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STATE-OF-THE-ART PAPER

Acute Coronary Syndrome

Emerging Tools for Diagnosis and Risk Assessment

Benjamin M. Scirica, MD, MPH

Boston, Massachusetts

Acute coronary syndrome encompasses a broad and heterogeneous population that challenges the clinician at each step of treatment in terms of: 1) diagnosis; 2) appropriate risk stratification; 3) therapeutic decision making; and 4) monitoring response to therapy. Although there are many established tools for diagnosis, prognosis, and clinical decision making, understanding the advantages and limitations of each tool according the clinical scenario is essential. Several emerging tools, such as novel biomarkers (e.g., high-sensitivity troponin and growth differential factor-15), ECG techniques (e.g., heart rate turbulence or T-wave alternans), and imaging modalities (computed tomography angiography and cardiac magnetic resonance) may potentially improve clinical care; however, they must be fully evaluated and validated in different scenarios and patient cohorts before they are incorporated into clinical practice. This review identifies promising new or emerging techniques, as well as established tools, and reviews their current or potential role in clinical practice. (J Am Coll Cardiol 2010;55: 1403–15) © 2010 by the American College of Cardiology Foundation

Acute coronary syndrome (ACS) encompasses a broad and heterogeneous population ranging from a patient with atypical chest discomfort, nonspecific electrocardiographic (ECG) changes, and normal cardiac biomarkers to the patient with a large ST-segment elevation, myocardial infarction (MI), and cardiogenic shock.

The diversity in clinical presentation of patients with suspected acute ischemic symptoms challenges the physician at each step of treatment in terms of: 1) diagnosis of ACS; 2) appropriate risk stratification; 3) therapeutic decision making; and 4) monitoring response to therapy (Fig. 1). When approaching a patient with suspected ACS, clinicians incorporate all available data to create a treatment plan. The bases for these decisions, even those that adhere to clinical guidelines, often rely on less than definitive data (1). The aim of this article is first to briefly review the statistical and analytical underpinnings that are used to evaluate new and emerging techniques for diagnosis, prognosis, and medical decision making and then to review how the clinical history, electrocardiography, biomarkers, and imaging modalities may be incorporated into clinical care.

From the TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts. Dr. Scirica has received research grants via the TIMI Study Group and Brigham and Women's Hospital from CV Therapeutics, Novartis, AstraZeneca, Daiichi-Sankyo, Merck, Johnson and Johnson, Bayer Healthcare, and Bristol-Myers Squibb. He has received honoraria for educational presentations from CV Therapeutics, Novartis, Merck, and Schering-Plough; and has served as a consultant for AstraZeneca, Novartis, CV Therapeutics, Congentus, Shionegi, and Gilead Sciences.

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Evaluating Novel Techniques for Clinical Care

Diagnosis. In the simplest terms, the goal of diagnosis is to correctly identify (or discriminate) patients with and without a particular disease. Diagnostic tests are evaluated according to their sensitivity (probability of a positive test result in a person with the disease) and specificity (probability of a negative test result in a person without the disease) and then compared with a gold standard. By incorporating both sensitivity and specificity, one can estimate likelihood ratios, receiver-operator characteristic curves, and overall accuracy to best understand the performance of a particular diagnostic test (2).

There are 2 related, although distinct, diagnostic questions in ACS. First, does the patient actually have unstable ischemic symptoms as opposed to nonischemic or noncardiac symptoms? Evaluating tools to identify patients with ACS without evidence of myocardial necrosis remains problematic because there is no true gold standard for the diagnosis of unstable angina. In contrast, the second question, did the patient have an MI, is more clearly defined according to consensus definitions based on the clinical scenario and the identification of myocardial necrosis by elevated levels of cardiac troponin (3) (Fig. 2).

Prognosis/risk stratification. Estimating prognosis is, by definition, based on probability and intends to predict future outcomes using clinical models that incorporate known risk features. Estimating, or discriminating, the relative strength of the relationship between clinical variables and clinical outcomes can be done using several

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Abbreviations and Acronyms

ACS = acute coronary syndrome
CAD = coronary artery disease
CK-MB = creatine kinase-myocardial bound
CMR = cardiac magnetic resonance
CRP = C-reactive protein
CTA = computed tomography angiography
ECG = electrocardiographic
GDF = growth differentiation factor
HRT = heart rate turbulence
HRV = heart rate variability
MDCT = multidetector computed tomography
MI = myocardial infarction
MPI = myocardial perfusion imaging
NP = natriuretic peptide
NSTE-ACS = non–ST-segment elevation acute coronary syndrome
STEMI = ST-segment elevation myocardial infarction

statistical techniques based on the addition of different risk variables to an accepted model. Traditionally, Cox models and receiver-operator characteristic curves have been used to identify variables independently associated with outcomes or to improve discrimination as determined with an increase in the C-statistic. However, these statistical techniques may underestimate the significance of a new variable in predicting relatively infrequent events such as cardiovascular death and recurrent ischemic episodes (2,4). Several new methods, such as integrated discriminating index (IDI), and net reclassification improvement (NRI), or reclassification calibration statistic, attempt to improve the integration of sensitivity and specificity and evaluate the proportion of patients who are reclassified to higher or lower risk categories based on a new technique (5). New risk stratification algorithms should be evaluated using several tests of discrimination and calibration, including these newly described techniques.

All guidelines strongly recommend that patients with ACS be accurately categorized into different risk categories using clinical models, but there remains substantial debate regarding the optimal method for determining whether a new risk factor improves the discrimination of future cardiac events (2,4,6).

Therapeutic implications/clinical decision making. The next and perhaps most challenging step in the evaluation of a new clinical technique is to determine whether using that tool changes practice based on its result. In other words, does the knowledge of the results of a particular test alter the treatment? The identification of a treatment that is of particular benefit in one group versus the other is most commonly identified within clinical trials when there is documented evidence of heterogeneity in the treatment effect based on a positive interaction between treatment and the clinical variable of interest. Confirming the relationship should then be evaluated prospectively in studies that specifically identifies patients based on that feature (e.g., cardiogenic shock, diabetic patients, elevated clinical risk score or troponin) to determine whether the proposed treatment improves outcomes in that population.

