CLINICAL: ACUTE CORONARY SYNDROMES

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I. OVERVIEW OF THE ACUTE CORONARY SYNDROME

A. Definition of Terms

*Acute coronary syndrome* (ACS) 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 non-traumatic chest symptoms presenting for emergency evaluation each year in the United States.\(^3\) 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 two major categories based on the 12-lead electrocardiogram at presentation; 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 upon a major divergence in the therapeutic approach to STEMI versus 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 of ACS

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 pro-coagulant contents of the atheroma core to circulating platelets and coagulation proteins, and culminating in formation of intra-coronary thrombus.6-8 In 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 approximately 30% of patients with ACS,9 the intra-coronary thrombus completely occludes the culprit vessel resulting in STEMI. Anti-thrombotic and anti-platelet 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 sub-group of patients with STEMI are 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, five 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).\textsuperscript{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.\textsuperscript{12} With the emergence of newer biomarkers that reflect the diverse pathobiology of acute ischemic heart disease, their use as non-invasive means to gain insight into the underlying causes and consequences of ACS is being investigated.\textsuperscript{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.\textsuperscript{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.\textsuperscript{1} It follows that the objectives of the initial evaluation of patients with non-traumatic chest pain are twofold: 1) To assess the probability that the patient’s symptoms are related to acute coronary ischemia; and 2) To assess the patient’s risk of recurrent cardiac events, including death and recurrent ischemia.\textsuperscript{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 MI

Class I

1. Biomarkers of myocardial necrosis should be measured in all patients who present with symptoms consistent with ACS.

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.

3. Cardiac troponin is the preferred marker for the diagnosis of MI. CK-MB by mass assay is an acceptable alternative when cardiac troponin is not available.

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, at 6 to 9 hours, and again at 12 –24 hours if the earlier samples are negative and the clinical index of suspicion is high.

5. In the presence of a clinical history suggestive of ACS, the following are considered indicative of myocardial necrosis consistent with MI:

   a. Maximal concentration of cardiac troponin exceeding the 99th percentile of values (with acceptable precision) for a reference control group on at least one occasion during the first 24 hours after the clinical event

   b. Maximal concentration of CK-MB exceeding the 99th percentile of values for a gender-specific reference control group on two successive samples (Values for CK-MB should rise and fall)

   c. In the absence of availability of a troponin or CK-MB assay, total CK greater than two times the gender-specific upper reference limit

Class Ila

1. For patients who present within 6 hours 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 studies marker for this purpose.
Class IIb

2. A rapid “rule-in” protocol with frequent early sampling of markers of myocardial necrosis may be appropriate if tied to therapeutic strategies.

Class III

1. Total CK, aspartate aminotransferase (AST, SGOT), beta-hydroxybutyric dehydrogenase, and/or lactate dehydrogenase should not be used as biomarkers for the diagnosis of MI.

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.

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), creatine kinase (CK), myoglobin, lactate dehydrogenase, and others. On the basis of improved sensitivity and superior tissue-specificity compared to 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 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, troponin I and T have isoforms that are unique to cardiac myocytes and may be measured by assays employing monoclonal antibodies specific to epitopes of the cardiac form.\textsuperscript{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,\textsuperscript{16,20,21} and also provides superior discrimination of myocardial injury when the concentration of CK-MB is normal or minimally increased.\textsuperscript{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 levels of CK-MB and suspected ACS has confirmed the clinical relevance of detecting circulating troponin in patients previously classified with unstable angina.\textsuperscript{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 concentration 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 fall are important to maintaining specificity for the diagnosis of acute MI.

While of historical significance, due to low specificity for cardiac injury and the availability of more specific alternative biomarkers of necrosis, total CK, lactate dehydrogenase (LDH), and aspartate aminotransferase (AST) should no longer be used for the diagnosis of MI. 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.\textsuperscript{27,28} Multi-marker strategies that include myoglobin appear to identify patients with MI more rapidly than laboratory based determination of a single marker.\textsuperscript{29,30} CK-MB sub-forms may also be used as an early rising indicator of MI but have not seen widespread clinical application due to logistic barriers.\textsuperscript{31}

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 hours after the onset of myocardial injury and falls to normal ranges by 48-72 hours. Cardiac troponin rises with a time course similar to CK-MB but can remain elevated for up to 10 - 14 days.
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. In contrast, myoglobin concentration begins to rise as early as 1 hour after onset of myocyte damage and returns to normal within 12-24 hours.

