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EXPERT CONSENSUS DOCUMENT

ACCF 2012 Expert Consensus Document on Practical Clinical Considerations in the Interpretation of Troponin Elevations

A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents

Developed in Collaboration With the American Association for Clinical Chemistry, American College of Chest Physicians, American College of Emergency Physicians, American Heart Association, and Society for Cardiovascular Angiography and Interventions

Writing Committee Members

L. Kristin Newby, MD, MHS, FACC, FAHA, *Co-Chair**
Robert L. Jesse, MD, PhD, FACC, FAHA, *Co-Chair**

Joseph D. Babb, MD, FACC, FSCAI†
Robert H. Christenson, PhD, DABCC, FACB‡
Thomas M. De Fer, MD, FACP§
George A. Diamond, MD, FACC*
Francis M. Fesmire, MD, FACEP‖
Stephen A. Geraci, MD, FACC, FCCP, FAHA, FACP¶
Bernard J. Gersh, MB, ChB, DPhil, FACC*
Greg C. Larsen, MD, FACC*
Sanjay Kaul, MBBS, FACC, FAHA#
Charles R. McKay, MD, FACC*
George J. Philippides, MD, FACC*
William S. Weintraub, MD, FACC, FAHA**

*American College of Cardiology Foundation Representative; †Society for Cardiovascular Angiography and Interventions Representative; ‡American Association for Clinical Chemistry Representative; §American College of Physicians Representative; ‖American College of Emergency Physicians Representative; ¶American College of Chest Physicians Representative; #ACCF Task Force on Clinical Expert Consensus Documents Representative, American Heart Association Representative.

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ACCF Task Force Members

Robert A. Harrington, MD, FACC, *Chair***
Deepak L. Bhatt, MD, MPH, FACC, *Co-Chair*

Jeffrey L. Anderson, MD, FACC
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David J. Moliterno, MD, FACC
Debabrata Mukherjee, MD, FACC**
Robert S. Rosenson, MD, FACC**
James H. Stein, MD, FACC**
Howard H. Weitz, MD, FACC
Deborah J. Wesley, RN, BSN**

**Former Task Force member during this writing effort.

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Preamble

This document has been developed as an Expert Consensus Document (ECD) by the American College of Cardiology Foundation (ACCF), American Association for Clinical Chemistry (AACC), American College of Chest Physicians (ACCP), American College of Emergency Physicians (ACEP), American College of Physicians (ACP), American Heart Association (AHA), and Society for Cardiovascular Angiography and Interventions (SCAI). Expert Consensus Documents are intended to inform practitioners, payers, and other interested parties of the opinion of ACCF and document cosponsors concerning the evolving areas of clinical practice and/or technologies that are widely available or new to the practice community. Topics chosen for coverage by ECDs are so designed because the evidence base, the experience with technology, and/or clinical practice are not considered sufficiently well developed to be evaluated by the formal ACCF/AHA Practice Guidelines process. Often the topic is the subject of considerable ongoing investigation. Thus, the reader should view the ECD as the best attempt of the ACCF and document cosponsors to inform and guide clinical practice in areas where rigorous evidence may not yet be available or evidence to date is not widely applied to clinical practice. When feasible, ECDs include indications or contraindications. Some topics covered by ECDs will be addressed subsequently by the ACCF/AHA Practice Guidelines Committee.

The ACCF Task Force on Clinical Expert Consensus Documents (TF CECD) makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that may be perceived as relevant to the writing effort. This information is documented in a table, reviewed by the parent task force before final writing committee selections are made, reviewed by the writing committee in conjunction with each conference call and/or meeting of the group, updated as changes occur throughout the document development process, and ultimately published as an appendix to the document. External peer reviewers of the document are asked to provide this information as well. The disclosure tables for writing committee members and peer reviewers are listed in Appendices 1 and 2, respectively, of this document. Additionally, in the spirit of complete transparency, writing committee members' *comprehensive disclosure information*—including relationships with industry and other entities that do not pertain to this document—are available online. Disclosure information for members of the ACCF Task Force on Clinical Expert Consensus Documents—as the oversight group for this document development process—is also available at www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx.

The work of the writing committee was supported exclusively by the ACCF without commercial support. Writing committee members volunteered their time to this effort. Meetings and/or conference calls of the writing committee were confidential and attended only by committee members.

Robert A. Harrington, MD, FACC
Chair, ACCF Task Force on Clinical Expert Consensus Documents

Deepak L. Bhatt, MD, FACC
Vice Chair, ACCF Task Force on Clinical Expert Consensus Documents

1. Introduction

1.1. Document Development Process

1.1.1. Writing Committee Organization

The writing committee was commissioned by the ACCF TF CECD and consisted of members representing 7 societies: ACCF, AACC, ACCP, ACEP, ACP, AHA, and SCAI. Prior to the commencement of the writing process, authors reported all relevant relationships with industry within the previous 24 months. Authorship reflects 1 chair and 5 additional members with no relevant RWI. Relationships were managed in accordance with the disclosure policy in place as of September 2009, as noted in the Preamble. The ACCF disclosure policy was subsequently revised, but it did not apply to this writing effort, which was already in progress. Coordination and staff support were provided by the ACCF.

1.1.2. Document Development Approval

The writing committee convened by conference call and e-mail to finalize the document outline, develop the initial draft, revise the draft per committee feedback, and ultimately sign off on the document for external peer review. All participating organizations participated in peer review, resulting in 22 reviewers representing 170 comments. Com-

ments were reviewed and addressed by the writing committee. A member of the ACCF TF CECD served as lead reviewer to ensure that all comments were addressed adequately. Both the writing committee and TF CECD approved the final document to be sent for board review. The ACCF Board of Trustees reviewed the document, including all peer review comments and writing committee responses, and approved the document in July 2012. This document is considered current until the TF CECD revises or withdraws it from publication.

1.2. Conceptual Model

Since the introduction of troponin testing in the early 1990s, there have been questions about the relationship between the physiological finding of elevated troponin as a marker of myocardial necrosis and the clinical significance of the finding and the nomenclature that should be attributed to it. This early experience with testing clearly demonstrated that an elevated troponin level identified patients at increased risk for adverse outcomes whether the clinical diagnosis was unstable angina, myocardial infarction (MI), or a noncoronary etiology. This experience taught us much about both analytical and clinical sensitivity and specificity of cardiac markers, especially in the absence of a putative operational standard (clinical, imaging, or laboratory), against which the clinical states of unstable angina and MI could be defined.

