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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

Table 1
Risk scores validated for accelerated ACS 'rule-out' with serial cTn sampling.

Risk score	Clinical features	Criteria for 'low risk' (eligible for early discharge)	Troponin criteria
ADAPT protocol (TIMI risk score)	One point for each of: Age <65 years; current aspirin use; known coronary artery disease; severe symptoms (>2 episodes of chest pain in 24 h); ≥3 risk factors for coronary artery disease; ST deviation >0.5 mm on the ECG	0 points (with a contemporary cTn assay); 1 point (with an hs-cTn assay)	cTn <99th percentile on arrival and at 2 h
EDACS score	Score as follows: Age (multiple criteria, ranging from 2 to 20 points) Male sex (6 points) Aged 18–50 and either known coronary artery disease or ≥3 risk factors (4 points) Diaphoresis (3 points) Pain radiates to arm or shoulder (5 points) Pain occurred or worsened with inspiration (−4 points) Pain is reproduced by palpation (−6 points)	<16 points plus no ECG ischemia	cTn <99th percentile on arrival and at 2 h
HEART pathway	Score as follows: **History**: highly suspicious[2]; moderately suspicious[1]; slightly suspicious (0) **ECG:** Significant ST depression[2]; non-specific repolarization disturbance[1]; normal (0) **Age**: ≥65 years[2]; 45–64[1]; <45 years (0) **Risk factors:** ≥3 risk factors or history of atherosclerotic disease[2]; 1–2 risk factors[1]; no risk factors (0) Low risk: <4 points	<4 points	cTn <99th percentile on arrival and at 3 h

cardiac events (MACE).[28] The small miss rate can be reduced by repeating troponin measurement after 3 h, although that strategy does remove the advantage of having a 'single test' rule out.[29,30] A cluster randomized controlled trial comparing use of the HEART score to usual care showed a non-inferior incidence of MACE when the HEART score was used, although the trial did not show an increase in early discharges from the ED.[31]

3.3. *Summary of progress*

This evidence demonstrates that it is now possible to 'rule out' ACS with a single blood test, and to both 'rule in' and 'rule out' ACS for even more patients following a second blood sample taken 1–3 h after arrival. This represents a substantial advance in diagnostic technology.

There is, however, still room for improvement in our diagnostic approach. The above single test rule out strategies identify less than 40% patients as eligible for early discharge, and cannot be used to 'rule in' the diagnosis of ACS. The LoD rule out strategy ignores the patient's history and vital signs, whereas the HEART score was developed based on the intuition of a single cardiologist. The algorithms are also static and unchanging. As patient demographics, troponin assays and medical practices change, we are likely to observe 'calibration drift', with decreasing accuracy of diagnostic pathways. Further, all the current algorithms use troponin cut-offs, thus treating the cardiac troponin concentration as a dichotomous variable. This risks losing important diagnostic information because it is evident that there is a clear correlation between the actual cardiac troponin concentration and the probability of AMI.[32]

4. Towards ACS diagnosis version 2.0

Following the recent advances in diagnostic technology in this field, our group faced the important challenge of considering what 'ACS diagnosis version 2.0' should look like. In doing so, we derived the 'Troponin-only Manchester Acute Coronary Syndromes (T-MACS)' decision aid, a bespoke clinical prediction model. The decision aid set out to achieve six key things:

1. Use a single blood test taken at the time of arrival to guide decision making in the ED
2. Consider elements of the patient's history, physical examination, ECG and biomarker concentrations, thus taking full advantage of all diagnostic information that is available to clinicians in the ED
3. Guide clinicians in their decision making for every patient, rather than only 'ruling out' ACS in a proportion of patients.
4. Consider cardiac troponin as a continuous variable, without imposing artificial cut-offs that risk losing important diagnostic information.
5. Calculate the probability of ACS for each patient. This probability could be used by clinicians and patients to make personalized decisions about a patient's care.
6. Use a rigorous machine learning approach to derive the model, thus ensuring that the final version is based on the strongest possible evidence.

