Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients with Non–ST-Segment Elevation Acute Coronary Syndromes

From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Non–ST-Segment Elevation Acute Coronary Syndromes:

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This clinical policy focuses on critical issues in the evaluation and management of patients with non–ST-segment elevation acute coronary syndromes. A writing subcommittee knowledgeable in acute coronary syndromes-related literature selected 4 areas of current interest and/or controversy:

1. Are serial ECGs useful during the emergency department (ED) evaluation of patients with suspected acute coronary syndromes?

2. Is there a preferred regimen of serum marker testing in the ED for the exclusion of non–ST-segment elevation acute myocardial infarction?
3. What are the indications for ED administration of glycoprotein IIb/IIIa inhibitors in patients with non–ST-segment elevation acute coronary syndromes?
4. What are the indications for ED administration of clopidogrel in patients with non–ST-segment elevation acute coronary syndromes?

MEDLINE searches were performed to select appropriate literature for inclusion. Subcommittee members and expert peer reviewers also supplied articles with direct bearing on this policy. Articles included in this policy were graded on the basis of a predetermined formula taking into account design and quality of the study. Recommendations for patient management are provided for each 1 of these 4 topics based on strength of evidence (Level A, B, or C). Level A recommendations represent patient management principles that reflect a high degree of clinical certainty; Level B recommendations represent patient management principles that reflect moderate clinical certainty; and Level C recommendations represent other patient management strategies based on preliminary, inconclusive, or conflicting evidence, or based on panel consensus. This guideline is intended for physicians working in hospital-based EDs or chest pain evaluation units.

INTRODUCTION

Patients with chest pain and other symptoms suggestive of acute coronary syndromes are among the most common reasons for which patients seek emergency department (ED) care. The etiologies for these symptoms range from minor disease processes such as chest wall strain, bronchitis, or indigestion to life-threatening conditions such as acute myocardial infarction (AMI), pulmonary embolism, or aortic dissection. Not only does missing a life-threatening condition result in potential serious morbidity and mortality to the patient, but this represents a frequent cause of malpractice suits against emergency physicians and the most dollars awarded.[1,2] For these reasons, the American College of Emergency Physicians (ACEP) chose chest pain as the topic of the first clinical policy that was published in 1990,[3] and revised in 1995.[4]

Over the last decade there has been an exponential growth in published research and development of new diagnostic modalities and therapies relating to evaluation and treatment of patients with acute coronary syndromes. These newer diagnostic and therapeutic modalities are being developed at a pace that far exceeds the ability of one physician to keep track. This current policy represents the first part of a 2 part revision of the 2000 ACEP clinical policy on AMI and unstable angina.[5] The second part will focus on critical issues in reperfusion therapy in patients with ST-segment elevation AMI. This policy focuses on critical issues in patients with non–ST-segment elevation acute coronary syndromes. This clinical policy was created after careful review and critical analysis of the peer-reviewed literature. A writing subcommittee knowledgeable in acute

coronary syndromes-related literature was selected to review the 2000 ACEP clinical policy[5] and other recent acute coronary syndromes clinical guidelines[6,7] in order to select key areas on which to focus this current policy. Four critical questions of current interest and/or controversy were chosen by the subcommittee:

1. Are serial ECGs useful during the ED evaluation of patients with suspected acute coronary syndromes?
2. Is there a preferred regimen of serum marker testing in the ED for the exclusion of non–ST-segment elevation AMI?
3. What are the indications for ED administration of glycoprotein IIb/IIIa inhibitors in patients with non–ST-segment elevation acute coronary syndromes?
4. What are the indications for ED administration of clopidogrel in patients with non–ST-segment elevation acute coronary syndromes?

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. Multiple MEDLINE searches were done. The medical literature was reviewed for articles that pertained to each critical question posed, and pertinent articles were selected. Those articles were evaluated, and those addressing the questions considered in this document were chosen for grading. Subcommittee members also supplied articles from bibliographies of initially selected articles or from their own files.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.[8] This policy is a product of the ACEP clinical policy development process and is based on the existing literature; where literature was not available, consensus of emergency physicians was used. Expert review comments were received from individual emergency physicians and individual members of the American College of Cardiology, the Emergency Medicine Cardiac Research and Education Group, and the Society of Chest Pain Centers. Their responses were used to further refine and enhance this policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly.

All articles used in the formulation of this clinical policy were graded by at least 2 subcommittee members for strength of evidence and classified by the subcommittee members into 3 classes of evidence on the basis of the design of the study, with design 1 representing the strongest evidence and design 3 representing the weakest evidence for therapeutic, diagnostic, and prognostic clinical reports respectively (Appendix A). Articles were then graded on 6 dimensions thought to be most relevant to the development of a clinical guideline: blinded versus nonblinded outcome assessment, blinded or randomized allocation, direct or indirect outcome measures (reliability and validity), biases (eg, selection, detection, transfer), external validity (ie, generalizability), and sufficient sample size. Articles received a final grade (I,

II, III) on the basis of a predetermined formula taking into account design and quality of study (Appendix B). Articles with fatal flaws were given an "X" grade and not used in the creation of this policy. Evidence grading was done with respect to the specific data being extracted, and the specific critical question being reviewed. Thus, the level of evidence for any one study may vary according to the question, and it is possible for a single article to receive different levels of grading as different critical questions are answered. Question-specific level of evidence grading may be found in the Evidentiary Table included at the end of this policy.

Clinical findings and strength of recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on strength of evidence Class I or overwhelming evidence from strength of evidence Class II studies that directly address all the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies).

Level C recommendations. Other strategies for patient management that are based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus.

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 heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs, and publication bias, among others, might lead to such a downgrading of recommendations.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. ACEP clearly recognizes the importance of the individual physician's judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the crucial questions addressed in this policy.

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

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with suspected non–ST-segment elevation acute coronary syndromes.

Exclusion Criteria. This guideline is not intended for pediatric patients, patients in cardiogenic shock, or patients with injury on the initial 12-lead electrocardiogram (ECG).

CRITICAL QUESTIONS

1. Are serial ECGs useful during the ED evaluation of patients with suspected acute coronary syndromes?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Perform repeat ECG or automated serial ECGs during the ED evaluation of patients in whom the initial ECG is nondiagnostic for injury and who have symptoms consistent with ongoing or recurrent ischemia.

No recommendations can be made in regards to the exact timing of repeat ECGs. Studies suggest that 30 to 60 minutes after baseline may be a reasonable time interval for repeat ECG.

Level C recommendations. None specified.

Early identification of patients with acute coronary syndromes, defined as AMI and unstable angina in the ED, is of paramount importance. However, establishing this diagnosis is often challenging, as patients' symptoms may be atypical in nature and the initial ECG in patients with AMI can be normal or nondiagnostic up to 55% of the time.[9] Complicating matters further is a mounting body of evidence indicating that ST-segment depression or elevation is frequently an unstable phenomenon in the early stages of AMI and unstable angina.[10,11] Thus, a single ECG represents a "snapshot" of what is actually a dynamic process, and may happen to be obtained at a moment when the ST-segment changes are nondiagnostic. Instability of ST-segments in patients with ongoing cardiac ischemia, as well as the potential for evolving changes, is the theoretical basis for the implementation of automated serial 12-lead ECG. There are currently several automated serial 12-lead ECG monitors on the market and most share the following features: (1) the ability to continuously monitor ST-segment trends in the standard 12-leads, (2) storage of ECGs at a predetermined interval (generally every 20 minutes or less), (3) frequent computer analysis of the ECGs (generally at intervals of less than or equal to 2 minutes), (4) the ability of the computer analysis to detect changes in ST-segment elevation or depression from an initial baseline reading, and (5) alarms to notify the clinician of ST-segment variability meeting preset criteria. Current serial 12-lead ECG monitors do not include T-wave morphology analysis and some have limited analysis of QRS area trends. Although the use of automated serial 12-lead ECG systems has the principal advantage of being nearly continuous, some of the same potential benefits may be reaped by routinely obtaining conventional serial 12-lead ECGs in chest pain patients with possible acute coronary syndromes at select time intervals after presentation to the ED.

In AMI patients receiving fibrinolytic therapy, automated serial 12-lead ECG or a repeat ECG at 60 to 180 minutes has been shown to be predictive of successful reperfusion and is used to alert clinicians to patients in whom reperfusion therapy is failing.[12-16] Automated serial 12-lead ECG monitoring also has been shown to have prognostic value in detecting complications after coronary artery bypass graft surgery, as well

as detecting episodes of silent ischemia in critical care unit patients.[17,18] Silent myocardial ischemia has been found to occur frequently in patients with unstable angina and has been shown to be a marker for unfavorable outcomes including death.[19-21] In a British study of 212 critical care unit patients that used serial 12-lead ECG monitoring for the first 48 hours of hospitalization, Patel et al[22] found that transient ST-segment changes predicted an increased risk of AMI or death. No patients with a normal ECG and without changes on serial 12-lead ECG monitoring died or had an AMI. More recently, a study of routine monitoring versus automated serial 12-lead ECGs in an intensive care unit setting found that routine monitoring failed to identify 12 patients with ischemic changes identified by serial 12-lead ECGs.[23]

Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines for ST-segment elevation AMI recommend as a Class I consensus recommendation (level of evidence C), serial ECGs at 5 to 10 minute intervals or continuous 12-lead ST-segment monitoring in patients with initial ECG nondiagnostic of injury but the patient has ongoing symptoms with high clinical suspicion for AMI .[7] To investigate utility of serial ECG in clinical practice, the ACEP Clinical Policies Subcommittee performed a MEDLINE search utilizing the following key words/phrases in combination with serial ECG or ST-segment monitoring: "myocardial infarction," "unstable angina," and "acute coronary syndromes," in order to determine the usefulness of serial ECGs in the ED. A review of potentially relevant abstracts was performed and chosen papers were subsequently graded by ACEP criteria according to the weight of evidence as it applies to this critical question. Only clinical studies that directly or indirectly investigated the utility of serial ECGs in the ED are listed in the Evidentiary Table. In the following section we will investigate clinical investigations in the use of serial 12-lead ECG or repeat ECG in the initial evaluation of patients with suspected acute coronary syndromes.

Clinical Investigations

Two studies evaluating the benefit of obtaining a second routine ECG on ED patients with possible acute coronary syndromes have been conducted.[24,25] Hedges et al[24] conducted a multicenter prospective observational study comparing 2 ECGs with serial creatine kinase-MB (CK-MB) in 261 patients with possible acute coronary syndromes. They found a repeat ECG at 3 to 4 hours had a 39% sensitivity and 88% specificity for AMI, and 25% sensitivity and 92% specificity for acute coronary syndromes. The study found that combining serial CK-MB with a repeat ECG was more sensitive and specific than either used alone. A second multicenter study of similar design enrolled 1,055 patients for serial cardiac markers and a second ECG. They reported that the second ECG diagnosed an additional 3% of myocardial infarction patients not diagnosed by the initial ECG and serial cardiac markers.[25]

Research in automated serial 12-lead ECG monitoring in the ED setting is limited. Fesmire et al[26] reported on 1,000 admitted chest pain patients (204 AMI patients, 295 unstable angina) who underwent serial 12-lead ECG monitoring during the initial ED evaluation. The study objective was to determine whether the use of serial 12-lead ECG monitoring was more sensitive and specific than a single 12-lead ECG in the detection of injury and ischemia in patients with acute coronary syndromes. The initial ECG was obtained on average 17 minutes after arrival in the ED, and the serial 12-lead ECG monitoring was initiated 46 minutes after arrival to the ED. The mean duration of serial 12-lead ECG monitoring was 128 minutes ±41 minutes. This study found serial 12-lead ECG monitoring was more sensitive and specific than the initial ECG for detection of AMI and acute coronary syndromes. Perhaps most importantly, serial 12-lead ECG detected injury in an additional 16.2% of AMI patients, which represented a relative increase of 34% in patients eligible for emergency reperfusion therapy. Also, when compared with patients who had no changes on their serial 12-lead ECG, those patients with diagnostic changes on serial 12-lead ECG had a 2.5 times greater risk of acute coronary syndromes, a 4.9 times greater risk of percutaneous transluminal coronary angioplasty/coronary artery bypass graft, a 9.6 times greater risk of life-threatening complications, and a 12.3 times greater risk of death.

Two studies have investigated utility of serial 12-lead ECG in various cardiac risk groups. Fesmire reported on 678 chest pain patients evaluated in an ED who had serial 12-lead ECG applied. He found that 14.6% of high-risk patients and 1.1% of low-risk patients had a change in therapy based on the serial 12-lead ECG findings.[27] Decker et al[28] reported on the use of automated serial 12-lead ECG in a low-to-intermediate risk chest pain unit population and found the application of this technology to be of little incremental benefit in this patient population. In a prospective observational study of 2,074 patients presenting to the ED with chest pain, Fesmire and colleagues[29] found serial 12-lead ECG modestly improved the incremental value of a multistep prognostic algorithm for chest pain patients in the ED. In a multicenter study, small variations of ST-segment shift in the first 4 hours of AMI were correlated with worse outcomes.[30]

In a retrospective study, Gibler et al[31] described 1,010 low-risk chest pain patients in whom serial 12-lead ECG monitoring was used as part of their chest pain unit evaluation protocol. In this study, only 11 patients were found to have evidence of ischemia or evolving AMI on serial 12-lead ECG. However, this was a population with a low prevalence of disease as evidenced by 43 of 1,010 patients ultimately being discharged with a diagnosis of acute coronary syndromes (12 AMI, 31 angina). Gibler et al[32] also reported on serial 12-lead ECG monitoring in 86 admitted patients who underwent serial 12-lead ECG monitoring during the ED evaluation. Of the 86 patients admitted, 18 (20.9%) were discharged with a cardiac-related diagnosis. Seven of those 18 patients had suggested abnormalities on serial 12-lead ECG monitoring. However, an additional 10 of the 86 patients had findings suggestive of unstable angina or AMI but were ultimately discharged with a

noncardiac diagnosis. Finally, a number of case reports demonstrate various aspects of the potential value of serial 12-lead ECG monitoring in the ED including diagnosis of AMI in the presence of left bundle branch block (LBBB).[9,10,33]

2. Is there a preferred regimen of serum marker testing in the ED for the exclusion of non–ST-segment elevation AMI?

Inclusion Criteria. Patients with symptoms suggestive of acute coronary syndromes presenting less than or equal to 12 hours of symptom onset.

Patient Management Recommendations

Level A recommendations. Do not utilize cardiac serum marker tests to exclude non-AMI acute coronary syndromes (ie, unstable angina).

