Clinical Chemistry 63:1
129–139 (2017)

Early Rule-Out and Rule-In Strategies for Myocardial Infarction

Louise A. Cullen,[1*] Nicholas L. Mills,[2] Simon Mahler,[3] and Richard Body[4]

BACKGROUND: Patients with chest pain comprise a large proportion of emergency presentations and place a major burden on healthcare resources. Therefore, efforts to safely and rapidly identify those with and without acute myocardial infarction (AMI) are needed. The challenge for clinicians is to accurately identify patients with acute coronary syndromes, while balancing the need to safely and rapidly reassure and discharge those without serious conditions.

CONTENT: This review summarizes the evidence to date on optimum accelerated strategies for the rule-in and rule-out of AMI, using strategies focused on optimum use of troponin results. Evidence based on both sensitive and highly sensitive troponin assay results is presented. The use of novel biomarkers is also addressed and the combination of biomarkers with other clinical information in accelerated diagnostic strategies is discussed.

SUMMARY: The majority of patients, who are not at risk of myocardial infarction or other serious harm, may be suitable for discharge directly from the emergency setting using approaches focused on troponin algorithms and accelerated diagnostic protocols. Evidence about the clinical and health economic impact of use of such strategies is needed, as they may have major benefits for both patients and healthcare providers.

The burden of assessment of patients with chest pain and other symptoms of possible acute coronary syndromes (ACS)[5] for emergency departments (EDs) is large, with this patient cohort representing between 5% and 10% of ED presentations *(1)*. ACS, encompassing the clinical entities of acute myocardial infarction (AMI) and unstable angina, remains the leading cause of death in most countries, and missed diagnoses are associated with significant morbidity and mortality *(2)*. The challenge for clinicians is to accurately identify patients with ACS or patients at risk for ACS within 30 days while balancing the need to safely and rapidly reassure and discharge those without. Early and accurate identification of those with AMI allows prompt use of evidence-based treatments to improve outcomes in those with the condition, while improved methods to identify patients without will have important benefits both to patients and health services.

The assessment process of patients with possible ACS is problematic and traditional methods to identify patients with an AMI are lengthy *(3)*. Clinicians' diagnostic acumen is challenged by the diverse symptoms and signs associated with ACS, hence the development of risk scores that combine clinical assessment with investigations such as the electrocardiogram (ECG) and biomarkers of myocardial necrosis (Fig. 1) *(4)*. Increasingly it is recognized that determination of patients' risk of ACS based on clinical gestalt alone is limited *(5)* and inferior to the use of some risk stratification tools. This has led to endeavors to improve risk stratification tools, with the search for the optimum rule continuing.

Biomarker evidence of AMI has evolved rapidly over the last two decades. Previously delayed serial testing of biomarkers such as creatine kinase MB isoenzyme (CK-MB), aspartate aminotransferase (AST), and lactate dehydrogenase (LD) over at least a 12-h period was required. However, this approach is now obsolete given the development of cardiac troponin assays with greater sensitivity and specificity *(6)*. High sensitivity troponin as-

[1] Royal Brisbane and Women's Hospital, Brisbane, Australia; [2] BHF Centre for Cardiovascular Sciences, University of Edinburgh, Edinburgh, UK; [3] Wake Forest School of Medicine, Winston-Salem, NC; [4] Central Manchester University Hospitals NHS Foundation Trust, UK.

* Address correspondence to this author at: Royal Brisbane and Women's Hospital, Butterfield St., Herston, Brisbane, Queensland 4029, Australia. Fax 61-73646–1643; e-mail louise.cullen@health.qld.gov.au.

Received June 6, 2016; accepted August 9, 2016.
Previously published online at DOI: 10.1373/clinchem.2016.254730

[5] Nonstandard abbreviations: ACS, acute coronary syndrome; EDs, emergency departments; AMI, acute myocardial infarction; ECG, electrocardiogram; CK-MB, creatine kinase MB isoenzyme; AST, aspartate aminotransferase; LD, lactate dehydrogenase; URL, upper reference limit; H-FABP, heart-type fatty acid binding protein; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; NPV, negative predictive value; GRACE, Global Registry of Acute Coronary Events; APACE, Advantageous Predictors of Acute Coronary Syndrome Evaluation Study; TRAPID-AMI, High-Sensitivity Cardiac Troponin T Assay for Rapid Rule Out of Acute Myocardial Infarction; ASPECT, ASia Pacific Evaluation of Chest pain Trial; ADP, accelerated diagnostic pathway; TIMI, thrombolysis in myocardial infarction; ADAPT, 2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker; RATPAC, Randomized Assessment of Treatment Using Panel Assay of Cardiac markers; hs-cTnT, high-sensitivity cardiac troponin T; MACS, Manchester Acute Coronary Syndromes; MACE, major adverse cardiac event; MIDAS, myeloperoxidase in diagnosis of ACS; EDACS, The Emergency Department Assessment of Chest Pain Score; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave MI.

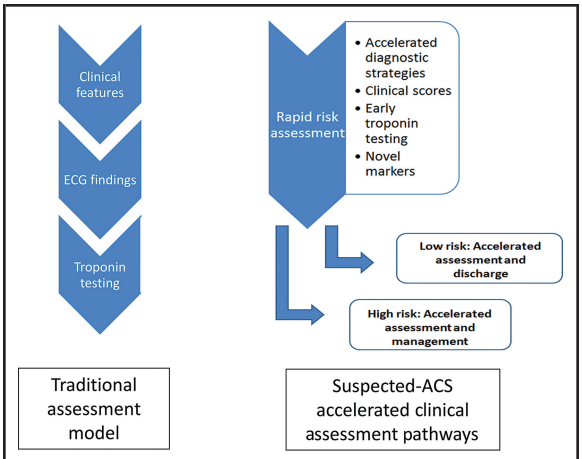

Fig. 1. Initial assessment of patients with suspected acute coronary syndromes.

Traditional models of assessment are based upon a sequential process incorporating the key elements of clinical features, ECG, and troponin testing. All patients undergo a similar assessment process. New suspected-ACS accelerated clinical assessment pathways also include all such elements and may include risk scores, early troponin testing, novel biomarkers, and accelerated protocols tailored toward refined assessment of the likelihood of AMI.

says are able to measure troponin concentrations well below the 99th percentile upper reference limit (URL) and have improved precision (coefficient of variation of <10%) at the URL in comparison to older assays. With the advent of high-sensitivity troponin assays, novel methods are being explored to improve the early recognition of patients with AMI. The role of newer biomarkers, including heart-type fatty acid binding protein (H-FABP) and copeptin, is also being explored *(7–9)*.

As we search for the optimum approach to accelerate the rule-in and rule-out of ACS, consideration of the acceptable error rate of new strategies is fundamentally important. Little, if anything, is certain in medicine, and our ability to identify all patients with and without ACS is not guaranteed. For clinicians a tolerable missed adverse event rate of <1% has been reported *(10)*, while for patients a higher miss rate may be acceptable *(11)*. Consideration of the results of the diagnostic accuracy (both point estimates and confidence intervals) of novel studies in this area is therefore fundamentally important, and the outcomes of small studies lacking the power to determine the safety of strategies should be viewed with caution.

