
The National Academy of Clinical Biochemistry

Presents

LABORATORY MEDICINE PRACTICE
GUIDELINES



BIOMARKERS OF ACUTE CORONARY SYNDROMES AND HEART FAILURE

EDITED BY
Robert H. Christenson

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EDITED BY
Robert H. Christenson

NACB Committee Members

Robert H. Christenson, Chair
University of Maryland School of Medicine,
Baltimore, Maryland, USA

Fred S. Apple
Hennepin County Medical Center and University
of Minnesota, Minneapolis, Minnesota, USA

Christopher P. Cannon
Brigham and Women's Hospital, Boston,
Massachusetts, USA

Gary S. Francis
Cleveland Clinic Foundation, Cleveland, Ohio,
USA

Robert L. Jesse
Medical College of Virginia, Richmond,
Virginia, USA

David A. Morrow
Brigham and Women's Hospital, Boston,
Massachusetts, USA

L. Kristin Newby
Duke University Medical Center, Durham, North
Carolina, USA

Jan Ravkilde
Aarhus University Hospital, Aarhus, Denmark

Alan B. Storrow
Vanderbilt University, Nashville, Tennessee,
USA

W. H. Wilson Tang
Cleveland Clinic Foundation, Cleveland, Ohio,
USA

Alan H. B. Wu
San Francisco General Hospital and University
of California at San Francisco, San Francisco,
California, USA

Ad Hoc members of the committee for selected sections

Allan S. Jaffe
Mayo Clinic, Rochester, Minnesota, USA

Mauro Panteghini
University of Milan, Milan, Italy

Alan S. Maisel
University of California at San Diego, San
Diego, California, USA

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National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Utilization of Biochemical Markers in Acute Coronary Syndromes and Heart Failure

Robert H. Christenson, Ph.D, Chair

National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Utilization of Biochemical Markers in Acute Coronary Syndromes and Heart Failure

The National Academy of Clinical Biochemistry's (NACB) Laboratory Medicine Practice Guidelines (LMPG) for use of cardiac markers in coronary artery diseases were published in July of 1999 (1). Since production of this initial document, numerous published studies and presented data have added significantly to the knowledge base for cardiac biomarkers. This increased knowledge has substantially expanded the scope of recommendations for cardiac biomarker utilization since the 1999 document, and in particular has required the inclusion of recommendations regarding biomarkers that extend beyond myocardial necrosis. Toward addressing these advances and their impact on biomarker utilization in clinical practice, the NACB appointed a chair and members of a LMPG committee that was charged with the overall objective of revising and extending the earlier recommendations by establishing modern guidelines for Utilization of Biomarkers in Acute Coronary Syndrome and Heart Failure. This LMPG is aimed at providing analytical and clinical guidance for the measurement and interpretation of cardiac biochemical markers of acute coronary syndromes (ACS), heart failure and point-of-care measurement and logistics of providing ACS biomarker data for patient care; guidance for interpretation of biomarkers in etiologies other than ACS and Heart Failure is included as well. For the ACS guidelines, the subset of patients having non-ST elevation on their electrocardiogram are the major focus because cardiac biomarkers have major impact on their diagnosis and care. As implied, sections of these guidelines contain analytical recommendations for important tests utilized in these clinical applications. We strongly encourage laboratory medicine professionals to share the analytical performance characteristics with clinicians; there is evidence that providing test performance characteristics to clinicians influenced certain decisions, sometimes in unexpected ways (2).

These guidelines and their recommendations are structured into six chapters that include Chapter 1: Clinical Utilization of Biomarkers in Acute Coronary Syndromes (ACS); Chapter 2:

Analytical Issues of ACS Biomarkers; Chapter 3: Clinical Utilization of Biomarkers of Heart Failure; Chapter 4: Analytical Issues of Heart Failure Biomarkers; Chapter 5: Point of Care Testing and Logistics; and Chapter 6: Cardiac Biomarkers and Other Etiologies. Each chapter was spearheaded by a writing group, which was a subset of the overall committee. In addition, other ad hoc expertise contributed to the writing group of some subsections and chapters to optimize the content and quality of the guidelines. The "questions" for each chapter are in the form of issues addressed and specified in the organization of each individual chapter. The chapter design of the guidelines was used to facilitate finding guidance by users; this format was also used, in part, to provide an easy and focused procedure for updating the guidelines in the future. Also, the chapter design allowed publication of sections in appropriate laboratory medicine and clinical specialty journals.

Stakeholder involvement in development and refinement of these guidelines was substantial. The guideline team was comprised of laboratory medicine professionals (Apple, Christenson, Wu), ACS cardiology experts (Cannon, Jesse, Morrow, Newby, and Ravkilde), and heart failure cardiology experts (Jesse, Francis, Tang). As these guidelines target acutely ill patients, Emergency Medicine stakeholders were represented by a specialist (Storrow); it is also noteworthy that all of the laboratory professionals and cardiology experts on the guideline committee have substantial interaction, knowledge, and publications in the area of laboratory and clinical medicine in the Emergency Medicine environment. To further enhance stakeholder input, draft revisions of the Guidelines were prepared and placed for comment on the NACB World Wide Web site (<http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/DraftGuidelines/BioHeartFailure/>). The draft LMPG and suggested revisions were also presented for public and stakeholder comment at the October 2004 Arnold O. Beckman Conference titled *Cardiac Markers: Establishing Guidelines and Improving Results*. Table 1 lists the various

Table 1. Stakeholder organizations, with contact addresses, that agreed to participate in guideline development

Agency for HealthCare Research Quality www.ahrq.gov
American Academy of Physician Assistants www.aapa.org
American Association of Critical Care Nurses www.aacn.org
American Association of Occupational Health Nurses www.aaohn.org
American College of Cardiology www.acc.org
American College of Chest Physicians www.chestnet.org
American College of Emergency Physicians www.acep.org
American Heart Association www.americanheart.org
American Red Cross www.redcross.org
Association of Black Cardiologists www.abcardio.org
College of American Pathologists www.cap.org
Centers for Disease Control and Prevention www.cdc.gov
Emergency Nurses Association www.ena.org
Food and Drug Administration www.fda.gov
Global Task Force for Revision of ESC/ACC MI Consensus Development
National Association of Emergency Medical Technicians www.naemt.org
National Association of EMS Physicians www.naemsp.org
National Association of State Emergency Medical Services Directors www.nasemsd.org
National Heart, Lung, and Blood Institute www.nhlbi.nih.gov
National Medical Association www.nmanet.org
Society for Academic Emergency Medicine www.saem.org
Society for Chest Pain Center Providers www.scpcp.org
Society for General Internal Medicine www.sгим.org

stakeholder groups that agreed to examine the documents and were represented at the conference. ACS and heart failure are worldwide problems, and therefore stakeholders are not limited to the United States. The analytical chapters of the guidelines were developed in collaboration with the International Federation for Clinical Chemistry and Laboratory Medicine (IFCC) through the IFCC's Committee on Standardization of

Markers of Cardiac Damage chaired by Dr. Apple. Several of the NACB committee members (Apple, Ravkilde, and Newby) were also members of the global task force for redefinition of myocardial infarction. Also, Dr. Allan Jaffe, chair of the biochemical markers section of the global task force, had substantial input into the guidelines and was a member of the writing group for two chapters. This international interaction provided an important and valuable venue for comment and input by colleagues and stakeholders.

Although the committee believed that the implications of cardiac biomarker testing addressed in these guidelines should be broad and international, the tradeoff was that designing, funding and conducting a appropriate pilot study for the recommendations in this guideline was extremely complicated and logistically impossible.

These guidelines refer to *in vitro* diagnostic testing and are intended for use by laboratory medicine professionals and caregivers of acutely ill ACS and heart failure patients as part of their diagnosis and management. In this context, there is currently no role for home or self-monitoring of testing addressed or advocated in this LMPG. The role of input from the perspective of patient preferences and values in development of these guidelines was modest, and the direct care clinicians on the committee expressed that they were able to represent patients adequately. In addition, several nursing organizations participated by reviewing the document from the perspective of patient representation. Although a patient was not a designated member of the guidelines committee, a mechanism for expressing views and preferences was available through the web posting above. Further, AACC and NACB believe that it is critical to inform patients about laboratory medicine testing and information facilitate patient interaction is available through such venues as LabTests Online (web address: www.labtestsonline.org).

These NACB guidelines were developed rigorously; however it was possible to include only papers published in the English language. The specified method for developing the evidence base for recommendations listed each chapter involved use of PubMed, EMBASE and other databases that were not necessarily published. Systematic methods were used whenever available; searches were first set to be sensitive to avoid missing papers of possible interest, and then narrowed to sort through the literature in order to enhance specificity. The writing group for each section contacted recognized experts to assure that important evidence had not been missed. Also, as stated above, certain experts were made ad hoc writing group members to help assure the rigor of guideline development. Finally, each of the guidelines have been published in the peer-reviewed literature, in clinical and laboratory medicine journals, to enhance dissemination and help assure rigor from stakeholder perspectives. The remaining sections involving other clinical and analytical issues for utilization of cardiac biomarkers is available at <http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines>.

Because these guidelines are intended for both laboratory medicine and clinical use, the strength of scientific data supporting each recommendation is characterized using a modified

**Table 2. Modified American College of Cardiology/
American Heart Association****Classifications: Summary of Indications**

- I Conditions for which there is evidence and/or general agreement that a given laboratory procedure or treatment is useful and effective
- II Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a laboratory procedure or treatment.
 - a Weight of evidence/opinion is in favor of usefulness/efficacy
 - b Usefulness/efficacy is less well established by evidence/opinion
- III Conditions for which there is evidence and/or general agreement that the laboratory procedure/treatment is not useful/effective and in some cases may be harmful.

Weight of Evidence

- A Data derived from multiple randomized or appropriately designed clinical trials that involved large numbers of patients
- B Data derived from a limited number of randomized or appropriately designed trials that involved small numbers of patients or from careful analyses of observational registries
- C Expert Consensus was the primary basis for the recommendation

form of the scoring criteria adopted from the American Heart Association/American College of Cardiology as summarized in Table 2. For each recommendation, the designations I, IIa, IIb and III describe the indications, and the upper case letters A through C describe the weight of evidence. Levels of evidence listed in the guidelines were determined by the full writing committee. Any issues regarding ratings were discussed in detail until consensus of the full writing committee was reached. In the discussion section of each chapter, the relative benefits, unintended consequences and risks were considered. The sections are cited such that there is an explicit link between the recommendations and the supporting evidence for each recommendation in the appropriate clinical and laboratory context.

Our aim was to assure that the recommendations in this guideline were presented specifically and unambiguously. To accomplish this, the recommendations are listed together in

bold lettering at the beginning of relevant sections within a chapter. Various options for utilization are presented when appropriate. Tools for application of the guideline involve close communication with local physician and other caregivers, as well as with the administrators responsible for each area. Collaboration with manufacturers and communication of clinical need as articulated in the guidelines are also critical for proper implementation. Many of these issues are of particular importance in Point of Care testing, and this chapter has several recommendations on how to assure that appropriate testing is available and for monitoring or auditing performance. Cost implications of the guidelines are discussed, however these issues could not be detailed because of the many local reimbursement policies and international funding issues involved.

Other than modest funding from the NACB/AACC, development of these guidelines was a volunteer activity. Thus the guidelines are editorially independent from any funding body. All potential conflicts of interest for the NACB guidelines committee and ad hoc members of the writing committees are listed at the following: <http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/ACSHeart/heartpdf.htm>.

In summary, these guidelines were developed utilizing best available evidence and incorporated substantial input from acknowledged experts and professional organizations. Except for education and dissemination, implementation of the recommendations should encounter very few barriers, and each of the recommendations should be viewed as key review or audited criteria. As such, these guidelines represent the current best practice for utilization of biochemical markers of ACS and heart failure.

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Chapter 1

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

NACB WRITING GROUP MEMBERS

David A. Morrow,¹ Christopher P. Cannon,¹ Robert L. Jesse,² L. Kristin Newby,³ Jan Ravkilde,⁴ Alan B. Storrow,⁵ Alan H.B. Wu,⁶ and Robert H. Christenson^{7}*

NACB COMMITTEE MEMBERS

*Robert H. Christenson, Ph.D, Chair
Fred S. Apple, Minneapolis, MN; Christopher P. Cannon; Gary Francis, Cleveland, OH;
Robert L. Jesse; David A. Morrow; L. Kristin Newby; Jan Ravkilde; Alan B. Storrow;
Wilson Tang, Cleveland, OH; and Alan H.B. Wu*

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¹Brigham and Women's Hospital, Harvard University, Boston, MA.

²Medical College of Virginia, Richmond, VA.

³Duke University Medical Center, Durham, NC.

⁴Aarhus University Hospital, Aarhus, Denmark.

⁵Vanderbilt University, Nashville, TN.

⁶University of California at San Francisco, San Francisco, CA.

⁷University of Maryland School of Medicine, Baltimore, MD.

All relationships with industry for the guidelines committee are reported online at <<http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/ACSHeart/heartpdf.htm>>.

The materials in this publication represent the opinions of the authors and committee members, and do not represent the official position of the National Academy of Clinical Biochemistry (NACB). The National Academy of Clinical Biochemistry is the academy of the American Association for Clinical Chemistry.

*Address correspondence to this author at: Director, Rapid Response Laboratories, University of Maryland School of Medicine, 22 S. Greene St., Baltimore, MD 21201. Fax 410-328-5880; e-mail rchristenson@umm.edu.

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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 non traumatic 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 (Figure 1-1): 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, NSTEMACS). The latter term (NSTEMACS) encompasses

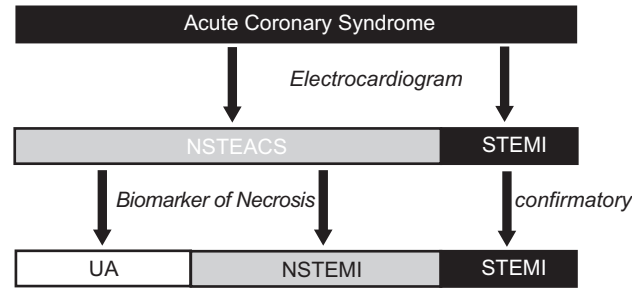


Figure 1-1 Categorization of acute coronary syndromes.

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 NSTEMACS (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 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 NSTEMACS (1, 11).

Including the most common etiology of ACS described above, 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

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⁸Nonstandard abbreviations: ACS, acute coronary syndrome; ECG, electrocardiogram; STEMI, ST-elevation myocardial infarction; NSTEMACS, 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.

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 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 may be 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)

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 1-1). 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

Table 1-1 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.

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 circulating troponin in patients previously classified with unstable angina. An example from one of several studies is shown in Figure 1-2 (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 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/or fall are important to

maintaining specificity for the diagnosis of acute MI. Alternatives to cardiac injury should be sought when CK-MB

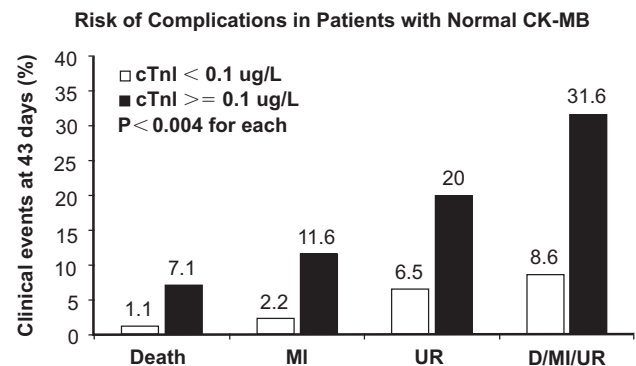


Figure 1-2 Risk of death and recurrent ischemic events among patients with NSTEMACS and normal serial CK-MB with and without increase baseline concentration of cardiac troponin I (Dimension RxL, Dade Behring). As discussed in section II-B1.c, the cut point applied in this study is specific to the assay used. Data from Morrow et al. (67). UR, urgent reagent revascularization prompted by recurrent ischemia.

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 (Figure 1-3). 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 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

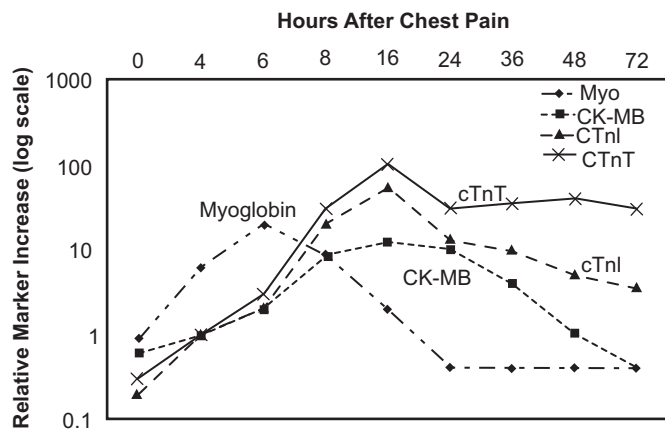


Figure 1-3 Temporal release of myoglobin, CK-MB, cTnI and cTnT. With permission, from Christenson RH, Azzazy HME. Biomarkers of necrosis: past, present and future. In Morrow DA, ed. Cardiovascular Biomarkers: Pathophysiology and Clinical Management. New York: Humana Press, 2006.