Level B recommendations. Utilize any of the following cardiac serum marker tests to exclude non–ST-segment elevation AMI as defined by the World Health Organization (WHO) or modified WHO criteria (Figure 1):*

1. A single negative CK-MB mass, Troponin I, or Troponin T measured 8 to 12[†] hours after symptom onset.[‡]
2. A negative myoglobin in conjunction with a negative CK-MB mass, or negative Troponin[§] when measured at baseline and 90 minutes in patients presenting less than 8 hours after symptom onset.[‡]
3. A negative 2-hour delta[‖] CK-MB mass in conjunction with a negative 2-hour delta[‖] Troponin[§] in patients presenting less than 8 hours after symptom onset.[‡]

Level C recommendations. None specified.

*There is insufficient evidence at this time to make any recommendations in regards to utilization of cardiac serum markers to exclude non–ST-segment elevation AMI using current Joint European Society of Cardiology(ESC)/ACC criteria for AMI (Figure 2).

†The exact timing of serum marker measurement as it relates to time of symptom onset should take into account the sensitivity, precision, and institutional norms of the assay being utilized, as well as the release kinetics of the marker being measured.

‡If time of symptom onset is unknown, unreliable, or more consistent with preinfarctional angina, then time of symptom onset should be referenced to the time of ED presentation.

§Only Troponin I has been investigated in the serial 90 minute multimarker protocol and the 2-hour delta protocol.

‖The appropriate delta values for exclusion of AMI should take into account the sensitivity and precision of the assay utilized and confirmed by in-house studies. It is also important that delta serum marker levels are measured on the same instrument due to subtle variations in calibration among individual instruments of the same model.

This section of the clinical policy is directed at the early exclusion of non–ST-segment elevation AMI in the ED setting. The exclusion of AMI is important in that one may consider immediate stress testing, admit for inpatient stress testing and/or coronary arteriogram, pursue an alternate diagnosis (eg, pulmonary embolism, aortic dissection), or discharge the patient home if no serious medical condition is thought to exist. Many medical centers have developed chest pain observation or

clinical decision units that can aid in the performance of extended diagnostic workups. Unfortunately, these resources are not universally available to all practicing emergency physicians. In order to generalize this policy for all types of EDs in the United States, some assumptions must be made about the ED length of stay for a patient with a complex medical problem or a diagnostic dilemma. For the purpose of this discussion, a length of stay of approximately 4 hours will be used for the ED length of stay. Using this parameter, the discussion will focus on serum marker performance characteristics and regimens that can be completed in this approximate time frame. Elevations in serum troponins and C-reactive protein (CRP) have been demonstrated to be predictive of long-term adverse cardiac events in ED patients under evaluation for possible ischemic symptoms[34,35] and B-type natriuretic peptide elevations have been shown to predict higher rates of morbidity and mortality

WHO Diagnostic Criteria for Acute Myocardial Infarction (One of following):

1. Definite ECG*, or
2. Symptoms† typical or atypical or inadequately described, together with probable ECG‡ and abnormal enzymes§, or
3. Symptoms typical† and abnormal enzymes§ with ischemic or noncodable ECG or ECG not available, or
4. Fatal case, whether sudden or not, with naked-eye appearance of fresh myocardial infarction and/or recent coronary occlusion found at necropsy.

*Definite ECG:
a) The development in serial records of a diagnostic Q wave and/or
b) The evolution of an injury current that lasts more than 1 day.

†Duration of more than 20 minutes

‡Probable ECG: Evolution of major ST-elevation, major ST-depression, and/or major T-wave inversion

§Abnormal enzymes: if at least one reading is more that twice the upper limit of normal

Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, et al. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation.* 1994;90:583-612. Reprinted with permission.

Figure 1. WHO diagnostic criteria for acute myocardial infarction.

in patients with AMI.[36] These applications of serum marker testing, however, are outside the scope of this policy.

Additionally, the use of LDH isoenzymes and CK-MB activity testing has become archaic and the use of CK-MB isoforms is increasingly uncommon,[37] therefore these markers will not be discussed further. This discussion focuses around the use of myoglobin, CK-MB mass (henceforth referred to as CK-MB), cardiac troponin I (cTnI), and cardiac troponin T (cTnT) for the exclusion of AMI. The ACEP Clinical Policies Subcommittee performed a MEDLINE search from 1985 through 2004 using the following key word/phrases in combination with myocardial infarction: "creatine kinase," "myoglobin," and "troponin." The subcommittee also reviewed current guidelines from the ACC/AHA, National Academy of Clinical Biochemistry, and other organizations for the use of cardiac markers in patients with suspected AMI. A review of potentially relevant abstracts was performed and chosen papers were subsequently graded by ACEP criteria according to the weight of evidence as it applies to this critical question. Only clinical studies that directly or indirectly investigated exclusion of AMI are listed in the Evidentiary Table with emphasis on studies with greater than or equal to 50 AMI patients.

Analytical Issues with Serum Markers

Each serum marker has a defined reference range, lower detection limit, and diagnostic cutoff. Ideally, these values must be determined in rigorous clinical studies comparing the new assays with a criterion standard test. In the case of the newer markers, the National Academy of Clinical Biochemistry has suggested that the reference range should set the upper limit of normal at the 99th percentile for the normal healthy population. Thus by definition, at least 1% of all people undergoing testing will have elevated serum troponin above the reference range. In reporting results, it has been recommended that the lower detection limit be set at the level at which a 10% coefficient of variation is maintained. Below this 10% coefficient of variation range, the results must be considered unreliable.[38,39] Once the reference ranges and lower detection limits are determined, diagnostic cutoff levels are best determined through clinical studies that construct receiver operating characteristic (ROC) curves to determine an optimal value based on analysis of sensitivity, specificity, and clinically meaningful likelihood ratios for the identification and/or exclusion of AMI. Methodologically, CK-MB and myoglobin assays are fairly similar from laboratory to laboratory, but there are no internationally standardized reference ranges for all assays. Interestingly, troponin assays utilize proprietary antibodies that bind to various epitopes of the troponin molecules and complexes of molecules. Because of this intrinsic variation in troponin assays, the reported results yielded by 2 different manufacturers' assays when testing aliquots of blood from the same sample may vary widely. Furthermore, the diagnostic cutoffs supplied by the manufacturers of troponin assays for AMI are frequently an order of magnitude higher than the upper end of the reference range, leaving a wide "gray-area"

Table 1. Recommended cutoff values for current commercial assays for acute myocardial infarction utilizing ESC/ACC criteria for redefinition of acute myocardial infarction.

Manufacturer/Assay	Generation	99th Percentile	Recommended Cutoff*
Troponin I Assays			
Abbott AxSYM	1st	0.5 ng/ml	0.8 ng/ml
Bayer Immuno 1	1st	0.1 ng/ml	0.35 ng/ml
Bayer ACS: 180	1st	0.1 ng/ml	0.35 ng/ml
Bayer Centaur	1st	0.1 ng/ml	0.35 ng/ml
Beckman-Coulter Access	2nd	0.04 ng/ml	0.06 ng/ml
Biosite Triage	1st	<0.19 ng/ml	0.5 ng/ml
Dade Behring Dimension RxL	2nd	0.07 ng/ml	0.14 ng/ml
Dade Behring Stratus CS	2nd	0.07 ng/ml	0.06 ng/ml
Dade Behring Opus/ OpusPlus	1st	0.1 ng/ml	0.3 ng/ml
DPC Immulite	1st	0.2 ng/ml	0.6 ng/ml
DPC Immulite Turbo	1st	<0.05 ng/ml	0.6 ng/ml
First Medical Alpha Dx	1st	0.15 ng/ml	0.3 ng/ml
i-STAT	1st	0.08 ng/ml	0.1 ng/ml
Ortho Vitros ECi	1st	0.08 ng/ml	0.12 ng/ml
Tosoh AIA	2nd	<0.06 ng/ml	0.06 ng/ml
Troponin T Assay			
Roche Elecsys	3rd	0.01 ng/ml	0.035 ng/ml

Modified from Apple FS, Wu AHB, Jaffe AS. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: How to use existing assays clinically and for clinical trials. *Am Heart J.* 2002;144:981-986. Reprinted with permission.
*Lowest cutoff value above 99% in which the assay imprecision is <10%.

of diagnostic uncertainty when evaluating results from a single sample of patient's blood. It is critical that the emergency physician knows and understands the reference ranges and diagnostic cutoffs for the cardiac marker assays used in each of his or her clinical sites. Lastly, over the past 12 years at least 3 "generations" of cTnT and cTnT assays have been released. Each generation appears to have gained sensitivity and specificity; therefore, studies reviewed for this policy may report lower predictive values than are obtainable with today's tests. Table 1 lists the 99th percentile of the most commonly available troponin assays as well as lowest cutoff above the 99th percentile with 10% coefficient of variation.[38]

Study Design Issues

When evaluating the available data on serum markers for the diagnosis of AMI, a number of issues arise that affect the quality of the evidence. First and foremost is the variability in the definition of AMI used in each study. The vast majority of published cardiac marker studies have used some variant of the WHO definition of AMI (Figure 1),[40] but they are far from uniform and may lack specificity. In 2000, the ESC and ACC published new guidelines for the definition of AMI with a diagnostic requirement for elevated cardiac markers in the absence of pathological findings of AMI (Figure 2).[41] The guidelines further recommend that the cutoff value for CK-MB

ESC/ACC Diagnostic Criteria for Acute Myocardial Infarction (One of following criteria):

1. Typical rise and gradual fall (troponin*) or more rapid rise and fall (CK-MB*) of biochemical markers of myocardial necrosis with at least one of the following:
   a. ischemic symptoms;
   b. development of pathologic Q waves on the ECG;
   c. ECG changes indicative of ischemia; or
   d. coronary artery intervention.

2. Pathological findings of acute myocardial infarction.

*An increased value for cardiac troponin or CK-MB should be defined as a value that exceeds the 99th percentile in a reference control group. In most situations, elevated values for biomarkers should be recorded from two successive blood samples to diagnose MI. Cardiac troponins are the preferred biomarker for myocardial damage.

Alpert JS, Thygesen K, Antman E, et al. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined – a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959-969. Reprinted with permission from the American College of Cardiology Foundation.

Figure 2. ESC/ACC diagnostic criteria for acute myocardial infarction.

Figure 3. Timing of release of common cardiac markers of necrosis. Peaks A, B, and C respectively demonstrate release of myoglobin, troponin, and CK-MB in acute myocardial infarction as defined by WHO diagnostic criteria. Peak D demonstrates troponin release in troponin positive/CK-MB negative acute coronary syndrome now defined as acute myocardial infarction by ESC/ACC diagnostic criteria.

Modified from Wu AHB, Apple FS, Gibler WB, et al. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery disease. *Clin Chem.* 1999;45:1104-1121. Reprinted with permission.

or troponin should be defined as the 99th percentile in a reference control group with cardiac troponin being the preferred biomarker. Surprisingly, this committee was unable to find any relevant cardiac marker studies that utilized the 99th percentile as the cutoff value. Furthermore, many of the studies reviewed defined AMI using circular definitions incorporating the very marker they are attempting to characterize resulting in significant incorporation bias.

The population of patients studied can have a drastic effect on patterns of cardiac marker elevations observed. Differences among patient populations studied (eg, ED versus critical care unit patients) can make the comparison of studies and pooling of data inappropriate. As this guideline applies to the ED use of cardiac markers, only those works studying ED patients were used in formulation of patient management recommendations. Studies of consecutive patients and prospective evaluations had less potential for selection bias and were assigned more favorable levels of evidence.

The timing of acquisition of the initial blood sample in relation to symptom onset will have a significant effect on the sensitivity of the test for AMI. Theoretically, studies that report results based on the 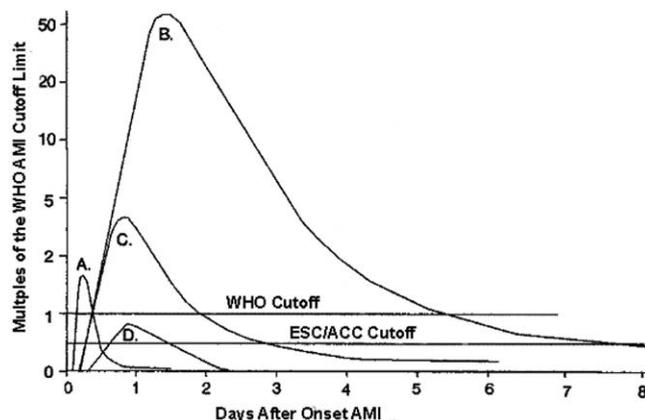timing of sample acquisition should give the most accurate depiction of test sensitivity to myocardial necrosis versus time. However, the subjective nature of patients' time perception and the unreliability of the patients' determination of the constancy of the symptoms (or lack thereof) makes the time of first medical contact (eg, ED arrival time) a more reliable time data point. Ideally, both the time of symptom onset and time of ED arrival should be reported in any study investigating the utility of a particular serum marker or markers. Figure 3 demonstrates the release kinetics of CK-MB, troponin (I or T), and myoglobin as a function of time from symptom onset.

The presence of an adequate patient sample size is critical in evaluating the performance of a serum marker regimen. Many studies on cardiac markers focus on low-risk patient populations that may include large groups of patients with a very small number of AMIs. The effect of this low prevalence is that although high sensitivity can be reported, there are sometimes very wide confidence intervals. For the purpose of this review, we focused our attention on studies that contained at least 50 patients that had the final diagnosis of AMI.

The 2000 ACEP clinical policy on AMI and unstable angina stated that the ideal cardiac serum marker should have a sensitivity and specificity greater than 90% and both reliably identify (positive likelihood ratio $\geq$ 10) and exclude (negative likelihood ratio $\leq$ 0.1) AMI.[5] The identification of AMI (ie, high specificity) is imperative for identification of patients requiring more intensive anti-ischemic therapy. The exclusion of AMI (high sensitivity) is important for selecting patients who may need further evaluation for presence of acute coronary

Table 2. Relationship of reported sensitivities of various serum markers in relationship to time of symptom onset.

