Diagnosing myocardial infarction in the era of high-sensitivity troponin: the High-STEACS trial

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Diagnosing myocardial infarction in the era of high-sensitivity troponin: the High-STEACS trial

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High-sensitivity cardiac troponin is central to the diagnosis of myocardial infarction when measured in patients with signs or symptoms consistent with myocardial ischaemia. In this context, the Universal Definition of Myocardial Infarction (UDMI) mandates a rise and/or fall in troponin concentrations with at least one measure above the 99th centile of a healthy reference population.[1] Increasing precision of cardiac troponin assays has allowed quantification of ever lower concentrations in the bloodstream, with detectable circulating levels present in over half of the healthy population.[2] Where previous diagnostic thresholds were limited by assay precision, the 99th centile defines myocardial infarction by non-conformity with the healthy state at a population level. However, this approach is subject to inconsistencies according to the gender balance, ethnicity, and stringency of screening for disease within reference populations.[3] Such controversies may have limited implementation of high-sensitivity assays and the full recommendations of the UDMI.[4]

While lowering the diagnostic threshold for myocardial infarction has previously been shown to improve patient outcomes,[5] many clinicians fear that increasingly sensitive assays may compromise specificity, as low levels of cardiac troponin may be released in the absence of acute plaque rupture and coronary thrombosis, the hallmarks of a type 1 myocardial infarction.[6] Until recently there have been no randomized trials of the UDMI or the introduction of high-sensitivity troponin assays, with guidance based solely on expert consensus and observational data.

The High-STEACS trial

The High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome (High-STEACS) cluster-randomized controlled trial assessed the impact of introducing a high-sensitivity cardiac troponin I (hs-cTnI) assay with sex-specific 99th centile diagnostic thresholds (16 ng/L in females, 34 ng/L in males).[7] The study included 48 282 consecutive patients in whom cardiac troponin was requested for suspected acute coronary syndrome across 10 hospitals in Scotland. Contemporary and hs-cTnI assays were run concurrently in two phases of the study: a validation phase in which the contemporary assay was used to guide clinical decisions and the hs-cTnI results were suppressed, and an implementation phase where this process was reversed and sex-specific 99th centile thresholds of the hs-cTnI assay were used to guide clinical care. Hospital sites were randomized to early or late implementation of hs-cTnI for clinical care. The primary endpoint of the trial was subsequent myocardial infarction or cardiovascular death at 1 year after initial hospital presentation. All events were independently adjudicated against UDMI criteria by two physicians using all available clinical information; disagreements were resolved by a third adjudicator.

The study population included 10 360 (21%) patients with hs-cTnI concentrations above sex-specific 99th centile thresholds, of whom 1771 (4%) patients were reclassified only through use of the high-sensitivity assay (i.e. concentrations above the 99th centile on high-sensitivity testing but below the diagnostic threshold of the contemporary troponin assay). Primary endpoint events did not vary between those reclassified in the validation and implementation phases of the study [15% vs. 12% respectively, adjusted odds ratio 1.10, 95% confidence interval (95% CI) 0.75–1.61, $P = 0.62$]. Patients reclassified by hs-cTnI were older than those identified by the contemporary test (mean age 75 ± 14 vs. 70 ± 15 years old) and 83% were female, reflecting in part the lower sex-specific 99th centile in women. Only one-third of those reclassified by hs-cTnI received an adjudicated diagnosis of type 1 myocardial infarction, compared to 60% of those identified by the contemporary assay.

Implications for clinical practice

Previous improvements in outcomes achieved by increasingly sensitive cardiac troponin assays[5] were not replicated following introduction of hs-cTnI assays and the 99th centile diagnostic threshold. This was despite reclassified patients having a similar cardiac risk profile to those identified by the contemporary assay and more than 1 in 9 reclassified patients sustaining a subsequent myocardial infarction or cardiac death within a year of index hospital presentation. There are several possible reasons for these observations. Two-thirds of reclassified patients did not sustain a type 1 myocardial infarction where evidence-based therapy exists to improve outcomes. Even including those with type 1 events, new secondary prevention therapy or coronary angiography was undertaken in fewer than 1 in 10 reclassified patients after implementation of the new

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assay, limiting the potential to improve outcomes. This may be related to the gender imbalance of reclassified patients, with several previous studies observing women receiving fewer investigations and treatments for heart disease than men.[8,9]

