National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical Characteristics and Utilization of Biochemical Markers in Acute Coronary Syndromes

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I. Overview of the Acute Coronary Syndrome

A. DEFINITION OF TERMS

Acute coronary syndrome (ACS)[8] refers to a constellation of clinical symptoms caused by acute myocardial ischemia *(1, 2)*. Owing to their higher risk for cardiac death or ischemic complications, patients with ACS must be identified among the estimated 8 million patients with nontraumatic chest symptoms presenting for emergency evaluation each year in the US *(3)*. In practice, the terms *suspected* or *possible* ACS are often used by medical personnel early in the process of evaluation to describe patients for whom the symptom complex is consistent with ACS but the diagnosis has not yet been conclusively established *(1)*.

Patients with ACS are subdivided into 2 major categories based on the 12-lead electrocardiogram (ECG) at presentation (Fig. 1): those with new ST-segment elevation on the ECG that is diagnostic of acute ST-elevation myocardial infarction (STEMI) and those who present with ST-segment depression, T-wave changes, or no ECG abnormalities (non–ST elevation ACS, NSTEACS). The latter term (NSTEACS) encompasses both unstable angina and non–ST elevation myocardial infarction (NSTEMI). This terminology has evolved along clinical lines based on a major divergence in the therapeutic approach to STEMI vs NSTEACS (see section IB). Unstable angina and NSTEMI are considered to be closely related conditions, sharing a common pathogenesis and clinical presentation but differing in severity *(1)*. Specifically, NSTEMI is distinguished from unstable angina by ischemia sufficiently severe in intensity and duration to cause irreversible myocardial damage (myocyte necrosis), recognized clinically by the detection of biomarkers of myocardial injury *(4)*.

B. PATHOGENESIS AND MANAGEMENT

It is important to recognize that ACS is a complex syndrome with a heterogeneous etiology, analogous to anemia or hypertension *(5)*. Nevertheless, the most common cause is atherosclerotic coronary artery disease with erosion or rupture of atherosclerotic plaque, exposing the highly procoagulant contents of the atheroma core to circulating platelets and coagulation proteins, and culminating in formation of intracoronary thrombus *(6–8)*. In
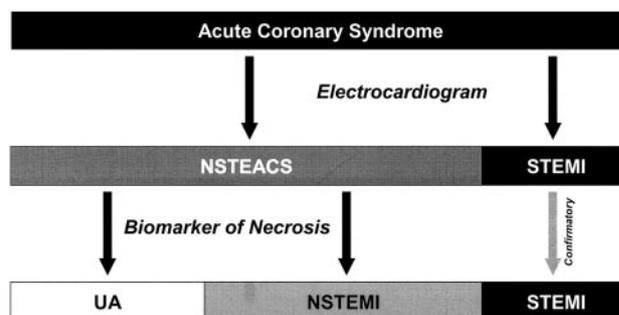

Fig. 1. Categorization of acute coronary syndromes.

the majority of patients presenting with ACS, the thrombus is partially obstructive, or only transiently occlusive, resulting in coronary ischemia without persistent ST-segment elevation (unstable angina or NSTEMI). In the remaining ~30% of patients with ACS *(9)*, the intracoronary thrombus completely occludes the culprit vessel, resulting in STEMI. Antithrombotic and antiplatelet therapies aimed at halting the propagation or recurrence of coronary thrombus are central to management of the majority of patients across the entire spectrum of ACS *(1, 2, 10)*. The subgroup of patients with STEMI consists of candidates for immediate reperfusion therapy with either fibrinolysis or percutaneous coronary intervention *(10)*. In contrast, fibrinolysis appears to be harmful in patients with NSTEACS *(1, 11)*.

Including the most common etiology of ACS described above, 5 principal causes have been described: *(1)* plaque rupture with acute thrombosis; *(2)* progressive mechanical obstruction; *(3)* inflammation; *(4)* secondary unstable angina (e.g., due to severe anemia or hyperthyroidism); and *(5)* dynamic obstruction (coronary vasoconstriction) *(12)*. It is rare that any of these contributors exists in isolation. Because patients with ACS vary substantially with respect to the mixture of contributions from each of these major mechanisms, and, as such, are likely to benefit from different therapeutic approaches, characterization of the dominant contributors for an individual patient can be valuable in guiding their care *(12)*. With the emergence of newer biomarkers that reflect the diverse pathobiology of acute ischemic heart disease, their use as noninvasive means to gain insight into the underlying causes and consequences of ACS is being investigated *(13)*.

Commensurate with the heterogeneous pathobiology of ACS, the risk of subsequent death and/or recurrent ischemic events also varies widely. As a result, effective risk stratification and targeting of therapy is a focus of contemporary clinical management of this condition *(14, 15)*. In addition, among patients with definite ACS, early treatment may reduce the extent of myocardial injury; therefore, rapid diagnosis and initiation of therapy is also a central tenet of management *(1)*. It follows that the objectives of the initial evaluation of patients with

[8] Nonstandard abbreviations: ACS, acute coronary syndrome; ECG, electrocardiogram; STEMI, ST-elevation myocardial infarction, NSTEACS, non-ST elevation ACS; NSTEMI, non-ST elevation myocardial infarction; MI, myocardial infarction; CK-MB, creatine kinase MB; cTnI, cardiac troponin I; cTnT, cardiac troponin T; hs-CRP, high-sensitivity C-reactive protein; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP; LLD, lower limits of detectability; CRP, C-reactive protein; IL-6, interleukin-6; IMA, ischemia modified albumin; and GP, glycoprotein.

nontraumatic chest pain are 2-fold: (a) to assess the probability that the patient's symptoms are related to acute coronary ischemia; and (b) to assess the patient's risk of recurrent cardiac events, including death and recurrent ischemia (1). When applied in conjunction with the clinical history, physical examination, and interpretation of the ECG, cardiac biomarkers are valuable in achieving both of these objectives.

II. Use of Biochemical Markers in the Initial Evaluation of ACS

A. DIAGNOSIS OF MYOCARDIAL INFARCTION

RECOMMENDATIONS FOR USE OF BIOCHEMICAL MARKERS FOR DIAGNOSIS OF MYOCARDIAL INFARCTION (MI)

CLASS I

1. Biomarkers of myocardial necrosis should be measured in all patients who present with symptoms consistent with ACS (Level of Evidence: C).
2. The patient's clinical presentation (history, physical exam) and ECG should be used in conjunction with biomarkers in the diagnostic evaluation of suspected MI (Level of Evidence: C).
3. Cardiac troponin is the preferred marker for the diagnosis of MI. Creatine kinase MB (CK-MB) by mass assay is an acceptable alternative when cardiac troponin is not available (Level of Evidence: A).
4. Blood should be obtained for testing at hospital presentation followed by serial sampling with timing of sampling based on the clinical circumstances. For most patients, blood should be obtained for testing at hospital presentation and at 6–9 h (Level of Evidence: C).
5. In the presence of a clinical history suggestive of ACS, the following are considered indicative of myocardial necrosis consistent with MI (Level of Evidence: C):
   a. Maximal concentration of cardiac troponin exceeding the 99th percentile of values (with optimal precision defined by total CV <10%) for a reference control group on at least 1 occasion during the first 24 h after the clinical event (observation of a rise and/or fall in values is useful in discriminating the timing of injury).
   b. Maximal concentration of CK-MB exceeding the 99th percentile of values for a sex-specific reference control group on 2 successive samples (values for CK-MB should rise and/or fall).

CLASS IIB

1. For patients who present within 6 h of the onset of symptoms, an early marker of myocardial necrosis may be considered in addition to a cardiac troponin. Myoglobin is the most extensively studied marker for this purpose (Level of Evidence: B).

2. A rapid "rule-in" protocol with frequent early sampling of markers of myocardial necrosis maybe appropriate if tied to therapeutic strategies (Level of Evidence: C).

CLASS III

1. Total CK, CK-MB activity, aspartate aminotransferase (AST, SGOT), β-hydroxybutyric dehydrogenase, and/or lactate dehydrogenase should not be used as biomarkers for the diagnosis of MI (Level of Evidence: C).
2. For patients with diagnostic ECG abnormalities on presentation (e.g., new ST-segment elevation), diagnosis and treatment should not be delayed while awaiting biomarker results (Level of Evidence: C).

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1. BIOCHEMICAL MARKERS OF MYOCARDIAL NECROSIS
Myocardial necrosis is accompanied by the release of structural proteins and other intracellular macromolecules into the cardiac interstitium as a consequence of compromise of the integrity of cellular membranes. These biomarkers of myocardial necrosis include cardiac troponin I and T (cTnI and cTnT), CK, myoglobin, lactate dehydrogenase, and others (Table 1). On the basis of improved sensitivity and superior tissue-specificity compared with the other available biomarkers of necrosis, cardiac troponin is the preferred biomarker for the detection of myocardial injury. The diagnosis of acute, evolving, or recent MI requires (in the absence of pathologic confirmation) findings of a typical rise and/or fall of a biomarker of necrosis, *in conjunction with clinical evidence (symptoms, or ECG) that the cause of myocardial damage is ischemia*. Because recognition of acute MI is important to prognosis and therapy, measurement of biomarkers of necrosis is indicated in all patients with suspected ACS. Important characteristics of these biomarkers are discussed in the remainder of this section.