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 (NTproBNP) 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)

Continued on next page

*Continued from previous page***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 NSTEMACS 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 NSTEMACS, 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 NSTEMACS and an increased concentration of troponin compared with patients with a normal troponin result (Figure 1-4) (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 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).

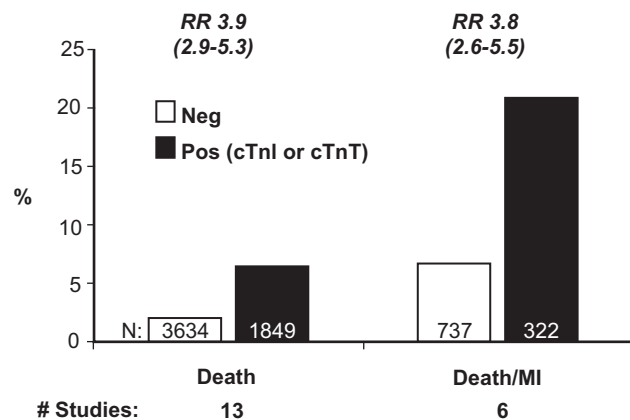


Figure 1-4 Risk of death or MI stratified by troponin result in patients with suspected ACS. Adapted with permission from Braunwald E, et al. American College of Cardiology/American Heart Association guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial 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.

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 (\geq LLD to <99th percentile, 10%CV), intermediate (\geq 99th percentile, 10%CV to < manufacturer’s suggested diagnostic limit for MI), and high (\geq 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 (Figure 1-5) (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

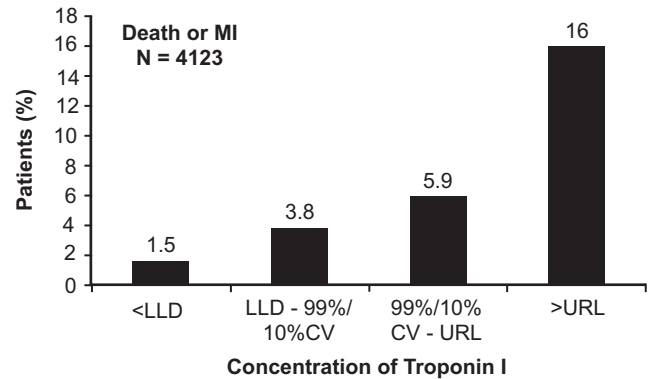


Figure 1-5 Prognostic implication of low-level troponin elevation in patients with chest pain suspicious for ACS. Data from Kontos, et al. (72). URL, upper reference limit supplied by manufacturer.

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 singlephoton 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.

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 1-2) (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

Table 1-2 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, with early no interaction 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.

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 NSTEMACS, a highly significant graded relationship between the concentration of BNP and subsequent 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 NTproBNP (85, 86, 89), including substudies of clinical trials and observational data from community-based cohorts (Figure 1-6).

Although the plasma concentration of BNP and NTproBNP 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 (Figure 1-7) (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 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 decisionlimits 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).

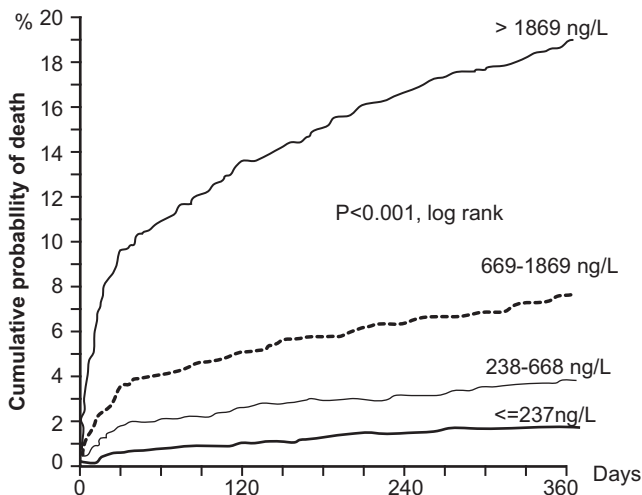


Figure 1-6 Risk of death in patients with NSTEMACS syndrome stratified by quartile of concentration of NT-proBNP (Elecsys 2010, Roche Diagnostics) at baseline. With permission from James et al. (89).

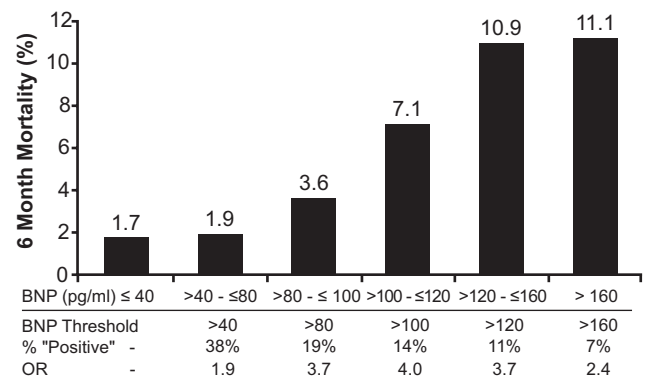


Figure 1-7 Mortality risk stratified by BNP concentrations over the range of 40–160 pg/mL (Triage, Biosite). The odds ratios (ORs) and χ^2 statistics in the table below the chart are based on BNP results dichotomized at the lower bound of the range. With permission from Morrow et al. (84).

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 pro-coagulant 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 1-3). 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 NSTEMI (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).

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

Table 1-3 Summary of Clinical Studies of CRP in ACS

A. NSTEMACS					
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)
Bazzino et al., 2001 (187)	Observational	139	>15	3 months	D/MI/RI, 2.1 (1.5–3.1)
Mueller et al., 2002 (125)	Observational	1042	>10	3 months	D/MI, 18.6 (4.5–77)
James et al., 2003 (60)	Substudy of RCT (GUSTO IV)	7108	>10	In-hospital	Death, 4.2 (1.6–10.9)
Oltrona et al., 2004 (188)	Observational	965	>10	1 month	Death, 1.2 (1.05–1.4)
Long-term					
de Winter et al., 1999 (189)	Observational	156	>5	1 month	D/MI, 2.0 (1.3–3.1)
Heeschen et al., 2000 (59)	Substudy of RCT (CAPTURE)	447	>10	6 months	D/MI/RI, 9.8 (1.5–65)
Mulvihill et al., 2001 (190)	Observational	91	>3	6 months	Death, 4.7 (1.3–16.9)
Bholasingh et al., 2003 (191)	Observational	382	>3	6 months	D/MI/RI, 9.8 (2.5–38.9)
Baldus et al., 2003 (128)	Substudy of RCT (CAPTURE)	1090	>10	6 months	D/MI, 5.6 (1.5–22.2)
Bodi et al., 2005 (192)	Observational	515	>11	6 months	D/MI, 1.25 (1.02–1.7)
Biasucci et al., 1999 (123)	Observational	53	>3	6 months	D/MI, 2.1 (1.2–3.8)
Lindahl et al., 2000 (124)	Substudy of RCT (FRISC)	917	>10	1 year	D/MI/RI, 4.7 (1.8–12.0)
Versaci et al., 2000 (193)	Observational	62	>5	3 years	Death, 2.5 (1.6–3.9)
Mueller et al., 2002 (125)	Observational	1042	>10	1 year	D/MI/RI, 22.2 (3.1–157)
Zebrack et al., 2002 (194)	Observational	442	>11	20 months	Death, 3.8 (2.3–6.2)
James et al., 2003 (60)	Substudy of RCT	7108	>10	3 years	D/MI, 2.6 (1.4–4.8)
Sanchez et al., 2004 (195)	Observational	83	>5	1 year	Death, 1.5 (1.1–1.9)
				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.

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 (\geq 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 pre-discharge 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 (\geq 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 anti-inflammatory 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 NSTEMACS

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)

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 (Figures 1-8 and 1-9). As such, patients with suspected ACS and abnormal troponin results should be treated in accordance 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 NSTEMACS. 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

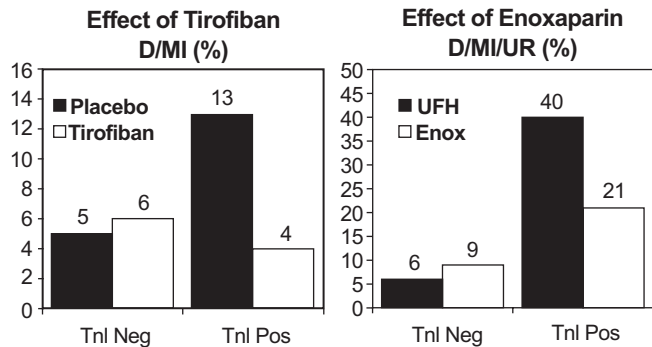


Figure 1-8 Effect of potent antithrombotic therapy on the risk of death and recurrent ischemic events. Left, effect of the platelet GPIIb/IIIa receptor inhibitor, tirofiban, among patients with NSTEMI/ACS enrolled in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial. Data from Heeschen et al. (162). Right, effect of the low-molecular-weight heparin, enoxaparin, among patients with NSTEMI/ACS enrolled in the TIMI 11B trial. Data from Morrow et al. (67). Neg, negative; Pos, positive; UR, urgent revascularization prompted by recurrent ischemia.

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.

a. 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).

b. 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 NSTEMI/ACS, 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, eptifibatid or tirofiban only) early cardiac catheterization and revascularization are planned (1).

c. 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 associated 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).

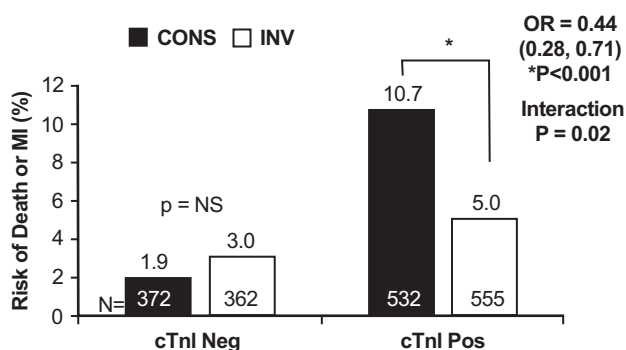


Figure 1-9 Benefit of an early invasive (Inv) vs conservative (Con) management strategy on the risk of death and new/recurrent MI at 6 months in patients with NSTEMI/ACS enrolled in the TACTICS-TIMI 18 trial. The early invasive strategy consisted of routine cardiac catheterization within 48 h of presentation 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.

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 × 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 II A

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 II B

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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Chapter 2

National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical Issues for Biochemical Markers of Acute Coronary Syndromes

NACB WRITING GROUP MEMBERS

Fred S. Apple,¹ Robert L. Jesse,² L. Kristin Newby,³ Alan H.B. Wu,⁴ And Robert H. Christenson^{5}*

NACB COMMITTEE MEMBERS

Robert H. Christenson, Chair

Fred S. Apple; Christopher P. Cannon, Boston, Ma; Gary Francis, Cleveland, Oh; Robert Jesse; David A. Morrow, Boston, Ma; L. Kristin Newby; Jan Ravkilde, Aarhus, Denmark; Alan B. Storrow, Nashville, Tn; Wilson Tang, Cleveland, Oh; And Alan H.B. Wu

IFCC COMMITTEE ON STANDARDIZATION OF MARKERS OF CARDIAC DAMAGE (C-SMCD) MEMBERS

Fred S. Apple, Chair

Robert H. Christenson; Allan S. Jaffe, Rochester, Mn; Johannes Mair, Innsbruck, Austria; Jordi Ordonez-Llanos, Barcelona, Spain; Franca Pagani, Brescia, Italy; Mauro Panteghini, Milan, Italy; Jillian Tate, Brisbane, Australia; and Alan H.B. Wu

¹ Hennepin County Medical Center, Minneapolis, MN.

² Medical College of Virginia, Richmond, VA.

³ Duke University Medical Center, Durham, NC.

⁴ University of California at San Francisco, San Francisco, CA.

⁵ University of Maryland School of Medicine, Baltimore, MD.

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*Address correspondence to this author at: Director, Rapid Response Laboratories, University of Maryland School of Medicine, 22 S. Greene St., Baltimore, MD 21201. Fax 410-328-5880; e-mail rchristenson@umm.edu.

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I. OVERVIEW OF ANALYTICAL ISSUES FOR ACUTE CORONARY SYNDROME (ACS) BIOMARKERS

A. Background

In 1999, the National Academy of Clinical Biochemistry (NACB)⁶ published the first standards of laboratory practice addressing analytical and clinical recommendations for use of cardiac markers in coronary artery diseases (1). The objectives were to recommend the appropriate implementation and utilization of cardiac biomarkers, specifically for cardiac troponin (cTn), which had just gained US Food and Drug Administration (FDA) clearance as a cardiac biomarker to aid in the diagnosis of acute myocardial infarction (AMI). In 2001, the IFCC Committee on Standardization of Markers of Cardiac Damage (C-SMCD) recommended quality specifications for analytical and preanalytical factors for cTn assays (2). The objectives were intended for use by the manufacturers of commercial assays and by clinical laboratories that use cTn assays. The overall goal was to establish uniform criteria so that all cTn assays could objectively be evaluated for their analytical qualities and clinical performance. These general principles can also be applied to creatine kinase MB (CK-MB) mass and myoglobin assays by use of the analytical recommendations in this document. In this report, we provide the background for establishing updated practice guidelines with recommendations addressing analytical issues for cardiac biomarkers based on 8 years of evidence-based medical and scientific observations since the publication of the initial recommendations (1).

⁶Nonstandard abbreviations: NACB, National Academy of Clinical Biochemistry; ACS, acute coronary syndrome; cTn, cardiac troponin; FDA, US Food and Drug Administration; AMI, acute myocardial infarction; C-SMCD, Committee on Standardization of Markers of Cardiac Damage; CK-MB, creatine kinase MB; cTnI, cardiac troponin I; cTnT, cardiac troponin T; CLSI, Clinical Laboratory Standards Institute; POC, point-of-care; TAT, turnaround time; MI, myocardial infarction; AHA, American Heart Association; ESC, European Society of Cardiology; ACC, American College of Cardiology; and WHF, World Heart Federation.

II. ANALYTICAL BIOMARKER ISSUES

Recommendations: Analytical Aspects of Acs Biomarkers

All Class I

1. Reference decision-limits should be established for each cardiac biomarker based on a population of normal, healthy individuals without a known history of heart disease (reference population). For cardiac troponin I (cTnI) and T (cTnT), as well as for CK-MB mass, the 99th percentile of the reference population should be the decision-limit for myocardial injury. The Clinical Laboratory Standards Institute (CLSI; formerly NCCLS) recommends a minimum of 120 individuals per group of healthy individuals for appropriate statistical determination of a normal reference limit cutoff. Sex-specific reference limits should be used in clinical practice for CK-MB mass. For myoglobin, the 97.5th percentile (with sex-specific reference limits) should be the decision-limit for myocardial injury. (Level of Evidence: B)
2. One decision-limit, the 99th percentile, is recommended as the optimum cutoff for cTnI, cTnT, and CK-MB mass. ACS patients with cTnI and cTnT results above the decision-limit should be labeled as having myocardial injury and a high-risk profile. (Level of Evidence: B)
3. Assays for cardiac biomarkers should strive for a total imprecision (%CV) of <10% at the 99th percentile reference limit. Before introduction into clinical practice, cardiac biomarker assays must be characterized with respect to potential interferences, including rheumatoid factors, human anti-mouse antibodies, and heterophile antibodies. Pre-analytical and analytical assay characteristics should include biomarker stability (over time and across temperature ranges) for each acceptable specimen type used in clinical practice and identification of antibody/epitope recognition sites for each biomarker. Analytical and preanalytical specifications developed by professional groups such as the IFCC should be followed. (Level of Evidence: C)
4. Serum, plasma, and anticoagulated whole blood are acceptable specimens for the analysis of cardiac biomarkers. Choice of specimen must be based on sufficient evidence and the known characteristics of individual biomarker assays. (Level of Evidence: C)

A. CTN Specifications

First, in the context of cTn, the epitopes recognized by the antibodies must be delineated. Epitopes located on the stable part of the cTnI molecule should be a priority. Specific relative responses need to be described for the following cTnI forms:

free cTnI, the I-C binary complex, the T-I-C ternary complex, and oxidized, reduced, and phosphorylated isoforms of the 3 cTnI forms. The effects of different anticoagulants on binding of cTnI also need to be addressed. Second, the source of material used to calibrate cTn assays, specifically for cTnI, should be reported. A cTnI standardization subcommittee of the AACC in collaboration with the NIST has developed a primary reference material (SRM #2921) (3). Although this material demonstrated commutability with only 50% of current cTn assays, it will be of use in harmonizing cTnI concentrations across different assays (4, 5). At present, it appears that the only way to achieve complete standardization for cTnI would be for all manufacturers to agree on using the same antibody pairs for all commercial assays as well as a common reference material for calibration (6, 7). The IFCC C-SMCD is currently exploring the development of a serum-based secondary reference material. For cTnT, as there is only one assay manufacturer, harmonizing between assay generations has been consistent. Third, manufacturers need to use methods advocated by the CLSI to characterize detection limit, functional sensitivity, and total imprecision (8, 9). Key characteristics for cTn assays include determination of the distribution of values in a healthy reference population, the statistical determination of the 99th percentile cutoff for the reference population, and determination of the concentration corresponding to the 10% CV (total imprecision). Preanalytical factors that should be described include effect of storage time and temperature, effect of glass vs plastic tubes and gel separator tubes, and the influence of anticoagulants for plasma and whole-blood measurements. As more assay systems are devised for point-of-care (POC) testing, identical analytical criteria must apply to both central laboratory methodologies and POC testing systems. When measuring cTn by different methodologies within the same institution, assay results should be harmonized or a strategy implemented to avoid interpretative confusion by clinicians.

