# Clinical Policy: Critical Issues in the Evaluation and Management of Emergency Department Patients With Suspected Non–ST-Elevation Acute Coronary Syndromes

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Approved by the ACEP Board June 27, 2018

Endorsed by the Emergency Nurses Association July 26, 2018

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0196-0644/$-see front matter
Copyright © 2018 by the American College of Emergency Physicians.
https://doi.org/10.1016/j.annemergmed.2018.07.045

[Ann Emerg Med. 2018;72:e65-e106.]


## ABSTRACT

This clinical policy from the American College of Emergency Physicians addresses key issues in the evaluation and management of patients with suspected non–ST-elevation acute coronary syndromes. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: (1) In adult patients without evidence of ST-elevation acute coronary syndrome, can initial risk stratification be used to predict a low rate of 30-day major adverse cardiac events? (2) In adult patients with suspected acute non–ST-elevation acute coronary syndrome, can troponin testing within 3 hours of emergency department presentation be used to predict a low rate of 30-day major adverse cardiac events? (3) In adult patients with suspected non–ST-elevation acute coronary syndrome in whom acute myocardial infarction has been excluded, does further diagnostic testing (eg, provocative, stress test, computed tomography angiography) for acute coronary syndrome prior to discharge reduce 30-day major adverse cardiac events? (4) Should adult patients with acute non–ST-elevation myocardial infarction receive immediate antiplatelet therapy in addition to aspirin to reduce 30-day major adverse cardiac events? Evidence was graded and recommendations were made based on the strength of the available data.


## INTRODUCTION

Chest pain is the chief complaint for approximately 10 million emergency department (ED) visits each year. Based on accepted protocols triggered by diagnostic ECG changes, individuals with ST-elevation myocardial infarction (STEMI) are quickly diagnosed and treated with reperfusion therapy. However, approximately 70% of the 625,000 patients who are diagnosed annually with an acute coronary syndrome (ACS) have a non–ST-elevation (NSTE) ACS.[1] The physician evaluating stable patients with symptoms suspicious for ischemia must strike a balance between increasing diagnostic certainty, the threat of malpractice lawsuits, and the judicious use of limited resources. Currently in the United States, approximately $10 billion is spent each year on these low-risk patients with less than 10% ultimately being found to have ACS.[2] In spite of the intensive use of resources including observation and stress testing, approximately 1% to 2% of patients with acute MI were missed at an ED visit.[3,4] Therefore, the purpose of this clinical policy is to aid the emergency physician in the initial evaluation and treatment of patients who present with potential NSTE ACS. This includes both NSTEMI and unstable angina, because these can be indistinguishable on presentation to the ED and represent a continuum of disease.

### Risk Tolerance

Any discussion of accuracy in ED testing for potential NSTEMI needs to include discussion of an acceptable rate of missed diagnosis. The test threshold, the point of probability at which the harms associated with elevated troponin testing and workup exceed the risks of untreated disease, has been estimated to be approximately 2% for ED patients presenting with suspected cardiac chest pain.[5] A limited survey of 1,029 emergency physicians internationally showed that 82% were willing to accept an arbitrary maximum of only 1% for missed diagnosis of major adverse cardiac events (MACE) within 30 days of ED discharge for a patient with symptoms suggestive of ACS.[6] The acceptable miss rate in this survey is lower than the test threshold of 2%, which suggests that many patients may be receiving extensive diagnostic workups for ACS in which the harms may exceed the potential benefit. When physicians are given permission to have a 1% to 2% acceptable missed diagnosis rate without medicolegal repercussions, there is a hypothetical 29% decrease in the rate of hospital admissions.[7] Also, when patients are engaged in shared decisionmaking, observation admissions for chest pain were reduced with no change in clinical outcomes.[8,9] Therefore, based on limitations in diagnostic technology and the need to avoid the harms associated with false-positive test results, the committee based its recommendations on the assumption that the majority of patients and providers would agree that a missed diagnosis rate of 1% to 2% for 30-day MACE in NSTE ACS is acceptable.

### Troponin Testing

Both diagnosis and risk stratification of patients with potential myocardial ischemia relies on troponin testing. Cardiac troponin I and T are components of the contractile apparatus of myocardial cells and are expressed almost exclusively in the heart. Although elevations of these biomarkers in the blood reflect injury leading to necrosis of myocardial cells, they do not indicate the underlying mechanism. Elevated or abnormal troponin levels are defined as exceeding the 99th percentile cutoff point for each specific assay[10]; however, not all studies clearly report the performance characteristics of the assays used. In addition, there is substantial variability in studies with respect to the use of troponin I versus T, high sensitivity versus standard conventional troponin, and bedside point-of-care versus lab-based testing.

More recently, high-sensitivity assays for troponin measurement have been developed. This designation refers

to the performance characteristics of the assay, and does not reflect the form of troponin measured. To be recognized as having "high sensitivity," an assay must meet 2 criteria: (1) have a coefficient of variation (imprecision) of less than or equal to 10% at the 99$^{th}$ percentile value; and (2) have measurable concentrations below the 99th percentile that are attainable with an assay at a concentration value above the assay's limit of detection for at least 50% (ideally >95%) of healthy individuals.[11] Although the increased sensitivity with these assays may offer earlier recognition of MI, their lack of specificity for coronary artery disease may result in a cascade of unnecessary diagnostic tests and/or hospital admission.[12] In addition, a single high-sensitivity troponin may not have adequate sensitivity for MACE. In a recent study the use of a single high-sensitivity troponin T test (<19 ng/L) to predict MACE had a sensitivity of only 86% (95% confidence interval [CI] 79.7% to 90.9%).[13] Lowering the cutoff to 6 ng/L improved sensitivity markedly, but at the expense of specificity. The authors concluded that although a single troponin test may not have adequate performance characteristics to exclude 30-day MACE, the combination of a single high-sensitivity troponin with a risk stratification tool should be explored.

### Clinical Outcome

The main clinical outcome of interest after initial ED evaluation of patients with suspected ACS is 30-day MACE. MACE includes Q-wave MI, non–Q-wave MI (ie, NSTEMI), death, or target lesion revascularization. The latter is controversial as many of these patients may undergo stenting without clear clinical benefit. Subjective ischemic endpoints such as revascularization are likely to be driven by local practices, and given that false-positive results may occur with troponin assays, it was difficult to consistently determine the effect of this source of incorporation or verification bias in the systematic review of the literature.

### Definitions

This policy refers only to adult (>18 years) patients presenting to the ED with a complaint or condition, usually chest pain, which could be related to cardiac ischemia. The major exclusion is acute STEMI based on the Third Universal Definition of Myocardial Infarction which defines ST elevation as >0.1 mV in 2 contiguous leads (except for leads $V_2$ -$V_3$ where the cut points are >0.2mV in men >40 years, >0.25 mV in men less than 40 years, and >0.15 mV in women).[14] Without these ECG changes, the primary goal in the ED is to diagnose NSTE ACS, which is a continuum of disease ranging from unstable angina to acute NSTEMI. NSTEMI is defined by a significant Δ increase in troponin level *without* ST-segment elevation, in the appropriate clinical context suggestive of myocardial ischemia.[15]

Therefore, the ultimate purpose of this policy is to address critical issues in the care of patients presenting to the ED with symptoms consistent with potential coronary ischemia but without STEMI. This is an update of the 2006 American College of Emergency Physicians clinical policy on NSTE ACS.[16] Based on feedback from the ACEP membership, this clinical policy will address 4 clinical questions relating to ED patients who present with chest pain. The first 3 questions focus on the initial identification of patients at low risk for MACE, using history and limited testing. The fourth question focuses on the role of early antiplatelet therapy in patients with acute NSTEMI.

## METHODOLOGY

This clinical policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of MEDLINE, MEDLINE InProcess, Scopus, Web of Science, and the Cochrane Database were performed. All searches were limited to English-language sources, adults, and human studies. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

This policy is a product of the ACEP clinical policy development process, including internal and external review, and is based on the existing literature; when literature was not available, consensus of Clinical Policies Committee members was used and noted as such in the recommendation (ie, consensus recommendation). Review comments were received from emergency physicians, individual members of EMCREG International, ACEP's Medical-Legal Committee, members of the Chest Pain Steering Committee of the ACEP Emergency Quality Network, nurses, and an advocate for patient safety. Comments were received during a 60-day open-comment period, with notices of the comment period sent in an e-mail to ACEP members, published in *EM Today*, and posted on the ACEP Web site. Review requests were also sent to organizations and other experts pertinent to the topic. The responses were used to further refine and enhance this clinical policy; however, responses do not imply endorsement. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

## Assessment of Classes of Evidence

Two methodologists independently graded and assigned a preliminary Class of Evidence for all articles used in the formulation of this clinical policy. Class of Evidence is delineated whereby an article with design 1 represents the strongest study design and subsequent design classes (ie, design 2 and design 3) represent respectively weaker study designs for therapeutic, diagnostic, or prognostic studies, or meta-analyses (Appendix A). Articles are then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and conflicts of interest. Using a predetermined process combining the study's design, methodological quality, and applicability to the critical question, articles received a Class of Evidence grade. An adjudication process involving discussion with the original methodologist graders and at least one additional methodologist was then used to address any discordance in original grading, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of robust evidence. Grading was done with respect to the specific critical questions; thus, the Class of Evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive a different Class of Evidence rating when addressing a different critical question. Question-specific Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

## Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence grading for each critical question (ie, Evidentiary Table), the subcommittee drafted the recommendations and the supporting text, synthesizing the evidence using the following guidelines:

***Level A recommendations.*** Generally accepted principles for patient care that reflect a high degree of clinical certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies).

***Level B recommendations.*** Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty (eg, based on evidence from 1 or more Class of Evidence II studies or strong consensus of Class of Evidence III studies).

***Level C recommendations.*** Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of adequate published literature, based on expert consensus. In instances in which consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

The recommendations and evidence synthesis were then reviewed and revised by the Clinical Policies Committee, which was informed by additional evidence or context gained from reviewers.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as consistency of results, uncertainty about effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient (Appendix C).

This policy is not intended to be a complete manual on the evaluation and management of patients with suspected NSTE ACS but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine. Potential benefits and harms of implementing recommendations are briefly summarized within each critical question.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain adequate empirical data to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical

strategies for which medical literature exists to answer the critical questions addressed in this policy.

***Scope of Application.*** This guideline is intended for physicians working in EDs or chest pain evaluation units.

***Inclusion Criteria.*** This guideline is intended for adult patients (>18 years) presenting to the ED with undifferentiated chest pain or other complaints or conditions that are suspicious for NSTE ACS.

***Exclusion Criteria.*** This guideline is not intended for pediatric patients or adults who receive a diagnosis of NSTE ACS incidentally. For example, atypical presentations of ACS such as individuals presenting with only dyspnea or with an alteration in mental status are generally excluded from the scope of this work. Also, MI (ie, ST-elevation ACS) diagnosed on arrival to the ED is excluded.

## CRITICAL QUESTIONS

**1. In adult patients without evidence of ST-elevation ACS, can initial risk stratification be used to predict a low rate of 30-day MACE?**

### Patient Management Recommendations

***Level A recommendations.*** None specified.

***Level B recommendations.*** In adult patients without evidence of ST-elevation ACS, the History, ECG, Age, Risk factors, Troponin (HEART) score can be used as a clinical prediction instrument for risk stratification. A low score (≤3) predicts 30-day MACE miss rate within a range of 0% to 2%.

***Level C recommendations.*** In adult patients without evidence of ST-elevation ACS, other risk-stratification tools, such as Thrombolysis in Myocardial Infarction (TIMI), can be used to predict rate of 30-day MACE.

Potential Benefit of Implementing the Recommendations: Decreased use of limited resources, including repeated laboratory testing, expeditious provocative testing, and decreased ED length of stay and admissions for chest pain patients at low risk for ACS.

Potential Harm of Implementing the Recommendations: Potential for missed cases of preventable MI or death.

Key words/phrases for literature searches: acute coronary syndrome, chest pain, decision support techniques, risk assessment, clinical protocols, risk factors, decision rule, clinical risk stratification, clinical risk, risk, biological models, confidence intervals, reproducibility of results, sensitivity and specificity, emergency, emergency service, emergency department, emergency room, risk score, and variations and combinations of the key words/phrases. Searches included January 1, 2005 to search dates of December 8, 2015, December 14, 2015, and December 8, 2017.

Study Selection: Six hundred sixty-five articles were identified in the searches. Ninety-one articles were selected from the search results for further review, with 2 Class I, 5 Class II, and 37 Class III studies included for this critical question.

The initial evaluation of patients presenting to the ED with chest pain is critical for identifying time-sensitive coronary disease. Although very few of these patients ultimately have NSTE ACS, they require further stratification based on risk factors, ECG, and screening laboratory results. With these tools, clinicians have tried to apply risk stratification to expedite the workup and discharge of low-risk patients. Such discharges are contingent on clinicians understanding the risk of their patients having a MACE within the subsequent 30 days. The ideal would be to have a clinical prediction instrument that expedites this process based on assessment and a single troponin-level test on ED presentation, which was defined as "initial" for this critical question. Pathways that rely on repeated troponin testing are addressed in question 2. In addition to providing some increase in accuracy over clinician gestalt or judgment, these tools also provide a structured format for documentation of medical decisionmaking.

Two Class I studies,[17,18] 5 Class II studies,[19-23] and 37 Class III studies[24-60] addressed this critical question. Most of the studies highlighted a single clinical prediction instrument for predicting the 30-day incidence of MACE. Some studies compared various prediction instruments, and a few examined physician gestalt. When such decision rules relied on troponin measurement, there were a variety of assays used, including conventional, high sensitivity, point of care, and even mixed testing within the same study.