Time (h)	CK-MB Mass %	Myoglobin %	cTnT %	cTnI %
0-2	7-49	22-53	11-55	16-47
2-4	12-64	27-84	34-55	36-59
4-6	58-87	55-90	58-73	41-58
6-8	72-94	61-95	78-84	71
8-10	90-98	76-98	87-95	92-93
10-12	97-100	71-98	94-100	88
12-24	89-100	41-66	79-99	83-100

Modified from American College of Emergency Physicians. Clinical Policy: critical issues in the evaluation and management of adult patients presenting with suspected acute myocardial infarction or unstable angina. *Ann Emerg Med.* 2000; 35:521-544. Reprinted with permission.

syndromes (eg, stress testing), evaluation for other potentially life-threatening medical conditions (eg, pulmonary embolism), or can be safely discharged. No single serum marker used alone has sufficient sensitivity or specificity to reliably identify or exclude AMI within 6 hours after symptom onset. Despite this statement, the measurement of CK-MB, cTnI, and/or cTnT at the time of ED presentation is useful because of the significant proportion of patients with delayed presentation to the ED after onset of symptoms. Numerous studies report that the initial sensitivities for AMI of CK-MB range from 14% to 60% and for cTnI or cTnT range from 9% to 65%.[42-56] When measured from time of symptom onset, sensitivities of CK-MB and the troponins for AMI improve in an incremental fashion and exceed 90% by 8 hours of symptom onset and approach 100% by 12 hours.[25,57-66] Table 2 summarizes the relationship of sensitivities of CK-MB, myoglobin, and the troponins in relationship to time of symptom onset. Neither CK-MB nor the troponins have a clear sensitivity advantage for the diagnosis of AMI in the initial 12 hours after symptom onset. Measurements of myoglobin in the first few hours after symptom onset appear to have better sensitivity with lower specificity when compared with CK-MB and the troponins.[45,47,49,52,56,59,64,65,67-69] Samples taken beyond 3 to 4 hours after symptom onset have declining sensitivity and specificity for AMI, and after 6 hours both CK-MB and the troponins are superior to myoglobin.[45,48,53,62,65,70] Because myoglobin has a declining sensitivity after approximately 6 hours of symptom onset, it should never be used alone to exclude AMI. A strong caveat in the 2000 ACEP policy states: *If time of symptom onset is unknown, unreliable, or more consistent with preinfarctional angina, then time of symptom onset should be referenced to the time of ED presentation.*[5]

The serial measurements of CK-MB and/or the cardiac troponins over an 8 to 12 hour period of observation is supported by several studies as a reliable method of identifying and excluding AMI.[43,45,48] Common testing intervals in serial regimens are 3 to 4 hours in duration to make early diagnosis of AMI possible prior to the completion of the entire observation period. Although serum markers

alone approach 100% sensitivity at 8 to 12 hours for AMI depending on cutoff values utilized,[44,45] it is important to recognize that clinical studies investigating the exclusion for AMI in the ED incorporate other technological modalities (eg, serial 12-lead ECG) and clinical decision rules to select low-risk subsets.[31] With proper patient selection, the posttest probability of missing an AMI in one of these low-risk patients after completing a negative 8 to 12 hour serial marker protocol should be significantly less than 1%.

Multimarker Approaches

Several investigators have attempted to demonstrate the reliable exclusion of AMI by combining several serum markers at time of ED presentation and within 3 to 6 hours to create "multimarker" regimens with greater sensitivity for AMI.[50,64,65,70] Combinations of CK-MB and the troponins have not been found to have significantly increased sensitivities, while the combinations of myoglobin with either CK-MB[60,64,65] or the troponins[64,65] have shown promise.

As part of a large study of 6,352 chest pain patients with 814 AMIs, Gibler et al[52] report that myoglobin, CK-MB, or the combination of CK-MB plus myoglobin demonstrated sensitivities for AMI on initial presentation of 64%, 52%, and 72%, respectively with specificities of 90%, 96%, and 88%. In a study of 519 chest pain patients with 76 AMIs, Esses et al[53] studied the combination of myoglobin and CK-MB testing. Myoglobin was measured on presentation, 2, and 6 hours later. CK-MB was measured on presentation, 6, 12, and 18 hours later. Initial sensitivities for myoglobin, CK-MB, or both were 46%, 42%, and 57%, respectively. At 6 hours, these sensitivities increased to 62%, 88%, and 96% with specificities ranging from 92% to 100%.

A study by McCord et al[65] of 817 chest pain patients with 65 AMIs reported on predictive values for combinations of myoglobin with either CK-MB or cTnI at presentation and at 90 minutes. The myoglobin/CK-MB combination yielded sensitivities and specificities of 84% and 70% at presentation and 92% and 68% at 90 minutes. The myoglobin/cTnI combination yielded sensitivities and specificities of 85% and 67% at presentation and 97% and 60% at 90 minutes. The lower specificities compared with other studies were likely due both to low specificity of myoglobin and a CK-MB-based definition of AMI.

The reduced specificity of the multimarker regimens versus the measurement of a later definitive marker obligates the physician to act cautiously when initiating treatment of the AMI at such early time points, and if used without a more lengthy testing protocol, the multimarker approach will predictably result in increased utilization of observation or inpatient resources.

Delta Measurements

Another piece of information available to the clinician when serial markers are measured is the rate of change of those

markers between samples. Also termed "deltas," these incremental changes may exhibit early patterns that are both sensitive and specific for AMI at early (less than or equal to 6 hours for symptom onset) time points in the course of an ED encounter. Newer assays can now reliably detect marker concentrations below the 99th percentile for the general population. Abnormal delta values may include sequential increases within the diagnostic "gray area" between normal levels and the diagnostic cutoff for AMI. The use of delta measurements appears to have predictive value for AMI. This concept has become increasingly important as the various assays continue to have more precision and ever lower detection limits.

Three studies meeting review criteria have specifically investigated algorithms using delta CK-MB for detection of AMI. The earliest publication with an adequate sample size (70 patients with AMI) comes from Marin and Teichman[43] who reported a sensitivity and a specificity of 94% and 91%, respectively, for 2-hour delta CK-MB where a positive test required either the baseline or 2-hour value to be greater than or equal to 5 ng/ml. Young et al[25] conducted a study of 1,042 chest pain patients (67 with AMIs) looking at 3-hour delta CK-MB measurements with a criteria for positivity of any value returning greater than or equal to 8 ng/ml or an interval change of greater than or equal +3 ng/ml. They report 93% sensitivity and 95% specificity for AMI at 3 hours from ED arrival. Sensitivity was significantly lower in the subset of patients with prompt presentation to the ED after symptom onset. Fesmire et al[61] performed baseline and 2-hour CK-MB measurements in 710 patients (113 patients with AMIs) in chest pain patients having negative CK-MB at presentation. Using a threshold of delta CK-MB of +1.6 ng/ml, they described a sensitivity of 92% and specificity of 95% at 2 hours after ED presentation for patients with a mean time to presentation of 108 minutes after symptom onset. In a retrospective study, Fesmire[63] found that a delta 2-hour CK-MB outperformed a delta 2-hour first generation cTnI with sensitivities of 88% and 61%, respectively. Fesmire et al[29] also report on the utility of a delta CK-MB in conjunction with a delta cTnI (first generation assay) in the identification and exclusion of AMI as part of the workup in a comprehensive chest pain evaluation protocol. In this study of 2,074 consecutive chest pain patients (179 AMI patients), the initial ECG in conjunction with baseline serum markers had a sensitivity and specificity for AMI of 58% and 99% respectively. The addition of a positive delta CK-MB and/or delta cTnI increased the sensitivity to 93% with specificity of 94% (+LR 15; −LR 0.07). The delta performance characteristics of the newer troponin assays have yet to be reported except in a small pilot study in which a delta 2-hour cTnI significantly outperformed a delta 2-hour CK-MB in identification of patients with acute coronary syndromes.[71]

Several studies have been performed on the utility of delta myoglobin testing; only 2 met the size criteria for review. Ng et al[68] performed a study on 1,285 chest pain patients (66

with AMIs) using multiple and serial markers. A 90-minute delta myoglobin in this population performed poorly with a sensitivity of 29% and specificity of 98%. These results may have been influenced by the fact that over 50% of the study population presented greater than 6 hrs after symptom onset. In a study of 817 patients (75 with AMIs), Sallach et al[69] in a retrospective analysis of the previously discussed investigation by McCord et al[65] reported 90-minute delta myoglobin sensitivity ranging from 58% to 92% depending on the cutpoints used to determine a change. At the delta cutpoint of +10 ng/ml change in myoglobin between the initial and 90-minute samples, sensitivity was 91.7% with a specificity of 79.7% in patients having initially normal markers. The strength of this evidence is severely limited by the small number of patients in this subset (27 with AMIs).

Fesmire et al,[56] in his most recent study of deltas, directly compared 2-hour delta CK-MB with 2-hour delta myoglobin. Although the study of 975 chest pain patients only included 44 AMIs, it is the only delta study to use a troponin standard similar to the new ESC/ACC AMI definition. A 2-hour delta CK-MB of greater than +0.7 ng/mL was found to have a sensitivity of 93% with specificity of 94% compared with a sensitivity of 77% and specificity of 84% for 2-hour delta myoglobin greater than 9.4 ng/ml.

Finally, the aforementioned study by Ng et al[68] investigated a combined delta myoglobin and multimarker approach using myoglobin, CK-MB, and cTnI. At 90 minutes from ED presentation, they reported 99% sensitivity and 98% specificity for delta myoglobin + cTnI, and 100% sensitivity and 94% specificity for delta myoglobin + cTnI + CK-MB. Delta CK-MB and delta cTnI values were not reported. The high specificity of myoglobin in this report is counter to all previous research on myoglobin and casts doubt on the results of this study.

3. What are the indications for ED administration of glycoprotein IIb/IIIa inhibitors in patients with non–ST-segment elevation acute coronary syndromes?

Exclusion Criteria: Contraindications for a glycoprotein inhibitor (bleeding disorder, renal insufficiency, etc).

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Consider administration of glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, or eptifibatide) prior to percutaneous coronary intervention to patients with positive troponin or ischemic ST-segment depression in whom an early interventional strategy is anticipated.* Studies suggest that benefit is greatest in patients in whom treatment was initiated within 6 hours of symptom onset and in patients in whom there will be a delay in percutaneous coronary intervention.

Level C recommendations. Consider administration of glycoprotein IIb/IIIa inhibitors (tirofiban, or eptifibatide) to patients with positive troponin or ischemic ST-segment depression in whom a *non-interventional* strategy is planned.*

*There is insufficient information at this time to make any recommendations in regards to the exact location or timing for initiation of glycoprotein IIb/IIIa inhibitor therapy (ie, ED versus inhospital).

The common pathway for platelet aggregation and thrombus formation is the crosslinking of platelet glycoprotein IIb/IIIa receptors by fibrinogen molecules. Glycoprotein IIb/IIIa inhibitors block this process by occupying these platelet receptors, thus preventing platelet-to-platelet crosslinking by fibrinogen. This action also promotes stabilization of the ruptured plaque and passivates the epithelium that decreases further adverse cardiac events. Finally, by inducing inhibition of platelet aggregation, these drugs may prevent thrombus formation during percutaneous coronary intervention, thereby attenuating or preventing acute coronary occlusion and embolization of microthrombi to the distal microvasculature.[72]

The ACC/AHA 2002 guidelines for the management of patients with non–ST-segment elevation acute coronary syndromes recommend as a class IA recommendation administration of glycoprotein IIb/IIIa inhibitors in addition to aspirin to patients in whom catheterization and percutaneous coronary intervention are planned.[6] The guidelines also provide a level IIb recommendation for administration of low-molecular weight glycoprotein IIb/IIIa inhibitors (ie, eptifibatide or tirofiban) in addition to aspirin and heparin to high-risk patients (eg, continuing ischemia, elevated troponin) in whom conservative management is planned.[6] Of note, the ACC/AHA guidelines state that the glycoprotein IIb/IIIa inhibitor may be administered "just prior to percutaneous coronary intervention" in patients managed with interventional strategy. This vague comment makes it unclear when such agents should be administered. Specifically should the glycoprotein IIb/IIIa inhibitor be exclusively administered in the cardiac catheterization laboratory by the interventional cardiologist; or should non-invasive cardiologists and/or emergency physicians initiate therapy with glycoprotein IIb/IIIa inhibitors once the patient has been appropriately risk-stratified into a high-risk acute coronary syndromes subgroup, even when the precise timing for percutaneous coronary intervention is unknown. In order to determine the indications for ED administration of glycoprotein IIb/IIIa inhibitors in patients with non–ST-segment elevation acute coronary syndromes, the ACEP Clinical Policies Subcommittee performed a MEDLINE search using the following key words/phrases in combination with glycoprotein inhibitors: "myocardial infarction," "unstable angina," "acute coronary syndromes," and "percutaneous coronary intervention." The subcommittee also reviewed current guidelines from the ACC/AHA for the treatment of non–ST-segment elevation acute coronary syndromes. A review of potentially relevant abstracts was performed and chosen

papers were graded by ACEP criteria according to the weight of evidence as it applies to this critical question. Only clinical trials that directly or indirectly investigated delay effects of glycoprotein IIB/IIIa inhibitors are listed in the Evidentiary Table.

Glycoprotein IIb/IIIa Inhibitors in Patients Medically Managed

Currently, 3 glycoprotein IIb/IIIa inhibitors are commercially available: abciximab, tirofiban, and eptifibatide. All require a 24- to 72-hour infusion to show a benefit. A number of large trials have evaluated glycoprotein IIb/IIIa inhibitors for use in patients with unstable angina or non-Q-wave AMI in both the percutaneous coronary intervention setting and in patients managed conservatively.

