis testing was used to evaluate two co-primary endpoints for efficacy and safety in an *a priori* defined hierarchical order*

Co-primary endpoints:

Length of stay (efficacy)

Myocardial infarction or cardiac death after discharge at 30 days (safety)

Secondary efficacy endpoint:

Proportion discharged from ED

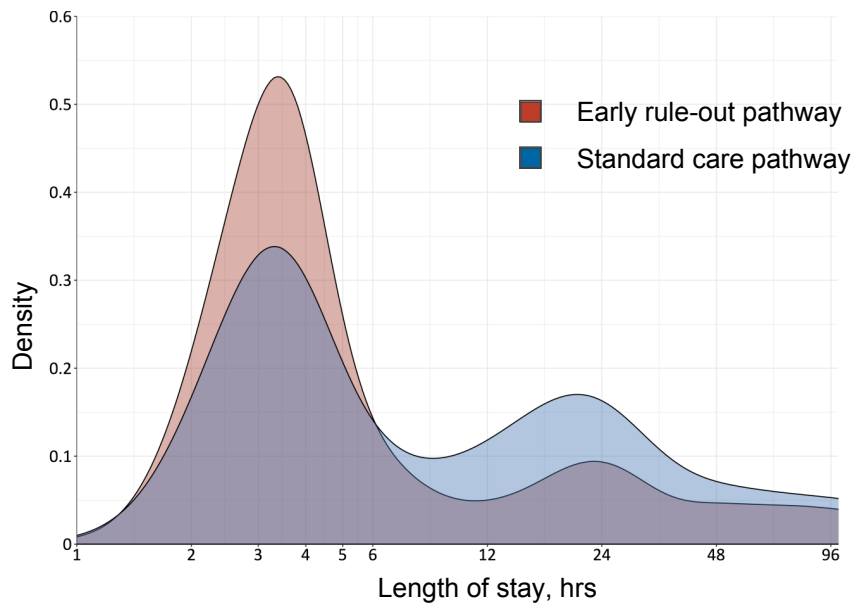**Secondary safety endpoint at 1 year:**

Myocardial infarction or cardiac death, myocardial infarction, cardiac death,

cardiovascular death,   all-cause death, unplanned revascularisation, re-attendance for any

reason

* Outcomes were compared using a linear mixed effects model adjusted for site, season, and time from start of study

Characteristics of the trial population

	All	Standard care	Early rule-out
No. of participants	31,492	14,700	16,792
Age, years	59±17	59±17	59±17
No. of women, %	14,252 (45)	6,575 (45)	7,677 (45)
Chest pain, %	26,590 (84)	12,566 (85)	14,024 (84)
Early presenters (≤2 hrs), %	5,664 (18)	2,859 (19)	2,805 (17)
Known ischaemic heart disease	7,346 (23)	3,834 (26)	3,512 (21)
Diabetes mellitus	1,912 (6)	1,002 (7)	910 (5)
Myocardial ischemia on ECG*	2,037 (13)	1,208 (14)	829 (11)
Presentation hs-cTnI, ng/L	3 [1-6]	3 [1-6]	3 [1-6]
Presentation to first test, mins	66 [45-97]	66 [46-97]	65 [43-97]
Serial (>2) tests	11,904 (38)	6,540 (44)	5,364 (32)

Primary efficacy endpoint

Reduced length of stay by 3.3 hrs

Increased discharge from ED by 57%

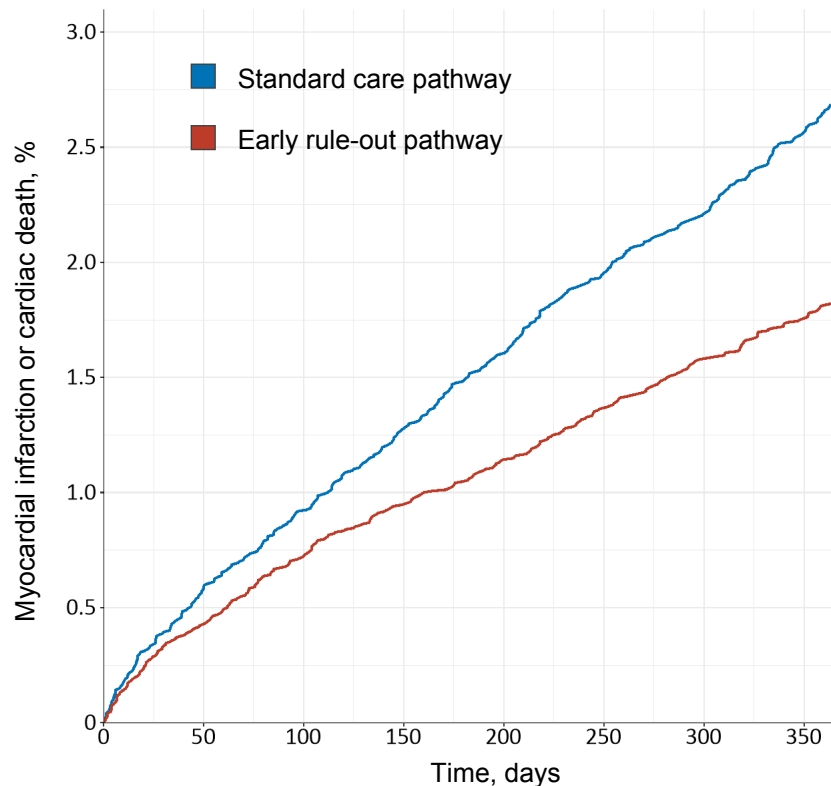|	Standard care	Early rule-out	Ratio (95% CI)*	P-value
No. of participants, n	14,700	16,792		
Length of stay, geo mean (SD) hrs	10.1±4.1	6.8±4.1	0.76 (0.73 to 0.83)	P<0.0001

