Session I. Recommendations for Markers in the Triage of Patients with Chest Pain

Introduction to Section I

Coronary artery disease remains today as the leading cause of morbidity and mortality throughout the western world. In the U.S. alone, 8 million out of the total of 95 million annual visits to the emergency department (ED)[7] is for a presentation of acute chest pain (Figure 1)(1). Of this total, 5 million are suspected of acute cardiac disease. The annual incidence of unstable angina (UA) and acute myocardial infarction (AMI) is 1.2 and 1.0 million, respectively. Sudden acute cardiac death occurs in about 300 thousand patients, while the remainder have a non-cardiac cause of chest pain and are discharged from the ED. The differential diagnosis of acute chest pain is summarized in Table 1. Several of the diagnoses listed have a low probability of being the etiology of the chest pain. Nevertheless, the ED physician must rule them out, as many carry a significant potential for producing morbidity and mortality.

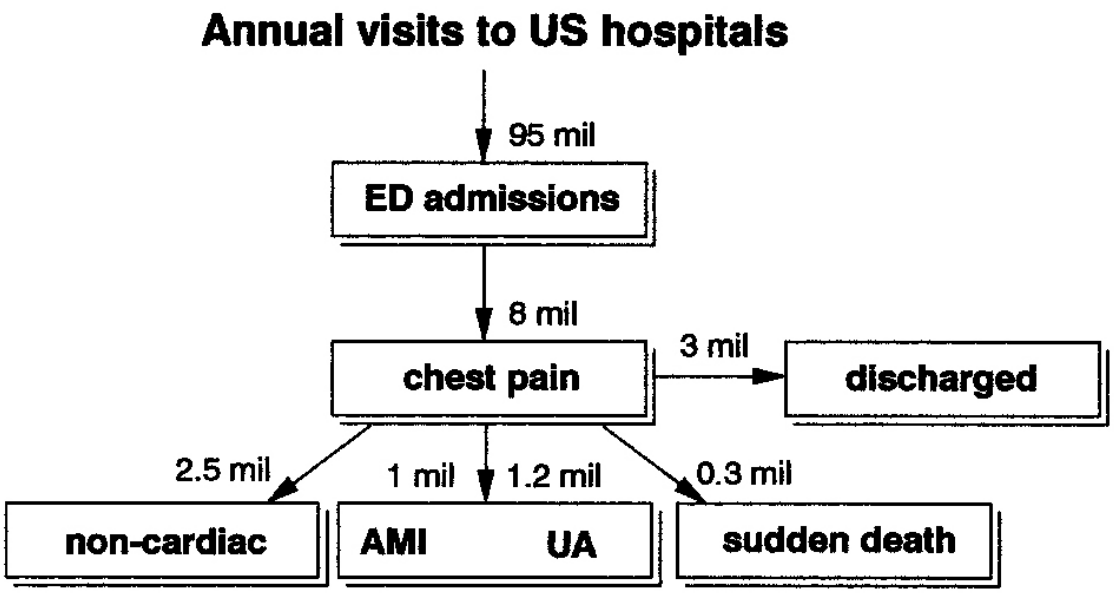

Fig. 1. Demographics and outcomes of patients who present to emergency departments in the U.S. with chest pain.

Table 1. Common cause of chest pain[a]

Cardiac	Pulmonary	Others
Ischemic syndromes	Bronchitis	*Vascular*
Stable angina	Bronchospasm	Aortic dissection
Unstable angina	Empyema	Pulmonary embolism
Variant angina	Pleural effusion	Pulmonary hypertension
AMI	Pleuritis	*Gastrointestinal*
Valvular disease	Pneumonia	Esophageal spasm
Mitral valve prolapse	Pneumothorax	Gastroesophageal reflux
Aortic stenosis	Pulmonary edema	Mallory-Weiss tear
Subaortic stenosis	Aortic dissection	Esophagitis/gastritis
Cardiomyopathy	Pulmonary embolism	Gastric/duodenal ulcer
Pericarditis	Pulmonary hypertension	Biliary colic
		Musculoskeletal
		Costochondritis
		Muscle strain/spasm
		Cervical radiculopathy
		Neurologic
		Herpes Zoster

aTaken from Green GB, Green SF. Markers of myocardial injury in the evaluation of the emergency department patient with chest pain. In: Wu et al. ed., Cardiac Markers, Totowa NJ: Humana Press, 1998, p. 77.