In patients with non–ST-segment elevation acute coronary syndromes treated medically there are 8 trials encompassing 30,006 patients.[73-80] The results of these trials showed a non-significant trend toward a reduction in risk of 30-day mortality [odds ratio (OR) 0.90, 95% confidence interval (CI) 0.80-1.02].[6,72] Overall, the administration of intravenous glycoprotein IIb/IIIa inhibitors as an initial bolus followed by a continuous infusion for at least 24 to 72 hours resulted in a modest benefit at 30 days in the composite endpoint of death and recurrent AMI (OR 0.91; 95% CI 0.85-0.98). The rate of mortality and recurrent AMI was 10.4% in the treatment group and 11.7% in the control group.[6,72] Therefore an additional 13 patients did not have the composite endpoint for every 1,000 patients treated. In this patient population, there was a small but significant increase in major bleeding from 3.7% in the treatment group from 3.6% in the control (OR 1.27, 1.12-1.44).[6,72]

Glycoprotein IIb/IIIa Inhibitors in Percutaneous Coronary Intervention

The use of glycoprotein IIa/IIIB inhibitors in the setting of a percutaneous coronary intervention was evaluated in 14 trials.[81-94] Data from these 14 trials with 17,788 patients showed that treatment with a glycoprotein IIb/IIIa inhibitor resulted in a reduction in mortality at 30 days (OR .71, 95% CI 0.52-0.97).[6,72] Consequently, an additional 4.4 patients were alive for every 1,000 treated with a glycoprotein IIb/IIIa inhibitor. At 30 days there was also a significant reduction in the composite endpoint of death and AMI (OR 0.62, 95% CI 0.55-0.70). The composite event rate was 5.6% in the treatment group and 8.8% in the controls.[6,72] Therefore an additional 31 patients were alive and did not have an AMI for every 1,000 patients treated with a glycoprotein IIb/IIIa inhibitor. It is important to note that in 3 of these studies, patients were revascularized in the setting of AMI with ST elevation.[81,88,91]

Meta-analysis of Glycoprotein IIb/IIIa Inhibitor Therapy

Boersma et al[95] performed a meta-analysis from 6 large, randomized, placebo-controlled trials (including GUSTO-IV

ACS[74]) encompassing 31,402 patients with acute coronary syndromes not routinely scheduled to undergo coronary revascularization. As previously mentioned, a statistically significant decrease in the endpoint of death or AMI was noted. Although not scheduled for coronary revascularization procedures, 11,986 (38%) of the 31,402 patients actually underwent percutaneous coronary intervention or coronary artery bypass graft within 30 days. In this late interventional subgroup, the OR for death or AMI in the treated patients was 0.89 (95% CI, 0.80 to 0.98). In the 19,416 patients in this analysis who did not undergo percutaneous coronary intervention or coronary artery bypass graft, the OR for death or myocardial infarction in the glycoprotein IIb/IIIa group was 0.95 (95% CI, 0.86 to 1.05; $P=$not significant). Major bleeding complications were significantly more common in the glycoprotein IIb/IIIa group compared with those in the placebo group (2.4% vs 1.4%; $P<0.0001$). In patients with positive troponins (troponin T or I concentration greater than 0.1 g/L), glycoprotein IIb/IIIa inhibitors were associated with a 15% reduction in the odds of 30-day death or MI compared with placebo or control (10.3% vs 12.0% events; OR 0.85; 95% CI 0.71 to 1.03). In patients with negative troponins, no risk reduction was seen. The conclusion of this analysis was that glycoprotein IIb/IIIa inhibitors should be utilized in patients with non–ST-segment elevation acute coronary syndromes and high-risk features and considered in patients that are not scheduled for early revascularization.[95]

Of note, the GUSTO-IV ACS trial[74] randomized 7,800 non–ST-segment elevation acute coronary syndromes patients with positive troponin or ST-segment depression in whom early percutaneous coronary intervention was not planned to treatment with placebo or high molecular weight abciximab. At 30 days, death or AMI occurred in 8.0% of patients receiving placebo, 8.2% receiving 24-hour infusion of abciximab, and 9.1% of patients receiving 48-hour infusion [$P=$NS]. Lack of treatment benefit was seen in all patient subgroups. As a result, the ACC/AHA provide a level III recommendation (ie, not indicated, potentially harmful) for administration of abciximab in patients in whom percutaneous coronary intervention is not planned.

Timing of Glycoprotein IIb/IIIa Administration

Although the benefit of intravenous glycoprotein IIb/IIIa inhibitors is established for patients undergoing percutaneous coronary intervention, the optimum time to initiate therapy has not been clearly established. Specifically there are few data surrounding the benefit of these agents in terms of the time interval of symptom onset to drug initiation. Despite the fact that entry criteria for these studies required patients be enrolled within 12 to 24 hours of the last episode of chest pain, there is little analysis of this time frame on outcomes. The Platelet Glycoprotein IIb/IIIa in Unstable Angina Receptor Suppression Using Integrilin Therapy (PURSUIT) trial[79] was a multinational, randomized, placebo-controlled trial that demonstrated eptifibatide reduced the incidence of death or

AMI among non–ST-segment acute coronary syndrome patients. Because of differences in practice patterns among participating countries, a prospectively planned analysis of outcomes by regions of the world was performed. Patients were allocated to placebo or eptifibatide infusion for 72 to 96 hours. Other medical therapies and revascularization strategies were employed at the discretion of the treating physician. The mean time from symptom onset to randomization was 11 hours. Eptifibatide reduced the primary endpoint of death or AMI to 30 days from 15.4% to 11.9% ($P=0.003$) among patients in the United States and from 15.7% to 14.2% in the overall study population ($P=0.02$). The treatment effect was achieved early and maintained over a period of 6 months (18.9% vs 15.2%; $P=0.004$). Bleeding events were more common in patients receiving eptifibatide, but were predominantly associated with invasive procedures. A stabilization effect prior to percutaneous coronary intervention also was noted, with a 31% relative reduction in the incidence of preprocedural AMI from 9.8% to 6.8%, $P=0.052$.[96] Bhatt et al[97] presented an abstract that evaluated the impact of the time from symptom onset to drug administration on adverse cardiac events. They reported that the absolute reduction in death or AMI was greatest in those who received the drug within 6 hours of symptom onset (2.8%) compared with 6 to 12 hours (2.3%), and 12 to 24 hours (1.7%). Furthermore, they also noted that there was no absolute reduction in death or AMI in patients who receive the drug more than 24 hours after symptom onset.

The Platelet Receptor Inhibition in Ischemic Syndromes Management (PRISM) trial reported no significant difference in benefit of tirofiban based on the analysis of time-to-symptom onset when comparing patients who presented within 24 hours of symptom onset.[78] In the PRISM study, 3,232 patients were randomized to treatment with tirofiban or heparin for 48 hours in addition to the aspirin. The endpoints of death, AMI, or refractory ischemia at 48 hours was 32% lower in the tirofiban group. There was a reduction in the mortality rate up to 30 days.[78] When evaluating the time points of 0 to 6 hours, 6 to 12 hours, and 12 to 24 hours from time of symptom onset to drug administration there was no difference in the benefit of tirofiban compared to placebo. Registry data from the National Registry of Myocardial Infarction suggests that patients who receive a glycoprotein IIa/IIIb inhibitor within 24 hours of presentation have a decreased rate of mortality after adjusting for confounders (OR 0.88, 95% CI 0.79 to 0.97).[98] No analysis was performed regarding time from symptom onset until drug administration. In addition there was no analysis to evaluate the duration of treatment prior to percutaneous coronary intervention.

The other issue of time when evaluating the use of glycoprotein IIB/IIIa inhibitors is assessing the impact of the duration of treatment prior to percutaneous coronary intervention. Overall, the administration of glycoprotein IIb/IIIa inhibitors as a bolus immediately before percutaneous coronary intervention followed by a 12- to 24-hour infusion is

beneficial. Although associated with an increased risk of bleeding, this hazard is more than offset by the reduction in the 30-day mortality (4 patients per 1,000 treated); mortality or nonfatal AMI (31 patients per 1,000); and the combined endpoints of mortality, AMI, or urgent revascularization (42 patients per 1,000).[72] This early benefit of glycoprotein IIb/IIIa blockers is maintained during follow-up. In the CAPTURE trial, 1,265 patients with refractory unstable angina were randomized to abciximab or placebo prior to a percutaneous coronary intervention.[82] Patients were treated for 18 to 24 hours prior to percutaneous coronary intervention and 1 hour following the procedure. The patients who received abciximab had less death or AMI (11.3% versus 15.9%; $P=0.012$). O'Shea et al[87] randomized 2,064 patients to receive eptifibatide or placebo immediately prior to percutaneous coronary intervention and for 18 to 24 hours after the procedure. In the patients who received eptifibatide there was a reduction in death and AMI at 6 months (hazards ratio 0.63, 95% CI 0.47-0.84).

In conclusion, although there is data to support the use of glycoprotein IIb/IIIa inhibitors in patients with non–ST-segment elevation acute coronary syndromes undergoing invasive strategy, and use of low-molecular-weight glycoprotein IIb/IIIa inhibitors in medically managed high-risk patients, the exact timing is unclear. Preliminary abstract data from PURSUIT suggests that there is a treatment effect on outcomes based on time from symptom onset to drug initiation in patients initially medically managed.[97] However, the PRISM trial found no such time dependent benefit.[78] In addition, early administration prior to percutaneous coronary intervention appears to decrease the rate of preprocedural AMI. Also, data from percutaneous coronary intervention trials supports administration at the time of percutaneous coronary intervention or 12 hours prior. However, many of these trials were performed in patients undergoing elective percutaneous coronary intervention and thus are not generalizable to the ED population.

4. What are the indications for ED administration of clopidogrel in patients with non–ST-segment elevation acute coronary syndromes?

Exclusion Criteria: Aspirin allergy; contraindications for clopidogrel therapy (eg, bleeding disorder, other).

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Administer a loading dose of clopidogrel in patients with elevated troponin or ischemic ST-segment depression*:

1. In whom a non-interventional approach is planned
2. Prior to percutaneous coronary intervention in patients in whom an interventional approach is planned and who are not at significant risk for urgent coronary artery bypass graft.

Level C recommendations. None specified.

*There is insufficient information at this time to make any recommendations in regard to the exact location or timing for

administration of the initial clopidogrel loading dose (ie, ED versus inhospital administration). Studies in elective percutaneous coronary intervention suggest benefit is greatest if clopidogrel is administered at least 6 hours prior to percutaneous coronary intervention.

Although aspirin provides beneficial antiplatelet action during acute coronary syndromes by inhibiting platelet activation mediated by thromboxane A2, there still remains significant risk for recurrent ischemia and AMI. The development of thienopyridines, a class of antiplatelet drugs that reduces adenosine diphosphate mediated platelet activation, has received much attention in the management of patients with acute coronary syndromes and other occlusive vascular events.[99-101] Combination therapy using aspirin and an adenosine diphosphate receptor antagonist has been demonstrated to have greater platelet inhibition than either agent alone.[99] However, the use of ticlopidine, the first available drug in this class, was limited by frequent side effects including life-threatening neutropenia and thrombocytopenic purpura.[99,102] Since introduction of clopidogrel, a thienopyridine with an excellent safety profile, use of adenosine diphosphate receptor antagonists has become standard therapy following percutaneous coronary intervention and in the non-interventional management of patients with acute coronary syndromes.

Current ACC/AHA guidelines on unstable angina and non–ST-segment elevation AMI recommend as a class I recommendation administration of clopidogrel to hospitalized patients unable to take aspirin, hospitalized patients in whom a non-interventional approach is planned, and in patients in whom catheterization and percutaneous coronary intervention is planned.[6] However, ACC/AHA also recommend as a class I recommendation that patients in whom an elective coronary artery bypass graft is planned, clopidogrel should be withheld for at least 5 days. These ACC/AHA recommendations apply to hospitalized patients. No recommendations are made whether or not therapy should be initiated in the ED. In order to determine the indications for ED administration of clopidogrel in patients with non–ST-segment elevation acute coronary syndromes, the ACEP Clinical Policies Subcommittee performed a MEDLINE search utilizing the following key words/phrases in combination with clopidogrel: "myocardial infarction," "unstable angina," and "acute coronary syndromes." The subcommittee also reviewed current guidelines from the AHA/ACC for the treatment of non–ST-segment elevation acute coronary syndromes. A review of potentially relevant abstracts was performed and chosen papers were graded by ACEP criteria according to the weight of evidence as it applies to this critical question. Only clinical trials that directly or indirectly investigated delay effects of clopidogrel are listed in the Evidentiary Table.

Importance of Loading Dose

Cadroy et al[103] looked at the antiplatelet effects of 325 mg aspirin versus 325 mg aspirin + 75 mg clopidogrel versus 325 mg aspirin + clopidogrel (loading dose 300 mg followed by

75 mg). They demonstrated that the antiplatelet effects of aspirin + clopidogrel (75 mg) occurred within 6 hours, and that this combination therapy was significantly more potent than aspirin alone. The antiplatelet effects of clopidogrel were even more significant with the loading dose regimen. With a 300 mg loading dose, the antiplatelet effects of clopidogrel + aspirin appeared within 90 minutes, and after 6 hours, the antithrombotic effects were equivalent to those achieved after 10 days of therapy. Recent evidence suggests that a loading dose of 600 mg of clopidogrel in patients with known coronary disease provides additional platelet inhibition even in the subgroup of patients who are already on chronic clopidogrel therapy.[104]

Clinical Trials

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial showed that aspirin in conjunction with clopidogrel improves the outcome of patients with acute coronary syndromes compared with aspirin alone.[105] The CURE trial was a multicenter, randomized, double-blind, placebo-controlled trial in 12,562 patients to evaluate the effects of clopidogrel with aspirin versus aspirin alone in patients presenting with non–ST-segment elevation acute coronary syndromes. Patients were eligible if they presented within 24 hours of symptom onset and with either ECG changes suggestive of ischemia or elevation of cardiac markers at entry. CURE demonstrated that in patients with non–ST-segment elevation acute coronary syndromes, the combination of clopidogrel (loading dose 300 mg followed by 75 mg daily) and aspirin is superior to aspirin alone in reducing cardiovascular events over 3 to 12 months. At 12 months, the primary outcome (death from cardiovascular causes, stroke, or nonfatal reinfarction) was lower in the clopidogrel group [9.3% versus 11.4%, relative risk (RR) 0.80, 95% CI 0.72 to 0.90], with the most significant difference in the rate of AMI. The second primary outcome (the primary outcome components with the addition of refractory ischemia) was also improved in the clopidogrel group (16.5% versus 18.8%, RR 0.86, 95% CI 0.79 to 0.90). Major bleeding defined as substantially disabling bleeding, intraocular bleeding leading to vision loss, or bleeding requiring 2 units of blood transfusion was significantly higher in the clopidogrel group (3.7% versus 2.7%, RR 1.38, 95% CI 1.13 to 1.67). However, there were not significantly more episodes of life-threatening bleeding. In a follow-up study, Yusuf et al[106] explored the early effects of clopidogrel therapy in the CURE study and found that the benefits of clopidogrel emerged within 24 hours of initiation of treatment and continued throughout the ensuing 12 months. During the initial 24 hours after the start of therapy, there was a 20% relative risk reduction (RRR) in the primary outcome (RR 0.80; P=NS) and a 34% RRR in the secondary outcome (RR=0.66; P<0.003) with clopidogrel therapy as compared to placebo. Analysis of treatment benefit curves revealed a divergence as early as 4 hours after initiation of therapy. In another follow-up study, Budaj et al[107] demonstrated that the benefits seen in the CURE study were consistent in low-, intermediate-, and high-

risk patients as defined by the thrombolysis in myocardial infarction (TIMI) risk score. The authors conclude that use of clopidogrel is supported in all patients with documented non–ST elevation acute coronary syndromes. However, the entry criteria requiring elevated markers or ECG changes suggestive of ischemia limits the applicability of these findings to only patients with high-risk acute coronary syndromes.