This review summarizes the evidence to date on optimum accelerated strategies for the rule-in and rule-out of AMI, using troponin-only strategies. The use of novel biomarkers is also addressed and the combination of biomarkers in accelerated diagnostic strategies discussed.

Troponin-Only Strategies for Rapid Rule-In and Rule-Out AMI

Contemporary sensitive troponin assays cannot safely rule out AMI at presentation, and therefore international guidelines recommend serial troponin testing, which often requires admission to hospital including placement into observation units *(12)*. High-sensitivity troponin assays have excellent precision at very low concentrations and permit accurate quantification of troponin in the majority of healthy persons *(13, 14)*. These assays have the potential to transform the assessment of patients with chest pain through the development of safe and effective strategies to rule out myocardial infarction (MI) rapidly in the ED.

Until recently guidelines have recommended measuring troponin on presentation and 6 h later, or 10–12 h after the onset of symptoms, to coincide with the peak in plasma troponin concentrations *(12)*. This minimizes the risk of missing a small myocardial infarct and allows the assessment of infarct size. However, the majority of patients require admission for serial testing, placing pressure on crowded EDs and hospitals. Recently, the National Institute for Health and Care Excellence (NICE) compared troponin assays for the early rule-out of MI *(15)*. They concluded that the use of high-sensitivity troponin on presentation and at 3 h was a cost-effective strategy compared to admission of patients for conventional troponin testing at 10–12 h. The clinical effectiveness and safety of these pathways, as well as the optimal threshold and timing of sampling remain uncertain.

NINETY-NINTH CENTILE AND SERIAL TESTING AT PRESENTATION AND 3 h

International guidelines based on general consensus recommend that the 99th centile of a healthy reference population be used as the threshold to diagnose and rule out AMI *(6)*. There is controversy on how to precisely determine the 99th centile *(16)*. One of the main advantages of high-sensitivity assays is high precision (<10% coefficient of variation) at this threshold. A recent systematic review evaluated the diagnostic accuracy of the high-sensitivity troponin T (Roche) and high-sensitivity troponin I (Abbott) using the 99th centile at presentation and at 2–3 h as compared to a contemporary assay at presentation and 10–12 h after symptom onset *(17)*. High-sensitivity troponin T concentrations below the 99th centile (14 ng/L) at presentation had a sensitivity of 89% (95% CI 85%–92%, 13 cohorts), which increased to 95% (95% CI 92%–97%, 2 cohorts) when serial testing was performed at 2 h *(18, 19)*. The sensitivity of a high-sensitivity troponin I concentration below the 99th centile (26 ng/L) at presentation was 80% (95% CI 77% to 83%, 4 cohorts), but increased to 98% (95 CI 96%–

99%, 1 cohort) when serial testing was performed at presentation and 3 h *(20)*.

The majority of published studies are retrospective and observational involving selected patients and prospective clinical trials evaluating the implementation of high-sensitivity troponin assays are awaited. Some studies recruited low-risk patients and therefore the findings may not be generalizable to all patients presenting with suspected ACS. Most studies did not use the high-sensitivity assay as the reference standard for the primary analysis, and therefore the adjudication of the diagnosis of myocardial infarction was based on peak troponin testing using a conventional assay. This may lead to overestimation of both the sensitivity and negative predictive value (NPV) of the high-sensitivity assay. Finally, relatively few studies have addressed important subgroups of patients, such as those who present early and within 3 h of the onset of their symptoms. Interestingly, Pickering et al. using pooled data from 5 cohort studies recently reported lower sensitivities for both high-sensitivity troponin T at 94.8% (95% CI 89.6%–97.9%) and high-sensitivity troponin I at 93.2% (95% CI 87.5%–96.8%) measured at presentation and at 3 h, raising further questions about the safety of this approach in clinical practice *(21)*.

OPTIMAL THRESHOLD FOR RISK STRATIFICATION AT PRESENTATION

Despite these limitations in the evidence, the European Society of Cardiology recommend the use of high-sensitivity troponin and accelerated testing strategies, but these guidelines have been updated recently acknowledging that the reliance on a single threshold to rule out and diagnose MI may not be optimal *(22)*. Why should we use the same threshold to rule out and diagnose MI when high-sensitivity assays can quantify troponin concentrations well below the 99th centile? Recent studies have demonstrated that very low troponin concentrations at presentation can be used to risk stratify patients *(23–25)*. A recent metaanalysis found that high-sensitivity troponin T concentrations below the limit of blank (3 ng/L) or limit of detection (5 ng/L) ruled out approximately 1 in 4 patients with a pooled sensitivity of 97.4% (94.9%–98.7%) *(26)*. However, assay imprecision at the limit of blank may result in variation in the performance of this approach in practice, and influence the proportion of patients who could be identified as suitable for discharge.

The only high-sensitivity troponin I assay currently in clinical use (manufactured by Abbott Diagnostics) has enhanced high-sensitivity troponin I assay precision at very low concentrations, permits quantification of troponin in the majority of persons, and affords the opportunity to define a threshold to rule out MI based on clinical performance rather than analytical imprecision. In a prospective study of 4870 consecutive patients with suspected ACS, a troponin concentration <5 ng/L at presentation had a NPV of 99.6% (99.3%–99.8%) for MI during the index presentation, or MI or cardiac death at 30 days *(27)*. Furthermore, patients with troponin concentrations <5 ng/L at presentation had very low rates of adverse cardiac events at 1 year. This threshold identified two-thirds of patients with suspected ACS who are low-risk and may be suitable for immediate discharge. The NPV of this threshold remained high in all subgroups, including those patients known to have coronary heart disease, cardiovascular risk factors, or intermediate/high Global Registry of Acute Coronary Events (GRACE) risk scores. The only exception was in the group of patients who present within 2 h of symptom onset where the NPV was lower at 97.6% (95.8%–99.2%) and repeat testing is recommended.

RULE-OUT PATHWAYS INCORPORATING LOW THRESHOLDS AND SERIAL TESTING

The use of thresholds below the 99th centile to risk stratify patients at presentation and pathways that incorporate a change in troponin concentration on serial testing is likely to further improve the safety and effectiveness of early rule-out pathways. A number of pathways have been validated using both high-sensitivity troponin T and troponin I assays with serial testing as early as one hour after presentation. A pathway developed in the Advantageous Predictors of Acute Coronary Syndrome Evaluation Study (APACE) cohort *(28)* was prospectively validated in the multicentered, international observational High-Sensitivity Cardiac Troponin T Assay for Rapid Rule Out of Acute Myocardial Infarction (TRAPID-AMI) study demonstrating in 1282 patients that high-sensitivity troponin T concentrations <12 ng/L and a change from presentation to 1 h of <3 ng/L ruled out myocardial infarction in 63% of patients with a NPV of 99.1% (98.2%–99.7%) *(29)*. A subsequent analysis from the same cohort suggests the combination of a normal ECG and a troponin T concentration <5 ng/L at presentation can rule out MI with a higher NPV of 99.6% (98.5%–100.0%) *(30)*. Although this approach rules out fewer patients (44%), it has the advantage of requiring a single troponin measurement. Pathways incorporating high-sensitivity troponin I testing at presentation and one hour have also been validated in the APACE cohort *(31)* demonstrating that troponin I concentrations <5 ng/L at presentation and a change of <2 ng/L at 1 h rules out MI in 56% of patients with a NPV of 99.2% (98%–99.8%).