Recommendation 1

The triage of patients with chest pain from the emergency department is one of the most difficult challenges that face ED physicians today. Admission of patients with a low probability of acute coronary artery disease often leads to excessive hospital costs (2). A strategy that is too liberal with regard to ED discharges may lead to higher numbers of patients released with acute myocardial infarction (AMI). As summarized in Table 2, inappropriate discharge of ED patients who have AMI has been estimated to occur in 2-13% of patients and is the single most common cause of malpractice lawsuits against ED physicians today (3-11).

Table 2. Rate of inappropriate discharge from the ED for patients with AMI

Study	Year	Percentage
Pozen et al. (5)	1984	7%
Tierney et al. (6)	1986	13%
Lee et al. (7)	1987	4%
Rouan et al. (8)	1987	10%
McCarthy et al. (9)	1993	2%
Puleo et al. (10)	1994	5%
Graff et al. (11) 1997		4.5%

Recommendation: Members of emergency departments, divisions of cardiology, hospital administration, and clinical laboratories should work collectively to develop an accelerated protocol for use of biochemical markers for the evaluation of patients with possible acute coronary syndromes (ACS).

Strength/consensus of recommendation: Class I.[8]

For simplicity, this protocol should apply to either the facilitated diagnosis or the rule-out of AMI in the ED or to routine diagnosis from other areas of the hospital, should a patient develop symptoms consistent with acute coronary syndromes while hospitalized.

Strength/consensus of recommendation: Class II.

Many hospitals today have a dedicated area within the ED for the rapid rule-out of AMI. These areas have been designated as "chest pain centers", "heart emergency rooms", or some other terms to indicate that the efficient triage of chest pain patients is a major objective of that center. Figure 2 lists the necessary elements of a chest pain center. Essential for early AMI rule-out is frequent electrocardiographic (ECG) testing and blood collections for the measurement of cardiac markers. Patients with negative results for these tests most likely do not have an AMI. They may, however, have unstable angina or other forms of acute cardiovascular disease. For these patients, it is

appropriate to perform additional studies such as a stress test, echocardiogram, or radionuclide ventriculogram for risk stratification. Establishment of a clinical practice guideline for the evaluation of patients with chest pain will reduce the variability of practices among physicians and institutions, at the same time improving the accuracy of triaging decisions (13). The NACB Committee felt that for "routine AMI diagnosis" of patients who are already hospitalized for other reasons, the same principles and criteria should apply as are used in the ED.

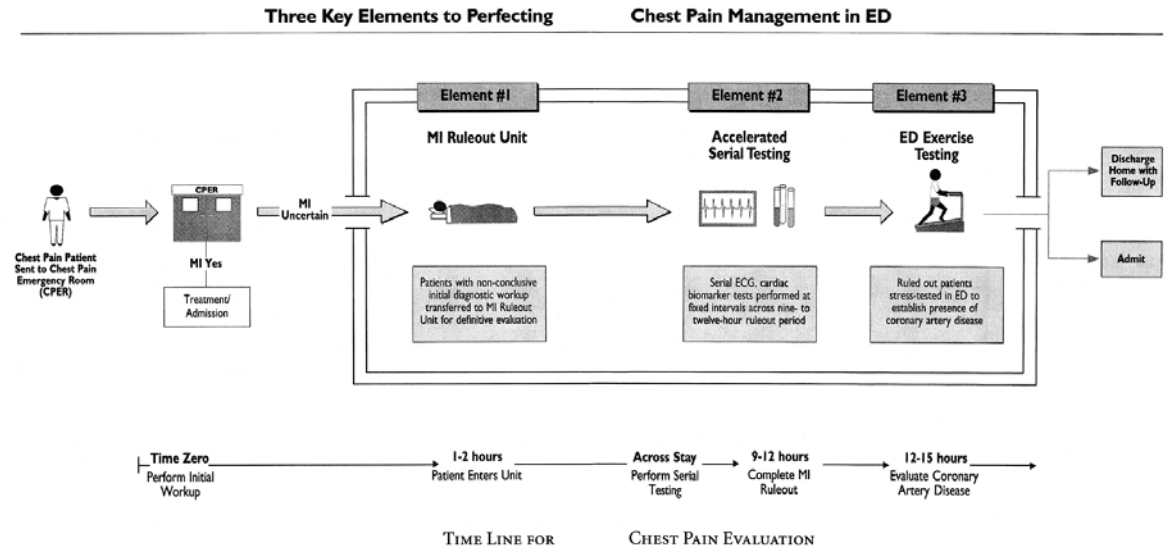

Fig. 2 Time line for chest pain evaluation centers. From perfecting MI Ruleout. Best Practices for emergency evaluation of chest pain. Cardiology Preeminence Roundtable, Wahington, DC, 1994, used with permission.

