High-sensitivity cardiac troponin tests for diagnosis of heart attack

A meta-analysis and a UK cohort study found that thresholds lower than those generally applied could be used with high-sensitivity cardiac troponin T or I tests to rule out myocardial infarction in people with chest pain.

Overview:
- A meta-analysis and a UK cohort study found that thresholds lower than those generally applied could be used with high-sensitivity cardiac troponin T or I tests to diagnose myocardial infarction in people with chest pain.
- Threshold such as these that fall at or below the 99th percentile for the normal population could potentially be used to rule out myocardial infarction in emergency departments.
- However, the improved sensitivity of lower thresholds with high-sensitivity cardiac troponin tests is at the expense of specificity.

Background: Cardiac troponins are proteins that are released into the bloodstream when heart muscle is damaged. A rise in serum troponin levels can signify that myocardial infarction has taken place in a person who has chest pain.

High-sensitivity troponin tests can be used in emergency settings to rule out non-ST-segment-elevation myocardial infarction (NSTEMI) in people with chest pain and suspected acute coronary syndrome (NICE 2014). These tests are able to detect lower levels of troponin in the blood earlier than older standard assays, leading to improved early detection of acute myocardial infarction.

The thresholds that are used to diagnose myocardial infarction with these tests are based on the troponin levels of a healthy reference population. A cardiac troponin level above the upper limit (99th percentile) seen in the reference population indicates myocardial infarction. However, the use of a single diagnostic threshold may result in the under-diagnosis of myocardial infarction in women (Apple et al. 2012).

Current advice: NICE has diagnostics guidance on myocardial infarction (acute): early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnl+3 assays).
The Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I assay are recommended as options for the early rule out of NSTEMI in people presenting to an emergency department with chest pain and suspected acute coronary syndrome. The AccuTnI+3 assay is only recommended for use in clinical research.

The assays are recommended for use with 'early rule-out protocols', which typically include taking a blood sample for cardiac troponin I or T at initial assessment in an emergency department and a second blood sample taken after 3 hours. Laboratories should report absolute values and the upper reference limit should be set at the 99th percentile.

Results should be interpreted along with clinical judgement and the results of clinical assessment. Healthcare professionals should take into account that 99th percentile thresholds for troponin I and T may differ between sexes.

The NICE pathway on acute coronary syndromes brings together all related NICE guidance and associated products on the conditions in a set of interactive topic-based diagrams.

**New evidence:** Shah et al. (2015) evaluated using sex-specific diagnostic thresholds for a high-sensitivity troponin I test to diagnose myocardial infarction. This prospective cohort study enrolled people who presented with suspected acute coronary syndrome to a single hospital in Scotland.

Serum cardiac troponin I concentrations were measured on admission and again 6 or 12 hours later using both a contemporary troponin I test (ARCHITECT STAT Troponin-I assay) and a high-sensitivity troponin I test (ARCHITECT STAT High Sensitive Troponin-I assay; both Abbott Laboratories).

A diagnostic threshold of 50 ng/l was used for the contemporary test. For the high-sensitivity test, a generic threshold of 26 ng/l based on the 99th percentile value for a mixed gender reference population was used for both men and women. Sex-specific thresholds of 34 ng/l for men and 16 ng/l for women based on 99th percentile limits for male only and female only reference populations were also used with the high-sensitivity test.

A total of 1126 consecutive patients with suspected acute coronary syndrome were enrolled, 504 (45%) of whom were women and 622 (55%) men. When the contemporary test was used, 55 women (11%) and 117 men (19%) were classified as having myocardial infarction.

When the high-sensitivity test was used, the number of women classified as having myocardial infarction increased significantly to 80 (16%) with the generic threshold and 111 (22%) with the sex-specific threshold (p<0.001 for both). The number of men diagnosed with myocardial infarction using the high-sensitivity test increased slightly to 142 (23%) with the generic threshold and to 131 (21%) with the sex-specific threshold (p<0.021).

