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Review Article

Acute coronary syndromes diagnosis, version 2.0: Tomorrow's approach to diagnosing acute coronary syndromes?

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ABSTRACT

Chest pain accounts for approximately 6% of Emergency Department (ED) attendances and is the most common reason for emergency hospital admission. For many years, our approach to diagnosis has required patients to stay in hospital for at least 6–12 h to undergo serial biomarker testing. As less than one fifth of the patients undergoing investigation actually has an acute coronary syndrome (ACS), there is tremendous potential to reduce unnecessary hospital admissions.

Recent advances in diagnostic technology have improved the efficiency of care pathways. Decision aids such as the Thrombolysis in Myocardial Infarction (TIMI) risk score and the History, Electrocardiogram, Age, Risk factors and Troponin (HEART) score enable rapid 'rule out' of ACS within hours of patients arriving in the ED. With high sensitivity cardiac troponin (hs-cTn) assays, approximately one third of patients can have ACS 'ruled out' with a single blood test, and up to two thirds could have an acute myocardial infarction 'ruled out' with a second sample taken after as little as 1 h.

Building on those recent advances, this paper presents an overview of the principles behind the development of the Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid. This clinical prediction model could be used to 'rule out' and 'rule in' ACS following a single blood test and to calculate the probability of ACS for every patient. The future potential of this approach is then addressed, including practical applications of artificial intelligence, shared decision making, near-patient testing and personalized medicine.

1. Acute coronary syndromes diagnosis, version 1.0

Chest pain is one of the most common reasons for patients to present to the Emergency Department (ED), accounting for approximately 6% of all attendances.[1] It is also a very common reason for hospital admission, although studies from around the world consistently demonstrate that less than 20% of the patients who are initially suspected to have a diagnosis of acute coronary syndrome (ACS) actually have that diagnosis.[2–5] Retaining all these patients in the ED or hospital wards for investigation is an inefficient use of resources, particularly given the growing problem of ED and hospital crowding.

However, our approach to diagnosing ACS has until recently relied on prolonged evaluations for 6–12 h. It is often impossible for clinicians to differentiate ACS from non-threatening illnesses such as dyspepsia and musculoskeletal chest pain without the use of biomarkers. For example, the nature of a patient's symptoms cannot be used to 'rule out' ACS.[6] Even grouping symptoms together as 'typical' or 'atypical' does not change the probability that a patient has ACS.[7,8] Although Framingham risk factors (hypertension, hyperlipidaemia, diabetes mellitus, tobacco smoking and family history of premature coronary artery disease) predict the future development of coronary artery disease they do not change the probability of ACS in patients presenting to the ED.[9]

Abbreviations: ED, Emergency Department; AMI, Acute myocardial infarction; cTn, Cardiac troponin; hs-cTn, High sensitivity cardiac troponin; MACE, Major adverse cardiac events; ECG, Electrocardiogram; AUC, Area under the receiver operating characteristic curve.

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Similarly, the ECG has a sensitivity of less than 50% for acute myocardial infarction (AMI).[10] Our inability to accurately 'rule out' ACS following a clinician's evaluation means that we place a heavy reliance on cardiac biomarkers.

Cardiac troponin (cTn) is now the biomarker of choice for diagnosing AMI. The third universal definition of myocardial infarction requires that patients must have a rise and/or fall of cTn with at least one concentration above the 99th percentile upper reference limit (URL) of the assay, in conjunction with one of several additional factors, in order to fulfil the criteria for diagnosis of AMI.[11] As cTn is the highly cardiac specific isoform of troponin (part of the contractile apparatus of the myocardium), the detection of a rise in cTn concentrations in the bloodstream is highly specific for myocardial injury. However, it can take many hours for concentrations to rise above the 99th percentile URL of contemporary cTn assays. Thus, until recently, patients routinely underwent prolonged in-hospital evaluation.[12,13]

2. Acute coronary syndromes diagnosis version 1.1: accelerated serial cTn sampling

The development of high sensitivity cardiac troponin (hs-cTn) assays represents a momentous advance in the approach to early diagnosis of ACS. Compared to 'contemporary' cTn assays, hs-cTn assays have improved analytical sensitivity and precision. Analytical sensitivity refers to the ability of the assay to detect small concentrations of cTn. Precision refers to the amount of variation that will be seen when the same sample is repeatedly tested. Specifically, an hs-cTn assay must be able to detect some cTn (rather than returning a result below the limit of detection of the assay) in over 50% of apparently healthy individuals. Further, the assay must have sufficient precision, which is defined as a coefficient of variation (CV, calculated as the standard deviation divided by the mean of the results when the same sample is repeatedly tested) < 10% when measuring a sample with a cTn concentration equal to the 99th percentile URL of the assay.[14]

The improved precision offered by hs-cTn assays means that the detection of a smaller change on serial sampling is more likely to be a genuine change in cTn concentration, rather than simply being due to the imprecision of the assay. In AMI, the cTn concentrations are changing over time (usually rising in patients presenting early after symptom onset). If a smaller change in cTn concentration is more likely to be genuine (as is the case with hs-cTn assays), then the time between serial samples can be reduced.