#### TIMI Score

One of the first structured tools applied to patients with chest pain to determine the potential for ACS was the TIMI score. The TIMI risk score was derived from a trial in which multivariate analysis was used to determine risk of MACE.[61] The risk score assigns 1 point for each of 7 predictors, allowing stratification for prognosis based on score (variables include age, risk factors, history of coronary stenosis, severe angina, ST-segment elevation, recent aspirin use, and elevated biomarkers).[61] There were 2 Class I,[17,18] 2 Class II,[19,20] and 16 Class III[24,25,27-33,35,36,38-42] studies that included performance data for TIMI score in ED patients with chest pain for predicting who would subsequently develop MACE (Table 1). Most of these

**Table 1.** Performance of cutoff TIMI score less than 1 for ruling out 30-day MACE.

| Source | Class of Evidence | Troponin | Sensitivity (%) | 95% CI | Test | Tn | Detection Cutoff | LOD | 99th Percentile | 10% COV |
|---|---|---|---|---|---|---|---|---|---|---|
| Than et al[17] | I | Conventional POC | 99.3 | 97.9 to 99.8 | TRIAGE CardioProfilER Assay | I | 0.05 μg/L | NA | NA | NA |
| Than et al[18] | I | Conventional | 97.0 | 94.4 to 98.4 | ARCHITECT DxI Access Accu | I | Δ 20% with one value >99th percentile (>0.03 and >0.04 μg/L) | <0.01 μg/L 0.01 μg/L | 0.028 μg/L 0.04 μg/L | 0.032 μg/L 0.06 μg/L |
| Hess et al[19] | II | Conventional | 96.6 | 91.5 to 99.0 | ROCHE | T | ≥0.01 ng/mL (with Δ ≥0.03 ng/mL if initial <0.2 ng/mL; Δ ≥20% if initial ≥0.2 ng/mL) | 0.01 ng/mL | <0.01 ng/mL | 0.035 ng/mL |
| Hess et al[20] | II | Conventional | 97.2 | 96.4 to 97.8 | Mixed | T, I, other | NA | NA | NA | NA |
| Pollack et al[24] | III | Conventional | 97.9 | 97.2 to 98.6 | Unknown | I | NA | NA | NA | NA |
| Campbell et al[25] | III | Conventional | 97.1 | 95.0 to 98.4 | NA | NA | NA | NA | NA | NA |
| Lee et al[27] | III | Conventional | 97.9 | 97.2 to 98.5 | NA | NA | NA | NA | NA | NA |
| Macdonald et al[28] | III | Conventional | 97.2 | 94.8 to 98.5 | Various | T, I | >99th centile cutoff | NA | NA | NA |
| Aldous et al[29] | III | POC+high | 93.4 | 89.6 to 96.0 | Abbott Architect | I | ≥1 Laboratory TnI ≥99th centile with a ≥20% rise/fall | 0.010 μg/L | 0.028 μg/L | 0.032 μg/L |
| Goodacre et al[30] | III | POC | 99.4 | Not available | Status CS Analyser | I | ≥0.02 μg/L | 0.02 μg/L | 0.07 μg/L | 0.03 to 0.22 μg/L (COV 4.3% to 5.1%) |
| Kelly[31] | III | Conventional | 98.9 | 93.4 to 99.9 | TnI-Ultra (Siemens) | I | ≤99th centile | 0.006 ng/mL | 0.04 ng/mL | 0.03 ng/mL |
| Cullen et al[32] | III | High sensitivity | 98.4 | 95.9 to 99.4 | ARCHITECT High Sensitivity | I | >26.2 ng/mL | 1.2 ng/L | 26.2 ng/L | COV <5% |
| Six et al[33] | III | Conventional | 98.9 | 96.2 to 99.1 | TRIAGE CardioProfilER Assay | T or I | >99th centile (or 0.05 μg/L) | NA | 0.05 μg/L | NA |
| Kelly and Klim[35] | III | Conventional | 100.0 | 97.9 to 100 | TnI-Ultra (Siemens) | I | >99th centile | 0.006 μg/L | 0.04 μg/L | 0.03 μg/L |
| Macdonald et al[36] | III | Conventional | 96.0 | 92 to 98 | Various | I or T | >99th centile | 0.006 to 0.05 μg/L | 0.028 to 0.05 μg/L | 0.03 μg/L |
| Lyon et al[38]* | III | Conventional | 96.6 | 94.5 to 100 | NA | NA | NA | NA | NA | NA |
| Scheuermeyer et al[39] | III | Conventional | 90.8 | 84.3 to 94.8 | Roche Elecsys | T | >0.4 ng/mL | NA | NA | NA |
| Carlton et al[40] | III | High sensitivity | 100 | 94.3 to 100 | Fourth-generation Roche Elecsys | T | >14 ng/L (index) (≤26.2 for discharge) | 1.9 ng/L | 14 ng/L | COV <5% |
| Chen et al[41]** | III | Conventional | 66.7 | 48.9 | Not stated | T | NA | NA | NA | NA |
| Leung et al[42] | III | High sensitivity | 100.0 | 91.6 to 100 | Roche Elecsys | T | >14 ng/L | NA | 14 ng/L | NA |
| Sun et al[60] | III | Conventional | 98.8 | 97.1 to 98.3 | Varied | NA | NA | NA | NA | NA |

*COV*, coefficient of variation; *LOD*, level of detection; *NA*, data not available in article; *POC*, point of care.
*Used cutoff of less than 2 rather than 1.
**Used cutoff of less than 3 rather than 1

studies used a cutoff score of zero as the threshold for defining low risk.

Two Class I studies[17,18] compared the TIMI score alone with a more comprehensive accelerated diagnostic pathway (ADP). In the first series of 3,582 consecutive patients with chest pain, any TIMI score greater than zero was 96.7% (95% CI 94.5% to 98.0%) sensitive for MACE.[17] A subsequent study of 1,975 patients with chest pain showed similar performance for TIMI score greater than zero, at 97.0% (95% CI 94.4% to 98.4%).[18] Because the lower bound of the 95% CI for MACE approached 94% sensitivity, the authors recommended repeating a troponin test at 2 hours before discharge for low-risk patients rather than relying on the initial TIMI score alone; however, the specificity using this repeat troponin strategy was only 27%.

Two Class II studies[19,20] examined the performance of TIMI score in predicting which ED patients with chest pain were at low risk for subsequent ACS. Both used conventional nonhigh-sensitivity troponin testing. Hess et al[19] published a prospective cohort study that included 1,017 patients with chest pain. Using a modified TIMI score, which included ST-segment deviation or troponin T (either at arrival and/or at $\geq$6 hours from pain onset), they assigned patients to a low-risk group who had a TIMI score of zero. The sensitivity of the tool with an initial TIMI score of zero was 96.6% (95% CI 91.5% to 99.0%) for 30-day MACE, but specificity was only 24%. Limitations of the study included enrollment of only 76% of eligible patients and 4.6% of patients lost to follow-up. A Class II meta-analysis by Hess et al[20] of 8 studies with 17,265 patients that used a TIMI score cutoff of less than or equal to 1 reported a pooled sensitivity of 97.2% (95% CI 96.4% to 97.8%), specificity of 25% (95% CI 24.3% to 25.7%), and a negative LR of 0.11 (95% CI 0.09 to 0.15) in predicting 30-day MACE. Limitations of the analysis included substantial statistical heterogeneity between studies and lack of consistent reporting of cardiac marker assays, types, and thresholds.

Twelve Class III studies[24-28,31,33,35,36,38,39,60] examined the utility of conventional, nonhigh-sensitivity troponins in formulating TIMI score for predicting 30-day MACE. One of the earliest was a secondary analysis of a prospective cohort of ED patients presenting with chest pain.[24] In this series of 3,326 patients, a TIMI risk score of zero (using troponin I as the biomarker), resulted in a 30-day MACE of 2.1% (29/1,388) (95% CI 1.4% to 2.8%). Limitations of this study included that it was a convenience sample. Another prospective observational study[38] of 760 patients in an urban academic hospital used a TIMI cutoff score of greater than 1 rather than zero. Therefore, it is not surprising that sensitivity was only 96.6% (95% CI 94.5% to 100%) for subsequent MACE. In the Class III study by Campbell et al[25] of 3,169 chest pain patients, the incidence of 30-day MACE for patients with a clinical impression of an alternative diagnosis and a TIMI score of zero was 2.9% (95% CI 1.6% to 5.0%). As in the study by Pollack et al,[24] there was good representation of blacks and women, but this may limit its applicability to other populations. In a series of 796 consecutive patients presenting with chest pain suspected to be cardiac, a TIMI score of zero missed 1 patient of the 137 (17.2%) who went on to have 30-day MACE.[26] This equates to a sensitivity of 99.3% (95% CI 96.0% to 99.9%), but the lower limit of confidence is beyond what is generally acceptable because of small sample size. Lee et al[27] performed a secondary analysis of previous prospectively collected cohort data. With 4,743 patients who presented with chest pain, a TIMI score cutoff of zero had a sensitivity of 97.9% (95% CI 97.2% to 98.5%); this study had a good representation of blacks and women. Six et al[33] performed a substudy of a prospective observational cohort from a large multicenter study with 14 hospitals in 9 countries. In 2,906 patients presenting with a minimum of 5 minutes of chest pain, sensitivity of TIMI score of zero for MACE was 98.1% (95% CI 96.2% to 99.1%). Technically, this was a retrospective analysis of an existing database. One Class III study[39] questioned the safety of relying on TIMI scoring for screening and discharging chest pain patients. Although this study was not designed to examine the utility of the TIMI score, the authors did find that of the 120 patients with ACS (unstable angina), 9.2% had a TIMI score of zero.[39] They suggested that TIMI score, designed for risk stratification of admitted cardiac patients, is not suitable alone for screening ED patients for possible ACS. Kelly[31] performed a substudy of prospective observational data with 651 patients. Using a TIMI score of zero with a conventional troponin test included, one case of MACE was missed, giving a sensitivity of 98.9% (95% CI 93.4% to 99.9%). The major limitation of this study was retrospective data collection at only one center. A repeated study by Kelly and Klim,[35] a prospective cohort study of atraumatic chest pain patients, showed that a TIMI score of zero had a sensitivity of 100% (95% CI 97.9% to 100%) for 30-day MACE. In this single-hospital study, there was not a single case of MACE among the patients. A retrospective analysis of greater than 8,000 patient visits at 8 different sites confirmed the acceptability of a TIMI of zero for predicting 30-day MACE; sensitivity was 98.8% (95% CI 97.1% to 98.3%).[60]

Two of the 11 Class III studies for the TIMI score were by Macdonald et al,[28,36] who used a mix of conventional serial troponin testing in patients with suspected ACS. The

first study[28] that included data on TIMI score was actually examining performance of the New Zealand score in 1,666 patients, 219 of whom had MACE. A TIMI score of zero was 97.2% sensitive (95% CI 94.8% to 98.5%) for the study outcome. Minor limitations of this study were failure to obtain initial troponin level for 2.5% of patients and loss to follow-up of 2.6% of patients. The second study[36] attempted to validate both the original TIMI score and a modified version that had increased weighting (×5) of elevated biomarkers and ST deviation (>0.5 mm) each. In a nonconsecutive series of 1,666 patients, with 219 (13%) having 30-day MACE, the sensitivity of either the original or modified TIMI score was 96% (95% CI 92% to 98%), not high enough in the authors' opinion to warrant widespread adoption.

In the interest of time efficiency, some studies used a point-of-care troponin test in determining TIMI score. A Class III study by Aldous et al[29] of 1,000 patients presenting with chest pain showed that an initial TIMI score of zero combined with ECG with normal point-of-care troponin testing on presentation was 99.6% sensitive (95% CI 97.4% to 100%) for subsequent MI within 30 days. Goodacre et al[30] (Class III) conducted a retrospective secondary analysis of 2,243 patients who presented with chest pain to an ED. Although not enough raw data were presented to calculate CIs, a cutoff of zero for TIMI score combined with normal point-of-care troponin testing resulted in a MACE rate of 0.6%. Limitations of the study included lack of complete data for 80% of patients and lack of firm follow-up for 28% of patients.

Three Class III studies[29,32,40] relied on high-sensitivity troponins for TIMI score determination. Aldous et al[29] also examined the performance of high-sensitivity troponins in their point-of-care study. The sensitivity in ruling out 30-day MI incidence with a normal troponin level and ECG, along with TIMI score of zero, was 99.6% (95% CI 97.3% to 100%). Cullen et al[32] evaluated 2 prospective cohorts of patients with chest pain suggestive of ACS. In the preliminary cohort of 2 academic EDs, the sensitivity of a TIMI score of zero for MACE at 30 days was 99.2% (95% CI 97.1% to 99.8%); in the secondary cohort, which was multinational and multicenter, sensitivity was 99.4% (95% CI 96.5% to 100%). Specificity approached 50% in both groups, with a population mainly limited to white race. The final Class III study, by Carlton et al,[40] was a prospective series of 959 patients with suspected ACS. A TIMI score cutoff of zero had a sensitivity of 100% (95% CI 94.3% to 100%) for MI at 30 days (no data on MACE). This study did include a comparison to using HEART; there was no statistical difference in test performance.

Many of the high-performing studies discussed above used high-sensitivity troponins, also known as fifth generation, which use the 99th percentile upper reference limit with a coefficient of variation of less than or equal to 10 for cardiac troponin I and T.[62] They were developed in 2007 and recently approved by the Food and Drug Administration for use in the United States. High-sensitivity troponins could improve the performance of any rule, but at the expense of specificity. In one Class III study[34] of 14,636 patients, only 39 patients (0.44%) with undetectable high-sensitivity cardiac troponin T went on to have an MI. Combining that with no signs of ischemia on initial ECG produced an absolute risk for MI of 0.17% (95% CI 0.09% to 0.27%). High-sensitivity troponins may not ultimately improve overall performance of the TIMI score. A study in Australia showed that randomization of 973 patients to high-sensitivity versus conventional troponin testing did not change clinical outcome for MACE at 12 months.[63] The authors recommended further validation in clinical trials before widespread adoption and reliance on a single high-sensitivity troponin result for risk stratification of chest pain patients.

Recent studies have examined the performance of TIMI score in novel populations. A Class III study[41] prospectively compared 4 different clinical risk scores in Chinese patients who presented with the chief complaint of chest pain or discomfort. In terms of area under the curve for sensitivity and specificity for 30-day MACE, the TIMI score performed as well as the HEART score. However, the sensitivity and specificity were poor, 66.7% (95% CI 55.9% to 76.3%) and 64.2% (95% CI >60.6% to 67.7%) respectively, which could be explained by the use of a TIMI score cutoff of greater than 2, rather than zero or 1 used in earlier studies. A repeated study (Class III) in Hong Kong, showed that with a high-sensitivity troponin T test, a TIMI score cutoff of zero had 100% sensitivity [95% CI 91.6% to 100%] for predicting 30-day MACE.[42] The lower limit of the CI was low even though the sample size was good, at 602 subjects.

In most of these studies, a TIMI score of zero that includes an ECG and a single biomarker approaches but does not consistently reach the threshold of a 2% miss rate for 30-day MACE (Table 1). Also, in most of these studies, a TIMI score cutoff of greater than zero consistently performed better than 97% sensitivity in predicting 30-day MACE; however, the 95% CIs extended the lower bound to 90% in some studies. Another limitation of using the TIMI score is that by virtue of anyone aged 65 years and

older being assigned a point, a cutoff of zero is a poor discriminator for initial decisionmaking in a large proportion of ED patients presenting with chest pain. The TIMI score was not designed for application to undifferentiated ED patients presenting with chest pain and suspected ACS.[61] Modifications are often made, such as substituting history of coronary artery disease for known coronary artery stenosis greater than 50%. Also, none of the studies examining the performance of TIMI score had a comparison with simple clinician gestalt. Based on the above data, most authors recommended not relying on TIMI score alone to predict MACE, and instead advocated for a short period of observation with repeated troponin testing.