B. Cardiac Biomarker Turnaround

Clinicians and laboratorians continue to support a goal for turnaround times (TATs) <60 min for cardiac bio-markers, but the largest study published to date has demonstrated that TAT expectations are not being met in a large proportion of hospitals (10). A College of American Pathologists Q-probe survey study of 7020 cTn and 4368 CK-MB determinations in 159 predominantly North American hospitals demonstrated that the median and 90th percentile TATs for troponin were 74.5 and 129min, and for CK-MB, 82 and 131min. In fact, fewer than 25% of hospitals were able to meet the <60-min TAT, defined as order-to-report time. A separate subanalysis of just POC testing systems was not reported. Recently published data have shown that implementation of POC cTn testing can decrease TATs to <30min in cardiology critical-care and short-stay units (11). These data highlight the continued need for laboratory services and healthcare providers to work together to develop better processes to meet a <60-min TAT as requested by physicians.

C. Biomarkers no Longer Recommended for Use in the Evaluation of ACS

Use of aspartate aminotransaminase, total lactate dehydrogenase, and lactate dehydrogenase isoenzymes are not recommended for evaluation of cardiac injury and detection of myocardial infarction (MI). The use of total CK or CK-MB activity is an acceptable alternative for evaluating cardiac injury in institutions where cTn or CK-MB mass assays are not available or feasible. Total CK can also assist in improving myocardial tissue specificity when the ratio of CK-MB to total CK is greater than previously established reference intervals. This concept is emphasized in a statement from the American Heart Association (AHA) Council on Epidemiology and Prevention regarding case definitions for acute coronary heart disease in epidemiology and clinical research studies (12). The following recommendations were made to allow for a more accurate interpretation of recent trends in ACS during implementation of cTn assays and use of the European Society of Cardiology (ESC)/American College of Cardiology (ACC) consensus MI definition (13, 14) predicated on cTn: (a) simultaneous use of traditional biomarkers with cTn to determine the performance of new biomarkers; and (b) use of adjustment factors in databases and retrospective studies seeking to determine incidence and trends of MI before and after cTn-derived studies.

D. Determining Biomarker Decision Cutoff Characteristics for ACS

The 99th percentile of a reference decision-limit (medical decision cutoff) for cTn assays should be determined in each local laboratory by internal studies using the specific assay that is used in clinical practice or validating a reference interval that is based on findings in the literature (13, 16). Desirable imprecision (expressed as %CV) of each cTn assay (and CK-MB mass assay) has been defined as <10% CV at the 99th percentile reference limit (13, 16). Unfortunately, the majority of laboratories have neither the resources to perform adequately powered 99th percentile reference studies nor the ability to carry out CLSI protocols to establish total imprecision criteria for the cTn assay that they plan to use in practice (17). Therefore, clinical laboratories must rely on the peer-reviewed published literature to assist in establishing both local reference limits and imprecision characteristics. Caution must be taken when comparing the findings reported in the manufacturers' package inserts, which have been cleared by the FDA, with the findings reported in journals because of differences in total sample size, distributions by sex and ethnicity, age ranges, and statistical methods used to calculate the 99th percentile reported.

To date, very few in vitro diagnostic companies have published 99th percentile limits in their package inserts. There is no established guideline set by the FDA or other regulatory agencies to mandate a consistent evaluation of the 99th percentile reference limit for cTns. The largest and most diverse reported reference value study to date shows plasma (heparin) 99th percentile reference limits for 8 cTn assays (7 cTnI and 1 cTnT) and 7 CK-MB mass assays (18). This study was performed in

696 healthy adults (ages 18–84 years) stratified by sex and ethnicity. There was a 13-fold difference between the lowest vs the highest measured cTnI 99th percentile limit. The lack of cTn assay standardization (there is no primary reference material that is commutable with all commercial methods, as noted earlier) and the differences in antibody epitope recognition between assays (different assays use different antibodies, as noted earlier) give rise to substantially discrepant concentrations. What is generally recognized, though, is that as long as one understands the characteristics of an individual assay and does not attempt to compare absolute concentrations between different assays, clinical interpretation should be acceptable for all assays.

For CK-MB (as has been recognized for years for total CK), all assays demonstrate a significant 2- to 3-fold higher 99th percentile limit for men vs women (18). Further, CK-MB can demonstrate up to 2- to 3-fold higher concentrations for African Americans vs Caucasians—differences attributed to between-race physiological differences in muscle mass. These data led to the class I recommendation that clinical laboratories should establish different CK-MB reference limits based on sex. Labs should also consider doing so for ethnic groups.

For cTn, expert consensus has emerged in support of the 99th percentile as the reference cutoff, in spite of whether the total imprecision of the assay is <10%. This has been supported by a recent study that has demonstrated that misclassification of patients who are ruled out using cTn assays with variable imprecision (10%–25%) at the 99th percentile does not lead to significant patient misclassification over serial cTn orders (19). Further, whereas the literature has been enriched with studies appropriately addressing the total imprecision of cTn assays, as to what the lowest concentration will be to attain a 10% CV, the manufacturers' package inserts often publish imprecision data primarily based on within-run or between-day precision. Again, there is no consistent regulatory specification regarding precision data that should be reported in the manufacturers' package inserts. To better address day-to-day clinical laboratory practice, early findings from an IFCC C-SMCD study demonstrated that the total imprecision for 13 commercial assays [based on a 20-day CLSI protocol (20)] was unable to experimentally achieve a 10% CV at their 99th percentile limit. Improved 2nd-generation assays, however, have recently demonstrated 10% CVs at the 99th percentile (21). The ultimate goal will be to have all cTn assays attain a 10% CV at the 99th percentile reference limit to reduce any potential of false-positive analytic results attributable to imprecision in the low concentration range.

For clinical trials, to avoid the confusion of multiple centers using multiple assays, several approaches are recommended for cTn testing (15, 16). First, analyze all samples from trial centers in a core, central lab with a precise, well-defined assay. Second, provide all trial centers with the same well-defined, FDA-cleared assay. Third, uniformly define each center's assays by using the 99th percentile concentration (assay-dependent), thus reducing reliance on local laboratory criteria for cTn decision cutoffs. Fourth, use a multiple (2- to 3-fold) of the 99th percentile. Fifth, if trials

decide to use cutoff values defined in earlier studies, the degree of imprecision at these concentrations should be reported.

E. European Society of Cardiology/American College of Cardiology Recommendations

An ESC/ACC consensus document along with the AHA/ACC guidelines for differentiating AMI and unstable angina codified the role of cTn by advocating that the diagnosis of AMI be based on increases of cTnI or T (preferred) or CK-MB mass above the 99th percentile cutoff in the appropriate clinical situation (14, 22). The guidelines recognized the reality that neither the clinical presentation nor the electrocardiogram had adequate clinical sensitivity and specificity. The guidelines do not suggest that all increases of these biomarkers should elicit a diagnosis of MI or high-risk profile, only those associated with the appropriate clinical, electrocardiogram, imaging, or pathological findings. When cTn increases are not due to acute ischemia, the clinician is obligated to search for another etiology for the elevation (6, 23). Updated guidelines addressing the revised universal definition of MI cosponsored by the Joint ESC-ACC-AHA-World Heart Federation (WHF) Task Force For The Redefinition of MI will soon be published. This document will support and coincide with the recommendations proposed in the current joint NACB IFCC document.

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Chapter 3

National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical Utilization of Cardiac Biomarker Testing in Heart Failure

WRITING GROUP MEMBERS

W. H. Wilson Tang MD, Gary S. Francis MD, David A. Morrow MD, L. Kristin Newby MD, Christopher P. Cannon MD, MHS, Robert L. Jesse MD Ph.D, Alan B. Storrow MD, Robert H. Christenson Ph.D

COMMITTEE MEMBERS

*Robert H. Christenson, Ph.D, Chair
Fred S. Apple, Ph.D; Christopher P. Cannon, MD; Gary S. Francis, MD;
Robert L. Jesse, MD, Ph.D; David A. Morrow, MD, MPH; L. Kristin Newby, MD MHS;
Jan Ravkilde, MD, Ph.D; Alan B. Storrow, MD; W. H. Wilson Tang, MD; Alan H.B. Wu, Ph.D*

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All relationships with industry for the writing group members are reported on-line at: <<http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/ACSHeart/heartpdf.htm>>.

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I. OVERVIEW OF HEART FAILURE

A. Context of Biochemical Marker Testing in Heart Failure

Biochemical marker testing has revolutionized the approach to diagnosis and management of heart failure over the past decade. There is an unsurpassed excitement in the heart failure community that significant advances in our understanding of currently available and future cardiac biomarkers will facilitate improved characterization of heart failure disease states and promote individualized therapy in heart failure and beyond. However, like most novel diagnostic tests, the promising findings from pivotal trials have met with ongoing challenges when applied in the clinical setting.

The material discussed in this guidelines document addresses clinical use of BNP/NT-proBNP and cardiac troponin testing in the context of heart failure diagnosis, risk stratification and management, including therapeutic guidance in adult (>18 year-old) patients. Together with the associated document titled “*National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical Issues for Biomarkers of Heart Failure*”, these recommendations are aimed at appropriate utilization of this testing by both practicing clinicians and laboratorians. The committee feels that dissemination of this guidance to the clinical and laboratory communities will improve communication and ultimately care and outcomes of patients with heart failure. Although providing specific tools for implementation is complicated, the guidelines are designed to be direct and succinct to facilitate implementation. The committee feels that education and dissemination are the major barriers to over- or under-use of natriuretic peptide testing. For this reason, there are plans for wide dissemination of the recommendations contained herein; the committee believes such dissemination will assist in educating users on the advantages and caveats of BNP and NT-proBNP measurement. Regarding costs as an example, the direct per-test cost for BNP or NT-proBNP measurement is approximately \$50 (2007 United States [U.S.] currency). Although somewhat controversial, there is evidence that use of natriuretic peptide testing in the context of heart failure decreases cost without increasing patient risk (1, 2). Costs were considered by the committee in formulating recommendations; however, the costs were considered modest compared with the total care of heart failure patients, and this view is supported by evidence (1, 2).

It is most important to emphasize that validity of test results must complement clinical findings to define a disease process. Thus, biochemical marker testing (such as BNP and NT-proBNP measurement) is not a stand-alone test, and must be used and interpreted in a larger clinical context, with confounding factors taken into account. Used appropriately in this context, the health benefits of testing far outweigh the side effects and risks of having knowledge of BNP and NT-proBNP levels. Use of cardiac troponin testing as it pertains to the heart failure population will also be discussed primarily in its role for risk stratification.

B. Background and Definition of Terms

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricles to fill with or eject blood (3). It is a growing and costly problem, affecting 2–3% of the total U.S. population. Moreover, it is estimated that only 50% of all patients survive up to 4 years (4). The increasing prevalence of heart failure is due to the aging population as well as the marked increase in survival of patients who suffered from myocardial infarction. Conservative estimates suggest that over 50% of cases have an ischemic origin, while up to 75% of cases have hypertension as a major contributing

factor. The cost of heart failure is estimated to be \$100 billion a year in Europe and the U.S., 70% of which is due to hospitalization (3–5).

The diagnosis of heart failure is a bedside diagnosis based on clinical signs and symptoms *rather* than any stand-alone test results. However, a substantial proportion of the patients referred to cardiologists from primary care physicians have been originally misdiagnosed with conditions other than heart failure. Therefore, clinical biomarker testing in the setting of heart failure has three important goals: 1) to identify possible underlying (and potentially reversible) causes of heart failure; 2) to confirm the presence or absence of the heart failure syndrome; and 3) to estimate the severity of heart failure and risk of disease progression.

Over the last decade, natriuretic peptides, particularly BNP and its amino-terminal co-metabolite, NT-proBNP, have been shown to be particularly useful in confirming or refuting the diagnosis of heart failure as well as stratifying long-term risk profiles. Several novel cardiac, metabolic and inflammatory biomarkers have emerged in the heart failure literature, such as C-type natriuretic peptide (6), endothelin-1 (7), cardiac troponin (8), high-sensitivity C-reactive protein (hsCRP) (9, 10), apelin (11, 12), myotrophin (13), urotensin-II (14–16), adrenomedullin (17, 18) and mid-regional pro-adrenomedullin (19), cardiotrophin-1 (20, 21), urocortin (22), soluble ST2 receptor (23), myeloperoxidase (MPO) (24), copeptin (19, 25), growth differentiation factor-15 (GDF-15) (26), lymphocyte G-protein coupled receptor kinases (GRK-2) (27), galectin-3 (28), mid-regional pro-A-type natriuretic peptide and other circulating forms (19, 29), and many others. However, their clinical role remains to be determined and validated (Table 1). Therefore, we will focus our discussion on the utility of testing BNP and its associated metabolite NT-proBNP in heart failure, with some mentioning of other cardiac biomarkers in specific contexts.

C. BNP and NT-proBNP Metabolism and Measurement

Since a large body of knowledge in biochemical marker testing specific to patients with heart failure will involve BNP and NT-proBNP, we will specifically discuss the metabolism and measurement of these markers. BNP and NT-proBNP belong to a family of naturally occurring hormones known as natriuretic peptides. Although BNP is co-expressed in secretory vesicles with A-type natriuretic peptide and the stimuli for expression is complex, BNP expression is augmented primarily by increase in wall tension in response to pressure (and volume) overload in both the atria and the ventricles. Therefore, elevated blood BNP and NT-proBNP levels occur in the setting of elevated filling pressures in patients with cardiac dysfunction, and can provide relatively reliable diagnostic and prognostic information (30).

It is clear from the existing literature that blood natriuretic peptide levels are reduced following long-term treatment with angiotensin converting enzyme (ACE) inhibitors (31, 32), angiotensin-II receptor blockers (33) and spironolactone (34, 35). This finding is most likely due to reduction in filling pressures

and/or reversal of the pathologic remodeling process that occurs following neurohormonal blockade. However, responses in natriuretic peptide levels to beta-adrenergic blockers have been mixed – while the majority of the literature points to reduction of blood natriuretic peptide levels with long-term treatment with beta-adrenergic blockers, transient elevation of blood natriuretic peptide levels have been observed with their initiation (36).

Several commercial laboratory platform-based and point-of-care assays have become available for BNP testing in the clinical setting as an aid to the diagnosis of heart failure and for providing prognostic information (Table 3-1). For example, blood BNP of <100 pg/mL or a blood NT-proBNP of <300 pg/mL have

Table 3-1 Selected Biochemical Markers Currently Available or Under Study for Clinical Diagnosis, Management and Risk Stratification of Heart Failure

Standard Laboratory Markers

Sodium
Blood urea nitrogen
Serum creatinine
Hemoglobin
Leukocyte count
Total lymphocyte count
Serum albumin
Total bilirubin
Uric acid
Red blood cell distribution width

Neurohormones

Catecholamines (norepinephrine, epinephrine)
Renin, ACE activity, angiotensin II, and aldosterone
Natriuretic peptides (ANP, BNP, C-type, N-terminal proANP, N-terminal proBNP, mid-regional pro-ANP)
Endothelin-1
Vasopressin / copeptin
Cardiotrophin-1
Novel vasodilators (adrenomedullin and mid-regional pro-adrenomedullin, urotensin-II, urocortin)

Inflammatory biomarkers

High-sensitivity C-reactive protein
Myeloperoxidase
Galectin-3
Fatty acid binding protein
Soluble ST2 receptor
Tumor necrosis factor alpha (TNF α) and receptors
Interleukin-6 (IL-6)
Growth differentiation factor 15 (GDF-15)
Osteopontin

Metabolic biomarkers

Leptin
Adiponectin
Ghrelin
Apelin
Insulin-like growth factor-1 (IGF-1)

Other Miscellaneous Biomarkers

G-Protein Coupled Receptor Kinase-2 (GRK-2)
Cardiac troponin I or troponin T
Myotrophin

high negative predictive values in ruling out the diagnosis of heart failure among patients presenting with dyspnea (37, 38). As stated earlier, in this document, the term “natriuretic peptide” in subsequent discussions will refer to both BNP and NT-proBNP unless otherwise specified.

There are several practical considerations in the use of blood natriuretic peptide testing in the clinical settings. First, the reference ranges for natriuretic peptides assays vary depending on the assay method employed and the nature of the control population. The units expressed in the natriuretic peptide literature including mol/L and pg/mL, and the commonly used research assay (Shionogi) often reports values that are 15–20% below that of the commercial assays (Biosite and Abbott) (39). Differences in results between these assays have been attributed to the different epitopes identified by antibodies used in different immunoassays (40). These variations have made direct comparison among study results difficult, and careful consideration of the type(s) of assay used when interpreting values reported in the literature is warranted (See *National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical Issues for Biomarkers of Heart Failure*).