Each of these strategies and pathways show promise, and are likely to improve on the sensitivity and NPV of conventional pathways that rely on the 99th centile to both diagnose and rule out MI. Implementation of these approaches is likely to reduce healthcare costs by avoiding unnecessary hospitalization. Prospective studies are now required that evaluate both the clinical and cost effective-

Table 1. GRACE, TIMI, HEART, and EDACS score variables.

GRACE	TIMI	HEART	EDACS
• Age	• Age	• History	• Age
• Heart rate	• ≥3 risk factors	• ECG	• Sex
• Systolic blood pressure	• Known CAD	• Age	• Known CAD or ≥3 risk factors
• Creatinine	• Aspirin use in past 7 days	• Risk factors	• Diaphoresis
• Killip class	• Severe angina	• Troponin	• Pain radiating to arm, shoulder, neck, or jaw
• Cardiac arrest at admission	• ST-segment deviation of ≥0.05 mV on first EKG		• Pain occurred or worsened with inspiration
• ST segment deviation	• Elevated troponin and/or CK-MB on initial blood tests		• Pain is reproducible by palpation
• Elevated cardiac enzymes			

CAD, coronary artery disease.

ness of implementing these novel pathways in practice. When clinical reliance rests on the accuracy of reported troponin values, especially at low concentrations, quality assurance measures including accuracy of assay calibration are of the utmost importance *(32, 33)*.

The Role of Novel Biomarkers in the Diagnosis of ACS

For many years there has been interest in additional biomarkers of ACS. Even using a high sensitivity assay, troponin concentrations may take several hours to increase in the circulation following the onset of an AMI. This creates a period in the first hours after onset where troponin values are below the 99th centile but rising and is the basis of the requirement for serial sampling. Biomarkers that can identify patients with ACS in this early phase could therefore either obviate the need for serial sampling altogether or reduce the time period over which serial sampling takes place.

CK-MB and myoglobin are 2 such biomarkers. In combination with troponin (the "triple panel"), their ability to rule out AMI with reasonable sensitivity has been noted almost since the dawn of the troponin era *(34)*. Two landmark trials have evaluated this strategy in emergency medicine settings. First, the ASia Pacific Evaluation of Chest pain Trial (ASPECT) was an observational cohort study including 3582 patients from 9 countries in the Asia–Pacific region *(35)*. ASPECT evaluated the accuracy of an accelerated diagnostic pathway (ADP) that would rule out ACS in patients who have a thrombolysis in myocardial infarction (TIMI) risk score (Table 1) of 0 as well as normal troponin I, CK-MB, and myoglobin concentrations measured at the point of care (manufactured by Alere) both on arrival and 2 h later. This ADP had a sensitivity of 99.3% (95% CI 97.9%–99.8%) and a NPV of 99.1% (95% CI 97.3%–99.8%). In total, the ADP classified 9.8% of patients as being at low risk, thus potentially avoiding hospital admission. However, subsequent work has shown that the use of central laboratory troponin testing alone (without other biomarkers) alongside this ADP can achieve similar sensitivity but greater specificity, thus avoiding more unnecessary admissions *(36)*.

The Randomized Assessment of Treatment using Panel Assay of Cardiac markers (RATPAC) trial randomly assigned patients to standard assessment including serial troponin testing or point of care testing for CK-MB, myoglobin, and troponin I on arrival and at 90 min *(37)*. However, while more patients in the intervention group were safely discharged from the ED, use of the ADP was more expensive than standard care and thus not cost-effective *(38)*.

Perhaps one explanation for the lack of cost-effectiveness of this ADP is that the additional biomarkers (CK-MB and myoglobin) are notoriously nonspecific for injury. The proportion of patients eligible for early discharge therefore is relatively small and the ADP could lead to clinicians overinvestigating and overtreating patients with positive results. Another biomarker of myocardial injury, which may overcome these limitations, is H-FABP. H-FABP is a cytoplasmic protein with low molecular weight, which is involved in fatty acid transport within myocytes *(39)*. It is abundantly expressed in the myocardium and, due to its small size, rapidly appears in plasma following the onset of myocardial ischemia *(40)*. These characteristics mean that H-FABP is a promising candidate as a biomarker of ACS.

The combination of H-FABP and troponin is superior to the combination of CK-MB, myoglobin and tro-

ponin, both in terms or improved sensitivity and improved specificity *(7)*. H-FABP has independently predicted long-term prognosis in patients with chest pain *(41)* and has a higher sensitivity than troponin in early presenters for AMI, with the combination of both biomarkers giving even greater early sensitivity *(9)*. However, while a metaanalysis of 8 studies including 2735 patients has confirmed that measuring H-FABP at the time of ED presentation improves diagnostic sensitivity compared to measuring troponin alone, the pooled sensitivity of this strategy remains suboptimal to rule out ACS, at 91% *(42)*.

Using a high-sensitivity cardiac troponin assay in combination with H-FABP may help further. This combination marginally improved diagnostic performance measured by the area under the receiver operating characteristic curve *(20, 43)*, although this evidence still does not suggest that ACS can be ruled out following a single blood test.

By combining clinical information and EKG findings with H-FABP and high-sensitivity cardiac troponin T (hs-cTnT) concentrations, the Manchester Acute Coronary Syndromes (MACS) clinical prediction model can stratify patients with acute chest pain into 4 risk groups. In the lowest risk group, the first external validation study suggested that ACS could be considered "ruled out" with a sensitivity of 98.0% for major adverse cardiac events (MACEs) within 30 days (100% sensitivity for AMI) *(44)*. Another external validation study showed a sensitivity of 100% (95% CI 95.4%–100.0%) for MACE at 30 days. Using MACS, 17.0% patients could have ACS "ruled out" following a single blood test *(45)*. The MACS prediction model could also enable ACS to be "ruled in" following a single blood test with >95% positive predictive value in the initial external validation study, although this dropped to 53.3% in the second study. A pilot randomized controlled trial comparing the use of MACS to standard care is due to report in the near future *(46)*.

Copeptin, a prohormone of vasopressin, has also attracted interest as a biomarker of ACS. Similar to H-FABP, concentrations rise early after the onset of AMI. Copeptin has been shown to have incremental value when used in combination with troponin for "ruling out" ACS following a single blood test *(8)*. A systematic review of 14 studies including 9244 patients found that the combination of copeptin and troponin has strikingly similar diagnostic performance to the combination of H-FABP and troponin, with a pooled sensitivity of 90.5% (95% CI 88.8%–92.1%) *(47)*. It is unlikely that clinicians would consider this sensitivity sufficient to safely "rule out" ACS. However, a second systematic review, which excluded patients with ST elevation myocardial infarction, showed a higher pooled sensitivity of 95.0% (95% CI 89.0%–98.0%) for the diagnosis of AMI, rising to 98.0% (95% CI 96.0%–100.0%) when a high sensitivity troponin assay was used *(48)*. Notably, the sensitivity for predicting MACE was not evaluated in this study. For a discharge diagnosis of ACS, the combination of hs-cTnT and copeptin has been shown to be lower (83%, 95% CI 74%–89%) in a more recent study *(49)*.