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 hours), and does not support maximal sensitivity of these markers until six or more hours after the onset of MI. Accurate determination of the timing of symptom onset is based on patient reporting and is often clinically very challenging. Therefore, for most patients, blood should be obtained for testing at hospital presentation, and at 6 to 9 hours to provide adequate clinical sensitivity for detecting MI. In patients for whom these initial samples are negative and there is a high clinical index of suspicion, repeat testing at 12-24 hours is appropriate. Among patients without ST-elevation, such serial testing increases the proportion of patients myocardial injury who are detected from 49% to 68% at 8 hours, and enhances the accuracy of risk assessment. 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. This strategy has also shown value in some studies for expedited exclusion of MI.
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 electrocardiogram 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.\(^4,39\) The tissue-specificity of cardiac troponin should not be confused with specificity for the mechanism of injury (e.g. MI vs. myocarditis).\(^40,41\) When an elevated 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 99\(^{th}\) percentile of a reference control group. Analytic variability at this concentration must be at an acceptable level. The criteria and assessment recommended to meet this analytic requirement are described elsewhere in these guidelines (see section \textit{X.X}). A maximal concentration of cardiac troponin exceeding this decision limit on at least one occasion during the index clinical event is indicative of myocardial necrosis. Similarly, the diagnostic limit for CK-MB is defined as the 99\(^{th}\) percentile (with acceptable imprecision) in a gender-specific reference control group. In light of the lower tissue-specificity compared to troponin, it is recommended that in most situations two consecutive measurements of CK-MB above this decision-limit are required to be considered sufficient biochemical evidence of myocardial necrosis. In the absence of availability of a troponin or CK-MB assay, total CK greater than two...
times the gender-specific upper reference limit may be used as biochemical evidence of myocardial necrosis. A characteristic rise and fall of CK-MB or total CK provides additional evidence supporting the diagnosis of acute MI.

4. Additional Considerations in the Use of Biomarkers for Diagnosis of MI

The criteria for myocardial infarction recommended in these and other guidelines\(^4\) are based upon the principle that any reliably detected myocardial necrosis, if caused by myocardial ischemia, constitutes a myocardial infarction. 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.\(^42\) 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.\(^43\) Elevated concentrations of cardiac troponin I and T have been observed in animal models of ischemia without histologic evidence of irreversible cellular injury.\(^44\) While 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.\(^45\) Nevertheless, based upon the aggregate evidence to date, the present guidelines reflect the prevailing consensus opinion\(^39\) that any reliably detected elevation of a cardiac troponin is abnormal and most likely represents
necrosis. The committee is supportive of 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 one 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. Patients presenting within 6 hours of symptom onset may not yet have detectable serum levels 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 upon an integrated assessment of symptoms, physical exam findings, ECG findings, and biomarkers.

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 concentration exceeding the 99th percentile of values for a reference control group (with acceptable precision) should be considered indicative of increased risk of death and recurrent ischemic events.

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, at 6 to 9 hours, and again at 12 –24 hours if the earlier samples are negative and the clinical index of suspicion is high.

Class IIa

1. Measurement of 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.

2. Measurement of 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.

3. Early repeat sampling of cardiac troponin (e.g. 2 to 4 hours after presentation) may be appropriate if tied to therapeutic strategies.

Class IIb

1. In patients with a high clinical probability of ACS, maximal concentrations of cardiac troponin exceeding the 99th percentile (without stringent requirements for precision) may be recognized as indicative of increased risk of death or recurrent ischemic events.
2. Measurement of markers of myocardial ischemia, in addition to cardiac troponin and ECG, may aid in the short-term risk stratification of patients with suspected ACS, and in excluding ACS in patients with a low clinical probability of myocardial ischemia.

3. A multi-marker strategy that includes measurement of two 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.

Class III
Biomarkers of necrosis should not be used for routine screening of patients with low clinical probability of ACS.