Based on these principles, we derived T-MACS by logistic regression. The final model includes seven variables. While T-MACS could be used as a simple checklist to 'rule out' ACS (Table 2), use with a computer or smartphone gives access to its full functionality. An example of a calculator is freely available online.[33]

T-MACS has been validated with both an hs-cTnT assay (Roche Diagnostics Elecsys)[34,35] and a contemporary cTnI assay (Siemens ADVIA Centaur TnI-Ultra) (36), the key results of which are summarised in Fig. 1. On external validation, T-MACS would have 'ruled out' 40.4% patients using hs-cTnT with a sensitivity and negative predictive value (NPV) of 98.8% and 99.7% respectively.[34] Using contemporary cTnI, T-MACS would have 'ruled out' ACS for 36.3% with a sensitivity and NPV of 98.7% and 99.3%, respectively (36). An

Table 2
Simplified checklist for using the T-MACS decision aid as a simple 'rule out' strategy based on the initial cardiac troponin concentration measured on arrival in the ED.

Variable	Score
Visible sweating	1 point
Systolic blood pressure <100 mmHg	1 point
Pain radiation to the right arm or right shoulder	1 point
Chest pain/discomfort associated with vomiting	1 point
Worsening (crescendo) angina	1 point
Acute ECG ischemia	1 point
cTn >9 ng/L	1 point
Total	
0 points: Eligible for immediate discharge	

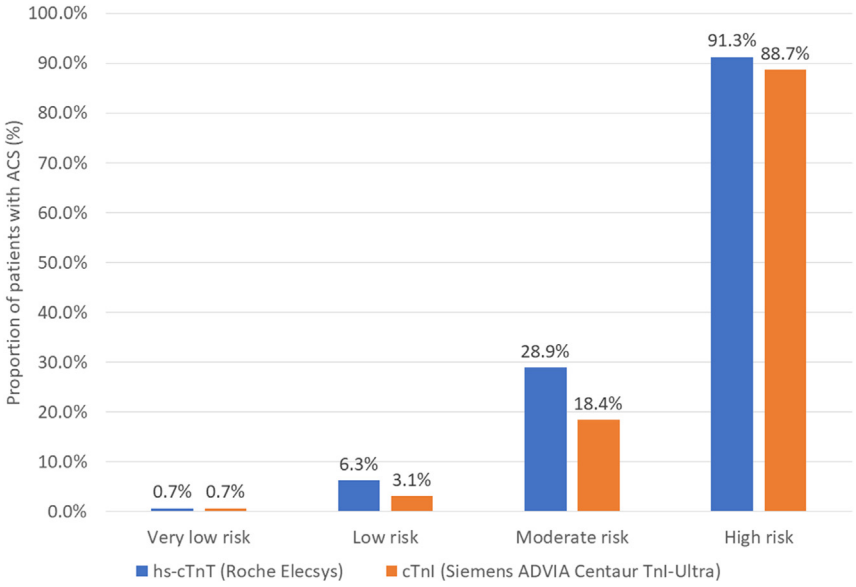

Fig. 1. Prevalence of ACS in each T-MACS risk group with hs-cTnT (original validation study, n = 1,459[34]) and contemporary cTnI (n = 405)[36].

Australasian validation study (n = 1715) found that T-MACS had lower sensitivity and NPV (99.1% and 99.2% respectively for AMI or emergency revascularization occurring within 30 days; 96.3% and 97.6% respectively for a broader definition of MACE including angiographic stenosis >70% identified within 30 days).[35] This may be due to heterogeneity in patient characteristics, or may be because this was a secondary analysis and relied on the use of surrogate variables ('prior angina' rather than 'worsening (or crescendo) angina' and 'diaphoresis' rather than specifically 'diaphoresis observed').

The original form of the T-MACS decision aid, which incorporated an additional biomarker (heart-type fatty acid binding protein) has also been evaluated in a pilot randomized controlled trial, in which clinical use of the decision aid was compared to standard practice involving serial troponin testing. Use of the decision aid led to an increase in the proportion of patients safely discharged from the ED within 4 h of arrival (adjusted odds ratio 5.5, 95% CI 1.7–17.1, p = 0.004), although the analysis was underpowered to specifically study the incidence of MACE in the 'very low risk' group.[37]

5. Future possibilities

This progress to date now opens the door to several important opportunities to further improve pathways to enhance the early diagnosis of ACS.