### Modifications of TIMI Score

Multiple studies examined a modification of the TIMI score to improve its performance, such as adding an early second troponin-level test. A Class II study[22] randomized 542 chest pain patients at a single institution to either a standard pathway with 12 hours of observation and repeated troponin I testing or an ADP that allowed early discharge of patients with a TIMI (modified with 7 criteria) score of zero, no ischemic changes in ECG, and negative troponin I test result at 0 and 2 hours after presentation. The ADP tool allowed almost twice as many patients to be discharged within 6 hours (19% versus 11%), with one missed case of MACE, which happened to be in the ADP group (n=270). In a secondary analysis (Class III study) of previously collected data from 7 US centers that included patients with TIMI scores of 0 to 2, Mahler et al[43] reported a sensitivity of 83.9% (95% CI 66.3% to 94.5%) when conventional troponin testing was done at presentation and at 2 hours. Another Class III study[44] of 1,000 patients showed that adding a second troponin test, regardless of type (routine or high sensitivity), and ECG at 2 hours postpresentation had a sensitivity of 99.2% (95% CI 97.5% to 99.8%) for MACE at 30 days.

A group in Manchester, United Kingdom, examined improving the performance of the TIMI score by increasing the point scores 5-fold for elevated cardiac markers and ischemic changes on ECG. One of the first studies examining this modified TIMI score was by Body et al[26] (Class III study). At a cutoff score of less than or equal to 1, the modified TIMI score performed no better than the original TIMI score. At a cutoff of less than or equal to 3, they maintained adequate sensitivity (96.4%; 95% CI 91.7% to 98.4%) while increasing specificity to 51%, better than with the original TIMI score. Although sample size was adequate (796 patients >25 years presenting with chest pain), it was retrospectively applied. Hess et al,[19] in a Class II study, found that although this modified TIMI score was superior to the original, it still had a sensitivity of only 91% and specificity of only 54% at a cutoff of less than or equal to 2 for 30-day MACE. A Class III study by Macdonald et al[36] used the same modified TIMI score in a cohort of 1,758 ED patients undergoing evaluation for ACS at 5 Australian hospitals. At a cutoff of less than or equal to 1, the modified TIMI score performed no better than the original TIMI score. Further increasing the cutoff to less than or equal to 2 or less than 3 showed no better performance for the modified TIMI score than the original TIMI score, with both missing greater than 10% of 30-day MACE. The authors concluded that neither the original nor the modified TIMI score is sufficiently sensitive at any score above zero to safely risk-stratify patients even if they have a normal ECG result and troponin level.

### HEART Score

The HEART score, developed in the ED setting, adds clinical judgment in the form of history as suspicious for ACS[64] (Table 2). In a Class III validation study,[47] HEART and TIMI scores were compared in a cohort of 2,440 chest pain patients from 10 hospitals. The low HEART score group (0 to 3 points) had a 1.7% (15/870; 95% CI 0.9% to 2.6%) incidence of MACE at 6 weeks, whereas the incidence of MACE among those with a low TIMI score (0 to 1) was 2.8% (95% CI 1.7% to 3.9%). A Class III

**Table 2.** HEART score for chest pain patients in the ED.[47] (Used with permission).

| Variable | Features | Points |
|---|---|---|
| History | • Highly suspicious<br>• Moderately suspicious<br>• Slightly or nonsuspicious | • 2<br>• 1<br>• 0 |
| ECG | • Significant ST-depression<br>• Nonspecific repolarization<br>• Normal | • 2<br>• 1<br>• 0 |
| Age, y | • ≥65<br>• >45 to <65<br>• ≤45 | • 2<br>• 1<br>• 0 |
| Risk factors (diabetes mellitus, smoker, hypertension, hypercholesterolemia, family history of coronary artery disease, obesity, history of significant atherosclerosis) | • ≥3 risk factors or history of atherosclerotic disease<br>• 1 or 2 risk factors<br>• No risk factors | • 2<br>• 1<br>• 0 |
| Troponin | • ≥3×normal limit<br>• >1 to <3×normal limit<br>• ≤Normal limit | • 2<br>• 1<br>• 0 |

multicenter validation study[33] including 2,906 patients demonstrated that the HEART score at a cutoff of less than or equal to 2 performed as well as the TIMI score. Based on 6-week MACE, a HEART score less than or equal to 2 had, for ruling out MACE, a sensitivity of 98.9% (95% CI 97.3% to 99.6%) and specificity of 14.7% (95% CI 13.4% to 16.2%) versus a TIMI score of zero with sensitivity of 98.1% (95% CI 96.2% to 99.1%) and specificity of 20.3% (95% CI 18.8% to 21.9%). A retrospective analysis of greater than 8,000 patient visits at 8 sites confirmed the performance of the HEART score; score less than or equal to 3 predicted 30-day MACE with sensitivity 98.2% (95% CI 97.8% to 98.6%).[60]

Adding high-sensitivity troponin testing did not appreciably improve performance of the HEART score. A prospective observational Class III study[40] of 959 patients presenting with suspected ACS confirmed these findings. They found that a HEART score of less than or equal to 2 had a sensitivity of 98.7% (95% CI 92.4% to 99.9%) for ruling out MI within 30 days; specificity was 14.1% (95% CI 13.5% to 14.2%). It performed as well as a TIMI score cutoff of zero. Limitations of this study included an incomplete 30-day endpoint of MI rather than MACE, and use of high-sensitivity troponin. A recent 9-hospital prospective study[56] (Class III) in the Netherlands examined the ability of the HEART score versus usual care, using high-sensitivity troponin for predicting MACE at 6 weeks. Of the 1,821 patients in the experimental group, a HEART score of 3 or less was associated with a miss rate for MACE of 2.0% (95% CI 1.2% to 3.3%). The HEART score performed slightly better (Δ 1.3%) than the usual care in predicting MACE, and at lower cost.

A recent meta-analysis (Class III) of 9 studies examined the performance of the HEART score in a pooled sample of 11, 217 patients of whom 15% went on to have MACE.[57] A HEART score of 0 to 3 had a sensitivity of 96.7% (95% CI 94.0% to 98.2%) for predicting MACE. If only the 5 studies that used a HEART score of 0 to 2 were included, the sensitivity was a more acceptable 99.4% (95% CI 96.8% to 99.9%) but at expense of a specificity of only 22% (95% CI 14.2% to 32.5%). Examining only the high-sensitivity-troponin studies did not improve outcome in terms of sensitivity. They recommend that a HEART score of 0 to 3 should not be used as the sole screening test for patients with undifferentiated chest pain in whom ACS is suspected.

The Class III study[41] mentioned earlier in TIMI also examined the performance of the HEART score in Chinese patients with chest pain as their chief complaint, using conventional troponins. The HEART score had the largest area under the receiver operator curve, compared with TIMI, the Global Registry of Acute Coronary Events, and Banach scores in predicting MACE at 30 days. But using a HEART score cutoff of greater than 5 led to poor sensitivity (48.9%), with specificity 83.7%. A repeated study[42] (Class III) in Hong Kong showed that a high-sensitivity troponin T test along with a modified HEART score at a cutoff of less than or equal to 2 had 100% sensitivity (95% CI 91.6% to 100%) for predicting 30-day MACE. The HEART score had a single modification: the presence of ST deviation greater than 0.05 mV was scored at 1 point, rather than 2, although specificity was still poor, at 17%.

Strengths of the HEART score include its excellent sensitivity (98% to 99%) in preliminary work at a cutoff of less than or equal to 2. Also, as opposed to the TIMI score, it was derived specifically for use in the ED setting. Substituting high-sensitivity for conventional troponin testing does not appear to improve prediction of 30-day MACE in low-risk patients (Table 3).

### Alternative Scoring Systems

There is an international variety of alternative clinical prediction instruments for risk stratification of chest pain patients (Table 4). Many perform well in differentiation of the low-risk patient who presents with chest pain. Some even have a zero-miss rate for 30-day MACE, and one was rated at a Class II level of evidence.[21]

No specific alternative scoring system can be recommended at this time. Although some perform well, the studies are limited to nondiverse populations or perform well only when high-sensitivity troponins are used. Many will require validation through successful replication in larger diverse cohorts before we can attest to their reliability.

### Clinical Judgment

For risk scores to improve practice, they must perform better than the comparator, or status quo, which is physician gestalt. A prospective study by Mitchell et al[23] (Class II), using an unstructured estimate of MACE at 45 days, found that clinicians identified 293 of 1,114 patients as low-risk (<2% pretest probability of MACE at 45 days). Two of these patients went on to have ACS, for a sensitivity of 96.1% (95% CI 86.5% to 99.5%).[64] A Class III post hoc secondary analysis by Chandra et al[54] recorded risk of ACS assigned by physicians in 10,145 patients who came in with chest pain or angina equivalent. Out of those deemed to be low

**Table 3.** Performance of HEART score (low risk) in ruling out 30-day MACE.

| Source | Score | Class of Evidence | Troponin | Sensitivity (%) | 95% CI | Test | Troponin | Detection Cutoff | LOD | 99th Percentile (URL) | 10% COV |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Poldevaart et al[56] | 0 to 3 | III | Conventional and high sensitivity | 98.0 | 96.7 to 98.8 | Multiple | T or I | 14 to 60 ng/L | Varied | Varied | Varied |
| Backus et al[47] | 0 to 3 | III | Conventional | 98.3 | 97.2 to 100 | Various | T or I | 0.01 to 0.100 μg/L | NA | 0.01 to 0.04 μg/L | NA |
| Six et al[33] | 0 to 2 | III | Conventional | 98.9 | 97.3 to 99.6 | TRIAGE CardioProfl ER Assay | T or I | >99th percentile (or 0.05 μg/L) | NA | 0.05 μg/L (for TRIAGE; NA for ER Assay) | NA |
| Carlton et al[40] | 0 to 2 | III | High sensitivity | 98.7 | 92.4 to 99.9 | Fourth-generation Elecsys (Roche) | T | >14 ng/L (index) (≤26.2 ng/L for discharge) | 1.9 ng/L | 14 ng/L | COV ≤5% |
| Van Den Berg and Body[57] | 0 to 2 | III | Conventional and high sensitivity | 99.4 | 96.8 to 99.9 | Varied | T or I | Varied | Varied | Varied | Varied |
| Chen et al[41] | 0 to 5 | III | Conventional | 48.9 | 38.2 to 59.7 | Not stated | T | <0.03 μg/L | NA | NA | NA |
| Leung et al[42] | 0 to 2 (modified) | III | High sensitivity | 100.0 | 91.6 to 100.0 | Elecsys Troponin (Roche) | T | 14 ng/L | NA | 14 ng/L | NA |
| Sun et al[60] | 0 to 3 | III | Conventional | 98.2 | 97.8 to 98.6 | Varied | Varied | Varied | NA | NA | NA |

*CI*, confidence interval; *COV*, coefficient of variation; *LOD*, level of detection; *NA*, data not available.

risk, only 2.2% (95% CI 1.8% to 2.6%) went on to have 30-day MACE. In another study with a population that clinicians identified as low risk (pretest probability of <2.5% for ACS), sensitivity for MACE was only 91% (95% CI 72% to 99%).[65] Therefore, clinician gestalt alone may not reach an acceptable sensitivity (≥98%) for ruling out potentially serious cardiac ischemia.

Body et al[55] (Class III) showed some improvement in gestalt by adding results of the ECG and conventional troponin T testing (fourth generation). In this series of 458 patients, no patient identified as "probably not" or "definitely not" having ACS with negative ECG result and a negative troponin result experienced MACE at 30 days (sensitivity 100% [95% CI 95.6% to 100%] and specificity 28% [95% CI 23.5% to 32.8%]). This suggests that although gestalt alone is not robust enough to discern ACS and subsequent MACE, when combined with objective cardiac biomarkers, it may be sensitive enough to reach the less than or equal to 2% miss rate threshold. A Class III study by Bracco et al[51] used a clinical pathway based on initial ECG result and clinical features on presentation. Based on clinical features, the study relied on a risk assignment by the emergency physician. The lowest-risk group, which was deemed to be clearly noncoronary chest pain, had a MACE outcome of 0.7% (95% CI 0% to 1%). All higher-risk groups had levels of MACE exceeding 3%. Part of the pathway's success is attributable to repeated testing at 12 hours after symptom onset, not feasible for most EDs. All of these studies suffer from variability in physician experience and lack of standardization, as well as a need for further validation of such approaches at other sites.

A systematic review by Fanaroff et al[66] (Class X) evaluated 58 articles that examined the predictive value of decision rules in determining the LR for a patient having the diagnosis of ACS. The most useful for identifying patients unlikely to have ACS were the low-risk-range HEART score (0 to 3), LR=0.20 (95% CI 0.13 to 0.30); low-risk TIMI score (0 to 1), LR=0.31 (95% CI 0.23 to 0.43); or low- to intermediate-risk designation by the Heart Foundation of Australia and Cardiac Society of Australia and New Zealand risk algorithm, LR=0.24 (95% CI 0.19 to 0.31). This was compared with clinical impression before ECG or troponin results were reviewed. The choice of "definitely not" ACS had a diagnostic LR of 0.36 (95% CI 0.05 to 2.8), which was not as low but not significantly different from the various risk-stratification tools.

A more recent study suggested that in ED patients presenting with chest pain and possible ACS, but no history of percutaneous coronary intervention (PCI) or coronary artery bypass graft, a simple

**Table 4.** Alternative clinical prediction instruments for risk stratification of chest pain patients.

| Score | Reference | Class | N | Outcome | MACE, No. (%) | Troponin | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| North American Chest Pain Rule | Hess et al[21] | II | 2,718 | 30-day MACE | 336 (12) | conv T | 100% (97.2% to 100%) | 20.9% (16.9% to 24.9%) |
| Manchester Acute Coronary Syndrome | Body et al[48] | III | 463 | 30-day MACE | 2 (1.6) | hs T | 98.0% (93.0% to 99.8%) | Not reported |
| | Body et al[37] | III | 456 | 30-day MACE | 2 (2.3) | hs T | 97.9% (92.8% to 99.8%) | 23.4% (92.8% to 99.9%) |
| | Body et al[58] | III | 1,459 | 30-day MACE/ACS | 212 (14.5) | hs T | 98.1% (95.22% to 99.5%) | 47.0% (44.2% to 49.8%) |
| Vancouver chest pain rule | Scheuermeyer et al[39] | III | 1,116 | 30-day ACS | 120 (10.8) | conv T | 100% (97.6% to 100%) | Not reported |
| | Scheuermeyer et al[49] | III | 960 | 30-day ACS | 119 (13.1) | hs T | 99.2% (95.4% to 100%) | 23.4% (20.6% to 26.5%) |
| | Carlton et al[40] | III | 867 | 30-day MI | 66 (7.6) | hs I | 100% (9.3% to 100%) | 16.7% (16.2% to 16.7%) |
| | Cullen et al[50] | III | 200 | 30-day ACS | 4 (1.9) | hs T | 98.8% (97% to 99.5%) | 15.8% (13.9% to 17.9%) |
| GRACE | Lyon et al[38] | III | 760 | 30-day MACE | 123 (16) | Not reported | 100% (96% to 100%) | Not reported |
| | Carlton et al[40] | III | 867 | 30-day MI | 66 (7.6) | hs I | 89.4% (79.1% to 95.2%) | 34.3% (33.5% to 34.8%) |
| | Lee et al[27] | III | 4,743 | 30-day MACE | 319 (6.7) | Not reported | 99.5% (97.4% to 99.9%) | Not reported |
| | Chen et al[41] | III | 833 | 30-day MACE | 90 (10.8) | conv T | 72.2% (61.8% to 81.1%) | 49.9% (46.3% to 53.6%) |
| NHF Australia/ New Zealand | Macdonald et al[28] | III | 1,666 | 30-day MACE | 219 (13.1) | conv various | 99% (97.3% to 99.7%) | Not reported |
| EDACS | Than et al[45] | III | 608 | 30-day MACE | 79 (13.0) | Not reported | 100% (94.2% to 100%) | 100% (94.2% to 100%) |
| | Stopyra et al[46] | III | 282 | 30-day MACE | 17 (6.0) | hs I | 88.2% (63.6% to 98.5%) | 70.2% (64.3% to 75.6%) |
| Banach | Chen et al[41] | III | 833 | 30-day MACE | 90 (10.8) | conv T | 75.6% (65.4% to 85.0%) | 44.8% (41.2% to 48.5%) |
| m-Goldman | Carlton et al[40] | III | 867 | 30-day MI | 66 (7.6) | hs I | 98.5% (91.0% to 99.9%) | 12.6% (12.0% to 12.7%) |

*ACS*, acute coronary syndrome; *CI*, confidence interval; *conv*, conventional; *EDACS*, Emergency Department Assessment of Chest pain Score; *GRACE*, Global Registry of Acute Coronary Events; *MACE*, major adverse cardiac event; *MI*, myocardial infarction; *NHF Australia/New Zealand*, National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand.

combination of normal ECG result and high-sensitivity troponin testing on presentation was more accurate than the TIMI or HEART score in predicting 30-day MACE.[59] Although a very-low-risk score missed only 3 out of 42 cases of MACE, with a sensitivity of 99.1% (95% CI 97.5% to 99.7%), the study has not been replicated and more than half of the eligible patients were excluded; therefore, the strategy of not using some kind of structured risk assessment cannot be recommended.

