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Understanding cardiac troponin part 2: early rule out of acute coronary syndrome

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ABSTRACT

Chest pain of suspected cardiac origin is a very common emergency department presentation. Over the past decade, there has been an exponential growth in strategies that promote blood sampling at earlier and earlier time points after presentation to facilitate the rule out of acute coronary syndrome.

In part 2 of this series, we examine key concepts from the recent literature with the aim of improving clinicians' understanding of the rule-out strategies available to them and provide a structured overview of strategies that facilitate discharge with blood testing over <3 hours.

CLINICAL CASE

A female aged 52 years presents to the ED having experienced 30 min of central chest discomfort radiating to the jaw 90 min prior to attendance. Physical examination and observations are unremarkable. She has a previous history of hypertension but no other risk factors for coronary artery disease. Current medications include ramipril. The ECG recorded at presentation to the ED shows no abnormalities. She remains pain free and feels well.

QUESTION

What are the options for ruling out of acute coronary syndrome (ACS) early (with blood testing over <3 hours) in this patient?

To answer that question, this work will provide an overview of current early rule-out strategies and a practical guide for clinical implementation based on current best evidence.

Key concepts

Emergency medicine literature is abundant in chest pain diagnostics research. Over the past decade, there has been an exponential growth in strategies that promote blood sampling at earlier and earlier time points after presentation to facilitate the rule out of ACS. Emergency physicians must have an accurate grasp of key concepts from the literature before implementing rapid rule-out strategies.

WHAT ARE WE TRYING TO RULE OUT?

ACS represents a spectrum of clinical conditions, which includes unstable angina (UA), non-ST-elevation myocardial infarction, ST-elevation myocardial infarction and cardiac death. It is imperative for the ED physician—and the patient—to understand that ruling out an acute myocardial infarction (AMI) is not the same as ruling out ACS. At least some patients with UA, who by definition will not have a troponin elevation, will derive prognostic benefit from early coronary intervention and are at a higher risk of adverse events.[1] The identification of these patients remains problematic but clinically essential.

It is important to understand that the chest pain diagnostic literature varies in selection of what constitutes an adverse cardiac event. Some large-scale analyses examining early rule-out strategies have chosen to exclude UA as an outcome and have only reported fatal or non-fatal AMI.[2–5] Others have used a broader definition of major adverse cardiac events (MACE) at 30 days, which includes the need for revascularisation.[6–8] In the absence of a universal definition of MACE, there is subtle variation in the reporting of revascularisation end points from including all patients with a coronary stenosis >50%, even if revascularisation did not take place,[8] to including only those who have undergone symptom-driven emergency revascularisation.[6] Clinicians should be mindful of the variations in outcome reporting when interpreting the diagnostic literature and consider whether an early rule-out strategy safely rules out the full spectrum of ACS.

WHAT IS THE ACCEPTABLE RISK OF MISSED EVENTS?

No diagnostic test in medicine is 100% accurate. However, when considering early rule-out strategies, it is generally considered that clinicians will accept a miss-rate for MACE between 0% and 1%.[9] This equates to a diagnostic sensitivity threshold of 99%. Importantly, patients themselves may be willing to accept a higher miss-rate (2%) when presented with the risk of missed events as part of shared decision-making.[10]

When presented with diagnostic accuracy statistics in analysis of early rule-out strategies, clinicians should also consider the lower bounds of the 95% CIs of sensitivity and consider if they would be satisfied with the safety of the strategy if the true sensitivity was around this lower bound. The width of the CIs will depend on the size of the study population and the incidence of adverse events. For example, one single-centre study of just under 1000 patients, examining an early rule-out strategy using a single high-sensitivity troponin (hs-cTn) in combination with a risk score presents an excellent point estimate of sensitivity for MACE of 99.0% but with the lower bound of the CIs at 93.7%.[11] Given the potential medical and medicolegal implications of missing MACE clinicians should evaluate both point estimates of sensitivity and 95% CIs and be encouraged to adopt a cautious approach.