While the observational studies report mixed evidence for copeptin, a randomized controlled trial of troponin-negative patients who were randomized to receive care guided by copeptin or standard care showed no difference in the incidence of MACE among patients whose care was guided by troponin *(50)*. Length of stay was significantly reduced in the copeptin group (median 4 h vs 7 h, $P < 0.001$). However, this noninferiority trial was only powered to demonstrate that the incidence of MACE was no more than 5% higher in the copeptin group, meaning that further large studies are required.

A further challenge to the clinical implementation of additional biomarkers is the logistic requirement for hospital laboratories. Copeptin requires a dedicated analyzer to run a single biomarker, which may be a difficult expense to justify. An automated immunoassay is available for H-FABP that can be run using conventional modular laboratory analyzers. However, this still requires additional maintenance and quality control. The development of point of care assays for additional biomarkers may assist with clinical implementation.

Strategies Combining Biomarkers with Additional Clinical Information

While troponin and novel biomarker combinations have high sensitivity for the detection of myocardial injury, several studies suggest that these measures alone are insufficient to identify patients who can be safely discharged from the ED *(36, 51, 52)*. For example, in the 2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker (ADAPT) trial, which included 1975 patients from the Asia–Pacific region, the sensitivity of serial contemporary troponin at 0 and 2 h (using the URL) for 30 days major adverse cardiac events was 87.4% *(36)*. In the myeloperoxidase in diagnosis of ACS (MIDAS) study, which included 1107 patients with possible ACS from 18 US EDs, the sensitivity of 0 and 3 h serial contemporary troponin measures for the detection of 30-day ACS was only 56% *(51)*. Studies evaluating serial high-sensitivity cardiac troponin measures have had similar findings. In the APACE cohort, a study of 909 patients with serial high-sensitivity cardiac troponin measures at 0 and 2 h yielded a sensitivity of 82.7% sensitivity for 30-day ACS events *(52)*. However, in each of these studies when troponin results were integrated with EKG data and clinical decision aids, the sensitivities

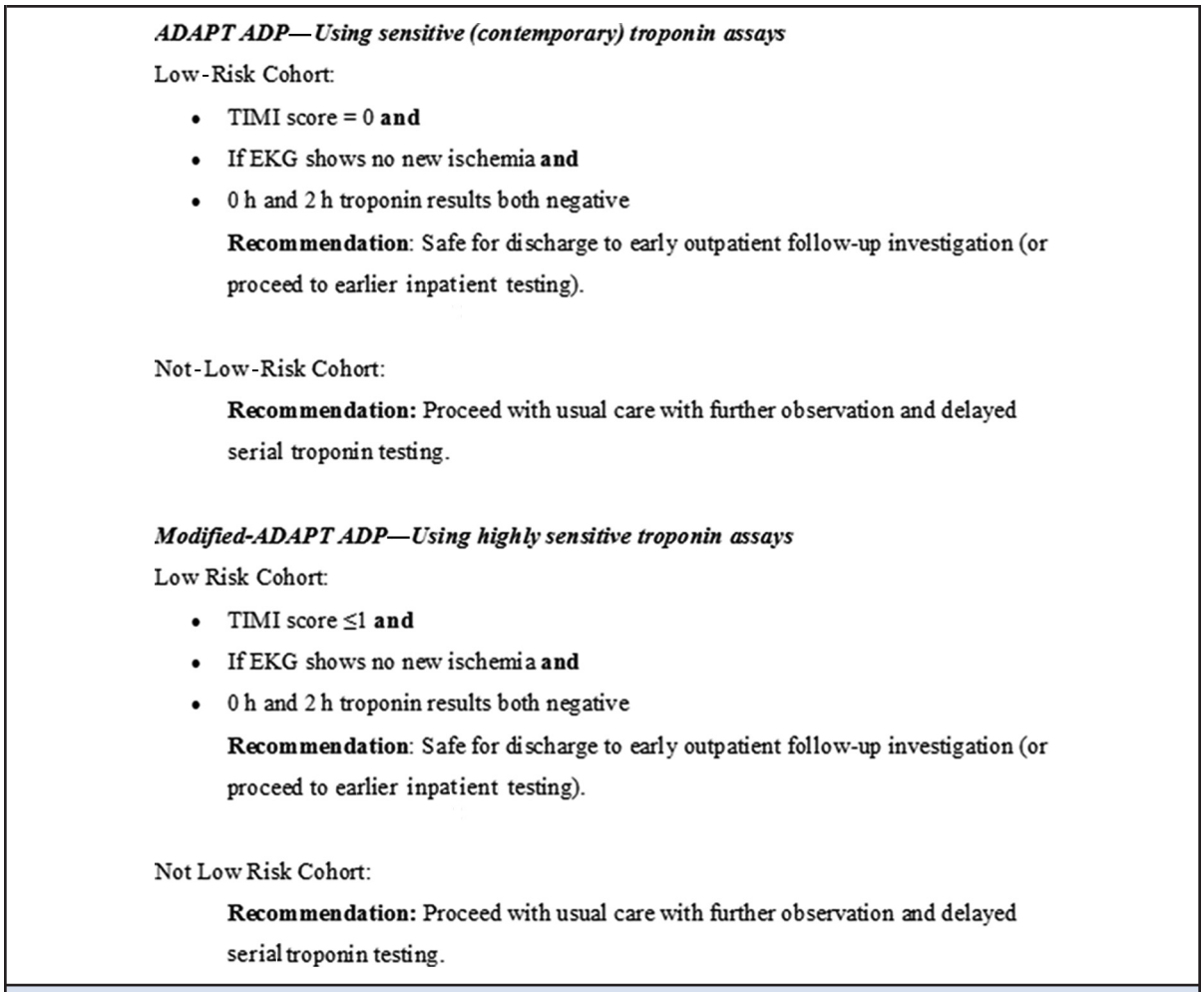

Fig. 2. ADAPT and Modified-ADAPT ADPs.

for adverse events improved to >99%. These studies underscore the importance of considering troponin results in combination with other key clinical data, such as the patient's chest pain features, past medical history, and electrocardiogram, particularly when contemporary assays are used.

Clinical decision aids and ADPs objectively combine key variables from the patient's history, electrocardiogram findings, and troponin measures to risk stratify patients with acute chest pain. These combinations include older commonly used decision aids (TIMI Risk Score and GRACE score, Table 1), which were first derived and validated among patients with ACS, and newer aids [ADAPT, HEART, and The Emergency Department Assessment of Chest Pain Score (EDACS); Table 1, Figs. 2–4], which were derived and validated in ED patients with undifferentiated chest pain and designed to identify patients for early discharge from the ED. These tools have been incorporated into the guidelines for the early risk stratification of patients with acute chest pain and are increasingly used by ED providers *(53)*.