Zhelev et al. (2015) conducted a systematic review and meta-analysis of studies that used cardiac troponin T tests to diagnose myocardial infarction. The authors identified cohort studies that used the Elecsys Troponin T high-sensitive assay (Roche Diagnostics) to evaluate a single blood sample drawn at presentation in people attending an emergency department with suspected acute coronary syndrome.

The analysis assessed two thresholds used for diagnosis of acute myocardial infarction: 14 ng/l (99th percentile reference value) and a lower limit of 3–5 ng/l, which was the lowest possible amount of cardiac troponin T that could be detected with the test (the limit of detection).

A total of 20 studies (23 papers) were included in the meta-analysis (n=9428). When all 20 studies that used a threshold of 14 ng/l were pooled, the assay correctly identified 89.5% of people who had myocardial infarction (sensitivity; 95% confidence interval [CI] 86.3 to 92.1%) and 77.1% of people who did not have the condition (specificity; 95% CI 68.7 to 83.7%).

If 100 people had been tested with a high-sensitivity cardiac troponin T assay and 21 actually had myocardial infarction (the median prevalence across the studies in the analysis), the threshold of 14 ng/l would have missed the diagnosis in 2 or 3 people who had the disease (false negatives). A total
of 13 to 25 people who did not have myocardial infarction would have been identified as having the condition (false positives).

When the 6 studies that used a diagnostic threshold of 3–5 ng/l were pooled, the sensitivity of the assay was 97.4% (95% CI 94.9 to 98.7%) and the specificity was 42.4% (95% CI 31.2 to 54.5%). If this threshold was used in the hypothetical group of 100 people, none to 1 person with myocardial infarction would have been missed (false negatives) and 36 and 54 would have been wrongly diagnosed with the condition (false positives).

Commentary by Dr Divaka Perera, Consultant Cardiologist and Reader in Cardiology, St Thomas' Hospital Campus, King's College London:

“The main finding of the study by Shah et al. was that the use of lower diagnostic thresholds with a high-sensitivity cardiac troponin I test increased the proportion of people with suspected acute coronary syndrome who were classified as having a myocardial infarction. This applied to both men and women when comparing the traditional threshold of 50 ng/l to the 99th percentile value of 26 ng/l, and also when using the gender-specific 99th percentile limits of 16 ng/l for women and 34 ng/l for men.

“The study is limited by the fact that the authors did not have an external reference for the diagnosis of myocardial infarction. Hence the clinical relevance of reclassifying people using the high-sensitivity test is not entirely clear. In fact, the only hard outcome measure in this study (death or recurrent myocardial infarction at 12 months) was not different in women classified as having a myocardial infarction using the 16 ng/l threshold versus the 50 ng/l threshold (25% versus 24%).

“It is already well established that using the 99th percentile reference value as a diagnostic threshold for troponin I or T tests improves their sensitivity compared with the previous thresholds that have been used (such as the 50 ng/l threshold in this study), hence their utility for ruling out myocardial infarction. However, the latter traditional thresholds may have higher specificity and are better for ruling in myocardial infarction.

“There is also a growing body of evidence that using values even lower than the 99th percentile, as low as the limit of detection, can improve sensitivity (such as the 5 ng/l threshold for troponin I used in the new Lancet study by Shah et al. 2015). In this context, exploring the utility of gender specific 99th percentile thresholds may no longer be relevant: using the limit of detection will improve sensitivity in both men and women.

“The meta-analysis by Zhelev et al. showed that using the limit of detection (5 ng/l) as a diagnostic threshold improved sensitivity for diagnosing myocardial infarction compared with use of the 99th percentile (14 ng/l). However, this improved sensitivity was at the cost of specificity when using a single baseline measurement.

“UK practice is likely to change to include the use of lower diagnostic thresholds, below the 99th percentile for the normal population, for ruling out myocardial infarction in emergency departments.”

Study sponsorship: Shah et al. (2015) was funded by the British Heart Foundation and the legacy of Violet Kemlo. Zhelev et al. (2015) was funded by the South West Academic Health Science Network (AHSN) and the National Institute for Health Research (NIHR).