High-Sensitive Troponin in the Evaluation of patients with Acute Coronary Syndrome (High-STEACS):
a stepped-wedge cluster-randomised controlled trial

Professor Nicholas L Mills on behalf of the High-STEACS Investigators
Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (I have received honoraria from Abbott Diagnostics, Singulex and Roche all of whom manufacture cardiac troponin assays )
- Research contracts (The HighSTEACS trial is funded in full by a research charity, the British Heart Foundation, but Abbott Diagnostics provided reagent without charge to support the trial. )
"The term myocardial infarction should be used when there is acute myocardial injury with clinical evidence of myocardial ischaemia and with detection of a rise and/or fall of cardiac troponin values with at least one value above the **99th centile upper reference limit** of a healthy population"
High-Sensitivity Cardiac Troponins

- Greater analytical precision at very low concentrations (<10% coefficient of variation at 99th centile)
- Cardiac troponin measurable in >50% of healthy men and women
- UDMI 4 recommends use of a sex-specific 99th centile upper reference limit as the diagnostic threshold

UDMI = Universal Definition of Myocardial Infarction; CV = coefficient of variation; URL = upper reference limit
~2,000 hospitals across 5 continents in 23 high and low to middle income countries

41% of hospitals use high-sensitivity cardiac troponin assays
18% use a sex-specific 99th centile threshold
Will the Introduction of High-Sensitivity Cardiac Troponin Testing Improve Clinical Outcomes in Patients with Suspected Acute Coronary Syndrome?
**Hypothesis:** Implementation of high-sensitivity cardiac troponin I assay and a sex-specific 99th centile diagnostic threshold will reduce subsequent myocardial infarction or cardiovascular death at one year in patients with suspected acute coronary syndrome.
Contemporary and High-Sensitivity Cardiac Troponin Assays

Both contemporary (standard care) and high-sensitivity (intervention) assays measured in all patients throughout both phases of the trial.

**Validation phase:** Contemporary troponin I (cTnI) assay (Abbott) used to guide care
Diagnostic threshold = 40 or 50 ng/L (10% CV)

**Implementation phase:** High-sensitivity troponin I (hs-cTnI) assay (Abbott) used to guide care
Diagnostic threshold = 16 ng/L (♀), 34 ng/L (♂) (99th)
Stratification by Cardiac Troponin Concentration

Patients grouped by peak high-sensitivity (hs-cTnI) and contemporary (cTnI) troponin concentrations

- **No injury**: hs-cTnI <99th centile
  - >16 ng/L (♀), 34 ng/L (♂)

- **Reclassified**: hs-cTnI >99th centile AND cTnI negative

- **Identified**: cTnI positive
  - (>40 or 50 ng/L)

hs-cTnI = high-sensitivity cardiac troponin I; cTnI = contemporary cardiac troponin I
Primary and Secondary Endpoints

Primary end point
Myocardial infarction or cardiovascular death at one year

Secondary efficacy end-points
Durations of stay
Myocardial infarction
Cardiovascular death
All-cause death
Unplanned coronary revascularisation

Secondary safety end-points
Major and minor haemorrhage
Recurrent hospitalization excluding acute coronary syndrome
Non-cardiovascular death

Outcomes were compared in reclassified patients admitted during the validation and implementation phases using a linear mixed effects model adjusted for patient covariates, site, season, and time.
Adjudication of Index Diagnosis and Endpoints According to the Universal Definition

- **ADJUDICATED DIAGNOSIS**
  1. Type 1 myocardial infarction
  2. Type 2 myocardial infarction
  3. Type 3 myocardial infarction
  4. Type 4a and 4b myocardial infarction
  5. Type 5 myocardial infarction
  - Myocardial injury
  - Unable to classify

* Electrocardiograms reviewed with summary of investigation including radiology results, stress testing and coronary angiography

---

ESC Congress Munich 2018

www.clinicaltrials.gov number: NCT01852123 📚@HighSTEACS #ESC2018
### Characteristics of the High-STEACS Trial Population