Clinical History and Evaluation

Clinical evaluation is fundamental to diagnosis, risk stratification, and decision making in patients with suspected ACS. The most important step in the evaluation of a patient with suspected ACS is to determine whether the clinical scenario is consistent with a spontaneous atherothrombotic lesion.

Diagnosis. Despite the advances in imaging and biochemical markers, obtaining a complete and detailed history remains the cornerstone of the evaluation of patients with suspected ischemic coronary syndromes. A diagnosis of ACS can be made based solely on history if there is a compelling clinical scenario in a patient with at least a moderate or high probability of an unstable syndrome.

Prognosis. Many clinical features assessed at presentation offer important prognostic information regarding the risk of death, MI, heart failure, or arrhythmic complications. Killip class, for example, which classifies the degree of heart failure, is one of the most powerful indicators of in-hospital risk. Clinical features, when combined with basic laboratory and ECG findings, have been incorporated into clinical risk scores that accurately stratify patients into different risk categories. The most widely used are the Thrombolysis In Myocardial Infarction (TIMI) risk score for non–ST-segment elevation acute coronary syndrome (NSTE-ACS), and ST-segment elevation myocardial infarction (STEMI), and the GRACE (Global Registry of Acute Coronary Event) risk score, which have all been derived or validated in large registry databases (7–9).

Clinical implications. Treatment decisions are often and appropriately based solely on the clinical evaluation. For example, according to the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, patients with ACS and evidence of cardiogenic shock benefit from immediate revascularization versus medical therapy (10). Clinical risk scores also identify patients who benefit from more aggressive treatment. Patients with NSTE-ACS with a moderate or high TIMI risk score have been shown to have a greater benefit with low molecular weight heparin (7), an early invasive strategy (11), and with the use of a glycoprotein IIb/IIIa inhibitors (12).

Current guidelines recommend calculating risk scores to evaluate risk and guide treatment decisions accordingly (13,14). Clinicians, however, tend to underestimate risk based on clinical evaluation. In the Canadian ACS Registry, treating physicians classified patients by their own estimation into low-, intermediate-, or high-risk groups. Patients at higher risk as determined by the treating physician did receive more aggressive therapy; however, there was poor correlation between physician-estimated risk and risk determined by the TIMI, GRACE, or PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin) risk scores (15). All 3 risk scores offered better discrimination in terms of predicting outcomes compared with the treating physician's classification

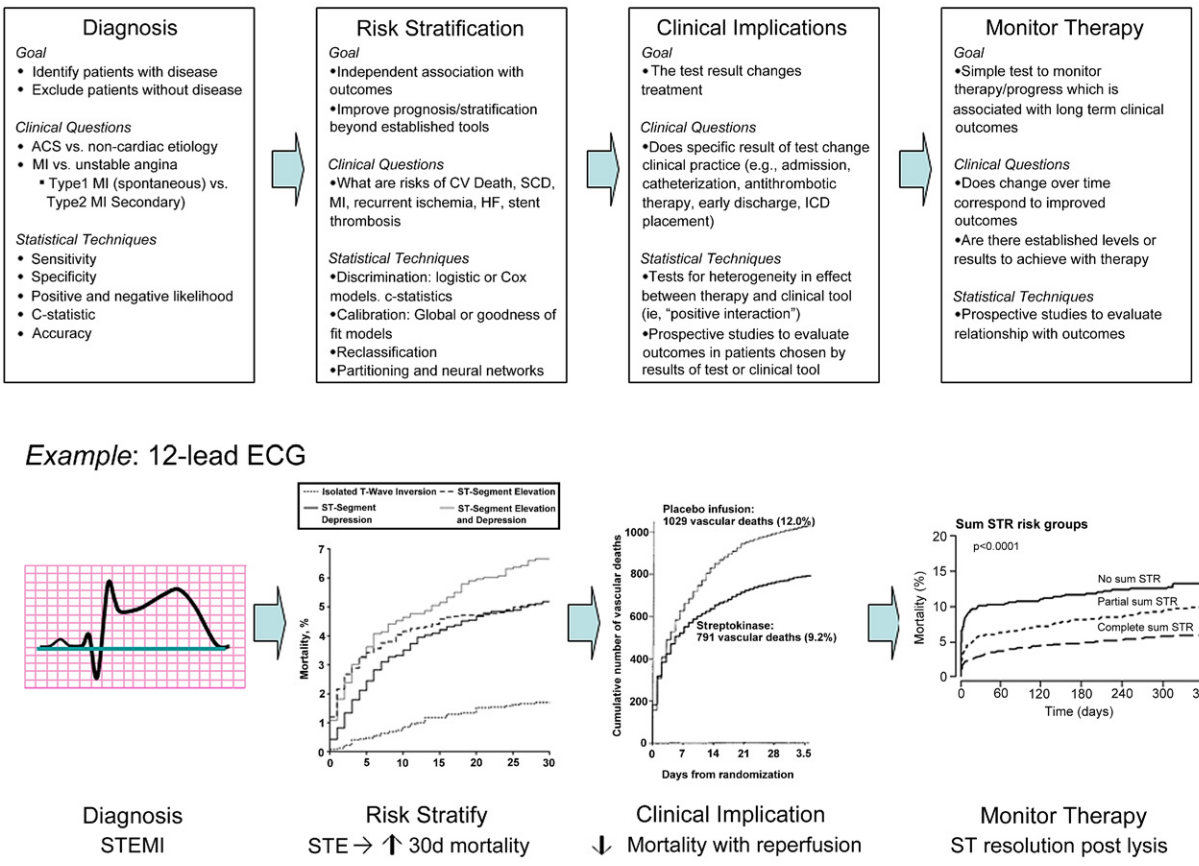

Figure 1 **Application of Clinical Techniques in Patients With Suspected ACS**

Ideally, a clinical tool is useful for diagnosis, risk stratification, clinical decision making, and monitoring therapy. Few existing tools address the statistical requirements of each stage of clinical use. The 12-lead electrocardiogram (ECG) is one exception and is central to each stage via diagnosis, in this example with ST-elevation (STE), prognosis (19), clinical decision making (fibrinolytics in patients with STEMI [ST-segment elevation myocardial infarction]), and monitoring therapy (degree of ST-segment resolution [STR] [25]). ACS = acute coronary syndrome; CV = cardiovascular; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; SCD = sudden cardiac death.