Discussion

Although the recommendation that laboratorians should work with ED physicians, cardiologists, and hospital administration may appear obvious, in actual practice, decisions on testing protocols are often made without input from the laboratory. Laboratory directors must be aggressive in requesting that qualified personnel be part of organizational and operating committees when such discussions are being conducted,

or should initiate the discussions themselves. Understanding the expanded role that the laboratory will play in creating these rule-out centers will enable justification to hospital administrators for the additional laboratory expenses that will be required. This argument will be particularly effective if the overall objective of reducing in-hospital lengths of stay and the numbers of unnecessary admissions or wrongful discharges from the ED can be demonstrated.

The diagnosis of AMI is not always made in the ED. Sometimes patients admitted for other reasons develop symptoms for AMI while in the hospital. Some physicians or administrators may believe that rapid AMI rule-out of hospitalized patients may not be as important as triage for ED patients. Nevertheless, the NACB Committee felt that the same protocol used in the ED is appropriate for routine AMI diagnosis because new therapies for acute coronary syndromes are available, and, when appropriate, should be delivered rapidly. The use of a rapid AMI rule-out protocol will simplify the steps needed from the laboratory's perspective and provide clinicians optimum diagnostic measures for all patients.

Recommendation 2

Although the time of onset of chest pain for AMI patients is often known, this information often is less available or reliable for those with unstable angina and other cardiac diseases. It is not uncommon for these patients to report multiple episodes of chest pain over the hours and days before ED presentation. Intermittent closure and spontaneous reperfusion of coronary arteries with ruptured atherosclerotic plaques reflect the dynamic nature of acute coronary syndromes. In the elderly or in patients with insulin-dependent diabetes mellitus type I, there may be altered thresholds or a blunted response to pain. Indeed, there are many patients with acute coronary syndromes who experience silent ischemia and infarction (i.e., no pain during occlusive episodes) (14).

Recommendation: For routine clinical practice, blood collections should be referenced relative to the time of presentation to the ED and (when available) the reported time of chest pain onset.

Strength/consensus of recommendation: Class I.

Discussion

In the early drafts of the Guidelines, the recommendations were that all blood collections should be referenced to the time of ED presentation only. However, many reviewers felt it important to also note the time of onset of chest pain, especially when there is a history of a single chest pain event (and not several events over many days) and when the time of onset as reported by the patient or family is deemed to be reliable. It may also provide an explanation as to why some clinical studies fail to document a consistent rise in the concentration of the marker, e.g., at 6 h, whereas other studies indicate that the markers were increased at this time point in all patients (e.g., when the majority of enrolled patients in the study present beyond 6 h of chest pain).

Recommendation 3

The ideal biochemical marker would be one that has high clinical sensitivity and specificity, appears early after AMI to facilitate early diagnosis, remains abnormal for several days after AMI, and can be assayed with a rapid turnaround time (15,16). Because there currently is no single marker that meets all of these criteria, a multianalyte approach has the most merit.

Because the interval between the onset of pain and ED presentation is variable from patient to patient, two markers are needed to enable detection of patients who present either early or late. Currently, myoglobin is the marker that most effectively fits the role as an early marker. A rise in myoglobin is detectable in blood as early as 1-2 h

after onset and can be highly effective for AMI rule-out (Fig. 3, peak A)(17). Moreover, automated immunoassays for myoglobin are commercially available. Myoglobin is not cardiac specific, and patients with renal failure, skeletal muscle injury, trauma, or disease can have abnormal concentrations in the absence of AMI (18). The creatine kinase MB (CK-MB) isoforms (also termed "subforms") have also been shown to be an early marker for AMI (10). Automated stat CK-MB isoform measurements are being used in some hospitals as an early measure of myocardial injury. Moreover, it may also be possible that troponin can be used as an early marker if new assays are developed that are more sensitive than current ones (19). In an ED study, qualitative measurement of cardiac troponin T and I (cTnT and cTnI) using point-of-care (POC) devices were reliable for ruling out AMI at 6 h after onset of symptoms (20). These studies, however, were not confirmed by a more recent study of chest pain patients that used quantitative laboratory-based assays for troponin (21). Clearly, more studies are needed to fully address the role of troponin T and I in early diagnosis.