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 elevated 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. In addition, elevated levels of troponin are associated with impaired myocardial tissue or “microvascular” perfusion and thus hypothesized to reflect embolization of platelet aggregates into the distal coronary artery. Furthermore, elevated levels of troponin have been associated with a higher likelihood of poor outcomes during angioplasty, including very slow flow (so-called “no re-flow”) despite a patent epicardial artery in a clinical syndrome believed to result from distal microvascular obstruction. Advances in our understanding of the pathobiology of ACS have pointed toward
these phenomena of micro-embolization and microvascular obstruction as important mediators of adverse outcomes.\textsuperscript{51} As such, the apparent link between micro-embolization and release of cardiac troponin may underlie, at least in part, the strong association between this biomarker and subsequent recurrent clinical events.\textsuperscript{48}

\textit{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.\textsuperscript{52} In addition, the blood concentration of biomarkers of necrosis shows a consistent graded relationship with the risk of short-and long-term mortality.\textsuperscript{53,54} 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 < ULN, to 3.3\% for those with a 1 to 2-fold increase above the ULN, to 8.3\% among those with >10-fold elevation.\textsuperscript{54} The availability of cardiac troponin has extended the spectrum of detectable myocardial injury and further enhanced the clinician’s ability to assess risk.\textsuperscript{24} Based upon evidence from more than 26 studies, that include 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.\textsuperscript{26} In aggregate, the available data indicate an approximately four fold higher risk of death and recurrent MI among patients presenting with suspected NSTEACS and an elevated concentration of troponin compared to patients with a normal troponin result.\textsuperscript{26,55,56} In patients with STEMI, an elevated concentration of troponin at presentation is also associated with significantly higher short-term mortality.\textsuperscript{57,58}
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.\textsuperscript{53,57,59-62} The higher risk of patients presenting with abnormal levels of cardiac troponin is also evident among patients with normal levels of CK-MB.\textsuperscript{63} As such, cardiac troponin is the preferred biomarker for risk assessment in patients presenting with suspected ACS. Cardiac troponin I and T appear to have similar value for risk assessment in ACS.\textsuperscript{26,64}

c. Decision-Limits
As the lower limits of detectability (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 that the upper limit of normal for cardiac troponin and CK-MB be defined by the 99\textsuperscript{th} percentile among a reference control population in conjunction with acceptable precision (<10% coefficient of variation) is aimed at avoiding the greater imprecision associated with the LLD for most assays. In most circumstances, this definition is likely to be optimal as it will minimize the proportion of patients who are incorrectly classified due to analytic false positive results.\textsuperscript{65}

However, operating under Bayesian principles, clinicians should recognize that in populations with a high clinical (pre-test) probability of ACS, increases in cardiac
troponin above an even lower decision limit (e.g. with less stringent criteria for analytic precision) may identify patients at high risk for adverse outcomes. 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. 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 level of cTnI in the range immediately above the 99th percentile for the assay used in the study (0.1 ng/ml, CV 20%) were at more than 3-fold higher risk of death or recurrent MI than those with cTnI < 0.1 ng/ml. This observation of the prognostic significance of low-level elevation of cardiac troponin has been independently confirmed using another assay for cTnI in two separate data sets from clinical trials (OPUS-TIMI 16 and FRISC II), as well as within a community-based study. Specifically, in the latter, patients presenting with chest pain were stratified into four groups according to peak cTnI level – negative (< LLD), low (≥LLD to < 99%ile, 10%CV), intermediate (≥99%ile, 10% to < manufacturer’s suggested diagnostic limit for MI), and high (≥ suggested diagnostic limit for MI) – revealing a six month mortality rate that increased in a stepwise fashion when compared to patients with negative cTnI results (Hazard Ratio of 2.5 (95% 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. With future improvements in the analytic performance of available assays, the association between troponin concentrations at
the lower limit of detectability and outcomes in ACS will require continued careful evaluation.

2. Natriuretic Peptides
   a. Pathophysiology

   Brain (B-type) natriuretic peptide (BNP) and the N-terminal fragment of its prohormone (NT-proBNP) are released from cardiac myocytes in response to increases in ventricular wall stress. 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 non-systolic 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.

   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. Hypoxia has also been
shown to trigger release of BNP. 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 SPECT imaging. After uncomplicated coronary angioplasty, BNP transiently increases even when intracardiac filling pressures remain unchanged. Together, these data provide a plausible basis to explain the strong association between (NT-pro)BNP (abbreviated to refer to both BNP and NT-proBNP where appropriate) and mortality in patients with unstable angina and normal left ventricular systolic function.

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. After presentation with transmural infarction, the plasma concentration of BNP rises rapidly and peaks at approximately 24 hours, with the peak concentration proportional to the size of the MI. 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. In patients with acute MI, higher levels of (NT-pro)BNP have been shown to predict a greater likelihood of death or heart failure, independent of other prognostic variables including left ventricular ejection fraction (LVEF). BNP and NT-proBNP are also elevated in high risk patients with unstable angina. When measured a median of 40 hours after presentation in approximately 1600 patients with NSTEACS, a highly significant graded relationship between the concentration of BNP and subsequent risk of short- and long-term mortality was evident.