48,282 consecutive patients with suspected acute coronary syndrome (61±17 years, 47% women)*

<table>
<thead>
<tr>
<th>No myocardial injury</th>
<th>Reclassified by hs-cTnI</th>
<th>Identified by c-TnI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>37,922 (79%)</td>
<td>1,771 (17%)</td>
</tr>
<tr>
<td>Age</td>
<td>58±17</td>
<td>75±14</td>
</tr>
<tr>
<td>No. of women</td>
<td>17,571 (46%)</td>
<td>1,470 (83%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>28,091 (84%)</td>
<td>1,074 (67%)</td>
</tr>
<tr>
<td>Known ischaemic heart disease</td>
<td>8,455 (22%)</td>
<td>645 (36%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2,040 (5%)</td>
<td>218 (12%)</td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>56±10</td>
<td>47±15</td>
</tr>
<tr>
<td>Myocardial ischemia on ECG</td>
<td>-</td>
<td>194 (14)</td>
</tr>
<tr>
<td>Peak hs-cTnI, ng/L</td>
<td>3 [1-6]</td>
<td>26 [20-37]</td>
</tr>
</tbody>
</table>

Presented as No. (%), mean ± SD or median [inter-quartile range]; eGFR = estimated glomerular filtration rate

* enlisted between June 10, 2013, and March 3, 2016
Primary Outcome Stratified by Troponin Concentration

Primary outcome = 5.8% (1,106/18,978) and 5.1% (1,480/29,304) in validation and implementation phases
Primary Outcome Stratified by Troponin Concentration

Primary outcome = 5.8% (1,106/18,978) and 5.1% (1,480/29,304) in validation and implementation phases

hs-cTnI <99th centile
367/14862 [2%] versus 479/23060 [2%]

ESC Congress
Munich 2018
Primary Outcome Stratified by Troponin Concentration

Primary outcome = 5.8% (1,106/18,978) and 5.1% (1,480/29,304) in validation and implementation phases

hs-cTnI <99th centile
367/14862 [2%] versus 479/23060 [2%]
Primary Outcome Stratified by Troponin Concentration

Primary outcome = 5.8% (1,106/18,978) and 5.1% (1,480/29,304) in validation and implementation phases

hs-cTnI <99th centile
367/14862 [2%] versus 479/23060 [2%]

Identification
[cTnI positive
634/3396 [19%] versus 870/5193 [17%]

ESC Congress
Munich 2018

@HighSTEACS #ESC2018
Primary Outcome Stratified byTroponin Concentration

Survival Free from Myocardial Infarction or Cardiovascular Death [%]

- **Validation phase**
- **Implementation phase**

<table>
<thead>
<tr>
<th>Troponin Status</th>
<th>Survival Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-cTnI &lt;99th centile</td>
<td>367/14862 (2%) versus 479/23060 (2%)</td>
</tr>
<tr>
<td>cTnI positive</td>
<td>634/3396 (19%) versus 870/5193 (17%)</td>
</tr>
</tbody>
</table>

No myocardial injury

Reclassified

Identified

* linear mixed effects model adjusted for patient covariates, site, season, and time

ESC Congress
Munich 2018

@HighSTEACS #ESC2018
Primary Outcome Stratified by Troponin Concentration

Adjusted odds ratio for implementation versus validation phase 1.10, 0.75-1.61; P=0.620 *

- **No myocardial injury**
  - hs-cTnl <99th centile
  - 367/14862 [2%] *versus* 479/23060 [2%]

- **Reclassified**
  - hs-cTnl >99th centile but cTnl negative
  - 105/720 [15%] *versus* 131/1051 [12%]

- **Identified**
  - cTnl positive
  - 634/3396 [19%] *versus* 870/5193 [17%]