Second, a wide variety of clinical factors have been shown to influence blood natriuretic peptide levels, including age and sex (39, 41–43), renal function (43–48), body habitus (49–51), thyroid function (52, 53), and anemia (54). Obesity, in particular, has been associated with lower blood BNP and NT-proBNP levels across the spectrum of heart failure, and should be interpreted with caution, especially in ruling out cardiac causes of dyspnea. Pre-existing cardiac conditions such as prior history of heart failure (55), rhythm abnormalities (42, 56–58), and underlying etiology of heart failure (59) may also influence the diagnostic accuracies. The relative influence of these factors in relation to the degree of cardiac dysfunction remains highly debated, and can be different in various clinical settings (overall, confounding effects are less apparent in the setting of acute exacerbation of heart failure). Furthermore, diastolic dysfunction, mitral regurgitation, right ventricular dysfunction, recent heart surgery, and other cardiac structural or functional abnormalities can significantly influence blood natriuretic peptide levels (60–63).

Third, although several studies have demonstrated excellent statistical correlations between the BNP and NT-proBNP assays (64, 65), there were noticeable differences, particularly with regard to their half-lives, intra- and inter-individual variability (66, 67), and differences in their production and renal clearance. However their overall diagnostic and prognostic abilities appeared to be comparable in the clinical setting. There are also differences in peptide stability. Currently, there is no direct “conversion” between the two assay types, let alone between different assays within the same peptide.

When applied in conjunction with the clinical history, physical examination and other tools available to physicians, cardiac biomarkers are valuable in achieving clinical objectives as outlined below.

II. USE OF BIOCHEMICAL MARKERS IN THE INITIAL EVALUATION OF HEART FAILURE

A. Diagnosis of Heart Failure

Recommendations for use of biochemical markers for diagnosis of Heart Failure

Class I

1. BNP or NT-proBNP testing can be used in the acute setting to rule out or to confirm the diagnosis of heart failure among patients presenting with ambiguous signs and symptoms. (Level of Evidence: A)

Class IIa

1. BNP and NT-proBNP testing can be helpful to exclude the diagnosis of heart failure among patients with signs and symptoms suspicious of heart failure in the non-acute setting. (Level of Evidence: C)

Class III

1. In diagnosing patients with heart failure, routine blood BNP or NT-proBNP testing for patients with an obvious clinical diagnosis of heart failure is not recommended. (Level of Evidence: C)
2. In diagnosing patients with heart failure, blood BNP or NT-proBNP testing should not be used to replace conventional clinical evaluation or assessment of the degree of left ventricular structural or functional abnormalities (e.g., echocardiography, invasive hemodynamic assessment). (Level of Evidence: C)

1. BNP and NT-proBNP for diagnosis of acute decompensated heart failure

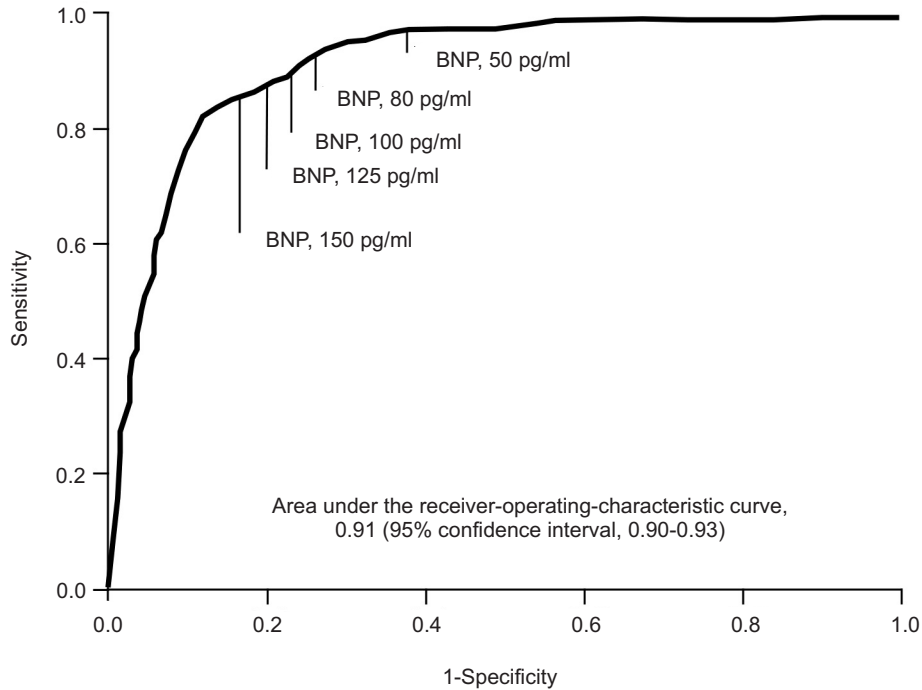
Most of the early studies of natriuretic peptides have focused on the diagnostic role of BNP or NT-proBNP testing among patients presenting with signs and symptoms of heart failure. The utility of blood BNP or NT-proBNP testing in the initial evaluation of patients with heart failure in the acute setting has been well established by several prospective multi-center clinical studies. In the multicenter Breathing-Not-Properly Study, using a BNP level of 100 pg/ml as a diagnostic “cut-off” gave a sensitivity of 90%, specificity of 76% and a diagnostic accuracy of 81% in determining a heart failure etiology of acute dyspnea, which was superior to clinical assessment alone in a series of 1,586 patients presenting to the emergency department with acute dyspnea (68) (Figure 3-1A). In a recent randomized controlled trial comparing a diagnostic strategy involving blood BNP testing versus clinical assessment alone, blood BNP testing in the emergency department improved the evaluation and treatment of patients with acute dyspnea, reducing the time to discharge and the total cost of treatment (1). Similar findings were reported in the primary care setting in which blood NT-proBNP testing improved the diagnostic accuracy of acute heart failure by general practitioners (69). The equivalent role of NT-proBNP

testing was confirmed in the PRIDE (ProBNP Investigation of Dyspnea in the Emergency Department) study, in which blood NT-proBNP testing was performed in 600 patients presenting to the Emergency Department with acute dyspnea. NT-proBNP at cut-points of >450 pg/ml (ages <50 years) and >900 pg/ml (ages ≥50 years) were highly sensitive and specific for the diagnosis of acute heart failure, while <300 pg/ml was optimal for ruling out acute heart failure (negative predictive value of 99%, Figure 3-1B) (70). Comparing natriuretic peptide levels longitudinally in previously stable patients with pre-existing heart failure is logical, although the precise extent of an increase that might be deemed clinically significant has not been established. At present, there are no national guidelines for the diagnosis and management of acute heart failure syndromes in North America.

There has been some skepticism regarding the clinical indications for *routine* use of blood natriuretic peptide testing in the initial evaluation of patients presenting with signs and symptoms heart failure, particularly in the non-acute setting (71). Moreover, a single-point measurement of blood natriuretic peptide with levels between 80 and 300 pg/mL using the Biosite assay has been reported to be less reliable in the setting of acute heart failure with “flash” pulmonary edema as the level of blood BNP or NT-proBNP may not have had sufficient time to rise (72). These natriuretic peptide “grayzones” in the diagnosis of heart failure may also be influenced by the presence of underlying history of heart failure, where the “dry” blood natriuretic peptide level may fall within this range (55, 73, 74). There are also challenges with the specific “cut-offs” in certain populations such as in the elderly (75). Furthermore, absolute values as well as changes in blood natriuretic peptide levels may correlate with clinical or echocardiographic parameters, but such correlations may vary considerably. There have been reports illustrating the lack of a tight relationship between blood natriuretic peptide levels and blood volume assessment (76), left ventricular ejection fraction (60), and hemodynamic parameters (77–79). Therefore, at this time, natriuretic peptide testing should still be considered only as part of the diagnostic evaluation in heart failure, and not the diagnostic definition.

2. BNP or NT-proBNP for confirmation of the heart failure diagnosis

There is a consensus among the latest American College of Cardiology (ACC)/American Heart Association (AHA), Heart Failure Society of America (HFSA), and other guidelines regarding the management of *chronic* heart failure that blood natriuretic peptide testing should be performed to confirm the diagnosis of heart failure among patients with suspected diagnosis of heart failure, but only in those who present with signs and symptoms that are ambiguous or which occur in the setting of confounding disease states (such as chronic obstructive pulmonary diseases (80)). Such levels can be valuable to improve the diagnostic accuracy for detecting heart failure. Furthermore, blood natriuretic peptide testing has found to be useful in differentiating different mechanisms of cardiac dysfunction (restrictive cardiomyopathy versus constrictive cardiomyopathy (81)), and in identifying cardiac involvement in systemic diseases (82, 83).



BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
50	97%	62%	71%	96%	79%
80	93%	74%	77%	92%	83%
100	90%	76%	79%	89%	83%
125	87%	79%	80%	87%	83%
150	85%	83%	83%	85%	84%

Figure 3-1A Receiver Operator Characteristic (ROC) Curve for B-type Natriuretic Peptide Testing in the Diagnosis of Heart Failure with Acute Dyspnea (68). With permission from Maisel A, et al. “Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure.” *N Engl J Med* 2002; 347(3): 161–7; Copyright © 2002 Massachusetts Medical Society. All rights reserved.

Careful prospective evaluation of the utility of blood natriuretic peptide testing has not been conducted in the non-acute ambulatory care setting. By deduction, the clinical utility of natriuretic peptide testing in confirming the diagnosis of heart failure in symptomatic patients in the ambulatory care setting should be comparable to the acute setting, where more of the existing data regarding natriuretic peptide testing are derived from. It is important to point out that among minimally or chronically symptomatic patients in the non-acute, ambulatory care setting, blood natriuretic peptide levels may vary, and the diagnostic ranges may be different from that in the acute setting (see Section III on “Screening”). Hence, the cut-off values used in the acute setting may not reliably translate into the ambulatory care setting among patients with chronic stable heart failure. There also have been reports that in the ambulatory care setting, patients with stable but symptomatic chronic heart failure can have blood natriuretic peptide levels that are relatively lower than would normally considered to be “diagnostic” of heart failure (e.g., Biosite BNP <100 pg/ml) (59). This is in direct contrast to the over 90% of patients presenting with blood BNP levels >100 pg/ml in the

acute care setting (84). Nevertheless, this cut-off is still likely to be helpful in excluding a diagnosis of heart failure when verified by a careful history and physical examination.

B. Risk Stratification of Heart Failure

Recommendations for use of biochemical markers for risk stratification of Heart Failure

Class IIa

1. Blood BNP or NT-proBNP testing can provide a useful addition to clinical assessment in selected situations when additional risk stratification is required. (Level of Evidence: A)
2. Serial blood BNP or NT-proBNP concentrations may be used to track changes in risk profiles and clinical status among patients with heart failure in selected situations where additional risk stratification is required. (Level of Evidence: B)

Class IIb

1. Cardiac troponin testing can identify patients with heart failure at increased risk beyond the setting of acute coronary syndromes. (Level of Evidence: B)

Class III

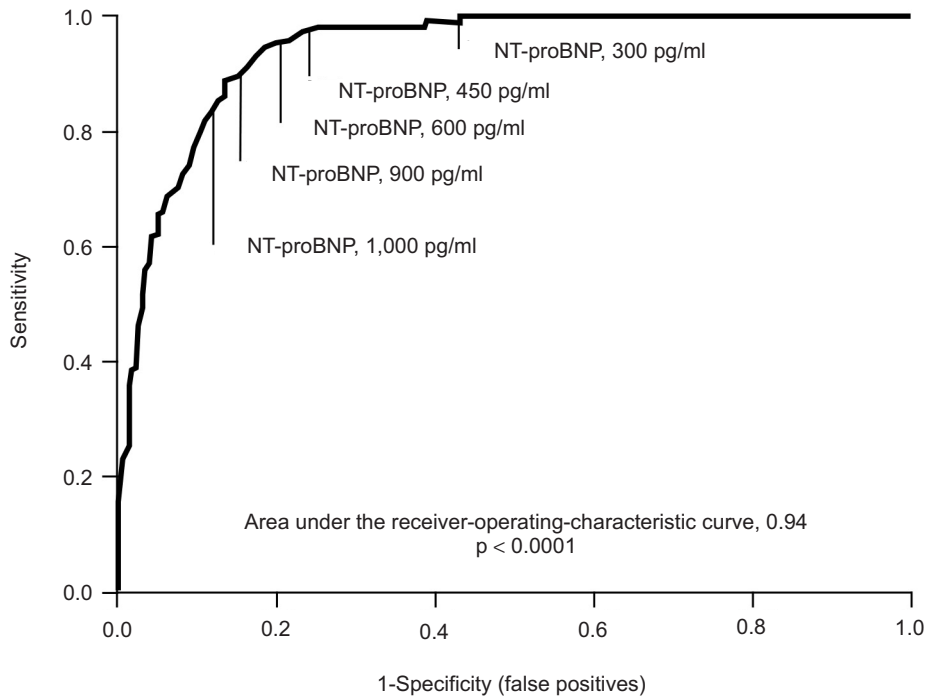
1. Routine blood biomarker testing for the *sole* purpose of risk stratification in patients with heart failure is not warranted. (Level of Evidence: B)

1. Risk stratification of patients with and without heart failure using BNP or NT-proBNP

There is a growing body of consistent literature supporting the utility of blood natriuretic peptide testing for risk stratification among patients with heart failure, or even those without prior history of heart failure (85). This applies to a wide variety of clinical settings, including acute coronary syndromes (86–89),

stable coronary artery disease (90–92), decompensated heart failure (93, 94), stable chronic heart failure (95), and even non-cardiac disorders such as pulmonary embolism (96, 97) or in the general population with no prior history of heart failure (85) or those at risk of developing heart failure (98). There have also been studies advocating the role of blood natriuretic peptide testing in selection for cardiac transplantation (8, 99, 100), as well as implantation of cardiac defibrillators (101) or cardiac resynchronization therapy (102–104). Furthermore, blood natriuretic peptide levels have been found to be an important independent predictor of sudden death (105) and equivalent in risk stratification to the Heart Failure Survival Score (106). Natriuretic peptides also provide incremental prognostic value with standard clinical and laboratory prognostic indicators (98, 107).

It is important to also point out that changes in blood natriuretic peptide levels have been associated with differences in long-term clinical outcomes (see Section IV on “Guiding Management”). In addition, it is also worthwhile to recognize that the absolute values of the ranges in different risk strata



Cut Point pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
300	99%	68%	62%	99%	79%
450	98%	76%	68%	99%	83%
600	96%	81%	73%	97%	86%
900	90%	85%	86%	94%	87%
1000	87%	86%	78%	91%	87%

Figure 3-1B Receiver Operator Characteristic (ROC) Curve for Aminoterminal proB-type Natriuretic Peptide Testing in the Diagnosis of Heart Failure with Acute Dyspnea (70). Reprinted from Januzzi JL Jr et al. “The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study.” *Am J Cardiol* 2006; 95(8): 948–954; Copyright © 2006, with permission from Elsevier.

reported in the literature vary considerably, depending on the patient population. Indeed, even when the blood natriuretic peptide levels were intermediate in the diagnosis of heart failure, their long-term prognostic values remained robust (74, 108). However, the prognostic value of natriuretic peptide testing is still limited by a lack of clear utility in guiding clinical management. The challenge is to better define the specific situations in which risk stratification can be clinically beneficial, and what is deemed to be “false positive” or “false negative” may reveal underlying pathophysiologic manifestations that are still not clinically apparent (109).

Current medical management of patients with heart failure relies on patients’ and physicians’ subjective clinical assessment and various non-specific laboratory measurements of organ dysfunction and fluid status. Blood natriuretic peptide levels fall rapidly following diuretic therapy in patients with decompensated heart failure (131–133), although these changes may vary widely and can be independent of hemodynamic changes (77). Furthermore, blood natriuretic peptides may correlate with symptom status in the outpatient setting (134). The intra-individual variability of serial natriuretic peptide levels remains highly debated (135–137). Recent literature from patient cohorts with chronic heart failure (138) and with acute coronary syndromes (139) have further illustrated that reduction in blood natriuretic peptide levels over time may be directly associated with corresponding reductions in long-term clinical events. Therefore, serial blood BNP or NT-proBNP concentrations may be used to track changes in risk profiles and clinical status among patients with heart failure in selected situations where additional risk stratification is required.

2. Risk stratification of patients with heart failure using cardiac troponin

Detectable serum levels of cardiac troponin represent evidence of myocardial necrosis, and have been extensively used in the setting of acute coronary syndromes (ACS). In patients presenting with acute heart failure, cardiac troponin testing has been used as part of the clinical work-up in the acute setting to rule out myocardial ischemia as the primary etiology (refer to Chapter 1 for recommendations). However, in the setting of advanced heart failure (8, 110) or in decompensated states (111–113), some patients may present with transient or persistent elevation of serum cardiac troponin I or troponin T levels in the absence of any obvious myocardial ischemia. Elevated serum troponin levels have been associated with poor long-term prognosis. Several clinical series have further illustrated a strong adverse prognostic effect of sustained elevation of serial serum troponin levels, which may indicate ongoing myocardial damage (114, 115). However, the utility of routine assessment of serum troponin levels in patients with acute or chronic heart failure, as well as the appropriate diagnostic and therapeutic approaches to elevated serum troponin levels in non-ACS setting remains to be determined. This is in part due to the lack of understanding as to whether cardiac troponin levels as markers of myocyte necrosis represents a risk marker versus a risk factor.