In contrast, cTnT and cTnI are currently the best markers for definitive AMI diagnosis. Troponins appear in the serum relatively early after the onset of symptoms (4-12 h) and remain abnormal for 4-10 days (Fig. 3, peak B). Results are not increased in the presence of skeletal muscle troponin (22,23). Early studies have questioned the clinical specificity of cTnT assays in patients with chronic renal failure (24,25). With the development of a second- and third-generation ELISA assay for cTnT, the frequency of positive results in these patients is lower than the frequency in the first-generation assay, although still higher than for cTnI (26,27). Western blot analysis on regenerating human skeletal muscle tissue showed that the cardiac isoforms of troponin T are expressed in pathologic conditions (such as renal disease, polymyositis and muscular dystrophy) (28). However, subsequent studies have shown that the antibodies used in the Roche commercial assays are specific for myocardial cTnT isoforms, do not detect

the cTnT isoforms expressed in diseased skeletal muscle, and therefore, do not produce false-positive cTnT results in renal patients (29,30).

Preliminary outcomes studies have shown that chronic renal failure patients who have high cTnT concentrations in blood have a higher incidence of cardiac death than those with normal concentrations, confirming the notion that troponin is measuring true myocardial injury that is not associated with or classified as an AMI (31). The importance of these findings is not completely known. Are there therapies that can be administered to reduce the short-term mortality of renal failure patients with a positive troponin result? How does risk stratification with troponin compare with other indicators of renal function? One study showed that measurement of the troponins in patients with both acute coronary syndromes and renal insufficiencies reduces the effectiveness for risk stratification of chest pain patients based on cTnT and cTnI monitoring (32). As more studies are completed in this area, a meta-analysis may be necessary to resolve these continuing issues.

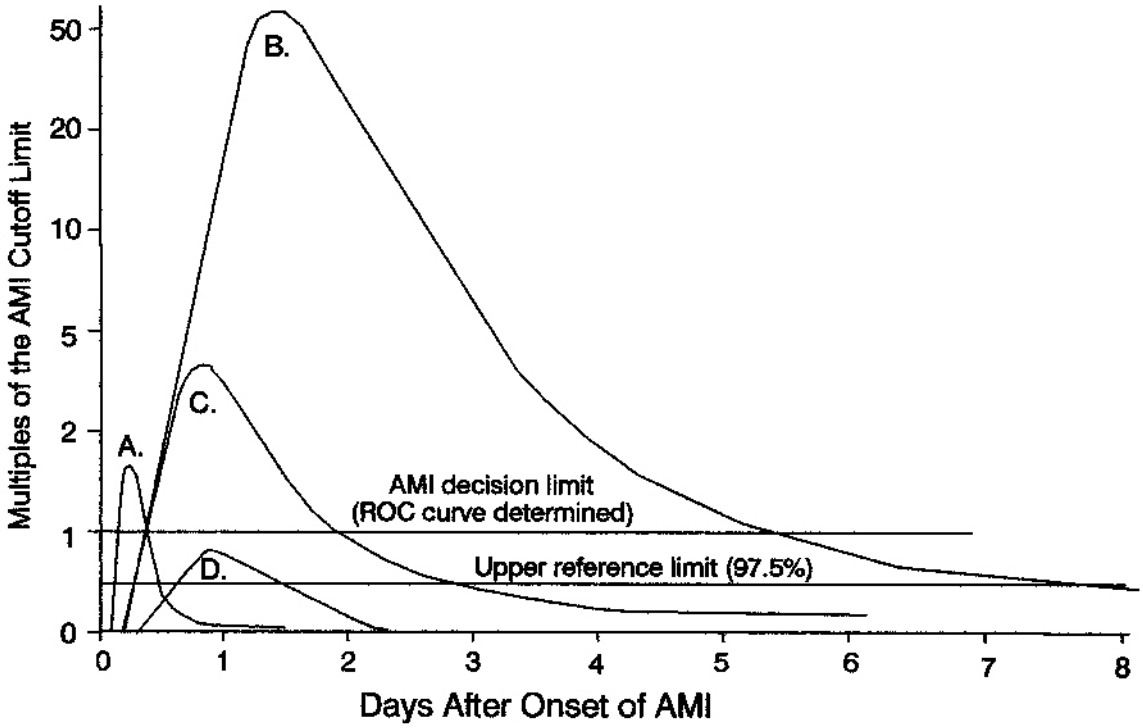

Fig. 3. Plot of the appearance of cardiac markers in blood vs time after onset of symptoms. Peak A, early release of myoglobin or CKMB isoforms after AMI; peak B, cardiac troponin after AMI; peak C, CK-MB after AMI; peak D, cardiac troponin after unstable angina. Data are plotted on a relative scale, where 1.0 is set at the AMI cutoff concentration.