As troponin assays become more sensitive, the issues plaguing clinicians will become more frequent and more complex. Although there are substantial discussions related to assay characteristics (e.g., sensitivity, precision, and reference limits), the distinction between diagnosis and prediction of risk in populations, and the consequences of false-positive and false-negative results, the common focus is on improving patient care and outcomes.

What has become extremely clear is that much of the interpretation of the test results must consider the clinical context in which the measurement was made. For example, the interpretation of a positive troponin in a patient presenting with ischemic chest pain will (and must) be different from that in the patient undergoing a procedure or presenting with acute onset dyspnea, fever and hypotension, or renal failure. Furthermore, there is an increasing appreciation for the nonischemic versus ischemic etiologies of troponin release, and for the latter, an appreciation for differentiating the nuances of acute coronary syndromes (ACS) versus non-ACS etiologies. The most important nuance to understand is that *an elevated troponin is a finding that represents the likely occurrence of myocardial necrosis and does not in and of itself provide any indication of the etiology.*

Figure 1 shows a conceptual model for clinical distribution of elevated troponin. The key to understanding this concept is to appreciate that not all elevated troponin results represent an MI and that not all myonecrosis results from an ACS event, even when ischemic in etiology. Although the finding of an elevated troponin carries an increased risk for subsequent adverse clinical outcomes in many circumstances, inappropriate treatments driven by troponin elevation alone could impart an even higher risk.

2. Interpretation

More than 30 years ago, a landmark Joint Report from the International Society and Federation of Cardiology and World Health Organization defined the criteria for the diagnosis of ischemic heart disease (1). In this report, the diagnosis of acute MI was based on a consensus of 2 of the following 3 features: 1) clinical history; 2) electrocardiographic findings; and 3) temporal changes in serum enzymes. A diagnosis based on a consensus was necessary due to the heterogeneity of clinical symptoms at presentation, the fact that the ECG is frequently equivocal, and because enzyme biomarkers available at the time were not specific for myocardial injury. However, in the early 1990s, the situation changed with the development of cardiac troponin T and I assays. Initial studies showed that with the exception of rare analytical false positives (2), the presence of cardiac troponin in blood indicated that cardiac injury had occurred. Therefore, clinicians rapidly came to consider cardiac troponin biomarkers to have virtually 100% predictive accuracy for MI.

Although early cardiac troponin assays were considered as a replacement test for creatine kinase (CK)-MB measurement, equivalence between the markers could not be demonstrated. In 12% to 39% of patients who were negative for CK-MB, cardiac troponin results were positive (3). These data raised the question as to whether discordant troponin and CK-MB results were falsely positive or indicative of a more sensitive test that classified patients more accurately. Subsequent meta-analyses answered this question by showing that patients with positive troponin results indeed had a higher risk for adverse outcomes (4,5) even in the absence of recurrent ischemic injury.

The question then became, what cutoff should be used for the diagnostic and prognostic interpretation of cardiac troponin? Several studies indicated that even minor elevations in cardiac troponin were associated with an increased risk in patients within the continuum of ACS (6–9). The notion that any amount of myocardial necrosis caused by ischemia should be labeled as MI, and the evolution of sensitive and specific technologies, including cardiac troponin assays, necessitated the re-evaluation of established definitions of MI (10). On the heels of a declaration made by the National Academy of Clinical Biochemistry (NACB) in reference to the need for incorporation of troponin into the diagnosis on MI (11), a joint committee of the European Society of Cardiology (ESC) and the American College of Cardiology Foundation was convened in 1999 to re-examine the MI definition. The result was a consensus that the preferred biochemical marker for detecting myocardial necrosis was cardiac troponin and that a maximal