III. USE OF BIOCHEMICAL MARKERS IN SCREENING FOR CARDIAC DYSFUNCTION

Recommendations for use of BNP and NT-proBNP in screening of Heart Failure

Class IIb

1. Blood BNP or NT-proBNP testing can be helpful to identify selected patients with left ventricular systolic dysfunction in the post-infarction setting or to identify patients at high risk of developing heart failure (e.g., history of myocardial infarction, diabetes mellitus). However, the diagnostic ranges and cost-effectiveness in different populations remain controversial. (Level of Evidence: B)

Class III

1. Routine blood natriuretic peptide (BNP or NT-proBNP) testing is not recommended for screening large asymptomatic patient populations for left ventricular dysfunction. (Level of Evidence: B)

A. BNP or NT-proBNP for Screening Heart Failure and Dysfunction

The diagnostic utility of blood natriuretic peptide levels in the acute heart failure setting has prompted interest in evaluation of these biomarkers as screening tools for patients with underlying cardiac dysfunction but no overt signs and symptoms – so-called “asymptomatic left ventricular dysfunction” (ALVD). According to the latest ACC/AHA guidelines for the management of chronic heart failure, a large majority of patients who develop heart failure may have preceding structural cardiac abnormalities (“Stage B heart failure”) that can be recognized before disease progression (116). Recent data from the general population from Olmsted County suggest that the prevalence of underlying cardiac structural abnormalities (including ALVD, diastolic dysfunction, valvular abnormalities, left ventricular hypertrophy, and regional wall motion abnormalities) was the highest among individuals within the highest tertile of both BNP and NT-proBNP. Higher NT-proBNP levels have also been associated with greater likelihood of detecting incident heart failure in a population with stable coronary artery disease (117). However, there have been inconclusive data regarding the role of screening for ALVD using natriuretic peptide testing in several studies (85, 118, 119). In general, the diagnostic accuracies are far lower compared with the detection of clinical heart failure, which is likely due to the relatively non-specific association with ALVD at ranges of blood natriuretic peptide levels observed in the general population (120, 121).

B. Approaches for Screening for Cardiac Dysfunction

There are two approaches to use of natriuretic peptide testing for screening purposes. In the first approach, blood natriuretic

peptide testing may be useful in the setting of acute myocardial infarction in the absence of overt heart failure. In this setting, blood natriuretic peptide levels have been inversely associated with post-infarction left ventricular ejection fraction. However, due to the heterogeneity of study populations and the timing of sampling, the accuracy of natriuretic peptide screening has been variable. Echocardiography is likely to remain the main method of assessing LV structural and functional abnormalities after a myocardial infarction.

The second approach is to combine natriuretic peptide testing with other screening modalities to increase the diagnostic accuracy of any single test. This “multi-marker” approach has been broadly studied for risk stratification in the setting of acute coronary syndromes. In this context, combining natriuretic peptide testing with myeloperoxidase or electrocardiography appeared to be promising (122, 123), but further studies are needed to better define these approaches. At this time, most guidelines do not support *routine* blood natriuretic peptide testing for screening large asymptomatic patient populations for left ventricular systolic dysfunction.

Some investigators have attempted to increase the yield to detect asymptomatic cardiac dysfunction by focusing on high-risk subgroups, a strategy that may be more cost-effective (124). A high prevalence of elevated blood natriuretic peptide levels has been observed in a patient population at risk of developing heart failure (“Stage A heart failure”), particularly among those with a history of long-term hypertension, diabetes mellitus (125, 126), coronary artery disease (92, 127), and in the elderly (128–130). It is conceivable that blood natriuretic peptide testing may be useful for screening these high-risk populations who may otherwise be referred for further echocardiographic screening for ALVD, although the “cut-off” levels may differ in different patient populations. Others have combined several cardiac biomarkers to increase the specificity of screening using inflammatory markers such as MPO or hsCRP (122). Until prospective studies are conducted to establish evidence for stratifying patients according to natriuretic peptide levels or to validate a multimarker approach with clinically available assays with cost-effectiveness justifications, broad clinical application of these approaches are still not warranted.

IV. USE OF BIOCHEMICAL MARKERS IN GUIDING MANAGEMENT OF HEART FAILURE

Recommendations for use of biochemical markers in guiding management of Heart Failure patients

Class III

1. Routine blood BNP or NT-proBNP testing is not warranted for making specific therapeutic decisions for patients with acute or chronic heart failure because of the still emerging but incomplete data as well as intra- and inter-individual variations. (Level of Evidence: B)

A. Monitoring Therapy Using BNP or NT-proBNP Guidance

The natural extension in natriuretic peptide testing beyond its diagnostic capabilities is to guide therapy in an objective manner. Indeed, this hypothesis has been tested in a small pilot study among patients with mild-to-moderate chronic heart failure. In this study ACE inhibitors and diuretic therapy were titrated to achieve a blood NT-proBNP level of <200 pmol/L by the Christchurch assay (equivalent to 1,680 pg/mL) without compromising other organ function (e.g., hypotension, renal insufficiency) (140). This study found significantly fewer total cardiovascular events (deaths, hospital admissions, or episodes of decompensated heart failure based on modified Framingham criteria) in the group randomized to NT-proBNP-guided therapy. These results have been confirmed in a multicenter French study that indicated significant improvement in clinical events following a natriuretic peptide-guided approach compared with standard clinical assessment (141). However, neutral results were also observed when a natriuretic peptide-guided approach was compared with standard clinical assessment (142, 143). Therefore, the concept of natriuretic peptide-guided management of heart failure is still being debated, and there is no general consensus in expert opinion regarding this issue.

Another potential use of blood natriuretic peptide testing in treatment monitoring is the assessment of adequacy of therapy in decompensated heart failure. Pre-discharge, but not initial blood natriuretic peptide levels have consistently been more strongly associated with post-discharge outcomes (93, 144), although the ranges of the changes in blood natriuretic peptides following therapeutic interventions also vary widely. However, the difficulty remains the determination of the “dry” natriuretic peptide levels, which is different from patient to patient. Over-aggressive diuresis based *solely* on blood natriuretic peptide levels may increase the risk of renal azotemia or extend length of stay without reducing morbidity and mortality.

Several problems have also emerged regarding the clinical feasibility of a natriuretic peptide-guided therapeutic strategy. The wide variation of single or sequential blood natriuretic peptide levels in chronic heart failure after long-term medical therapy have created difficulties in establishing a single “target” level (59, 60, 136, 145, 146). The frequency of natriuretic peptide testing and the utility of natriuretic peptide testing in monitoring patients with heart failure remain to be determined.

The ability to guide therapeutic decisions using a biomarker-guided approach is highly promising. Several prospective studies are currently underway to confirm the utility of a natriuretic peptide-guided therapeutic strategy (147, 148). However, until these results are available, all clinical guidelines agreed that routine blood BNP or NT-proBNP testing is still not warranted for therapeutic decisions for patients with acute or chronic heart failure, primarily due to the mixed results from clinical studies and inter- and intra-individual as well as inter-assay variabilities.

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Chapter 4

National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical Issues for Biomarkers of Heart Failure

WRITING GROUP MEMBERS

Fred S. Apple,¹ Alan H.B. Wu,² Allan S. Jaffe,³ Mauro Panteghini,⁴ and Robert H. Christenson⁵

NACB COMMITTEE MEMBERS

Robert H. Christenson, Chair

*Fred S. Apple; Christopher P. Cannon, Boston MA; Gary Francis, Cleveland OH;
Robert L. Jesse; David A. Morrow, Boston, MA; L. Kristen Newby, Durham, NC;
Alan B. Storrow, Nashville, TN; Wilson Tang, Cleveland, OH; and Alan H.B. Wu*

IFCC COMMITTEE ON STANDARDIZATION OF MARKERS OF CARDIAC DAMAGE (C-SMCD) MEMBERS

Fred S. Apple, Chair

*Robert H. Christenson; Allan S. Jaffe; Franca Pagani, Brescia, Italy;
Jillian Tate, Brisbane, Australia; Jordi Ordóñez-Llanos, Barcelona, Spain; and
Johannes Mair, Innsbruck, Austria*

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¹ Hennepin County Medical Center, Minneapolis MN.

² University of California at San Francisco, San Francisco CA.

³ Mayo Clinic, Rochester MN.

⁴ University of Milan, Milan Italy.

⁵ University of Maryland School of Medicine, Baltimore MD.

All relationships with industry for the writing group members are reported on-line at: <<http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/ACSHeart/heartpdf.htm>>.

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I. OVERVIEW OF ANALYTICAL ISSUES FOR HEART FAILURE BIOMARKERS

A. Background

In 2005, the IFCC C-SMCD recommended analytical and pre-analytical quality specifications for natriuretic peptide and their related co-metabolites assays (1). The objectives developed were intended to guide manufacturers of commercial assays and clinical laboratories that utilize these assays. The overall goal was to establish uniform criteria so that the analytical qualities and clinical performance of assays natriuretic peptide and their related co-metabolites could be evaluated objectively. As B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) become more heavily integrated into clinical practice as diagnostic and prognostic biomarkers, understanding the differences between individual assays becomes important. Further, the influence of clinical, analytical and preanalytical factors on the growing number of BNP and NT-proBNP assays commercially available begs for a better understanding of how to interpret findings of different studies predicated on BNP or NT-proBNP concentrations monitored by different assays. The Laboratory Medicine community must also work closely with the in-vitro diagnostics companies to assist in defining all of the assay characteristics (1), a process that was poorly orchestrated during the developmental phase of cardiac troponin assays. When BNP or NT-proBNP assays are used as biomarkers for diagnosis, therapy decisions, and prognosis, or used in clinical trials or studies, they should be well characterized, as suggested by the list of recommendations that follow. We recommend that when designing studies that will use BNP or NT-proBNP assays, investigators should review the STARD (Standards for Reporting Diagnostic Accuracy) initiative (2) for both assay characterization issues as well as for clinical study design and patient enrollment issues. We also advocate that both analytic and clinical assay validation studies, including reference (“normal”) interval studies, be published in detail in the peer reviewed literature. Assays that do not provide adequate information for evaluation should be used with caution. To our knowledge these recommendations are the first international recommendations addressing the analytical aspects of BNP and NT-proBNP for clinical use in heart failure.

II. ANALYTICAL BIOMARKER ISSUES

A. Issues Related to B-type Natriuretic Peptide (BNP) and N-Terminal proB-type Natriuretic Peptide (NT-proBNP) Measurement

Recommendations for analysis of biochemical markers of Heart Failure

Class I

1. Before introduction into clinical practice, BNP and NT-proBNP assays must be characterized with

respect to the following preanalytical and analytical issues.

Preanalytical:

- a) sample type; including type of biological sample: serum, plasma, whole blood; and type of specimen collection tubes;
- b) effect of storage time and temperature.

Analytical:

- a) identification of antibody recognition epitopes;
 - b) description of calibration material used; with identification of source and the concentration value assignment. Until a clear determination of the clinically relevant molecules is established and a corresponding reference system is defined, results for both BNP and NT-proBNP should be reported in ng/L, rather than pmol/L;
 - c) determination of cross reactivity characteristics with related NPs, especially for BNP, NT-proBNP and proBNP, as well as for, atrial natriuretic peptide, NT-proANP, C-type natriuretic peptide;
 - d) evaluation of dilution response;
 - e) evaluation of interferences such as heterophile antibodies, rheumatoid factors, human anti-mouse antibodies. (Level of Evidence: C)
2. Upper reference limits, at the 97.5th percentile of the reference value distribution, should be independently established for both BNP and NT-proBNP based on age, by decade, and by gender. Each commercial assay should be validated separately. (Level of Evidence: C)
 3. Patients specimen comparisons and regression analysis should be performed, along CLSI (formerly NCCLS) guidelines, to establish the degree of or lack of harmonization across the dynamic range of each assay. Harmonization has been proposed around the current presumed optimal diagnostic medical decision cutoff for heart failure of 100 ng/L for BNP, as found in the Breathing Not Properly Trial using the Biosite assay (3). This may not be ideal for other non-heart failure clinical situations. More formal harmonization efforts might well be necessary along the lines done for other analytes, i.e. cardiac troponin and creatine kinase MB. Since there is only one source of antibodies and calibrators for NT-proBNP (Roche), harmonization of NT-proBNP assays should not be a problem. (Level of Evidence: C)
 4. ROC curves should be established to evaluate the clinical effectiveness and to establish optimal medical decision cutoffs for both BNP and NT-proBNP assays for diagnostic usefulness. Data need to be reported in concentration numbers to allow for consensus between assays and not only in quartiles and tertiles. (Level of Evidence: C)

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*Continued from previous page***Class IIa**

1. Assays for BNP and NT-proBNP should have a total imprecision (%CV) of <15% at concentrations corresponding to their age and gender defined upper reference limits. (Level of Evidence: C)
2. The effect of ethnicity needs to be evaluated as a possible independent variable. (Level of Evidence: C)
3. Caution should be exercised in interpreting <50% concentration changes as being related to medical therapy because a consistently high biological variation for both BNP and NT-proBNP exists. However, consistent trends should be followed as clinically important. (Level of Evidence: B)

1. Scope of BNP and NT-proBNP assays

The growing diversity of BNP and NT-proBNP assays used worldwide emphasizes the need for both analytical and clinical validation of all commercial assays prior to the clinical acceptance of these new biomarkers. At present, four companies (Biosite, Bayer, Abbott, and Beckman Coulter using Biosite reagents) have BNP assays cleared by the Food and Drug Administration (FDA) and four companies have FDA cleared NT-proBNP assays (Roche, Dade Behring, Ortho-Clinical Diagnostics, and Nanogen; all using Roche antibodies and calibrator material); with Response Biomedical (a point of care assay) available in Japan. Research and development is also in progress towards release of additional NT-proBNP assays using Roche antibodies and calibrator material on both central laboratory platforms (DPC) as well as point of care (POC) platforms (bioMerieux, Mitsubishi Kagaku Iatron, Inverness Medical, Radiometer). The number of assays will only continue to grow, making it even more essential that appropriate clinical and analytical assay criteria are uniformly adapted. The accurate clinical performance of each BNP or NT-proBNP assay, which may serve as the basis for life and death medical decisions, sets the stage to establish recommendations for assay criteria as indispensable.

2. Biological implications for assays of BNP and NT-proBNP

BNP and NT-proBNP concentrations are determined by various immunoassays using antibodies directed to different epitopes located on the antigen molecules. For BNP one antibody binds to the ring structure and the other antibody to either the carboxy- or amino-terminal end. Degradation of BNP (amino acid residues 77 to 108) is known to occur by proteolytic cleavage of serine and proline residues at the amino-terminal end in-vivo and in-vitro (1, 4, 5). This degradation may effect BNP recognition by antibodies and thus be responsible for differences in stabilities of BNP measured by different commercial BNP assays (6). Experimental observations have shown that proBNP, the precursor peptide that splits into BNP and NT-proBNP, cross reacts with commercial BNP assays

(7, 8, 9). For NT-proBNP (amino acid residues 1–76) measurement, an improved understanding of potential crossreactivity with split products of NT-proBNP and proBNP (amino acid residues 1–108) itself are needed, as preliminary evidence demonstrates cross reactivity of proBNP in an NT-proBNP assay (8, 10). For both BNP and NT-proBNP assays blocking antibody strategies minimizing interferences from heterophilic antibodies and rheumatoid factor, for example, need to be described.

3. Specimen collection for BNP and NT-proBNP measurement

The stabilizing or destabilizing influence of anticoagulant additives, as well as the type of collection tube, have also been addressed (11, 12). For BNP, EDTA anticoagulated whole blood or plasma appears to be the only acceptable specimen choice. Presently, only one system, the Biosite Triage meter, allows for the direct measurement of whole blood (EDTA) BNP; with the Abbott's Point-of-Care i-STAT BNP assay in development. Samples should ideally be collected in iced tubes and processed rapidly to avoid in vitro degradation. For NT-proBNP, serum or heparin plasma is the specimen of choice on the larger instruments in clinical laboratories. EDTA plasma gives a consistent negative bias (8 to 10%) compared with matched serum samples for NT-proBNP. At least four whole blood assays (Roche Cardiac Reader, Dade Behring Stratus CS, Synx Pharma (Nanogen) StatusFirst, and Mitsubishi Pathfast) are commercially available for NT-proBNP determination. Blood collected in plastic tubes is necessary for BNP, while for NT-proBNP, either glass or plastic are acceptable. For proBNP a research assay has been developed (7).

