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

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1. Biomarkers after cardiac surgery

VII. REFERENCES

Preamble

Over the past decade, cardiac troponin (cTn) has become the cornerstone laboratory medicine measurement for assessment of myocardial infarction (MI) in suspected acute coronary syndrome (ACS) patients. In the past 5–7 years, methods for measuring the natriuretic peptide B-type natriuretic peptide (BNP) and its inert cometabolite N-terminal proBNP (NT-proBNP) have become available, and much knowledge has accumulated regarding their clinical use in the context of heart failure and hemodynamic stress. In addition to ACS and heart failure, there are common and clinically important patient cohorts in whom these measurements can aid in diagnosis and management. For this reason, the National Academy of Clinical Biochemistry (NACB) formed a Laboratory Medicine Practice Guidelines (LMPG) committee to extend cardiac biochemical marker recommendations and establish modern guidelines for utilization in etiologies other than ACS and heart failure. During development, updated 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/BioHearFailure/) beginning in August 2004. The draft LMPG and suggested revisions were presented for public and stakeholder comment at the October 2004 Arnold O. Beckman Conference titled Cardiac Markers: Establishing Guidelines and Improving Results. The resulting draft guidelines can be viewed in their entirety at on the NACB World Wide Web site (http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/ACSHeart/heartpdf.htm).

The scope of the guidelines presented here represent the writing group's recommendations for cTn, BNP, and NT-proBNP in the rapidly evolving area of etiologies other than ACS and heart failure in adult patients. Other sections of the biochemical cardiac marker guidelines involving clinical and analytical issues of ACS and heart failure and issues of logistics and point-of-care testing are available at http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/ACSHeart/heartpdf.htm. More explicit detail on guideline development and the groups providing stakeholder input is available in the Preamble to the overall guideline, which is available at http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/ACSHeart/heartpdf.htm.

Currently available cardiac biomarkers can define cell death, damage, or dysfunction to particular organ sys-

<table>
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<th>Table 1. American College of Cardiology/American Heart Association classifications.</th>
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<td><strong>Summary of indications</strong></td>
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<th>Weight of evidence</th>
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10 Nonstandard abbreviations: cTn, cardiac troponin; MI, myocardial infarction; ACS, acute coronary syndrome; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; NACB, National Academy of Clinical Biochemistry; LMPG, Laboratory Medicine Practice Guidelines; cTnT, cardiac troponin T; cTnI, cardiac troponin I; AMI, acute MI; ESRD, end-stage renal disease; ED, emergency department; PE, pulmonary embolism; NRMI, National Registry of Myocardial Infarction; CK, creatine kinase; OR, odds ratio; PCI, percutaneous coronary intervention.
tems 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), BNP, and NT-proBNP are specific only to the presence of ACS and heart failure, and imply diagnosis of ACS and heart failure, and their etiology. Although 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 MI (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 cutoff values are used, such as the 99th percentile limit of a healthy population, which detect a variety of more subtle abnormalities (1). Table 2 shows a list of conditions that can cause an increase in cTn in the absence of overt ischemic heart disease (2).