## Conclusion

Limitations in regard to the applicability of the above studies include the use of different entry criteria and variation in the types of troponin testing. Although all studies included patients with suspected ischemic heart disease, the definition and duration of symptoms varied. Laboratory testing often involved different cutoffs and coefficients of variation and some used high-sensitivity troponin testing, whereas others used conventional troponin. Finally, most of the decision rules lack prospective impact analyses and have not been validated or compared with physician gestalt in large, diverse populations.

Despite their limitations, risk scores have become increasingly popular in the ED management of chest pain, with the most data available for the TIMI and HEART scores. Regardless of the clinical prediction instrument system used, they can be recommended only as a tool to assist in the risk stratification of undifferentiated patients presenting with chest pain or other symptomatology suggestive of ACS. Risk stratification is also a useful way to standardize care and decrease variability because physician gestalt is often poorly structured and inconsistently applied.[55] In fact, a structured clinical decision rule is now mandatory for accreditation as an American College of Cardiology (ACC) chest pain center.

Physicians must still use good clinical judgment based on subjective individual patient characteristics that may or may not be captured by these tools. In the setting of ruling out NSTE ACS and the prospects of more observation or testing, it is important to include the patient in shared decisionmaking because many of them will prefer quick risk stratification and avoidance of further diagnostic testing and a lengthy ED stay.[8,9] Of course, health literacy of the individual patient has to be taken into account. Finally, it is important not to ignore continued or recurrent symptoms during the ED stay, which should prompt one to re-evaluate the patient and consider repeated ECG and perhaps additional troponin testing.

## Future Research

Future research should focus on prospective validation of these clinical prediction instruments in diverse populations and compare them with physician judgment.

In addition, the effect of novel biomarker testing in improving the accuracy of these rules will be an area of continued interest.

**2. In adult patients with suspected acute NSTE ACS, can troponin testing within 3 hours of ED presentation be used to predict a low rate of 30-day MACE?**

**Patient Management Recommendations**

***Level A recommendations.*** None specified.

***Level B recommendations.*** None specified.

***Level C recommendations.***

(1) In adult patients with suspected acute NSTE ACS, conventional troponin testing at 0 and 3 hours among low-risk ACS patients (defined by HEART score 0 to 3) can predict an acceptable low rate of 30-day MACE.

(2) A single high-sensitivity troponin result below the level of detection on arrival to the ED, or negative serial high-sensitivity troponin result at 0 and 2 hours is predictive of a low rate of MACE.

(3) In adult patients with suspected acute NSTE ACS who are determined to be low risk based on validated ADPs that include a nonischemic ECG result and negative serial high-sensitivity troponin testing results both at presentation and at 2 hours can predict a low rate of 30-day MACE allowing for an accelerated discharge pathway from the ED.

Potential Benefit of Implementing the Recommendations: The application of an accelerated serial troponin testing protocol in patients with suspected NSTE ACS has the potential to decrease the ED length of stay and avoid further unnecessary testing or hospitalization.

Potential Harm of Implementing the Recommendations: Despite the very low risk of 30-day MACE after a negative ADP, there will be a few patients who go on to MI or experience other MACE. Alternatively, the low specificity of ADPs will result in false positives, which may lead to further unnecessary testing or hospital admission in a subset of patients without disease.

Key words/phrases for literature searches: acute coronary syndrome, chest pain, myocardial infarction, cardiac arrhythmia, biological markers, troponin, negative troponin, predictive value of tests, risk assessment, risk factors, time factors, risk, ROC curve, emergency service, emergency and variations and combinations of the key words/phrases. Searches included January 1, 2005, to search dates of December 8, 2015; December 14, 2015; and December 7, 2017.

Study Selection: Six hundred twenty-six articles were identified in the searches. Seventy-two articles were selected from the search results for further review, with 1 Class I, 4 Class II, and 26 Class III studies included for this critical question.

Emergency physicians frequently evaluate patients for NSTE ACS in the ED with a protocol that entails testing for 2 troponin levels 6 hours apart. The ability to evaluate these same patients with an accelerated pathway that includes a repeated troponin test within 3 hours while maintaining high sensitivity and a low rate of MACE would improve ED flow and length of stay for patients. In an attempt to identify the ideal pathway, a number of studies have been conducted using a variety of biomarkers (conventional and high-sensitivity troponins) in a variety of time frames (single troponin, repeated at 1, 2, and 3 hours) and in combination with a variety of decision aids (eg, TIMI score, HEART pathway). It is important to keep in mind that some of these studies introduced the concept of "below level of detection." Typically, troponin tests have a negative range and a positive range. With high-sensitivity troponin, some researchers have added an additional stratification that includes undetectable troponin, or "below level of detection."

The literature search identified 1 Class I study,[18] 4 Class II studies,[13,17,67,68] and 26 Class III studies[29,31,34,35,40,43,44,46,47,60,69-84] that addressed the critical question.

Conventional Troponin

Mahler et al[67] (Class II) conducted a randomized trial at a single center in the United States with adult patients with suspected ACS without ST elevations on ECG, comparing the HEART Pathway with usual care. The HEART Pathway entails stratifying patients based on the HEART score as low risk (score 0 to 3) or high risk (score $\geq$4), followed by testing with conventional troponins at 0 and 3 hours. Two hundred eighty-two patients were enrolled, and among the 141 randomized to the HEART pathway, 66 were in the low-risk cohort; 56 of these patients were discharged at 3 hours and none had MACE at 30 days. In this study, serial troponin testing at 0 and 3 hours achieved a zero MACE rate when applied to patients with a low HEART score. Not surprisingly, a secondary analysis of the above study performed with high-sensitivity troponin yielded identical test characteristics for the HEART Pathway.[74]

The HEART Pathway also performed well in a secondary analysis when applied to 1,005 ACS patients in the Myeloperoxidase In the Diagnosis of Acute coronary syndromes Study (MIDAS), a prospective observational cohort of ED patients enrolled from 18 sites in the United States; there was a 1% MACE miss rate and 99% sensitivity for ACS when conventional troponin levels were negative at 0 and 3 hours among low-risk patients (HEART score 0 to 3).[76]

Another ADP that has been validated is the Emergency Department Assessment of Chest pain Score (EDACS). Flaws et al[82] (Class III) demonstrated a sensitivity of 100% among a North American population in Vancouver, Canada, with an EDACS score less than 16 using a conventional troponin T test at 0 and 2 hours. Other decision aids such as the Vancouver CP Rule have had difficulty getting validated in subsequent studies.[84]

In the absence of structured risk stratification, can conventional troponins rule out MI in less than 3 hours? Goodacre et al[78] conducted a multicenter randomized trial in the United Kingdom and found MACE to be similar when using point-of-care conventional troponin I testing at presentation and at 90 minutes compared with standard care (3% versus 2%). A 3% risk of MACE would be considered unacceptable in the United States.

### High-Sensitivity Troponin With Decision Aid

The single Class I study[18] that addressed the critical question was the prospective 2-hour Accelerated Diagnostic protocol to Assess Patients with chest pain symptoms using Troponins as the only biomarker (ADAPT) trial, conducted in Australia and New Zealand using a high-sensitivity troponin at time zero and 2 hours. Among patients enrolled, the primary endpoint of 30-day MACE occurred in 15.3%, whereas only 1 patient experienced MACE among the subgroup determined to be at low risk (N=392), defined as those with a TIMI score of zero, no ischemic changes on the ECG, and 2 negative troponin values. Thus, application of the ADP resulted in a sensitivity of 99.7% (95% CI 98.1% to 99.9%) and a specificity of 23.4% (95% CI 21.4% to 25.4%).

The Class II Asia-Pacific Evaluation of Chest pain Trial (ASPECT)[17] was similar to the ADAPT Trial except that it included a panel of biomarkers (high sensitivity troponin, creatine kinase MB, and myoglobin), which was collected from 3,582 consecutive patients recruited from 14 urban EDs spanning 9 countries in the Asia-Pacific region. Low risk (N=352) was again defined as a TIMI score of zero, no ischemic changes on the ECG, and negative biomarkers at 0 and 2 hours. Based on the primary endpoint of 30-day MACE, the ADP had a sensitivity of 99.3% (95% CI 97.9% to 99.8%) and a specificity of 11.0% (95% CI 10.0% to 12.2%). In a Class III post hoc analysis of the ASPECT study, Aldous et al[44] applied various published ADPs to their previously collected data and determined that the TIMI score provided the highest sensitivity, along with identifying the largest cohort of "low-risk" patients.

Although the majority of studies using high-sensitivity troponin are conducted in Europe and other places where its use has been approved for many years, Peacock et al[13] (Grade II) recently published a 4-year prospective, observational study in 15 US EDs, demonstrating a negative predictive value (NPV) of 99.4% for patients with high-sensitivity cardiac troponin T level below 6 ng/L and an NPV of 99.3% for those with a high-sensitivity cardiac troponin T level less than 19 ng/L at 0 and 3 hours.

There were 5 Class III studies that attempted to validate the ADP established by ADAPT and ASPECT.[29,31,35,43,46] Kelly[31] performed a substudy of a prospective cohort of potential ACS patients (N=651) in Australia, using repeated conventional troponin (not high-sensitivity) testing and identified only 1 MACE (revascularization within 7 days) among 215 low-risk patients, resulting in a sensitivity of 98.9% (95% CI 93.4% to 99.9%). A subsequent study by Kelly and Klim,[35] conducted as a formal prospective validation of the ADAPT trial, did not identify any MACE among the 177 patients (21%) deemed to be at low risk.

Five additional Class III studies evaluated accelerated serial troponin testing in a variety of methods, with similar results: when high-sensitivity troponin was used, there was a low MACE rate and a very high sensitivity (>98% when applied to certain low-risk cohorts)[40,44,69-71]

Although there is high-quality evidence for successful application of a 2-hour ADP using high-sensitivity troponins, similar results could not be achieved using conventional troponins in the United States. In a secondary analysis of a previous trial, Stopyra et al[46] (Class III) reported sensitivity for the 2-hour ADP of 88.2% (95% CI 63.6% to 98.5%). In another secondary analysis of previously collected data from 7 US centers that included patients with TIMI scores 0 to 2, Mahler et al[43] reported a sensitivity of 83.9% (95% CI 66.3% to 94.5%) when conventional troponin levels were obtained at presentation and at 2 hours.

Repeated conventional troponin testing at 3 to 4 hours may yield a lower MACE at 30 days, as suggested by a post hoc analysis performed by Kelly and Klim.[72] Among patients stratified as non-high-risk using the Australasia Heart Foundation guidelines and who had a negative troponin result at 3 to 4 hours, only 1 MACE (0.26%) occurred.

### Single Troponin

The HEART score was designed to identify patients at very low risk of ACS in the ED by using a single troponin test. Six et al[64] originally developed the HEART score based on data from 122 patients. Backus et al[85] then conducted a retrospective multicenter validation of the HEART score, which yielded a 1% MACE rate among patients with a low-risk HEART score (0 to 3). Backus

et al[47] were unable to replicate the very low rate of MACE in a prospective validation of the HEART score in the Netherlands (multicenter study at 11 hospitals), using a single conventional troponin applied to greater than 2,400 patients. Among those with a low-risk HEART score (36.4% of the entire cohort), the MACE rate at 30 days was 1.7%, with upper range of the CI greater than 2%. A systematic review and meta-analysis by Van Den Berg and Body[57] pooled 9 studies, yielding greater than 11,000 patients and found the HEART score to be predictive of MACE but the low-risk cohort still had an unacceptably high 3.3% rate of MACE. HEART score performs well, but it has not been able to consistently demonstrate a MACE rate less than 1%; therefore, the creators developed the HEART Pathway, which includes a second troponin test at 3 hours.

Marcoon et al[77] attempted to further reduce the MACE rate to below 1% by applying the HEART score to a cohort already risk stratified with the TIMI score. Among 8,815 adult patients with suspected ACS, application of the HEART score lowered the MACE rate at every level of TIMI score; however, only those patients with a TIMI score of 0 and a HEART score of 0 had a MACE risk of less than 1%. Whether emergency physicians should use decision aids preferentially incorporating the TIMI score, HEART score, or both remains unclear; both have demonstrated utility. One study comparing the 2 scores in a large registry (N=8,255) concluded that the HEART score has more discriminatory power[60]; however, this was a Class III retrospective study without a prospective clinical application of the scores. Patients who did not have adequate data to calculate a TIMI or HEART score were excluded.

## Single High-Sensitivity Troponin

In a low-risk cohort based on history and ECG, Mokhtari et al[79] demonstrated very high sensitivity for the high-sensitivity cardiac troponin T test. From a total of 1,138 patients, almost one third had a troponin level less than 5 ng/L (the limit of detection), with a sensitivity of 99% (0.3% risk of MACE). Two thirds of patients had a negative troponin test result using the 99$^{th}$ percentile cutoff of 14 ng/L; however, sensitivity decreased to 92% (1.3% risk of MACE).