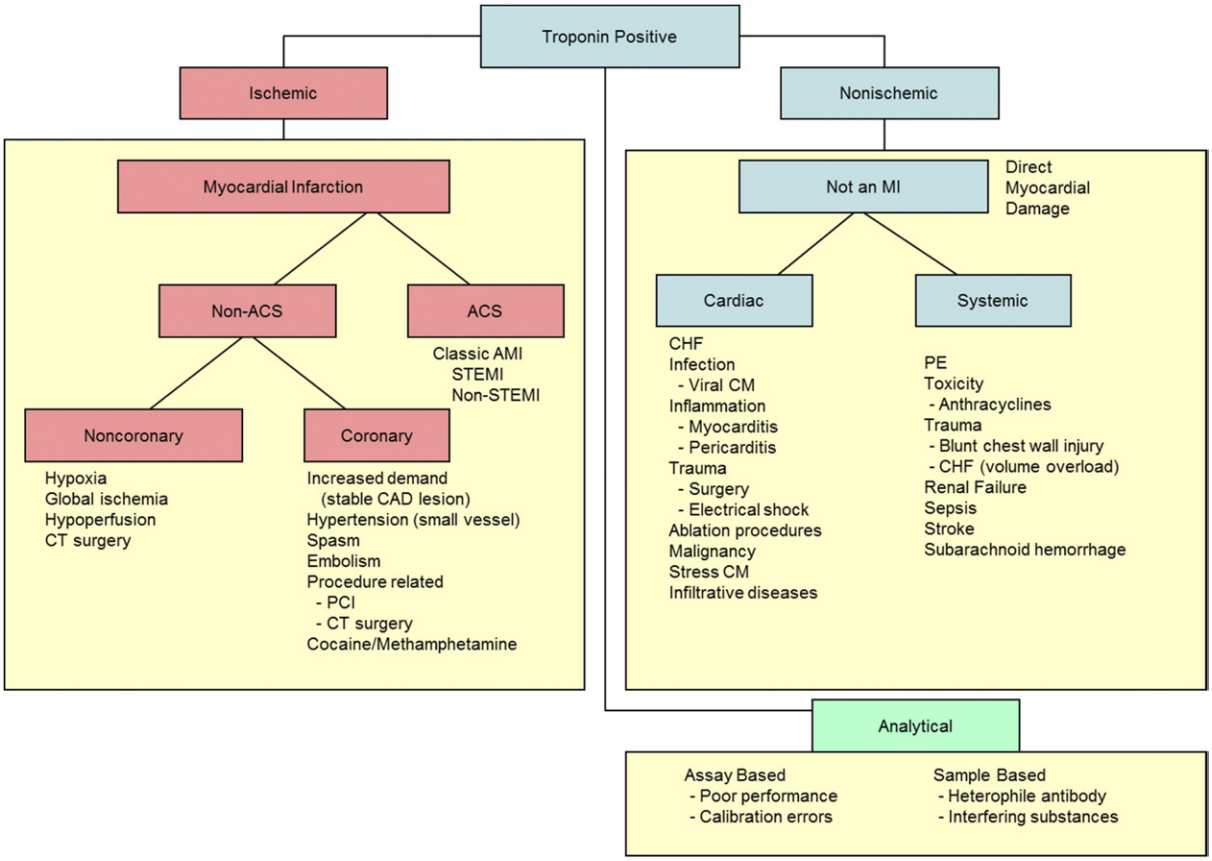

Figure 1. Conceptual Model for Clinical Distribution of Elevated Troponin

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure; CM = cardiomyopathy; CT = cardiothoracic; PCI = percutaneous coronary intervention; PE = pulmonary embolism; STEMI = ST-segment elevation myocardial infarction.

concentration of troponin T or I that exceeded the operative threshold on at least 1 occasion during the first 24 h after an index clinical ischemic event indicated MI (12). The operative threshold was defined as the 99th percentile of the values for a reference control group and was based on the consensus that an acceptable false-positive rate would be approximately 1%.

The emerging role of cardiac troponin as a powerful tool for MI diagnosis and risk stratification led professional organizations to issue guidance statements on its usage. From the laboratory medicine perspective, the NACB recommended cardiac troponin as the preferred marker for risk stratification of suspected ACS patients and for establishing the diagnosis of MI (11). A low cutpoint at the 99th percentile of a reference control population was championed by the NACB guidelines, in agreement with the earlier statement by the ACC/ESC/AHA on redefinition of MI (10).

In 2007, a second global task force comprised jointly of representatives from the ESC, ACCF, AHA, and WHF was convened to update the 2000 consensus document on redefinition of MI (12). This task force concluded that the term *MI* should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia and in association with the following criteria for diagnosis of MI: 1) A rise and/or fall of biomarkers (preferably troponin); 2) sudden cardiac death; 3) elevations in biomarkers after percutaneous coronary intervention (PCI) in patients having normal pre-intervention troponin levels; 4) elevations in biomarkers in patients following coronary artery bypass grafting (CABG) and with normal baseline troponin levels; or 5) pathological findings of an acute MI. This document defined MI according to 5 classifications, as shown in Figure 2: Type 1 is termed spontaneous MI, which is related to ischemia due to a primary coronary event such as plaque rupture, erosion/fissuring or dissection; Type 2 is ischemia related to either increased oxygen demand or decreased supply; Type 3 is related to sudden unexpected cardiac death; Type 4a is associated with PCI, and 4b is associated with documented stent thrombosis; and Type 5 is associated with CABG. A major refinement in the 2007 document was the stipulation that a rise and/or fall of cardiac biomarkers (preferably troponin) is necessary. Not included in the earlier global task force document, but consistent with the NACB guidelines, this stipulated rise and/or fall mandates serial sampling of troponin in all patients suspected of having an acute spontaneous (Type 1) MI. Although the global task force

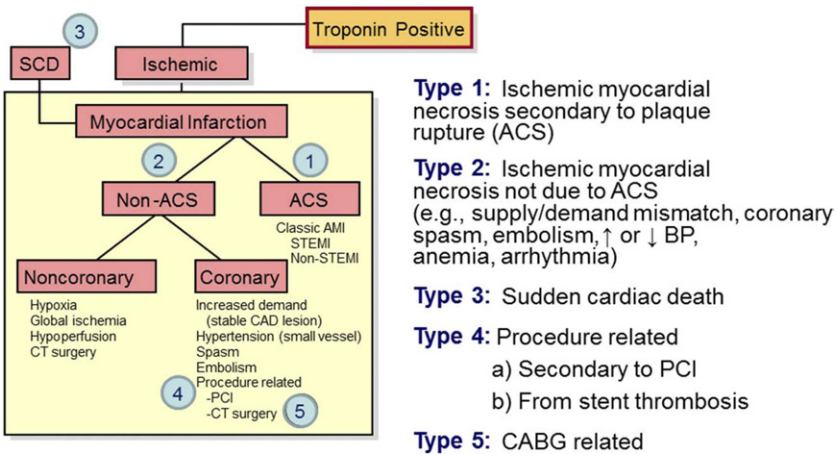

Figure 2. Troponin Positivity and the Universal Definition of MI (13) Classification of MI Type

ACS = acute coronary syndromes; AMI = acute myocardial infarction; BP = blood pressure; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CT = cardiothoracic; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCD = sudden cardiac death; STEMI = ST-segment elevation myocardial infarction.

document did not specify the degree of rise or fall that would be diagnostic of Type 1 MI, the earlier NACB document recommended a change of 20% at 3 to 6 h from a previous sample. Both documents recommended sampling at the baseline, approximately 6 to 9 h later, and again between 12 and 24 h from the baseline. To consider 2 troponin measures to be different requires them to vary by a difference of >3 standard deviations of the variance of the measures. For most robust assays, the variance is approximately 5% to 7%. Therefore, although empirical data supporting this degree of change are limited, a 20% change between successive values should be statistically different and also produce a value >99th percentile. However, other factors, including interindividual variability, may affect this parameter and become more important as increasingly precise assays are available. Point-of-care testing may be useful as a screening tool, but most point-of-care assays are only semiquantitative. To confirm a rise and/or fall from an initially positive assay would require serial quantitative testing, and in general, high-quality quantitative assays are preferred.

Most recently, the "Third Universal Definition of Myocardial Infarction" document was published in 2012 (13). Although refinements have been made to the thresholds and supporting information needed for the use of troponin to define MI in the setting of PCI and CABG, the general classification framework created by the 2007 Universal Definition of MI (12) document was carried forward. Figure 2 aligns the model presented in Figure 1 with the framework for the universal definition of MI. It is incumbent on all practitioners to fully understand the implications of an elevated troponin level in a given patient in order to initiate the appropriate treatment and to optimize outcomes. This is extremely important, not only in distinguishing Type 1 from Type 2 MI, but also in distinguishing ischemic from nonischemic causes and in understanding the non-MI cohort of patients denoted on the right side of Figure 1.