* linear mixed effects model adjusted for patient covariates, site, season, and time
## Primary and Secondary Efficacy Outcomes in Patients Reclassified by High-Sensitivity Cardiac Troponin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Validation</th>
<th>Implementation</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction or CV death</td>
<td>105 (14.6%)</td>
<td>131 (12.5%)</td>
<td>1.10 (0.75-1.61)</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>56 (7.8%)</td>
<td>62 (5.9%)</td>
<td>1.33 (0.81-2.20)</td>
</tr>
<tr>
<td>Unplanned revascularisation</td>
<td>18 (2.5%)</td>
<td>25 (2.4%)</td>
<td>1.77 (0.72-4.36)</td>
</tr>
<tr>
<td>All cause death</td>
<td>167 (23.2%)</td>
<td>187 (17.8%)</td>
<td>0.71 (0.46-1.10)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>54 (7.5%)</td>
<td>75 (7.1%)</td>
<td>0.86 (0.51-1.45)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>32 (4.4%)</td>
<td>59 (5.6%)</td>
<td>1.13 (0.61-2.09)</td>
</tr>
<tr>
<td>Hospitalisation with heart failure</td>
<td>91 (12.6%)</td>
<td>113 (10.8%)</td>
<td>1.34 (0.84-2.16)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>24 (3.3%)</td>
<td>17 (1.6%)</td>
<td>0.85 (0.33-2.18)</td>
</tr>
</tbody>
</table>

*Validation better* or *Implementation better*
Adjudication of index diagnosis and sex

Total population (n = 48,282)

- **NO INJURY** (n = 37,922)
- **RECLASSIFIED** (n = 1,771)
- **IDENTIFIED** (n = 8,589)

**SEX**

**DIAGNOSIS**

- TYPE 1 MI
- TYPE 2 MI
- INJURY

@HighSTEACS #ESC2018
Management and Safety Endpoints

<table>
<thead>
<tr>
<th></th>
<th>No myocardial injury</th>
<th>Reclassified by hs-cTnI assay</th>
<th>Identified by cTnI assay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Validation</td>
<td>Implementation</td>
<td>Validation</td>
</tr>
<tr>
<td>No. of participants</td>
<td>14,862 (39)</td>
<td>23,060 (61)</td>
<td>720 (41)</td>
</tr>
<tr>
<td></td>
<td>3,396 (40)</td>
<td>5,193 (60)</td>
<td></td>
</tr>
<tr>
<td>Duration of stay, hrs</td>
<td>7 (3-24)</td>
<td>4 (3-20)</td>
<td>21 (4-101)</td>
</tr>
<tr>
<td></td>
<td>82 (19-186)</td>
<td>78 (37-164)</td>
<td></td>
</tr>
<tr>
<td>Coronary angiography at 30d</td>
<td>204 (1)</td>
<td>329 (1)</td>
<td>29 (4)</td>
</tr>
<tr>
<td></td>
<td>1008 (33)</td>
<td>2,177 (42)</td>
<td></td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>112 (1)</td>
<td>187 (1)</td>
<td>23 (3)</td>
</tr>
<tr>
<td></td>
<td>706 (21)</td>
<td>1,535 (30)</td>
<td></td>
</tr>
<tr>
<td>New anti-platelet agent</td>
<td>795 (5)</td>
<td>976 (4)</td>
<td>64 (9)</td>
</tr>
<tr>
<td></td>
<td>1,408 (41)</td>
<td>2,428 (47)</td>
<td></td>
</tr>
<tr>
<td>New dual anti-platelet therapy</td>
<td>248 (2)</td>
<td>336 (1)</td>
<td>35 (5)</td>
</tr>
<tr>
<td></td>
<td>1,144 (34)</td>
<td>2,080 (40)</td>
<td></td>
</tr>
<tr>
<td>New statin therapy</td>
<td>419 (3)</td>
<td>608 (3)</td>
<td>32 (4)</td>
</tr>
<tr>
<td></td>
<td>660 (19)</td>
<td>1,263 (24)</td>
<td></td>
</tr>
<tr>
<td>New ACE inhibitor or ARB</td>
<td>287 (2)</td>
<td>479 (2)</td>
<td>34 (5)</td>
</tr>
<tr>
<td></td>
<td>671 (20)</td>
<td>1,163 (22)</td>
<td></td>
</tr>
<tr>
<td>New beta-blocker</td>
<td>765 (5)</td>
<td>1,092 (5)</td>
<td>65 (9)</td>
</tr>
<tr>
<td></td>
<td>828 (24)</td>
<td>1,502 (29)</td>
<td></td>
</tr>
</tbody>
</table>