TIMI RISK SCORE

The TIMI risk score (Table 1) was derived in the late 1990s from the Thrombolysis in Myocardial Infarction 11B trial and Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave MI (ESSENCE) trial *(54–56)*. Participants in these trials had ACS; angina at rest; and either transient ST-elevation or depression, a history of coronary artery disease, or increased cardiac biomarker concentrations. These cohorts were not representative of an all comers ED chest pain population. However, despite not being derived in ED patients, TIMI is frequently used for the early risk stratification of ED patients. Multiple studies have demonstrated that while TIMI is predictive of 30-day adverse outcomes among ED patients with undifferentiated chest pain, it is insufficiently sensitive to be used

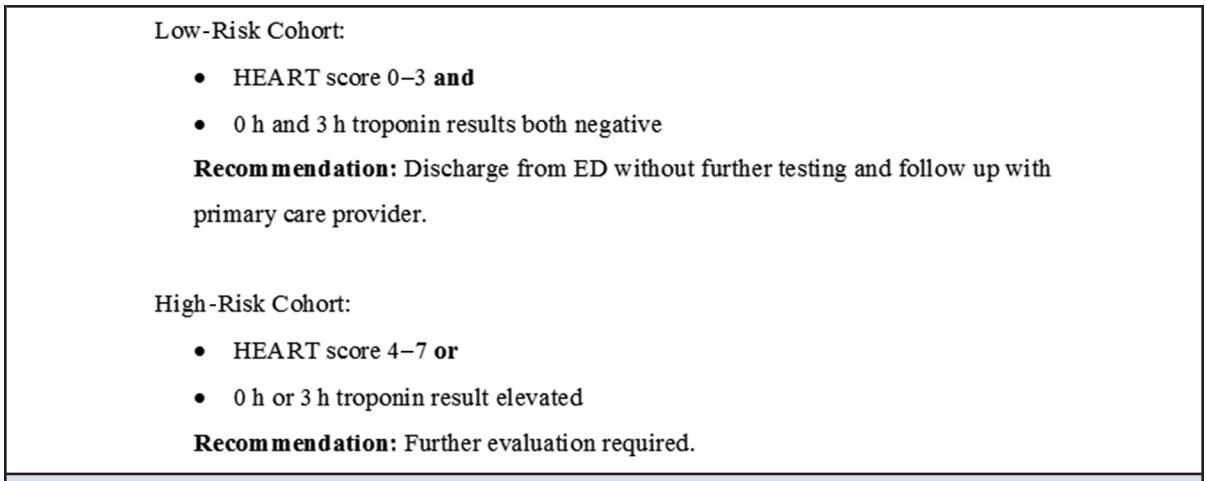

Fig. 3. The HEART Pathway.

to identify ED patients for early discharge *(57, 58)*. Therefore, patients with a TIMI score of 0 require further diagnostic testing if used alone.

GRACE

Like TIMI, the GRACE score (Table 1) was derived from a large cohort with confirmed ACS *(59)*. GRACE consists of 2 separate risk stratification scores; the first is composed of 8 variables and is designed to predict in-hospital mortality *(60)*, while the second predicts 6-month mortality *(61)*. The GRACE score has been validated in an undifferentiated ED chest pain population. In a study by Lyon et al. *(62)*, patients in the lowest risk group had a 4% event rate, and the highest risk group with 71% event rate. As with TIMI, the GRACE score is predictive of short term outcomes, but is not sensitive enough in to identify ED patients for discharge without further testing.

THE ADAPT TRIAL

ADAPT (Fig. 2) is an ADP that combines a TIMI risk score of 0, a nonischemic EKG, and negative serial troponin measures at 0 and 2 h to identify patients at low risk for MACE at 30 days. The ADAPT trial *(36)* was an observational study evaluating 1975 ED patients with chest pain. In this study, 20% of patients were identified

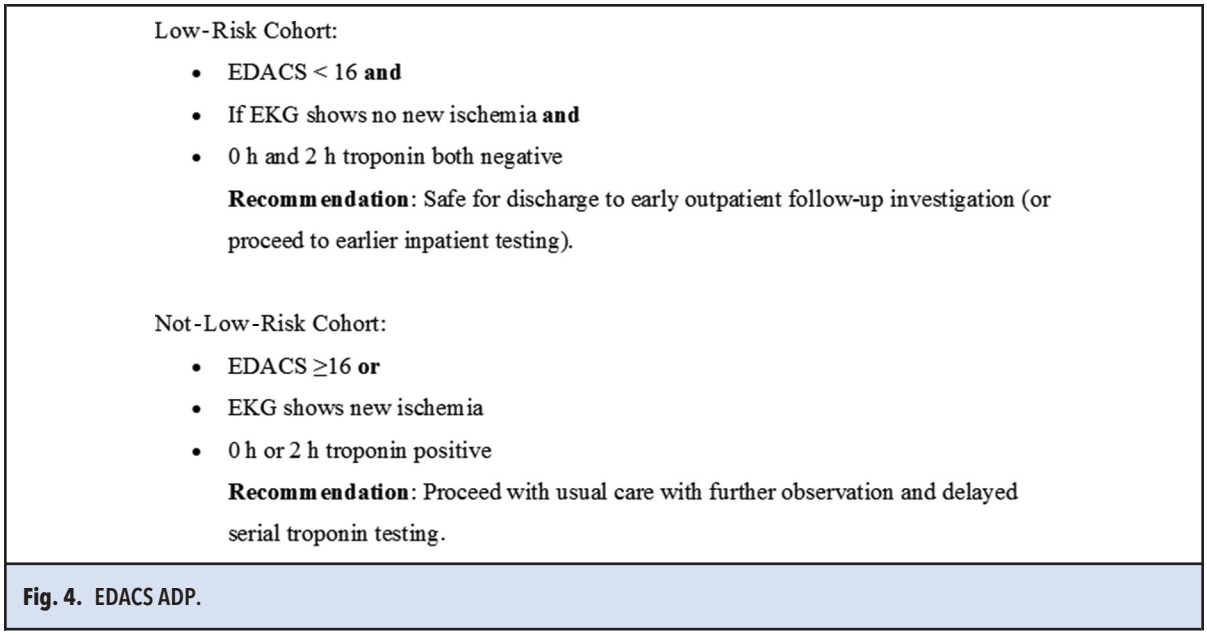

Fig. 4. EDACS ADP.

as low-risk and potentially eligible for ED discharge, with only one low-risk patient suffering an adverse event (an MI with subsequent revascularization). The tool was 99.7% sensitive (CI 98.1%–99.9%) with a 99.7% NPV (CI 98.6%–100.0%). ADAPT was subsequently validated in the Asia–Pacific region and Europe. *(52, 63)* However, in the first retrospective validation study in a North American cohort, in a cohort of 1140 patients, ADAPT correctly identified 26 of 31 patients with MACE, for a sensitivity of 83% (CI: 66.3%–94.5%) and NPV of 99.1 (CI 97.9%–99.7), below what was reported in other studies; however as this was a secondary analysis of the ACRIN trial, there were differences in EKG data definitions compared to the ADAPT study *(64)*. In a recent randomized trial, ADAPT increased the early discharge rate by only 8.3% compared to usual care *(63)*. This limitation may be a result of use of the TIMI risk score, which classifies patients with aspirin use or 2 episodes of chest pain in 24 h as non-low-risk. The Modified ADAPT ADP incorporating patients with TIMI scores of $\leq$1 and high sensitivity troponin results, doubled the number of patients identified as low-risk (40%) (Fig. 2). It was validated in the APACE cohort and reported sensitivity of 99.2 (95% CI: 97.1%–99.8%) and 99.4% (95% CI: 96.5%–100%) and NPV of 99.7(95% CI: 98.9%–99.9%) and 99.7% (95% CI: 98.4%–100%) in the primary and secondary cohorts respectively. A potential limitation of both studies is that some TIMI variables (i.e., >3 risk factors) may be difficult to accurately ascertain in the ED setting.