The percutaneous coronary intervention-CURE study, a prospective randomized double-blind placebo controlled trial, included the 2,658 patients from the CURE study who underwent percutaneous coronary intervention.[108] They found that treatment with clopidogrel prior to percutaneous coronary intervention was associated with less cardiovascular death, AMI, and urgent revascularization within 30 days (4.5% versus 6.4%, RR=0.70, 95% CI 0.50 to 0.97). This benefit was mostly seen in reduction of Q wave myocardial infarction. Benefit was seen both in patients undergoing percutaneous coronary intervention less than or equal to 72 hours and greater than 72 hours after study enrollment. In this population, the median time from entry into the study until percutaneous coronary intervention was 5 days during initial hospital stay (median 10 days if include percutaneous coronary intervention after initial hospital stay). It is important to realize that the 2,658 patients in the percutaneous coronary intervention-CURE substudy comprise only a small percentage of the 12,562 patients in the overall CURE study, and that when percutaneous coronary intervention was performed, it was at a median of 10 days. This is not consistent with therapeutic strategy in the United States. Furthermore, no information regarding outcome in patients whose clopidogrel therapy was initiated in the ED versus after admission is provided in the CURE and percutaneous coronary intervention-CURE studies.

The Clopidogrel for the Reduction of Events During Observation (CREDO) study looked at loading dose clopidogrel prior to elective percutaneous coronary intervention.[109] In this randomized double-blind placebo-controlled trial, pretreatment with a loading dose of 300 mg of clopidogrel was not associated with significant reduction in primary endpoint of cardiovascular death, AMI, or urgent target vessel revascularization [6.8% in clopidogrel group versus 8.3% in placebo group, RRR 18.5%, 95% CI −14.2% to 41.8%]. The median time to percutaneous coronary intervention post pretreatment with clopidogrel was 9.8 hours, and only 45% of patients received pretreatment with a glycoprotein IIb/IIIa antagonist. Subgroup analysis showed a trend toward an improved outcome for patients who received a loading dose at least 6 hours prior to percutaneous coronary intervention (RRR =38.6%, 95% CI −1.6% to 62.9 %). It should be kept in mind that the CREDO population was undergoing elective percutaneous coronary intervention, and these findings do not necessarily apply to the ED acute coronary syndromes population.

Clopidogrel Prior to Coronary Artery Bypass Graft

A potential problem that results from initiating clopidogrel prior to knowledge of future treatment plan or coronary

anatomy are the bleeding complications that frequently occur in patients who require urgent coronary artery bypass graft. Patients in the CURE study, who had stopped clopidogrel within 5 days of coronary artery bypass graft, had a trend toward more major bleeding complications as compared to placebo (9.6% versus 6.3%; $P=0.06$ [NS]).[105] Hongo et al[110] showed that patients with exposure to clopidogrel within 7 days of coronary artery bypass graft had statistically significantly higher rates of postoperative bleeding, transfusion requirements, and a ten-fold higher re-operation rate. A more recent study found that clopidogrel treatment less than or equal to 72 hours prior to coronary artery bypass graft resulted in statistically higher rates of postoperative bleeding, transfusion requirements, and re-operation rates.[111]

As discussed earlier, current ACC/AHA guidelines recommend that clopidogrel be withheld for 5 days in patients in whom an elective coronary artery bypass graft is planned. Ideally clopidogrel should be withheld in all ED patients with acute coronary syndromes who are at significant risk for urgent coronary artery bypass graft. In the CURE study, 912 patients (7.3%) had coronary artery bypass graft in less than or equal to 5 days of discontinuation of clopidogrel therapy.[105] Undoubtedly, rates of urgent coronary artery bypass graft are much higher in the United States where a more aggressive interventional approach is utilized. Identification of these acute coronary syndrome patients at risk for urgent coronary artery bypass graft is extremely difficult in the ED setting. In many instances patients with coronary artery disease have had a recent prior arteriogram indicating absence of multivessel disease, and thus would potentially benefit from early clopidogrel therapy. Also, younger patients with localized ischemia on functional stress testing may be assumed to be at low risk of multivessel disease and likewise candidates for early clopidogrel therapy. Sadanandan et al,[112] in a retrospective analysis of 2,220 patients enrolled in the TACTICS-TIMI-18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis in Myocardial Infarction) trial, developed a simplified risk score that may assist physicians in estimating the likelihood of coronary artery bypass surgery in patients with non-ST-segment elevation acute coronary syndromes. They found the following 5 variables associated with an increased risk of coronary artery bypass surgery: elevated troponin (OR 3.9; risk score 3), prior stable angina (OR 1.8; risk score 1); ST-segment deviation >0.5 mm (OR 1.7; risk score 1); male gender (OR 1.6; risk score 1), and history of peripheral artery disease (OR 1.6; risk score 1). Patients with history of prior coronary artery bypass surgery were significantly less likely to undergo inhospital coronary artery bypass surgery (OR 0.34; risk score -2). The risk score generated by summing the numerical value of each individual risk score predicted the risk of inhospital coronary artery bypass surgery: 6% for risk score <3; 22% for risk score 3 to 5, and 55% for risk score >5. These findings were validated in the TIMI-11B trial and TIMI-III registry.

In summary, early clopidogrel therapy combined with aspirin reduces the incidence of cardiovascular death, myocardial infarction, AMI, cerebrovascular accident, and refractory ischemia, with benefits arising as early as 6 hours post therapy. However, these benefits may occur at the expense of major bleeding, especially if the patient will undergo coronary artery bypass graft within 5 to 7 days of clopidogrel therapy. At the present time, there is no direct data that elucidates whether or not there is a time-dependent benefit from initiating clopidogrel therapy in the ED in patients who are going to be admitted for further treatment and evaluation of non–ST-segment elevation acute coronary syndromes. Also, subgroup analysis of patients in the CURE, percutaneous coronary intervention-CURE, and CREDO studies,[105,108,109] as well as more recent studies,[113-115] suggest that the use of platelet glycoprotein IIb/IIIa agents in addition to clopidogrel and aspirin provides additional platelet inhibition. In patients in whom coronary anatomy is unknown, and who may be at greater risk for urgent coronary artery bypass graft, clopidogrel treatment should be used cautiously until coronary arteriogram has been performed. In cases where rapid reversal of clopidogrel effects is required, platelet transfusion may be utilized.[99] Larger studies are needed to help delineate appropriate use of triple antiplatelet therapy. Future studies also are needed comparing outcomes in patients with clopidogrel therapy initiated in the ED versus early inhospital administration and in better defining patient subgroups who benefit the most from early clopidogrel therapy.

REFERENCES

1. Karcz A, Holbrook J, Burke MC, et al. Massachusetts emergency medicine closed malpractice claims: 1988-1990. *Ann Emerg Med.* 1993;22:553-559.
2. Rusnak RA, Stair TO, Hansen K, et al. Litigation against the emergency physician: Common features in cases of missed myocardial infarction. *Ann Emerg Med.* 1989;18:1029-1034.
3. American College of Emergency Physicians, Standards Task Force. Clinical policy for management of adult patients presenting with a chief complaint of chest pain, with no history of trauma. Dallas, American College of Emergency Physicians, 1990.
4. American College of Emergency Physicians. Clinical policy for the initial approach to adults presenting with a chief complain of chest pain, with no history of trauma. *Ann Emerg Med.* 1995;25:274-299.
5. American College of Emergency Physicians. Clinical Policy: critical issues in the evaluation and management of adult patients presenting with suspected AMI or unstable angina. *Ann Emerg Med.* 2000;35:521-544.
6. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). 2002. Available at: www.acc.org/clinical/guidelines/unstable/unstable.pdf. Accessed March 2, 2006.
7. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of

Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). 2004. Available at: www.acc.org/clinical/guidelines/stemi/index.pdf. Accessed March 2, 2006.

8. Schriger DL, Cantrill SV, Greene CS. The origins, benefits, harms, and implications of emergency medicine clinical policies. *Ann Emerg Med.* 1993;22:597-602.

9. Fesmire FM, Percy RF, Wears RL, et al. Initial ECG in Q wave and non-Q wave myocardial infarction. *Ann Emerg Med.* 1989;18:741-746.

10. Fesmire FM, Wharton DR, Calhoun FB. Instability of ST segments in the early stages of acute myocardial infarction in patients undergoing continuous 12-lead ECG monitoring. *Am J Emerg Med.* 1995;13:158-163.

11. Fesmire FM, Bardoner JB. ST-segment instability preceding simultaneous cardiac arrest and AMI in a patient undergoing continuous 12-lead ECG monitoring. *Am J Emerg Med.* 1994;12:69-76.

12. Krucoff MW, Croll MA, Pope JE, et al. Continuous 12-lead ST-segment recovery analysis in the TAMI 7 study: performance of a noninvasive method of real-time detection of failed myocardial reperfusion. *Circulation.* 1993;88:437-446.

13. Klootwijk P, Langer A, Meij S, et al. Non-invasive prediction of reperfusion and coronary artery patency by continuous ST-segment monitoring in the GUSTO-I trial. *Eur Heart J.* 1996;17:689-698.

14. Col J, Pirenne B, Decoster O, et al. Basic components and patterns of acute ischemia recovery assessed from continuous ST monitoring in acute myocardial infarction treated by thrombolytic therapy. *J Electrocardiol.* 1994;27S:241-248.

15. Schroder R, Wegscheider K, Schroder K, et al. Extent of early ST segment resolution: a strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens. *J Am Coll Cardiol.* 1995;26:1657-1666.

16. Purcell IF, Newall N, Farrer M. Change in ST segment elevation 60 minutes after thrombolytic initiation predicts clinical outcome as accurately as later electrocardiographic changes. *Heart.* 1997;78:465-471.

17. Yazigi A, Richa F, Gebara S, et al. Prognostic importance of automated ST-segment monitoring after coronary artery bypass graft surgery. *Acta Anaesthesiol Scand.* 1998;42:532-535.

18. Drew BJ, Adams MG, Pelter MM, et al. ST-segment monitoring with a derived 12-lead electrocardiogram is superior to routine cardiac care unit monitoring. *Am J Crit Care.* 1996;5:198-206.

19. Gottlieb SO, Weisfeldt ML, Ouyang P, et al. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. *N Engl J Med.* 1986;314:1214-1219.

20. Nademanee K, Intarachot V, Josephson MA, et al. Prognostic significance of silent myocardial ischemia in patients with unstable angina. *J Am Coll Cardiol.* 1987;10:1-9.

21. Johnson, SM, Mauritson DR, Winniford MD, et al. Continuous electrocardiographic monitoring in patients with unstable angina pectoris: identification of high-risk subgroup with severe coronary disease, variant angina, and/or impaired early prognosis. *Am Heart J.* 1982;103:4-12.

22. Patel DJ, Holdright DR, Knight CJ, et al. Early continuous ST-segment monitoring in unstable angina: Prognostic value additional to the clinical characteristics and the admission electrocardiogram. *Heart.* 1996;75:222-228.

23. Martinez EA, Kim LJ, Faraday N, et al. Sensitivity of routine intensive care unit surveillance for detecting myocardial ischemia. *Crit Care Med.* 2003;31:2302-2308.

24. Hedges JR, Young GP, Henkel GF, et al. Serial ECGs are less accurate than serial CK-MB results for emergency department diagnosis of myocardial infarction. *Ann Emerg Med.* 1992;21:1445-1450.

25. Young GP, Gibler WB, Hedges JR, et al. Serial creatine kinase-MB results are a sensitive indicator of acute myocardial infarction in chest pain patients with nondiagnostic electrocardiograms: the second Emergency Medicine Cardiac Research Group Study. *Acad Emerg Med.* 1997;4:869-877.

26. Fesmire FM, Percy RF, Bardoner JB, et al. Usefulness of automated serial 12-lead ECG monitoring during the initial emergency department evaluation of patients with chest pain. *Ann Emerg Med.* 1998;31:3-11.

27. Fesmire FM. Which chest pain patients potentially benefit from continuous 12-lead ST-segment monitoring with automated serial ECG? *Am J Emerg Med.* 2000;18:773-778.

28. Decker WW, Prina LD, Smars PA, et al. Continuous 12-lead electrocardiographic monitoring in an emergency department chest pain unit: an assessment of potential clinical effect. *Ann Emerg Med.* 2003;41:342-351.

29. Fesmire FM, Hughes AD, Fody EP, et al. The Erlanger chest pain evaluation protocol: a one-year experience with serial 12-lead ECG monitoring, two-hour delta serum marker measurements, and selective nuclear stress testing to identify and exclude acute coronary syndrome. *Ann Emerg Med.* 2002;40:584-594.

30. Johanson P, Svensson AM, Dellborg M. Clinical implications of early ST-segment variability. A report from the ASSENT 2 ST-monitoring sub-study. *Coron Artery Dis.* 2001;12:277-283.

31. Gibler WB, Runyon JP, Levy RC, et al. A rapid diagnostic and treatment center for patients with chest pain in the emergency department. *Ann Emerg Med.* 1995;25:1-8.

32. Gibler WB, Sayre MR, Levy RC, et al. Serial 12-lead electrocardiographic monitoring in patients presenting to the emergency department with chest pain. *J Electrocardiol.* 1993;26S:238-243.

33. Fesmire FM. ECG diagnosis of acute myocardial infarction in the presence of left bundle-branch block in patients undergoing continuous ECG monitoring. *Ann Emerg Med.* 1995;26:69-82.

34. Sabatine MS, Morrow DA, de Lemos JA, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation.* 2002;105:1760.

35. Hamm CW, Goldmann BU, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med.* 1997;337:1648-1653.

36. James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy *Circulation.* 2003;108:275-281.

37. Wu AH, Apple FS, Gibler WB, et al. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. *Clin Chem.* 1999;45:1104-1121.

38. Apple FS, Wu AH, Jaffe AS. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: how to use existing assays clinically and for clinical trials. *Am Heart J.* 2002;144:981-986.

39. Apple FS, Quist HE, Doyle PJ, et al. Plasma 99th percentile reference limits for cardiac troponin and creatine kinase MB mass for use with European Society of Cardiology/American

College of Cardiology consensus recommendations. *Clin Chem.* 2003;49:1331-1336.

40. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, et al. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation.* 1994;90:583-612.

41. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined–a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Amer Coll Cardiol.* 2000; 36:959-969.

42. Mair J, Artner-Dworzak E, Dienstl A. Early detection of acute myocardial infarction by measurement of mass concentration of creatine kinase-MB. *Am J Cardiol.* 1991;68:1545-50.

43. Marin MM, Teichman SL. Use of rapid serial sampling of creatine kinase MB for very early detection of myocardial infarction in patients with acute chest pain. *Am Heart J.* 1992; 123:354-61.