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IMPLICATIONS OF STUDY DESIGN

A common theme among studies evaluating early rule-out strategies using hs-cTn is that the vast majority are observational and data are reported in patients who were not actually discharged based on hs-cTn results. Evaluating new diagnostic technology with observational research alone has important limitations. It is possible that beneficial effects will be diluted because clinicians do not abide by their recommendations. Furthermore, unanticipated effects such as rebound overuse of resources have previously been reported and have meant that apparently safe strategies are not cost-effective.[12 13] Therefore, the clinical effectiveness and cost-effectiveness of the majority of these strategies remains unknown. Furthermore, there remains a paucity of research evaluating the acceptability of very early discharge to patients, in what is likely to be a high anxiety presentation. Further interventional research is required, which incorporates assessment of clinical effectiveness and cost-effectiveness, together with patient views and shared decision-making, prior to the widespread implementation of the majority of early rule-out strategies.

EARLY RULE-OUT STRATEGIES USING HIGH-SENSITIVITY TROPONIN TESTING IN <3 HOURS

Clinicians rely on three elements to rule out ACS: clinical findings, ECG and cardiac biomarkers. Although some elements of the history and examination have been shown to be excellent predictors of ischaemia and are used successfully within risk scores,[8 11] history alone is an unreliable predictor of AMI.[14] Few patients (14%) have an ECG that is diagnostic.[15] Therefore, the majority of patients require cardiac biomarker testing. For many years, patients who present to the ED with suspected cardiac chest pain have required serial troponin testing over 3–12 hours before ACS can be safely ruled out. This prolonged assessment has been driven by limitations in cardiac biomarker analysis. In part 1 of this series, we discussed how cardiac troponin is central to the diagnosis of AMI and how hs-cTn assays have recently been developed. These assays can detect troponin in over 50% of healthy individuals[16] and this improved analytical sensitivity has transformed the way we rule out ACS. There are now a number of early rule-out strategies available to ED clinicians, who have access to hs-cTn assays, to facilitate early discharge of low-risk patients using either single hs-cTn testing or serial testing in under 3 hours (table 1).

SINGLE TEST RULE-OUT STRATEGIES

Clearly, in busy and crowded EDs the ability to 'rule out' ACS with a single blood test at the time of arrival has advantages over a strategy involving serial testing. Many such strategies show considerable promise.

The 'limit of detection' rule-out strategy

'Ruling out' ACS for patients with troponin concentrations below the limit of detection (LoD; lowest analyte concentration at which detection is feasible) of a high-sensitivity assay (<5 ng/L for Roche hs-cTnT or <2 ng/L for Abbott hs-cTnI) appears safe (sensitivity approaching 98% for AMI and MACE) and may allow discharge between 20% and 30% of patients depending on the assay used.[2 5 17–19] However, caution should be exercised prior to widespread implementation of this strategy. The assay precision at the very low cut-off concentration is variable[16] and as such the proportion of patients eligible for discharge using this approach may vary widely between centres. Furthermore, no interventional data currently exist to support its use and it remains relatively untested against revascularisation end points. Of note, although some contemporary (ie, not meeting the criteria for being high-sensitivity) troponin assays can detect troponin concentrations below the 99th percentile upper reference limit, the sensitivity is lower (97.1%), which currently means that they are not recommended for use in clinical practice.[20]

For other rule-out strategies that use a single hs-cTn result, such as those using higher cut-offs above the LoD or combining hs-cTn results with a risk score, clinicians should ascertain whether it has been validated and remains effective using the assay available to them. For example, one suggested strategy uses a cut-off concentration above the LoD but below the 99th percentile for Abbott hs-cTnI at 5 ng/L.[3] This cut-off concentration may allow the discharge of over 60% of patients, with the authors citing a high negative predictive value of >99%.[3] However, the sensitivity has been consistently shown to be relatively low at 93.8% in the original derivation cohort, 94.3% on internal validation and 94.5% (95% CI 91.1% to 96.7%) on subsequent external validation in 3155 patients.[5] The evidence is similar with the alternative Roche hs-cTnT assay. At cut-offs above the LoD but below the 99th percentile, the point estimate sensitivities for MACE <97%.[21]

THE MANCHESTER ACUTE CORONARY SYNDROMES DECISION AID

The Manchester Acute Coronary Syndromes decision aid (MACS) is a clinical prediction model that was prospectively derived specifically for use in patients presenting to the ED with suspected cardiac chest pain. It combines information from a patient's history with ECG findings and troponin concentrations measured at the time of arrival to calculate the probability that a patient has ACS. Based on that probability, patients can be 'ruled out' immediately (probability <2%), 'ruled in' immediately (probability >95%) or triaged to one of two levels of inpatient care ('low risk' and 'moderate risk') to await serial troponin sampling. As such, it could be combined with other rule-out strategies involving serial sampling.