5.1. Incorporation of artificial intelligence

All clinical decision rules are subject to the phenomenon of 'calibration drift', whereby diagnostic performance deteriorates over time due to changes in patient demographics and clinical practice.[38] Thus all of the decision aids described above will soon need to be updated, refined or replaced. Further, our current approach is to provide healthcare with a 'one size fits all' approach, regardless of whether the decision aid is applied to a healthy 20 year-old patient or an 80 year-old patient with multiple co-morbidities. With the use of a computerized prediction model such as T-MACS, the data collected during routine clinical practice can be saved. If those data can be linked to other routinely collected data providing details of patient outcomes, the machine learning approach used to derive T-MACS can be extended to update and refine the model as time passes. This process can be fully or partially automated, thus introducing an artificial intelligence (AI) function that will help to protect the prediction model from calibration drift. As this approach will enable the accrual of vast amounts of data, the analyses will ultimately have sufficient statistical power to enable the consideration of new predictor variables. Importantly, it may be possible to identify subgroups of patients for whom existing clinical prediction models are suboptimal, and may be able to tailor the algorithm for those patients, thus enabling an increasing personalization of healthcare.

5.2. Shared decision making

The T-MACS model calculates the probability of ACS for each individual patient. This information is visible to clinicians, but there is an opportunity to also share this with patients, which could be used to fully inform patients of the advantages and disadvantages of different approaches to their healthcare, thus enabling a personalized approach to shared decision making. It has been demonstrated that patients who are given an opportunity to engage in shared decision making are more likely to choose to terminate all further investigations without any apparent effect on patient outcomes.[39] This suggests that patients may have a more pragmatic approach to risk than clinicians, and this approach may help to safeguard healthcare resources, which is vital given the increasing demand for emergency care.

5.3. Precision medicine

To date, clinical prediction models in this field have focused on guiding 'rule in' and 'rule out' decisions only. By using a computerized clinical prediction model, it is possible to guide more decisions including decisions about patient treatment. For example, the model could be used to calculate the probability of benefit and harm with each possible treatment option, based on the available data about the patient's background and current clinical status. Thus, treatment decisions (such as the decision to prescribe antiplatelet medication or to proceed to coronary angiography) can be increasingly personalized, targeting treatments to those who stand

to benefit most and reducing the potential for adverse effects.

5.4. Point of care testing

To date, existing clinical prediction models have been validated using laboratory-based assays. However, algorithms such as T-MACS and the HEART score rely on a single measurement of cardiac troponin to guide decision making. If these algorithms could be validated using portable point of care troponin assays, then it may not be necessary to transport patients to hospital for investigations to take place. Thus, patients may be cared for in the ambulance or in ambulatory environments close to home.

6. Summary

There has been tremendous recent progress in our approach to the early 'rule in' and 'rule out' of ACS in emergency settings. It is now possible to use serial troponin sampling over as little as 1 h to 'rule in' and 'rule out' the diagnosis of AMI for the majority of patients. ACS could be immediately 'ruled out' for a substantial proportion of patients following a single blood test by using the limit of detection of an hs-cTn assay as a 'rule out' threshold, by using the HEART score or the T-MACS algorithm. Recent successful validation of the T-MACS algorithm demonstrates that it is safe and feasible to use a machine learning approach, integrating elements of the history, ECG and cardiac troponin concentrations measured on arrival in the ED to guide clinical decision making. As well as enhancing the care that can be provided now, these recent advances demonstrate that there is tremendous future potential to further improve care pathways in this field. The future use of artificial intelligence, shared decision making, novel applications of precision medicine and portable near-patient testing promise to increasingly personalize healthcare, while reducing unnecessary healthcare resource utilization.

Declarations

The authors declare the following interests: Richard Body has undertaken research involving donation of reagents without charge by Roche, Abbott, Alere, Siemens, Randox, FABPulous BV and Singulex. Richard Body has accepted speaker fees from Singulex, Alere and Siemens and provision of travel and accommodation to present research findings at conferences from Roche and Randox.

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