In contrast to CK, cTnI and cTnT have isoforms that are unique to cardiac myocytes and may be measured by assays employing monoclonal antibodies specific to epitopes of the cardiac form (16–19). The advantage of cardiac troponin over other biomarkers of necrosis has been firmly established in clinical studies. Testing for cardiac troponin is associated with fewer false-positive results in the setting of concomitant skeletal muscle injury, e.g., after trauma or surgery (16, 20, 21) and also provides superior discrimination of myocardial injury when the concentration of CK-MB is normal or minimally increased (16, 22, 23). Moreover, the association between an increased concentration of cardiac troponin and a higher risk of recurrent cardiac events in patients with normal serum concentration of CK-MB and suspected ACS has confirmed the clinical relevance of detecting

Table 1. Properties of biomarkers of myocardial necrosis.

Biochemical marker	Molecular weight, g/mole	Cardiac specific?	Advantage	Disadvantage	Duration of elevation
Myoglobin	18 000	No	High sensitivity and negative predictive value. Useful for early detection of MI and reperfusion.	Low specificity in presence of skeletal muscle injury and renal insufficiency. Rapid clearance after necrosis.	12–24 h
h-FABP	15 000	+	Early detection of MI	Low specificity in presence of skeletal muscle injury and renal insufficiency.	18–30 h
CK-MB, mass assays	85 000	+++	Ability to detect reinfarction. Large clinical experience. Previous gold standard for myocardial necrosis	Lowered specificity in skeletal muscle injury.	24–36 h
CK-MB isoforms	85 000	+++	Early detection of MI	Lack of availability/ experience	18–30 h
cTnT	37 000	++++	Tool for risk stratification. Detection of MI up to 2 weeks. High specificity for cardiac tissue	Not an early marker of myocardial necrosis. Serial testing needed to discriminate early reinfarction.	10–14 days
cTnI	23 500	++++	Tool for risk stratification. Detection of MI up to 7 days. High specificity for cardiac tissue	Not an early marker of myocardial necrosis. Serial testing needed to discriminate early reinfarction. No analytical reference standards.	4–7 days

Time of first increase for the markers are 1–3 h for myoglobin, 3–4 h for CK-MB mass, 3–4 h for cTnT, and 4–6 h for cTnI. h-FABP, heart fatty acid–binding protein. Adapted from Christenson RH and Azzazy HME. Biomarkers of necrosis: past, present and future. In Morrow DA, ed. *Cardiovascular Biomarkers: Pathophysiology and Clinical Management*. New York: Humana Press, 2006.

circulating troponin in patients previously classified with unstable angina. An example from one of several studies is shown in Fig. 2 (*24–26*).

When cardiac troponin is not available, the next best alternative is CK-MB (measured by mass assay). Although total CK is a sensitive marker of myocardial damage, it has poor specificity due to its high concentra-

Risk of Complications in Patients with Normal CK-MB

Fig. 2. Risk of death and recurrent ischemic events among patients with NSTEACS and normal serial CK-MB with and without increase baseline concentration of cardiac troponin I (Dimension RxL, Dade Behring).

As discussed in section II-B1.c, the cut point applied in this study is specific to the assay used. Data from Morrow et al. (*67*). UR, urgent revascularization prompted by recurrent ischemia.

tion in skeletal muscle. By virtue of its greater concentration in cardiac vs skeletal myocytes, the MB isoenzyme of CK offers an improvement in sensitivity and specificity compared with total CK. Nevertheless, CK-MB constitutes 1%–3% of the CK in skeletal muscle, and is present in minor quantities in intestine, diaphragm, uterus, and prostate. Therefore, the specificity of CK-MB may be impaired in the setting of major injury to these organs, especially skeletal muscle. Serial measurements documenting the characteristic rise and/or fall are important to maintaining specificity for the diagnosis of acute MI. Alternatives to cardiac injury should be sought when CK-MB is increased in the presence of a troponin concentration below the 99th percentile. Assays for CK-MB mass offer superior analytical and diagnostic performance and thus are strongly preferred to assays for CK-MB activity (see *Analytical Issues for Biomarkers in ACS* in separate guidelines).

Although they are of historical significance, total CK, lactate dehydrogenase, and aspartate aminotransferase should no longer be used for the diagnosis of MI because they have low specificity for cardiac injury and more specific alternative biomarkers of necrosis are available. Myoglobin shares limitations with these markers due to its high concentration in skeletal muscle. However, because of its small molecular size and consequent rapid rise in the setting of myocardial necrosis, it has retained value

as a very early marker of MI. Clinical studies have shown that the combined use of myoglobin and a more specific marker of myocardial necrosis (cardiac troponin or CK-MB) may be useful for the early exclusion of MI *(27, 28)*. Multimarker strategies that include myoglobin have been shown to identify patients with MI more rapidly than laboratory-based determination of a single marker *(29, 30)*. However, this potential advantage of myoglobin may be diminished with use of contemporary decision-limits and improving sensitivity of newer troponin assays *(31)*. CK-MB subforms may also be used as an early rising indicator of MI *(32)* but are not used today, as there are no commercial platforms available.

2. OPTIMAL TIMING OF SAMPLE ACQUISITION

The optimal timing of sample acquisition for measurement of biomarkers for the diagnosis of MI derives from both properties of the available biomarkers and patient-related factors (timing and duration of symptoms relative to presentation and overall probability of ACS). CK-MB begins to rise within 3–4 h after the onset of myocardial injury and falls to normal ranges by 48–72 h (Fig. 3). Cardiac troponin rises with a time course similar to CK-MB but can remain increased for up to 4–7 days for cTnI and 10–14 days for cTnT. The initial release of cardiac troponin that exists in the cellular cytosol (3%–8%) followed by the slower dispersion of troponin from degrading cardiac myofilaments is responsible for this extended kinetic profile *(33)*. In contrast, myoglobin concentration begins to rise as early as 1 h after onset of myocyte damage and returns to normal within 12–24 h.

By virtue of these kinetics, the temporal rise of the serum concentration of CK-MB and cardiac troponin typically does not permit detection of myocardial necrosis very early (1–3 h) and does not support maximal sensitivity of these markers until 6 or more hours after the onset of MI *(34–36)*. Accurate determination of the timing of symptom onset is based on patient reporting and is

Hours After Chest Pain

Fig. 3. Temporal release of myoglobin, CK-MB, cTnI and cTnT.

With permission, from Christenson RH, Azzazy HME. Biomarkers of necrosis: past, present and future. In Morrow DA, ed. Cardiovascular Biomarkers: Pathophysiology and Clinical Management. New York: Humana Press, 2006.

often clinically very challenging *(10)*. Therefore, for most patients, blood should be obtained for testing at hospital presentation and at 6–9 h after presentation (unless the timing of symptoms is reliably known) to provide adequate clinical sensitivity for detecting MI. Given improvements in the analytic performance of troponin assays, testing up to 6–9 h after symptom onset is expected to deliver optimal sensitivity in most patients. However, in patients for whom these initial samples are negative and there is an intermediate or high clinical index of suspicion, or in whom plausibly ischemic symptoms have recurred, repeat testing at 12–24 h should be considered. Among patients without ST elevation, such serial testing increases the proportion of patients with myocardial injury who are detected from 49% to 68% at 8 h and enhances the accuracy of risk assessment *(37)*. More frequent early testing of cardiac troponin and/or CK-MB, particularly in combination with myoglobin, may be considered as an approach to increase early detection of infarction and to facilitate rapid initiation of treatment *(38, 39)*. This strategy has also shown value in some studies for expedited exclusion of MI *(40)*, as has use of the change in markers of necrosis repeated over an interval of 2 h *(41, 42)*.

3. CRITERIA FOR DIAGNOSIS OF MI

Detection of increased blood concentrations of biomarkers of myocardial necrosis in the setting of a clinical syndrome consistent with myocardial ischemia is necessary for the diagnosis of acute, evolving, or recent MI. Clinical information from the history and ECG must be integrated with data from measurement of biomarkers in determining whether the myocardial necrosis manifested by increased concentration of these markers is due to myocardial ischemia or some other cause *(4, 43)*. The tissue specificity of cardiac troponin should not be confused with specificity for the mechanism of injury (e.g., MI vs myocarditis) *(44, 45)*. When an increased value is encountered in the absence of evidence of myocardial ischemia, a careful search for other possible etiologies of cardiac damage should be undertaken.

An increased concentration of cardiac troponin is defined as exceeding the 99th percentile of a reference control group. Recommendations regarding analytic evaluation and performance are described in separate guidelines (see *Analytical Issues for Biomarkers in ACS*). A maximal concentration of cardiac troponin exceeding this decision-limit on at least 1 occasion during the index clinical event is indicative of myocardial necrosis. Similarly, the diagnostic limit for CK-MB is defined as the 99th percentile (with acceptable imprecision) in a sex-specific reference control group. In light of the lower tissue specificity compared with troponin, it is recommended that in most situations 2 consecutive measurements of CK-MB above this decision-limit are required to be considered sufficient biochemical evidence of myocardial necrosis. Use of total CK for diagnosis of MI is not recommended. However, *in the absence of availability of data*
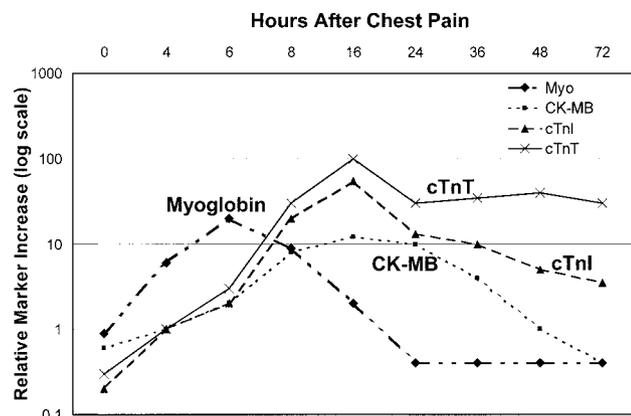
using a troponin or CK-MB assay (mass or activity), when only total CK values are available, the recommended decision-limit is >2 times the sex-specific upper reference limit. A rise and/or fall of CK-MB or total CK provides additional evidence supporting the diagnosis of acute MI. In addition, for values of cardiac troponin between the 10% CV and the 99th percentile, as well as for potential chronic elevations (e.g., renal failure), the use of a rising and/or falling pattern is often useful in facilitating the discrimination of patients with acute events.