The original MACS decision aid derived by multivariate analysis included two biomarkers: hs-cTnT and heart-type fatty acid binding protein (h-FABP), a biomarker of myocardial injury that is known to rise early after the onset of ischaemia.[22] On external validation, the original algorithm had 100.0% sensitivity for AMI (95% CI 95.4% to 100.0%) and 98.0% (93.0%–99.8%) sensitivity for MACE. Both of the missed MACEs were isolated coronary stenoses that did not require coronary intervention, emphasising the importance of noting the details of study design and outcome definition when appraising the evidence. The decision aid was later validated with an automated assay for h-FABP, which is commercially available and can be run on modular analysers in most hospital laboratories.[23] This refined algorithm was then evaluated in a pilot randomised controlled trial. Patients receiving care guided by the MACS rule were significantly more likely to be safely discharged within 4 hours of arrival in the ED (adjusted OR 5.5, 95% CI 1.71 to 17.11, P=0.004) with no missed MACEs.[24]

However, to further increase usability, the algorithm was again refined to evaluate its diagnostic performance without h-FABP. This troponin-only MACS decision aid (T-MACS) was externally validated in 1459 patients. The sensitivity was not significantly different to the original MACS model (98.1%, 95% CI 95.2 to 99.5, vs 100.0%, 95% CI 95.4% to 100.0%) but would allow more patients to have ACS ruled out immediately (40.4% vs 18.0%).[8]

Table 1 Early rule-out strategies using high-sensitivity troponin testing in under 3 hours externally validated in large cohort studies or recommended by current consensus guidelines