Recommendation: Two biochemical markers should be used for routine AMI diagnosis: an early marker (reliably increased in blood within 6 h after onset of symptoms) and a definitive marker (increased in blood after 6-9 hours but has high sensitivity and specificity for myocardial injury, remaining abnormal for several days after onset).

Strength/consensus of recommendation: Class II.

Discussion

The merits of myoglobin, as the early marker, have been debated by many reviewers and conference participants. Although there is ample literature suggesting that myoglobin is an early marker (33-35), there are reports that support the view that

myoglobin is not any earlier than CK-MB mass assays (36). These critics feel that the poor specificity of myoglobin (in the presence of skeletal muscle disease or renal failure) does not justify its routine use as a cardiac marker. However, there is increasing pressure by ED physicians and hospital administrators to rule out AMI sooner. Some chest pain centers have begun to discharge patients within 6 h of ED presentation. CK-MB is not reliably increased at this interval after AMI, and myoglobin may have a role in this situation. As an alternative to myoglobin, a minority of laboratories have begun using CK-MB isoforms as an early AMI marker (21,37). (In a poll taken during the AACC Annual Meeting, <1% of conference participants indicated that they were currently using isoforms.) Currently, CK-MB isoforms are most effectively measured by high-voltage electrophoresis (38). With improvements in analytical methodologies, the number of laboratories routinely using isoforms might increase. The NACB Committee recognizes the limitations of myoglobin and CK-MB isoforms and encourages continued research into earlier markers, particularly if they are more specific for myocardial necrosis. In the meantime, the NACB Committee believes that myoglobin is an earlier marker than CK-MB mass and is more conveniently measured on automated immunoassay analyzers than CK-MB isoforms.

Recommendation 4

Large studies in New York and Texas have shown that about 50% of AMI patients will present to the ED with evidence of acute myocardial infarction on the electrocardiogram (ECG) (39). Acute intervention with thrombolytic therapy or angioplasty should be considered in those patients who present within 12 h after the onset of symptoms (40,41). Specific ECG changes are highly diagnostic for AMI when interpreted by well-trained physicians (42).

Recommendation: In patients with a diagnostic ECG on presentation (ST-segment elevations, presence of Q waves or left bundle branch block in two or more contiguous leads), the diagnosis of AMI can be made and acute treatment initiated without results of acute cardiac marker testing.

Strength/consensus of recommendation: Class I.

In AMI patients with diagnostic ECGs, biochemical marker testing at a reduced frequency of blood collection (e.g., twice per day) is valuable for confirmation of diagnosis, to qualitatively estimate the size of the infarction, and to detect the presence of complications such as a reinfarction.

Strength/consensus of recommendation: Class I.

Discussion

The NACB Committee sought advice from ED physicians and cardiologists as to why cardiac markers are still being ordered on patients with ECG-documented AMI, when in many cases, therapy had already been initiated before results of tests were available from the laboratory. Although most physicians recognize that in this context, these tests do not serve a diagnostic role, many felt that biochemical documentation of AMI was necessary to complete the triad of criteria established by WHO for AMI diagnosis (43). It is also likely that a positive result for a cardiac marker in these patients provided a level of comfort and confidence to the attending staff. Many physicians also felt that knowing the peak concentration of a cardiac marker provided a qualitative estimate of infarct size (without calculating the area under the curve of marker

concentration vs time). This information might have a role in the future management of surviving AMI patients.