44. Bakker AJ, Gorgels JP, van Vlies B, et al. Contribution of creatine kinase MB mass concentration at admission to early diagnosis of acute myocardial infarction. *Br Heart J.* 1994;72: 112-118.

45. de Winter RJ, Koster RW, Sturk A, et al. Value of myoglobin, troponin T, and CK-MB mass in ruling out an acute myocardial infarction in the emergency room. *Circulation.* 1995;92:3401-3407.

46. D'Costa M, Fleming E, Patterson MC. Cardiac troponin I for the diagnosis of acute myocardial infarction in the emergency department. *Am J Clin Path.* 1997;108:550-555.

47. Kontos MC, Anderson FP, Schmidt KA, et al. Early diagnosis of acute myocardial infarction in patients without ST-segment elevation. *Am J Cardiol.* 1999;83:155-158.

48. Zimmerman J, Fromm R, Meyer D, et al. Diagnostic marker cooperative study for the diagnosis of myocardial infarction. *Circulation.* 1999;99:1671-1677.

49. Apple FS, Anderson FP, Collinson P, et al. Clinical evaluation of the first medical whole blood, point-of-care testing device for detection of myocardial infarction. *Clin Chem.* 2000;46:1604-1609.

50. Jurlander B, Clemmensen P, Wagner GS, et al. Very early diagnosis and risk stratification of patients admitted with suspected acute myocardial infarction by the combined evaluation of a single serum value of cardiac troponin-T, myoglobin, and creatine kinase MB(mass). *Eur Heart J.* 2000; 21:382-389.

51. Porela P, Pulkki K, Helenius H. Prediction of short-term outcome in patients with suspected myocardial infarction. *Ann Emerg Med.* 2000;35:413-420.

52. Gibler WB, Hoekstra JW, Weaver WD, et al. A randomized trial of the effects of early cardiac serum marker availability on reperfusion therapy in patients with acute myocardial infarction: the serial markers, acute myocardial infarction and rapid treatment trial (SMARTT). *J Amer Coll Cardiol.* 2000;36:1500-1506.

53. Esses D, Gallagher EJ, Iannaccone R, et al. Six-hour versus 12-hour protocols for AMI: CK-MB in conjunction with myoglobin. *Am J Emerg Med.* 2001;19:182-186.

54. Zarich SW, Qamar AU, Werdmann MJ, et al. Value of a single troponin T at the time of presentation as compared to serial CK-MB determinations in patients with suspected myocardial ischemia. *Clin Chim Acta.* 2002;326:185-192.

55. Capellan O, Hollander JE, Pollack C Jr, et al. Prospective evaluation of emergency department patients with potential coronary syndromes using initial absolute CK-MB vs. CK-MB relative index. *J Emerg Med.* 2003;24:361-367.

56. Fesmire FM, Christenson RH, Fody EP, et al. Delta creatine kinase-MB outperforms myoglobin at two hours during the emergency department identification and exclusion of troponin positive non-ST-segment elevation acute coronary syndromes. *Ann Emerg Med.* 2004;44:12-19.

57. Gibler WB, Young GP, Hedges JR, et al. Acute myocardial infarction in chest pain patients with nondiagnostic ECGs: serial CK-MB sampling in the emergency department. The Emergency Medicine Cardiac Research Group. *Ann Emerg Med.* 1992;21: 504-512.

58. Bakker AJ, Koelemay MJ, Gorgels JP, et al. Failure of new biochemical markers to exclude acute myocardial infarction at admission. *Lancet.* 1993;342:1220-1222.

59. Castaldo AM, Ercolini P, Forino F, et al. Plasma myoglobin in the early diagnosis of acute myocardial infarction. *Eur J Clin Chem Clin Biochem.* 1994;32:349-353.

60. Lindahl B, Venge P, Wallentin L. Early diagnosis and exclusion of acute myocardial infarction using biochemical monitoring. The BIOMACS Study Group. Biochemicals Markers of Acute Coronary Syndromes. *Coron Artery Dis.* 1995;6:321-328.

61. Fesmire FM, Percy RF, Bardoner JB, et al. Serial creatinine kinase (CK) MB testing during the emergency department evaluation of chest pain: utility of a 2-hour delta CK-MB of +1.6ng/ml. *Am Heart J.* 1998;136:237-244.

62. Apple FS, Maturen AJ, Mullins RE, et al. Multicenter clinical and analytical evaluation of the AxSYM troponin-I immunoassay to assist in the diagnosis of myocardial infarction. *Clin Chem.* 1999;45:206-212.

63. Fesmire FM. Delta CK-MB outperforms delta troponin I at 2 hours during the ED rule out of acute myocardial infarction. *Am J Emerg Med.* 2000;18:1-8.

64. Stork TV, Wu AH, Muller-Bardorff M, et al. North-Wurttemberg Infarction Study (NOWIS) Group. Diagnostic and prognostic role of myoglobin in patients with suspected acute coronary syndrome. North-Wurttemberg Infarction Study (NOWIS) Group. *Am J Cardiol.* 2000;86:1371-1374.

65. McCord J, Nowak RM, McCullough PA, et al. Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. *Circulation.* 2001;104:1483-1488.

66. Collinson PO, Stubbs PJ, Kessler AC. Multicentre Evaluation of Routine Immunoassay of Troponin T Study. Multicentre evaluation of the diagnostic value of cardiac troponin T, CK-MB mass, and myoglobin for assessing patients with suspected acute coronary syndromes in routine clinical practice. *Heart.* 2003;89:280-286.

67. de Winter RJ, Lijmer JG, Koster RW, et al. Diagnostic accuracy of myoglobin concentration for the early diagnosis of acute myocardial infarction. *Ann Emerg Med.* 2000;35:113-120.

68. Ng SM, Krishnaswamy P, Morissey R, et al. Ninety minute accelerated critical pathway for chest pain evaluation. *Am J Cardiol.* 2001;88:611-617.

69. Sallach SM, Nowak R, Hudson MP, et al. A change in serum myoglobin to detect acute myocardial infarction in patients with normal troponin I levels. *Am J Cardiol.* 2004;94:864-867.

70. Apple FS, Christenson RH, Valdes R Jr, et al. Simultaneous rapid measurement of whole blood myoglobin, creatine kinase MB, and cardiac troponin I by the triage cardiac panel for detection of myocardial infarction. *Clin Chem.* 1999;45:199-205.

71. Fesmire FM, Fesmire CE. Improved identification of acute coronary syndromes with second generation cardiac troponin I

assay: utility of 2-hour delta cTnI ≥ +0.02 ng/ml. *J Emerg Med.* 2002;22:147-152.

72. Bosch X, Marrugat J. Platelet glycoprotein IIb/IIIa blockers for percutaneous coronary revascularization, and unstable angina and non-ST-segment elevation myocardial infarction. *The Cochrane Database of Systematic Reviews* 2001, Issue 4. Art. No.: CD002130. DOI: 10.1002/14651858.CD002130.

73. Theroux P, Kouz S, Roy L, et al. Platelet membrane receptor glycoprotein IIb/IIIa antagonism in unstable angina. The Canadian Lamifiban Study. *Circulation.* 1996;94:899-905.

74. Simoons ML. The GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularization: the GUSTO IV-ACS randomized trial. *Lancet.* 2001;357:1915-1924.

75. Moliterno DJ. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. The PARAGON Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. *Circulation.* 1998;97:2386-2395.

76. The Paragon B Investigators. Dose-adjusted Lamifiban, a nonpeptide, platelet glycoprotein IIb/IIIa antagonist for acute coronary syndrome without ST-segment elevation [abstract]. *J Am Coll Cardiol.* 2001;2 [suppl.]:343A.

77. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med.* 1998;338:1488-1497.

78. Bazzino O, Aylward P, Hains A, et al. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med.* 1998;338:1498-1505.

79. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med.* 1998;339:436-443.

80. Schulman SP, Goldschmidt-Clermont PJ, Topol EJ, et al. Effects of integrelin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina. A randomized multicenter trial. *Circulation.* 1996;94:2083-2089.

81. Montalescot G, Barragan P, Wittenberg O, et al. ADMIRAL Investigators. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med.* 2001;344:1895-1903.

82. Simoons ML, Rutsch W, Vahanian A, et al. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet.* 1997;349:1429-35.

83. EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *N Engl J Med.* 1994;330:956-961.

84. Topol EJ, Califf RM, Lincoff AM, et al. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPILOG Investigators. *N Engl J Med.* 1997;336:1689-1696.

85. Topol EJ, Lincoff AM, Califf RM, et al. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. The EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet.* 1998;352:87-92.

86. The ERASER Investigators. Acute platelet inhibition with abciximab does not reduce in-stent restenosis (ERASER study). *Circulation.* 1999;100:799-806.

87. O'Shea JE, Hafley GE, Greenberg S, et al. Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention. The ESPRIT trial: a randomized controlled trial. *JAMA.* 2001;285:2468-2473.

88. Neumann FJ, Kastrati A, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade with abciximab on clinical and angiographic reestenosis rate after the replacement of coronary stents following an acute myocardial infarction. *J Am Coll Cardiol.* 2000;35:915-921.

89. Tcheng JE, Harrington RA, Kottke-Marchant K, et al. Multicenter, randomized, double-blind, placebo-controlled trial of the platelet integrin glycoprotein IIb/IIIa blocker Integrelin in elective coronary intervention. IMPACT Investigators. *Circulation.* 1995; 91:2151-2157.

90. Tcheng JE, Lincoff AM, Sigmon KN, et al. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lancet.* 1997; 349:1422-1428.

91. Brener SJ, Barr LA, Burchenal JE, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators. *Circulation.* 1998;98:734-741.

92. Hanrath P, vom DJ, Paulus O, et al. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation.* 1997;96:1445-1453.

93. Kereiakes DJ, Kleiman NS, Ambrose J, et al. Randomized, double-blind, placebo-controlled dose-ranging study of tirofiban (MK-383) platelet IIb/IIIa blockade in high risk patients undergoing coronary angioplasty. *J Am Coll Cardiol.* 1996;27: 536-542.

94. Simoons ML, de Boer MJ, van Den Brand MJ, et al. Randomized trial of a GPIIb/IIIa platelet receptor blocker in refractory unstable angina. European Cooperative Study Group. *Circulation.* 1994;89:596-603.

95. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet.* 2002;359:189-198.

96. Lincoff AM, Harrington RA, Califf RM, et al. Management of patients with acute coronary syndromes in the United States by platelet glycoprotein IIb/IIIa inhibition. Insights from the platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy (PURSUIT) trial. *Circulation.* 2000;102: 1093-1100.

97. Bhatt DL, Marso SP, Houghtaling P, et al. Does earlier administration of eptifibatide reduce death and MI in patients with acute coronary syndromes? [abstract]. *Circulation..* 1998; 98(Suppl 1):I560-I561.

98. Peterson ED, Pollack CV Jr, Roe MT, et al. Early use of glycoprotein IIb/IIIa inhibitors in non-ST-elevation acute myocardial infarction: observations from the National Registry of Myocardial Infarction 4. *J Am Coll Cardiol.* 2003;42:45-53.

99. Lubbe DF, Berger PB. The thienopyridines. *J Interv Cardiol.* 2002;15:85-93.

100. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324:71-86.

101. Braunwald E. Application of current guidelines to the management of unstable angina and non-ST-elevation

myocardial infarction. *Circulation.* 2003;108[suppl III]:III-28-III-37.

102. Casella G, Ottani F, Pavesi PC, et al. Safety and efficacy evaluation of clopidogrel compared to ticlopidine after stent implantation: an updated meta-analysis. *Ital Heart J.* 2003;4: 677-684.

103. Cadroy Y, Bossavy JP, Thalamas C, et al. Early potent antithrombotic effect with combined aspirin and a loading dose of clopidogrel on experimental arterial thrombogenesis in humans. *Circulation.* 2000;101:2823-2828.

104. Kastrati A, von Beckerath N, Joost A, et al. Loading with 600 mg clopidogrel in patients with coronary artery disease with and without chronic clopidogrel therapy. *Circulation.* 2004;5;110: 1916-1919.

105. Yusuf S, Zhao F, Mehta SR, et al. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001; 345:494-502.

106. Yusuf S, Shamir RM, Zhao F, et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation.* 2003;107:966-972.

107. Budaj A, Yusuf S, Mehta SR, et al. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. *Circulation.* 2002;106:1622-1626.

108. Mehta SR, Yusuf S, Peters RJG, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet.* 2001;358:527-533.

109. Steinhubl SR, Berger PB, Mann JT III, et al. CREDO Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA.* 2002;288:2411-2420.

110. Hongo RH, Ley J, Dick SE, et al. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. *J Am Coll Cardiol.* 2002;40:232-237.

111. Englberger L, Faeh B, Berdat PA, et al. Impact of clopidogrel in coronary artery bypass grafting. *Eur J Cardiothorac Surg.* 2004; 26:96-101.

112. Sadanandan S, Cannon CP, Gibson CM et al. TIMI Study Group. A risk score to estimate the likelihood of coronary artery bypass surgery during the index hospitalization among patients with unstable angina and non–ST-segment elevation myocardial infarction. *J Am Coll Cardiol.* 2004;44:799-803.

113. Dalby M, Montalescot G, Bal dit Sollier C, et al. Eptifibatide provides additional platelet inhibition in non-ST-elevation myocardial infarction patients already treated with aspirin and clopidogrel: Results of the Platelet Activity Extinction in Non-Q-Wave Myocardial Infarction with Aspirin, Clopidogrel, and Eptifibatide (PEACE) Study. *J Am Coll Cardiol.* 2004;43:162-168.

114. Krastrati A, Mehilli J, Schunhlen H, et al for the Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) Study Investigators. A clinical trial of Abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med.* 2004;350:232-238.

115. Chan AW, Moliterno DJ, Berger PB, et al. Triple antiplatelet therapy during percutaneous coronary intervention is associated with improved outcome including one-year survival: Results from the Do Tirofiban and ReoProGive Similar Efficacy Outcome Trial (TARGET). *J Am Coll Cardiol.* 2003;42:1188-1195.

Evidentiary Table.