(16). Underestimation of risk was primarily due to discounting the significance of older age and previous coronary artery bypass graft, and an overemphasis on biomarkers and ST-segment depressions. One-third of all patients were not referred for catheterization because they were thought to be at "not high enough risk." In fact, almost 60% of these patients were in an intermediate or high TIMI risk category, for which an invasive strategy is recommended (17).

Electrocardiography

The standard 12-lead electrocardiogram remains the single most important diagnostic tool in the evaluation of ACS and as such should be performed within 10 min of the first contact with medical personnel. The integrated role of that the admission electrocardiogram plays in the diagnosis, triage, and treatment of patients with ACS is shown in Figure 1. In addition, continuous ECG monitoring after admission may provide additional information regarding arrhythmia or recurrent ischemia and can be used for more novel and complex analyses (Table 1).

Diagnosis. The presence of ST-segment elevation identifies the first branch point in the identification and diagnosis of ACS. ST-segment elevation is the most specific finding for MI and, together with a compatible clinical scenario, is sufficient to make the diagnosis of MI. Any question regarding the diagnosis of STEMI can be confirmed with echocardiography to assess wall motion abnormalities. Although not specific enough to be diagnostic for MI, ST-segment depression, especially if dynamic and captured during ischemic symptoms, greatly increase the likelihood of ACS. Capturing additional leads (right-sided and V_7 to V_9) improves both the sensitivity and specificity of the electrocardiogram in the diagnosis ACS and MI. More extensive monitoring with body surface mapping with 80-lead electrocardiograms has also been shown to improve the detection of myocardial ischemia, in particular, for ischemia in high right anterior, posterior, and right ventric-

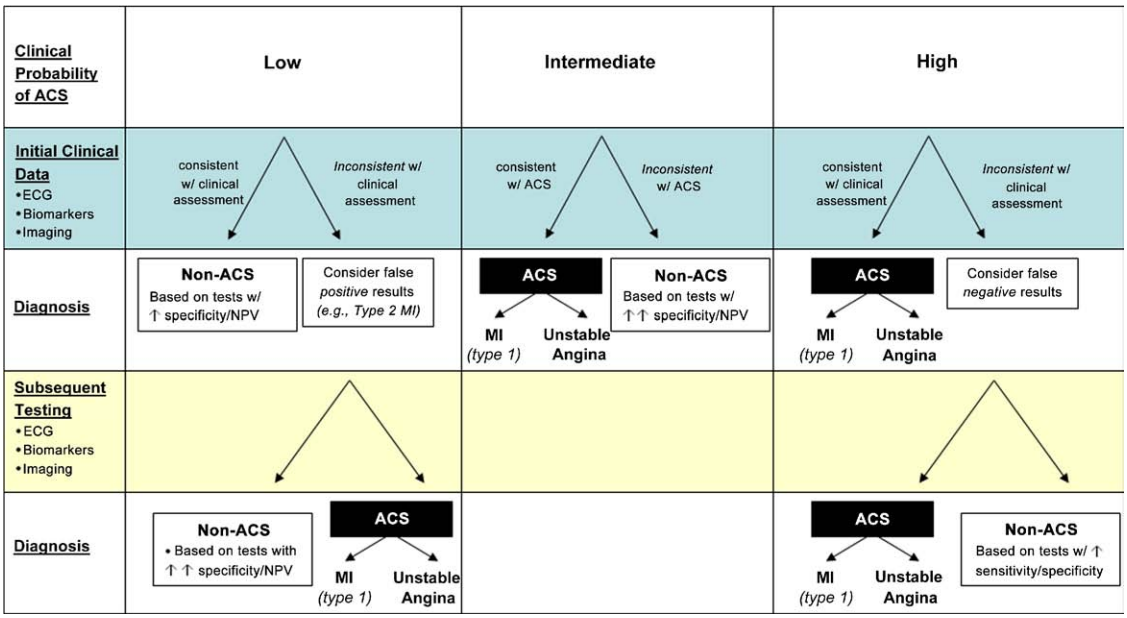

Figure 2 **Incorporation of Clinical, Electrocardiographic, Biomarker, and Imaging Data in the Diagnosis of ACS and MI**

Diagnosis of suspected acute coronary syndrome (ACS) begins with the clinical evaluation and decision regarding the likelihood of ACS. Depending of that likelihood, tests with different sensitivities and specificities should be used to confirm or reject the diagnosis. The diagnosis of myocardial infarction (MI) must incorporate clinical scenario to determine whether it is an ACS-related MI (type 1 or spontaneous) or non–ACS-related myonecrosis (type 2 or secondary). ECG = electrocardiogram; NPV = negative predictive value.

ular territories (18). Whether a patient has unstable angina or non-STEMI will depend on any elevation in markers of necrosis.

Prognosis. **ST-SEGMENTS.** In addition to aiding in diagnosis, different aspects of the electrocardiogram also provide prognostic information (19,20). Patients with NSTE-ACS and ST-segment deviation >0.5 mV were at greater 1-year risk of death or MI than patients with T-wave inversion or no ECG changes (21). Even when including cardiac biomarkers such as troponin, N-terminal pro–B-type natriuretic peptide (NP), and C-reactive protein (CRP), the degree of ST-segment depression in patients with NSTE-ACS was the strongest prognostic variable for death or MI (22).