Early rule-out strategy	Clinical implementation	Sensitivity (95% CI)	% Eligible for early rule out	Critique
Single hs-cTn test				
Limit of detection (LoD) of high-sensitivity troponin*	Discharge if hs-cTnT (<5 ng/L) or hs-cTnI (<2 ng/L) at presentation and a non-ischaemic ECG	**hs-cTnT**: 99.1% (96.7 to 99.9) for AMI[17] 99.2% (95.6 to 100) for 30-day MACE[18] 100% (95.4 to 100) for AMI[19] **hs-cTnI:** 99.0% (96.8 to 99.7) for non-fatal/fatal AMI[5]	**hs-cTnT**: 36.7%[17] 29.2%[18] 17.3%[19] **hs-cTnI**: 18.8%[5]	Few studies test LoD in combination with ECG findings. Variation in outcomes (AMI vs MACE). High sensitivity (>99%) but with wide CIs. Variance in proportion suitable for discharge and clinical effectiveness unknown.
Higher cut-offs of high-sensitivity troponin (above the LoD but below the 99th percentile): *High-STEACS*[3]	**hs-cTnT**: not recommended **hs-cTnI**: discharge after a single result <5 ng/L and >2 hours from pain onset	**hs-cTnT**:<97% for MACE[21] **hs-cTnI**: 98.6% (97.7 to 99.4).[3] 94.5% (91.1 to 96.7)[5]	**hs-cTnT**: not applicable **hs-cTnI**: 61%,[3] 66.5%[5]	High proportion suitable for early discharge but at cost of sensitivity. Relatively untested against full spectrum of ACS). Caution in early presenters (<2 hours from pain onset). Assay specific (hs-cTnI only).
Troponin-only Manchester Acute Coronary Syndromes decision aid[8]	**hs-cTnT**: clinical variables (worsening angina, radiation of pain to right arm, vomiting, sweating, hypotension and ECG ischaemia) in combination with hs-cTnT concentration. Computer algorithm generates predicted probability of ACS. Discharge if very low risk. 'Rule in' ACS if high risk **hs-cTnI**: not currently validated	**hs-cTnT**: 98.7% (95.3 to 99.8) for 30-day MACE in derivation cohort. 98.1% (95.2 to 99.5) in validation set.[8] **hs-cTnI**: unvalidated therefore unknown	**hs-cTnT**: 37.7% in derivation cohort. 40.4% in validation set.[8]	Sensitivity high (>98%) but wide CIs. High proportion suitable for discharge (>35%). Allows rule in (10% ruled in with 100% specificity for ACS). Unvalidated with hs-cTnI.
HEART Care	The HEART score combining variables from the history, ECG, age, risk factors and troponin results. Studies have evaluated various troponin assays. Only one study has evaluated the HEART score with hs-cTnI[38]	Pooled sensitivity 96.7% (95% CI 94.0% to 98.2%) from 11 studies including 11 217 patients[26] In a cluster RCT of 3648 patients, the incidence of MACE in low-risk patients (HEART score 0–3) was 2.0% (1.2 to 3.0)[13]	39.3% classified as low risk and eligible for early discharge. Non-adherence to strategy in 41.0% of low-risk patients.[13]	Systematic review: sensitivity below acceptability.[26] Interventional trial: demonstrates non-adherence to strategy. No improvements demonstrated in early discharge rates or downstream resource use.[13]
0/1 hour hs-cTn tests				
European Society of Cardiology 0/1 hour rule-out and rule-in algorithm[32]	Discharge if the hs-cTn concentration is <LoD and pain >3 hours ago. Or discharge if 0 hour hs-cTn low and the lack of a relevant increase within 1 hour (see guideline for increase[32]).	**hs-cTnT**: 96.7 % (93.4 to 98.7) for AMI.[4 37] **hs-cTnI** : 98.8 % (96.4 to 99.7) for AMI.[4 37]	**hs-cTnT**: 63.4 %.[4 37] **hs-cTnI**: 54.2 %.[4 37]	High proportion ruled out (> 50%). May not meet required sensitivity threshold. Revascularisation end points not reported. Allows rule in with good positive predictive value.
0/2 hours hs-cTn tests				
ADAPT Accelerated Diagnostic Protocol.[27–29]	**hs-cTnT**: discharge if hs-cTnT <14 ng/L at 0 and 2 hours and TIMI score ≤1 and ECG normal.[27] **hs-cTnI**: discharge if hs-cTnI <26 ng/L at 0 and 2 hours and TIMI ≤1† and ECG normal.[6]	**hs-cTnT:** 100 % (98.2 to 100) for 30-day MACE in derivation cohort. 97.4 (94.5 to 98.8) in validation set.[27] **hs-cTnI:** 99.2 (97.1 to 99.8) for 30-day MACE in derivation cohort. 99.4 % (96.5 to 100) in validation set.[6 27]	**hs-cTnT:** 34.5 % in derivation cohort. 40.3 % in validation set.[27] **hs-cTnI**: 41.5 % in derivation cohort. 38.6 % in validation set.[6]	Implementation evidence available.[28 29] Most patients will not be discharged until at least 4 hours after ED attendance.[28 29]

*In the UK, NICE recommends that the LoD strategy can be used with both hs-cTnI and hs-cTnT. However, NICE recommends that only patients who also have a low TIMI risk score can be discharged.[36] This strategy remains unvalidated.
†Sex-specific cut-offs may be used for the Abbott hs-cTnI assay; 16 ng/L for women and 34 ng/L for men. The Emergency Department Assessment of Chest Pain Score can be used in place of TIMI.[37]
hs-cTnT, Roche high-sensitivity cardiac troponin T; ADAPT, 2-hour accelerated diagnostic protocol; AMI, acute myocardial infarction; hs-cTn, single high-sensitivity troponin; HEART, History, ECG, Age, Risk factors and Troponin; High-STEACS, High-sensitivity Troponin in the Evaluation of patients with Acute Coronary Syndrome; hs-cTnI, Abbott high-sensitivity cardiac troponin I; MACE, major adverse cardiac events; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; TIMI, Thrombolysis in Myocardial Infarction.

The algorithm has also been validated in an Australasian cohort of 1244 patients. Sensitivity was maintained for AMI within 30 days (99.1%, 95% CI 95.2% to 100.0%). Fewer patients would have been 'ruled out' with T-MACS (19.8%) but this may be because of the use of surrogate variables in this secondary analysis from previous cohort studies.[25] T-MACS has not yet been validated for use with hs-cTnI.