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
Martinez et al[23]	2003	Prospective cohort	Continuous 12-lead ECG vs. routine monitoring	Identification of cardiac ischemia	Superiority of serial ECG, automated	Indirect outcome;small sample	II
Hedges et al[24]	1992	Prospective observational	Repeat ECG at 4 hours in ED chest pain patients	CK-MB measurements	CK-MB superior to repeat ECG to identify AMI	Does not measure incremental value of repeat ECG	II
Young et al[25] (source - serial ECG section)	1997	Prospective observational	Repeat ECG at 3 hours in ED chest pain patients	Serial CK-MB measurements	CK-MB superior to repeat ECG to identify AMI	Does not measure incremental value of repeat ECG	II
Young et al[25] (serum marker section)	1997	Prospective	3 hour repeat and delta CK-MB in ED chest pain patients	WHO criteria	CK-MB at time 0 and 3-h in ED patients; CK-MB (0,3 h, delta), sensitivity 57, 88, 93; specificity 97, 97, 95	Convenience sample	I
Fesmire et al[26]	1998	Prospective observational	Continuous 12-lead ECG in ED chest pain patients	New diagnostic changes on ECG	Serial 12-lead ECG more sensitive and specific than a single ECG for AMI and ACS	Only inhospital outcome data	II
Fesmire[27]	2000	Prospective observational	Continuous serial 12-lead ECG in ED chest pain patients	Significant change in therapy	High-risk chest patients benefit more from serial 12-lead ECG monitoring than low-risk patients	Indirect outcomes; no control group	II
Decker et al[28]	2003	Prospective observational	Continuous 12-lead ECG in low risk ED observation unit patients	30-day adverse outcomes	Little incremental value of serial 12-lead ECG in low-risk ED observation unit	Small sample size; no comparison group	II
Fesmire et al[29] (source - serial ECG section)	2002	Prospective observational	Continuous 12-lead ECG in ED chest pain patients for 2 h evaluation	30-day adverse outcomes	99% sensitivity for 30 day ACS when combined with serum markers	No comparison group	II
Fesmire et al[29] (serum marker section)	2002	Prospective	Serial and delta CK-MB	Modified WHO criteria using positive CK-MB or cTnI as marker standard	N=2,074 patients; 179 AMIs; comprehensive report of a 6-step accelerated chest pain protocol for identification of AMI and ACS. Addition of a positive delta CK-MB and/or positive delta cTnI to baseline markers and ECG increased sensitivity to 93% with specificity 94% for identification of AMI	Study not intended to study markers alone for diagnosis of AMI	II
Johanson et al[30]	2001	Prospective cohort	Serial 12-lead ECG in CCU in AMI	30-day adverse outcomes	Small variations in ST segments in first 4 h of AMI predict poor outcomes	Substudy of ASSENT II trial	II
Gibler et al[31]	1995	Retrospective review	Evaluate ED chest pain unit	Result of chest pain unit evaluation	Effective method to evaluate low-risk chest pain in ED	Retrospective; no 30-day outcomes	III

Clinical Policy

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
Mair et al[42]	1991	Prospective	CK-MB	WHO diagnosis of AMI blinded to CK-MB mass results	CK-MB mass had average sensitivity of 57%, specificity of 95% on initial measurement at ED presentation; 51 AMIs	Relatively small	II
Marin and Teichman[43]	1992	Prospective	CK-MB, delta CK-MB	CK >225 w/ MB% 5+% or ECG changes in chest pain patients	N=313 patients; 70 AMIs; initial sensitivity/specificity of CK-MB were: 76%/72%, 2-h delta rule sensitivity/specificity: 94%/91%	Loose AMI definition	I
Bakker et al[44]	1994	Prospective	CK-MB	AMI; blinded cardiologist using WHO class	N=297 patients; 154 AMIs; CK-MB mass at presentation studied; sensitivity 45% <4 h after presentation; 76% 4-12 h later	Numbers in tables do not seem to add up correctly	II
de Winter et al[45]	1995	Prospective	Myoglobin, CK-MB, troponin T	AMI; clinical history, ECG, peaking CK-MB pattern	N=309 patients; 163 AMIs; myoglobin better 3-6 h after symptom onset, then CK-MB or troponin are better; myoglobin: 68% sensitivity w/ 98% specificity at 3 h after symptom onset	No ROC determinations and 2 different cutoffs analyzed	II
D'Costa et al[46]	1997	Prospective	Myoglobin, CK-MB, troponin	Modified WHO	N=316 patients; 62 AMIs; troponin I at cutoff of 1.0 ng/ml showed sensitivity of 79% at presentation vs. 44% for CK-MB; myoglobin was 100% sensitive	This high sensitivity of cTnI is inconsistent with all other trials; onset of chest pain not always noted	II
Kontos et al[47]	1999	Prospective/ retrospective	Myoglobin, CK-MB	Modified WHO	N=2,093 patients; 186 AMIs; sensitivity initial myoglobin 46%, specificity 89% 3-h CK-MB w/ relative index >4: sensitivity 93%, specificity 86%	Reports of CK-MB relative index rather than CK-MB	III
Zimmermann et al[48]	1999	Prospective, multicenter	Serial myoglobin, troponin T, troponin I, CK-MB, CK-MB subforms	MI defined by CK-MB; 7 ng/ml in >1 sample	N=955 patients; 119 AMIs; CK-MB had highest sensitivity for AMI at all timepoints with exception of 2- and 4 h where myoglobin and CK-MB subforms had a small advantage	CK-MB-based definition biases results in highest predictive values for CK-MB; troponin cutoffs were not determined using ROC and used relatively high level	III
Apple et al[49]	2000	Prospective, multicenter	Myoglobin, CK-MB, troponin I	Modified WHO w/ either CK-MB or troponin I	N=369 patients; 89 AMIs; study comparing different CK-MB, trop I, and myoglobin assays; sensitivity (0-4h) after symptom onset: myoglobin – 61%, CK-MB – 50%, cTnI – 29%	Not all sensitivity results reported for all time intervals	I

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
Jurlander B et al[50]	2000	Prospective	Myoglobin, CK-MB, troponin T	Modified WHO	N=155 patients; 83 AMIs; single markers at ED presentation; no significant difference in any marker within 6 h of symptom onset; sensitivity range 35%-86%	Addition of ECG to diagnostic criteria was done retrospectively	I
Porela et al[51]	2000	Prospective with some retrospective elements	CK-MB, troponin I	Modified WHO based on peak CK-MB >11	N=311 patients; 132 AMIs; median delay to presentation 4 h; sensitivity/specificity: CK-MB – 60%/92%, cTnI – 53%/91%, marker + ECG – 90%/54%	Nonstandard; study published 7 y after the data collection; cannot tell from text how much of this was retrospective	II
Gibler et al[52]	2000	Prospective study with primary endpoint on decision-making regarding reperfusion; treatment as it is influenced by initial serum markers	Myoglobin, CK-MB	"cardiac marker elevations and ECG changes"	N=6,352 patients; 814 AMIs; sensitivity/specificity of initial markers: myoglobin - 64%/90%, CK-MB – 52%/96%, either – 72%/88%	Marker results were reported but were not the primary endpoint of this study; largest number of AMIs in any marker study; multimarker	II
Esses et al[53]	2001	Prospective	CK-MB, myoglobin	WHO criteria with 18–h CK-MB	N=519 patients; 76 AMIs; CK-MB + myoglobin 0 and 6 h sensitivity of 57% and 96% respectively	Some circularity with CK-MB-based AMI definition	II
Zarich et al[54]	2002	Prospective	Troponin T, serial CK-MB	WHO definition; blinded to troponin results	N=267 patients, 60 AMIs; initial CK-MB vs troponin T sensitivity/specificity: CK-MB: 46.6%/82.6%, cTnT: 86.7%/93.7%	Study included some late presenters >12 h that could skew results to favor troponin	II
Capellan et al[55]	2003	Prospective	CK-MB and CK-MB relative index	WHO definition of AMI	CK-MB and CK-MB RI at time of ED presentation; CK-MB sensitivity 52%; specificity 93%	Time of test was median 240 min after symptom onset; data not reported by time of onset	II
Fesmire et al[56]	2004	Prospective	CK-MB, delta CK-MB, myoglobin	Chest pain plus rising troponin >1.0, new Q waves, or death	N=975 patients, 44 AMIs; 2-h delta CK-MB vs delta myoglobin; delta CK-MB: sensitivity/specificity 93% and 94%, respectively	Relatively small	II

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
Gibler et al[57]	1992	Prospective	Serial CK-MB	WHO definition	N=616 patients; 108 AMIs; sensitivity time 0: 44%; time 3-h: 79.7 in non-diagnostic ECG group; in all patients, 67.2% and 88.4%	None	I
Bakker et al[58]	1993	Prospective	Myoglobin, CK-MB, troponin T	WHO criteria by blinded cardiologist, CK-MB-based	N=290 patients, 153 AMIs; sensitivity troponin T >CK-MB >myoglobin at all timepoints	CK-MB-based definition; CCU patient population; reports results by time of symptom onset	I
Castaldo et al[59]	1994	Prospective	Myoglobin	WHO definition	N=157 patients; 58 AMIs; sensitivity/specificity for myoglobin 3, 6, 9 h after symptom onset; myoglobin sensitivity/specificity: 3-h – 38%/100%, 6-h – 90%/100%, 9-h – 100%/100%	No confidence intervals expressed	II
Lindahl et al[60]	1995	Prospective	Myoglobin, CK-MB, troponin I	Modified WHO	N=142 patients; 59 AMIs; CK-MB and myoglobin had best early performance at 0-6 h; troponin equivalent at 6 h	Relatively small, unblended assessments	II
Fesmire et al[61]	1998	Prospective	CK-MB, delta CK-MB	WHO definition of AMI	N=710 patients; 113 AMIs; study of predictive value of CK-MB, initial and 2-h and delta CK-MB; sensitivity initial – 18%, 2-h – 75%, delta – 92%	Time from symptom onset not reported	I
Apple et al[62]	1999	Laboratory investigation	Troponin I	WHO definition of AMI	122 AMI patients; sensitivity for cTnI for AMI peaks at about 24 h	Diagnostic cutoffs for cTnI set at exceedingly high level	III
Fesmire[63]	2000	Retrospective	CK-MB, delta CK-MB, troponin I	Modified WHO definition of AMI with positive CK-MB and/or cTnI being gold standard	N=578 patients; 57 AMIs; 0, 2-h and delta CK-MB and cTnI; delta CK-MB at 2 h is most sensitive for diagnosis of AMI (88%); combination of 2-h values and deltas yields sensitivity of 91%	Retrospective review; relatively small; differences seen between STEMI and non–ST-segment elevation MI subsets, but the subsets are too small to generate significance	II
Stork et al[64]	2000	Prospective	Myoglobin	CK >100 w/CK-MB relative index >6% on 1 measurement	N=253 patients; 66 AMIs; sensitivity/specificity at admission, 4h: myoglobin – 62/81, 85/71 CK-MB – 41/100, 85, 100 cTnT – 46/89, 73/81 myoglobin + CK-MB – 74/81, 96/71 myoglobin + troponin – 70/75, 88/62	Circular definition with CK-MB's statistics; strange AMI definition	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
McCord et al[65]	2001	Prospective	Myoglobin, troponin I	Cardiologist opinion + CK-MB	N=817 patients; 65 AMIs; 90–min sensitivity/specificity: myoglobin 85%/73%, CK-MB 83%/83%, troponin I 77%/79%, myoglobin + CK-MB 92%/68%, myoglobin + troponin I 97%/60%	Median delay from symptoms to presentation 4.3 h; multimarker study	II
Collinson et al[66]	2003	Multicenter, prospective, observational	Troponin T, CK-MB, myoglobin	ECG +/- doubling of CK-MB or MB>5	Third generation troponin T for diagnosis of AMI; sample size: 1,105 patients; 467 AMIs; TNT >0.03 ng/ml best predictor by AUC; CK-MB and troponin T equivalent at 2-6 h	Not much discussion of myoglobin or CK-MB	I
de Winter et al[67]	2000	Prospective	Serial myoglobin	WHO using CK-MB peak of >15 ng/ml	N=309 patients; 162 AMIs; ROC curve analysis of myoglobin determined optimal cutoff for myoglobin at 50 ng/ml giving sensitivity/specificity at 3 h and 5 h after symptom onset of 77%/90% and 98%/86% respectively	High CK-MB cutoff for diagnosis of AMI; low myoglobin cutoff	II
Ng et al[68]	2001	Prospective	Delta myoglobin, CK-MB, troponin I	WHO definition of AMI	N=1,285 patients; 66 AMIs; 90–min protocol using multimarkers (myoglobin, CK-MB, cTnI) with high sensitivity for AMI	40% of patients discharged without complete reporting of outcome; 98% male patients; >50% of patients presented after 6 h of symptoms; myoglobin in conjunction with cTnI demonstrated specificity of 98%; this is inconsistent with all other myoglobin studies and casts doubts on results	III
Sallach et al[69]	2004	Prospective/ retrospective	Serial myoglobin and troponin I	AMI defined by CK-MB elevation during 9-h protocol plus cardiologist opinion	N=817 patients; 75 AMIs; highest sensitivity with 90-min myoglobin + cTnI + delta myoglobin (97.3%); specificity not reported	Same population as McCord,[65] now with delta myoglobin and multimarker; second publication with same patient group suggests post-hoc analysis	III
Apple et al[70]	1999	Prospective	Myoglobin, CK-MB, troponin I	Modified WHO definition of AMI	N=192 patients; 59 AMIs; biosite triage panel of myoglobin, CK-MB, troponin compared with other standard assays; multimarker strategy showed highest sensitivity (87%) at <6 h with 67.4% specificity	Time reported as after ED presentation, not symptom onset	I