HEART SCORE

Unlike previously discussed risk scores, the HEART score was not derived by logistical regression or recursive partitioning multivariate analysis, instead, relying on literature and clinical experience. It is made up of 5 factors: history, EKG, age, risk factors, and troponin (Table 1). Each factor is scored 0, 1, or 2, making the scoring system easy to remember and utilize without a computer. The original evaluation of the HEART score, in 120 patients identified about one-third of the cohort as low-risk, with 1 missed adverse event *(65)*. A retrospective validation in 880 patients from 4 hospitals in the Netherlands identified roughly one third of patients as low-risk with a NPV of 99.1% *(66)*. Prospective validation studies have demonstrated the score's ability to risk stratify, with <2% MACE rates in those with HEART score 0–3 *(67, 68)*. However, in many practice settings, an adverse event rate >1% is frequently considered unacceptable *(10)*. Other potential limitations of HEART are that some variables (i.e., >3 risk factors) may be difficult to accurately ascertain in the ED setting, the evaluation of typicality of the history is clinician-dependent and patients with troponin elevations may not all be considered high-risk.

HEART PATHWAY

The HEART Pathway is an ADP that combines the HEART score with serial troponin, designed to improve on the sensitivity and NPV of the HEART score alone (Fig. 3). To be considered low-risk and eligible for early discharge the HEART Pathway requires a HEART Score of 0–3 and negative serial troponins. The first study evaluating the HEART Pathway included 1070 patients admitted into an ED-based observation unit for stress testing *(69)*. In this cohort, the HEART Pathway was 100% sensitive (CI 72%–100%) with a NPV of 100% (CI 94.6%–100%) for MACE and could have identified 82% for early discharge (CI 80%–84%). While the HEART Pathway had no cases of missed MACE, use of the HEART Score alone would have missed 5 patients a 0.6% missed MACE rate. Validation of the HEART Pathway occurred in the MIDAS cohort, demonstrating a sensitivity of for MACE of 99% (CI 97%–100%) with a NPV of 99% (CI 96%–100%), while identifying 20% (95% CI 18%–23%) as eligible for early discharge *(51)*. Additional validation occurred in a randomized trial of 282 patients to the HEART Pathway or usual care based on American College of Cardiology/American Heart Association guidelines *(70)*. In this study, 39.7% of patients in the HEART Pathway group were discharged early, compared to 18.4% receiving usual care. Patients in the HEART Pathway group had a median reduction in hospital length of 12 h and were less likely to have stress testing (12% reduction at 30 days). No patients identified as low-risk by the HEART Pathway experienced MACE at 30 days.

EDACS

EDACS was developed from 37 patient variables in a derivation cohort of 1974 patients in the ED with possible cardiac ischemia *(71)*. It combines clinical variables identified as independent predictors for MACE to identify a subgroup of patients who are at low risk of such an event within 30 days (Fig. 4). The EDACS ADP, incorporating EDACS, 0- and 2-h troponin results, and EKG findings, classified more than 50% of ED patients as low-risk for 30-day events, with sensitivity $\geq$99%.

OTHER DECISION AIDS AND ACCELERATED DIAGNOSTIC PROTOCOLS

Several other decision aids have also been developed, and additional decision aids are sure to emerge. The new Vancouver Chest Pain Rule incorporates troponin sampling over 2 h, although recent reports suggest disappointing sensitivity *(72, 73)*.The MACS decision rule, which uses a single blood test at the time of arrival to "rule in" and "rule out" ACS, has been discussed above *(44, 45)*.

THE VALUE OF CLINICAL JUDGMENT

Even without a structured scoring system, clinicians may be able to combine troponin concentrations, EKG findings, and their own "gestalt" or clinical judgement to rapidly rule out ACS. In a cohort of 458 patients, a strategy to "rule out" ACS in patients who had an initial hs-cTnT concentration below the 99th centile, no EKG ischemia, and in whom the treating clinician felt the diagnosis was "probably not" or "definitely not" ACS (using a 5-point Likert scale) had 100% sensitivity for MACE at 30 days *(5)*.

Accounting for clinical judgement may also help to improve the diagnostic performance of troponin-based algorithms. For example, the one-hour rule out strategy described with hs-cTnT has recently been shown to have a sensitivity of just 87.6% for MACE within 30 days in a Swedish cohort. Incorporating clinician judgement into an extended algorithm markedly improved that sensitivity, to 97.5% *(74)*.

CLINICAL USE OF RAPID RULE-IN AND RULE-OUT STRATEGIES

The ultimate proof of both the safety and clinical acceptability of accelerated strategies for the rule-in and rule-out of AMI lies in outcomes of implementation of novel methods into clinical practice. As the majority of studies in this area have been observational in nature, such reports are key to determining the ability to translate change into actual patient care and assess the overall utility of novel methods, as findings of observational research may overestimate the effect of intervention. It is likely though that there will not be a single strategy that is widely applicable in all healthcare setting nor acceptable to all clinicians.

To date, studies reporting outcomes of the translation of troponin-only strategies into clinical practice are absent. Reports of combined strategies in use are emerging. The impact of the stepped wedged trial of the HEART score, "HEART Care," included a calculation of the HEART score in every individual patient and a recommendation for further management, specifically, early discharge, in low-risk patients (HEART score of $\leq$3). The preliminary findings show the decrease in healthcare resource use following the initial assessment was small *(75)* and warrants further exploration.

The ADAPT protocol has been widely translated into routine clinical practice in some regions, including Australia, with the outcomes in terms of both the ability to define low-risk patients and safely facilitate early hospital discharge reported *(76, 77)*. Overall, similar proportions of patients were defined as low-risk in clinical practice when compared to the original study (19% vs 20% respectively) *(36)*. The EDACS ADP has also been assessed in the clinical setting, using a prospective pragmatic randomized controlled trial *(78)*, and is in clinical use widely in New Zealand.

Future Directions

Despite great advances in our understanding of accelerated rule-in and rule-out strategies for AMI, there are areas requiring ongoing investigation. Due to the lack of standardization of troponin assays and as many approaches depend on assay-specific values, new troponin assays require investigation to define the optimum safe approach for the rule-in and rule-out of AMI. In patients who present early with symptoms of a possible AMI, current evidence suggests that our ability to define those at risk is hampered by our dependence on troponin, a biomarker of myocardial necrosis, that takes time to be released. In the future, novel biomarkers that identify vascular injury or plaque rupture before the development of symptoms or onset of myocardial injury may allow clinicians to initiate treatment earlier and prevent presentations with ACS.

While efforts to define safer, faster methods to assess patients with possible ACS continue, strategies that have already been developed may be able to be incorporated into clinical care. Reported outcomes of the translation of accelerated strategies into clinical practice are needed.