4. Clinical impact of BNP and NT-proBNP metabolism

In the clinical setting, BNP and NT-proBNP assay characteristics need to be better understood or better established for optimal consideration as diagnostic and prognostic biomarkers. Recent observations report that proBNP appears to show cross reactivity with at least the Biosite, and Bayer BNP assays (7, 8), conflicting with a report demonstrating that neither the Biosite or Shionogi BNP assays detect proBNP (13). This may explain why at least one study describes difficulty for detecting BNP (amino acid residues 77–108) in plasma of patients with severe heart failure and increased BNP concentrations by Biosite assay, when a non-immunological measurement approach (i.e. liquid chromatography (LC)-electrospray ionization Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry) was used (14). Release of intact proBNP in its glycosylated and deglycosylated forms in blood may, therefore, have substantial implications regarding clinical utilization of BNP and NT-proBNP assays (7, 8, 9, 10, 13).

5. Other effects and considerations for BNP and NT-proBNP values

The influence of age, gender, ethnicity, and non-HF pathologies have been shown to substantially influence what may

otherwise be considered a physiological concentration (15, 16). Renal impairment has been shown to increase NT-proBNP concentrations and increase BNP to a lesser extent (17–19). Obesity has also been shown to have an impact on BNP and NT-proBNP concentrations, with an inverse relationship between body mass index (BMI) and BNP and NT-proBNP concentrations in patients with and without CHF (20–22). It appears some of this variability is related to lean body mass, perhaps as a manifestation of testosterone metabolism. It appears that androgens reduce BNP and NT-proBNP levels (23). HF patients who receive the drug nesiritide (Natracor, human recombinant BNP) for therapy and management may have confounding BNP results, since nesiritide is molecularly identical to endogenously released BNP. Thus, if BNP concentrations were to be monitored for regulation of nesiritide infusion within a time window before an appropriate decrease of BNP could occur (theoretical half-life ~22 minutes), the potential for false increased concentrations could arise. Conversely, Nesiritide does not directly confound NT-proBNP measurements. Changes in NT-proBNP in response to nesiritide have not been marked in most studies (24, 25).

Finally, a lack of definitive understanding of the biological variability of BNP and NT-proBNP may cause clinicians to misinterpret changing (increasing or decreasing) BNP and NT-proBNP concentrations in the context of establishing the success or failure of therapy. Both BNP and NT-proBNP have been shown to exhibit a high intra-individual biological variability (26–29). Thus when considering what is significantly different between serial BNP or NT-proBNP concentrations for clinical use, a change of approximately 85% for increases and 46% for decreases could at minimum be necessary. This implies that changes in BNP or NT-proBNP concentrations must be used cautiously and reemphasizes their role as confirmation biomarkers and not as stand alone tests that clinicians should solely rely upon to manage HF patients.

The literature is scattered with home-brewed BNP and NT-proBNP assays that may add to the confusion of clinicians when interpreting and comparing data from different clinical studies. To avoid misinterpretation of results, one must consider the assay used, the available clinical evidence based on that individual assay, together with the clinical aim of an individual biomarker based study. Due to the lack of a single molecular natriuretic peptide or metabolic entity in the serum, plasma or whole blood matrix tested and the cross-reactivity of the antibodies used towards these various NP forms, results for both BNP and NT-proBNP should be reported in ng/L, rather than pmol/L. No peer-reviewed literature has demonstrated that two NP assays are analytically equivalent. Until large studies are available, caution is suggested before the conclusions based on one BNP or one NT-proBNP assay-based study are translated to another assay-based context. Indeed, studies directed towards different clinical populations will often have very different cutoff concentrations. A synthesis of the rule in and rule out cutoffs for each clinical scenario is needed for the heart failure field to advance (30).

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Chapter 5

National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Point of Care Testing, Oversight and Administration of Cardiac Biomarkers for Acute Coronary Syndromes

WRITING GROUP MEMBERS

Alan B. Storrow, M.D., Section Leader

Fred S. Apple, Ph.D., Alan H.B. Wu, Ph.D., Robert L. Jesse, M.D., Ph.D.,

Gary S. Francis, M.D., Robert H. Christenson, Ph.D

COMMITTEE MEMBERS

Robert H. Christenson, Ph.D, Chair

Fred S. Apple, Ph.D; Christopher P. Cannon, MD; Gary S. Francis, MD;

Robert L. Jesse, MD, Ph.D; David A. Morrow, MD, MPH; L. Kristin Newby, MD;

Jan Ravkilde, MD, Ph.D; Alan Storrow, MD; Wilson Tang, MD; Alan H.B. Wu, Ph.D

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I. OVERVIEW OF BIOMARKER NEED	
A. Definition and Scope	
The disposition of patients with chest pain from the emergency department (ED) is one of the most difficult challenges that face caregivers. Admission of patients with a low probability of acute coronary syndrome (ACS) often leads to excessive hospital costs (1). A strategy that is too liberal with regard to ED discharges may lead to higher numbers of patients released with acute myocardial infarction (AMI). Inappropriate discharge of ED patients who have AMI has	

been estimated to occur in 2–5% of patients and is the single most common cause of malpractice lawsuits against ED physicians (2, 3).

The scope of these recommendations focus on utilization of cardiac biomarkers of cardiac injury in the ED. Organizational aspects of providing results, administrative logistics and cost-effectiveness, as well as timing needs for performance cardiac biomarkers are addressed in this guidance. Note that an overview of ACS containing definitions, pathogenesis and management from the perspective of biochemical markers are presented in Chapter 1 (4). Chapter 1 also includes specific recommendations for the use of biochemical markers for the diagnosis AMI, early risk stratification of ACS patients and clinical decision making in the context of ACS (4). Recommendations addressing analytical issues for cardiac biomarkers are presented separately in Chapter 2 (5). Guidance provided in other sections of the overall guideline, particularly Chapters 1 and 2, must be integrated with the recommendations to improve global care of suspected ACS patients.

II. ORGANIZATION OF CARDIAC BIOMARKER SERVICES

A. Collaboration on Providing Cardiac Biomarker Measurements

Recommendations for Stakeholder Collaboration on Cardiac Biomarker Services

Class I

1. Members of emergency departments, divisions of cardiology, primary care physicians, hospital administrations, and clinical laboratories should work collectively to develop an accelerated protocol for the use of biochemical markers in the evaluation of patients with possible ACS. (Level of Evidence: C)
2. Members of emergency departments, divisions of cardiology, primary care physicians, hospital administrations, and clinical laboratories should work collaboratively to use quality-assurance measures, evidence-based guidelines, and monitoring to reduce medical error and improve the treatment of patients with possible ACS. (Level of Evidence: C)

Class IIa

1. For simplicity, protocols for cardiac biomarker testing should apply to either the facilitated diagnosis or the rule-out of AMI in the ED or to routine diagnosis from other areas of the hospital, should a patient develop symptoms consistent with ACS while hospitalized. (Level of Evidence: C)

1. Stakeholders for providing cardiac biomarker services

No clinical trials have examined the outcome of collaborative development of accelerated protocols versus development of such protocols by one specific group. Although the recommendation that laboratorians should work with ED physicians, primary care physicians, cardiologists, and hospital administration may appear obvious (6), in actual practice decisions on testing protocols are often made without input from laboratory medicine. Laboratory directors must be assertive in requesting that qualified personnel be part of organizational and operating committees when such discussions are being conducted, or should initiate the discussions themselves.

Many institutions today have a dedicated area within the ED for the rapid evaluation of patients with potential ACS. These areas are frequently designated as “chest pain centers”, “heart emergency rooms”, or some other term to indicate that the efficient evaluation and management of patients with chest pain, or other signs and symptoms of ACS, is a major objective of that center (7–9). Essential for early AMI rule-out is frequent electrocardiographic testing and blood collections for the measurement of cardiac biomarkers. Patients with negative results for these tests on a serial basis most likely do not have an AMI. They may, however, have unstable angina (UA) or other forms of acute cardiovascular disease. For these patients, it is appropriate to perform additional studies such as a stress test, echocardiogram, or radionuclide myocardial perfusion imaging for risk stratification (7–12). Establishment of a clinical practice guideline for the evaluation of patients with chest pain will reduce the variability of practices among physicians and institutions, and at the same time improve the accuracy of disposition decisions (13). Consensus on the merits of this approach was overwhelmingly favorable.

2. Use of accelerated protocols

No clinical trials have been performed to examine the outcome of accelerated protocols in the ED versus other patient care locations. Consensus from the committee and feedback from conferences and reviewers is that for “routine AMI diagnosis” of patients who are already hospitalized for other reasons, the same criteria should apply as are used in the ED. Some physicians or administrators may believe that rapid AMI rule-out of hospitalized patients is less important than rapid evaluation and disposition of ED patients. Nevertheless, the committee felt that the same protocol used in the ED is appropriate for routine AMI diagnosis because new therapies for ACS are available, and, when appropriate, should be delivered rapidly (2, 14). The use of a rapid AMI rule-out protocol will simplify the steps needed from the laboratory’s perspective and provide clinicians optimum diagnostic measures for all patients. Consensus on the merits of this approach was favorable overall.

3. Quality Assurance of Processes

In addition to being an important aspect of regulatory compliance, registry data (15–19) have suggested that quality assurance

activities improve patient outcomes. Approaches to quality assurance should be a multidisciplinary; consensus on the merits of this approach was overwhelmingly favorable.

B. Responsibility for Providing and Monitoring Cardiac Biomarker Measurements

Class I

1. Laboratory personnel must be involved in selection of devices, the training of individuals to perform the analysis, the maintenance of POC equipment, the verification of the proficiency of operators on a regular basis, and assuring compliance and documentation of all requirements by regulatory agencies. (Level of Evidence: C)
2. The multidisciplinary team involved in cardiac biomarker testing must include personnel knowledgeable about local reimbursement. Vendors should work with customers to help optimize cost-effective provision of biomarker testing. (Level of Evidence: B)

1. Responsibility for biomarker performance

POC devices are designed for testing to be performed at or near the bedside by primary caregivers. However, the responsibility for such testing must reside with laboratory medicine; involvement must include selection of POC devices, education, training, maintenance, and quality assurance (20, 21). The success of POC testing programs will depend on cooperation and the acknowledgment of the laboratory's responsibility by hospital administrations, nursing staff, and the appropriate units within the institution.

When the laboratory staff recognizes a situation of non-compliance, they must have the authority to remove POC testing devices and, at a minimum, suspend testing until the deficiencies have been satisfactorily corrected and documented.

2. Reimbursement for cardiac biomarker services

Biomarker testing cannot be justified if the laboratory or hospital cannot receive reasonable reimbursement for the service. Thus an important issue that must be resolved at each institution is reimbursement for testing. For example, the Center for Medicare and Medicaid Services announced that "it is not necessary to use troponin in addition to creatine kinase (CPT codes 82550–82554) (which includes the MB isoenzyme) in the management of patients with myocardial infarctions", suggesting that reimbursement will not be allowed when both tests are ordered (22). Private insurance companies may also limit reimbursements for cardiac biomarkers. Guidelines recommend use of cardiac troponin as the new standard for myocardial injury, but there is still may be role for both CK-MB and cardiac troponin (see Chapter 1; NACB Clinical ACS guidelines (4).)

III. LOGISTICS OF CARDIAC BIOMARKER SERVICES

A. Cardiac Biomarker Testing: Preanalytical, Analytical and Postanalytical Aspects

Recommendations for cardiac biomarker measurements

Class I

1. The specimen of choice for analysis of biochemical markers of cardiac injury is plasma or anticoagulated whole blood to facilitate a more rapid turnaround time for testing. (Level of evidence: C)
2. For routine clinical practice, blood collections should be referenced relative to the time of presentation to the emergency department and (when available) the reported time of chest pain onset. (Level of evidence: C)
3. The laboratory should perform cardiac marker testing with a turnaround time of 1 hour, optimally 30 minutes, or less. The turnaround time is defined as the time from blood collection to the reporting of results. (Level of evidence: B)
4. Performance specifications and characteristics for central laboratory and POC platforms must not differ. (Level of evidence: C)

Class IIa

1. Institutions that cannot consistently deliver cardiac marker turnaround times of approximately 1 hour should implement POC testing devices. (Level of evidence B)

Class IIb

1. While it is recognized that qualitative systems do provide useful information, it is recommended that POC systems provide quantitative results. (Level of Evidence: C)

1. Providing cardiac biomarker testing: the "need for speed"

Rapid cardiac marker testing may lead to earlier detection and use of appropriate therapies. Most (75%) of the 1352 ED physicians surveyed in a recent Q-probes study by the College of American Pathologists believed that the results of tests measuring myocardial injury should be reported back to them in 45 minutes or less, using as the reference point the test ordering time (6). Consensus of the committee and feedback on draft documents is that providing rapid testing will lead to more time-efficient, and therefore cost-effective, disposition decisions.

Although patients with non-ST elevation AMI (NSTEMI) have been shown to benefit from early percutaneous intervention (17, 23, 24) or glycoprotein IIb/IIIa inhibitors (23, 25), treatment of NSTEMI patients with glycoprotein IIb/IIIa inhibitors within 16 hours of presentation failed to demonstrate

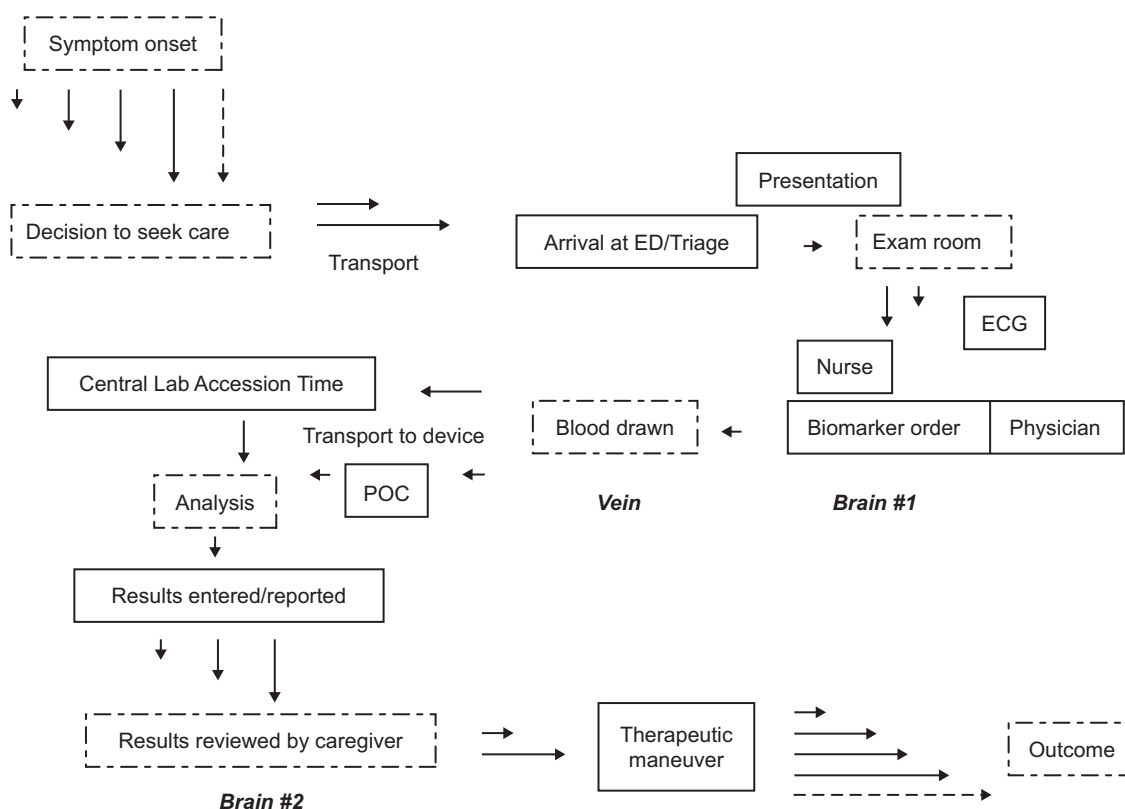


Figure 5-1 Time point options available to define turnaround time (TAT). Solid boxes indicate times generally recorded or known (hard times), while dashed boxes indicate times generally not, or variably, recorded (soft times). Arrow length grossly represents time duration; dashed arrows indicate times with large variability. Brain #1 = time physician decides to order a biomarker, Vein = time of blood draw, Brain #2 = time physician reviews result.

clinical outcome benefit (26). Therefore, justifying rapid measurement of cardiac biomarkers based on evidence clearly suggesting improved clinical outcomes is, at present, not appropriate. However rapid testing and reporting of cardiac biomarker concentrations may produce other benefits for cardiac patients. For example, identification of high-risk patients by rapid cardiac troponin testing has been suggested to improve outcome in those patients eligible for advanced therapies (2, 14, 23).

It is complicated for laboratories to consistently (>90%) deliver cardiac biomarker results in <30 min, using laboratory-based serum or plasma assays. Results of cardiac marker testing are not used to guide thrombolytic therapy and as stated earlier there is no clear evidence that availability of rapid biomarker results leads to better patient outcomes. Moreover, rule-out of AMI from the ED requires results of serial sampling, which does not support need for a very rapid turnaround time (TAT) on any single sample. The committee recognizes the controversy surrounding time from as well as the need for a standard definition of TAT. Nonetheless, caregiver consensus clearly indicates that rapid result availability is desirable and that time to patient disposition is expedited by rapid availability of cardiac biomarkers. Thus the recommendations involving logistics of providing cardiac biomarker testing focus on optimizing (minimizing) the time from blood collection to provision of testing results to the physician and caregiver team

responsible for direct care of the patient. The factors that affect TATs include the *preanalytical* phase necessary to collect the sample and deliver and process it in the testing area, the *analytical* phase necessary to produce the valid test result, and the *postanalytical* phase necessary to deliver results to the ordering physician and caregiver team (Figure 5-1).