4. ADDITIONAL CONSIDERATIONS IN THE USE OF BIOMARKERS FOR DIAGNOSIS OF MI

The criteria for MI recommended in these and other guidelines (4) are based on the principle that any reliably detected myocardial necrosis, if caused by myocardial ischemia, constitutes an MI. The development of more sensitive and specific biomarkers of necrosis, such as cardiac troponin, has enabled detection of quantitatively much smaller areas of myocardial injury (46). Moreover, it is likely that future generations of assays for cardiac troponin will push this limit even lower. Elegant histologic work in animal models of coronary ischemia has provided strong evidence that release of CK from cardiac myocytes occurs in setting of myocyte necrosis but not in the setting of reversible myocyte injury. In contrast, data in this regard for cardiac troponin have been mixed (47). Increased concentrations of cTnI and cTnT have been observed in animal models of ischemia without histologic evidence of irreversible cellular injury (48). Whereas the potential to miss small amounts of patchy necrosis during microscopic examination is a significant limitation of all such experimental results, it is also possible that such release of cardiac troponin into the circulation may result from reversible injury to the myocyte cellular membrane leading to egress of troponin residing in the cytosol (49). Nevertheless, based on the aggregate evidence to date, the present guidelines reflect the prevailing consensus opinion (43) that any reliably detected elevation of a cardiac troponin is abnormal and most likely represents necrosis. The committee supports additional investigation to determine whether current or future generations of assays for cardiac troponin may detect release of the protein that occurs during reversible injury due to ischemia without infarction.

Measurement of more than 1 specific biomarker of myocardial necrosis (e.g., cardiac troponin and CK-MB) is not necessary for establishing the diagnosis of myocardial infarction and is not recommended. The use of serial measurements of CK-MB to provide information during the management of MI after diagnosis is discussed in Section IV-B. Determination of an early marker of necrosis in combination with cardiac troponin may be appropriate in some circumstances as described in Section II-A1.

Despite the central role for biomarkers of necrosis in establishing the diagnosis of acute MI, other diagnostic tools remain vital to clinical care. In particular, acute ST-segment elevation on the ECG in conjunction with a consistent clinical syndrome has a very high positive predictive value for acute STEMI and should prompt initiation of appropriate strategies for coronary reperfusion (10). Patients presenting within 6 h of symptom onset may not yet have a detectable serum concentration of biomarkers of necrosis. However, given the critical relationship between rapid therapy and outcomes in patients with STEMI, therapy should *not* be delayed waiting for confirmatory biomarker measurements.

B. EARLY RISK STRATIFICATION

RECOMMENDATIONS FOR USE OF BIOCHEMICAL MARKERS FOR RISK STRATIFICATION IN ACS

CLASS I

1. Patients with suspected ACS should undergo early risk stratification based on an integrated assessment of symptoms, physical exam findings, ECG findings, and biomarkers (Level of Evidence: C).
2. A cardiac troponin is the preferred marker for risk stratification and, if available, should be measured in all patients with suspected ACS. In patients with a clinical syndrome consistent with ACS, a maximal (peak) concentration exceeding the 99th percentile of values for a reference control group should be considered indicative of increased risk of death and recurrent ischemic events (Level of Evidence: A).
3. Blood should be obtained for testing on hospital presentation followed by serial sampling with timing of sampling based on the clinical circumstances. For most patients, blood should be obtained for testing at hospital presentation and at 6–9 h (Level of Evidence: B).

CLASS IIA

1. Measurement of high-sensitivity C-reactive protein (hs-CRP) may be useful, in addition to a cardiac troponin, for risk assessment in patients with a clinical syndrome consistent with ACS. The benefits of therapy based on this strategy remain uncertain (Level of Evidence: A).
2. Measurement of brain-type (B-type) natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) may be useful, in addition to a cardiac troponin, for risk assessment in patients with a clinical syndrome consistent with ACS. The benefits of therapy based on this strategy remain uncertain (Level of Evidence: A).

CLASS IIB

1. Measurement of markers of myocardial ischemia, in addition to cardiac troponin and ECG, may aid in excluding ACS in patients with a low clinical probability of myocardial ischemia (Level of Evidence: C).
2. A multimarker strategy that includes measurement of 2 or more pathobiologically diverse biomarkers in addition to a cardiac troponin may aid in enhancing risk stratification in patients with a clinical syndrome consistent with ACS. BNP and hs-CRP are the biomarkers best studied using this approach. The benefits of therapy based on this strategy remain uncertain (Level of Evidence: C).
3. Early repeat sampling of cardiac troponin (e.g., 2–4 h after presentation) may be appropriate if tied to therapeutic strategies (Level of Evidence: C).

CLASS III

Biomarkers of necrosis should not be used for routine screening of patients with low clinical probability of ACS (Level of Evidence: C).

1. BIOCHEMICAL MARKERS OF CARDIAC INJURY

a. Pathophysiology

The presence of cardiac troponin in the peripheral circulation is indicative of myocardial injury (see Section II-A1). Additional pathophysiologic correlates of troponin elevation have been identified in clinical studies of ACS. Angiographic data from trials enrolling patients with NSTEACS have shown increased concentrations of troponin to be associated with greater lesion complexity and severity, more frequent visible thrombus, and more severely impaired blood flow in the culprit artery (50–53). In addition, an increased concentration of troponin is associated with impaired myocardial tissue or "microvascular" perfusion and thus hypothesized to reflect embolization of platelet aggregates into the distal coronary artery (52). Furthermore, increased concentrations of troponin have been associated with a higher likelihood of poor outcomes during angioplasty, including very slow flow (so-called "no reflow") despite a patent epicardial artery in a clinical syndrome believed to result from distal microvascular obstruction (54). Advances in the understanding of the pathobiology of ACS have pointed toward these phenomena of microembolization and microvascular obstruction as important mediators of adverse outcomes (55). As such, the apparent link between microembolization and release of cardiac troponin may underlie, at least in part, the strong association between this biomarker and subsequent recurrent clinical events (52).

b. Relationship to clinical outcomes

The presence of myocardial necrosis detectable with creatine kinase is established as an important prognostic factor in the assessment of patients with ACS (56). In addition, the blood concentration of biomarkers of necrosis shows a consistent graded relationship with the risk of short- and long-term mortality (57, 58). Specifically, among patients with NSTEACS, the concentration of CK-MB at hospital presentation establishes a gradient of 30-day mortality risk from 1.8% in patients with CK-MB less than the upper limit of the reference interval to 3.3% for those with a 1- to 2-fold increase above the upper limit of the reference interval, to 8.3% among those with >10-fold increase (58). The availability of cardiac troponin has extended the spectrum of detectable myocardial injury and further enhanced the clinician's ability to assess risk (24). Based on evidence from more than 26 studies, including both clinical trials and observational studies from community-based cohorts, cardiac troponin has proven to be a potent independent indicator of the risk of death and recurrent ischemic events among patients presenting with ACS (26). In aggregate, the available data indicate an ~4-fold higher risk of death and recurrent MI among patients presenting with suspected NSTEACS and an increased concentration of troponin compared with patients with a normal troponin result (Fig. 4) (26, 59, 60). In patients with STEMI, an increased concentration of troponin at presentation is also associated with significantly higher short-term mortality (61, 62).

The prognostic information obtained from measurement of cardiac troponin is independent of and complementary to other important clinical indicators of risk including patient age, ST deviation, and presence of heart failure (57, 61, 63–66). The higher risk of patients presenting with an increased concentration of troponin is also
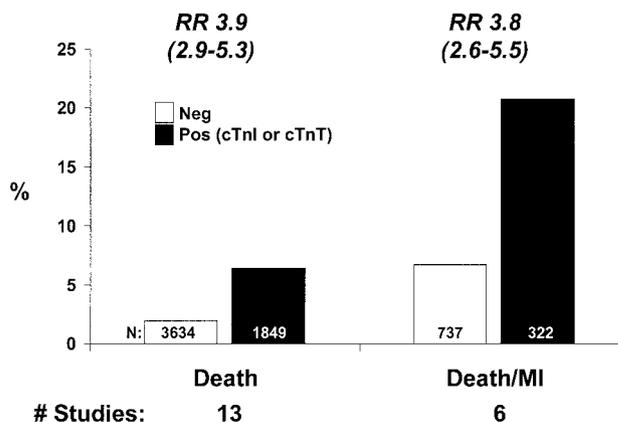
Fig. 4. Risk of death or MI stratified by troponin result in patients with suspected ACS.