Conclusions

As patients with chest pain comprise a large proportion of ED presentations and place a major burden on healthcare resources, efforts to safely and rapidly identify those with and without AMI are needed. The majority of patients, who are not at risk of myocardial infarction or other serious harm, may be suitable for discharge directly from the ED using approaches including troponin-only protocols and accelerated diagnostic protocols. Evidence about their clinical and health economic impact is needed with such strategies having potential for major benefit to patients and healthcare providers.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: S. Mahler, Decision Point Informatics; L. Cullen, guest editor, *Clinical Chemistry*, AACC.
Consultant or Advisory Role: L.A. Cullen, Abbott Diagnostics, Siemens, and Novartis; S. Mahler, Roche Diagnostics.
Stock Ownership: None declared.
Honoraria: L.A. Cullen, Abbott Diagnostics, Siemens, Alere, and AstraZeneca; N.L. Mills, Abbott Diagnostics, Roche, and Singulex.
Research Funding: N.L. Mills, the Butler Senior Clinical Research Fellowship (FS/16/14/32023) from the British Heart Foundation; S. Mahler, the Donaghue Foundation and NHLBI (1 R01 HL118263-01,

L30 HL120008); R. Body, funding to institution from Abbott Point of Care (CMFT), FABPulous BV (CMFT), Abbott Laboratories (CMFT), Roche (CMFT), and Siemens (CMFT); and the National Institute for Health Research (NIHR), which supports the salary of R. Body through a personal fellowship (PDF-2012-05-193).

Expert Testimony: R. Body, Roche Diagnostics.
Patents: None declared.
Other Remuneration: Roche provided remuneration of travel expenses for presentation of R. Body's research findings at the European Society of Cardiology Congress, 2015.

References

1. Goodacre S. The health care burden of acute chest pain. Heart 2005;91:229–30.
2. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000;342:1163–70.
3. Cullen L, Greenslade J, Merollini K, Graves N, Hammett CJ, Hawkins T, et al. Cost and outcomes of assessing patients with chest pain in an Australian emergency department. Med J Aust 2015;202:427–32.
4. Fanaroff AC, Rymer JA, Goldstein SA, Simel DL, Newby LK. Does this patient with chest pain have acute coronary syndrome?: the Rational Clinical Examination Systematic Review. JAMA 2015;314:1955–65.
5. Body R, Cook G, Burrows G, Carley S, Lewis PS. Can emergency physicians 'rule in' and 'rule out' acute myocardial infarction with clinical judgement? Emerg Med J 2014;31:872–6.
6. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35.
7. Body R, McDowell G, Carley S, Wibberley C, Ferguson J, Mackway-Jones K. A FABP-ulous 'rule out' strategy? Heart fatty acid binding protein and troponin for rapid exclusion of acute myocardial infarction. Resuscitation 2011;82:1041–6.
8. Wildi K, Zellweger C, Twerenbold R, Jaeger C, Reichlin T, Haaf P, et al. Incremental value of copeptin to highly sensitive cardiac Troponin I for rapid rule-out of myocardial infarction. Int J Cardiol 2015;190:170–6.
9. McCann CJ, Glover BM, Menown IB, Moore MJ, McEneny J, Owens CG, et al. Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponin T. Eur Heart J 2008;29:2843–50.
10. Than M, Herbert M, Flaws D, Cullen L, Hess E, Hollander JE, 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.
11. Pierce MA, Hess EP, Kline JA, Shah ND, Breslin M, Branda ME, et al. The Chest Pain Choice trial: a pilot randomized trial of a decision aid for patients with chest pain in the emergency department. Trials 2010;11:57.
12. Skinner JS, Smeeth L, Kendall JM, Adams PC, Timmis A, Chest Pain Guideline Development G. NICE guidance. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. Heart 2010;96:974–8.
13. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem 2012;58:1574–81.
14. Apple FS, Collinson PO, Biomarkers ITFoCAoC. Analytical characteristics of high-sensitivity cardiac troponin assays. Clin Chem 2012;58:54–61.
15. National Institute for Health and Care Excellence (NICE). Myocardial infarction (acute): early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays): DG15. London: National Institute for Health and Care Excellence; 2014. https://www.nice.org.uk/guidance/dg15 (Accessed May 2016).
16. Sandoval Y, Apple FS. The global need to define normality: the 99th percentile value of cardiac troponin. Clin Chem 2014;60:455–62.
17. Westwood M, van Asselt T, Ramaekers B, Whiting P, Thokala P, Joore M, et al. High-sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction in people with acute chest pain: a systematic review and cost-effectiveness analysis. Health Technol Assess 2015;19:1–234.
18. Melki D, Lind S, Agewall S, Jernberg T. Diagnostic value of high sensitive troponin T in chest pain patients with no persistent ST-elevations. Scand Cardiovasc J 2011;45:198–204.
19. Aldous SJ, Richards M, Cullen L, Troughton R, Than M. Diagnostic and prognostic utility of early measurement with high-sensitivity troponin T assay in patients presenting with chest pain. CMAJ 2012;184:E260–8.
20. Keller T, Zeller T, Ojeda F, Tzikas S, Lillpopp L, Sinning C, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA 2011;306:2684–93.
21. Pickering JW, Greenslade JH, Cullen L, Flaws D, Parsonage W, George P, et al. Validation of presentation and 3 h high-sensitivity troponin to rule-in and rule-out acute myocardial infarction. Heart 2016;102:1270–8.
22. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, 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.
23. Body R, Carley S, McDowell G, Jaffe AS, France M, Cruickshank K, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. J Am Coll Cardiol 2011;58:1332–9.
24. Rubini Gimenez M, Hoeller R, Reichlin T, Zellweger C, Twerenbold R, Reiter M, et al. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. Int J Cardiol 2013;168:3896–901.
25. Bandstein N, Ljung R, Johansson M, Holzmann MJ. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. J Am Coll Cardiol 2014;63:2569–78.
26. Zhelev Z, Hyde C, Youngman E, Rogers M, Fleming S, Slade T, et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-analysis. BMJ 2015;350:h15.
27. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015;386:2481–8.
28. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arc Intern Med 2012;172:1211–8.
29. Mueller C, Giannitsis E, Christ M, Ordonez-Llanos J, de-Filippi C, McCord J, 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 e74.
30. Body R, Mueller C, Giannitsis E, Christ M, Ordonez-Llanos J, de Filippi CR, 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.
31. Rubini Gimenez M, Twerenbold R, Jaeger C, Schindler C, Puelacher C, Wildi K, et al. One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac troponin I. Am J Med 2015;128:861–70.e4.
32. Parsonage WA, Tate JR, Greenslade JH, Hammett CJ, Ungerer JP, Pretorius CJ, et al. Effect of recalibration of the hs-TnT assay on diagnostic performance. Clin Chem Lab Med 2014;52:e25–7.
33. Wildi K, Twerenbold R, Jaeger C, Rubini Gimenez M, Reichlin T, Stoll M, et al. Clinical impact of the 2010–2012 low-end shift of high-sensitivity cardiac troponin T. Eur Heart J Acute Cardiovasc Care [Epub ahead of print 2016 Apr 7].
34. McCord J, Nowak RM, McCullough PA, Foreback C, Borzak S, Tokarski G, et al. Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. Circulation 2001;104:1483–8.
35. Than M, Cullen L, Reid CM, Lim SH, Aldous S, Ardagh MW, 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.
36. Than M, Cullen L, Aldous S, Parsonage WA, Reid CM, Greenslade J, 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.
37. Goodacre SW, Bradburn M, Cross E, Collinson P, Gray A, Hall AS, 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.
38. Fitzgerald P, Goodacre SW, Cross E, Dixon S. 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.
39. Glatz JF, Vork MM, van der Vusse GJ. Significance of cytoplasmic fatty acid-binding protein for the ischemic heart. Mol Cell Biochem 1993;123:167–73.
40. Glatz JF, van Bilsen M, Paulussen RJ, Veerkamp JH, van der Vusse GJ, Reneman RS. Release of fatty acid-binding protein from isolated rat heart subjected to ischemia and reperfusion or to the calcium paradox. Biochim Biophys Acta 1988;961:148–52.