Pickering et al[86] confirmed the value of a single high-sensitivity troponin result below the limit of detection (<5 ng/L) through a meta-analysis of patients with a nonischemic ECG result to exclude the possibility of an acute MI. Eleven studies with 2,825 patients resulted in a pooled sensitivity of MACE at 98%. Although many of the studies in the meta-analysis were very low quality, there were several higher-quality studies with consistent results.[18,78,79] Although not included in the meta-analysis, the study by Bandstein et al[34] also found a very low 30-day MACE rate of 0.17% among patients with a nonischemic ECG result and an initial undetectable high-sensitivity troponin T level.

## Novel Algorithms

Given that there is likely a subset of patients who can be ruled out for MI with a single troponin test and a separate subset who would require a second troponin test, Lindahl et al[83] derived and validated a stepwise algorithm using high-sensitivity cardiac troponin I; one third of the patients were able to be ruled in (high enough troponin level) or ruled out (low enough troponin level) with initial troponin level and another one third were able to be ruled out with a 2-hour troponin test. In total, 54.6% of patients were ruled out for acute MI within 2 hours, with an NPV of 99.4% and sensitivity of 97.7%, using a high-sensitivity troponin T test.

In a large, multicenter, international study, Mueller et al[68] validated a 0- and 1-hour algorithm with high-sensitivity cardiac troponin T, using a cutoff and a Δ troponin level; rule-out required an initial level less than 12 ng/L and a 1-hour Δ less than 3 ng/L, and a rule-in required an initial level greater than 52 ng/L or 1-hour Δ greater than 5 ng/L. Although the NPV was impressive at 99.1%, the sensitivity was only 96.7%, meaning more than 3 patients of every 100 would have false-negative results.

Than et al[73] performed a large study with greater than 31,000 patients in 7 New Zealand hospitals and demonstrated that having an ADP (repeated troponin testing within 3 hours) could significantly improve the ED discharge rates without increasing the 30-day MACE; a couple of institutions used a conventional troponin test and some used high-sensitivity troponins, with no difference in results. The authors concluded that the implementation of the clinical pathway was the primary driver of the reduced ED length of stay. Risk stratification in addition to type and timing of troponin testing is critical in identifying patients with non-ST elevation MI.

In summary, although the studies varied a great deal in the type of troponin test used and whether a repeated test was performed, a few reasonable conclusions are possible. At least in the Asia-Pacific region, a 2-hour ADP applied to a select group of low-risk ACS patients that uses a high-sensitivity troponin test can identify those with a low 30-day rate of MACE. A single high-sensitivity troponin test result below the level of detection, a single high-sensitivity troponin test result applied to a low-risk cohort, or serial

high-sensitivity troponin test results within 3 hours have all been demonstrated to reduce MACE.

**Future Research**

With the approval of high-sensitivity troponin in the United States, validation of ADPs in a diverse multicenter US study is needed. Ideally, such a validation study would include the HEART score as a clinical prediction instrument included within an ADP.

**3. In adult patients with suspected NSTE ACS in whom acute MI has been excluded, does further diagnostic testing (eg, provocative, stress test, computed tomography [CT] angiography) for ACS prior to discharge reduce 30-day MACE?**

**Patient Management Recommendations**

***Level A recommendations.*** None specified.

***Level B recommendations.*** Do not routinely use further diagnostic testing (coronary CT angiography, stress testing, myocardial perfusion imaging) prior to discharge in low-risk patients in whom acute MI has been ruled out to reduce 30-day MACE.

***Level C recommendations.*** Arrange follow-up in 1 to 2 weeks for low-risk patients in whom MI has been ruled out. If no follow-up is available, consider further testing or observation prior to discharge (Consensus recommendation).

Potential Benefit of Implementing the Recommendations: Limiting complex, expensive, and time-consuming testing can reduce patient cost, ED and hospital length of stay, and patient anxiety caused by unnecessary stress testing and potentially false-positive results once adequate risk stratification and cardiac rule-out have occurred.

Potential Harm of Implementing the Recommendations: Current literature continues to show that patients may still have a 30-day MACE after presenting with chest pain to an ED. Without more conclusive studies, providers should be aware of current American Heart Association (AHA)/ACC guidelines stating it is "reasonable" to obtain stress testing, and work within their hospital systems to establish an agreed-on approach to minimize medicolegal risk.

Key words/phrases for literature searches: acute coronary syndrome, chest pain, coronary artery disease, myocardial infarction, stress echocardiography, exercise test, myocardial perfusion imaging, coronary angiography, cardiac imaging techniques, diagnostic imaging, provocative test, diagnostic test, diagnostic test accuracy study, diagnostic value, decision support techniques, risk factor, risk, predictive value, confidence, emergency service, emergency, emergency department, emergency room, and variations and combinations of the key words/phrases. Searches included January 1, 2005, to search dates of December 8, 2015; December 14, 2015; and December 11, 2017.

Study Selection: Five hundred twenty-five articles were identified in the searches. Forty-one articles were selected from the search results for further review, with 1 Class II and 2 Class III studies included for this critical question.

Once acute MI has been ruled out by an adequate evaluation including troponin and ECG measurement, the question remains whether patients should undergo further testing to reduce 30-day MACE. Very few published studies directly address this question, which may be related to 2 issues: (1) current 2014 AHA/ACC guideline recommendations,[15] and (2) many studies that address only a certain risk population rather than all patients in whom MI has been ruled out.

The current 2014 AHA/ACC guidelines[15] provide the following Class IIA (b) recommendations: "It is reasonable for patients with possible ACS who have normal serial ECGs and cardiac troponins to have a treadmill ECG (Level of Evidence: A), stress myocardial perfusion imaging, or stress echocardiography before discharge or within 72 hours after discharge. (Level of Evidence: B)"

Although the recommendation states "it is reasonable" to obtain stress testing before discharge or within 72 hours, this does not provide emergency providers with guidance on whether it is recommended based on 30-day outcomes. Additionally, the articles used to support this recommendation were all published in 2003 or earlier, bringing into question their validity in the age of modern troponin use.

One Class II[87] and 2 Class III[88,89] studies directly addressed this critical question. Lim et al[87] published a randomized trial evaluating the effect of stress myocardial perfusion imaging on 30-day outcomes. In their study, all patients underwent 6-hour serial cardiac troponin T rule-out testing. After this 6-hour rule out, patients without elevated cardiac markers or ST changes were randomized to either their standard management arm (in which emergency physicians evaluated the patients' history, discharged those they deemed low risk, and admitted remaining patients for further testing) or to the stress myocardial perfusion imaging arm. Both groups had very low 30-day MACE rates, with only 0.4% in the stress myocardial perfusion imaging group and 0.8% in the standard management group (relative risk=0.50; 95% CI 0.13 to 2.00), thus demonstrating that stress myocardial perfusion imaging did not significantly reduce 30-day MACE once patients already had negative serial troponin testing results.

Frisoli et al[89] (Class III) randomized 105 patients with modified HEART scores less than or equal to 3 and reassuring 0- and 3-hour cardiac troponin I values to either immediate discharge or stress testing in the ED. None of their patients had 30-day MACE events. In addition, the immediate-discharge patients had markedly shorter length of stay, and a 3-fold reduction in 30-day total charges of care.

A Class III study by Poon et al[88] followed patients for 30-day MACE rates after NSTEMI was ruled out with ECG and serial troponins. Although this study did not directly address our study question of randomizing to stress testing or not after cardiac rule-out, they reported MACE rates of patients who did not routinely receive ED stress testing. They used coronary CT angiography and evaluated 30-day MACE rates before and after. They performed a matched propensity score to evaluate 894 comparative patients who received either coronary CT angiography or standard evaluation (including ED stress testing, discharge with outpatient stress testing referral, or admission). Patients discharged from the ED were instructed to contact a cardiologist for possible stress testing within 72 hours, yet only 9.9% of their discharged standard evaluation cohort underwent stress testing. The overall 30-day MACE rates, including the index visit, were 2.9% in both groups. However, all MIs were diagnosed during the index ED visit, and none of their 483 discharged patients had an MI between the index visit and 30 days afterward.

Although not included in this study question (Class X due to retrospective claims-based study), an analysis by Sandhu et al[90] assessed the use of outpatient cardiac testing for patients who had an ED visit for chest pain and were discharged without a diagnosis suggesting acute MI. They looked at privately insured patients younger than 65 years, examining over 900,000 such visits. They reported that further cardiac testing (including coronary angiography or noninvasive testing such as exercise electrocardiography, stress echocardiography, myocardial perfusion scan, or CT coronary angiography) between 2 and 30 days after discharge from an ED visit for chest pain did not appear to improve outcomes. Based on this retrospective analysis, the authors concluded that such "cardiac testing in patients with chest pain was associated with increased downstream testing and treatment without a reduction in AMI [acute MI] admissions, suggesting that routine testing may not be warranted."

The literature search also identified a few studies that reported on the false-positive rates with respect to stress testing low-risk patients; however, due to methodological limitations, all 3 studies were graded as Class X.[91-93] Khare et al[91] and Winchester et al[92] evaluated all patients who underwent routine cardiac stress testing after initial rule-out and reported a high false-positive rate, with associated costs approximately 5 times that of those who had negative stress test results. Poldervaart et al[93] evaluated stress test results after a single troponin result and a HEART score calculation. Patients in their low-risk HEART score cohort had a 2.4% MACE rate, yet the addition of exercise stress testing did not identify any of the patients who had a MACE. Among the intermediate- and high-risk HEART groups that were examined, the addition of exercise testing only modestly improved the accuracy of clinical diagnosis, whereas 50% of stress tests in all groups combined were false positives.

The problems associated with false-positive test results may be even more profound in younger patients. Several Class X studies[94-96] have noted that stress testing had a much higher false- than true-positive rate in patients younger than 40 years. Hermann et al[97] and Hamilton et al[98] were 2 other Class X studies that noted similar outcomes in young patients.

## Future Research

Given the paucity of evidence for this critical question, future randomized trials of low-risk patients comparing an approach based on stress testing during the index ED visit versus ED discharge with appropriate follow-up are needed to make recommendations that provide more informative guidance. This work should stratify 30-day MACE outcomes and include cost-effectiveness analysis, taking into account the harms and costs associated with false-positive provocative testing or advanced imaging.

### 4. Should adult patients with acute NSTEMI receive immediate antiplatelet therapy in addition to aspirin to reduce 30-day MACE?

**Patient Management Recommendations**

***Level A recommendations.*** None specified.

***Level B recommendations.*** None specified.

***Level C recommendations.*** P2Y12 inhibitors and glycoprotein IIb/IIIa inhibitors may be given in the ED or delayed until cardiac catheterization.

Potential Benefit of Implementing the Recommendations: Beyond the administration of aspirin, the emergency physician does not need to make an immediate decision in regard to the administration of the various antiplatelet agents to patients with NSTEMI and can defer this decision to local cardiologists. This may help avoid delays in transitions of care, as well as increased costs and potential adverse effects (ie, bleeding) from excessive use of antiplatelet agents in the ED.

Potential Harm of Implementing the Recommendations: If these guidelines are erroneously applied to patients with ST-elevation ACS, there is the potential for increased mortality. Physicians should be cognizant that this recommendation applies only to those patients with a diagnosis of NSTEMI.

Key words/phrases for literature searches: acute coronary syndrome, myocardial ischemia, myocardial infarction, aspirin, antithrombins, heparin, low-molecular-weight heparin, peptide fragments, recombinant proteins, platelet activation, platelet aggregation inhibitors, platelet function tests, decreased platelet hyperfunction, time factors, time dependence of antithrombin initiation, odds ratio, confidence intervals, immediate, emergency service, emergency, emergency room, emergency department, and variations and combinations of the key words/phrases. Searches included January 1, 2005, to search dates of December 8, 2015; December 14, 2015; and December 11, 2017.

Study Selection: One hundred twenty articles were identified in the searches. Thirty-three articles were selected from the search results for further review, with 3 Class I, 2 Class II, and zero Class III studies included for this critical question.

The literature search identified 3 Class I[99-101] and 2 Class II[102,103] studies that addressed this critical question. For patients diagnosed with NSTEMI with a positive troponin test result, this question addresses whether emergency physicians should give additional antiplatelet agents as soon as the diagnosis is made, rather than deferring the administration of these drugs to time of admission or cardiology evaluation. For this critical question, "immediate" administration was the time frame shortly after the diagnosis of NSTEMI during which the patient was still under the care of the physician in the ED.

There are conflicting data from major studies in regard to the efficacy and safety of adenosine diphosphate–induced platelet aggregation inhibitors (P2Y12 inhibitors). A Class I randomized placebo-controlled trial[99] found that in patients with NSTE ACS who were scheduled to undergo catheterization, administration of a dose of prasugrel before angiography did not reduce 30-day MACE. Major bleeding episodes were increased in the prasugrel group at 30 days (2.8% versus 1.5%, hazard ratio 2.0; 95% CI 1.3 to 3.1). Although patients in this study received the drug before PCI, this was up to a 48-hour period, and the study did not address whether receiving the drug immediately on diagnosis had an effect on mortality. An earlier Class I placebo-controlled randomized study[100] evaluating the use of clopidogrel in patients with NSTE ACS found a reduction in MI during the 12-month study period (5.2% versus 6.7%; relative risk 0.8; 95% CI 0.7 to 0.9). Patients in the study received clopidogrel immediately and then daily for 3 months. However, this study did not differentiate between patients with positive troponin results and patients with ECG changes and is therefore less generalizable to the specific population of NSTEMI. Although the study period was 12 months, the benefits of clopidogrel were apparent as early as 24 hours after randomization and continued throughout the 12-month follow-up period. The risk of bleeding complications was increased in the clopidogrel group (8.5% versus 5.0%; relative risk 1.7; 95% CI 1.5 to 1.9). Although P2Y12 inhibitors cannot be recommended for routine administration in addition to aspirin in the ED for NSTEMI, these antiplatelet agents could be considered as an aspirin alternative in patients with an aspirin allergy.

In the Class I Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO) IV-ACS Trial,[101] the antiplatelet glycoprotein IIb/IIIa inhibitor abciximab was compared with placebo. For patients not scheduled for early coronary intervention (within 48 hours), the trial showed no difference in the 30-day composite endpoint of death or MI (odds ratio 1.0; 95% CI 0.83 to 1.24) for the difference between placebo and 24-hour abciximab, and 1.1 (95% CI 0.94 to 1.39) for the difference between placebo and 48-hour abciximab; however, increased mortality was reported at 48 hours for patients receiving a 24- or 48-hour infusion of abciximab.[101] The Class II 2007 Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Timing Trial[102] found that immediate glycoprotein IIB/IIIa inhibitor (eptifibatide or tirofiban) administration, compared with deferral until the time of PCI for patients undergoing PCI within 72 hours did not confer additional benefit, but caused increased bleeding. The main limitation in regard to the ACUITY Timing Trial was that it included all patients with ACS and did not differentiate between those with ECG changes versus those with positive troponin results. A third trial by Giugliano et al[103] (Class II) showed no added benefit of early versus late eptifibatide in patients with ACS without ST elevation; however, by waiting until after catheterization, there was a reduction in non-life-threatening bleeding and blood transfusions. One issue in all 3 of these trials is that patients were concomitantly anticoagulated with either heparin or bivalirudin.