THE HEART SCORE

The History, ECG, Age, Risk factors and Troponin (HEART) Score has been tested within an interventional study, allowing discharge after a single troponin (both high-sensitivity and contemporary troponins were used) result.[13] This randomised controlled trial was designed to measure the effect of the use of

this strategy (termed HEART Care) on patient outcomes and use of healthcare resources. Importantly, while the strategy tested appeared as safe as standard care (incidence of MACE in low-risk patients was 2.0%), its implementation did not lead to significant differences in early discharge rates or downstream resource use. ED clinicians appear reticent to adhere to this rule-out strategy in facilitating early discharge. A recent meta-analysis of 9 studies including 11 217 patients found that the pooled sensitivity of the HEART score is 96.7% (95% CI 94.0% to 98.2%) for MACE, suggesting a miss-rate that may be unacceptable to clinicians.[26] The majority of studies included in this analysis were contemporary rather than high-sensitivity troponin assays.

THE 2-HOUR ACCELERATED DIAGNOSTIC PROTOCOL

Perhaps the best validated early rule-out strategy is the 2-hour accelerated diagnostic protocol (ADAPT), which combines the TIMI score for UA with troponin assay results taken at presentation and 2 hours later.[27–31] This strategy has been successfully tested within two interventional studies. The first compared use of ADAPT with the TIMI score to 6–12 hours troponin testing and found a significant increase in successful discharges within 6 hours with ADAPT (19.3% vs 11.0%, OR 1.92, 95% CI 1.18 to 3.13).[30] The second was a pragmatic trial comparing the use of the TIMI score with the Emergency Department Assessment of Chest Pain Score (EDACS), which was derived specifically for use in patients with suspected cardiac chest pain.[28] In that trial, the proportion of patients successfully discharged within 6 hours was similar for both TIMI and EDACS (32.3% vs 34.4%). This approach has been successfully implemented across Queensland, Australia with subsequent evaluation demonstrating both clinical effectiveness and cost-effectiveness.[29] Importantly, ADAPT has also been tested using both high-sensitivity[6 27] and contemporary[31] troponin assays. While safety is maintained using either high-sensitivity or troponin assays, the use of contemporary troponin leads to significantly fewer patients being eligible for early discharge (40% vs 20%). Therefore, ADAPT remains a viable option for implementation, yet clinicians should be aware that due to limitations clinical and laboratory processing times with strategies reliant on two blood tests, most patients will still not be discharged until at least 4 hours after ED attendance.[28]

Caution in early presenters

Strategies reliant on low cut-offs of high-sensitivity troponin at presentation have been shown to have an unacceptable diagnostic performance in early presenters, that is, where a sample is taken <2 hours from chest pain onset.[3–5] To this end, current European Society of Cardiology guidelines recommend that the LoD strategy only be applied using testing 3 hours after chest pain onset,[32] and higher cut-offs of high-sensitivity troponin (above the LoD but below the 99th percentile) such as the High-STEACS strategy only be applied 2 hours after chest pain onset.[3] Given that the median time to chest pain onset in one UK study was 2 hours 20 min,[11] this may have implications for the applicability of these strategies in facilitating very early discharge.

EARLY RULE-OUT STRATEGIES USING CONTEMPORARY TROPONIN TESTING IN UNDER 3 HOURS

Globally, many EDs will not have access to hs-cTn assays. For example, in the USA the hs-cTnT assay has only recently (January 2017) been approved by the Food and Drug Administration for clinical use (with caveats that prevent the use of the LoD) and the hs-cTnI assay is still awaiting approval. To overcome the limitations of contemporary troponin assays, prior studies examining rapid rule-out strategies have combined such assays with a panel of traditional cardiac biomarkers such as creatine kinase MB and myoglobin.[33 34] The ASia-Pacific Evaluation of Chest Pain Trial aimed to prospectively validate the safety of a predefined 2-hour accelerated diagnostic protocol combining the TIMI score and negative point-of-care biomarker results.[33] A total of 3582 patients were enrolled, of which only 10% were considered low risk and eligible for discharge. This strategy had a sensitivity for of 99.3% (97.9–99.8) for 30-day MACE. In subsequent analysis, when creatine kinase MB and myoglobin were removed from the analysis and only contemporary troponin was used, the proportion of patients eligible for early discharge rose to 20% with a similar diagnostic sensitivity.[31] In a recently published interventional trial (Improved Assessment of Chest pain Trial), recruiting 1366 participants at a single centre in Australia, using negative contemporary troponin results at 0/2 hours in low-risk patients facilitated the early discharge (median length of stay 5.1 hours) of 17.9% of patients with suspected cardiac chest pain with no missed 30-day events.[34]