Adapted with permission from Braunwald E, et al. American College of Cardiology/American Heart Association guidelines 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). J Am Coll Cardiol 2000;36:970–1062.

evident among patients with normal concentrations of CK-MB *(67)*. As such, cardiac troponin is the preferred biomarker for risk assessment in patients presenting with suspected ACS. cTnI and cTnT appear to have similar value for risk assessment in ACS *(26, 68)*.

c. Decision-limits

As the lower limits of detection (LLD) have decreased with incremental improvements in commercially available assays for cardiac troponin, the potential prognostic implications of quantitatively modest ("low-level") increases in cardiac troponin have attained greater clinical relevance. The consensus recommendation is that the upper limit of normal for cardiac troponin and CK-MB be defined by the 99th percentile among a reference control population *(69)*. Details regarding the determination of this cut point and analytic performance of the assay are discussed elsewhere in these guidelines (see *Analytical Issues for Biomarkers in ACS*).

When conducted among patients with a compelling clinical history suggesting ACS (e.g., in clinical trials of ACS), prospective analyses have documented that troponin concentrations at the low end of the detectable range are associated with higher risk of recurrent cardiac events than patients without detectable troponin *(66, 70)*. For example, in the Treatment with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18 study, patients with a baseline concentration of cTnI in the range immediately above the 99th percentile for the assay used in the study (0.1 μg/L, CV 20%) were at more than 3-fold higher risk of death or recurrent MI than those with cTnI <0.1 μg/L *(66)*. This observation of the prognostic significance of low-level increase of cardiac troponin has been independently confirmed using another assay for cTnI in 2 separate data sets from clinical trials (OPUS-TIMI 16 and FRISC II) *(70, 71)*, as well as within a community-based study *(72)*. Specifically, in the latter, patients presenting with chest pain were stratified into 4 groups according to peak cTnI concentration—negative (<LLD), low (≥LLD to <99th percentile, 10%CV), intermediate (≥99th percentile,

10%CV to < manufacturer's suggested diagnostic limit for MI), and high (≥ suggested diagnostic limit for MI)—revealing a 6-month mortality rate that increased in a stepwise fashion compared with patients with negative cTnI results [hazard ratio 2.5; 95% confidence interval (CI) 1.4–4.4] in the low cTnI group, 3.9 (95% CI 2.3–6.8) in the intermediate cTnI group, and 6.1 (95% CI 4.2–8.7) in the high cTnI group (Fig. 5) *(72)*. With future improvements in the analytic performance of available assays, the association between troponin concentrations at the lower limit of detection and outcomes in ACS will require continued careful evaluation.

d. Therapeutic decision-making

The application of cardiac troponin to guide specific therapeutic choices for patients with ACS is well studied and is discussed in section IIIA.

2. NATRIURETIC PEPTIDES

a. Pathophysiology

BNP and NT-proBNP are released from cardiac myocytes in response to increases in ventricular wall stress *(73)*. Wall stress in a chamber is directly related to the diameter of the chamber and the transmural pressure and inversely related to the thickness of the wall. Therefore, increases both in the diameter of and pressure within the left ventricle during remodeling after a transmural infarction, or as a consequence of prior ischemic damage, may contribute to elevation of natriuretic peptides observed in patients with acute MI. In addition, impairment of ventricular relaxation and consequent nonsystolic ventricular dysfunction is one of the earliest consequences of myocardial ischemia, preceding angina and ST-segment deviation. This well-described pathophysiology, together with a strong relationship between BNP and NT-proBNP with mortality in patients with unstable angina (see below), has supported the hypothesis that myocardial ischemia can also elicit the release of BNP in absence of necrosis *(74)*.

The concept that ischemia may be an important stimulus for BNP synthesis and release is supported by several lines of evidence. In experimental models of myocardial infarction, BNP gene transcription is increased both in infarcted tissue and in the surrounding ischemic but viable myocardium *(75)*. Hypoxia has also been shown to trigger release of BNP *(76)*. BNP rises early after exercise in patients with coronary disease, and the magnitude of BNP increase is proportional to the size of the ischemic territory as assessed with nuclear single-photon emission computed tomography imaging *(77)*. After uncomplicated coronary angioplasty, BNP transiently increases even when cardiac filling pressures remain unchanged *(78)*. Together, these data provide a plausible basis to explain the strong association between BNP and NT-proBNP with mortality in patients with unstable angina and normal left ventricular systolic function.
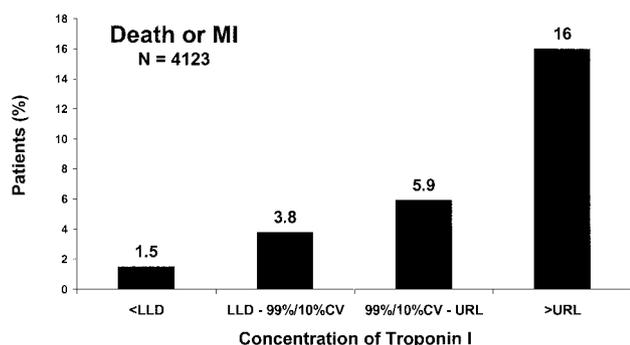

Fig. 5. Prognostic implication of low-level troponin elevation in patients with chest pain suspicious for ACS.

Data from Kontos, et al. *(72)*. URL, upper reference limit supplied by manufacturer.

b. Relationship to clinical outcomes

In aggregate there are now more than 10 studies showing a strong association between BNP or NT-proBNP and outcomes in patients with ACS (Table 2) *(79–89)*. After presentation with transmural infarction, the plasma concentration of BNP rises rapidly and peaks at ~24 h, with the peak concentration proportional to the size of the MI *(90, 91)*. In some patients, particularly those who eventually develop severe heart failure, a second peak may occur after 5 days, likely reflecting the development of adverse ventricular remodeling *(92)*. In patients with acute MI, a higher concentration of BNP and NT-proBNP have been shown to predict a greater likelihood of death or heart failure, independent of other prognostic variables including left ventricular ejection fraction *(80, 81, 83, 93, 94)*. BNP and NT-proBNP are also increased in high-risk patients with unstable angina *(83, 84, 95)*. When measured a median of 40 h after presentation in ~1600 patients with NSTEACS, a highly significant graded relationship between the concentration of BNP and subse-

Table 2. Summary of clinical studies of BNP and NT-proBNP in ACS.

Author, year	Study	Subjects	Marker	Follow-up	Findings
Arakawa et al., 1996 *(79)*	Observational	70	BNP	18 months	RR not reported, BNP at admission independently associated with mortality.
Darbar et al., 1996 *(183)*	Observational	75	BNP	20 months	Increase in OR for death by 7.3 (1.9–10.1) per each 10 pmol/L increase in BNP
Richards et al., 1998 *(81)*	Observational	121	NT-proBNP	24 months	RR 5.9 (1.8–19) associated with BNP above vs below median
Crilley and Farrer, 2001 *(184)*	Observational	133	BNP	1 year	BNP higher in patients who died by 1 year (675 vs 365 pg/mL)
de Lemos et al., 2001 *(83)*	Substudy of RCT (OPUS-TIMI 16)	1698	BNP	10 months	RR 12.5 for mortality in highest vs lowest quartile of BNP in NSTEMI
					RR 7.9 for mortality in highest vs lowest quartile of BNP in unstable angina
Jernberg et al., 2002 *(86)*	Observational	755	NT-proBNP	4 years	RR 26.6 for mortality in highest vs lowest quartile of BNP
Omland et al., 2002 *(87)*	Observational	405	NT-proBNP	52 months	RR 5.6 for mortality with BNP above vs below median in NSTEMI
					RR 3.0 for mortality with BNP above vs below median in unstable angina
Omland et al., 2002 *(85)*	Substudy of RCT (TIMI 11B)	681	NT-proBNP	6 weeks	Higher baseline biomarker concentrations in patients that died (299 pmol/L) than in survivors (138 pmol/L)
Morrow et al., 2003 *(84)*	Substudy of RCT (TACTICS-TIMI 18)	1676	BNP	6 months	Increased risk of death at 7 days (2.5% vs 0.7%) and 6 months (8.4% vs 1.8%) in patients with BNP >80 pg/mL, no interaction with early invasive strategy
Jernberg et al., 2003 *(88)*	Substudy of RCT (FRISC II)	775	NT-proBNP	2 years	RR 4.1 for mortality in highest tertile of BNP compared to lowest (invasive)
					RR 3.5 for mortality in highest tertile of BNP compared to lowest (conservative)
James et al., 2003 *(89)*	Substudy of RCT (GUSTO IV)	6809	NT-proBNP	1 year	RR 10.6 for mortality in highest vs lowest quartile of BNP
Richards et al., 2003 *(94)*	Observational	666	BNP/NTproBNP	3 years	RR 3.6 (2.5–53) and 4.9 (2.9–8.2) for BNP above the median among those with and without ejection fraction <40%, respectively
Heeschen et al., 2004 *(97)*	Substudy of RCT (PRISM)	1791	NT-proBNP	30 days	RR 2.68 (1.66–4.34) for death or MI at 30 days in patients with NT-proBNP >250 pg/mL

OR, odds ratio; RCT, randomized clinical trial; RR, relative risk.

quent risk of short- and long-term mortality was evident *(83)*. The rate of death increased from <1% among patients with BNP concentrations in the lowest quartile to 15% in those with a BNP concentration in the highest quartile (*P* < 0.0001) *(83)*. This finding has been corroborated in multiple studies of both BNP *(83, 84)* and NT-proBNP *(85, 86, 89)*, including substudies of clinical trials and observational data from community-based cohorts (Fig. 6).