The High-STEACS trial represents a challenge to the research field and fundamentally questions the current approach to the diagnosis of myocardial infarction. This should not prompt rejection of hs-cTnI assays, which are highly specific markers of myocardial injury and have major potential to improve patient care. This is demonstrated in the effective adoption of pathways for the rapid exclusion of myocardial infarction using low troponin concentrations well below the 99th centile, only measureable using high-sensitivity assays.[10–12] Such low-level concentrations also have an emerging role in the estimation of future cardiovascular risk.[13,14] It is clear that elevations of cardiac troponin must be central to the diagnosis of myocardial infarction as objective evidence of myocardial necrosis. However, assessment against a binary 99th centile threshold may be too simplistic and ignore the information provided by a continuous marker of myocardial injury.[15]

We argue that new approaches should be considered to support clinicians assessing patients with suspected acute coronary syndrome. In the absence of gold-standard invasive coronary imaging, the evaluation of type 1 myocardial infarction is a probabilistic evaluation of troponin concentrations in the context of patient signs, symptoms, electrocardiographic, non-invasive, and invasive imaging. With appropriate statistical modelling using large consecutive patient cohort studies such as High-STEACS, established cardiovascular risk factors and high-sensitivity troponin measures can be combined to estimate the positive predictive value for the diagnosis of type 1 myocardial infarction in an individual. In a low-risk setting, the negative predictive value of low troponin concentrations may guide early safe exclusion of a cardiac event. This approach has been adopted in the recently described myocardial-ischaemic-injury-index (MI^3), which uses a machine-learning algorithm trained across multiple international cohorts to predict the risk of type 1 myocardial infarction in an individual from their age, sex, and serial cardiac troponin concentrations.[16]

The role of cardiac troponin in the assessment of patients with suspected acute coronary syndrome is evolving. The precision of high-sensitivity assays at very low troponin concentrations enable the use of separate risk stratification and diagnostic thresholds for the evaluation of patients with suspected acute coronary syndrome. We have previously demonstrated the safety and effectiveness of a risk stratification threshold at 5 ng/L for the exclusion of myocardial infarction.[10,17] The diagnostic threshold remains at the 99th centile in the 4th UDMI,[1] but modelling may allow individual refinement of risk based on additional clinical characteristics. Additional blood biomarkers may improve diagnostic discrimination, such as in distinguishing between myocardial injury secondary to active coronary disease from left ventricular hypertrophy or systolic dysfunction. Further research is ongoing and much needed in this area.[15]

Between the low-risk stratification and diagnostic thresholds are patients at intermediate risk, where the optimum treatment pathway is uncertain. The SCOT-HEART trial suggested that CT coronary angiography (CTCA) could improve targeting of therapy and long-term outcomes in patients with stable angina by identification of underlying coronary artery disease.[18] We are prospectively assessing the role of CTCA for this intermediate-risk group with suspected acute coronary syndrome, in whom myocardial infarction has been excluded, as part of the Troponin in Acute chest pain to Risk stratify and Guide EffecTive use of Computed Tomography Coronary Angiography (TARGET-CTCA) randomized controlled trial (clinicaltrials.gov NCT03952351).

In conclusion, the High-STEACS trial is the first randomized trial to evaluate the impact of adopting the UDMI and 99th centile diagnostic threshold in practice. Introduction of hs-cTnI increased the diagnosis of myocardial infarction but did not reduce the risk of subsequent myocardial infarction or cardiac death. To improve the clinical utility of high-sensitivity cardiac troponin in the assessment of patients with suspected acute coronary syndrome, we suggest troponin should no longer be considered a binary test. The use of separate risk stratification and diagnostic thresholds or probabilistic modelling could improve decisions in individual patients, and such an approach now requires prospective evaluation in future clinical trials.

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Biography: Professor Nicholas L. Mills is the British Heart Foundation Butler Senior Clinical Research Fellow, and Professor of Cardiology at the University of Edinburgh. He is also a Consultant Interventional Cardiologist at the Royal Infirmary of Edinburgh working for the National Health Service in Scotland. His research aims to improve our understanding of the mechanisms of myocardial injury in patients with coronary heart disease, and to identify new approaches to improve risk stratification, diagnosis and outcomes for these patients. He is the chief investigator of a series of multi-centred data-enabled randomized trials evaluating the impact of a high sensitive cardiac troponin testing in patients with suspected acute coronary syndrome (High-STEACS, HiSTORIC). He also leads a data driven innovation in health and social care programme in Scotland, which is harnessing routinely collected data to better understand care and outcomes for people with acute and chronic health conditions.