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

Louise A. Cullen,¹ Nicholas L. Mills,² Simon Mahler,³ and Richard Body⁴

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) 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.

© 2016 American Association for Clinical Chemistry

© 2016 American Association for Clinical Chemistry

© 2016 American Association for Clinical Chemistry

© 2016 American Association for Clinical Chemistry

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 Predictions 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-cTnI, high-sensitivity cardiac troponin I; 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.
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.

NI 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%–

**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.

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.
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-
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-
Copeptin, both in terms of 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 “ruled 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, 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 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 APACHE 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
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...
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. 3. The HEART Pathway.**

**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 ≤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 a NPV of 99.1% (40%) (Fig. 2). 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 typicity 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 ≥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 ≤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.