In critically examining the results of these trials in clinical context for the emergency physician, it is reasonable to defer starting glycoprotein IIb/IIIa inhibitor infusion until the time of cardiac catheterization or hospital admission. This is in agreement with current guidelines of the AHA, ACC, and European Society of Cardiology that

recommend delay by selectively using these drugs only in patients going for invasive or ischemic guided strategy.[15,104]

A limitation in regard to all of the included studies addressing this critical question on antiplatelet agents in NSTEMI is that few isolate the effect of a single agent because most included other standard treatments such as aspirin and heparin. Although 3 Class I studies[99-101] were included, a recommendation higher than level C was not made because none of the studies directly addressed the critical question in terms of immediacy of administration. As for the 2 Class II studies,[102,103] neither showed a benefit from early intervention. Ultimately, the critical determinant of drug selection and route of administration often hinges on the need for urgent cardiac catheterization and the potential for emergency cardiac bypass. In addition, it is not always apparent to the emergency physician whether a patient with a diagnosis of NSTEMI will proceed to catheterization. Ultimately, the decision about the selection and timing of these antiplatelet agents should be made in collaboration with local cardiovascular specialists.

## Future Research

Future research focusing on the use of nonaspirin antiplatelet agents in the highest-risk NSTEMI patients, such as those with ongoing chest pain, with significant ischemic changes on ECG, or determined by cardiologists to be candidates for urgent PCI, may help identify a subset of patients in whom immediate administration of these agents in the ED improves patient-important outcomes.

***Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic.***

***Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical question.***

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**Appendix A.** Literature classification schema.*

| Design/Class | Therapy† | Diagnosis‡ | Prognosis§ |
|---|---|---|---|
| 1 | Randomized, controlled trial or meta-analysis of randomized trials | Prospective cohort using a criterion standard or meta-analysis of prospective studies | Population prospective cohort or meta-analysis of prospective studies |
| 2 | Nonrandomized trial | Retrospective observational | Retrospective cohort<br>Case control |
| 3 | Case series | Case series | Case series |

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

**Appendix B.** Approach to downgrading strength of evidence.

| | Design/Class | | |
|---|---|---|---|
| **Downgrading** | **1** | **2** | **3** |
| None | I | II | III |
| 1 level | II | III | X |
| 2 levels | III | X | X |
| Fatally flawed | X | X | X |

**Appendix C.** Likelihood ratios and number needed to treat.*

| LR (+) | LR (-) | |
|---|---|---|
| 1.0 | 1.0 | Does not change pretest probability |
| 1-5 | 0.5-1 | Minimally changes pretest probability |
| 10 | 0.1 | May be diagnostic if the result is concordant with pretest probability |
| 20 | 0.05 | Usually diagnostic |
| 100 | 0.01 | Almost always diagnostic even in the setting of low or high pretest probability |