2.1. Analytical Issues

Clinicians must be aware that all troponin assays are not created equal, and they must understand the characteristics and potential limitations of the specific assay used in their practice. This is because the susceptibility of troponin assays to potential interfering substances, such as heterophile antibodies and rheumatoid factor, can vary widely. Cardiac troponin is a complex analyte, and the regions of the troponin molecule targeted by the antibodies comprising these immunoassays are an important consideration for assay performance. Furthermore, assays have become, over time, increasingly sensitive, with improved analytical precision. This has resulted in a wide spectrum of assay quality in practice. Ultimately, this variability in quality has led to confusion in clinical practice and in the literature because varying cutoffs and decisions limits have been used. These decision limits have not always been the same for a given assay or between users of the same assay, and some have changed between earlier and later generations of the same assay. Thus, one study may not be comparable to the next in a similar population, and a test in one hospital may not have the same meaning in another. Assays are heterogeneous in their ability to accurately and reliably measure in the range of the 99th percentile of troponin values (i.e., the 95% confidence interval [CI] can be rather narrow for some assays but much wider for others) (14). Different interpretations of a "reference control population" upon which the 99th percentile of cardiac troponin values is based further complicates interpretation. Finally, measurement of cardiac troponin is not currently standardized. Therefore, unlike glucose, total cholesterol, and many other common measurements, troponin values vary from assay to assay, and assays have very different values for 99th percentile of normal. The NACB has developed analytical recommendations for troponin assays (15), and 1 publication has proposed a system of "grading" assays (16). With a centrally

maintained, continuously updated database of assays, their functional characteristics and overall "grade" on these parameters would facilitate assay selection through competitive pressure to promote assay quality. Importantly, for the multiple troponin I assays in existence, regulations to ensure standardization of assays to the National Institute of Standards and Technology reference material (NIST #2921) would make it more feasible for clinicians to readily compare troponin levels measured in different laboratories or hospitals with different assays or generations of assays. This may be particularly important as patients are transferred from one facility to another. It is recommended that reference interpretive thresholds should be established for each cardiac biomarker, based on a population of normal, healthy individuals without a known history of heart disease. Creation of a healthy subject sample bank—such that all assay manufacturers could establish the 99th percentile of their assay against a common standard population of uniform size and clinical characteristics—would eliminate variability related to the population selected and obviate the need for each hospital or clinic to independently carry out this task. The NACB analytical document also recommends 1 threshold for optimal use of the cardiac biomarkers, troponin I and troponin T. Importantly, assays for cardiac biomarkers should improve towards a total imprecision (% coefficient of variation) of <10% at the 99th percentile reference limit. Even now, "high-sensitivity" troponin assays are being developed and are in use in some areas of the world. These assays have substantially lower limits of detection (in the picogram per milliliter range versus the current fourth-generation assays in the nanogram per milliliter range) as well as improved assay precision. Clinicians, laboratorians, clinical pathologists, and other users must communicate to assure that their troponin assays are in sufficient compliance with these recommendations and that all groups understand the characteristics of the assay in clinical use at a given facility.

2.2. Statistical Issues

Determining whether a troponin elevation represents a Type 1 MI is dependent upon the pre-test probability of ACS due to atherothrombosis (i.e., atherosclerotic plaque rupture, fissuring, and erosion). The concept of pre-test probability has been well understood for several decades. Pre-test probability for obstructive coronary artery disease (CAD) has been formally quantified in reference to coronary angiography, based on observable clinical characteristics such as age, sex, risk factors, and the quality of presenting symptoms (17). Similarly, factors that suggest a high pre-test probability of ACS include typical symptoms (rest or crescendo angina), ischemic ECG changes (ST-segment depression of >1.0 mm or T-wave inversion) or wall-motion abnormalities on echocardiography (or other imaging tests), and the presence of CAD risk factors or history of CAD (18). Because troponin elevation may be due to myocardial necrosis from causes other than atherothrombosis, there is no single putative standard for defining the presence or absence of MI as reliably as that of coronary angiography for the diagnosis of obstructive CAD. Furthermore, many of the same demographic factors that suggest a higher probability of ACS are also implicated in patients with non-ACS causes of troponin elevation, including heart failure, which often coexists. As a result, interpretation of the results of troponin testing for diagnosis of MI must be considered in the context of the pre-test probability of ACS, which is less formally quantitative than the pre-test probability of CAD.

Despite this limitation, Bayes' theorem is equally operative, if less precise. Thus, assuming a sensitivity of 100% among patients with a high pre-test probability of atherothrombotic ACS, in the range of 90% (typical chest pain with clinical and electrocardiographic evidence of ischemia), the post-test probability (predictive accuracy) for positive troponin is over 95%, even if the false-positive rate is as much as 40% (point B in Fig. 3). On the other hand, if pre-test probability is low, in the range of only 10% (as for patients with atypical symptoms and nonspecific ECG changes), the post-test probability is around 50%, even if the false-positive rate is only 10% (point A in Fig. 3). The difference in post-test probabilities becomes more pronounced at low pre-test probabilities, highlighting the impact of specificity of troponin in patients presenting with low pre-test probability of ACS. Thus, although myocardial necrosis is present, even high values of troponin do not establish a diagnosis of ACS with confidence if the pre-test probability is low. Conversely, low values do not reliably exclude the diagnosis of ACS if pre-test probability is high.

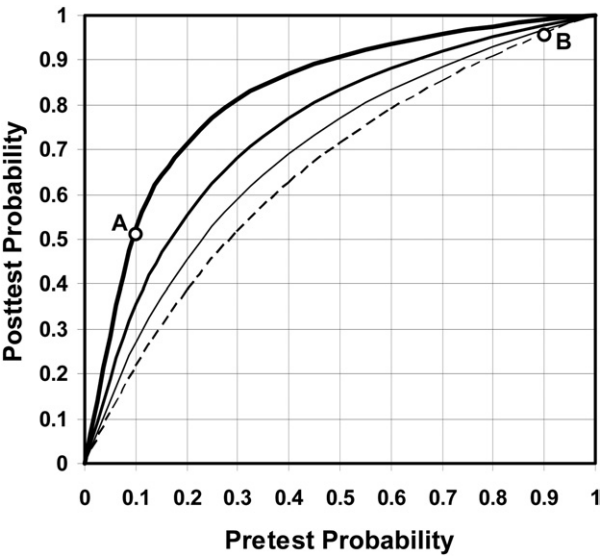

Figure 3. Relation Between Pre-Test And Post-Test Probability According to Bayes' Theorem for Troponin Test With 100% Sensitivity

The curves are shown for a specificity of 60% (lowermost) to 90% (uppermost). See text for further discussion. Modified with permission from Diamond and Kaul (19).