2. Preanalytical aspects of cardiac biomarker measurements

Use of plasma for measurement of cardiac biomarkers eliminates extra time necessary for the clotting process involved in producing serum and therefore reduces the overall TAT for cardiac biomarker testing. Further, use of an anticoagulated whole blood specimen for cardiac biomarker testing simplifies processing by eliminating the need for centrifugation of the specimen prior to testing. Also, the fact that treatments for suspected ACS patients may involve anticoagulant therapies that extend clotting times underscores the need for measurement using a plasma or whole blood matrix. Therefore, manufacturers should target their assays for use of plasma or anticoagulated whole blood; however use of any specimen type must be based on sufficient evidence and the known characteristics of individual biomarker assays, in accordance with the recommendations of the NACB's Analytical Issues for Biomarkers of Acute Coronary Syndromes (see Chapter 2) (5).

Although the time of chest pain onset for AMI patients is sometimes known, this information is less available or reliable for those with UA or other cardiac diseases. It is common for these patients to report multiple episodes of chest pain over the hours or days before ED presentation. The pathophysiology of ACS is dynamic and includes intermittent closure and spontaneous reperfusion of coronary arteries with ruptured atherosclerotic plaques. In the elderly, or in patients with diabetes mellitus, there may be altered thresholds or a blunted response to pain (27). Indeed, there are many patients with ACS who experience silent ischemia and infarction (i.e., no pain during occlusive episodes) (27). The time of presentation is most reliable as a reference point; however additional information may be added when the actual time of chest pain (or equivalent signs and symptoms) is available. Thus many reviewers felt it important to also note the time of chest pain onset, especially when there is a history of a single chest pain event (and not several events over many days), and when the time of onset by patient or family report is deemed reliable. Reporting time of symptoms onset may also provide an explanation as to why some clinical studies fail to document a consistent rise in marker concentration, e.g., at 6 hours, whereas other studies indicate that the markers were increased at this time point in most patients (e.g., when the majority of enrolled patients presented to the ED well beyond 6 hours after onset of chest pain).

An important factor that impacts TATs includes delays in the delivery of the sample to the laboratory (Figure 1). The committee acknowledges that the time taken for the delivery of samples to the laboratory is not always under the control of laboratory medicine or the ED. Nevertheless, laboratory personnel should work closely with hospital administrators, physicians, specimen couriers and nursing staff to minimize delays. TATs can be improved with the implementation of pneumatic tubes that deliver samples directly and rapidly to the central laboratory or testing area. The use of satellite laboratories is another mechanism to reduce delivery time reporting TATs, improve clinician satisfaction and decrease length of patient stay in the ED (28).

3. Analytical aspects: Turnaround time requirements of cardiac biomarker testing

Patients presenting with ST-segment elevation myocardial infarction (STEMI) can be effectively treated with thrombolytic therapy or percutaneous coronary intervention (PCI), particularly if therapy is initiated within 12 h after the onset of symptoms. Delays in implementation will reduce the success of this treatment. As such, the National Heart Attack Alert Program has made a recommendation to physicians to treat all AMI patients within 60 min of their arrival in the ED (29). However, results for serum cardiac markers are not needed in making acute treatment decisions in STEMI patients.

The clinical and analytical specifications of various biomarkers are covered in the Clinical ACS (4) (Chapter 1) and Analytical ACS (5) (Chapter 2) guideline sections. It seems obvious that specifications and performance characteristics for assays must be consistent, regardless of performance platform.

Thus it is worthwhile to reiterate that performance specifications and characteristics for central laboratory and POC platforms must not differ from the characteristics and specifications outlined in these recommendations (4, 5). This is based on clear consensus of the committee and feedback from reviewers; any compromise in performance based on location or technology has the potential to negatively impact patient care. Here logistics of testing are the focus and it must be acknowledged that laboratories at some laboratories do not have automated immunoassay analyzers, rapid tube delivery systems, or staffing to deliver results within 1 hour on a continuous or consistent basis. Unfortunately, it has been suggested that laboratory based TATs for myocardial injury do not meet the expectations of either laboratory medicine personnel or emergency physicians (6).

Qualitative as well as quantitative point-of-care (POC) testing devices are now available for myoglobin, CK-MB, cTnT, and cTnI (30–46), many in multimarker formats. These assays make use of anticoagulated whole blood and have analyzer times of <20 minutes. Eliminating the need to deliver samples to the central laboratory and centrifugation enables TATs of <30 min (42). Results obtained with POC cardiac marker testing, compared with central laboratories, have universally suggested significant decreases in TAT (20, 21, 28, 40, 42, 44–53). In addition, the introduction of POC testing has been reported to reduce costs and total ED length of stay (53–55).

The committee recognizes the lack of evidence supporting cardiac POC testing in the pre-hospital setting, although this use has shown some promise (21, 56). Likewise, remote location testing, such as on cruise ships or during disasters, may offer unique advantages but needs further investigation (57, 58).

Although outcome studies have shown that rapid availability of testing and reporting of results for cardiac markers, as well as B-type natriuretic peptide, reduces hospital length of stay and laboratory costs for cardiac patients (38, 40, 55, 59–61), there are no outcome studies to validate the specific need for a 1 hour (or less) TAT.

However, there is some evidence that earlier treatment of high-risk ACS with GP IIb/IIIa inhibitors improves outcome (17, 23, 24), as well as early intervention with PCI (24, 62–68). With the development of new therapeutic strategies for unstable angina and non-Q-wave AMI (14), the committee anticipates that early detection of any myocardial injury will also be beneficial in the management of these patients. For those patients who are ruled out for ACS, it is expected that rapid TATs for laboratory data will lead to expedited patient discharge and a reduction in overall hospital costs. The NACB Committee encourages prospective outcome studies to examine the putative advantage of reporting TATs within 1 hour.

In addition, it is not clear what impact POC cardiac marker testing might have on patient satisfaction, a notoriously multifactorial issue (69–83). However, consensus indicates that a shorter ED length of stay clearly improves patient satisfaction. Whether such satisfaction is at least partially a function of POC testing remains to be investigated.

4. Postanalytical aspects: Minimizing potential for medical error

Reporting of cardiac biomarker results should be interfaced with the electronic medical record to minimize human error, and utilize the institutions usual method of providing information to the treating physician and caregiver team. Results of cardiac biomarker testing in an institution should be in harmony to allow accurate serial monitoring to facilitate interpretation. The NACB Committee believes that both of these measures reduce the probability of medical error.

5. Reporting qualitative versus quantitative cardiac biomarker results

The committee recognizes the lack of evidence suggesting improved outcomes by reporting results as quantitative systems versus qualitative. However, quantitative results offer particular strengths in risk stratification and low end sensitivity (84, 85, 86).

IV. EVOLVING TECHNOLOGY IN CARDIAC BIOMARKERS

A. Process for Adapting Evolving Biomarker Technology

Recommendations for Adapting Evolving Technologies

Class I

1. Early in the process, manufacturers are encouraged to seek assistance and provide support to professional organizations such as the AACC or IFCC to develop committees for the standardization of new analytes. These organizations will determine the need for analyte standardization based on the potential clinical importance of the marker and gather the necessary scientific expertise for the formation of a standardization committee. (Level of Evidence: C)

1. Process for adapting new cardiac biomarkers

New biomarkers will continue to be developed and examined for use in patients with possible ACS. When a marker such as cardiac troponin demonstrates major advantages over existing markers, there is an urgency of manufacturers to develop and market commercial assays. In the specific cases of CK-MB mass and cTnI assays, there were no cooperative attempts to develop reference materials or to standardize results.

The NACB Committee acknowledges that the exclusive release of new markers may be in the manufacturer's best interests in terms of profitability, and therefore, they may be reluctant to share ideas and needs with their colleagues. Nevertheless, the implementation of new tests is more easily integrated into the laboratory when these markers are available

on a wide spectrum of analyzers, and it is in the best interests of the medical community and the in vitro diagnostic industry that assays correlate to one another.

Assays for cardiac markers for early diagnosis, rule-out, triaging of patients from the ED, or for determination of successful reperfusion require markers that have a short assay TAT. Irrespective of how the testing is performed (i.e., laboratory-based or POC testing), assays must meet minimum precision requirements. Imprecise assays at or near cutoff concentrations will adversely affect the clinical performance of the test. The committee understands the importance of establishing objective analytical goals for assays for new cardiac markers. This will assist manufacturers in the construction of new assays.

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Chapter 6

National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Use of Cardiac Troponin and B-type Natriuretic Peptide or N-terminal proB-type Natriuretic Peptide for Etiologies other than Acute Coronary Syndromes and Heart Failure

WRITING GROUP MEMBERS

*Alan H.B. Wu, Ph.D., Section Leader
Allan S. Jaffe, M.D.; Fred S. Apple, Ph.D.; Robert L. Jesse, MD, Ph.D.; Gary L. Francis, MD;
David A. Morrow, MD, MPH; L. Kristin Newby, MD, MHS; Jan Ravkilde, MD, Ph.D;
W. H. Wilson Tang, MD; and Robert H. Christenson, Ph.D*

COMMITTEE MEMBERS

*Robert H. Christenson, Ph.D, Chair
Fred S. Apple, Ph.D; Christopher P. Cannon, MD; Gary L. Francis, MD;
Robert L. Jesse, MD, Ph.D; David A. Morrow, MD, MPH; L. Kristin Newby, MD, MHS;
Jan Ravkilde, MD, Ph.D; Alan B. Storrow, MD; W. H. Wilson Tang, MD; Alan H.B. Wu, Ph.D*

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I. OVERVIEW OF OTHER ETIOLOGIES

A. Background and Scope

Presently available cardiac biomarkers can define cell death, damage or dysfunction to particular organ systems but cannot define the mechanisms of the effects seen. Cardiologists, emergency medicine physicians and clinical laboratorians have often acted as if cardiac biomarkers such as cardiac troponins T (cTnT) and I (cTnI) and B-type natriuretic peptide (BNP) and N-terminal B-type natriuretic peptide (NT-proBNP) are specific only to the presence of acute coronary syndrome and heart failure, and imply diagnosis of acute coronary syndrome and heart failure, and their etiology. While it is true that release of cTn into blood is the result of myocardial damage, it is not necessarily damage related to a coronary artery abnormality, or even the result of acute myocardial ischemia. Therefore the diagnosis of acute myocardial infarction (AMI) must always be framed in the correct clinical context; this includes the caveat that the combination of ischemia plus necrosis does not in and of itself imply a coronary etiology. This is particularly more important when lower cut off values are used such as the 99th percentile limit of a healthy population, which detect a variety of more subtle abnormalities (1). Table 6-1 shows a list of conditions that can cause an increase in cTn in the absence of overt ischemic heart disease (2).

In a similar manner, increases in BNP and NT-proBNP concentrations are not specific for heart failure alone. Table 6-2 lists conditions other than heart failure than can cause an increase in BNP and NT-proBNP (3–22). Renal dysfunction is a confounder for both cTnT and cTnI as well as BNP and NT-proBNP. Cardiac surgery will release cardiac biomarkers into blood due to the damage of the heart during the procedure itself. Although increased concentrations of cTn and natriuretic peptides are not specific to ischemic damage or heart failure, a detectable increase in these cardiac biomarkers has been associated with worse prognosis regardless of the etiology of the increase.

Finally, it must also be clinically recognized that false positive increases in cTn, BNP and NT-proBNP can occur, although very infrequently, as a result of analytical errors. Although the incidence of assay interferences caused by atypical antibodies has been reduced, all immunoassays have the potential for both false positive and false negative interferences (23, 24).

The scope of the recommendations in this section will focus on other etiologies that can affect the interpretation of cTn and the natriuretic peptides. Where there is sufficient scientific and medical evidence, recommendations will be provided. Note that an overview of acute coronary syndrome (ACS) and heart failure containing definitions, pathogenesis and management from the perspective of biochemical markers are presented in Chapter 1 and 3. Chapters 1 and 3 also includes specific recommendations for the use of biochemical markers for the diagnosis and risk stratification of patients and

clinical decision in the context of ACS and heart failure. Recommendations addressing analytical issues for cardiac biomarkers of ACS and heart failure are presented in Chapter 2 and 4, respectively.

Table 6-1 Elevations of Cardiac Troponins without Overt Ischemic Heart Disease¹

-
- Trauma (including contusion, ablation, pacing, ICD firings including atrial defibrillators, cardioversion, endomyocardial biopsy, cardiac surgery, after interventional closure of ASDs)
 - Congestive heart failure—acute and chronic
 - Aortic valve disease and HOCM with significant LVH
 - Hypertension
 - Hypotension, often with arrhythmias
 - Postoperative noncardiac surgery patients who seem to do well
 - Renal failure
 - Critically ill patients, especially with diabetes, respiratory failure, gastrointestinal bleeding, sepsis
 - Drug toxicity, e.g., adriamycin, 5-fluorouracil, herceptin, snake venoms, carbon monoxide poisoning
 - Hypothyroidism
 - Abnormalities in coronary vasomotion, including coronary vasospasm
 - Apical ballooning syndrome
 - Inflammatory diseases e.g., myocarditis, eg. parvovirus B19, Kawasaki disease, sarcoid, smallpox vaccination, or myocardial extension of BE
 - Post PCI patients who appear to be uncomplicated
 - Pulmonary embolism, severe pulmonary hypertension
 - Sepsis
 - Burns, especially if total surface burn area (TBSA) > 30%
 - Infiltrative diseases including amyloidosis, hemachromatosis, sarcoidosis and scleroderma
 - Acute neurological disease, including cerebrovascular accident, subarachnoid bleeds
 - Rhabdomyolysis with cardiac injury
 - Transplant vasculopathy
 - Vital Exhaustion
-

¹Babu L, Jaffe AS. Troponin: the biomarker of choice for the detection of cardiac injury. CMAJ 2005;173:1191–202.

Table 6-2 Increased Concentrations of BNP/NT-proBNP without Overt Heart Failure (references)

-
- Inflammatory cardiac diseases (3–5)
 - Systemic arterial hypertension with LVH (6–8)
 - Pulmonary hypertension (9–11)
 - Acute or chronic renal failure (12, 13)
 - Ascitic liver cirrhosis (14–16)
 - Endocrine disorders
 - Hyperaldosteronism (17, 18)
 - Adrenal Tumors (19)
 - Hyperthyroidism (20–22)
-

II. USE OF CARDIAC BIOMARKERS IN THE EVALUATION OF PATIENTS WITH CHRONIC RENAL FAILURE

A. Utilization of Cardiac Biochemical Marker in the Setting of Chronic Renal Failure

Recommendations for use of biochemical markers in the setting of chronic renal failure

Class I

1. In renal failure patients with symptoms (e.g., acute chest pain), electrocardiographic (ECG) or other clinical evidence suggesting myocardial ischemia, measurement of cTn is warranted for evaluation of MI. (Level of evidence A)
2. For end-stage renal disease (ESRD) patients, as for all patients who may have baseline elevations of cTn, who present with possible ACS, relying on dynamic changes in the cTn values of 20% or more should be used to define those with acute myocardial infarction. (Level of evidence B)

Class IIb

1. cTnT and cTnI can be used as aids for defining the risk for mortality in ESRD patients and to provide baseline values for comparison when measured in the setting of an acute clinical change. (Level of evidence B)
2. In renal failure patients, BNP or NT-proBNP testing can be used in the acute setting to *rule out* or to *confirm* the diagnosis of heart failure among patients presenting with ambiguous signs and symptoms. However different decision point (cutoff) values must be used compared to patients with estimated glomerular filtration rate >60 mL/min/1.73m². (Level of evidence B)

Class III

1. Routine BNP/NT-proBNP measurement is not warranted in asymptomatic end-stage renal disease patients. (Level of Evidence B)

1. Biomarkers in chronic renal failure

Increases in the concentration of cTnT and cTnI in the setting of end stage renal disease (ESRD) represent cardiac damage. In patients with suspected ACS, a dynamic change in the cTnI indicates a diagnosis of AMI (25, 26) and warrant further investigation/treatment. A recommended cutoff cTn value of 20% or more in the 6–9 hours after presentation represents a significant (3 SD) change in cTn based on a 5–7% analytical CV typical for most assays in concentration range indicating AMI. Patients with ESRD who have increased cTn concentrations have a higher (long-term) risk for death than corresponding patients without increases in cTn in this setting. Using a cutpoint of 0.03 µg/L for cTnT (10% coefficient of variance,

CV), Aviles et al. reported a 2.7-fold higher (95% CI: 1.9–3.8) risk of myocardial infarction or death at 30 days among patients with suspected acute coronary syndromes in the lowest quartile for creatinine clearance (27). Recent data suggest that even if there is an increased baseline concentration, further increase above that baseline occurs in acute ischemic damage. Thus acute increases can be discriminated from more chronic elevations, when a rising pattern of results is observed (28–30). Given the prognostic importance of the acute increases, which is similar to that seen in the absence of ESRD, some have suggested that the use of acute pharmacologic or invasive interventions in patients with evidence of ischemia and increased cTn outweigh the risks of bleeding and increased renal dysfunction (31).