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of death increased from <1% among patients with BNP levels in the lowest quartile to 15% in those with BNP levels in the highest quartile (p<0.0001).\textsuperscript{79} This finding has been corroborated in multiple studies of both BNP\textsuperscript{79,80} and NT-proBNP,\textsuperscript{81,82,85} including sub-studies of clinical trials and observational data from community-based cohorts.

Although plasma concentration of (NT-pro)BNP in ACS is associated with older age, female gender, 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 these biomarkers and mortality is independent of these other clinical risk indicators.\textsuperscript{83,92} Importantly, (NT-pro)BNP identifies patients without systolic dysfunction or signs of heart failure who are at higher risk of death and heart failure, and provides prognostic information that is complementary to cardiac troponin.\textsuperscript{80,85}

c. Decision-limits

When evaluated in ACS, (NT-pro)BNP shows a graded relationship with risk for short- and long-term mortality.\textsuperscript{80,85} As such, the absolute plasma concentration of (NT-pro)BNP 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 for one BNP assay and may be used for assays that are similarly calibrated (see Section X.X).\textsuperscript{80} 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 gender-related decision-limits in ACS. It is possible that different decision limits should be applied for risk stratification in ACS compared to diagnostic assessment of the patient with shortness of breath. A detailed discussion analytic issues that may impact the selection and reporting of decision limits for BNP and NT-proBNP is presented in Section X.X of these guidelines.

Whether there is an optimal timing for measurement also warrants additional investigation. When measured at admission,93 <24 hours after symptom onset,80 or 2 to 5 days after the index event, BNP and/or NT-proBNP maintain prognostic performance.79 However, the concentration of natriuretic peptides change over time after presentation and it is possible that the association with clinical risk may vary based upon the time of ascertainment. Serial measurements may serve to provide information that reflects the patient’s risk at presentation, as well as the response to therapy and effects of ventricular remodeling.

d. Therapeutic Decision-making

Few studies have evaluated the effects of specific therapies on ameliorating the risk associated with elevated (NT-pro)BNP in ACS (see Section III-A2). Two studies have evaluated whether (NT-pro)BNP is helpful for identifying candidates for early routine referral for coronary revascularization ("early invasive strategy") following ACS. In the first of these studies, patients with an elevated plasma concentration of BNP experienced a similar benefit of the early invasive approach compared to
patients with BNP < 80 pg/ml. In the second, a trend toward greater benefit with the early invasive strategy was apparent in patients in the highest tertile of NT-proBNP.84

Although convincing data for a strong interaction between the biomarker and specific therapeutic strategies do not yet exist for (NT-pro)BNP as they do for troponin, BNP does 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 (NT-pro)BNP, it has been proposed that less aggressive management strategies may be employed for such patients.95

3. Biochemical Markers of Inflammation
   a. Pathophysiology

Multiple lines of investigation have converged to implicate inflammation as a central contributor to plaque compromise. 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.97,98 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.\textsuperscript{99} As the prototypical acute phase reactant, C-reactive protein (CRP) has been the focus of much of the clinical investigation.\textsuperscript{100}

Elevated levels of inflammatory biomarkers such as C-reactive protein, serum amyloid A, and IL-6 are detectable in a substantial proportion of patients presenting with ACS, including those without evidence of myocyte necrosis.\textsuperscript{100-104} 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.\textsuperscript{105} 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.\textsuperscript{100,102,104} CRP has also been implicated as a potential direct participant in atherothrombosis rather than a mere by-stander. 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.\textsuperscript{96} Lastly, 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\textsuperscript{106} and patient-specific responses to inflammatory stimuli.\textsuperscript{107}
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. Data restricted to patients with STEMI are few; in one cohort study, patients with elevated CRP were more likely to suffer complications of acute MI (myocardial rupture, left ventricular aneurysm, and death by 1 year). 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 NSTE ACS. Specifically, measurement of hs-CRP appears to yield additional prognostic value in patients with negative testing of cardiac troponins 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. While hs-CRP is the best studied of the inflammatory markers in the setting of ACS, others such as IL-6 and myeloperoxidase are also associated with prognosis and may eventually prove to add or supercede hs-CRP (see section II-B6).