Continuous ECG monitoring in patients hospitalized with ACS allows detailed assessment of recurrent ischemia. In more than 6,300 patients with NSTE-ACS who underwent 7-day continuous ECG monitoring, an episode of recurrent ischemia (>1 mm depression lasting at least 1 min) was associated with a significant increase in the risk of ischemic events including cardiovascular death. Patients with more than 2 episodes were at greatest risk, and the association was similar regardless of medical therapy or revascularization during the index hospitalization (23).

ST-SEGMENT RESOLUTION AFTER FIBRINOLYSIS. In patients with STEMI, close monitoring of the ST-segment after reperfusion provides a noninvasive method of assessing reperfusion after fibrinolysis and the degree of ST-segment resolution after reperfusion is closely associated with prognosis. Patients with failed reperfusion detected as poor ST-segment resolution should be urgently triaged to more intensive medical and interventional procedures (22). As described by deLemos et al. (24) and Schröder et al. (25,26), the degree of maximal ST-segment deviation on presentation and the extent ST-segment resolution after reperfusion are independent indicators of short- and long-term outcomes. ST-segment resolution after primary percutaneous intervention has also been associated with worse outcomes, although the therapeutic implication is not well defined.

NOVEL ELECTROCARDIOGRAPHIC PARAMETERS. Standard evaluation of the electrocardiogram is limited mostly to identifying the underlying cardiac rhythms and recognizing the typical wave patterns of cardiac ischemia. The ECG signal, however, provides a vast amount of additional data on the overall health of the heart that is currently not extracted because clinicians lack the tools and technology to interpret subtle abnormalities. Several ECG techniques such as heart rate variability (HRV) (27), deceleration capacity (28), heart rate turbulence (HRT) (29), T-wave alternans (30–32), and signal-averaged electrocardiography (31), among others, have been proposed to evaluate different aspects of ECG signals.

As opposed to ST-segment and T-wave deviations, which assess ischemia, these novel ECG metrics primarily attempt to identify patients at greatest risk of arrhythmic death and thus focus on overall mortality and sudden cardiac

Table 1 Established and Novel Biomarkers

Biomarkers		Diagnosis		Prognosis	Clinical Implications	Monitor Therapy
		ACS (Without Evidence of Myocardial Necrosis)	MI			
Troponin	Necrosis	+++	+++	+++	+++	
Natriuretic peptides	Ventricular stress	+		+++	++	+
Creatine kinase-myocardial bound	Necrosis	++	++	+++	++	
Myoglobin	Necrosis	++	+		+	
High-sensitivity troponin	Necrosis/ischemia	++	++	++		
Ischemia-modified albumin	Ischemia	+		+		
Fatty acid binding protein	Ischemia	+		++		
Growth differential factor-15	Ischemia/reperfusion	++		++	+	
C-reactive protein	Inflammation: nonspecific marker	++		+++		+
Pregnancy-associated plasma protein-A	Inflammation: matrix metalloproteinase-9/plaque instability	+				
Myeloperoxidase	Inflammation: neutrophil activation, reactive oxygen species	+		++		
ST2	Inflammation: regulatory protein in times of myocardial stress	+		+		
Lysosomal phospholipase A2	Cholesterol trafficking	+		++	+	
Copeptin	Stress: vasopressin prohormone	+		+		
Soluble CD40 ligand	Platelet activation	+		+		
Fibrinogen	Thrombosis	+		++		
Plasminogen activator inhibitor-1	Endogenous fibrinolytic system	+				
D-Dimer	Thrombosis	+		+		
Platelet aggregation	↓ Response to antiplatelet therapy			++	++	+
CYP2C19 polymorphism	↓ Response to clopidogrel			++	++	
Metabolite profile	Early signs of metabolic dysregulation	+	+			

ACS = acute coronary syndrome; MI = myocardial infarction; + = limited or contradictory evidence; ++ = compelling but not conclusive evidence; +++ = strong/validated evidence for use.

death rather than recurrent ischemic events (33). Most studies therefore focus on patients with the greatest risk of sudden cardiac death, in particular, patients with a history of MI and heart failure or depressed left ventricular function. HRV, HRT, deceleration capacity, signal-averaged electrocardiography, and T-wave alternans have all been shown to be associated with increased overall mortality or sudden cardiac death.

HRT, which assesses autonomic tone on heart rate recovery after premature ventricular beats, has been shown in more than 6,000 patients with a recent MI to be closely associated with mortality, even after adjusting for clinical features. The predictive accuracy of HRT was similar to left ventricular ejection fraction in terms of predicting sudden cardiac death (29). Other ECG techniques, such as deceleration capacity, which focuses principally on the vagal rather than sympathetic compenents of HRV, also have good discrimination for identifying patients at high risk of death after MI (C-statistic improvement from 0.74 to 80), which was better than an ejection fraction <30% or standard HRV parameters (28). Further studies to best assess the predictive value of novel ECG techniques are needed.

Clinical implications. The identification of ST-segment elevation or a new left bundle branch block is one the most straightforward examples of how a diagnostic test drives clinical decision making. Few other findings are quite as straightforward in cardiology. Similarly, although not as specific, dynamic ST-segment depressions or transient ST-segment elevations are high-risk features that should prompt more aggressive medical and invasive therapy in patients with NSTE-ACS (13,14).

Although there has been great hope in developing an ECG parameter to guide therapy and identify patients at greatest risk of sudden cardiac death, none of the novel ECG parameters such as HRT, deceleration capacity, or even T-wave alternans have conclusively been shown to provide information that should alter therapy. Adequately powered trials that prospectively identify patients according to a novel high-risk feature (e.g., low HRT or increased T-wave alternans) followed by randomization to therapy (e.g., implantable cardioverter-defibrillator placement or antiarrhythmic therapy) are needed to define whether these new techniques should be incorporated into clinical care (34,35).

