Institution: University of Edinburgh		
Unit of Assessment: 1		
Title of case study: H: High-sensitivity cardiac troponin testing enables earlier and more accurate diagnosis of myocardial infarction		
Period when the underpinning research was undertaken: 2011 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Nicholas Mills	Personal Chair of Cardiology	2003 – present
Anoop Shah	Honorary Senior Lecturer in Cardiology	2010 – 2020
David Newby	BHF Duke of Edinburgh Chair of Cardiology	2000 – present
Alasdair Gray	Chair of Emergency Medicine	2001 – present
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Andrew R Chapman	Clinical Lecturer	2015 – present
Period when the claimed impact occurred: 2014 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Underpinning Research: University of Edinburgh (UoE) researchers demonstrated that high-sensitivity cardiac troponin assays, rather than the less sensitive previous standard assays, enable more patients with suspected myocardial infarction (MI) to be correctly diagnosed, and that the use of sex-specific diagnostic thresholds addresses a systematic under-diagnosis in women. Based on this approach, the researchers developed a safe and effective pathway (the HighSTEACS pathway) that enables safe early rule-out of MI, and demonstrated that this halves the rate of hospitalisation when implemented in routine pratice.

Significance and Reach of Impact: The UK's National Institute for Health and Care Excellence (NICE, 2014 and 2018), Scottish Intercollegiate Guidelines Network (2016), and the Fourth Universal Definition of MI (2018) all recommend high-sensitivity cardiac troponin and sex-specific diagnostic thresholds, citing UoE publications. In 2020, NICE and the European Society of Cardiology recommended the HighSTEACS pathway, alongside others, for ruling out MI. High-sensitivity troponin assays, rather than previous standard assays, are now in routine use in 110 NHS hospitals and in 41% of 1,902 surveyed hospitals in 23 countries. Use of these pathways helps to reduce diagnostic uncertainty and associated anxiety for patients.

2. Underpinning research

The Challenge: How to effectively rule out and diagnose MI

Patients with symptoms suggestive of MI account for 1 in 10 of all presentations to the Emergency Department and up to 40% of unplanned admissions. However, the majority of patients ultimately have MI ruled out and could potentially have avoided hospital admission. UoE researchers have developed and evaluated novel strategies to either rule out or diagnose MI more effectively using high-sensitivity assays to detect cardiac troponin, a protein that is released into the bloodstream during an MI.

More sensitive troponin assays improve survival in patients with MI

More sensitive assays allow the accurate quantification of cardiac troponin in the blood at lower concentrations than the previous standard tests, and therefore enable the use of lower diagnostic thresholds and the identification of MIs that were previously missed as the rise in troponin was not detectable. However, in 2008, when the UoE team began their research programme, lowering the diagnostic threshold was a highly controversial issue among clinicians who were concerned that 1) increases in *sensitivity* would compromise *specificity*, leading to false positives and 2) that an increase in false positive results could lead to inappropriate treatment and harm.

To understand the validity of these concerns, the UoE researchers introduced a novel, more

sensitive assay into routine clinical practice at 1 hospital, allowing a lower diagnostic threshold to be used. By linking multiple routinely collected electronic health data sources, they tracked clinical management and outcomes of patients (n=2,092), before and after implementation. The use of a lower diagnostic threshold was associated with an increase in the use of evidence-based therapies and reduction in the risk of death and recurrent MI (from 39% to 21%). There was no evidence of an increase in false positives or harm to patients [3.1].

High-sensitivity assays show distinct thresholds should be used for men and women
Having demonstrated that lowering the diagnostic threshold identified additional patients with MI due to increased sensitivity, the team worked together with Abbott Laboratories to develop and evaluate the next generation of high-sensitivity troponin assays [5.9]. Using this newly developed assay, they demonstrated that the 99th centile upper reference limit (recommended as the diagnostic threshold in the 3rd Universal Definition of Myocardial Infarction) is 2-fold lower in women than in men, suggesting that different thresholds are needed to provide equivalent diagnostic sensitivity for women and men. They demonstrated that the use of the high-sensitivity assay and sex-specific diagnostic thresholds could double the proportion of women diagnosed from 11% to 22% compared with using the previous standard assay with a uniform threshold for men and women. They demonstrated the importance of this observation by showing that, after 1 year, the women whose increases in troponin levels were missed by the previous standard assay had the highest rate of death or recurrent MI [3.2].