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Therefore, from a Bayesian perspective, troponins are no different from any other imperfect diagnostic test, and even putative "high-sensitivity" troponin assays must obey the mathematical laws of probability. Just as a tool is only as good as its operator, a diagnostic test can be only as good as its interpretation. Expecting troponin testing to provide all the answers without including the proper clinical context can lead to erroneous diagnoses (19).

A semiquantitative summary of positive and negative predictive accuracies of troponin measurement is displayed in Table 1, recognizing that these parameters are also influenced by the prevalence of the disease in the population studied. If troponin (or any other laboratory test) is applied indiscriminately in broad populations with a low pre-test probability of atherothrombotic disease, given its high sensitivity but low specificity for ACS among these patients, the positive predictive value (PPV) for non–ST-segment elevation MI is greatly diminished. Thus, from a diagnostic standpoint, even when the troponin is "positive"—especially a weak positive—the post-test probability for atherothrombotic ACS is still low in a patient with low pre-test probability of atherothrombotic ACS (e.g., a young woman with atypical symptoms or an elderly patient with nonspecific symptoms admitted with pneumonia). Although looking for a characteristic rise and/or fall in troponin is essential for the diagnosis of MI as proposed by both the NACB and the universal definition of MI as discussed earlier, ignoring pre-test probability often results in a high rate of misdiagnosis, especially when clinical symptoms are less typical.

Although some have advocated floating cutpoints in different clinical contexts (lowered cutpoints trading specificity for increased sensitivity, and higher cutpoints trading sensitivity for increased specificity) (20), the superior strategy would be to determine the patient-specific post-test probability of infarction given the patient-specific estimate of pre-test probability and the patient-specific observed troponin level. An algorithm that takes into consideration the pre-test probability based on clinical presentation and ECG changes, age, renal function, and a higher troponin T cutpoint was claimed to allow for more accurate diagnosis of ACS (20). However, the formal integration of pre-test probabilities with clinical predictors and troponin levels awaits validation in prospective studies.

Another feature that might help discriminate ischemia-induced cardiac injury from nonspecific myocardial damage is the kinetics of the marker. An elevated troponin level that is relatively constant over an appropriate sampling interval (e.g., baseline at 6 to 9 h and again at 12 to 24 h; a so-called "smoldering" pattern) is more likely to be caused by chronic diseases, such as renal failure, heart failure, myocarditis, or amyloidosis. However, episodic and lower-level changes, even below the reference limit, could represent ischemia-induced injury. By contrast, although data are limited in clinical practice, a dynamic change from the baseline value may be more suggestive of an acute MI. Primarily on the basis of assay characteristics (which are in flux) and statistical considerations, the NACB has recommended a 20% change at 3 to 6 h from the baseline value to be suggestive of an MI that is either evolving (a troponin increase) or resolving (a troponin decrease) (11). However, although using such a change may discriminate acute myocardial injury, it does not discriminate acute injury as a result of ACS from other causes of acute myocardial injury (e.g., pulmonary embolus or myocarditis). Further, the degree of elevation above the reference limit may also provide clues as to the etiology of the infarction (21), and further study will be needed to understand whether the same degree of change is relevant at low levels of baseline troponin elevation as at higher levels.

With the high analytical and clinical specificity of cardiac troponin assays and the pragmatic need for early management decisions, clinicians commonly diagnose acute MI on the basis of a single abnormal troponin value, especially those derived from highly sensitive troponin assays. Although in certain circumstances (e.g., a patient presents with their last chest pain >24 h prior, or for patients who present with moderate to high pre-test probability of MI), a single troponin may be sufficient. This is especially the case when the timing of symptoms is uncertain or in the setting of low pre-test probability for ACS. Relying on a single troponin value should be avoided in favor of serial testing as recommended by the 2012 ESC/ACCF/AHA/WHF consensus document (13). Of course, treatment for clear ST-segment elevation MI based on clinical and ECG criteria should not be delayed for troponin testing or the results of even a single test.

In summary, the major challenge of troponin testing in clinical practice, as for any other laboratory test, is often an inappropriate request and improper interpretation of the results, not the marker itself. Troponin evaluation should be performed only if clinically indicated, and elevated troponin must always be interpreted in the context of the clinical

Table 1. Semiquantitative Summary of Positive and Negative Predictive Accuracies of Troponin Testing in Various Scenarios

Typical Anginal Symptoms	Ischemic ECG or Echocardiogram Findings	History of Risk Factors for Coronary Artery Disease	Pre-Test Likelihood of Acute Myocardial Ischemia	Cardiac Troponin	Predictive Value for Acute Myocardial Infarction	Diagnostic Evaluation for Nonthrombotic Etiology	Prognostic Information
Yes	Yes	Yes	High (>80%)	Positive	High PPV	No	Yes
				Negative	High NPV	No	Yes
No	No	No	Low (<10%)	Positive	Low PPV	Yes	Yes
				Negative	High NPV	No	Yes

ECG = electrocardiogram; NPV = negative predictive value; PPV = positive predictive value.

presentation. Only by doing so will troponin evaluation allow for optimal interpretation, diagnosis, risk stratification, and patient management.