*Linear mixed effects regression model adjusting for site, season, and time since start of study. **

Primary safety endpoint

	Standard care	Early rule-out
No. of participants	14,700	16,792
30 days	57 (0.4)	56 (0.3)

At 30 days unable to conclude non-inferiority at 0.5% margin (adjusted risk difference 0.02% to 0.70%)*

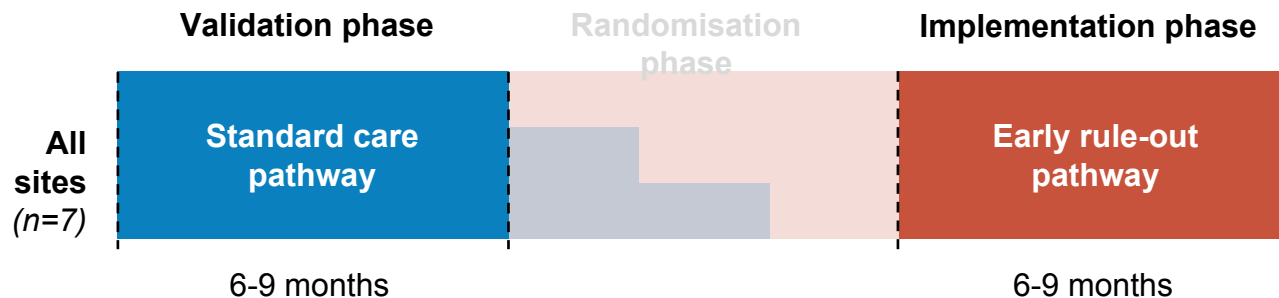At 1 year no evidence of adverse cardiac events (adjusted odds ratio 1.02, 95% CI 0.74 to 1.40)*

*Linear mixed effects regression model adjusting for site, season, and time since start of study

Secondary safety endpoints

	Standard care		Early rule-out		Adjusted odds ratio*	P-value
	n	%	n	%	95% CI	
Secondary outcomes at 1 year						
Myocardial infarction	238	1.6	184	1.1	1.10 (0.72 to 1.68)	P=0.646
Cardiac death	176	1.2	143	0.9	1.07 (0.69 to 1.64)	P=0.771
Cardiovascular death	249	1.7	203	1.2	0.93 (0.66 to 1.32)	P=0.692
All-cause death	852	5.8	868	5.2	0.92 (0.75 to 1.12)	P=0.385
Unplanned revascularisation	119	0.8	103	0.6	0.60 (0.35 to 1.03)	P=0.065
Re-attendance for any reason	5,770	39.2	6,536	38.9	0.93 (0.84 to 1.02)	P=0.112

*Linear mixed effects regression model adjusting for site, season, and time since start of study

# Pre-specified sensitivity analysis – calendar matched

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	Validation phase	**Randomisation phase**	**Implementation phase**
All sites *(n=7)*	**Standard care pathway**		**Early rule-out pathway**
	6-9 months		6-9 months

	Validation	Implementation	Ratio (95% CI)*	P-value for superiority
No. of participants, n	8,840	9,407		
Primary efficacy endpoint				
Length of stay, geo mean (SD) hrs	10.4 (4.1)	6.7 (3.9)	0.65 (0.62 to 0.68)	P<0.0001
Primary safety endpoint				
MI or cardiac death at 30 days, %	49 (0.5%)	27 (0.2%)	0.48 (0.29 to 0.80)	P=0.005
MI or cardiac death at 1 year, %	308 (2.8%)	181 (1.6%)	0.58 (0.47 to 0.71)	P<0.0001