Implementation of high-sensitivity assays and sex-specific thresholds
Between 2013 and 2017, the UoE team conducted the definitive clinical trial to evaluate the impact of implementing high-sensitivity cardiac troponin assays into routine clinical practice. In a stepped-wedge, cluster randomised trial of 48,282 consecutive patients with suspected MI across 10 hospitals, they linked multiple routinely collected electronic health data sources to compare the diagnosis, management and outcomes between two phases: first, a validation phase, during which the previous standard assay with a single threshold was used to guide care, and subsequently an implementation phase, during which the high-sensitivity assay with sex-specific thresholds was used [3.3]. The results showed that implementation of the high-sensitivity assay reduced length of hospital stay by a third, and was not associated with misdiagnosis or adverse outcomes.

Optimal approach to rule out MI at presentation
During the running of the trial, the UoE team developed an efficient approach to safely rule out MI using a single high-sensitivity cardiac troponin test at presentation and a separate rule-out threshold of 5 ng/L, which could avoid the need for hospital admission and serial testing in 50% of patients [3.4]. A subsequent individual patient-level meta-analysis revealed that this approach was effective in 23 different cohorts from 9 countries [3.5].

Combining this rule-out threshold with sex-specific diagnostic thresholds, the team formulated an integrated diagnostic pathway, the High-STEACS pathway, illustrated in **Figure 1** below. In another data-enabled trial (HiSTORIC; 31,492 consecutive patients across 7 hospitals) the researchers demonstrated that implementing the HighSTEACS pathway in routine care reduced the length of hospital stay by more than 3 hours and increased the proportion of patients discharged directly from the Emergency Department by 50%, with no increase in MI or cardiac death at 30 days or 1 year [3.6]. This was the first time the safety and efficacy of any early rule-out pathway had been tested in a randomised controlled trial.

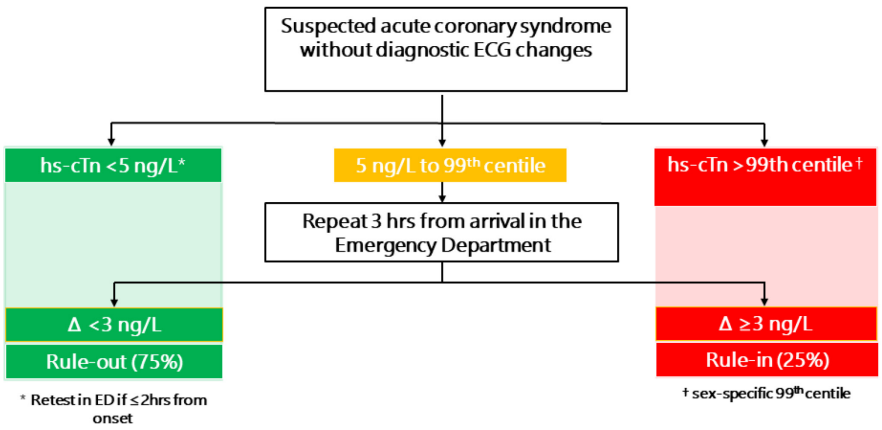

Figure 1: The High-STEACS pathway for safely ruling out MI. hs-cTn = high-sensitivity cardiac troponin

3. References to the research:

[3.1] Mills NL, Churchhouse AM, Lee KK, Anand A, Gamble D, Shah AS, Paterson E, MacLeod M, Graham C, Walker S, Denvir MA, Fox KA, Newby DE. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA*. 2011;305(12):1210-6. doi:10.1001/jama.2011.338

[3.2] Shah AS, Griffiths M, Lee KK, McAllister DA, Hunter AL, Ferry AV, Cruikshank A, Reid A, Stoddart M, Strachan F, Walker S, Collinson PO, Apple FS, Gray AJ, Fox KA, Newby DE, Mills NL. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ*. 2015; 350:g7873. doi: 10.1136/bmj.g7873

[3.3] Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Chapman AR, Sandeman D, Stables CL, Adamson PD, […], Newby DE, Mills NL; High-STEACS Investigators. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *The Lancet 2018. 392: 919-928.* doi: 10.1016/S0140-6736(15)00391-8

[3.4] Shah ASV, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, Chapman AR, Langdon T, Sandeman D, Vaswani A, Strachan FE, Ferry A, Stirzaker A, Reid A, Gray AJ, Collinson PO, McAllister DA, Apple FS, Newby DE, Mills NL; the High-STEACS Investigators. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome. *Lancet*. 2015; 386(10012): 2481-8. doi:10.1016/S0140-6736(15)00391-8