3. Troponins in Acute Coronary Syndromes

In addition to providing diagnostic information, troponin elevation in the setting of a clinical presentation with ACS is independently associated with worse clinical outcomes (6,9), irrespective of the result of CK-MB testing (22,23). The yield of serial testing, both diagnostically and prognostically, in this setting is small beyond 8 h (24). In ACS, cardiac troponins also offer clinicians a valuable tool for therapeutic decision making. The underlying rationale, or so-called "troponin hypothesis," is predicated on observations that ACS patients who are troponin-positive are more likely than troponin-negative patients to have more complex lesions with greater thrombus burden, a greater propensity for platelet embolization and distal microvascular obstruction that will lead to impaired epicardial coronary and myocardial tissue perfusion, as well as depressed left ventricular (LV) function (25–27). Treatment strategies such as intravenous glycoprotein (GP) IIb/IIIa inhibitors (abciximab, tirofiban, and lamifiban) (8,26,28,29), the low-molecular-weight heparins (enoxaparin and dalteparin) (30,31), and an early invasive strategy (27,32) appeared to be more beneficial in troponin-positive patients than in troponin-negative patients. However, when the troponin hypothesis was examined prospectively in the GUSTO IV (Global Use of Strategies to Open Occluded Coronary Arteries) trial—assessing whether benefit from upfront initiation and sustained treatment with abciximab was limited to troponin-positive patients—treatment with abciximab offered no benefit in patients with elevated levels of troponin undergoing primarily conservative medical management (33). Furthermore, in contrast to low-molecular-weight heparins and GP IIb/IIIa inhibitors, the benefit of treatment with clopidogrel was not shown to differ among patients with and without elevated troponin in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial (34). Thus, the troponin hypothesis may not be applicable in the setting of all therapeutic interventions for ACS.

Similarly, randomized trials evaluating early versus selective invasive strategy in ACS have yielded inconsistent results. The results from the ICTUS (Invasive versus Conservative Treatment in Unstable Coronary Syndromes) trial, which only enrolled patients with elevated troponins, showed no apparent treatment advantage for the early invasive strategy, but also no harm, and may have been limited by selecting only on troponin status and entering lower global risk patients (35). Disparate responses to an invasive strategy in patients with elevated troponin levels across trials (harm in Vanquish [Veterans Affairs Non–Q-Wave Infarction Strategies In-Hospital], neutral effect in ICTUS, and benefit in FRISC II [Fragmin and Fast Revascularisation during Instability in Coronary artery disease], TACTICS–TIMI 18 [Treat Angina with aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18], and VINO [Value of First Day Angiography/Angioplasty in Evolving Non–ST-Segment Elevation Myocardial Infarction] trials) highlight the limitations of cardiac biomarkers used as a dichotomous variable as a single risk index. However, in aggregate, meta-analyses have demonstrated benefit from an early invasive strategy among troponin-positive patients (36,37). Still, additional risk stratification beyond troponin alone may help to refine populations that benefit. In retrospective analysis of the FRISC II data (38), there was a 40% relative risk reduction in death or MI only in patients with both troponin T >0.03 ng/ml and ST-segment depression on admission ECG, whereas participants with only 1 of these variables had no benefit. In the RITA-3 [Third Randomised Intervention Treatment of Angina] trial, 9 factors besides the treatment group emerged as multivariate predictors of outcomes at 5 years (39). Patients derived the greatest benefit from an early invasive strategy in the highest quartile of risk score based on these predictor variables. These observations underscore the importance of global risk assessment rather than using any single risk marker for therapeutic triage. The 2011 focused update on Unstable Angina/Non–ST-Elevation Myocardial Infarction guidelines reflected these findings by recommending the early invasive strategy as Class I, Level of Evidence: A in patients identified to be at high risk, based on a "combination" (not "any 1") of several risk variables, including elevated troponin (18).

Ideally, refinement of the use the troponin testing should ensure that it is an important element of global risk assessment in a clinically driven management algorithm. One such algorithm is shown in Figure 4. Patients with elevated troponin and a high pre-test probability of ACS (based on presenting symptoms, risk factors, history of CAD, ECG, or wall motion changes) are most likely to derive benefit from a treatment strategy aimed at coronary thrombosis (e.g., aggressive antiplatelet therapy, coronary angiography, and revascularization). Patients, then, could be further stratified based on the risk characteristics into those likely to benefit from an early invasive strategy (for high-risk characteristics) or early conservative strategy (for low-risk characteristics). Patients with elevated troponin and a low pre-test probability of ACS are unlikely to derive a large incremental benefit from aggressive treatment strategy. In such patients, the main goal would be to identify the underlying cause of the troponin elevation—conditions such as myocarditis, pericarditis, cardiac contusion, sepsis, pulmonary embolism (PE), and heart failure. Therapy in these circumstances should target the underlying cause. Treatment in patients without troponin elevation, but with a high pre-test probability of ACS, should be directed by identification of other markers of risk. Those with high-risk features should be considered for early invasive manage-

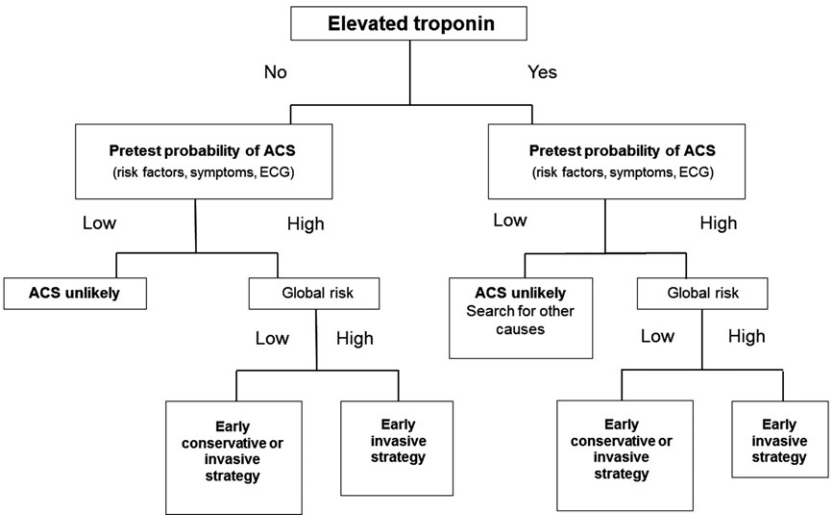

Figure 4. Proposed Algorithm for Troponin in Therapeutic Decision Making

Global risk should be estimated via formal clinical risk scores (TIMI, GRACE, or PURSUIT) or a combination of the following high-risk features: recurrent angina/ischemia at rest or low-level activity, heart failure or worsening mitral regurgitation, high-risk stress test, hemodynamic instability, sustained ventricular tachycardia, diabetes mellitus, PCI within 6 months, prior CABG or LV ejection fraction <0.40. ACS = acute coronary syndromes; CABG = coronary artery bypass grafting; ECG = electrocardiogram; LV = left ventricular; PCI = percutaneous coronary intervention.

ment, whereas those with low-risk features could be managed with either an invasive strategy or conservative strategy that is dictated by clinical course and functional testing and depends on clinical judgment of the individual patient circumstances.