c. Decision-limits

The preferred unit for reporting hs-CRP results is mg/L. Multiple decision-limits for hs-CRP, ranging from 3 to 15 mg/L, have been evaluated for risk assessment in ACS with few comparative studies. The optimal decision-limit remains to be determined; however, consensus opinion is that it is likely higher (e.g. 10 or 15 mg/L) than that used in candidates for primary prevention. In one 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.\textsuperscript{113}

The best timing for measurement of hs-CRP for risk stratification in ACS also remains uncertain. Potential confounding by the inflammatory response to necrosis must be considered when samples are drawn late after presentation of patients with MI.\textsuperscript{123,124} Studies with samples drawn both early after presentation,\textsuperscript{102,112} at discharge,\textsuperscript{111,114} and during the convalescent phase of recovery (>3 months post-MI)\textsuperscript{125} have all demonstrated independent associations with subsequent outcomes. In two comparative studies of samples drawn at admission versus discharge, a modest advantage of the pre-discharge assessment was evident (but not statistically heterogeneous).\textsuperscript{111,114} Additional research aimed at resolving these issues is needed.

d. Therapeutic Decision-making

The appropriate therapeutic response to elevated markers of inflammation in patients with ACS is not yet clear. Treatment with HMG-CoA reductase inhibitors ("statins") is effective in lowering CRP in patients with recent or prior ACS.\textsuperscript{126,127} However, since all patients with established CAD should be treated with these agents, any utility of hs-CRP for targeting statin therapy after ACS is not defined. 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.\textsuperscript{128-130} It is possible that future work investigating more aggressive anti-inflammatory
therapies for 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. 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 two 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 elevated has the potential to add substantially to available clinical tools.

Several biomarkers of myocardial ischemia are under investigation. Albumin cobalt binding is among the most thoroughly studied of these markers. This test 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 hours. Reduced albumin cobalt binding also occurs in patients with spontaneous coronary ischemia, with abnormal levels detectable prior to subsequent elevation of cardiac troponin. The precise mechanisms for production of ischemia-modified albumin (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.\textsuperscript{134,137}

The clinical specificity of IMA, as well as other potential markers of ischemia such as unbound free fatty acid\textsuperscript{138} and whole blood choline,\textsuperscript{139} in the broad population of patients with non-traumatic chest pain and suspected ACS remains an area for further investigation. Elevated levels of IMA have been demonstrated 24-48 hours after endurance exercise and postulated to relate to delayed gastrointestinal ischemia.\textsuperscript{140} A deletion defect of the N-terminal causing reduced cobalt binding (a “false positive” test for ischemia) has also been reported.\textsuperscript{136} Studies of IMA, and other proposed tests for ischemia, evaluating the prognostic implications and/or interaction with specific therapies 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.\textsuperscript{80,141} Accumulating evidence indicates that a multi-marker strategy, employing a pathobiologically diverse set of biomarkers, adds to biomarkers of necrosis for risk assessment in ACS.\textsuperscript{13} To date, the majority of evidence regarding this strategy entails newer markers paired with troponin, and hs-CRP and (NT-
pro)BNP are the most extensively studied. Although promising, few studies have examined strategies incorporating 2 or more markers in addition to troponin.\textsuperscript{121,141}

Consistent data from multiple studies indicate that elevated levels of CRP and BNP at presentation identify patients who are at higher mortality risk irrespective of whether or not there is detectable elevation of troponin.\textsuperscript{80,85,102,115,117} Thus, application of either of these markers along with a biomarker of necrosis (cardiac troponin) enhances risk assessment.\textsuperscript{79-82,85,102,115} Moreover, in one study (with internal validation from two separate trials), a simple multi-marker 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 three markers were elevated.\textsuperscript{141} Additional research evaluating this and other strategies for combining two or more pathobiologically diverse biomarkers will clarify the appropriate clinical role for such an approach. In particular, two 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 one 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 elevated levels of these “novel” markers, more information is needed to formulate an evidence-based management strategy tied to multi-marker testing. Nevertheless, as new markers and therapies are discovered, a multi-marker paradigm employing a
combination of biomarkers for risk assessment and clinical decision-making has the potential to improve outcomes for patients with ACS.  

6. **Other Novel Markers**

Other biomarkers such as soluble CD40 ligand, (a marker of platelet activation and potential direct participant in plaque destabilization), metalloproteinases, (enzymes that disrupt the integrity of the atheroma’s protective cap) and myeloperoxidase (released by leukocytes during activation in the coronary bed) 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. Newer technologies that have facilitated proteomic and genomic strategies for novel marker discovery are likely to extend this approach.