Acute changes in cTn are an important consideration in those ESRD patients with chronic increases which are not in and of themselves benign. These abnormal concentrations have been significant predictors of an adverse short- and/or long-term prognosis in nearly every available study. In a study of 224 subjects, increased concentrations of cTnT were strongly associated with diffuse coronary artery disease and an independent predictor of death (32). Virtually identical results were obtained for the outcome of death by cTnT levels at 1, 2, and 3 years of follow-ups for cTnT among 733 patients; odds ratios ranged from 2.2 to 2.5 and there was a gradation of risk related to the magnitude of the increases (33). The incidence of abnormal values in this cohort was considerably higher for cTnT than for cTnI; 82% of ESRD patients had an increase in cTnT compared with only 6% for cTnI when the 99th percentile cutoff limit was used (33). Further, the prevalence of increased cTn concentrations varied by which assay was used for measurement. A substantially greater number of patients had an increased cTnT (85%) compared with cTnI by either cTnI method (19% Beckman, 5% Dade). Percent agreement between the Beckman and Dade assays for increased cTnI was 85% ($\kappa = 0.32$). Two-year mortality rates based on an increased cTnI regardless of cTnT status was 61% for the Dade assay and 47% for the Beckman assay (34). Therefore both markers are predictive of risk in ESRD. However, cTnI appears to be less useful on a routine basis, because the frequency of increased values associated with increased risk of adverse events is markedly lower.

Although the exact reason for this difference is unknown, it is likely related to the mechanism by which cTn are differentially released into the circulation, degraded, and/or cleared from the circulation. There is some suggestion that the dialysis process itself may affect cTn values, although changes in cTn concentrations due to the procedure are not large (35). Recently, the Food and Drug Administration has cleared cTnT as a biomarker for risk stratification in ESRD patients for all cause death and the use of cTnT for this indication is suggested by the Kidney Disease Outcomes Quality Initiative (29). In the absence of myocardial ischemia, there are no specific therapeutic interventions known to reduce cardiovascular risk that can be recommended solely based upon the results of cTn testing in

patients with ESRD. However, the availability of such a baseline values would simplify the care of patients with ESRD who present with a variety of problems for emergency department (ED) and/or hospital evaluation and care.

Increases in the concentration of BNP and NT-proBNP have also been observed to have prognostic significance in patients with ESRD. Zoccali et al. reported a relative odds of 6.72 (95% CI: 2.44–18.54) for cardiovascular death among patients on dialysis with an increased concentration of BNP (36). Several investigators have combined the results of biomarkers to determine if they provide additive risk stratification information. In an analysis of cTnT, cTnI, atrial and brain natriuretic peptides in chronic dialysis patients, only cTnT was an independent predictor of death (37). However, Apple et al. found that cTnT, cTnI, and high sensitivity C-reactive protein were each independent predictors of death in ESRD patients (34). In his study, NT-proBNP had prognostic value but that was not independent to the cTn. Comparing BNP results directly against NT-proBNP in patients with chronic kidney disease, Vickery et al. suggested that NT-proBNP concentrations were more affected by declining kidney function (38). NT-proBNP does not have receptors and is not degraded by neutral endopeptidases but is excreted in the urine (39).

III. USE OF BIOMARKERS IN THE EVALUATION OF OTHER NON-ISCHEMIC ETIOLOGIES

A. Use of Cardiac Biomarkers in the Setting Non-ischemic Etiologies

Recommendations for use of biochemical markers in other non-ischemic etiologies

Class IIb

1. Increased cardiac telemetry may be warranted for patients who have increased cTn values following blunt chest trauma. (Level of evidence B)
2. The measurement of cTn can be used to define risk among patients who are critically ill. (Level of evidence A)
3. Increased cTn values identify individuals at increased risk for the development of congestive heart failure when treated with adriamycin therapy for cancer. (Level of evidence B)
4. Increased cTn values identify individuals at increased risk with acute pulmonary embolism. (Level of evidence B)
5. Routine BNP/NT-proBNP measurements may be warranted among patients with non-ischemic etiologies such as sepsis, myocarditis, or pulmonary embolism. (Level of evidence C)

Class III

1. Release of cTn from patients with cancer undergoing cardiotoxic chemotherapies represents myocardial damage, which may be associated with a worse prognosis (Level of evidence B). However routine cTnT or cTnI measurements are not warranted among cancer patients undergoing chemotherapies that are toxic to the heart (except those receiving adriamycin). (Level of evidence C)

1. cTn and BNP/NTproBNP in other non-ischemic etiologies

Years after the release of the first commercial cTn assays, there have been no basic or clinical studies that have shown that cTn can be released from any other tissues except the heart. Therefore, cTn found in concentrations exceeding the 99th percentile of a reference population reflect recent myocardial damage. However, increases in cTnT or cTnI neither imply an ischemic etiology for the damage nor are necessarily associated with an acute coronary event. cTn can be observed in non-ischemic injuries to the heart, among patients with critical illnesses (40–47), chemotherapy (48–53), myocarditis (54), blunt chest trauma (55, 56), stroke (57), pulmonary emboli (58–62), sepsis (63–65), and other conditions (66, 67). These findings are believed to represent ongoing myocardial damage. Regardless, there are several situations in which detection of increased cTn values may be clinically helpful. In a meta-analysis conducted on 6 studies of blunt chest trauma in which myocardial contusion was suspected (56), it was concluded that cTn was a sensitive indicator of myocardial damage. Since myocardial contusion is known to cause QTc prolongation which can be associated with malignant life threatening arrhythmias, monitoring such individuals for arrhythmias is a rational but as yet unproven adjunct to care. Troponin can also be released in patients undergoing chemotherapy such as with the anthracyclines and who can develop heart failure. Recent studies suggest that for patients with an increased cardiac troponin, treatment with angiotensin converting enzyme inhibitors dramatically reduces the frequency of heart failure (68).

2. cTn and BNP/NTproBNP in pulmonary embolism

Among patients with pulmonary emboli (PE), data substantiate the association of cTn increases with worse prognosis. La Vecchia et al. demonstrated that when cTnI was ≤ 0.6 $\mu\text{g/L}$, the mortality was 4.8% versus 36% for cTnI > 0.6 $\mu\text{g/L}$ (59). In a study of 56 consecutive patients with confirmed PE, in-hospital mortality was 44% among patients who were cTnT positive (>0.1 $\mu\text{g/L}$) versus 3% among those in whom TnT was ≤ 0.1 ng/mL (59). In addition to mortality, the use of inotropic drugs, need for resuscitation, and mechanical ventilation were all significantly higher among the cTnT-positive patients. This is likely because increases in cTn correlate with the degree of right ventricular dysfunction, a factor known to be associated with

prognosis among patients with pulmonary emboli (60). Although the therapeutic implications of such increases is not clear, it is important to assign the correct diagnosis in these patients, since mortality among cTn-positive PE patients is substantially higher than that among AMI patients, with the exception of those with cardiogenic shock. In both of the studies cited above, the rate of cTn-positive PE patients was approximately 30%, whereas only approximately 5% of AMI patients developed cardiogenic shock in the NRMI-2 and NRMI-3 registries (1994–2000). It is unlikely that AMI risk adjustment models would reflect the high PE mortality rates: while mortality for cardiogenic shock is high, the incidence of shock is low. Thus assigning the diagnosis of AMI to patients with PE would most probably result in a skewed observed/expected AMI mortality ratio that could contribute to a mortality outlier status for the facility.

What to do therapeutically in response to such increases and whether cTn and/or BNP or NT-proBNP increases provide more information is unclear at present. Some experts have recommended consideration of fibrinolytic therapy or invasive thrombectomy for those identified as high risk on the basis of increased cTn and/or BNP or NT-proBNP among patients with sub-massive pulmonary emboli (62).

3. cTn in critical care patients

Increases of cTn are common among critically ill patients, e.g., those with sepsis. While closely related to the extent of left ventricular dysfunction and the need for inotropic support and prognosis (63, 64), the therapeutic implications of such increases have not yet been fully defined. These principles may hold for many other situations in which there are increases of cTn. However, until systematic studies are conducted addressing the utility of the cTn for diagnosis, prognosis, and treatment in these non-ischemic etiologies, the relationship will remain unclear. BNP and NT-proBNP have also been used in many of these same clinical conditions (65–67) but these studies are less extensive at present than those with cTn.

IV. USE OF BIOMARKERS AFTER NON-CARDIAC SURGERY

A. Use of Cardiac Biochemical Markers After Non-cardiac Surgery

Recommendations for use of cardiac markers after non-cardiac surgery

Class IIb

1. cTnT and cTnI are recommended for patients undergoing non-cardiac surgery if there is a question of cardiac ischemia. Cutoff concentrations that are used for diagnosis of MI are appropriate. (Level of evidence C)

2. cTnT and cTnI are recommended for post-surgical assessment of patients undergoing vascular surgery given the high frequency of underlying coronary artery disease and associated perioperative events. Such increases appear to be due to ischemia and are highly prognostic for both short- and long-term mortality. Cutoff concentrations that are used for diagnosis of MI are appropriate. (Level of evidence B)
3. Increases of cTn post operatively are associated with adverse prognosis and should prompt clinical follow up. (Level of evidence B)

Class III

1. Routine BNP/NT-proBNP measurements are not warranted among patients undergoing non-cardiac surgery. (Level of evidence C)

1. Biomarkers after non-cardiac surgery

Ischemic myocardial damage can occur in patients undergoing surgery that does not involve the myocardium (66). Creatine kinase (CK) and CK-MB are less reliable biomarkers compared with cTn for assessing ischemic myocardial complications because these enzymes are released from skeletal muscle damage as the result of the surgery. cTn is specific to heart damage and is not normally released in non-cardiac surgery (70). Therefore, increased cTn concentrations after non-cardiac surgery are a marker of myocardial damage and are predictive of an adverse outcome at 6 and 12 months (71–73). Increases in cTnT above 0.03 µg/L (10% CV cut-point) were indicative of occult myocardial necrosis, and an independent marker of mortality (odds ratio 14.9, 95% CI: 3.7–60.3) (74). Similar results have been shown for cTnI (OR 9.8, 95%CI: 3.0–32) (75). Although it appears that increases of cTn provide prognostic information in many surgical settings, the etiology of increases, the absolute value of the increases, and whether there is short- or long-term prognostic significance may vary. For example, in vascular surgery patients, increases of cTn correlate closely with severity and duration of ST-segment changes in a group of patients known to have a high incidence of underlying coronary artery disease and these increases are highly prognostic (76). Furthermore, increases are associated with both early and late clinical consequences, suggesting the need for intervention acutely when increases occur in the hospital (69). It is only for vascular surgery patients that present evidence suggests a role for the routine monitoring of cardiac markers. Though less well studied, increases in orthopedic patients (depending on the age and other characteristics) might not be as likely related to ischemic heart disease but might more likely be associated with pulmonary emboli which are frequent post-operative complications (77). Thus, each surgical group that should be evaluated individually. It is only for vascular surgery patients that the present evidence suggests a role for monitoring of cTn. Currently, there is no evidence for the potential role of BNP/NT-proBNP in non-cardiac surgery.

V. BIOMARKER USE AFTER PERCUTANEOUS CORONARY INTERVENTION (PCI)

A. Use of Cardiac Biochemical Markers after PCI

Recommendations for use of biomarkers after PCI

Class IIb

1. It is appropriate to measure cTnT or cTnI before and after percutaneous coronary intervention to determine the presence of ischemic cardiac damage if the baseline pre-procedural value is less than 99th percentile for the reference control population. Any increase is indicative of cardiac damage. However, there is currently insufficient evidence to recommend the specific cTn cutoff concentration. (Level of Evidence C)

Class III

1. Routine BNP/NT-proBNP measurements are not warranted among patients undergoing PCI. (Level of Evidence C)
2. If the pre-procedural baseline cTn is increased above the 99th percentile of a reference control population, then biochemical markers should not be used to estimate whether increases are related to the procedure or to progression of the underlying disease state that caused the need for the procedure. If serial preprocedural cTn values are available, a falling trend followed by a post-procedural increase of 20% or more may be indicative of new myocardial injury, even if any or all of the pre-procedural results are above the 99th percentile. (Level of Evidence C)

1. Biomarkers after PCI

Peri-procedural myocardial damage has been the subject of debate since the inception of the technique 30 years ago (78). cTn release following PCI ranges in incidence from 14 to 48% (79–83). This wide variation is caused by both the assay and corresponding cutoff concentrations used, as well as the underlying indication for the revascularization procedure (e.g., acute versus elective) and the type of procedure performed. In the majority of these studies, cTnT or cTnI cutoff concentrations were higher than either the 99th percentile or 10% CV value. These and other studies have consistently shown that post-procedural increases in cTn and/or CK-MB are associated with major adverse clinical events. Indeed, minor increases in CK-MB are associated with an increase in 6-month mortality, a risk similar to that observed with spontaneous AMI at any given CK-MB concentration (84). In a study of elective PCI, increased cTnI (13.6% of patients) was associated with the presence of procedural side branch occlusions and thrombus formation (81). In the 481 patients with ACS and PCI enrolled in the SYMPHONY Trial, 48% had increased cTnI, which was associated with 90-day events of MI, severe recurrent ischemia, and the combination of

death or MI (80). Similar results have been reported for cTnT, in which abnormal concentrations resulted in odds ratio for death or MI of 2.64 (95% CI 1.37–5.10) (79). Postprocedural increases in cTnI were also correlated with decreased tissue-level perfusion as measured by angiography using TIMI (thrombolysis in myocardial infarction) myocardial perfusion grade, and intracoronary myocardial contrast echocardiography (82). While the mechanism is unknown, decreased tissue perfusion in patients with high cTn may be responsible for the increased incidence of adverse cardiac events.

Recent data have challenged the concept that post-procedure cTn increases carry prognostic significance. When one uses the baseline cTn in the analysis, the prognostic significance of the post-procedure values is totally obviated, suggesting that it is the pre-procedure value that defines risk. When the baseline cTn value is normal, increases in both cTn and CK-MB are modest and unassociated with long term events (85). The European Society of Cardiology (ESC) Task Force on Invasive Cardiology recommended a CK-MB cutoff concentration of 5 times the upper limit of normal (86). The previous convention has been the use of a 3-fold increase (87).

VI. USE OF BIOMARKERS AFTER CARDIAC SURGERY

A. Use of Cardiac Biochemical Markers after Cardiac Surgery

Recommendations for use of biomarkers after cardiac surgery

Class IIa

1. The higher the cTn values post operatively, the greater the risk of adverse cardiac events events. (Level of Evidence B)
2. In addition to greater than 5-fold increase in cTn after the procedure, clinical and other (non-lab medicine) diagnostic testing criteria should be used to distinguish components related to the operative procedure and cardioprotection from vascular events. (Level of Evidence C)
3. Preprocedural baseline cTn increases help to define risk among patients undergoing cardiac surgery. (Level of Evidence C)

Class III

1. At this time, there is insufficient evidence to recommend routine measurement of BNP/NT-proBNP before or after cardiac surgery. (Level of Evidence C)

1. Biomarkers after cardiac surgery

It has been recognized for many years that patients undergoing cardiac surgery release some amount of cardiac proteins such as CK and cTn. There is a relationship between increases of

biomarkers and the details of the procedure itself, such as the duration of the cross clamp and cardiopulmonary bypass times, the nature of the cardioplegic solution, cold versus warm solutions, and so on (88–96). Recent magnetic resonance imaging (MRI) data suggest that most of the damage observed after bypass surgery is subendocardial and apical and likely is a result of issues related to cardiac preservation (92). Transmural damage is observed only with very marked increases of cTn that are potentially related to a primary vascular event (92, 97). Therefore, if the diagnosis of MI must reflect a primary vascular event, finding an appropriate cutoff value is difficult to define. Several clinical studies have demonstrated that cTnT and cTnI concentrations that are much greater than the AMI cutoffs are associated with in-hospital and long-term morbidity and mortality (98–104). In general, the higher the value, the worse the prognosis (105). In addition, the higher the value, the greater the likelihood of transmural involvement which some might equate to a vascular event as opposed to cardiac damage related to the procedure itself (97). However, studies using angiography to define graft and/or native vessel occlusion have found that there remains substantial overlap between the values in those with graft occlusion and those without (106). In a recent series that used a marked increase of cTn to define possible graft occlusion (107), only 67 of 118 patients had a primary vascular event. Thus, additional criteria over and above markers are needed to define a vascular event after bypass surgery. Given that fact and the need to evaluate patients with a variety of surgical types (off pump for example), using a low cut off value (for example a 5-fold increase) together with other criteria might be advised. Nonetheless, regardless of the mechanism, the higher the value, the greater the likelihood of subsequent adverse clinical events.

At present, there is little data on the use of BNP and NT-proBNP for risk stratification for adverse events after cardiac surgery. In contrast to cTn, most studies on BNP have focused on the predictive value of preoperative concentrations. One study suggested that preoperative values of BNP predicted the need for intra-aortic balloon pumps, prolonged hospital length of stay and 1-year mortality (108). In another study, increase preoperative BNP predicted postoperative atrial fibrillation (109). Such studies address the suitability of patients undergoing cardiac surgery and not peri-operative complications or events.

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