*LR*, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

**Evidentiary Table.**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Peacock et al[13] (2017) | II for Q2 | Prospective study of ED patients in 15 EDs in the U.S. | Adults with suspected ACS were evaluated with high-sensitivity troponin T; outcome: 30-day MACE | NPV of single high-sensitivity troponin T below 6 ng/L and both 0- and 3-hour levels below 19 ng/L is greater than 99% (<1% risk of MACE) | Real-world implications unclear because treating physicians were blinded to results of high-sensitivity troponin |
| Than et al[17] (2011) | I for Q1 and II for Q2 | Prospective validation study, observational cohort; 14 urban EDs, mostly academic | Entered patients 18 y and older with at least 5 min of chest pain; the 2-h ADP included use of a structured pretest probability scoring method (TIMI score), ECG, and biomarker panel of troponin, CK-MB, and myoglobin; the primary endpoint was MACE within 30 days | N=3,582 with 421 (11.8%) having MACE; the ADP classified 352 (9.8%) patients as low risk and potentially suitable for early discharge; MACE occurred in 3 (0.9%) of these patients, giving the ADP a sensitivity of 99.3% (95% CI 97.9% to 99.8%), an NPV of 99.1% (95% CI 97.3% to 99.8%), and a specificity of 11.0% (95% CI 10.0% to 12.2%) | Very low specificity |
| Than et al[18] (2012) | I for Q1 and I for Q2 | Prospective observational study; 2 urban academic EDs | Adult patients had data collected for 2-h ADP that included pretest probability scoring by TIMI score, electrocardiography, and 0 to 2-h values of laboratory troponin I as the sole biomarker; outcome: MACE within 30 days | N=1,975, 302 (15.3%) had a MACE; ADP classified 392 patients (20%) as low risk; 1 (0.25%) of these patients had MACE, giving ADP sensitivity of 99.7% (95% CI 98.1% to 99.9%), NPV of 99.7% (95% CI 98.6% to 100.0%), specificity of 23.4% (95% CI 21.4% to 25.4%) | Observational retrospective analysis; mainly white patients |
| Hess et al[19] (2010) | II for Q1 | Prospective cohort study; urban academic ED | Patients >24 y with chest pain were assessed with modified TIMI score that included ST-segment deviation or troponin elevation as high-risk outcome; 30-day MACE | N=1,017; >0 sensitivity 96.6%, specificity 23.7%; lowest cut point (TIMI/modified TIMI score >0) was the only cut point to predict cardiac events with sufficient sensitivity to consider early discharge; the sensitivity and specificity of the modified and original TIMI risk scores at this cut point were identical | Only 72% of eligible patients enrolled; 4.6% lost to follow-up; rule did not include pain descriptors |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Hess et al[20] (2010) | II for Q1 | Systematic review and meta-analysis | Included prospective cohort studies that validated the TIMI risk score in ED patients; conducted meta-regression to determine whether a linear relation exists between TIMI risk score and the cumulative incidence of cardiac events; outcome 30-day cardiac arrest | N=8 prospective cohort studies (with a total of 17,265 patients); TIMI score of zero, 1.8% had a cardiac event within 30 days: sensitivity 97.2% (95% CI 96.4% to 97.8%); specificity 25.0% (95% CI 24.3% to 25.9%) | Small number of studies included; statistical heterogeneity between studies; lack of reporting of the characteristics of the cardiac biomarker assays and the thresholds used to define acute MI |
| Hess et al[21] (2012) | II for Q1 | Prospective cohort study; 3 urban academic EDs | Enrolled patients >24 y with anterior chest pain who had troponin testing; physicians completed standardized data collection forms before diagnostic testing; they used recursive partitioning to derive the rule and validated the model with 5,000 bootstrap replications; outcome: 30-day MACE | N=2,718 with 12% (336) having cardiac event in last 30 days; rule was 100% sensitive (95% CI 97.2% to 100%) and 20.9% specific (95% CI 16.9% to 24.9%) for a cardiac event within 30 days | Needs prospective evaluation |
| Than et al[22] (2014) | II for Q1 | Prospective RCT; urban university hospital | Experimental pathway using an ADP (TIMI score 0; electrocardiography; and 0- and 2-h troponin tests) or a standard-care pathway (troponin test on arrival at hospital, prolonged observation, and a second troponin test 6-12 h after onset of pain) serving as the control; used ARCHITECT TnI assay; outcome 30-day MACE | N=542; discharges: 30 (11%) in the control standard care group; 52 (19%) in the ADP group; MACE was only 1 (0.4%) in the ADP group | Single center; underpowered |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Mitchell et al[23] (2006) | II for Q1 | Prospective cohort study; 3 university-based EDs | Consecutive patients evaluated for ACS as part of a chest pain unit evaluation; evaluation of physician unstructured estimate, attribute matching, and a quantitative logistic regression prediction tool to estimate pretest probability; pretest probability >2% was considered "positive"; outcome 45-day MACE | N=1,114; 4.5% MACE within 45 days; 0.4% (4/991) discharged after negative chest pain unit evaluation result with 45-day MACE; unstructured assessment: 96% sensitive (95% CI 87% to 100%); 27% specific (95% CI 25% to 30%); attribute matching: 98% sensitive (95% CI 90% to 100%); 26.1% specific (95% CI 24% to 29%); ACI-TIPI: 100% sensitive (95% CI 93% to 100%); 6% specific (95% CI 5% to 8%) | Small number of patients with MACE (N=51), which limits sensitivity estimates; academic centers only, may limit generalizability |
| Pollack et al[24] (2006) | III for Q1 | Secondary analysis of a prospective cohort study; academic urban ED | Patients presenting with chest pain syndrome and warranting evaluation with an ECG; patients had TIMI risk scores determined at ED presentation; outcome: 30-day MACE | N=3,326; TIMI risk score at ED presentation successfully risk-stratified this unselected cohort of chest pain patients with respect to 30-day adverse outcome, with a range from 2.1%, with a score of 0% to 100%, with a score of 7 | Convenience sample; disproportionate number of blacks and women |
| Campbell et al[25] (2009) | III for Q1 | Urban academic hospital; prospective cohort study of ED patients with potential ACS | Assigned TIMI risk score and if clear-cut alternative diagnosis for the chest pain; outcome: 30-day MACE | N=3,169; prevalence of MACE in TIMI score zero and alternative diagnosis was 2.9% (95% CI 1.6% to 5%) | Larger than expected proportion of women and blacks |
| Body et al[26] (2009) | III for Q1 | Prospective cohort study; academic urban hospital | Patients with suspected chest pain; applied modified TIMI score (increased weight to ECG and troponin at 12 h after onset of pain); outcome: death, acute MI, and urgent revascularization within 30 days | N=796; modified TIMI score of >2 points had sensitivity of 96.4% (95% CI 92% to 98%), but specificity of only 51% | TIMI risk score extracted retrospectively |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Lee et al[27](2011) | III for Q1 | Secondary analysis of a prospective cohort study; university academic | Demographics, history, and components of the TIMI, GRACE, and PURSUIT scores were obtained on patients who presented with chest pain and had ECG done; outcome: 30-day MACE | N=4,743; at the lowest strata of TIMI, GRACE, and PURSUIT scores, the event rates were 2.0% (95% CI 1.4% to 2.7%), 0.5% (95% CI 0% to 2.6%), and 2.4% (95% CI 1.6% to 3.3%), respectively; for AUC at predicting MACE, TIMI score had the best AUC, 0.76 (95% CI 0.73 to 0.79) | Skewed toward blacks and women; convenience sample |
| Macdonald et al[28] (2011) | III for Q1 | Prospective cohort study (substudy); 2 tertiary and 3 urban hospitals | Compared NHF/CSANZ versus TIMI score in patients having serial troponin tests for suspected ACS; outcome: 30-day MACE | N=1,666; in the initial troponin group only, event rates between NHF/CSANZ guideline combined low or intermediate groups and TIMI risk score <2 were 3% vs 7%, *P*<.001 | 2.5% had no initial troponin test; 2.6% lost to follow-up |
| Aldous et al[29] (2012) | III for Q1 and III for Q2 | Secondary analysis of a prospective cohort study; single center | Patients ≥18 y with at least 5 min of chest pain; blood samples (including TnI, CK-MB, myoglobin, and high-sensitivity TnT) were collected at 0 and 2 h, and were combined with TIMI score, and ECG score; outcome 30-day MACE | N=1,000, outcome was ACS 36% (MI 24% and unstable angina 12%); there were 12.3% identified as low risk by the original ADP, with sensitivity for ACS of 99.2% (95% CI 97.5% to 99.8%); the ADP with the point-of-care TnI only or high sensitivity TnT had the same sensitivity, but identified more patients for discharge (15.0% versus 12.3%); including patients with a TIMI risk score of 1 identified more patients as low risk (19.7%), but with a lower sensitivity (97.0% versus 99.2%) | Secondary analysis of ASPECT trial (Than 2011[17]); single center with predominantly white population; limited generalizability |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Goodacre et al[30] (2012) | III for Q1 | Retrospective secondary analysis of the RATPAC data evaluating the TIMI and GRACE risk scores; 6 academic EDs | Retrospective assignment of TIMI and GRACE scores to ED patients with chest pain and normal or nondiagnostic ECG result; outcome: death, emergency revascularization, life-threatening arrhythmia, hospitalization for ACS, or nonfatal acute MI | N=2,243; mean age 54.5 y; 58% male); the major adverse event rate was 43 of 2,243 (2%) after 30 days; the C statistics for 30-day events were 0.72 (95% CI 0.70 to 0.74) for GRACE score and 0.68 (95% CI 0.66 to 0.70) for TIMI score | Many lost to follow-up |
| Kelly[31] (2013) | III for Q1 and III for Q2 | Substudy of prospective cohort study; urban teaching hospital | Adult patients with possible ACS; used TIMI score 0 and initial TnI <99% to predict 7-day MACE (primary outcome) and 30-day MACE | N=651 total; 215 met low-risk criteria; 1 (0.47%) MACE in low-risk group (revascularization) within 7 days; NPV of low-risk classification at 7 and 30 days was 99.5% (95% CI 97% to 100%) | Low outcome prevalence; may influence NPV estimates; single site; limited generalizability |
| Cullen et al[32] (2013) | III for Q1 | Prospective cohort study; 2 urban academic EDs | TIMI score and 2 troponin tests at 0 and 6 h; outcome: 30-day MACE | N=1,635; sensitivity, specificity, and NPV for TIMI score ≤1 in the primary cohort were 99.2% (95% CI 97.1% to 99.8%), 48.7% (95% CI 46.1% to 51.3%), and 99.7% (95% CI 98.9% to 99.9%), respectively; sensitivity, specificity, and NPV for TIMI score ≤1 in the secondary cohort were 99.4% (95% CI 96.5% to 100%), 46.5% (95% CI 42.9% to 50.1%), and 99.7% (95% CI 98.4% to 100%), respectively | Primarily white patients; high-sensitivity troponin |
| Six et al[33] (2013) | III for Q1 | Substudy of prospective observational cohort; 14 hospitals in 9 countries, mainly academic urban | Patients presenting with chest discomfort of at least 5-min duration suggestive of ACS, who received serial biomarker tests; HEART score calculated retrospectively on data for each patient at ED admission; outcome: 30-day MACE | N=2,906 of whom 374 had MACE; sensitivity: HEART score ≤2: 98.9% (95% CI 97.3% to 99.6%), HEART score ≤3: 96.3% (95% CI 93.8% to 97.8%), versus TIMI score ≤0: 98.1% (95% CI 96.2% to 99.1%), and TIMI score ≤1: 87.4% (95% CI 83.7% to 90.4%) | Retrospective analysis of study not designed for testing HEART |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Bandstein et al[34] (2014) | III for Q1 and III for Q2 | Retrospective cohort study; 2 academic urban hospitals | Patients >25 y with chest pain and a high-sensitivity cTnT test; included all patients with a high-sensitivity cTnT test ordered; compared different cutoff values of high-sensitivity cTnT, measuring MI or death at 30 days | N=14,636; of whom 8,907 (61%) had an initial high-sensitivity cTnT result of <5 ng/L; 21% had 5 to 14 ng/L, and 18% had >14 ng/L; during 30-day follow-up, 39 (0.44%) patients with undetectable high-sensitivity cTnT results had an MI, of whom 15 (0.17%) had no ischemic ECG changes; the NPV for MI within 30 days in patients with undetectable high-sensitivity cTnT result and no ischemic ECG changes was 99.8% (95% CI 99.7% to 99.9%); the NPV for death was 100% (95% CI 99.9% to 100%) | Follow-up data from national registries; low prevalence of outcome; high NPVs influenced by low prevalence |
| Kelly and Klim[35] (2014) | III for Q1 and III for Q2 | Prospective cohort study; community teaching hospital in Australia; patients with suspected ACS | Goal of validating a 2-h troponin pathway; used TIMI score 0 and contemporary sensitive troponin assay to predict 30-day MACE | Zero occurrences of MACE at 30 days; NPV=100% | Low outcome prevalence; may influence NPV estimates; single site; limited generalizability |
| Macdonald et al[36] (2014) | III for Q1 | Multicenter prospective cohort study; 2 tertiary and 3 general hospitals | Applied modified TIMI score (range 0-10) with increased weighting to ECG changes and troponin elevation was applied to ED patients with suspected ACS; used routine (not high-sensitivity) troponin; outcome: 30-day MACE | N=1,666, with 219 having study outcome; for TIMI score 0, sensitivity and specificity for the composite outcome were 96% (95% CI 92% to 98%) and 23% (95% CI 20% to 26%), respectively; for TIMI and modified TIMI score <2, sensitivity and specificity were 82% (95% CI 77% to 87%) and 53% (95% CI 51% to 56%), and 74% (95% CI 68% to 79%) and 54% (95% CI 51% to 56%), respectively | Nonconsecutive enrollment |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Body et al[37] (2015) | III for Q1 | Prospective cohort study; university urban hospital | Patients presenting to ED with chest pain; used modified TIMI score that included laboratory testing at 12 h for h-FABP assay and high sensitivity; outcome: MACE at 30 days | N=456; modified MACS rule TIMI score at >2 points had sensitivity of 97.9% (95% CI 92.8% to 99.8%) | Reliant on testing not readily available |
| Lyon et al[38] (2007) | III for Q1 | Observational prospective cohort; urban academic hospital | Consecutive patients presenting with chest pain were enrolled into the study during a 2-mo period; epidemiologic data were collected for each patient; TIMI and GRACE scores were calculated retrospectively; outcome: 30-day MACE | N=760; the event rate for TIMI score 0 to 1 (N=446) was 3%; for GRACE score 1 to 5, 4% | Excluded 161 patients from GRACE scoring because of lack of measured creatine level |
| Scheuermeyer et al[39] (2012) | III for Q1 | Prospective cohort study; inner-city academic hospital ED | Patients with potential ischemic chest pain without ECG or biomarker evidence of ischemia were discharged home after 2 to 6 h of observation; had follow-up study within 48 h; outcome: 30-day ACS | N=1,116; 197 (17.7%) were admitted at the index visit and 254 (22.8%) received outpatient testing on discharge; the 30-day ACS event rate was 10.8%, and the 30-day missed ACS rate was 0% (95% CI 0% to 2.4%) | Required 48-h follow-up |
| Carlton et al[40] (2015) | III for Q1 and III for Q2 | Urban hospital; prospective observational study of patients with suspected ACS | High-sensitivity troponin testing and risk scoring done on arrival; outcome: 30-day MI | N=959; a TIMI score $\leq$1 and modified Goldman score $\leq$1 with high-sensitivity troponin T, and TIMI score of 0 and HEART score $\leq$3 with high-sensitivity troponin I had potential to achieve an NPV $\geq$99.5% while identifying >30% of patients as suitable for immediate discharge | Based on whether physician thought patient warranted troponin test; used only high-sensitivity troponin testing; MI only endpoint; risk scoring done at later date according to chart |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Chen et al[41] (2016) | III for Q1 | Prospective 2-academic-center study | Compared prognostic value of 4 risk scores; outcome: 30-day MACE | N=833; sensitivity to predict 30-day MACE:<br>Heart score >5: 48.9% (95% CI 38.2% to 59.7%)<br>TIMI score >2: 66.7% (95% CI 55.9% to 76.3%)<br>GRACE score >109: 72.2% (95% CI 61.8% to 81.1%)<br>Banach score >0: 75.6% (95% CI 65.4% to 84.0%) | Used higher cutoffs for TIMI and HEART scores than other studies recommend; excluded any non-Chinese patients |
| Leung et al[42] (2017) | III for Q1 | Prospective academic center | Validated diagnostic accuracy of TIMI score with single troponin result (≤14 ng/L) compared with modified HEART score;<br>outcome: 30-day MACE | N=602; sensitivity to predict 30-day MACE:<br>TIMI score: 100% (95% CI 91.6% to 100%)<br>modified HEART score: 100% (95% CI 91.6% to 100%) | Convenience sample daytime weekdays; modified HEART score for ECG interpretation |
| Mahler et al[43] (2015) | III for Q1 and III for Q2 | Secondary analysis of patients prospectively enrolled in ACRIN trial | Patients ≥30 y and with possible ACS; secondary analysis of ACRIN trial to determine whether 2-h troponin protocol can be validated in a US population, using 30-day MACE as outcome measure | N=1,140; 30-day MACE: 5/551 (0.9%) with 1 MI and all the rest with revascularizations;<br>sensitivity 83.9% (95% CI 66.3% to 94.5%) | Limited sample size; wide precision estimates; low outcome prevalence |
| Aldous et al[44] (2012) | III for Q1 and III for Q2 | Secondary analysis of a prospective cohort study; single center | Patients stratified based on 0- and 2-h cTnI and TIMI score; outcome 30-day MACE | N=1,000; outcome was ACS 36% (MI 24% and unstable angina 12%); sensitivity for 0- or 2-h cTnI and TIMI was 99.2% (95% CI 97.5% to 99.8%) | Secondary analysis of ASPECT trial (Than 2011[17]); single center with predominantly white population; limited generalizability |
| Than et al[45] (2014) | III for Q1 | Prospective observational study; 2 urban academic EDs | Enrolled consecutive patients ≥18 y with at least 5 min of symptoms consistent with ACS, such that physician planned to perform further investigations; used logistic regression in derivation of EDACS, which was combined with ECG and troponin level at 0 and 2 h for EDACS ADP; the score was then validated | In the derivation (N=1,974) and validation (N=608) cohorts, the EDACS ADP classified 42.2% (sensitivity 99.0%, specificity 49.9%) and 51.3% (sensitivity 100.0%, specificity 59.0%) as low risk of MACE, respectively | Derivation and validation cohorts recruited from same centers; retrospective analysis |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Stopyra et al[46] (2015) | III for Q1 and III for Q2 | Secondary analysis of another study; single urban academic ED | Eligibility criteria were chest pain or other symptoms suggestive of ACS, ≥21 y, and the provider ordering an ECG and troponin for the evaluation of ACS; EDACS ADP decision rule was applied to all of the study participants to risk stratify patients into low-risk or at-risk groups; outcome 30-day MACE | N=282; the EDACS ADP identified 188/282 patients, 66.7% (95% CI 60.8% to 72.1%) as low risk; of these, 2/188 patients (1.1%; 95% CI 0.1% to 3.9%) had MACE at 30 days; EDACS ADP was 88.2% (95% CI 63.6% to 98.5%) sensitive for MACE, identifying 15/17 patients with MACE | 10 patients lost to follow-up; small sample size and low MACE rate |
| Backus et al[47] (2013) | III for Q1 and III for Q2 | Multicenter (10 urban university affiliated hospitals); prospective cohort study | Patients with chest pain presenting to ED; planned comparison of HEART score versus TIMI score versus GRACE score versus troponin alone; outcome: 6-week MACE | N=2,440, of whom 407/2,388 went on to have MACE; HEART scores (0 to 3) excluded MACE in 98.3% of patients; it outperformed all other score systems or tests | 45 lost to follow-up; all chest pain patients had scoring assessed after troponin and ECG results |
| Body et al[48] (2014) | III for Q1 | Prospective cohort study; 1 academic urban and 1 suburban center | Patients >25 y with chest pain (<24 h) followed by external validation of new clinical decision rule; logistic regression for predictors of outcomes of acute MI or MACE within 30 days | Derivation N=698; validation N=463; internally the new rule, MACS, had sensitivity of 99.4% (95% CI 96.5% to 100%) for the very-low-risk group; validation sensitivity of 98% (95% CI 93% to 99.8%) | Not only does the MAC rule use a high-sensitivity troponin T test but also h-FABP; rule not simple; needs computational analysis to determine risk level |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Scheuermeyer et al[49] (2014) | III for Q1 | Prospective cohort study; university tertiary care urban hospital | Patients with anterior or lateral chest pain of potential ischemic nature enrolled in 2000-2003 (development cohort) and in 2006 (validation cohort); the primary outcome was 30-day ACS diagnosis; a recursive partitioning model incorporated reliable and predictive cardiac risk factors, pain characteristics, ECG findings, and cardiac biomarker results | N=1,669; in the derivation cohort, 165 of 763 patients (21.6%) had a 30-day ACS diagnosis; the derived prediction rule (Vancouver Chest Pain Rule) was 100.0% sensitive and 18.6% specific; in the validation cohort, 119 of 906 patients (13.1%) had ACS, and the prediction rule was 99.2% sensitive (95% CI 95.4% to 100.0%) and 23.4% specific (95% CI 20.6% to 26.5%) | Single center; 207 patients who qualified not entered |
| Cullen et al[50] (2014) | III for Q1 | Prospective cohort study; 2 urban academic EDs | Used new Vancouver Chest Pain Rule; low-risk patients were identified with ECG results, cardiac history, nitrate use, age, pain characteristics, and troponin results at 2 h after presentation; outcome: ACS within 30 days | N=1,635 with 20.4% positive for ACS at 30 days | Convenience recruitment of patients |
| Bracco et al[51] (2010) | III for Q1 | Urban academic hospital; observation study of adults with chest pain | Used clinical pathway criteria based on risk factors, pain characteristics, and ECG; outcome: 30-day MACE | N=813; of the 338 patients discharged, 0.4% (95% CI 0.06% to 0.7%) had adverse outcome; using the pathway decreased adverse events to 0.27% | Observational, noncontrolled |
| Fuller et al[52] (2013) | III for Q1 | Single academic ED; prospective observational study | Used patients admitted to ED observation unit for chest pain; had 3 cTnI tests every 6 h and then retrospective application of cardiac score; 30-day outcomes recorded | N=1,276; 692 patients had zero score; 1.5% (95% CI 0.8% to 2.7%) of those with a score of 0 experiencing MI, stent, or CABG | Only 70% follow-up; only used observation patients |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Lorenzoni et al[53] (2006) | III for Q1 | Prospective cohort study; 23 community and academic hospitals | 12-h rule-out, computer protocol for the evaluation and management of patients presenting to an ED with chest pain and nondiagnostic ECG result; outcome: 1-mo MACE | N=472; incidence of coronary events for patients defined by the protocol as being at low, medium-low, medium-high and high; overall probability was 1.9%, 12.8%, 13.5% and 68.0%, respectively | Poor follow-up |
| Chandra et al[54] (2009) | III for Q1 | Post hoc analysis of registry of adults presenting with ACS symptoms | Examined unstructured treating physician estimate of risk; outcome: 30-day MACE | N=10,145; adverse cardiac events were 2.2% (95% CI 1.8% to 2.6%) for low risk, and to 1.8% (95% CI 1.4% to 2.4%) for noncardiac | Possible inclusion bias |
| Body et al[55] (2014) | III for Q1 | Prospective cohort study | Patients with suspected cardiac chest pain; assigned gestalt using Likert scale for ACS at presentation along with troponin (high and regular sensitivity); outcome: acute MI within 30 days | N=458; patients with normal initial regular troponin level and ECG in whom diagnosis was "probably not" or "definitely not" had sensitivity of 100% (95% CI 95.6% to 100%) for predicting no acute MI | Acute MI defined as only based on troponin rise |
| Poldervaart et al[56] (2017) | III for Q1 | Prospective RCT analysis at 9 Dutch EDs | Patients presenting with chest pain randomized to usual care versus HEART score care; outcome: 6-week MACE | N=3,648; in low-risk patients (HEART score $\leq$3) incidence of MACE was 2.0% (95% CI 1.2% to 3.3%); 6-week incidence of MACE during HEART score care was 1.3% lower than during usual care | Noninferiority study |
| Van Den Berg et al[57] (2018) | III for Q1 | Meta-analysis of 12 studies | HEART score at arrival; outcome: MACE | N=11,217; pooled sensitivity and specificity of the HEART score ($\leq$3) for predicting MACE; were 96.7% (95% CI 94.0% to 98.2%) and 47.0% (95% CI 41.0% to 53.5%), respectively | Mix of contemporary and high-sensitivity troponins; overall heterogeneity was relatively high |
| Body et al[58] (2017) | III for Q1 | Secondary analysis of 4 prospective cohorts | Patients presenting to ED with suspected ACS; outcome: 30-day MACE | N=703; 98.7% (95% CI 95.3% to 99.8%) sensitivity for 30-day MACE | Secondary analysis of existing cohorts; high-sensitivity troponin |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Ranier et al[59] (2016) | III for Q1 | Prospective observational study in academic ED | Patients with chest pain <24 h with suspected ACS and no history of PCI or CABG; outcome: 30-day MACE | N=602; 42 (7%) with MACE; very-low-risk (n=350) criteria, hs-cTnT with ECG was 99.1% (95% CI 97.5% to 99.7%) sensitive for excluding MACE | Same data as study by Leung et al[42]; relies on subjective assessment of possible ACS and ECG; more than half of the eligible patients were excluded |
| Sun et al[60] (2016) | III for Q1 and III for Q2 | Retrospective analysis of 8 academic EDs | Patients presenting to the ED with suspected ACS; outcome: 30-day MACE | N=4,039 for TIMI: sensitivity 98.2% (95% CI 97.8% to 98.6%); N=2,361 for HEART: sensitivity 98.8% (95% CI 97.1% to 98.3%) | Retrospective analysis |
| Mahler et al[67] (2015) | II for Q2 | Randomized trial in the US | ED patients randomized to HEART Pathway or usual care; outcomes: cardiac testing, length of stay, early discharge, 30-day MACE | HEART Pathway reduced cardiac testing by 12%, reduced length of stay by 12 h, and increased early discharges by 21%, and there was 0% MACE | Single center with N=282 (141 patients in each arm) |
| Mueller et al[68] (2016) | II for Q2 | Prospective international, multicenter study | Evaluation of patients presenting to the ED with suspected ACS using high-sensitivity troponin; outcome: MI | Using a 0- and 1-h high-sensitivity troponin test, the negative troponin zone had NPV of 99.1% and positive zone had PPV of 77.2% | Real-world implications unclear because treating physicians were blinded to results of high-sensitivity troponin |
| Conde et al[69] (2013) | III for Q2 | Prospective cohort study; chest pain unit in Argentina | Patients with probable ACS using regular troponin protocol followed by another 300 patients using high-sensitivity troponin (arrival and at 3 h), all of whom were discharged; outcome: MACE at 30 days | N=600; 100% follow-up obtained; MACE at 30 days: 3 (1.2%) in high-sensitivity troponin group and 5 (1.7%) in control group of regular troponin (nonsignificant difference) | Low-prevalence outcome; may influence NPV estimates |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Cullen et al[70] (2014) | III for Q2 | Secondary analysis of prospectively collected data; 1 urban academic ED in Australia; compared the diagnostic accuracy of early biomarker strategies and 2-h Δ cTnI with risk stratification to later biomarker testing | Patients included if presenting with chest pain suggestive of ACS; serial blood draw at 0, 2, and 6 h for cTnI measurements, as well as collection of the NHFA/CSANZ guidelines; outcome: acute MI and MACE within 30 days | N=685 with 7% positive for 30-day acute MI or death and 11% positive for 30-day MACE; using NHFA/CSANZ, patients were stratified into low-, intermediate-, and high-risk groups; among low- and intermediate-risk patients, there were comparable rates of acute MI and MACE between 0/2 h and 0/6 h cTnI results: 0.2% (95% CI 0% to 1.2%) and 0.2% (95% CI 0% to 1.2%) for AMI, respectively; and 2.4% (95% CI 1.3% to 4.5%) and 2.5% (95% CI 1.3% to 4.6%) for MACE, respectively | Convenience recruitment of patients; all patients completed 30-day follow-up; outcomes independently assessed and formal adjudication process performed, when necessary, by cardiologists masked to the results of index biomarkers |
| Greenslade et al[71] (2015) | III for Q2 | Secondary analysis of a prospective cohort study; 2 university teaching EDs | Adults with suspected ACS; secondary analysis to determine whether undetectable high-sensitivity troponin or negative high-sensitivity troponin and normal glucose results could predict 30-day ACS (outcome) | N=1,412; 182 (13%) with acute MI; sensitivity of 100% (95% CI 98% to 100%) for index acute MI for both groups; sensitivity similar with 98.1% (undetectable) and 96.5% (dual approach) | Secondary analysis; spectrum bias in that patients had to have chest pain on presentation, removing sub-groups that present atypically; convenience sampling |
| Kelly and Klim[72] (2014) | III for Q2 | Substudy of prospective cohort study; urban teaching hospital | Adult patients with possible ACS; 30-day MACE as primary outcome and stratified by high- and low-risk patients | N=460; 30-day MACE: 1 NSTEMI with revascularization and 5 additional revascularizations within 30 days (1.3%); 0 MACE among non-high-risk patients (0%; 95% CI 0% to 1.5%) and 1 revascularization (0.4%; 95% CI 0.07% to 2.17%) | Low outcome prevalence; may influence NPV estimates; some retrospective chart review methods; 84% follow-up; single site; limited generalizability |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Than and Pickering[73] (2018) | III for Q2 | Prospective before- and after trial in 7 New Zealand acute care hospitals | EDs were asked to implement a clinical pathway for patients with suspected ACS; outcome: length of stay and early discharge rate | 6-h discharge rate increased from 8.3% to 18.4% with no change in MACE; length of stay decreased by 2.9 h among patients without ACS | Convenience sample |
| Mahler et al[74] (2016) | III for Q2 | Secondary analysis of RCT conducted in the US at a single academic ED | Nonadherence defined and effects of nonadherence analyzed from existing RCT data; outcome: nonadherence rate to HEART Pathway protocol | 20% nonadherence rate mostly from overtesting resulted in a decreased discharge rate; overtesting was unnecessary as none of the patients had MACE | Secondary analysis was not powered for analyses related to overtesting |
| Mahler et al[75] (2017) | III for Q2 | Secondary analysis of RCT conducted in the US at a single academic ED | Test characteristics of various troponin measures were analyzed from existing RCT data | No difference in test characteristics with cTnI or high-sensitivity troponin I; 100% sensitivity and NPV for both | Small sample size; N=133; secondary analysis was not powered for comparison of different troponin test characteristics |
| Mahler et al[76] (2013) | III for Q2 | Secondary analysis of prospective study conducted in the US at 18 sites | Comparison of HEART score with NACPR score; outcome: early discharge rate and sensitivity for ACS | NACPR identified 4.4% for early discharge with 100% sensitivity and HEART score identified 20% with 99% sensitivity | Secondary analysis of data where NACPR and HEART scores were not calculated in the original study |
| Marcoon et al[77] (2013) | III for Q2 | Secondary analysis of prospective study of ED patients with suspected ACS | Further risk stratified patients with TIMI score of 0 or 1, using the HEART score to achieve 30-day MACE of <1% | Application of HEART score identified lower-risk cohorts; HEART score of 0 among patients with TIMI of 0 had <1% risk for MACE | HEART score was calculated based on secondary analysis data |
| Goodacre et al[78] (2011) | III for Q2 | Randomized trial in 6 hospitals in the United Kingdom | Assessment of patients with suspected ACS using point-of-care cardiac biomarkers at 0 and 90 min; outcome: discharge home within 4 h and no MACE at 3 mo | Increased rate of successful discharge when point-of-care biomarkers used (32% versus 13%) | Not powered to detect difference in adverse event rate |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Mokhtari et al[79] (2016) | III for Q2 | Prospective observational study in the ED | Application of a single high-sensitivity troponin test in combination with history and ECG; outcome: 30-day MACE | Cutoff of 5 ng/L for high-sensitivity troponin T resulted in sensitivity of 99.2% and cutoff of 14 ng/L resulted in sensitivity of 92% | Single center with convenience sample |
| Body et al[80] (2016) | III for Q2 | Prospective cohort study at 12 sites in 9 countries | External validation that a single high-sensitivity troponin T test and normal ECG result could rule out acute MI; outcome: 30-day MACE | Among the 36.7% of patients who had no ischemia on ECG and high-sensitivity troponin result below the level of detection, sensitivity was 99.1% for acute MI | Convenience sample |
| Carlton et al[81] (2016) | III for Q2 | Prospective observational cohort at 5 centers in 3 countries | Application of a single high-sensitivity troponin test in combination with nonischemic ECG result; outcome: 30-day MACE | Single troponin result below level of detection resulted in a sensitivity for acute MI of 99% | Classification of MI based on available troponin assays (non-high sensitivity) |
| Flaws et al[82] (2016) | III for Q2 | Retrospective validation study | EDACS-ADP protocol applied to a North American population; outcome: 30-day MACE | EDACS-ADP classified 41.6% of patients as low risk, with 100% sensitivity for MACE | Retrospective study design |
| Lindahl et al[83] (2017) | III for Q2 | Cross-sectional study with derivation and validation of ACS algorithm in 2 separate international cohorts | Algorithm using a high-sensitivity troponin I test at 0 and 2 h was derived and validated; outcome: 30-day MACE | Algorithm ruled out 54.6% of patients for MI after 2 h with a sensitivity of 97.7% | Algorithms were retrospectively applied and not used for clinical decisionmaking |
| Ong et al[84] (2017) | III for Q2 | Secondary analysis of Asian patients with suspected ACS at a single ED in Singapore | Application of the Vancouver Chest Pain Rule in Asian patients; outcome: 30-day MACE | Sensitivity for MACE was 78% when Vancouver Chest Pain Rule was applied to an Asian cohort | Vancouver Chest Pain Rule was applied retrospectively to prospectively collected data |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Lim et al[87] (2013) | II for Q3 | Prospective RCT; single academic hospital | Patients ≥25 y who presented to ED with acute chest pain and with nondiagnostic ECG result; randomized to stress myocardial perfusion imaging after a negative 6-h observation result versus clinical assessment; outcome: 30-day cardiac events, defined as cardiac-related death, ventricular fibrillation, MI, cardiogenic shock, acute pulmonary edema requiring endotracheal intubation, or significant coronary artery disease | N=1,690 (1,126 intervention; 564 to control); of 1,126, 1,004 completed 6-h observation and underwent stress myocardial perfusion imaging, with outcome prevalence of 0.4%; of 564, 504 completed 6-h observation and underwent disposition based on clinical assessment, with outcome prevalence of 0.8%; sensitivity and specificity of stress myocardial perfusion imaging 85% (95% CI 70% to 94%) and 93% (95% CI 92% to 95%); LR+ 13 (95% CI 10 to 17); LR- 0.2 (95% CI 0.08 to 0.3); sensitivity and specificity of clinical assessment 58% (95% CI 36% to 77%) and 84% (95% CI 80% to 87%); LR+ 4 (95% CI 2 to 6); LR- 0.5 (95% CI 0.3 to 0.9) | Unblinded; outcomes objective |
| Poon et al[88] (2013) | III for Q3 | Secondary analysis of 2 retrospective risk-matched cohorts; single ED | Compared risk-matched cohorts who presented to the ED for chest pain and received either standard care or CCTA; outcome: 30-day MACE | N=1,788; no deaths in either group; acute MI: 6 (1%) in standard group and 3 (<1%) in CCTA group but all occurred on index visit (so really zero in subsequent 30 days); revascularization: 23 (3%) standard group versus 19 (2%) in CCTA group | |
| Frisoli et al[89] (2017) | III for Q3 | Prospective randomized trial at 2 academic EDs | ED patients with symptoms suspicious for AMI had AMI excluded based on 2 negative troponin results >3 h apart and modified HEART score ≤3 randomized to early discharge without cardiac testing versus admission to an observation unit for cardiac testing; outcome: 30-day charges and length of stay | N=105; no MACE in either group; patients in early discharge had lower charges and length of stay | Single health care system; small sample size; selection bias; primary end-point, charges |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Montalescot et al[99] (2013) | I for Q4 | Multicenter, randomized, double blind, placebo-controlled trial | NSTE ACS, were scheduled to receive angiography and possible PCI 2 to 48 h after admission; randomized to pretreatment with prasugrel (before PCI) or placebo and then prasugrel if PCI was indicated after angiography; outcome composite of death from cardiovascular causes, MI, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue through day 7 | N=4,033; no evidence for reduction in the rate of major ischemic events up to 30 days, HR=1.02 (95% CI 0.84 to 1.25; *P*=.81); increased major bleeding at day 7: HR=1.90 (95% CI 1.19 to 3.02) and at 30 days, HR=1.97 (95% CI 1.26 to 3.08) | Suggests P2Y antagonists can be given after coronary angiography and not in the ED |
| Yusuf et al[100](2001) | I for Q4 | Multicenter, randomized double blind, placebo-controlled trial | Patients with NSTE ACS randomized to clopidogrel versus placebo (all received aspirin); outcomes: composite of death from cardiovascular causes, nonfatal MI, or stroke; composite of first primary outcome or refractory ischemia; secondary outcome: refractory ischemia, heart failure, need for revascularization, assessed at 1 and 3 mo | N=12,562; the rate of the first primary outcome was lower in the clopidogrel group within the first 30 days after randomization RR=0.8 (95% CI 0.7 to 0.9) | |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Simoons et al, GUSTO IV-ACS Investigators[101] (2001) | I for Q4 | Multicenter, international, randomized, placebo-controlled trial | NSTEMI or unstable angina without planned early revascularization allocated to: abciximab for 24 h + 24 h placebo, abciximab for 48 h, placebo for 48 h;<br>primary outcome: 30-day outcome of all-cause death or MI;<br>secondary outcome: 30-day MACE | N=7,800; abciximab for 24 h versus placebo: OR 1.0 (95% CI 0.83 to 1.2);<br>abciximab for 48 h versus placebo: OR 1.1 (95% CI 0.94 to 1.4); no significant difference in 30-day MACE | In subgroup analysis, effect was similar in patients with NSTEMI and unstable angina |
| Stone et al[102] (2007) | II for Q4 | Prospective, randomized, controlled trial; 450 academic and community EDs | Patients with unstable angina with ST-segment changes (not elevation) and/or troponin increase; randomized to routine upstream versus deferred selective glycoprotein IIb/IIIa inhibitor;<br>outcome: MACE at 30 days | N=9,207; time to randomization from admission: routine upstream 6.6 h; deferred selective 10.6 h;<br>no difference for 30-day MACE, but less 30-day bleeding in the deferred group | Secondary analysis of previous study |