III. **USE OF BIOCHEMICAL MARKERS IN THE MANAGEMENT OF NSTE ACS**

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.

**Class III**

1. Application of management guidelines for ACS should not be based solely upon measurement of natriuretic peptides.
2. Application of management guidelines for ACS should not be based solely upon measurement of C-reactive protein.

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 anti-coagulant, anti-platelet, and invasive therapies. As such, patients with suspected ACS and abnormal troponin results should be treated in accord with the American Heart Association/American College of Cardiology\(^1\) and European Society of Cardiology\(^2\) guidelines for the management of high risk patients with NSTE ACS. The reader should recognize that the data guiding this recommendation originate from patients with a high clinical probability for ACS. Aggressive treatment with potent anti-thrombotic therapies, and early invasive evaluation are 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 elevated cardiac troponin are discussed below.

*Low molecular weight heparin (LMWH)*

Two studies indicate that potent anti-thrombotic therapy with low molecular heparin offers particular benefit among patients with elevated levels 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 to unfractionated heparin. In contrast, there was no demonstrable advantage of enoxaparin compared to unfractionated heparin in patients without detectable cTnI. 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 elevated cardiac troponin. 

*Glycoprotein IIb/IIIa (GP IIb/IIIa) Inhibition*

Four studies provide evidence for an interaction between troponin results and the efficacy of potent platelet inhibition with intravenous GPIIb/IIIa antagonists. In the first of these studies, among patients treated with abciximab for 24 hours prior to percutaneous intervention, those with an elevated 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. Similar results have been obtained with two other glycoprotein IIb/IIIa inhibitors. Discordant results from one study are notable. In a trial which 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 ACC/AHA Guidelines for the Management of Patients with Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction recommend the use of GPIIb/IIIa antagonists in patients with elevated troponin.
whether (Class I) or not (Class IIa, eptifibatide or tirofiban only) early cardiac catheterization and revascularization are planned.\textsuperscript{151}

\textit{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 elevated levels of troponin at presentation, a strategy of early angiography (4-48 hours) and revascularization (if appropriate) achieved a \~55\% reduction in the odds of death or MI compared with a conservative management strategy.\textsuperscript{62} Early angiography and revascularization was not associated with a detectable benefit in patients who did not have elevated levels 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 ng/ml and cTnT 0.01-0.05 ng/ml).\textsuperscript{62} These data, along with similar results from the FRISC II trial,\textsuperscript{152} support the recommendation for early angiography in patients with suspected ACS and elevated levels of troponin.\textsuperscript{151}

2. \textit{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). 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 PCI.\textsuperscript{126,127} However, testing for a differential impact of treatment among those with or without higher concentrations of CRP has been negative.\textsuperscript{55} 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 interleukin-6); 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. Additional data in this regard are mixed and more research is needed before a role for (NT-pro)BNP in therapeutic-decision making is clearly defined.

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 is made.

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; however, data with more sensitive markers of
necrosis are mixed\textsuperscript{154} and the implications for peri-procedural 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).

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. Non-invasive 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 non-invasive 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.\textsuperscript{155,156} 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. \(^{157-159}\) Rapid “washout” of myoglobin, troponin T or I, or CKMB have positive predictive values (PPV) >90% for infarct artery patency. \(^{158-161}\)

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. \(^{159,161}\) Second, the logistical challenges of performing multiple measurements in “real-time” has limited use of this strategy. Lastly, 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 is valuable to qualitatively estimate the size of the infarction, and to detect the presence of complications such as re-infarction.

Class IIa

2. CK-MB is the preferred marker for detection of re-infarction early after the index event when the concentration of cardiac troponin is still increased.

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 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 re-infarction.

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.\textsuperscript{162-164} Although cardiac troponin may provide comparable data regarding infarct size and reperfusion, the clinical meaning of peak values remains less familiar to clinicians.\textsuperscript{165-167} In addition, by virtue of the release kinetics already described, it is reasonable to expect that troponin is less useful for detection of early re-infarction, particularly when frequent serial samples are not obtained to document the precise trajectory of decline. In comparison, CK-MB falls to the normal range by 48-72 hours and thus is more easily used for detection of re-infarction beyond that period. Myoglobin may be used when reinfarction is suspected very early (12-24 hours) after the index event. Measurement of CK-MB and/or myoglobin in conjunction with troponin may also be useful in determining the timing of recent MI. 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.
V. REFERENCES