Although the plasma concentration of BNP and NT-proBNP in ACS is associated with older age, female sex, renal insufficiency, left ventricular dysfunction, clinical evidence of heart failure, presence of myocardial necrosis, and more severe angiographic coronary artery disease, the prognostic relationship between the biomarkers and mortality is independent of these other clinical risk indicators *(87, 96)*. Importantly, BNP and NT-proBNP identify patients without systolic dysfunction or signs of heart failure who are at higher risk of death and heart failure and provide prognostic information that is complementary to cardiac troponin *(84, 89)*.

c. Decision-limits

When evaluated in ACS, serum concentrations of BNP and NT-proBNP have a graded relationship with risk for short- and long-term mortality *(84, 89)*. As such, the absolute plasma concentration of BNP or NT-proBNP carries information with respect to the magnitude of risk, and thus should be considered by the clinician. Nevertheless, for convenient clinical use, a decision-limit of 80 pg/mL has been validated in patients with high clinical suspicion for ACS using 2 BNP assays and may be used for assays that are similarly calibrated (Fig. 7) *(84)*. An evidence-based approach with specific assays studied and validated in clinical studies is thus possible. However, results for specific cut points may not be extrapolated to
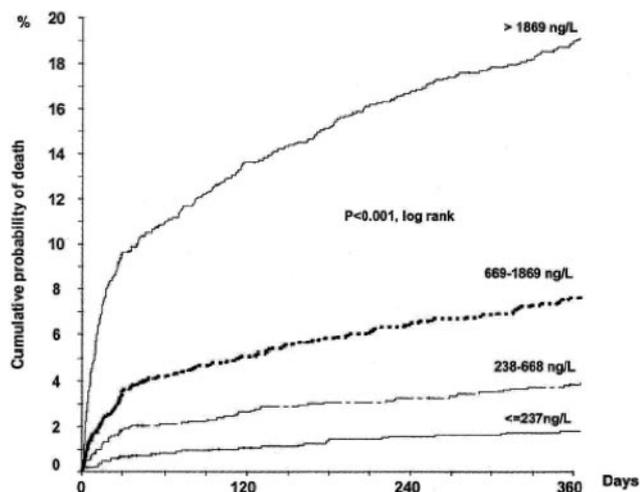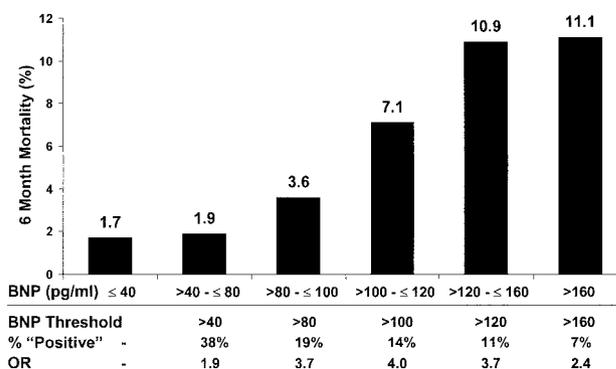
Fig. 7. Mortality risk stratified by BNP concentrations over the range of 40–160 pg/mL (Triage, Biosite).

The odds ratios (ORs) and χ^2 statistics in the table below the chart are based on BNP results dichotomized at the lower bound of the range. With permission from Morrow et al. *(84)*.

BNP (pg/ml)	≤ 40	>40 - ≤ 80	>80 - ≤ 100	>100 - ≤ 120	>120 - ≤ 160	>160
BNP Threshold		>40	>80	>100	>120	>160
% "Positive"	-	38%	19%	14%	11%	7%
OR	-	1.9	3.7	4.0	3.7	2.4

other assays. NT-proBNP has also been evaluated in clinical studies; cut points have been individually derived within each study, and no specific cut point has yet undergone separate validation in patients with ACS. The committee encourages additional investigation prospectively evaluating the optimal decision-limits for BNP and NT-proBNP in ACS, including evaluation of an approach that incorporates more than one decision-limit to stratify patients into low, intermediate, and high risk, as well as assessment of the need for age- and sex-related decision-limits in ACS. It is possible that different decision-limits should be applied for risk stratification in ACS compared with diagnostic assessment of the patient with shortness of breath, and that the prognostic decision-limits in ACS will be refined when studied in more heterogeneous patient populations presenting with suspected ACS. A detailed discussion of analytic issues that may impact the selection and reporting of decision limits for BNP and NT-proBNP is presented in separate guidelines (*Analytic Issues in Heart Failure Biomarkers*). These, and other issues discussed below, require additional study before *routine* use of BNP and NT-proBNP for risk assessment in ACS can be recommended.

Whether there is an optimal timing for measurement also warrants additional investigation. When measured at admission *(86)*, <24 h after symptom onset *(84)*, or 2–5 days after the index event, BNP and/or NT-proBNP maintain prognostic performance *(83)*. However, the concentrations of natriuretic peptides change over time after presentation and it is possible that the association with clinical risk may vary based on the time of ascertainment. Serial measurements appear to provide additional information that may reflect the patient's risk at presentation as well as the response to therapy and effects of ventricular remodeling *(97–99)*.

Fig. 6. Risk of death in patients with NSTEAC syndrome stratified by quartile of concentration of NT-proBNP (Elecsys 2010, Roche Diagnostics) at baseline.

With permission from James et al. *(89)*.

d. Therapeutic decision-making

Few studies have evaluated the effects of specific therapies on ameliorating the risk associated with increased

BNP or NT-proBNP in ACS (see Section III-A2). Two studies have evaluated whether BNP/NT-proBNP is helpful for identifying candidates for early routine referral for coronary revascularization ("early invasive strategy") after ACS. In the first of these studies, patients with an increased plasma concentration of BNP experienced a similar benefit of the early invasive approach compared to patients with BNP <80 pg/mL (84). In the second, a trend toward greater benefit with the early invasive strategy was apparent in patients in the highest tertile of NT-proBNP (88). This latter observation is supported by a nonrandomized evaluation of patients with increased NT-proBNP who did and did not undergo revascularization (100). One study has shown a significant reduction in the risk of death or new heart failure in patients with increased BNP treated with intensive statin therapy (101).

Although convincing data for a strong interaction between the biomarker and specific therapeutic strategies do not yet exist for natriuretic peptides as they do for troponin, BNP and NT-proBNP do assist in an assessment of absolute global risk and may therefore still inform clinical decision-making. For example, owing to the very low mortality rate observed for patients with negative troponin results and low concentrations of BNP or NT-proBNP, it has been proposed that less aggressive management strategies may be employed for such patients (102). In addition, studies of both BNP and NT-proBNP have demonstrated that a decline to a lower concentration of natriuretic peptides over time after presentation with ACS is associated with more favorable outcomes and thus raised the possibility that natriuretic peptides may be useful as a tool to monitor the response to preventive interventions (98, 99).

3. BIOCHEMICAL MARKERS OF INFLAMMATION
a. Pathophysiology
Multiple lines of investigation have converged to implicate inflammation as a central contributor to plaque compromise (103). Inflammatory processes participate in the earliest stages of atherogenesis in response to insults to the vascular endothelium, as well as to the development of the intermediate and mature atheromatous plaque. Ultimately, inflammatory cells and mediators participate in compromising the protective fibrous cap that maintains separation between the highly procoagulant contents of the atheroma core and circulating platelets and coagulation proteins (104, 105). Thus, several mediators of the inflammatory response, including acute-phase proteins, cytokines, and cellular adhesion molecules, have been evaluated as potential indicators of the risk of a first acute atherothrombotic event, as well as of recurrent complications after presentation (106). As the prototypical acute-phase reactant, C-reactive protein (CRP) has been the focus of much of the clinical investigation (107).

Increased concentrations of inflammatory biomarkers such as CRP, serum amyloid A, myeloperoxidase, and interleukin-6 (IL-6) are detectable in a substantial proportion of patients presenting with ACS, including those without evidence of myocyte necrosis (107–112). It is plausible that elevation of circulating markers of inflammation during ACS is a manifestation of intensification of the focal inflammatory processes that contribute to destabilization of vulnerable plaque. Nevertheless, the precise basis for the relationship between inflammatory markers and risk in ACS has not been conclusively established. CRP certainly rises as a consequence of the inflammatory response to myocardial necrosis (113). However, studies demonstrating elevation of CRP and IL-6 during ACS in the absence of myocyte necrosis refute the position that the rise in these markers is solely a response to necrosis (107, 109, 110). CRP has also been implicated as a potential direct participant in atherothrombosis rather than a mere bystander. CRP promotes uptake of LDL cholesterol by monocytes, induces the production of tissue factor, activates complement within arterial plaque, stimulates the expression of adhesion molecules, and may also recruit monocytes via a monocyte-CRP receptor (103). Nevertheless, in light of limitations to the experimental data, there remains a need for additional investigation of the role of CRP as a potential direct mediator (114). Last, the clinical importance of identifying inflammatory activation in ACS may have less to do with the particular inciting culprit and more to do with the widespread presence of vulnerable plaques (115) and patient-specific responses to inflammatory stimuli (116).

b. Relationship to clinical outcomes
There have now been more than 12 clinical studies demonstrating the prognostic capacity of hs-CRP determined either at presentation or at discharge after ACS (Table 3). Data restricted to patients with STEMI are few; in 1 cohort study, patients with increased CRP were more likely to suffer complications of acute MI (myocardial rupture, left ventricular aneurysm, and death by 1 year) (117). However, in at least 9 studies, multivariable analysis revealed hs-CRP to be an independent predictor of short- and/or long-term outcome among patients with NSTEACS (59, 60, 118–125). Specifically, measurement of hs-CRP appears to yield additional prognostic value in patients with negative testing of cardiac troponins (109, 124) and adds to information obtained from the clinical history and ECG. Several, but not all, studies indicate that the relationship between hs-CRP and outcome is strongest with respect to mortality with a weaker relationship to recurrent MI (60, 109, 119). Whereas hs-CRP is the best studied of the inflammatory markers in the setting of ACS, others such as IL-6 (126, 127) and myeloperoxidase (111, 128) are also associated with prognosis and may eventually prove to add or supercede hs-CRP (see section II-B6).