With hs-cTn assays, there is now good evidence that the use of two samples taken 1 h apart can 'rule out' AMI in the majority of patients with high negative predictive value (NPV). For example, with the hs-cTnT assay (Roche Diagnostics Elecsys), the prospective TRAPID-AMI study including 1282 patients at 14 centres in 9 countries showed that a 1-h algorithm has 96.7% sensitivity and 99.1% NPV for AMI.[15] With this algorithm, AMI is 'ruled out' in patients with an initial hs-cTnT concentration <12 ng/L in the absence of a change >3 ng/L after 1 h. There is also evidence for the diagnostic accuracy of 1-h algorithms with hs-cTnI (Abbott Architect STAT). In a large study of 2828 patients, for example, a sensitivity of 98.4% was achieved with 99.5% NPV.[16]

One key advantage of the 1-h algorithm is that, in addition to 'ruling out' AMI in a large proportion of patients, the algorithm can also be used to 'rule in' the diagnosis. For example, evidence from the TRAPID-AMI study showed that the algorithm could 'rule in' AMI for 14.4% patients with 77.2% positive predictive value.[17]

Even with a contemporary cTn assay, a high sensitivity and NPV can be achieved with the use of a validated risk score and serial sampling over 2–3 h. For example, a sensitivity and an NPV of 99.7% were achieved with an accelerated diagnostic protocol (ADP) by which patients with cTn concentrations below the 99th percentile on arrival and 2 h later could have ACS 'ruled out' if they scored zero points with the Thrombolysis in Myocardial Infarction (TIMI) risk score.[18] The Emergency Department Acute Coronary Syndromes (EDACS) score, which was derived in the same cohort, may have similar sensitivity but greater specificity.[19] The score is calculated based on a patient's demographics and symptoms. Patients who score <16 points, who have a normal ECG and cTn concentrations below the 99th percentile on arrival and 2 h later may have ACS 'ruled out' (Table 1).

3. Acute coronary syndromes diagnosis, version 1.2: single test 'rule out'

Even when the time between blood samples is as little as 1 h, drawing two blood samples from all patients with suspected ACS has some important disadvantages. First, patients must still wait in the hospital for several hours awaiting the tests and their results. With the growing problem of ED crowding and its association with increased patient mortality and patient safety incidents, 'ruling out' ACS without the need for a second blood sample is clearly preferable if it can be safely achieved. Second, serial sampling is relatively resource intensive. An ED with 100,000 patient visits per year should expect to see approximately 3000 patients with suspected cardiac chest pain per year, or 8 patients per day. A single venipuncture may be expected to take approximately 30 min of staff time. Thus avoiding serial sampling for even 40% of patients with suspected cardiac chest pain would be expected to save 1.5 h of staff time per day.

3.1. The 'limit of detection (LoD)' rule out strategy

The improved analytical sensitivity of hs-cTn assays means that it is now possible to measure smaller concentrations of cardiac troponin. Thus the limit of detection (LoD) of the assays, which refers to the lowest concentration of cardiac troponin that can be detected, is lower with contemporary assays. After the onset of AMI, cardiac troponin concentrations will increase over time. It may take several hours for the cardiac troponin concentration to exceed the conventional 99th percentile cut-off, meaning that it is not possible to 'rule out' the diagnosis with a single test at the time patients arrive in the ED. However, it may be possible with a lower cut-off.

There is now a plethora of research to demonstrate that patients with cardiac troponin concentrations below the LoD of a high sensitivity assay are highly unlikely to have AMI, particularly in the absence of ECG ischemia. For example, the Roche hs-cTnT assay has an LoD of 5 ng/L. Numerous large studies have shown that the sensitivity and negative predictive value of this cut-off for AMI are over 99% in patients who do not have ECG ischemia.[2,20–23] Setting the cut-off at the LOD of the Abbott Architect hs-cTnI or Beckman Accu-TnI assays yields similar diagnostic accuracy.[24–26] This 'rule out' strategy has been recommended for use by the European Society of Cardiology.[27]

3.2. The HEART score

The HEART (History, ECG, Age, Risk factors, Troponin) score was also designed to 'rule out' ACS following a single blood test in the ED. It was developed using the intuition of a cardiologist and scores patients from 0 to 2 points based on each of the five variables included in the acronym 'HEART'. Patients who score less than 4 points could be immediately discharged. A meta-analysis of 12 studies including 11,217 patients showed that the HEART score had a pooled sensitivity of 96.7% (95% CI 94.0–98.2%) for major adverse

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