### Table 2. Elevations of cardiac troponins without overt ischemic heart disease.

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Trauma (including contusion, ablation, pacing, implantable cardioverter defibrillator firings including atrial defibrillators, coronaryversion, endomyocardial biopsy, cardiac surgery, after interventional closure of atrial septal defects)</td>
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<tr>
<td>Congestive heart failure—acute and chronic</td>
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<td>Aortic valve disease and hypertrophic obstructive cardiomyopathy with significant left ventricular hypertrophy</td>
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<td>Hypertension</td>
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<td>Hypotension, often with arrhythmias</td>
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<tr>
<td>Postoperative noncardiac surgery patients who seem to do well</td>
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<tr>
<td>Renal failure</td>
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<td>Critically ill patients, especially with diabetes, respiratory failure, gastrointestinal bleeding, sepsis</td>
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<td>Drug toxicity, e.g., adriamycin, 5-fluorouracil, herceptin, snake venoms, carbon monoxide poisoning</td>
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<tr>
<td>Hypothyroidism</td>
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<td>Abnormalities in coronary vasomotion, including coronary vasospasm</td>
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<td>Apical ballooning syndrome</td>
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<tr>
<td>Inflammatory diseases, e.g., myocarditis, parvovirus B19, Kawasaki disease, sarcoid, smallpox vaccination, or myocardial extension of bacterial endocarditis</td>
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<tr>
<td>Post-PCI patients who appear not to have complications</td>
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<tr>
<td>Pulmonary embolism/PE, severe pulmonary hypertension</td>
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<tr>
<td>Sepsis</td>
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<tr>
<td>Burns, especially if total surface burn area is &gt;30%</td>
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<tr>
<td>Infiltrative diseases, including amyloidosis, hemochromatosis, sarcoidosis, scleroderma</td>
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<tr>
<td>Acute neurological disease, including cerebrovascular accident, subarachnoid bleeds</td>
</tr>
<tr>
<td>Rhabdomyolysis with cardiac injury</td>
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<tr>
<td>Transplant vasculopathy</td>
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<tr>
<td>Vital exhaustion</td>
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### Table 3. Increased concentrations of BNP/NT-proBNP without overt heart failure (references).

- Inflammatory cardiac diseases (3–5)
- Systemic arterial hypertension with left ventricular hypertrophy (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)

In a similar manner, increases in BNP and NT-proBNP concentrations are not specific for heart failure alone. Table 3 lists conditions other than heart failure than can cause an increase in BNP and NT-proBNP (3–22). Renal dysfunction is a confounder for cTnT and cTnI as well as BNP and NT-proBNP. Cardiac surgery will release cardiac biomarkers into blood because of the damage to 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 analysis 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 interference (23, 24).

The recommendations in this section will focus on other etiologies that can affect the interpretation of cTn and the natriuretic peptides. Recommendations will be provided where there is sufficient scientific and medical evidence. Note that an overview of ACS and heart failure containing definitions, pathogenesis, and management from the perspective of biochemical markers is presented in Chapters 1 and 3. Chapters 1 and 3 also include specific recommendations for the use of biochemical markers for the diagnosis and risk stratification of patients and clinical decisions in the context of ACS and heart failure. Recommendations addressing analytical issues for cardiac biomarkers of ACS and heart failure are presented in Chapters 2 and 4, respectively.

### 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) or electrocardiograph 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 AMI (Level of evidence B).

CLASS II B

1. cTnT and cTnI can be used as aids for defining the risk of mortality in ESRD patients and 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 than in patients with estimated glomerular filtration rate >60 mL·min⁻¹·(1.73 m²)⁻¹ (Level of evidence B).

CLASS III

1. Routine BNP/NT-proBNP measurement is not warranted in asymptomatic ESRD patients (Level of evidence B).

1. BIOMARKERS IN CHRONIC RENAL FAILURE

Increases in the concentration of cTnI and cTnT can be used as aids for defining the risk of mortality in ESRD patients and provide baseline values for comparison when measured in the setting of an acute clinical change (Level of evidence B).

In patients with suspected ACS, a dynamic change in the cTnI indicates a diagnosis of AMI (25, 26) and warrants further investigation/treatment. A recommended cutoff cTn value of ≥20% in the 6–9 h after presentation represents a significant (3 SD) change in cTnT on the basis of a 5%–7% analytical CV typical for most assays in the concentration range indicating AMI. Patients with ESRD who have increased cTn concentrations have a higher (long-term) risk of death than corresponding patients without increases in cTn in this setting. Using a cut point of 0.03 μg/L for cTnT (10% CV), Aviles et al. (27) reported a 2.7-fold higher (95% CI 1.9–3.8) risk of MI or death at 30 days among patients with suspected ACS in the lowest quartile for creatinine clearance. 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 differentiated 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 benefits 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 that 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 individuals, increased concentrations of cTnI 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 concentrations at 1, 2, and 3 years of follow-up for cTnT among 733 patients; odds ratios (ORs) 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). Furthermore, 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). Percentage of agreement between the Beckman and Dade assays for increased cTnI was 85% (κ 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.

cTnI appears to be less useful on a routine basis, however, 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 cTns 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 cTnI as a biomarker for risk stratification in ESRD patients for all-cause death, and the use of cTnI 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 based solely on the results of cTn testing in patients with ESRD. However, the availability of such 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; however,
recommended reference intervals for BNP and NT-proBNP have not been validated for patients with chronic renal failure.