Table 3. Summary of clinical studies of CRP in ACS.

A. NSTEACS

Author, year	Study	Subjects	CRP cut point, mg/L	Follow-up	End point, risk relationship for high CRP
Short-term					
Liuzzo et al., 1994 *(107)*	Observational	31	>3	In-hospital	D/MI/RI/UR, 4.5 (1.4–17.5)
Oltrona et al., 1997 *(185)*	Observational	140	>10	21 days	D/MI/RI, 0.46 (0.19–1.11)
Toss et al., 1997 *(119)*	Substudy of RCT (FRISC)	965	>10	5 months	D/MI, 1.19 (0.97–1.64)
Morrow et al., 1998 *(109)*	Substudy of RCT (TIMI 11A)	437	>15	14 days	Death, 18.3 (2.2–150)
Rebuzzi et al., 1998 *(120)*	Observational	102	>3	3 months	MI, 6.0 (1.4–25.3)
Oltrona et al., 1998 *(186)*	Observational	91	>3	In-hospital	D/MI, 1.94 (0.46–8.3)
Benamer et al., 1998 *(134)*	Observational	100	>6	In-hospital	D/MI/RI/UR, 0.65 (0.17–2.1)
Ferreiros et al., 1999 *(122)*	Observational	105	>15	In-hospital	D/MI/RI, 0.83 (0.29–2.4)
				3 months	D/MI/RI, 2.1 (1.5–3.1)
Bazzino et al., 2001 *(187)*	Observational	139	>15	3 months	D/MI, 18.6 (4.5–77)
Mueller et al., 2002 *(125)*	Observational	1042	>10	In-hospital	Death, 4.2 (1.6–10.9)
James et al., 2003 *(60)*	Substudy of RCT (GUSTO IV)	7108	>10	1 month	Death, 1.2 (1.05–1.4)
Oltrona et al., 2004 *(188)*	Observational	965	>10	1 month	D/MI, 2.0 (1.3–3.1)
Long-term					
de Winter et al., 1999 *(189)*	Observational	156	>5	6 months	D/MI/RI, 9.8 (1.5–65)
Heeschen et al., 2000 *(59)*	Substudy of RCT (CAPTURE)	447	>10	6 months	Death, 4.7 (1.3–16.9)
Mulvihill et al., 2001 *(190)*	Observational	91	>3	6 months	D/MI/RI, 9.8 (2.5–38.9)
Bholasingh et al., 2003 *(191)*	Observational	382	>3	6 months	D/MI, 5.6 (1.5–22.2)
Baldus et al., 2003 *(128)*	Substudy of RCT (CAPTURE)	1090	>10	6 months	D/MI, 1.25 (1.02–1.7)
Bodi et al., 2005 *(192)*	Observational	515	>11	6 months	D/MI, 2.1 (1.2–3.8)
Biasucci et al., 1999 *(123)*	Observational	53	>3	1 year	D/MI/RI, 4.7 (1.8–12.0)
Lindahl et al., 2000 *(124)*	Substudy of RCT (FRISC)	917	>10	3 years	Death, 2.5 (1.6–3.9)
Versaci et al., 2000 *(193)*	Observational	62	>5	1 year	D/MI/RI, 22.2 (3.1–157)
Mueller et al., 2002 *(125)*	Observational	1042	>10	20 months	Death, 3.8 (2.3–6.2)
Zebrack et al., 2002 *(194)*	Observational	442	>11	3 years	D/MI, 2.6 (1.4–4.8)
James et al., 2003 *(60)*	Substudy of RCT	7108	>10	1 year	Death, 1.5 (1.1–1.9)
Sanchez et al., 2004 *(195)*	Observational	83	>5	2 years	Death, 4.5 (1.6–12.5)

B. STEMI

Author, year	Study	Subjects	CRP cut point, mg/L	Follow-up	End point, risk relationship for high CRP
Short-term					
Liuzzo et al., 1994 *(107)*	Observational	29	>3	In-hospital	RR not provided
Pietila et al., 1996 *(196)*	Observational	188	None	6 months	RR not provided
Anzai et al., 1997 *(117)*	Observational	220	>20		Death, 6.59 (2.7–1.61)
Tommasi et al., 1999 *(121)*	Observational	64	>25	1 year	D/MI/angina, 3.55 (1.56–8.04)
Nikfardjam et al., 2000 *(197)*	Observational	729	Quintiles	3 years	Death, no relationship
Oltrona et al., 2004 *(188)*	Observational	808	>10	30 days	D/MI, 1.9 (1.1–3.2)
Mega et al., 2004 *(198)*	Substudy of RCT	483	>15	30 days	Death, no relationship

RR, relative risk; RI, recurrent ischemia; UR, urgent revascularization.

c. Decision-limits

The preferred unit for reporting hs-CRP results is mg/L *(129)*. Multiple decision-limits for hs-CRP, ranging from 3–15 mg/L, have been evaluated for risk assessment in ACS with few comparative studies. Consensus opinion is that the optimal decision limit for ACS is higher than that used in candidates for primary prevention *(129)*. In 1 prospective evaluation of multiple cut points using receiver-operating characteristics, 15 mg/L was the optimal decision-limit for prediction of a composite of death and

recurrent ischemic events (122). A cut point of 10 mg/L has also been validated in published studies and thus the optimal decision limit remains to be determined (59, 60, 124). When tested 1 or more months after presentation with ACS, use of cut points recommended for patients at risk for or with stable coronary artery disease (low: <1 mg/L; intermediate 1–3 mg/L; high: >3 mg/L) is appropriate (129, 130). Additional comparative studies of decision-limits for hsCRP in ACS are likely to be useful. In addition, recognition of differences in the distribution of hs-CRP based on race and ethnicity may warrant specific reporting of decision-limits (131–133).

The best timing for measurement of hs-CRP for risk stratification in ACS remains uncertain. Potential confounding by the inflammatory response to necrosis must be considered when samples are drawn late after presentation of patients with MI (134, 135). Studies with samples drawn early after presentation (109, 121), at discharge (120, 123), and during the convalescent phase of recovery (≥months postMI) (130, 136) have all demonstrated independent associations with subsequent outcomes. In 2 comparative studies of samples drawn at admission vs discharge, a modest advantage of the predischarge assessment was evident (but not statistically heterogeneous) (120, 123). It is plausible that values of CRP obtained early during the presentation with ACS reflect different pathophysiologic contributors and relationships to risk than those manifest by determination of CRP after resolution of the acute-phase response. Data raising the potential value of late measurement (≥1 month after ACS) for monitoring therapy (discussed below) may indicate greater clinical utility to values obtained later rather than early after ACS (130). Additional research aimed at resolving these issues is needed.

d. Therapeutic decision-making
The appropriate therapeutic response to increased markers of inflammation in patients with ACS is not yet clear. Treatment with hydroxymethylglutaryl (HMG)-CoA reductase inhibitors (statins) is effective in lowering CRP in patients with recent or prior ACS (137, 138). Observations from randomized trials of aggressive vs moderate statin therapy support a possible role for measurement of hs-CRP during follow-up after ACS as a guide for monitoring the success of therapy (130, 139). The effect of aspirin on inflammatory markers is controversial but not likely to impact therapeutic selection, as aspirin therapy is administered to all patients with ACS (140–142). It is possible that future work investigating more aggressive antiinflammatory therapies for the acute management of ACS may lead to a role for inflammatory markers in guiding such therapy.

4. BIOCHEMICAL MARKERS OF ISCHEMIA
Approximately 40%–60% of patients with definite ACS present with an initial troponin concentration below the clinical decision-limit for the assay (64). Some are presenting early after onset of an acute MI for which cTnI/T is not yet detectable by serum/plasma testing; the remainder are presenting with acute myocardial ischemia without necrosis (i.e., unstable angina). Discriminating these 2 groups from patients with chest pain syndrome of an etiology other than coronary ischemia is a major clinical challenge. Thus, a biomarker that reliably detects myocardial ischemia in the absence of necrosis, and/or before cardiac troponin is increased, has the potential to add substantially to available clinical tools (143, 144).

Several biomarkers of myocardial ischemia are under investigation (144). Ischemia-modified albumin (IMA) is among the most thoroughly studied of these markers and has been approved by the US Food and Drug Administration for clinical use (145–148). The albumin cobalt-binding test for detection of IMA is based on the observation that the affinity of the N-terminus of human albumin for cobalt is reduced in patients with myocardial ischemia. Detectable changes in albumin cobalt binding have been documented to occur minutes after transient occlusion and reperfusion of a coronary artery during angioplasty and return toward baseline within 6 h (146). Reduced albumin cobalt binding also occurs in patients with spontaneous coronary ischemia (145, 147, 149), with an abnormal concentration detectable before demonstrable increase of cardiac troponin (147). The precise mechanisms for production of IMA during coronary ischemia are not known, but have been localized to modifications of the N-Asp-Ala-His-Lys sequence of human albumin and are proposed to be related to production of free radicals during ischemia and/or reperfusion, reduced oxygen tension, acidosis, and cellular alterations such as disruption of sodium and calcium pump function (146, 150).