The Randomised Assessment of Treatment using Panel Assay of Cardiac markers Trial sought to evaluate point-of-care biomarkers tested measured at presentation and after 90 min.[35] In an interventional trial of 2243 ED patients with chest pain, this strategy was found to be potentially safe with a 3% rate of MACE in those discharged, allowing 32% of patients to be discharged within 4 hours. Yet, limitations in the availability of the diagnostic equipment used (Beckmann Access Triple Panel) and a failure to demonstrate effectiveness in terms of downstream resource use have meant widespread uptake of this strategy has been limited. Furthermore, subsequent analysis of this cohort found that measurement of contemporary troponin alone is sufficient for diagnosis.[36]

Centres that do not have access to high-sensitivity troponin assays may still be able to apply rapid rule-out strategies that incorporate troponin sampling over <3 hours, yet the proportion of patients eligible for early discharge may be reduced.

CLINICAL CASE: OUTCOME

Returning to the clinical case, the presentation is clearly compatible with a suspected ACS and focus of this encounter will be on ruling out this important diagnosis. The use of low cut-off concentration of high-sensitivity troponin (at the LoD for either hs-cTnT or hs-cTnI, or a cut-off of 5 ng/L for hs-cTnI) in combination with a non-ischaemic ECG taken at presentation may allow the safe rule out of AMI in this case. However, given the safety of strategies that rely on very low cut-off of hs-cTn have been questioned in very early presenters (90 min in this case), it would be prudent to wait until at least 3 hours after chest pain onset before applying such a strategy. Furthermore, the assessing clinician also needs to consider whether this approach will safely rule out the full spectrum of ACS, namely UA. Therefore, the addition of a risk stratification such as TIMI, T-MACS, EDACS or HEART, which have been tested against revascularisation end points, would allow the consideration of this diagnosis and may prompt further testing. For sites without access to high-sensitivity troponin assays, early rule out may still be possible with serial testing over 0/2 hours, although formal risk stratification is again recommended. We would therefore need to know a few more details about the character of chest pain and there will be benefit from clinical interpretation of the history and examination findings before reliably calculating each score. There are several options to confidently rule out an ACS event using blood testing over <3 hours in this case.

MAKING A CHOICE OF WHICH RAPID RULE-OUT STRATEGY TO USE

When selecting a rule-out strategy for clinical use, emergency physicians should follow the following five principles:

1. Understand the troponin assay you have available and only apply strategies that have been validated using your assay.
2. Consider using a formal risk-stratification tool such as TIMI or T-MACS. These may allow improved detection of patients across the whole spectrum of ACS.
3. It is important to take account of both sensitivity and negative predictive value when appraising diagnostic accuracy, as the latter is heavily influenced by prevalence. Ideally, these measures should be reported for MACE occurring within 30 days. Consider the lower bounds of the CIs (table 1).
4. Efficacy, as measured by the proportion of patients who may be eligible for early discharge, may not translate to clinical effectiveness, whereby patients are actually discharged early and downstream resource uses are saved.
5. Be wary of blindly applying consensus guidelines, some of which have demonstrated suboptimal accuracy on external validation.[32 37] Consider the alternatives.

THE EXPERT'S CHOICES

Edd Carlton's ED uses the 0/2 hours ADAPT strategy in combination with the Roche hs-cTnT assay. For him, this remains the best validated and applicable early rule-out strategy. It will also allow robust comparison with a single testing strategy (The Limit of Detection and ECG Diagnostic Strategy), when he commences this National Institute for Health Research funded multicentre randomised controlled trial in late 2017.