Zoccali et al. (36) reported a relative OR of 6.7 (95% CI 2.4–18.5) for cardiovascular death among patients on dialysis with an increased concentration of BNP. Several investigators have combined the results of biomarkers to determine whether they provide additive risk stratification information. In an analysis of cTnT, cTnI, and atrial and BNP in chronic dialysis patients, only cTnT was an independent predictor of death (37). However, Apple et al. (34) found that cTnT, cTnI, and high-sensitivity C-reactive protein were each independent predictors of death in ESRD patients. In his study, NT-proBNP had prognostic value, but it was not independent of cTn. Comparing BNP results directly against NT-proBNP in patients with chronic kidney disease, Vickery et al. (38) suggested that NT-proBNP concentrations were more affected by declining kidney function. 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 Nonischemic Etiologies

A. USE OF CARDIAC BIOMARKERS IN THE SETTING OF NONISCHEMIC ETIOLOGIES

Recommendations for use of biochemical markers in other nonischemic etiologies

CLASS IIb

1. Increased cardiac telemetry may be warranted for patients who have increased cTn values after 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 of acute pulmonary embolism (Level of evidence B).
5. Routine BNP/NT-proBNP measurements may be warranted among patients with nonischemic 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 NONISCHEMIC 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 tissues except the heart. Therefore, cTn found in concentrations exceeding the 99th percentile of a reference population reflects 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 nonischemic injuries to the heart, among patients with critical illnesses (40–47), chemotherapy (48–53), myocarditis (54), blunt chest trauma (55, 56), stroke (57), pulmonary embolism (PE) (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 metaanalysis 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. Because myocardial confusion 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, who can develop heart failure. Recent studies suggest that for patients with increased cTn, treatment with angiotensin-converting enzyme inhibitors dramatically reduces the frequency of heart failure (49).

2. cTN AND BNP/NTPROBNP IN PE

Among patients with PE, data substantiate the association of cTn increases with worse prognosis. La Vecchia et al. (59) demonstrated that when cTnI was >0.6 μg/L, the mortality was 4.8% vs 36% for cTnI >0.6 μg/L. In a study of 56 consecutive patients with confirmed PE, in-hospital mortality was 44% among patients who were cTnT positive (>0.1 μg/L) vs 3% among those in whom cTnT was <0.1 μg/L (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 result 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 PE (60). Although the therapeutic implications of such increases are not clear, it is important to assign the correct diagnosis in these patients, because 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 National Registry of Myocardial Infarction (NRMI)-2 and NRMI-3 registries (1994–2000). It is unlikely that AMI risk adjustment models would reflect the high PE mortality rates; although 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 produce a skewed observed:expected AMI mortality ratio that could contribute to a mortality outlier status for the facility.

It is unclear at present what to do therapeutically in response to such increases and whether cTn and/or BNP or NT-proBNP increases provide more information. 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 submassive PE (62).

3. CTN IN CRITICAL CARE PATIENTS

Increases of cTn are common among critically ill patients, e.g., those with sepsis. Although 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 nonischemic 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 Noncardiac Surgery

A. Use of Cardiac Biochemical Markers after Noncardiac Surgery

Recommendations for use of cardiac markers after noncardiac surgery

CLASS II B

1. cTnT and cTnI are recommended for patients undergoing noncardiac 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 may be considered for postsurgical 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 postoperatively 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 noncardiac surgery (Level of evidence C).