The clinical specificity of IMA, as well as other potential markers of ischemia such as unbound free fatty acid (151) and whole blood choline (152), in the broad population of patients with nontraumatic chest pain and suspected ACS remains an area for further investigation. Increased concentrations of IMA have been demonstrated 24–48 h after endurance exercise and postulated to relate to delayed gastrointestinal ischemia (153). A deletion defect of the N-terminal causing reduced cobalt binding (a false-positive test for ischemia) has also been reported (149). The concentration of albumin has also been shown to influence albumin cobalt binding in some but not all studies (154). IMA may be considered for use in conjunction with the ECG and cardiac troponin for the diagnostic assessment of suspected ACS to exclude ACS in patients with a low clinical probability (148). Available data highlight the potential for false-positive results when used as a diagnostic tool for ACS. In addition, the concentration of IMA is no longer increased by 6–12 h after provoked ischemia and thus the negative predictive value may be diminished in patients who do not present early after an ischemic event (146). Studies of IMA, and other proposed tests for ischemia, evaluating the prognostic implications

and/or interaction with specific therapies as well as the kinetics, analytic performance, and underlying pathophysiology will be important to defining their clinical role.

5. MULTIMARKER APPROACH

Advances in our understanding of the pathogenesis and consequences of ACS have stimulated development of new biomarkers and created the opportunity for an expanded role of multiple biomarkers in the classification and individualization of treatment *(84, 155)*. Accumulating evidence indicates that a multimarker strategy, employing a pathobiologically diverse set of biomarkers, adds to biomarkers of necrosis for risk assessment in ACS *(13)*. To date, the majority of evidence regarding this strategy entails newer markers paired with troponin, hs-CRP, and BNP are the most extensively studied. Few studies have examined strategies incorporating 2 or more markers in addition to troponin *(128, 155)*.

Consistent data from multiple studies indicate that increased concentrations of CRP and BNP or NT-proBNP at presentation identify patients who are at higher mortality risk irrespective of whether there is detectable elevation of troponin *(60, 84, 89, 109, 124)*. Thus, application of either of these markers along with a biomarker of necrosis (cardiac troponin) enhances risk assessment *(83–86, 89, 109, 124)*. Moreover, in one study (with internal validation from 2 separate trials), a simple multimarker approach combining each of these markers (BNP, CRP, cTnI) identified a 6- to 13-fold gradient of mortality risk between those without elevation of any marker and those in whom all 3 markers were increased *(155)*. Additional research evaluating this and other strategies for combining 2 or more pathobiologically diverse biomarkers will clarify the appropriate clinical role for such an approach. In particular, 2 important issues require exploration. First, because the relative risk relationships between the individual biomarkers and specific endpoints differ, the optimal weighting of each marker for assessment of 1 clinical outcome (e.g., mortality risk) may differ from that for evaluating another outcome (e.g., the risk of recurrent MI). Second, given the present lack of a robust database to guide treatment in response to increased concentrations of these "novel" markers, more information is needed to formulate an evidence-based management strategy tied to multimarker testing. Nevertheless, as new markers and therapies are discovered, a multimarker paradigm employing a combination of biomarkers for risk assessment and clinical decision-making has the potential to improve outcomes for patients with ACS *(13)*.

6. OTHER NOVEL MARKERS

Other biomarkers such as soluble CD40 ligand, (a marker of platelet activation and potential direct participant in plaque destabilization) *(156)*, metalloproteinases (enzymes that disrupt the integrity of the atheroma's protective cap) *(157)*, and myeloperoxidase (released by leukocytes during activation in the coronary bed) *(111, 128)* are newer markers that have shown potential for risk stratification in ACS. These and other emerging biomarkers that also reflect the underlying pathobiology of atherothrombosis are the substrate of ongoing investigation aimed at determining the optimal combination of biomarkers for characterizing patients with ACS *(158)*. Newer technologies that have facilitated proteomic and genomic strategies for novel marker discovery are likely to extend this approach. Careful evaluation of such novel markers relative to appropriate use of contemporary tools, avoiding limitations to the methodology cited as prevalent in studies of novel biomarkers, is essential to evaluating their potential to add to clinical use *(159)*. In addition, collaborative pooled analyses that evaluate the diagnostic accuracy and prognostic performance of new and established biomarkers across multiple studies are likely to be useful in the critical assessment of their individual and combined clinical value.

III. Use of Biochemical Markers in the Management of NSTEACS

A. CLINICAL DECISION-MAKING

RECOMMENDATIONS FOR THE USE OF BIOCHEMICAL CARDIAC MARKERS FOR THERAPEUTIC DECISION-MAKING

CLASS I

Among patients with a clinical history consistent with ACS, an increased concentration of cardiac troponin should prompt application of ACS management guidelines for patients with indicators of high risk (Level of Evidence: B).

CLASS III

1. Application of management guidelines for ACS should not be based solely on measurement of natriuretic peptides (Level of Evidence: C).
2. Application of management guidelines for ACS should not be based solely on measurement of CRP (Level of Evidence: C).

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1. BIOCHEMICAL MARKERS OF CARDIAC INJURY

The recommendation for measurement of cardiac troponin in all patients with suspected ACS derives not only from the importance of biomarkers of necrosis for risk assessment but also from the established value of cardiac troponin, in particular, for therapeutic decision-making. Consistent with the observation that patients with an increased concentration of troponin are more likely to have complex thrombotic coronary lesions, they also derive greater benefit from more aggressive anticoagulant, antiplatelet, and invasive therapies (Figs. 8 and 9). As such, patients with suspected ACS and abnormal troponin results should be treated in accordance with the
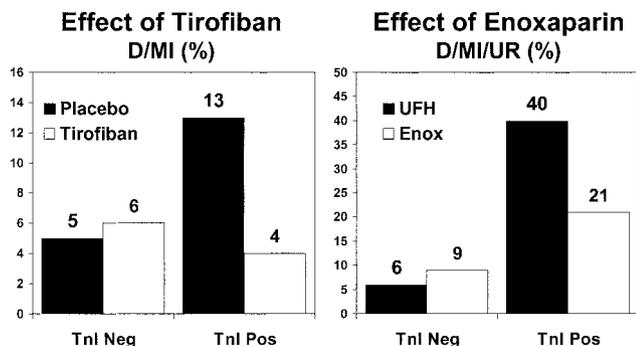
Fig. 8. Effect of potent antithrombotic therapy on the risk of death and recurrent ischemic events.

Left, effect of the platelet GPIIb/IIIa receptor inhibitor, tirofiban, among patients with NSTEAC syndrome enrolled in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial. Data from Heeschen et al. *(162)*. *Right*, effect of the low-molecular-weight heparin, enoxaparin, among patients with NSTEAC syndrome enrolled in the TIMI 11B trial. Data from Morrow et al. *(67)*. Neg, negative; Pos, positive; UR, urgent revascularization prompted by recurrent ischemia.

American Heart Association/American College of Cardiology *(1)* and European Society of Cardiology *(2)* guidelines for the management of high-risk patients with NSTEACS. These guidelines for the management of ACS are expected to be dynamic over time as new experience and evidence emerge. The reader should recognize that the data guiding this recommendation originate from patients with a high clinical probability for ACS. Aggressive treatment with potent antithrombotic therapies and early invasive evaluation is often *not* appropriate for patients with abnormal troponin results due to mechanisms other than ACS (e.g., myocarditis or sepsis). Data regarding the efficacy of specific therapies in patients with increased cardiac troponin are discussed below.
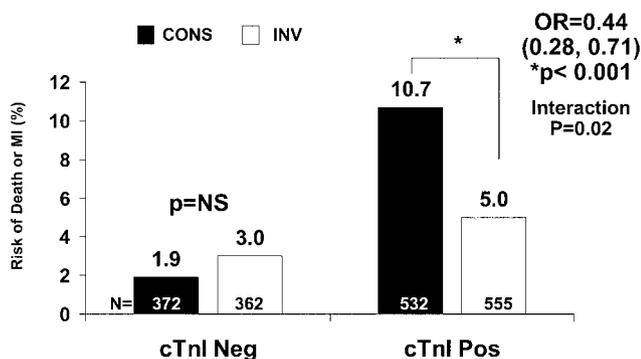

Fig. 9. Benefit of an early invasive *(Inv)* vs conservative *(Con)* management strategy on the risk of death and new/recurrent MI at 6 months in patients with NSTEAC syndrome enrolled in the TACTICS-TIMI 18 trial.

The early invasive strategy consisted of routine cardiac catheterization within 48 h of presentation and revascularization when appropriate regardless of clinical course. The conservative strategy included coronary angiography and revascularization only when prompted by recurrent spontaneous or provoked ischemia. Data from Morrow et al. *(66)*. Neg, negative; Pos, positive.

Low-molecular-weight heparin

Two studies indicate that potent antithrombotic therapy with low-molecular-weight heparin offers particular benefit among patients with an increased concentration of troponin. In the TIMI 11B trial, patients with an increased serum concentration of cTnI at presentation experienced a 50% reduction in death, MI, or recurrent ischemia at 14 days when treated with enoxaparin compared with unfractionated heparin. In contrast, there was no demonstrable advantage of enoxaparin compared with unfractionated heparin in patients without detectable cTnI *(67)*. In the Fragmin during Instability in Coronary Artery (FRISC) trial, extended treatment with dalteparin (Fragmin) after the initial hospitalization conferred a benefit only among patients with increased cardiac troponin *(160)*.