Rick Body's ED uses the T-MACS decision aid with the Roche hs-cTnT assay. This algorithm was derived specifically for use in patients presenting to the ED and could allow immediate 'rule out' with a single blood test, and risk stratification of the other patients. The highest risk patients are considered 'ruled in' with high positive predictive value while the remainder can be effectively triaged to either an ambulatory care unit or an acute medical unit. As the algorithm calculates the probability of ACS and uses a computer interface ensuring that all data can be saved, using T-MACS opens up numerous possibilities to develop innovative future care models. Communicating the probability of ACS with patients, for example, could enable a personalised approach to shared decision-making and help both patients and clinicians to adopt more objective, realistic and sustainable approaches to handling uncertainty and risk.

SUMMARY

There are a number of options available to emergency physicians in facilitating the early rule out of ACS in patients with chest pain using blood testing over <3 hours. The advent of high-sensitivity cardiac troponin testing may allow improved efficacy of such strategies, even allowing discharge after a single troponin taken at presentation. However, the clinical effectiveness of these strategies may be variable and many strategies are assay-specific. Caution in clinical implementation and local audit for safety and effectiveness is advised.

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REFERENCES

1 Hamm CW, Bassand JP, Agewall S, *et al*. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999–3054.
2 Bandstein N, Ljung R, Johansson M, *et al*. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. *J Am Coll Cardiol* 2014;63:2569–78.
3 Shah AS, Anand A, Sandoval Y, *et al*. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet* 2015;386:2481–8.
4 Mueller C, Giannitsis E, Christ M, *et al*. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med* 2016;68:76–87.
5 Carlton E, Greenslade J, Cullen L, *et al*. Evaluation of High-Sensitivity Cardiac Troponin I Levels in Patients With Suspected Acute Coronary Syndrome. *JAMA Cardiol* 2016;1:405–12.
6 Cullen L, Mueller C, Parsonage WA, *et al*. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol* 2013;62:1242–9.
7 Backus BE, Six AJ, Kelder JC, *et al*. A prospective validation of the HEART score for chest pain patients at the emergency department. *Int J Cardiol* 2013;168:2153–8.
8 Body R, Carlton E, Sperrin M, *et al*. Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid: single biomarker re-derivation and external validation in three cohorts. *Emerg Med J* 2017;34:349–56.
9 Than M, Herbert M, Flaws D, *et al*. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. *Int J Cardiol* 2013;166:752–4.
10 Hess EP, Knoedler MA, Shah ND, *et al*. The chest pain choice decision aid: a randomized trial. *Circ Cardiovasc Qual Outcomes* 2012;5:251–9.
11 Carlton EW, Cullen L, Than M, *et al*. A novel diagnostic protocol to identify patients suitable for discharge after a single high-sensitivity troponin. *Heart* 2015;101:1041–6.
12 Fitzgerald P, Goodacre SW, Cross E, *et al*. Cost-effectiveness of point-of-care biomarker assessment for suspected myocardial infarction: the randomized assessment of treatment using panel Assay of cardiac markers (RATPAC) trial. *Acad Emerg Med* 2011;18:488–95.
13 Poldervaart JM, Reitsma JB, Backus BE, *et al*. Effect of Using the HEART Score in Patients With Chest Pain in the Emergency Department: A Stepped-Wedge, Cluster Randomized Trial. *Ann Intern Med* 2017;166:689–97.
14 Carlton EW, Than M, Cullen L, *et al*. 'Chest pain typicality' in suspected acute coronary syndromes and the impact of clinical experience. *Am J Med* 2015;128:1109–16.
15 Goodacre S, Cross E, Arnold J, *et al*. The health care burden of acute chest pain. *Heart* 2005;91:229–30.
16 Apple FS, Collinson PO. IFCC Task Force on Clinical Applications of Cardiac Biomarkers. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem* 2012;58:54–61.
17 Body R, Mueller C, Giannitsis E, *et al*. The Use of Very Low Concentrations of High-sensitivity Troponin T to Rule Out Acute Myocardial Infarction Using a Single Blood Test. *Acad Emerg Med* 2016;23:1004–13.
18 Mokhtari A, Lindahl B, Smith JG, *et al*. Diagnostic Accuracy of High-Sensitivity Cardiac Troponin T at Presentation Combined With History and ECG for Ruling Out Major Adverse Cardiac Events. *Ann Emerg Med* 2016;68:649–58.
19 Body R, Burrows G, Carley S, *et al*. High-sensitivity cardiac troponin t concentrations below the limit of detection to exclude acute myocardial infarction: a prospective evaluation. *Clin Chem* 2015;61:983–9.
20 Body R, Burrows G, Carley S, *et al*. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a sensitive troponin I assay. *Ann Clin Biochem* 2015;52(Pt 5):543–9.
21 Carlton E, Kendall J, Khattab A, *et al*. Low concentrations of high-sensitivity troponin T at presentation to the emergency department. *Clin Chem* 2017;63:431–2.
22 Body R, Carley S, McDowell G, *et al*. The Manchester Acute Coronary Syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. *Heart* 2014;100:1462–8.
23 Body R, Burrows G, Carley S, *et al*. The Manchester Acute Coronary Syndromes (MACS) decision rule: validation with a new automated assay for heart-type fatty acid binding protein. *Emerg Med J* 2015;32:769–74.