Many conference participants also felt that continued measurement of markers was helpful in detecting the presence of a reinfarction, estimated to be 17% of AMI patients (44). If the reinfarction occurs before there is complete clearance of the marker from the original infarct, it might not be possible to detect the presence of the reinfarction because the markers released from the second event might be indistinguishable from that released by the initial event. For this reason, the use of cardiac markers that return to baseline concentrations early may have an advantage over the use of markers that are slow to clear from the circulation. For example, myoglobin and CK-MB isoforms return to reference values typically within 24 h after AMI (Fig. 3, peak A). If a reinfarction were to occur after this time, increases in the concentration or activity of these proteins would enable detection of a second necrotic event. CK-MB mass can also be considered as a reinfarction marker that returns to baseline concentration reasonably early (but not as early as myoglobin). Many reinfarctions occur between 7 and 14 days after the initial event. Because CK-MB remains abnormal for 3-4 days (Fig. 3, peak C), CK-MB may be useful to detect a reinfarction even if the event is not immediately suspected by the medical staff. CK-MB mass would show a secondary increase, whereas myoglobin and CK-MB isoforms could have returned to baseline concentrations (Fig. 3, peak A). Alternatively, one could request that the laboratory retrieve a stored specimen for myoglobin or isoform testing if available because serum myoglobin is stable for several days if refrigerated (45), and isoforms are stable when collected with EDTA (46).

Recommendation 5

For AMI rule-out of patients who have equivocal ECG changes, cardiac markers play an essential diagnostic role in non-Q-wave AMIs. Unfortunately, there is great

variability between hospitals in the frequency of blood collections. In 1986, the American College of Physicians recommended a conservative testing guideline based on total CK and CK-MB for blood collected on admission and at 12 and 24 h after admission, and the use of lactate dehydrogenase isoenzymes when admission is >24 h after onset (47). The NACB Committee believes that this strategy is no longer adequate to meet the current triaging needs.

Rule-out of AMI requires serial collection and testing of blood for cardiac markers. When an early marker such as myoglobin is used, acute myocardial necrosis can be effectively ruled out within 6-9 h after ED presentation (48,49), and a decision to discharge the patient to home or a to low care level bed can be considered. On the other hand, for AMI rule-in, a single positive result for either troponin T or I would trigger a diagnosis of AMI and triage of the patient to the appropriate level of care (14), without the need for necessarily completing this algorithm (50,51). This recommendation was made because, unlike myoglobin, CK, CK-MB, and lactate dehydrogenase, positive results for cTnT and cTnI are highly indicative of myocardial damage, with no release of these proteins from skeletal muscles or other tissues (52,53).

Recommendation: For detection of AMI by enzyme or protein markers, in the absence of definitive ECGs, the following sampling frequency is recommended:

marker	admission	2-4 h	6-9 h	12-24 h
early (<6 h)	x	x	x	(x)
late (>6 h)	x	x	x	(x)

(x) indicates optional determinations.

Strength/consensus of recommendation: Class II.

Discussion

The need to perform the 2-4 h blood collection for the late marker can be questioned. In particular, negative results at admission and at 2-4 h after admission for myoglobin, and a negative result for cardiac troponin at admission would obviate the need for measuring troponin in the 2-4 h sample. The NACB Committee felt that most laboratories do not currently have a mechanism for automatic "reflex testing" (i.e., testing that involves the ordering or cancellation of follow-up tests on a given sample based on results of preliminary tests). Therefore, it is more convenient for the laboratory to perform testing for both markers on all samples, rather than to hold specimens until results of preliminary tests (i.e., the early markers) are known.

Among chest pain centers, there are many variations to the protocol for blood sampling and the total number of samples needed for AMI rule-out. Some centers use intervals of every 3 h, whereas others use every 4 h. In one study using POC devices, chest pain patients were triaged on the basis of only two samples collected: one at admission and one at 4 h (20), with a third sample collected only on patients presenting with a 2 h history of chest pain. Because of the unreliability of the chest pain history, the NACB Committee has taken a more conservative approach of recommending the collection of at least three blood samples during the early triage period. A blood collection at 12-24 h may be useful for the detection of reinfarction or myocardial extension or for risk stratification of patients with unstable angina. Investigators have found that a 16-h blood sample adds additional value for risk stratification over the initial blood sample (54).

Recommendation 6

Some EDs have not yet developed a rapid rule-out chest pain center because of financial limitations, space, and/or a lack of knowledge of the potential benefits. In these centers, the extra laboratory tests bring additional costs without benefits in terms of

reduced hospital lengths of stay or frequency of inappropriate discharges of patients with AMI.

Recommendation: For those Eds in which patient triage decisions are not made within the first few hours after ED presentation, the use of an early marker such as myoglobin may be unnecessary. In this case, only one definitive marker such as cardiac troponin is needed. The frequency of blood collection should also be reduced.

Strength/consensus of recommendation: Class I.