Biomarkers

The discovery and evaluation of cardiac biomarkers continues at a rapid pace. Two biomarkers—cardiac troponin and NPs—have been fully incorporated into clinical care for many years; however, there remains substantial confusion regarding their application in ACS with regards to diagnosis and clinical decision making (3,36). Moreover, there are literally dozens of additional biomarkers reflecting different

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Table 2 Established and Emerging Electrocardiographic Tools

Electrocardiographic Test		Diagnosis		Prognosis	Clinical Implications	Monitor Therapy
		ACS (Without Evidence of Myocardial Necrosis)	MI			
12-lead electrocardiogram						
ST-segment elevation	Injury current	+++	+++	+++	+++	+++
Dynamic ST-segment depression	Ischemia	++	++	+++	+++	+++
Dynamic T-wave changes	Ischemia	++	+	++	++	+
Continuous electrocardiographic monitoring						
ST-segment shift	Ischemia			+++	+	+
Ventricular ectopy	Arrhythmia			+++	+	+
Heart rate variability	Autonomic nervous system modulation of sinus node			++		
Deceleration capacity	Vagal modulation of sinus node			++		
Heart rate turbulence	Short-term fluctuation of sinus cycle after VPB; possibly reflects baroreflex sensitivity			++		
T-wave alternans	Repolarization abnormalities			++	+	
Signal-averaged electrocardiography	QRS variability and late potentials			+		
Morphologic variability	Beat-to-beat energy differences			+		

VPB = ventricular premature beat; other abbreviations as in Table 1.

physiologic pathways that have been proposed to improve diagnosis or prognosis (Table 2).

Cardiac troponin. DIAGNOSIS. An elevated concentration of cardiac troponin is central to the universal definitions of MI. Values that are above the 99th percentile of a normal population should be considered as an indication of myocardial necrosis (3). Ideally, an assay should have a precision (or imprecision) of <10% coefficient of variation at the 99th percentile level. Despite a clear consensus on the definition of MI that is based on elevated cardiac troponin, several factors still lead to substantial confusion in clinical practice.

First, there are multiple commercially available assays, each with an individual decision limit based on the assay's performance. Second, many laboratories still report several cut points, often labeling them "normal," "indeterminate," and "suggestive of myocardial injury." With the current generation of commercial assays, there should be no "indeterminate" values, only results above or below the specific assay cut point. The third area of confusion is the most clinically challenging and due to the widespread use of troponin assays in a broader population than patients with suspected ACS. Cardiac troponins are extremely specific for cardiac injury; however, myocardial damage is not specific to ACS. Central to the diagnosis of ACS and MI is a clinical scenario consistent with myocardial ischemia. Thus, an elevated troponin in a patient with sepsis, hypertensive emergency, or pulmonary embolism indicates that there has been myocardial damage—*type 2* or *secondary MI* as defined by the Universal Definition of MI—and likely indicates a worse prognosis, but it does not mean that patient has ACS and therefore should not receive ACS-directed care. Overreliance on troponin as a diagnostic tool can lead to misdiagnosis and inappropriate, and potentially dangerous, treatment. Conversely, in a patient with a clinical scenario consistent with myocardial ischemia, an elevated troponin, even at levels just above the 99th percentile, fulfills the criteria for MI (type 1 or spontaneous MI) and identifies a patient who should be treated accordingly.

In patients presenting with ACS, creatine kinase-myocardial bound (CK-MB) should not be used for diagnostic purposes if troponins are also measured. Given the sensitivity and specificity of troponin for myocardial damage, elevated CK-MB in the setting of a normal troponin indicates a false-positive CK-MB. Both CK-MB and troponin can be used to detect episodes of reinfarction if the biomarker increases >20% above the level measured at the time of the recurrent symptoms (3).

HIGH-SENSITIVITY TROPONIN ASSAYS. There are several new troponin assays under development with reported detection limits and reproducibility that are considerably better than the current commercially available assays (37–39). These high-sensitivity assays detect pg/ml as opposed to ng/ml levels of circulating troponin and offer the possibility of not only greater sensitivity in identifying myocardial necrosis but also earlier detection. For example, in a study of patients with documented myocardial injury, 64% of the initial samples with negative results using a standard troponin assay actually had detectable levels of troponin using one of the high-sensitivity assays (37). In 2 studies of patients presenting with chest pain, several high-sensitivity troponin assays demonstrated impressive improvements in the diagnostic accuracy for MI, in particular among patients who presented early after the onset of symptoms. For example, 1 high-sensitivity assay improved the *c*-statistic for MI from 0.85 to 0.96 compared to a standard troponin assay (40,41).

The incorporation of high-sensitivity assays into clinical care will require a considerable amount of research and education. High-sensitivity assays will increase the sensitiv-

ity for detecting myocardial injury, but will reduce specificity for identifying ACS. Many more patients with an ischemic syndrome will have detectable levels of troponin and thus fulfill the criteria for MI. Placing the laboratory data within the clinical context will become even important because a greater number of patients *without* ACS will also have detectable levels of troponin due to other etiologies such as heart failure, renal disease, or myocarditis (type 2 or secondary MI). Moreover, due to the greater sensitivity in detecting even lower concentrations of circulating troponin, identifying the appropriate cut point will be dependent on the makeup of the "healthy" population and could differ significantly from one cohort to another. The recommendations in the current universal MI definition to evaluate the pattern of serial troponin measurements in patients with persistently elevated levels (e.g., renal failure) will become even more relevant with the introduction of highly sensitive troponin assays that will identify even more patients with detectable basal levels of troponin (3,42).

The development of more sensitive troponin assays may also require a reassessment of the currently held belief that troponin is only released from permanently injured myocardial cells. In a study of 120 patients referred for exercise stress testing, transient stress-induced ischemia, as detected by nuclear imaging, was associated with a detectable increase in troponin using one of the new high-sensitivity assays. There was no corresponding increase detected with conventional troponin assays (43). The entire paradigm of troponin "positive" or "negative" in ACS may need to change if and when high-sensitivity assays become commercially available.