[3.5] Chapman AR, Lee KK, […] Newby DE, Shah ASV, Mills NL. Association of High-Sensitivity Cardiac Troponin I Concentration With Cardiac Outcomes in Patients With Suspected Acute Coronary Syndrome. *JAMA*. 2017;318(19):1913-1924. doi: 10.1001/jama.2017.17488

[3.6] Anand A, Lee KK, Chapman AR, Ferry AV, Adamson PD, Strachan FE, Berry C, Findlay I, Cruickshank A, Reid A, Collinson PO, Apple FS, McAllister DA, Maguire D, Fox KAA, Newby DE, Tuck C, Harkess R, Keerie C, Weir CJ, Parker RA, Gray A, Shah ASV, Mills NL, HiSTORIC Investigators. High-sensitivity cardiac troponin on presentation to rule out myocardial infarction: a stepped-wedge cluster randomised controlled trial. medRxiv 2020.09.06.20189308; doi: 10.1101/2020.09.06.20189308

4. Details of the impact:

Impact on UK clinical guidelines

In October 2014, the UK National Institute for Health and Care Excellence (NICE) published Diagnostic Guidance 15: “Myocardial infarction (acute): Early rule out using high-sensitivity troponin tests”. This recommended 3 high-sensitivity troponin assays, including the Abbott assay that the UoE team helped to develop, and advised healthcare professionals to be aware that the thresholds for troponin may differ between the sexes [5.1a]. The recommendations

were based on clinical effectiveness and cost-effectiveness analyses from an independent diagnostics assessment report [5.1b], which cited 5 UoE papers, including using [3.1] to calculate mortality rates following use of the previous standard or high-sensitivity troponin assays. The recommendation for high-sensitivity troponin assays with sex-specific thresholds was retained in a 2018 review of DG15, which cited [3.4] as one of the new sources of evidence in favour of high-sensitivity troponin assays [5.2].

The Scottish Intercollegiate Guidelines Network (SIGN) Guideline 148 recommended both high-sensitivity assays and sex-specific thresholds in April 2016, citing 2 UoE publications as evidence for their clinical benefit [5.3].

In August 2020, the NICE Diagnostics Assessment Programme published novel guidance on "High-sensitivity troponin tests for the early rule out of NSTEMI [Non-ST-segment-elevation MI]". The HighSTEACS and HiSTORIC trials were the only 2 randomised controlled trials included in the evidence review [5.4]. The guidance recommends 11 options for high-sensitivity troponin assays (all of which have distinct thresholds for men and women), and 3 main types of sampling strategy, one of which was the HighSTEACS pathway. The committee concluded that "*recommending a range of early rule-out strategies would enable hospitals to use strategies that worked with the set-up of their emergency department*" but "*considered that strategies in which people could be safely discharged after the first test* [such as the High-STEACS pathway] *could be beneficial because fewer people would have to remain in the emergency department for a second test*." [5.4].

Impact on international guidelines

UoE research is cited in the Fourth Universal Definition of Myocardial Infarction published by the Global Task Force for the World Heart Federation, European Society of Cardiology, American College of Cardiology and American Heart Association in August 2018. This definition, considered the definitive global authority on MI, now explicitly recommends the use of sex-specific ranges of troponin concentration when using high-sensitivity assays, and cites paper [3.2] as one of 2 sources of evidence for its clinical benefit [5.5].

The European Society of Cardiology guidelines for the "management of acute coronary syndromes in patients presenting without persistent ST-segment elevation", published in 2020, recommend the HighSTEACS pathway as an alternative to their main 0/1h pathway (Class IIa, level B recommendation; "should be considered"), citing 2 UoE papers [5.6].

UoE research is also cited in the 2017 International Federation of Clinical Chemistry (IFCC) Taskforce on Clinical Applications of Cardiac Biomarkers review [5.7a] and in the 2017 Asia-Pacific consensus statement [5.7b], both of which recommend using sex-specific thresholds.

Impact on clinical practice

In the UK, high-sensitivity cardiac troponin assays are now in routine use in the majority of NHS Trusts. In April 2019, an independent research group sent a survey to 131 NHS hospitals, and found that, of the 125 responding hospitals, 110 (88%) reported using high-sensitivity assays, 92 of them (84%) for early rule-out of MI. 16 Trusts used the Abbott assay and 25 hospitals were using sex-specific thresholds [5.8].