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
PRISM Study Investigators[78]	1998	Randomized, double blind, multicenter	Randomized to tirofiban or heparin for 48 h	Composite outcome of death, MI, or refractory ischemia at 48 h; secondary endpoints were composite outcome at 7 and 30 days	In this study there were 3,232 patients within 24 h of the chest discomfort with ST-segment depression, elevated cardiac biomarkers, or history of AMI, PCI within 6 mo, a positive functional study or angiogram with >50% lesion; all patients were on aspirin; at 48 h there was a significant difference in the composite endpoint in patients on tirofiban (RR 0.67, 95% CI 0.48-0.92); there was no difference between the groups at 7 and 30 days; at 30 days 62% of patients underwent angiography; there was no difference in bleeding between the 2 groups	The protocol allows for inclusion of a number of patients with a broad definition of unstable angina; in a subgroup analysis the study noted no difference in outcome based on time from symptom onset	II
PURSUIT investigators[79]	1998	Multicenter, randomized, double-blind, placebo-controlled trial	Randomized to receive placebo or high or low dose eptifibatide for 72 h (extending to 96 h if PCI was performed at 72 h)	Primary endpoint was a composite of death, or nonfatal AMI at 30 days; secondary endpoint was a composite death or nonfatal AMI at 96 h and 7 days	The study cohort was comprised of 10,948 patients with ACS defined as ischemic chest pain within 24 h and ECG changes of ischemia or elevated creatine kinase; all patients received aspirin and heparin; the mean length of time to randomization from symptom onset was 11 h; cardiac catheterization was performed in 59% of the patients; at 30 days there was a significant difference in the composite endpoint between the eptifibatide group and the placebo group (14.2% vs 15.7%, $P=0.02$); there was no difference in death or AMI when analyzed independently; subgroup analysis of the composite endpoint prior to PCI favored the eptifibatide group (1.7% vs 5.5%, $P<0.001$); there was an increase in transfusion in patients on eptifibatide (RR1.3, 95% CI 1.1-1.4)	The greatest decrease in the composite outcome appeared to be in patients undergoing PCI; although this was a pre-specified subgroup analysis, these patients were not randomized and there is subject to bias; treatment initiation with mean time of 11 h from symptom onset may be relevant to patients in the ED setting	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
CAPTURE Investigators or Simoons et al[82]	1997	Multicenter, randomized, placebo-controlled trial	Randomized to receive abciximab or placebo prior to and after cardiac catheterization	Composite endpoint of death, recurrent AMI, or urgent revascularization at 30 days	This is a trial of 1,265 patients with refractory unstable angina; refractory angina was defined as chest pain at rest with ECG changes or typical pain on medical management; patients were treated for 18-24 h prior to PTCA and >1 h after the procedure; the composite endpoint favored the abciximab group (11.3 vs 15.9, P=0.012); there was an increased risk of bleeding and transfusion in the abciximab group	This trial studies a specific group of patients that are going to have a PTCA, therefore the results of this trial cannot be used to support or refute the use of GP IIb/IIIa inhibitors in the ED setting	III
O'Shea et al[87]	2001	Multicenter, randomized, placebo-controlled trial	Randomized to receive eptifibatide or placebo immediately prior to PCI with stent placement and 18-24 h following the procedure	Death, AMI, target vessels revascularization at 6 mo	2,064 patients were randomized and followed 6 mo for the primary outcome; patients were undergoing nonurgent stenting; at 6 mo there was a decrease in death and AMI (hazards ratio 0.63, 95% CI 0.47-0.84); the composite outcome was decreased in eptifibatide group 14.2% vs 18.3% (hazards ratio 0.75, 95% CI 0.63-0.93).	Anatomy already defined therefore difficult to generalize to the ACS patient population	III
Peterson et al[98]	2003	Retrospective review of multicenter, registry data of patients with non–ST-segment elevation MI	None	GP IIb/IIIa inhibitor use within 24 h; inhospital events defined as all cause mortality, reinfarction, and major bleeding	60,770 patients from the NRMI registry, 25% of eligible patients received a GP IIb/IIIA; elderly, women, and minority patients were less likely to get treated with a GP IIb/IIIA inhibitor within 24 h; early (within 24 h) use was associated with decreased mortality after adjusting for covariates OR 0.88 (95% CI 0.79-0.97)	Utilizing registry data it is difficult to adjust for all treatments; patients who received no GPIIb/IIIA inhibitor were considered in the analysis as "late" use; the difference in mortality may be a result of the treatment not the time factor	III

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
Cadroy et al[103]	2000	Randomized, double blind, non-placebo controlled, crossover study; in vitro study using model of thrombo-genisis	325 mg aspirin vs 325 mg aspirin + 75 mg clopidogrel vs. 325 mg aspirin +300 mg loading dose clopigogrel followed by 75 mg	Thrombus formation was determined on a collagen-coated surface; fibrin deposition was quantified by immunological determination of fibrin degradation products of plasmin-digested thrombi, and platelet deposition was determined by measurement of a specific alpha-granule membrane protein p-selectin	On day 10, there was 24% and 35% reduction in platelet and fibrin deposition with aspirin alone, while there was a 71% and 74% reduction with aspirin and clopidogrel ($P<0.001$); aspirin did not fully express its antithrombotic effects on day 1; on day 1 aspirin decreased platelet deposition by $<10\%$, while on day 10 platelet deposition was decreased by 24% ($P=0.03$); without loading dose, clopidogrel + aspirin developed moderate antithrombotic effects within 6 h, with reduction of 34% in platelet and 60% in fibrin deposition ($P=0.042$ and $P<0.001$); with loading dose clopidogrel, antithrombotic effects of clopidogrel + aspirin appeared within 90 min; as early as 6 h after the first dose it was very potent; there was 61% and 75% platelet and fibrin reduction ($P<0.001$) and comparable to levels reached at 10 days	Small sample size; sample population (young healthy males) is not a representation of the general population; in vitro model of human thrombogenisis	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
Yusuf et al[105]	2001	Multicenter, randomized, double blind, placebo-controlled trial	Clopidogrel vs placebo	Abnormal laboratory tests, ECG abnormalities, transfusion requirements, neurological physical examination, and death; co-primary outcomes: composite of cardiovascular death, AMI, or stroke; the composite of cardiovascular death, AMI, stroke or refractory ischemia; life-threatening bleeding, fatal bleed, leading to 5 g/dl drop in hemoglobin, substantial hypotension requiring inotropes, surgical intervention or requiring 4 units of PRBC, or resulting in intracranial bleed; major bleeding, substantially disabling bleed, intraocular bleeding leading to loss of vision, bleeding requiring 2 units of PRBC	At 12 mo, the first primary outcome, a composite of death from cardiovascular causes, MI, or stroke, occurred less often in the clopidogrel group (9.3% vs 11.4%, $P<0.001$, RR 0.80, 95% CI 0.72 to 0.90); the second primary outcome-composite of the first primary outcome or refractory ischemia was lower in the clopidogrel group (16.5% vs 18.8%, $P<0.001$, RR 0.86%, 95% CI .79 to 0.90); the percentage of patients with inhospital refractory or severe ischemia, heart failure, and revascularization procedures were also significantly lower with clopidogrel; major bleeding episodes were higher in the clopidogrel group than the placebo group (3.7% vs 2.7%, $P=0.001$, RR 1.38, 95% CI 1.13-1.67), but there was no statistically significant increase in life-threatening bleeds in the clopidogrel group (2.1% vs 1.8%, $P=0.13$); in patients undergoing CABG, 910 stopped clopidogrel >5 days prior to CABG and showed no increase in the rate of major bleeds; while, 912 stopped clopidogrel within 5 days of CABG; in the second group 9.6% in the clopidogrel group and 6.3% in the placebo group had major bleeding ($P=0.06$)	Not a study looking at starting clopidogrel in the ED; a relatively small amount of patients received early PCI, thus results are more applicable to patients receiving only medical management; applies to ACS patients who have ECG changes on presentation or elevation in cardiac markers 2x upper limit of normal at presentation; results are not statistically significant in the CABG group	II

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
Yusuf et al[106]	2003	Multicenter, randomized, double blind, placebo-controlled trial; subdivision analysis of the CURE study analyzing the endpoints at different times 24 h, 30 days, and at 12 mo	Clopidogrel vs placebo	Abnormal laboratory tests, ECG abnormalities, transfusion requirements, neurological physical examination, and death; co-primary outcomes: 1) composite of cardiovascular death, AMI, or stroke; 2) the composite of cardiovascular death, AMI, stroke, refractory ischemia, or severe ischemia	Mean time from pain onset to randomization 14.2 h; from randomization to 30 days, the first primary outcome occurred less in the clopidogrel group (4.3% vs 5.4%, $P<0.004$); the second primary outcome was lower in the clopidogrel group (7.7% vs 9.2%, $P<0.002$); at 24 h after randomization, the secondary outcome was significantly lower in the clopidogrel group (1.4% vs 2.1%, $P<0.003$); there was a trend toward reduction of the primary outcomes, with a 20% RRR and a 34% RRR in the secondary outcome; within 24 h, in the clopidogrel group, only the secondary outcome results were statistically significant; there was no increase in the number of major bleeds within the first 24 h with clopidogrel; the number of major vascular events prevented during any period was much greater than the risk of bleeding	Not a study looking at starting clopidogrel in the ED; a relatively small number of patients received early PCI, thus results are more applicable to patients receiving only medical management; applies to ACS patients who have ECG changes on presentation or elevation in cardiac markers 2 times the upper limit of normal at presentation	II

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
Mehta et al[108]	2001	Prospective, double blind study; 2,658 patients from the CURE study who had PCI	Clopidogrel vs placebo treatment prior to PCI	Primary endpoint, cardiovascular death, MI, or urgent target vessel revascularization within 30 days of PCI	1,730 patients had PCI during initial hospital stay at a median of 6 days post randomization; 928 patients had PCI post initial discharge; the overall median time from randomization to PCI was 10 days; the primary endpoint occurred less in the group pretreated with clopidogrel (4.5% vs 6.4%, RR 0.70, P=0.03, 95% CI 0.50-0.97); the rate of cardiovascular death in the 2 groups was similar; there was more minor bleeding in the clopidogrel group; subgroup analysis of clopidogrel group showed that in patients who received PCI <72 h post randomization the clopidogrel group did better 8.5% vs 13.5%; however, no P value is presented; long-term treatment with clopidogrel after PCI was associated with lower rate of primary endpoint; before PCI significantly fewer patients in the clopidogrel group had AMI or the composite of AMI or refractory ischemia	Possible selection bias as there was no randomization of who was going to receive PCI; 25% of patients in both groups received open label thienopyridine prior to PCI, this may decrease the benefit calculated in the clopidogrel group	II

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
Steinhubl et al[109]	2002	Randomized, double-blind, placebo-controlled trial	Clopidogrel vs placebo treatment prior to elective PCI	Death, laboratory tests, abnormal ECG, or revascularization by PCI or CABG	Mean time clopidogrel administration prior to PCI was 9.8 h; pretreatment with clopidogrel was associated with nonsignificant 18.5% RRR in AMI death, and urgent target vessel revascularization at 28 days (6.8% vs 8.3%, RRR 18.5%, $P=0.23$, 95% CI −14.2% to 41.8%); 51% of patients received clopidogrel 3-6 h prior to PCI; 49% of patients received clopidogrel 6-24 h prior to PCI; subgroup analysis: patients who received loading dose 3-6 h prior to PCI showed no benefit from pretreatment; patients who received loading dose 6-24 h prior to PCI showed a RRR 38.6% ($P=0.051$, 95% CI −1.6%-62.9%), suggesting that 300 mg loading dose more than 6 h prior to PCI may provide benefit; trend toward benefit was suggested in patients who received pretreatment glycoprotein IIbIIIa; long-term clopidogrel therapy was associated with 26.9% RRR of death, AMI, or stroke ($P=0.02$)	Patients were not having ACS, they were scheduled for elective PCI, this is not the population that we see in the ED; post PCI group not randomized thus long term effects could possibly be secondary to pretreatment; 7,684 pts excluded from study for "other" reasons; more glycoprotein IIbIIIa was used in the clopidogrel group than placebo group, although the difference was not statistically significant	III

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/ Criterion Standard	Results	Limitations/ Comments	Class
Hongo et al[110]	2002	Prospective cohort; 224 patients undergoing nonemergent CABG	Preoperative clopidogrel within 7 days of nonemergent CABG vs. no clopidogrel exposure within 7 days of CABG	Postoperative bleeding measures: chest tube output, need for transfusion; clinical outcome measures included: reoperation for bleeding, severe low cardiac output, AMI, stroke and postoperative atrial fibrillation; severe low cardiac output = need of multiple pressors, or intraaortic balloon pump for longer than 24 h	The clopidogrel group had higher mean chest tube output at both 8 h (775 ml vs 516 ml, P= 0.005) and 24 h (1,224 ml vs 840 ml, P=0.001); only 15 % of patients in the clopidogrel group were free of blood products, while approximately 39% of patients in the no clopidogrel group were spared from transfusion; the clopidogrel group had a 10 fold higher incidence of need for re-operation secondary to bleeding (6.8% vs 0.6%, P=0.018); within the clopidogrel group those with preoperative aspirin use did show higher chest tube output and need for transfusion than those without aspirin exposure; however, the findings were not statistically significant, possibly because the number of patients receiving only clopidogrel was small	2 groups being compared were not the same in that the patients in the clopidogrel group were sicker patients (71.1% vs 47.9% had class III-IV angina); confounding variable: more patients in the clopidogrel group were on aspirin than in the placebo group (86.4% vs 47.3%)	II
Englberger et al[111]	2004	Prospective cohort study; 505 consecutive patients undergoing CABG looking at exposure to clopidogrel within 72 h vs no exposure	Clopidogrel exposure within 72 h of CABG vs no exposure	Postoperative bleeding measures: chest tube output, need for platelet or fresh frozen plasma transfusion; clinical outcome measures: need for re-exploration, duration of ICU stay, duration of total hospital stay, duration of mechanical ventilation	Patients on clopidogrel had higher chest tube drainage in 24 h (1,485 vs 780 ml, P=0.03); patients on clopidogrel had more platelet and PRBC requirement; re-exploration rates were higher in the clopidogrel group, 5.9 % vs 1.2%, P<0.01; 30-day mortality and clinical outcome measures were comparable for the 2 groups	Confounding variables: the clopidogrel group was a sicker population than the control group; 67% vs 39% had class III/IV angina, and 57% vs 13% had prior PTCA with stent, respectively	II

ACS, acute coronary syndrome; *AMI*, acute myocardial infarction; *ASSENT*, Assessment of Safety and Efficacy of a New Thrombolytic; *CABG*, coronary artery bypass graft; *CI*, confidence interval; *CCU*, cardiac care unit; *CK-MB*, creatine kinase-MB; *CURE*, Clopidogrel in Unstable angina to prevent Recurrent Events; *RR*, relative risk; *ED*, emergency department; *ECG*, electrocardiogram; *h*, hour; *ICU*, intensive care unit; *MI*, myocardial infarction; *min*, minute; *mo*, month; *NRMI*, National Registry of Myocardial Infarction; *OR*, odds ratio; *PCI*, percutaneous coronary intervention; *PRBC*, packed red blood cells; *PTCA*, percutaneous transluminal coronary angioplasty; *ROC*, receiver operating characteristic; *RRR*, relative risk reduction; *STEMI*, ST-segment elevation myocardial infarction; *WHO*, World Health Organization.

Appendix A. Literature classification schema.*

Design/Class	Therapy[†]	Diagnosis[‡]	Prognosis[§]
1	Randomized, controlled trial or meta-analyses of randomized trials	Prospective cohort using a criterion standard	Population prospective cohort
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
[†]Objective to measure therapeutic efficacy comparing ≥2 interventions.
[‡]Objective to determine the sensitivity and specificity of diagnostic tests.
[§]Objective to predict outcome including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

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