Prognosis. Myocardial damage, as detected by elevated levels of cardiac troponin, clearly increases the risk of recurrent cardiovascular events with a graded relationship between the absolute elevation and outcomes. Overall, an elevated troponin is associated with roughly a 4-fold increase in the risk of death or recurrent MI compared with patients with a normal troponin concentration (44–46). Cardiac troponin is complementary to other risk factors such as age, renal function, and ECG changes. Even among patients with STEMI in whom biomarkers should not be used for diagnostic purposes, elevated troponin on admission is associated with worse outcomes (47,48), and peak troponin concentrations correlate with infarct size as determined by nuclear imaging (49).

Even low-level troponin elevations, at concentrations below what would be considered an appropriate MI cut point, are associated with worse clinical outcomes. Several studies of patients with chest pain or NSTE-ACS have shown that patients with initial concentrations of troponin that were detectable but still below the 99th percentile/10% coefficient of variation MI cut point were at greater risk of death or recurrent MI compared with patients with concentrations below the lower limit of detection (50,51).

As more sensitive troponin assays are introduced, further research regarding the prognostic risk associated with extremely small troponin elevations will be needed; however, it is likely that any elevation in troponin will likely identify patients at greater risk compared to patients with a nondetectable level.

CLINICAL IMPLICATIONS. Together with the initial electrocardiogram, cardiac troponin is one of the central decision-making nodes in the treatment of patients with ACS. Ischemia severe enough to induce necrosis is typically the result of more complex and thrombotic coronary lesions (52,53), and not unexpectedly, patients with elevated concentrations of troponin derive the greatest benefit from more aggressive antithrombotic therapy with low molecular weight heparins and the glycoprotein IIb/IIIa inhibitors (13,14) Several studies in patients with NSTE-ACS have shown that patients with elevated levels of troponin receive the greatest benefit from an invasive strategy compared with patients with no detectable necrosis, although 1 trial, the ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes) trial, prospectively enrolled patients with NSTE-ACS and an elevated troponin and did not demonstrate any benefit of an early invasive strategy compared with initial medical management, although there was high crossover to catheterization from the medical therapy group (54). Overall, a meta-analysis of 7 trials comparing an invasive and conservative strategies, which included the ICTUS trial, did demonstrate an overall reduction in short- and long-term outcomes with an invasive strategy (55), and current guidelines recommend this strategy in patients at high risk based on elevated levels of troponin. With the introduction of higher sensitivity troponin assays, many of the treatment implications associated with elevated levels of troponin, including early invasive strategy, will require re-evaluation.

NPs. NPs are released from the ventricular myocardium in response to stress. There are commercially available assays for both B-type NP and N-terminal-pro–B-type NP, and although there are differences in terms of kinetic and analytic parameters, their clinical role can be addressed together.

DIAGNOSIS. As a marker of myocardial stress, NPs are elevated in many cardiovascular conditions, most commonly heart failure, but also pulmonary hypertension, pulmonary embolism, cardiac arrhythmias, and cardiac ischemia. Thus, as a diagnostic tool, NP is sensitive but lacks specificity to either include or exclude patients with ACS.

PROGNOSIS. Among patients with ACS, elevated levels of NP are strongly associated with clinical outcomes across the spectrum of ACS (56) including NSTE-ACS (57) and STEMI (58,59). NP levels typically peak in the hours after the initiation of an ACS episode and then gradually decrease over the subsequent days; however, the pattern and speed of decrease are not uniform. Persistently elevated levels of an NP in the days and weeks following ACS may then identify patients at particularly high risk of cardiovas-

cular death or heart failure, even in the setting of normal ejection fraction (60–62).

CLINICAL IMPLICATIONS. In contrast to troponins and despite the ample evidence linking elevated levels of NP and cardiovascular outcomes, there are no clear clinical implications of how an elevated NP level should guide specific therapy or treatment in ACS (36). In terms of deciding on an early invasive strategy, one study found a nonsignificant trend toward greater benefit in patients with elevated levels of NP (63); however, another found no difference in the benefit of an early invasive versus compared with medical therapy (64). Studies specifically designed to evaluate whether a specific strategy or medication targeted at patients with an elevated NP level can modify the associated risk, or determine if NPs are useful to monitor therapy, are needed to better define the utility of routine measurement of the NP level in ACS (36).

CRP. CRP, a nonspecific marker of inflammation, has been evaluated extensively in ACS. Although not specific enough to aid in the diagnosis of ACS or MI, elevated levels of CRP at the time of admission have been shown in multiple studies to be associated with poor outcomes in patients with ACS (36,65,66). The strength of that relationship varies depending of the degree of myocardial necrosis, the cut point applied, the timing of measurement, and the patient population (36). CRP may be most useful when it is measured soon after the index event where the inflammation represents the underlying inflammatory precipitant as opposed to later when it may be confounded by necrosis, and when using disease-specific cut points (67). Assessing levels of CRP several weeks after ACS, when the acute inflammatory phase has subsided, may be more useful than in the acute setting. Patients with a CRP level >2 mg/l 1 month after admission for ACS were at significantly greater risk of death (68,69) and heart failure (62) compared with those with a low levels of CRP. The strategy of targeting patients with elevated concentrations of CRP with specific therapy, as was done in the primary prevention JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), is an example of how novel risk markers should be prospectively evaluated (70).

Novel biomarkers. There are literally dozens of biomarkers reflecting a variety of pathophysiologic pathways that have been reported to be elevated in patients with ACS and potentially associated with increased risk. These include markers of ischemia and inflammation (ischemia-modified albumin, heart fatty acid binding protein, myeloperoxidase), vascular dysfunction (matrix metalloproteinase-9, pregnancy-associated plasma protein A0, biomechanical stress (copeptin, ST2, growth differentiation factor [GDF]-15), hemostasis (fibrinogen, plasminogen activator inhibitor-1), and lipid metabolism (lipoprotein-associated phospholipase A2). For a variety of reasons, most are unlikely to reach widespread clinical use (36). Few of the novel biomarkers have been shown to consistently improve on established markers, and many lack confirmation in varied cohorts. In a study of 664 patients admitted with suspected ACS, for example, none of the more than 10 novel markers tested approached the sensitivity of cardiac troponin in diagnosing MI (71). Several authors have proposed analytical and clinical criteria that novel biomarkers must successfully meet before they can be fully integrated into clinical care (4,72,73).

