High-Sensitivity cardiac Troponin at presentation to Rule out myocardial Infarction (HiSTORIC): a stepped-wedge cluster-randomised controlled trial

Professor Nicholas L Mills on behalf of the HiSTORIC Investigators
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

Reference range studies
Expert consensus

Diagnostic performance in large prospective cohort studies

Meta-analysis of 22,457 from 22 cohorts across 9 countries


#HiSTORIC
@HighSTEACS
#ESC2019
Defining the optimal risk stratification threshold to rule out myocardial infarction at presentation

NPV of $\geq 99.5\%$ for myocardial infarction or cardiac death at 30 days and identifies the largest proportion of patients as low-risk.

Lancet 2015;386:2481-8

@HighSTEACS
#HiSTORIC
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

@HighSTEACS
#HiSTORIC
#ESC2019
The High-STEACS early rule-out pathway

Suspected acute coronary syndrome without diagnostic ECG changes

hs-cTnI at presentation *

hs-cTnI <5 ng/L**
- Low-risk
  - Out-patient (75%)

5 ng/L to 99th centile
- Intermediate
  - Re-test 3 hrs from presentation
    - <3 ng/L
    - ≥3 ng/L

>sex-specific 99th centile
- High-risk
  - 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
Aim: To evaluate the efficacy and safety of implementing the High-STEACS early rule-out pathway in consecutive patients with suspected acute coronary syndrome.

*Standard care rule-out if hs-cTnI <99th centile at presentation if >6 hrs symptoms, or serial testing 6-12 hrs from symptom onset.

www.clinicaltrials.gov NCT01852123
Screening, enrollment and outcomes via DataLoch™

- Suspected acute coronary syndrome
- Presenting symptom
- Time of onset of presenting symptom
- Screening by electronic order for cardiac troponin
  - Location of patient
  - Date and time of order
  - Emergency Department
  - Primary Assessment Area
  - Linkage in NHS Safe Haven
  - Unique study ID allocated
  - Anonymised data transferred to analysis platform

- CHI number
- hs-cTnI concentration
- Assay platform
- Blood tests (SCI store)
- Haematology (SCI store)
- Clinical chemistry (SCI store)
- Electrocardiography (MUSE)
- Coronary angiography (TOMCAT)

- Investigations
- Electronic patient record
  - Discharge prescriptions (TrakCare)
  - Community prescriptions and dispensing (PIS)
  - Patient demographics
  - Age
  - Sex
  - Ethnicity
  - Deprivation (SIMD)

- Treatments
  - Deaths - National Health Services Central Register (NHSCR)
  - Adjudication of trial outcomes
  - Hospitalisations - Scottish Morbidity Record (ICD-10)
31,492 consecutive patients with suspected acute coronary syndrome and hs-cTnI concentrations <99th centile at presentation were enrolled between Dec 2014 and Dec 2016.

Eligible participants with hs-cTnI <99th centile (n=31,696)

Included participants (n=31,492)

Excluded for cardiac arrest or STEMI (n=154)

Validation phase (n=10,724)

Randomization phase (n=9,336)

Implementation phase (n=11,432)

Standard-care pathway (n=14,700)

Early rule-out pathway (n=16,792)
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

<table>
<thead>
<tr>
<th>All</th>
<th>Standard care</th>
<th>Early rule-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>31,492</td>
<td>14,700</td>
</tr>
<tr>
<td>Age, years</td>
<td>59±17</td>
<td>59±17</td>
</tr>
<tr>
<td>No. of women, %</td>
<td>14,252 (45)</td>
<td>6,575 (45)</td>
</tr>
<tr>
<td>Chest pain, %</td>
<td>26,590 (84)</td>
<td>12,566 (85)</td>
</tr>
<tr>
<td>Early presenters (≤2 hrs), %</td>
<td>5,664 (18)</td>
<td>2,859 (19)</td>
</tr>
<tr>
<td>Known ischaemic heart disease</td>
<td>7,346 (23)</td>
<td>3,834 (26)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1,912 (6)</td>
<td>1,002 (7)</td>
</tr>
<tr>
<td>Myocardial ischemia on ECG*</td>
<td>2,037 (13)</td>
<td>1,208 (14)</td>
</tr>
<tr>
<td>Presentation hs-cTnI, ng/L</td>
<td>3 [1-6]</td>
<td>3 [1-6]</td>
</tr>
<tr>
<td>Serial (≥2) tests</td>
<td>11,904 (38)</td>
<td>6,540 (44)</td>
</tr>
</tbody>
</table>
**Primary efficacy endpoint**