*Linear mixed-effects regression model adjusting for site

Adherence to early rule-out pathway

Adherence to three pre-specified components of the early rule-out pathway was excellent and observed in 86% to 92% of trial participants following implementation
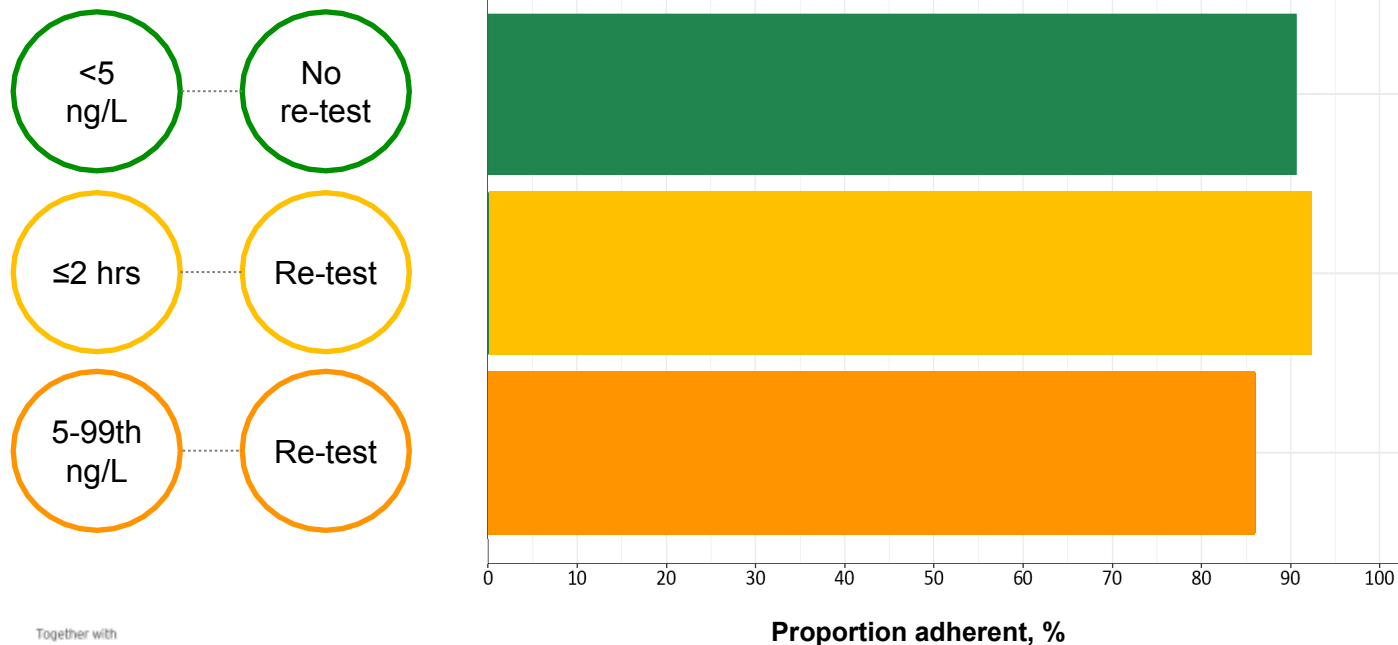
Summary and conclusions

- The HiSTORIC trial evaluated the effectiveness and safety of implementing an early rule-out pathway in 31,493 consecutive patients with suspected acute coronary syndrome

- Our early rule-out pathway, incorporating a single high-sensitivity cardiac troponin test at presentation with separate risk stratification and diagnostic thresholds, was more effective than the 99th centile and serial testing 6-12 hours from symptom onset

- Implementation reduced length of stay by 3.3 hours, and increased the proportion of patients discharged directly from the Emergency Department by 57%

- Whilst unable to conclude non-inferiority at 30 days there was no increase in the primary safety outcome or any secondary safety outcome measure at 1 year

- We conclude that implementation of this early rule-out pathway is both effective and safe

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Supplementary Materials

High-sensitivity Troponin and the Application of Risk Stratification Thresholds in Patients with Suspected Acute Coronary Syndrome

Anda Bularga, Kuan Ken Lee, Stacey Stewart, Amy V. Ferry, Andrew R. Chapman, Lucy Marshall, Fiona E. Strachan, Anne Cruickshank, Donogh Maguire, Colin Berry, Iain Findlay, Anoop S.V. Shah, David E. Newby, Nicholas L. Mills, and Atul Anand

on behalf of the High-STEACS Investigators

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