Of the novel markers, GDF-15, a member of the transforming growth factor family that is released by myocytes during ischemia and reperfusion, is one of the most promising. In several cohorts, including patients with chest pain (74) and NSTE-ACS (75,76), elevated levels of GDF-15 are associated with increased risk of death and MI, independent of ECG changes, troponin level, or NP level. In one study, there was an interaction between randomization to an invasive strategy and elevated levels of GDF-15, which suggests that an invasive strategy may be preferential in patients with an increased concentration (75), although prospective confirmatory studies are needed.

Proteomics, metabolomics, genomics, and pharmacogenomics. Advances in proteomic, metabolic, and genomic profiling with high-throughput screening technology combined with advanced bioinformatic and statistical techniques may dramatically expand the number of novel markers, traits, or patterns of cardiac metabolism and pathology. For example, a study of serial blood samples from patients undergoing alcohol septal ablation, in other words a "planned MI," revealed a specific profile of metabolites in pyrimidine metabolism, the tricarboxylic acid cycle, and the pentose phosphate pathway that were present within 10 min of the induced MI. The pattern was also present in patients with ACS undergoing percutaneous coronary intervention but not in patients with stable coronary artery disease (CAD) undergoing percutaneous coronary intervention (77). Candidate-gene studies, which focus on predefined genetic loci, and genomewide association studies, which evaluate hundreds of thousands of single nucleotide polymorphisms have identified several potential variants such as those at chromosome 9p21 that are associated with an increased risk of incident cardiovascular disease (78–80). Further studies are needed to determine whether individuals with single nucleotide polymorphisms at chromosome 9p21 are also at increased risk of secondary events after ACS.

Identification of reduced-function polymorphisms in the cytochrome P-450 *CYP2C19* gene is one of first examples of a potential treatment implications based on genetic analysis. Several studies of patients with ACS treated with clopidogrel found that the risk of recurrent ischemic events, including stent thrombosis, was greatly increased in patients with a reduced-function polymorphism in the gene that encodes CYP2C19, which is responsible for the conversion of clopidogrel, a prodrug, into its active metabolites (81–83). Genetic testing for this allele, as well as other single nucleotide polymorphisms, is commercially available,

Table 3 Established and Emerging Imaging Techniques

Imaging Modality	Diagnosis		Prognosis	Clinical Implications	Monitor Therapy
	ACS (Without Evidence of Myocardial Necrosis)	MI			
Coronary angiography	++	+++	+++	+++	+
Echocardiography	++	++	+++	++	+
Myocardial perfusion imaging	++		++	+	
Ischemic memory	+				
Computed tomography					
Perfusion	++	+	++	+	
Angiography	++		+	+	
Cardiac magnetic resonance	+	+	++		

Abbreviations as in Table 1.

and a new of section in the U.S. Food and Drug Administration prescribing information for clopidogrel specifically identifies this genetic cohort as potentially not responding to clopidogrel therapy.

Imaging

With advances in technology, cardiac imaging will play a greater role in the diagnosis of ACS and further improve prognostic capabilities (Table 3). As with cardiac biomarkers, understanding the clinical history and placing the results of any imaging modality in the context of other data are required to avoid misinterpretation of results.

Diagnosis. No imaging test alone is either 100% sensitive or specific for a diagnosis of ACS, and thus their clinical utility is greatest in patients with an intermediate probability of ACS. In patients with a high probability of ACS or MI (e.g., typical symptoms, documented CAD, elevated cardiac biomarker level, or dynamic ECG changes), results of imaging tests are unlikely to offer incremental clinical information and will only lead to unneeded exposure and resource utilization. Conversely, in patients with a very low probability of ACS based on other clinical features, further testing only increases the chance of false-positive results, requiring unnecessary follow-up testing.

ISCHEMIA. To aid in the diagnosis of ACS or acute infarct, imaging modalities can evaluate either ventricular function or coronary anatomy. Objective evidence of ischemia by cardiac imaging reduces the time to treatment in patients with suspected ACS. In the urgent setting, echocardiography is useful to identify wall-motion abnormalities in patients with nondiagnostic ECG changes and persistent chest discomfort. Resting myocardial perfusion imaging (MPI) in patients with ongoing chest discomfort and nondiagnostic ECG or biomarker results will also identify active ischemia. However, MPI cannot distinguish between recent and older infarcts; thus, abnormal MPI is not specific for ACS. Among 2,475 patients who presented with chest pain, randomization to a strategy with acute resting MPI did not affect triage decisions in patients in whom the eventual clinical diagnosis was MI or unstable angina; however, among those patients *without* acute coronary ischemia (>85% of the patients), MPI did reduce the rate of admission (84).

Both MPI with single-photon emission computed tomography and contrast echocardiography using molecularly modified contrast agents have been shown to identify areas of recent myocardial ischemia in the absence of necrosis. New techniques to identify recent ischemia, in other words, an "ischemic memory," will require further evaluation testing but could improve the early diagnosis of ACS in patients with recent, but not ongoing, rest symptoms (85–87).

CMR has also been evaluated in the acute setting of ACS and extensively reviewed (88). CMR can provide substantial information regarding ventricular function, ongoing ischemia/perfusion, early and late regions of infarction, and coronary anatomy. In a prospective study of 162 patients with suspected ACS but nondiagnostic electrocardiogram and biomarkers, CMR had a sensitivity and specificity for ACS of 84% and 85%, respectively, which was more sensitive than ECG or troponin and more specific than abnormal ECG findings (89). T2-weighted images, which identify edema associated with acute infarcts, may also be useful to discriminate between old and new infarcts and increase the specificity and positive predictive value of CMR in evaluating ACS (90). An added benefit of CMR is that in more than one-half of patients who do not have ACS, CMR does identify the etiology of elevated cardiac markers or ventricular dysfunction.