**Evidentiary Table (continued).**

| Study & Year Published | Class of Evidence | Setting & Study Design | Methods & Outcome Measures | Results | Limitations & Comments |
|---|---|---|---|---|---|
| Giugliano et al[103] (2009) | II for Q4 | Prospective randomized, double-blind, clinical trial | Patients at high risk for ACS without ST-segment elevation, but with plan for invasive evaluation and possible treatment, were randomly allocated to early eptifibatide versus placebo, both with provisional administration of eptifibatide after angiography but before PCI; primary outcome: 96 h-MACE; secondary outcome: 30-day death or MI | N=9,492; primary outcome occurred in 9% of patients in the early eptifibatide group versus 10% in the delayed group, OR 0.9 (95% CI 0.8 to 1.1; *P*=.20); secondary outcome occurred in 11% of the early group and 12% of the delayed group, OR 0.9 (95% CI 0.8 to 1.0; *P*=.08); patients in the early group had a significantly higher rate of bleeding and transfusion requirement (3% versus 2%) OR 1.4 (95% CI 1.1 to 1.9; *P*=.02) | Patients could be randomized up to 12 h after presentation, calling into question whether administration of the study drug should be considered "immediate"; large imbalance in the treatment protocols in the US versus non-US sites, making it difficult to assess effects in the US |

*ACI-TIPI*, Acute Coronary Insufficiency-Time Insensitive Predictive Instrument; *ACRIN*, American College of Radiology Imaging Network; *ACS*, acute coronary syndrome; *ADP*, accelerated diagnostic protocol; *ASPECT*, ASia-Pacific Evaluation of Chest pain Trial; *AUC*, area under the curve; *CABG*, coronary artery bypass graft; *CCTA*, coronary computed tomography angiography; *CI*, confidence interval; *CK-MB*, creatine kinase MB; *cTnI*, cardiac troponin I; *cTnT*, cardiac troponin T; *ECG*, electrocardiogram; *ED*, emergency department; *EDACS*, Emergency Department Assessment of Chest pain Score; *GRACE*, Global Registry of Acute Coronary Events; *GUSTO*, Global Use of Strategies to Open Occluded Coronary Arteries; *h*, hour; *HEART*, History, ECG, Age, Risk factors and Troponin; *h-FABP*, heart-type fatty acid binding protein; *HR*, hazard ratio; *LR*, likelihood ratio; *MACE*, major adverse cardiac event; *MACS*, Manchester Acute Coronary Syndromes; *MI*, myocardial infarction; *min*, minute; *mo*, month; *NACPR*, North American Chest Pain Rule; *NHFA/CSANZ*, National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand; *NPV*, negative predictive value; *NSTE*, non–ST-elevation; *OR*, odds ratio; *PCI*, percutaneous coronary intervention; *PPV*, positive predictive value; *PURSUIT*, Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; *RATPAC*, Randomized Assessment of Triage using Point-of-care Assay of Cardiac markers; *RCT*, randomized controlled trial; *RR*, relative risk; *TIMI*, thrombolysis in myocardial infarction; *TnI,* troponin I; *US*, United States; *y*, year.