A 2017 telephone survey of 1,902 hospitals in 23 countries across 5 continents found that worldwide, 41% hospitals have adopted high-sensitivity assays, with wide variation from 7% in North America (where the Food and Drug Administration had not approved the use of high-sensitivity testing at the time of the survey) to 60% in Europe. 18% of hospitals worldwide were using sex-specific thresholds at the time of the survey (before publication of the Fourth Universal Definition recommendations but after publication of UoE papers [3.2] and [3.4] and the IFCC and Asia Pacific consensus statements) [5.9].

Since its launch in 2013, over 115,000,000 Abbott high-sensitivity troponin assays have been conducted by healthcare professionals globally. Abbott confirms the role of UoE research on

the success of this assay: "*The collaboration with academic and research institutions such as University of Edinburgh on research studies specifically around hsTnI (High-STEACS pathway) helped the design and launch of Abbott hsTnI product, as well as successful adoption within medical community for acute coronary syndrome patient management*." [5.10].

Impact on health and welfare

Patients attending hospitals that use high-sensitivity assays and sex-specific thresholds benefit from avoiding unnecessary hospitalisation if they do not have MI, or, if they do, from being correctly diagnosed and more rapidly directed towards appropriate treatment. As noted in the 2016 SIGN guidelines, "*Use of a high-sensitivity cardiac troponin assay permits the use of lower diagnostic thresholds than standard troponin assays, and allows earlier testing that may reduce unnecessary hospital admissions, waiting times for test results and associated anxiety in patients and carers.*" [5.3]. With 80,000 patients presenting with MI in the UK annually, this benefit is felt by approximately 70,400 patients (88%) each year.

Economic impact

The NICE Diagnostics Assessment committee assessed the cost-effectiveness of the different recommended assays and testing strategies, and concluded that high-sensitivity troponin test strategies were cost-effective: each quality-adjusted life year gained using a high-sensitivity troponin strategy was calculated to cost GBP7,000, which is markedly cheaper than the GBP20,000 per quality-adjusted life year threshold that NICE typically considers cost-effective [5.4].

The HiSTORIC trial indicated that implementation of the HighSTEACS pathway into routine practice results in substantial cost-savings for the NHS through reducing the length of hospital stay by more than 3 hours, and increasing the proportion of patients discharged from the Emergency Department without hospitalisation by 50%, without an increase in adverse cardiac events [3.6]. Were these gains to be realised across healthcare systems, the benefits for both patients and providers would be substantial; for example, in the United States alone, more than 20,000,000 patients with suspected MI attend Emergency Departments each year. Based on independently published economic models, a reduction in the length of stay of 3 hours could save more than USD3,600,000,000 (GBP2,634,698,940; 01-21) per annum on bed occupancy alone [5.11].

5. Sources to corroborate the impact:

[5.1] a. NICE Diagnostic Guidance 15: Myocardial infarction (acute): Early rule-out using high-sensitivity troponin tests, October 2014 b. Systematic review by Westwood et al., used by NICE Diagnostics Assessment Committee
[5.2] Review of NICE Diagnostic Guidance 15, 2018 (UoE research cited on p. 11–12; p. 21)
[5.3] SIGN Guideline 148, 2016 (p. 8–9)
[5.4] NICE Diagnostics Assessment Programme diagnostics guidance 2020: High-sensitivity troponin tests for the early rule-out of NSTEMI; quotes on p. 37 and cost-effectiveness analysis on p. 35.
[5.5] Fourth Universal Definition of Myocardial Infarction (p. 20)
[5.6] ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (2020) doi:10.1093/eurheartj/ehaa575
[5.7] a. IFCC Taskforce on Clinical Applications of Cardiac Biomarkers review (2017) b. Asia-Pacific consensus statement (2017)
[5.8] Thapa et al. 2020 *Emerg Med* doi: 10.1136/emermed-2019-209100
[5.9] Anand, A, Shah, ASV, Beshiri, A, Jaffe, AS & Mills, NL 2019, 'Global Adoption of High-Sensitivity Cardiac Troponins and the Universal Definition of Myocardial Infarction' *Clinical Chemistry* 65(3) doi: 10.1373/clinchem.2018.298059
[5.10] Letter from Abbott re: collaboration with UoE researchers
[5.11] Probst MA, McConnell JK, Weiss RE, Laurie AL, Yagapen AN, Lin MP, et al. Estimating the Cost of Care for Emergency Department Syncope Patients: Comparison of Three Models. *West J Emerg Med* 2017; 18: 253–257. doi: 10.5811/westjem.2016.10.31171