24 Body R, Boachie C, McConnachie A, *et al*. Feasibility of the Manchester Acute Coronary Syndromes (MACS) decision rule to safely reduce unnecessary hospital admissions: a pilot randomised controlled trial. *Emerg Med J* 2017;34:586–92.
25 Greenslade JH, Nayer R, Parsonage W, *et al*. Validating the Manchester Acute Coronary Syndromes (MACS) and Troponin-only Manchester Acute Coronary Syndromes (T-MACS) rules for the prediction of acute myocardial infarction in patients presenting to the emergency department with chest pain. *Emerg Med J* 2017;34:517–23.
26 Van Den Berg P, Body R. The HEART score for early rule out of acute coronary syndromes in the emergency department: a systematic review and meta-analysis. *Eur Heart J Acute Cardiovasc Care* 2017:204887261771078.
27 Meller B, Cullen L, Parsonage WA, *et al*. Accelerated diagnostic protocol using high-sensitivity cardiac troponin T in acute chest pain patients. *Int J Cardiol* 2015;184:208–15.
28 Than MP, Pickering JW, Aldous SJ, *et al*. Effectiveness of EDACS versus ADAPT Accelerated Diagnostic Pathways for Chest Pain: a pragmatic randomized controlled trial embedded within practice. *Ann Emerg Med* 2016;68:93–102.
29 Parsonage WA, Milburn T, Ashover S, *et al*. Implementing change: evaluating the Accelerated Chest pain Risk Evaluation (ACRE) project. *Med J Aust* 2017;207:201–5.
30 Than M, Aldous S, Lord SJ, *et al*. A 2-hour diagnostic protocol for possible cardiac chest pain in the emergency department: a randomized clinical trial. *JAMA Intern Med* 2014;174:51–8.
31 Than M, Cullen L, Aldous S, *et al*. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. *J Am Coll Cardiol* 2012;59:2091–8.
32 Roffi M, Patrono C, Collet JP, *et al*. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267–315.
33 Than M, Cullen L, Reid CM, *et al*. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. *Lancet* 2011;377:1077–84.
34 Cullen L, Greenslade JH, Hawkins T, *et al*. Improved Assessment of Chest pain Trial (IMPACT): assessing patients with possible acute coronary syndromes. *Med J Aust* 2017;207:195–200.
35 Goodacre SW, Bradburn M, Cross E, *et al*. The Randomised Assessment of Treatment using Panel Assay of Cardiac Markers (RATPAC) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. *Heart* 2011;97:190–6.
36 Collinson P, Goodacre S, Gaze D, *et al*. Very early diagnosis of chest pain by point-of-care testing: comparison of the diagnostic efficiency of a panel of cardiac biomarkers compared with troponin measurement alone in the RATPAC trial. *Heart* 2012;98:312–8.
37 Pickering JW, Greenslade JH, Cullen L, *et al*. Assessment of the european society of cardiology 0-hour/1-hour algorithm to rule-out and rule-in acute myocardial infarction. *Circulation* 2016;134:1532–41.
38 Carlton EW, Khattab A, Greaves K. Identifying patients suitable for discharge after a single-presentation high-sensitivity troponin result: a comparison of five established risk scores and two high-sensitivity assays. *Ann Emerg Med* 2015;66:635–45.

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Notes