41. Kilcullen N, Viswanathan K, Das R, Morrell C, Farrin A, Barth JH, et al. Heart-type fatty acid-binding protein predicts long-term mortality after acute coronary syndrome and identifies high-risk patients across the range of troponin values. J Am Coll Cardiol 2007;50: 2061–7.
42. Lippi G, Mattiuzzi C, Cervellin G. Critical review and meta-analysis on the combination of heart-type fatty acid binding protein (H-FABP) and troponin for early diagnosis of acute myocardial infarction. Clin Biochem 2013;46:26–30.
43. Inoue K, Suwa S, Ohta H, Itoh S, Maruyama S, Masuda N, et al. Heart fatty acid-binding protein offers similar diagnostic performance to high-sensitivity troponin T in emergency room patients presenting with chest pain. Circ J 2011;75:2813–20.
44. Body R, Carley S, McDowell G, Pemberton P, Burrows G, Cook 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.
45. Carlton E, Body R, Greaves K. External Validation of the Manchester Acute Coronary Syndromes Decision Rule. Acad Emerg Med 2016;23:136–43.
46. Body R. Reducing unnecessary admissions for chest pain with the Manchester Acute Coronary Syndromes (MACS) decision rule. 2013. www.isrctn.com/isrctn86818215 (Accessed April 2016).
47. Lipinski MJ, Escarcega RO, D'Ascenzo F, Magalhaes MA, Baker NC, Torguson R, et al. A systematic review and collaborative meta-analysis to determine the incremental value of copeptin for rapid rule-out of acute myocardial infarction. Am J Cardiol 2014;113:1581–91.
48. Raskovalova T, Twerenbold R, Collinson PO, Keller T, Bouvaist H, Folli C, et al. Diagnostic accuracy of combined cardiac troponin and copeptin assessment for early rule-out of myocardial infarction: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care 2014;3:18–27.
49. Thelin J, Borna C, Erlinge D, Öhlin B. The combination of high sensitivity troponin T and copeptin facilitates early rule-out of ACS: a prospective observational study. BMC Cardiovasc Disord 2013;13:42.
50. Mockel M, Searle J, Hamm C, Slagman A, Blankenberg S, Huber K, et al. Early discharge using single cardiac troponin and copeptin testing in patients with suspected acute coronary syndrome (ACS): a randomized, controlled clinical process study. Eur Heart J 2015; 36(6):369–76.
51. Mahler SA, Miller CD, Hollander JE, Nagurney JT, Birkhahn R, Singer AJ, et al. Identifying patients for early discharge: performance of decision rules among patients with acute chest pain. Int J Cardiol 2013;168: 795–802.
52. Cullen L, Mueller C, Parsonage WA, Wildi K, Greenslade JH, Twerenbold R, 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.
53. O'Connor RE, Al Ali AS, Brady WJ, Ghaemmaghami CA, Menon V, Welsford M, et al. Part 9: Acute Coronary Syndromes: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015; 132(18 Suppl 2):S483–500.
54. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, Salein D, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. Circulation 1999;100:1593–601.
55. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000;284:835–42.
56. Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. N Engl J Med 1997;337:447–52.
57. Pollack CV, Jr., Sites FD, Shofer FS, Sease KL, Hollander JE. Application of the TIMI risk score for unstable angina and non-ST elevation acute coronary syndrome to an unselected emergency department chest pain population. Acad Emerg Med 2006;13:13–8.
58. Hess EP, Agarwal D, Chandra S, Murad MH, Erwin PJ, Hollander JE, et al. Diagnostic accuracy of the TIMI risk score in patients with chest pain in the emergency department: a meta-analysis. CMAJ 2010;182:1039–44.
59. Investigators G. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. Am Heart J 2001;141: 190–9.
60. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163:2345–53.
61. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004;291:2727–33.
62. Lyon R, Morris AC, Caesar D, Gray S, Gray A. Chest pain presenting to the Emergency Department–to stratify risk with GRACE or TIMI? Resuscitation 2007;74:90–3.
63. Than M, Aldous S, Lord SJ, Goodacre S, Frampton CM, Troughton R, 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.
64. Mahler SA, Miller CD, Litt HI, Gatsonis CA, Snyder BS, Hollander JE. Performance of the 2-hour accelerated diagnostic protocol within the American College of Radiology Imaging Network PA 4005 cohort. Acad Emerg Med 2015;22:452–60.
65. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. Neth Heart J 2008;16(6):191–6.
66. Backus BE, Six AJ, Kelder JC, Mast TP, van den Akker F, Mast EG, et al. Chest pain in the emergency room: a multicenter validation of the HEART Score. Crit Pathw Cardiol 2010;9:164–9.
67. Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol 2013;168:2153–8.
68. Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, et al. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. Crit Pathw Cardiol 2013;12:121–6.
69. Mahler SA, Hiestand BC, Goff DC, Jr., Hoekstra JW, Miller CD. Can the HEART score safely reduce stress testing and cardiac imaging in patients at low risk for major adverse cardiac events? Crit Pathw Cardiol 2011;10: 128–33.
70. Mahler SA, Riley RF, Hiestand BC, Russell GB, Hoekstra JW, Lefebvre CW, et al. The HEART pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. Circ Cardiovasc Qual Outcomes 2015;8:195–203.
71. Than M, Flaws D, Sanders S, Doust J, Glasziou P, Kline J, et al. Development and validation of the Emergency Department Assessment of Chest pain Score and 2 h accelerated diagnostic protocol. Emerg Med Australas 2014;26:34–44.
72. Cullen L, Greenslade JH, Than M, Brown AF, Hammett CJ, Lamanna A, et al. The new Vancouver Chest Pain Rule using troponin as the only biomarker: an external validation study. Am J Emerg Med 2014;32:129–34.
73. Greenslade JH, Cullen L, Than M, Aldous S, Chu K, Brown AF, et al. Validation of the Vancouver Chest Pain Rule using troponin as the only biomarker: a prospective cohort study. Am J Emerg Med 2013;31:1103–7.
74. Mokhtari A, Borna C, Gilje P, Tyden P, Lindahl B, Nilsson HJ, et al. A 1-h combination algorithm allows fast rule-out and rule-in of major adverse cardiac events. J Am Coll Cardiol 2016;67:1531–40.
75. Poldervaart JM. Risk stratification in chest pain patients [Dissertation]. UMC Repository: Utrecht University; 2016.
76. George T, Ashover S, Cullen L, Larsen P, Gibson J, Bilesky J, et al. Introduction of an accelerated diagnostic protocol in the assessment of emergency department patients with possible acute coronary syndrome: the Nambour Short Low-Intermediate Chest pain project. Emerg Med Australas 2013;25:340–4.
77. Queensland Government, Queensland Health. Healthcare Improvement Unit: the Accelerated Chest Pain Risk Evaluation (ACRE) Project. Queensland Health; 2015. https://www.health.qld.gov.au/caru/html/acre.asp (Accessed September 2016).
78. Than MP, Pickering JW, Aldous SJ, Cullen L, Frampton CM, Peacock WF, 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.