Glycoprotein iib/iiia receptor inhibition

Four studies provide evidence for an interaction between troponin results and the efficacy of potent platelet inhibition with intravenous glycoprotein (GP) IIb/IIIa receptor antagonists *(161–164)*. In the first of these studies, among patients treated with abciximab for 24 h before percutaneous intervention, those with an increased concentration of troponin experienced a 70% relative reduction in the risk of death or MI, while those with negative troponin results had no benefit compared with placebo *(161)*. Similar results have been obtained with 2 other GPIIb/IIIa receptor inhibitors *(162–164)*. Discordant results from one study are notable *(165)*. In a trial that tested abciximab as medical therapy in patients being managed conservatively (without early coronary angiography) for NSTEACS, there was no benefit of abciximab, including among patients with increased concentration of troponin. These results are not yet well explained, but may derive from the specific medical strategy and dosing in this trial. Accordingly, the 2002 update to the American College of Cardiology/American Heart Association Guidelines for the Management of Patients with Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction recommends the use of GPIIb/IIIa receptor antagonists in patients with increased troponin whether (Class I) or not (Class IIa, eptifibatide or tirofiban only) early cardiac catheterization and revascularization are planned *(1)*.

Early invasive strategy

The TACTICS-TIMI 18 trial prospectively examined the value of cardiac troponin for identifying patients who would benefit from an early invasive management strategy. Among patients with an increased concentration of troponin at presentation, a strategy of early angiography (4 to 48 h) and revascularization (if appropriate) achieved a ~55% reduction in the odds of death or MI compared with a conservative management strategy [Fig. 9 *(66)*]. Early angiography and revascularization was not associ-

ated with a detectable benefit in patients who did not have an increased concentration of troponin. Importantly, the advantage of an early invasive strategy was evident even among patients with the lowest level of troponin elevation (cTnI 0.1–0.5 μg/L and cTnT 0.01–0.05 μg/L) *(66)*. These data, along with similar results from the FRISC II trial *(166)*, support the recommendation for early angiography in patients with suspected ACS and an increased concentration of troponin *(1)*.

2. OTHER BIOCHEMICAL MARKERS

Consistent and compelling evidence for interactions between other available biomarkers (e.g., BNP and hs-CRP) and specific treatment strategies in ACS are not yet available (see Section II-B for discussion of individual markers/classes). A number of interventions, such as early treatment with statins and use of GPIIb/IIIa antagonists, have been shown to reduce the serum concentration of hs-CRP after presentation with ACS and/or in response to percutaneous coronary intervention *(137, 138)*. However, testing for a differential impact of treatment among those with or without higher concentrations of CRP has been negative *(59)*. A substudy of the FRISC II trial has demonstrated the potential for greater benefit of early invasive management in patients with evidence of systemic inflammation (increased IL-6) *(127)*; however, more data are needed before this application of inflammatory biomarkers can be advocated. Similarly, a trend toward greater efficacy of early invasive management has been manifest among patients with a higher plasma concentration of NT-proBNP *(88)*. Additional data in this regard are mixed, and more research is needed before a role for natriuretic peptides in therapeutic decision-making is clearly defined *(84)*. There is some evidence for promise of novel markers for selection of therapy, such as the use of GPIIb/IIIa receptor antagonists in patients with increased concentrations of soluble CD40 ligand *(156)*.

B. Biochemical Marker Measurement After the Initial Diagnosis

After the initial diagnosis of unstable angina or NSTEMI is established, measurement of biomarkers is useful for updating the initial assessment of risk, qualitative assessment of the size of infarction, and detection of new or recurrent myocardial injury. See section IV-B for guidelines regarding the serial collection of biomarkers of injury after an initial diagnosis of MI.

For patients in whom the index event is established to be unstable angina, cardiac troponin is the preferred marker for the detection of new infarction. Diagnostic criteria are as described for the index event (section II-A). Repeat sampling of cardiac troponin should be guided by the patient's clinical status and obtained when recurrent symptoms consistent with ischemia of sufficient duration to cause myocardial necrosis have occurred. Routine measurement of biomarkers of necrosis after uncomplicated percutaneous coronary revascularization may aid in assessment of long-term risk *(1)*; however, data with more sensitive markers of necrosis are mixed *(167)*, and the implications for periprocedural management are uncertain.

IV. Use of Biochemical Markers in the Management of STEMI

The diagnosis of STEMI is made by recognition of acute ST-segment elevation (or reciprocal depression) on the 12-lead electrocardiogram. Therefore, appropriate therapy should be instituted on the basis of a diagnostic ECG (See section II-A4) *(10)*. Confirmation of myocardial necrosis is subsequently made using specific biomarkers of necrosis. In addition to this confirmatory application, biomarkers may be used for several other purposes in the management of patients with STEMI.

A. NONINVASIVE ASSESSMENT OF REPERFUSION

One of the most challenging decisions in the acute care of patients with STEMI is when (and if) to perform urgent cardiac catheterization following fibrinolytic therapy. The pattern of rise and fall of biomarkers of necrosis can assist in a noninvasive assessment of the success of reperfusion of the infarct-related coronary artery. In the early experience with fibrinolytics, it was noted that reperfusion of an occluded artery was accompanied by an abrupt increase in serum CK followed by an early peak, findings that were attributed to washout of proteins from injured cells at the time of restoration of blood flow *(168, 169)*. Investigators thus recognized that the rate of rise in biomarkers of necrosis over the first few hours after reperfusion therapy provided information regarding patency of the infarct-related artery. Myoglobin has attracted the most attention for this purpose because of its small molecular size and consequent rapid release *(170–172)*. Rapid washouts of myoglobin, cTnT or cTnI, or CKMB have positive predictive values (PPV) >90% for infarct artery patency *(171–174)*.

However, a number of factors have limited the clinical application of these findings. First, absence of biomarker washout appears to overestimate the likelihood of an occluded artery and cannot accurately distinguish slow from normal flow *(172, 174)*. Second, the logistical challenges of performing multiple measurements in real time have limited use of this strategy. Last, with the steady trend toward more frequent use of primary angioplasty (where there is direct angiographic assessment of the artery) for the treatment of STEMI, the relevance of this application to contemporary practice is diminishing.

B. BIOCHEMICAL MARKER MEASUREMENT AFTER THE
DIAGNOSIS OF ACUTE MI
RECOMMENDATIONS FOR MEASUREMENT OF
BIOCHEMICAL MARKERS OF CARDIAC INJURY AFTER
THE DIAGNOSIS OF MI

CLASS I
1. Once the diagnosis of acute MI is ascertained, testing of biochemical markers of injury at a reduced frequency (e.g., Q6–10 h $\times$ 3) is valuable to qualitatively estimate the size of the infarction and to facilitate the detection of complications such as reinfarction (Level of Evidence: C).

CLASS IIA
2. CK-MB is the preferred marker for detection of reinfarction early after the index event when the concentration of cardiac troponin is still increased (Level of Evidence: C).

CLASS IIB
3. Cardiac troponin may be used as an alternative to CK-MB for detection of reinfarction early after the index event. Serial measurement of troponin is usually necessary to facilitate the discrimination of a new increase in concentration (Level of Evidence C).

During the course of management after the diagnosis of acute MI is ascertained, serial measurements of biomarkers of myocardial necrosis are useful in demonstrating the characteristic rise and/or fall that aids in confirming the diagnosis of MI, providing qualitative information with respect to infarct size and surveying for ongoing or recurrent myocardial ischemia causing reinfarction.

Among patients admitted with MI, the magnitude and temporal course of CK-MB elevation and decline have been shown to correlate strongly with infarct size (175–177). Although experimental and clinical data (using magnetic resonance imaging) demonstrate that cardiac troponin may provide comparable, if not superior, data regarding infarct size and reperfusion (178–181), the clinical meaning of peak values remains less familiar to clinicians. Increases in troponin are demonstrable in cases of early reinfarction (182). However, the scope of available evidence is significantly limited compared with that for CK-MB. In addition, cTnT is known to exhibit a bimodal distribution, and the kinetics for multiple available assays for cTnI have not been studied. Serial testing is usually necessary to discriminate a new increasing pattern of troponin if the concentration is not known to have returned to normal. Because CK-MB falls to the reference interval by 48–72 h, it may aid in the rapid discrimination of reinfarction when symptoms recur between 72 h and 2 weeks after the index MI, when troponin may still be increased from the initial cardiac event. Measurement of CK-MB in conjunction with troponin

may also be useful in determining the timing of recent MI. The committee encourages further investigation of the kinetics of available troponin assays, as well as concurrent evaluation of troponin and CK-MB for the diagnosis of early reinfarction. Data directly comparing these biomarkers for detection of reinfarction are few and may help guide deliberation as to whether CK-MB should continue to have a role in the routine care of patients with acute MI.

The value of biomarkers of necrosis to discriminate very early reinfarction (e.g., <18 h) during a period when the concentration of these markers is typically still increasing is limited. As discussed in greater detail in separate guidelines (*Cardiac Biomarkers and Other Etiologies*), the diagnosis of very early reinfarction rests predominantly on clinical grounds (symptoms and electrocardiographic changes). Routine serial acquisition of surveillance sampling for biomarkers of necrosis after they have returned to the normal range from the index event is not recommended.

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