CORONARY ANATOMY. The original and gold standard method to identify significant lesions is coronary angiography, which continues to have a central role in the diagnosis of ACS. In patients with an atypical symptoms but worrisome ST-segment elevation, urgent angiography will identify any potential lesions that require intervention. In patients with persistent angina and equivocal ECG or biomarker data, it may be better to proceed to urgent catheterization to identify potentially electrocardiographically silent lesions rather than pursue other imaging modalities.

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Computed tomography angiography (CTA) with multidetector computed tomography (MDCT) technology provides excellent spatial resolution of the coronary anatomy. Although not yet at the same level as traditional angiography, resolution is approaching <0.5 mm with 64-slice MDCT technology. In multiple studies comparing MDCT with coronary angiography, the sensitivity of MCDT ranges from 73% to 100% and the specificity from 91% to 97% (91–93).

The great challenge in incorporating imaging evidence into an algorithm for evaluating patients with ACS is that it in many cases, it is difficult to determine solely based on anatomy whether a particular lesion is the cause of the presenting symptoms. Patients may have both chest discomfort from a noncardiac source and a lesion on CTA that is not responsible for their presentation. To avoid the problem of "true, true, and unrelated," the clinical history must be compelling to act on a potential lesion detected by CTA. Similarly, in a patient with a high probability of ACS in whom catheterization is likely, CTA will only increase contrast and radiation exposure because there is less chance of excluding disease due to the patient's high pre-test probability of detectable CAD and likely need for coronary angiography.

Thus, the greatest benefit of noninvasive CTA is to exclude CAD in patients with a low to intermediate probability of ACS (94). Several studies have demonstrated that in patients with suspected ACS, the absence of significant coronary stenosis (>50%) and nonsignificant coronary atherosclerotic plaque on MDCT successfully identified most or all patients without ACS (up to 100% negative predictive value), although the specificity and positive predictive value of CTA were substantially lower (94–96).

Evaluating new imaging modalities requires careful attention to any potential biases in patient selection or selective use of post-test assessment of the gold standard catheterization, which would fundamentally, and possibly erroneous, alter the reported performance of the new modality (97).

Prognosis. A variety of data collected from cardiac imaging can help to risk stratify patients after ACS. Assessing ischemia by a stress test in low- to intermediate-risk patients or in patients medically managed after MI is clearly indicated in practice guidelines (13,97,98). Assessment of infarct size, residual ischemia, and left ventricular function have all been shown to identify patients at greatest risk of recurrent ischemic events or cardiac death. Echocardiography remains the most commonly used modality to assess ventricular function and assess for any complications of MI because it is widely available; however, other modalities such as single-photon emission computed tomography and especially CMR provide substantial information regarding infarct size and function (88).

Decision making. There are several treatment decisions that are routinely based on echocardiography, specifically the early initiation of inhibitors of the renin-angiotensin-aldosterone system or future consideration of implantable cardioverter-defibrillator implantation in patients with evidence of depressed left ventricular function (99). As discussed previously, the absence of coronary lesions detected on CTA can significantly improve disposition in terms of early discharge from an emergency department. Another study using early single-photon emission computed tomography to quantify infarct size and residual ischemia suggested that it may also identify patients at such low risk of recurrent events after MI that they could be safely discharged early (100).

Table 4 Questions Regarding Novel Diagnostic Tools in ACS

1. Can the tool be quantified or measured?
a. Biological relationship established
b. Accurate and reproducible method(s)
c. Preanalytical issues (including stability) evaluated and manageable
d. Technique is accessible and easy to implement
e. Widely available with rapid turnaround
f. Reasonable cost
g. Acceptable risk/side effects
2. Does tool add new information?
a. Strong and consistent association between the results of tool and the outcomes in multiple studies
b. Information adds to or improves on existing test or replaces more costly/risky test
c. Reference ranges and decision limits are validated in multiple studies
d. Evaluation includes data from community-based populations, and not just clinical trial cohort
3. Will tool help the clinician to manage patients?
a. Performance superior to that of existing diagnostic tools, or
b. Improved risk stratification, or
c. Evidence that test-guided triage or therapy improves care or,
d. Evidence that associated risk is modifiable with specific therapy, or
e. Tools can be used to monitor therapy

Adapted from Morrow and de Lemos (73).

An Integrated Approach

The goal and greatest challenges are the integration of multiple techniques and tests into clinical practice in a logical and cost-effective strategy. The optimal approaches will include a combination of clinical, ECG, biomarker, and imaging techniques. Which individual modality to include in a specific strategy will depend greatly on the clinical scenario and the question that is being asked. Does this patient have ACS or can he or she be discharged immediately? Should this patient undergo early catheterization? What is this patient's risk of sudden cardiac death and should an implantable cardioverter-defibrillator be placed before discharge? Each scenario will require different tests but also may weigh the relative results of one particular test differently depending on the clinical situation. The incorporation of new tools will require careful evaluation of their technical and clinical benefit and limitations before they are integrated into practice (Table 4).

Integration of multiple test results occurs via clinical risk scores or by combining multiple biomarkers into a multimarker strategy; however, there is always the conflict between simplicity of application and improved model performance. For example, creating a binary cut point with

biomarkers that have a linear or graded relationship with outcome enhances clinical applicability but reduces the discriminatory power of that test. More complex models, the use of Bayesian approaches, artificial neural networks, or support vector machines may substantially improve the discriminatory capacity of a particular tool or strategy. The question is how easily these more sophisticated techniques can be implemented in clinical care, especially when most clinicians may not understand the complex underlying statistical or decision-tree basis for the results.

There is unlikely to be one "perfect" tool that will be sufficient to answer all the questions related to patients with ACS; however, the clinical need for improved methods to diagnose, risk stratify, guide treatment, and evaluate therapy remains great.

Reprint requests and correspondence: Dr. Benjamin M. Scirica, TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: bscirica@partners.org.

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