- **Reduced length of stay by 3.3 hrs**
- **Increased discharge from ED by 57%**

<table>
<thead>
<tr>
<th></th>
<th>Standard care</th>
<th>Early rule-out</th>
<th>Ratio (95% CI)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants, n</td>
<td>14,700</td>
<td>16,792</td>
<td></td>
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</tr>
<tr>
<td>Length of stay, geo mean (SD) hrs</td>
<td>10.1±4.1</td>
<td>6.8±4.1</td>
<td>0.76 (0.73 to 0.83)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

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

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

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**Early rule-out pathway**

**Standard care pathway**

<table>
<thead>
<tr>
<th>No. of participants</th>
<th>Standard care</th>
<th>Early rule-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>57 (0.4)</td>
<td>56 (0.3)</td>
</tr>
<tr>
<td>1 year</td>
<td>396 (2.7)</td>
<td>307 (1.8)</td>
</tr>
</tbody>
</table>

**Primary safety endpoint**

- 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

<table>
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<th>Early rule-out</th>
<th>Adjusted odds ratio*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
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<tr>
<td><strong>Secondary outcomes at 1 year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>238</td>
<td>1.6</td>
<td>184</td>
<td>1.1</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>176</td>
<td>1.2</td>
<td>143</td>
<td>0.9</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>249</td>
<td>1.7</td>
<td>203</td>
<td>1.2</td>
</tr>
<tr>
<td>All-cause death</td>
<td>852</td>
<td>5.8</td>
<td>868</td>
<td>5.2</td>
</tr>
<tr>
<td>Unplanned revascularisation</td>
<td>119</td>
<td>0.8</td>
<td>103</td>
<td>0.6</td>
</tr>
<tr>
<td>Re-attendance for any reason</td>
<td>5,770</td>
<td>39.2</td>
<td>6,536</td>
<td>38.9</td>
</tr>
</tbody>
</table>

*Linear mixed effects regression model adjusting for site, season, and time since start of study*
Pre-specified sensitivity analysis – calendar matched

<table>
<thead>
<tr>
<th>Validation phase</th>
<th>Randomisation phase</th>
<th>Implementation phase</th>
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<tbody>
<tr>
<td><strong>Standard care</strong></td>
<td></td>
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<tr>
<td>path</td>
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<td></td>
</tr>
<tr>
<td>All sites</td>
<td></td>
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<tr>
<td>(n=7)</td>
<td></td>
<td></td>
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<tr>
<td>6-9 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Early rule-out</strong></td>
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<td></td>
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<tr>
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<th>Ratio (95% CI)*</th>
<th>P-value for superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants, n</td>
<td>8,840</td>
<td>9,407</td>
<td></td>
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<tr>
<td><strong>Primary efficacy endpoint</strong></td>
<td></td>
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<tr>
<td>Length of stay, geo mean (SD) hrs</td>
<td>10.4 (4.1)</td>
<td>6.7 (3.9)</td>
<td>0.65 (0.62 to 0.68)</td>
<td>P&lt;0.0001</td>
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<tr>
<td><strong>Primary safety endpoint</strong></td>
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<tr>
<td>MI or cardiac death at 30 days, %</td>
<td>49 (0.5%)</td>
<td>27 (0.2%)</td>
<td>0.48 (0.29 to 0.80)</td>
<td>P=0.005</td>
</tr>
<tr>
<td>MI or cardiac death at 1 year, %</td>
<td>308 (2.8%)</td>
<td>181 (1.6%)</td>
<td>0.58 (0.47 to 0.71)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

*Primary efficacy endpoint:
Length of stay, geo mean (SD) hrs

*Primary safety endpoint:
MI or cardiac death at 30 days, %
MI or cardiac death at 1 year, %
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.
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.
Acknowledgements

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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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