In summary, the troponin test should be integrated with assessment of other clinical factors that influence diagnosis and prognosis to provide a foundation for selection of the most clinically appropriate treatment strategy in patients with ACS without ST-segment elevation. Global risk assessment rather than any single risk marker should be the main driver of therapeutic decision making.

3.1. Impact of Improved Sensitivity Troponin Assays

Previously, the commercially available troponin assays used in clinical practice lacked the stringent precision (10% coefficient of variation at the 99th percentile cutoff) advocated by the universal definition of MI (11). However, so-called high-sensitivity (or ultrasensitive) assays have been developed that meet these requirements. Several studies have reported enhanced diagnostic and prognostic accuracy of these high-sensitivity troponin assays across a spectrum of patients with cardiovascular disease, including ACS (40,41), heart failure (42), and chronic stable CAD without LV systolic dysfunction (43). In comparison with standard assays, the high-sensitivity assays used in the studies by Reichlin and Keller (44) showed remarkably increased sensitivity and increased early detection of myocardial necrosis, but this was associated with decreased specificity. The discrimination from the reference population was favorable, and overall diagnostic accuracy was driven by the increased sensitivity. If, as in previous studies, the prognostic value of small elevations of troponin remains, we may soon use them in new ways. Rapidly repeated determinations may accelerate triage, especially in the emergency department. Also, the ability to detect incremental changes at levels below those previously detectable may lead to identification of patients with ischemic events who previously would have gone unrecognized and for whom additional testing for diagnostic clarification, risk stratification, or treatment may be indicated. Extending the range of detection may also lead to the use of continuous elevations instead of cutpoints in risk models.

However, the utility of high-sensitivity troponin testing for rapid triage or incremental identification of ACS patients with previously subclinical ischemic events may be limited by delays in patient awareness and travel to acute care facilities (45) as well as influenced by the pre-test likelihood of ACS (19). In addition, it is unclear what the prognostic or therapeutic implications of these increasingly sensitive and precise assays will be in general clinical use. Cohort studies show that as the definition of MI includes lower-risk patients, the number of outcome events decreases (46), and the case fatality rate decreases for the same diagnosis, thus creating an "era" effect (i.e., confounding by year of testing) (47). Still, for patients with detectable troponin levels and a clinical presentation consistent with moderate- to high-risk ACS, even if early intervention with antithrombotic therapy or an invasive assessment is not clearly indicated, it may identify a referral group for stress testing or other noninvasive means for further risk assessment.

Routine detection of troponin levels using high-sensitivity assays that yield a continuous gradient in apparently normal subjects may make it difficult to differentiate myocardial necrosis related to plaque rupture in ACS patients (those who might benefit from aggressive treatment

strategies) from necrosis in non-ACS patients. As an example, Venge et al. (48) detected troponin I in 95% of a normal healthy reference population with values that overlapped those in a random subsample of ACS patients in the GUSTO IV trial. Although cardiac events were significantly more frequent in the GUSTO IV patients, the discrimination was affected by case mix. Other studies suggest that low-level troponin elevations will be commonly detected by high-sensitivity assays, particularly in populations with stable coronary disease and heart failure; therefore, this finding reflects a shift, as assays become more sensitive, from detecting acute illness to identifying underlying chronic illness. In the Val-Heft (Valsartan Heart Failure) trial on heart failure and the PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) trial on chronic coronary disease, nearly all patients had detectable troponin by high-sensitivity assays, which were associated with subsequent risk of mortality and heart failure (43,49). Such widespread low levels of detectable troponin in populations with these assays will make it challenging to interpret low-level troponin elevations. However, these same features may open an era of population screening for subclinical disease and monitoring for disease tempo. In 1 population random sample, troponin T was detectable by high-sensitivity troponin T assay in 25% of the cohort, including 16% of the cohort after restricting to those without known chronic illnesses (such as diabetes, chronic kidney disease [CKD], hypertension, or coronary disease) (50). These levels correlated with the measures of subclinical cardiovascular disease, including high coronary calcium scores and greater LV mass adjusted for body surface area.

In another population study of community-dwelling individuals over age 65 years who had no prior documented heart failure, 66% of subjects had detectable troponin levels by high-sensitivity troponin T assay, which were strongly associated with subsequent death or heart failure events (51). Furthermore, changes in troponin levels correlated with changes in risk, such that those with initially detectable troponin whose levels increased by >50% on subsequent testing had increased risk. However, those whose levels fell >50% on serial testing had a reduction in risk in comparison with those patients with >50% change. These results suggest a potential role for high sensitivity in monitoring treatment response and will potentially usher in a new era of directed therapy. In addition, high-sensitivity troponin may have a role as part of a biomarker score for population screening as suggested by the MORGAM (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease [MONICA], Risk, Genetics, Archiving, and Monograph) biomarker project—where a combination of high-sensitivity troponin I, N-terminal pro-brain natriuretic peptide (NT-proBNP), and high-sensitivity C-reactive protein contributed significantly to clinical features in stratifying risk for long-term cardiovascular events (52).

Prospective studies are needed to determine the clinical effect of using new high-sensitivity assays, both in respect to their relationships with outcomes in population screening and for patients with suspected ACS and chronic disease populations, as well as in regard to risk–benefit tradeoffs for treatment or additional testing in such populations.

4. Non-ACS Ischemic Troponin Elevations

The 2007 Joint ESC/ACCF/AHA/WHF consensus document on "Universal Definition of Myocardial Infarction" defined Type 2 MI as myocardial necrosis secondary to ischemia from either "increased oxygen demand or decreased supply" (12). This designation has been maintained in the 2012 version of the universal definition of MI document (13). How frequently Type 2 MI occurs is unclear, in part because of reporting variability. There are only a few cohort studies (all retrospective) that have attempted to quantify the incidence of non-ACS causes of ischemia-mediated troponin elevations. In the largest series to date, 1.6% of 1,093 patients had Type 2 MI when the 2007 Joint ESC/ACCF/AHA/WHF criteria were applied (53). The reported causes for non-ACS ischemic troponin elevations vary by study and include paroxysmal atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, hypoxia, severe anemia, or gastrointestinal hemorrhage (20,53,54). All of these studies suffered from inadequate characterization for the rate of underlying CAD in the population studied, without which it is difficult to estimate the true frequency of Type 2 MI.