No difference in safety endpoints between the validation and implementation phases in those reclassified: major haemorrhage (1% versus 1%), unplanned hospital admission at 30 days excluding acute coronary syndrome (29% versus 23%), and non-cardiovascular death (16% versus 11%)

Presented as No. (%), PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting
Conclusions

• The High-STEACS trial is the first randomised controlled trial to evaluate the recommendations of the Universal Definition of Myocardial Infarction

• Implementation of high-sensitivity cardiac troponin and the 99\textsuperscript{th} centile reclassified one in six patients, but only a third had a diagnosis of type 1 myocardial infarction, and the rate of subsequent myocardial infarction or cardiovascular death at one year was unchanged

• Length of stay was doubled in reclassified patients, but halved in those without myocardial injury, and there was no evidence of excess treatment, bleeding or misdiagnosis

• Should the diagnosis of myocardial infarction be based on a statistical threshold derived from a reference population, or an approach that optimizes diagnostic accuracy?
Acknowledgments

Support
British Heart Foundation Project Grants (SP/12/10/29922 and PG/15/51/31596), BHF Butler Senior Clinical Research Fellowship (FS/16/04/32023)
Abbott Diagnostics (reagent)

High-STEACS Steering Committee
Professor Ian Ford (Chair)
Professor Nicholas L Mills (CI)
Dr Shannon Amoiles
Professor Fred S Apple
Professor Paul Collinson
Dr Simon Walker
Professor Colin Berry
Professor Keith Fox
Professor David Newby
Professor Alasdair Gray
Dr Iain Findlay
Dr Anne Cruikshank
Dr Donogh Maguire
Dr Colin Fischbacher
Professor John Norrie
Professor Christopher Weir

Edinburgh Clinical Trials Unit
Mr Christopher Tuck (Trial Manager)
Dr Catriona Keerie
Mr Ronald Harkness
Dr Richard Parker

University of Edinburgh
Dr Anoop SV Shah
Dr Atul Anand
Dr Fiona Strachan
Ms Amy V Ferry
Dr Kuan Ken Lee
Dr Andrew R Chapman
Dr Philip Adamson
Mr Dennis Sandeman
Dr Catherine L Stables
Dr Jack PM Andrews
Dr Mohamed S Anwar
Dr John Hung
Dr Alastair J Moss
Ms Rachel O’Brien

University of Glasgow
Dr Roma Armstrong
Professor Colin Berry
Dr Alan Reid
Dr David McAllister

Data Monitoring Committee
Colin M Fischbacher
Bernard L Croal
Stephen J Leslie

www.highsteacs.com
ESC Congress Munich 2018
@HighSTEACS #ESC2018
High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial


Summary

Background High-sensitivity cardiac troponin assays permit use of lower thresholds for the diagnosis of myocardial infarction, but whether this improves clinical outcomes is unknown. We aimed to determine whether the introduction of a high-sensitivity cardiac troponin I (hs-cTnI) assay with a sex-specific 99th centile diagnostic threshold would reduce subsequent myocardial infarction or cardiovascular death in patients with suspected acute coronary syndrome.

Methods In this stepped-wedge, cluster-randomised controlled trial across ten secondary or tertiary care hospitals in Scotland, we evaluated the implementation of a hs-cTnI assay in consecutive patients who had been admitted to the