1. Biomarkers after Noncardiac Surgery

Ischemic myocardial damage can occur in patients undergoing surgery that does not involve the myocardium. Creatine kinase (CK) and CK-MB are less reliable biomarkers than cTn for assessing ischemic myocardial complications because these enzymes are released from skeletal muscle damage as the result of the surgery (68). cTn is specific to heart damage and is not normally released in noncardiac surgery (69). Therefore, increased cTn concentrations after noncardiac surgery are a marker of myocardial damage and are predictive of an adverse outcome at 6 and 12 months (70–72). Increases in cTnT above 0.03 μg/L (10% CV cut point) were indicative of occult myocardial necrosis and an independent marker of mortality (OR 14.9, 95% CI 3.7–60.3) (73). Similar results have been shown for cTnI (OR 9.8, 95% CI 3.0–32) (72). 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 are closely associated 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 (74). Furthermore, increases are associated with both early and late clinical consequences, suggesting the need for intervention acutely when increases occur in the hospital (68). 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 age and other characteristics) might not be related to ischemic heart disease but might more likely be associated with pulmonary emboli, which are frequent postoperative complications (75). Thus, each surgical group 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 noncardiac surgery.

V. Biomarker Use after Percutaneous Coronary Intervention

A. Use of Cardiac Biochemical Markers after Percutaneous Coronary Intervention

Recommendations for use of biomarkers after percutaneous coronary intervention
CLASS IIb

1. It is appropriate to measure cTnT or cTnI before and after percutaneous coronary intervention (PCI) to determine the presence of ischemic cardiac damage if the baseline preprocedural value is less than the 99th percentile for the reference control population. Any increase is indicative of cardiac damage. 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 preprocedural 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 (Level of evidence C). If serial preprocedural cTn values are available, a falling trend followed by a postprocedural increase of 20% or more may be indicative of new myocardial injury, even if any or all of the preprocedural results are above the 99th percentile.

1. BIOMARKERS AFTER PCI

Periprocedural myocardial damage has been the subject of debate since the inception of the technique 30 years ago (76). cTn release after PCI ranges in incidence from 14% to 48% (77–82). This wide variation is caused by the assay and corresponding cutoff concentrations used, as well as the underlying indication for the revascularization procedure (e.g., acute vs 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 the 10% CV value. These and other studies have consistently shown that postprocedural 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 (82). 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 (79). 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 (78). Similar results have been reported for cTnT, in which abnormal concentrations resulted in an OR for death or MI of 2.6 (95% CI 1.4–5.1) (77). Postprocedural increases in cTnI were also associated with decreased tissue-level perfusion as measured by angiography using TIMI (thrombolysis in MI) myocardial perfusion grade and intracoronary myocardial contrast echocardiography (80). Although 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 postprocedure biomarker elevations carry prognostic significance. When one uses baseline cTn in the analysis, the prognostic significance of postprocedure values is totally obviated, suggesting that it is the preprocedure value that defines risk. If the baseline cTn value is increased, attempting to distinguish PCI-induced injury from the injury leading to the admission is probably not something that can be accomplished unless there is substantial time (2 samples at least 6 h apart) before the PCI. Similar principles should be applied for CK-MB, whose rise may not be detected due to its substantial lack of sensitivity compared with troponin. In this situation, the baseline value predicts subsequent risk (83). If the cTn values are stable over time, using criteria for reinfarction is suggested. When the baseline cTn value is normal, increases in both cTn and CK-MB are modest and unassociated with long-term events (83) but at least in this situation, the mechanism can be more clearly ascertained. The European Society of Cardiology Task Force on Invasive Cardiology recommended a CK-MB cutoff concentration of 5 times the upper limit of normal (84). The previous convention has been the use of a 3-fold increase (85).

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. In addition to >5-fold increase in cTn after the procedure, clinical and other (nonlaboratory medicine) diagnostic testing criteria should be used to distinguish components related to the operative procedure and cardioprotection from vascular events (Level of evidence C).

2. 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 vs warm solutions, and so on (86–94). Recent 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 (90). Transmural damage is observed only with very marked increases of cTn that and are potentially related to a primary vascular event (88, 90). Therefore, if the diagnosis of MI must reflect a primary vascular event, 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 (95–100); in general, the higher the value, the worse the prognosis (89). 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 (88). 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 (101). In a recent series that used a marked increase of cTn to define possible graft occlusion (102), 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 cutoff 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 are few 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 intraaortic balloon pumps, prolonged hospital length of stay, and 1-year mortality (103). In another study, increase preoperative BNP predicted postoperative atrial fibrillation (104). Such studies address the suitability of patients undergoing cardiac surgery and not perioperative complications or events.

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