Many non-ACS, demand-mediated ischemic conditions may cause increased troponin levels (see Fig. 1 for examples). Case reports and case series tend to focus on patients with elevated troponin and normal coronary arteries, but it is important to understand that these non-ACS ischemia-mediated conditions may also unmask underlying CAD. For example, though cocaine is thought to elevate troponin acutely from a combination of coronary spasm and sympathomimetic effects, it also accelerates the development of epicardial CAD. Coronary arteriograms in these patients have revealed that approximately 80% of such patients have significant underlying CAD (55,56). Two studies have investigated causes of troponin elevations in patients with normal coronary arteriograms. In a study of 144 patients, non-ACS ischemic causes of elevated troponins included 35 patients (24%) with tachyarrhythmia, 2 (1.4%) with LV hypertrophy, 1 (0.7%) with malignant hypertension, 2 (1.4%) with coronary vasospasm, and 9 (7%) with gastrointestinal bleeding (57). In another study of 21 patients, causes of elevated troponin were tachycardia in 6 patients (28.5%) and extreme physical exertion in 2 patients (9.5%) (58).

In summary, there is insufficient evidence to provide strict guidelines as to how to differentiate between ACS and non-ACS ischemia-induced troponin elevations without taking into account the clinical presentation. Though dis-

ruption of epicardial blood supply from emboli or coronary spasm can result in ischemic ECG changes and serial troponin changes indistinguishable from an MI caused by plaque rupture, the other causes of non-ACS ischemic troponin elevations may result in a more subtle increase with less change evident on serial determinations. When deciding whether or not to further investigate the possibility of CED in these patients, it is necessary to make an assessment of pre-test probability that the troponin elevation is due to underlying CAD versus one of the many non-ACS causes of troponin elevations.

5. Troponins in PCI and CABG

In this section, we review and define the current status of troponin assays for detection of periprocedural myonecrosis and clinical MI. In this context, "procedures" refers to both PCI and cardiac surgery procedures, primarily CABG. The ESC/ACCF/AHA/WHF Task Force for Redefinition of MI have reviewed and revised the universal definition of MI (13). Our discussion of post-revascularization troponin adheres to these newly established and widely adopted definitions and is confined to Type 4a and Type 5 MI, which are relevant to PCI and CABG, respectively.

The occurrence and adverse consequences of periprocedural MI for both PCI and CABG are well known. Early assessments depended predominantly upon a combination of clinical observations, ECG changes, and cardiac biomarkers such as total CK. With development of the relatively myocardium-specific marker CK-MB and troponins, detection became more accurate and precise. However, what level of biomarker elevation reflects "clinically significant injury" and whether this laboratory threshold is related to immediate adverse outcomes or delayed adverse events remains uncertain.

5.1. Biomarkers With PCI Procedures

Several studies have linked post-PCI CK or CK-MB elevation in the 3× to 8× upper limit number (ULN) range to increased mortality (59–61). The 2011 update of the PCI guidelines noted that more frequent requirements for revascularization procedures and a higher risk of death or subsequent MI were associated with elevated cardiac biomarkers (62). These guidelines recommended that for patients in whom a clinically driven CK-MB determination was made—a CK-MB increase of >3× ULN should be treated as signifying an MI—and provided a Class IIb recommendation that post-PCI enzymes levels be measured in all patients. It is recognized that the threshold specified in the PCI guidelines may change in accordance with the recently published 2012 update to the Universal Definition of MI that now specifies a >5× ULN troponin elevation and clinical evidence of MI to define a PCI-related MI (13). There were no recommendations for further workup of smaller elevations in an otherwise asymptomatic patient.

Several studies have examined the relevance of PCI-related troponin elevations (63–68). The results and conclusions of these studies, like the CK-MB data that preceded them, have been inconsistent secondary to small sample sizes, different elevation thresholds, and varying analytic techniques. Two meta-analyses, one using older and less sensitive troponin assays (68) and the other using a newer generation with more sensitive assays (based on the 99th percentile criteria) (65), concluded that post-procedure troponin elevations were associated with adverse outcomes, including long-term death or MI. Troponin elevations might have particularly important prognostic implications in circumstances where intraprocedural complications have occurred and result in angiographic evidence of flow impairment (e.g., side branch closure, transient decreased TIMI flow grade, or embolization).

A report from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial suggested that spontaneous MI (i.e., clinical ischemic events unrelated to a procedure, not including periprocedural MI) was significantly associated with subsequent mortality (66). Consistent with these observations, a consecutive cohort study at a single institution of 2,352 patients with pre- and post-PCI biomarkers for elective or urgent PCI found that long-term prognosis was most closely related to the baseline, pre-procedure troponin value rather than the post-PCI value (69). Post-procedure cardiac troponin T values did not contribute to the prediction of death or MI when added to the pre-procedure risk estimates. Of particular importance was that this report used the fourth-generation troponin T assay, an important difference from earlier reports in which earlier generation, less sensitive assays were used. Similar findings were also reported in a single-center cohort study of 5,847 consecutive patients treated with nonemergency PCI and who were assayed with a third-generation troponin T assay (70). However, in another study of ACS patients, elevated troponin I levels post-PCI remained prognostically significant even after adjusting for pre-procedure troponin elevation (63). Thus, although some studies suggest that periprocedural MI may be more related to baseline risk, atherosclerotic burden, and procedural complexity, without being an independent mortality prognosticator, it is premature to exclude the prognostic importance of detecting post-PCI troponin elevations.

A particular challenge with these studies is that they examine only relative increases above the ULN. This is particularly problematic with the very low ULNs of newer generation troponin assays with which even a 5× elevation may still be a very low absolute troponin level. Considering this and conflicting results from prior studies, the examination of the relationships for PCI-related troponin elevation with outcomes may be best assessed using absolute elevations, and further study is needed to understand whether there is a threshold effect. Although there is general consensus that large troponin elevations are associated with negative prognostic implications, it is less clear what con-

stitutes a large elevation and whether the negative prognosis is limited to in-hospital, is short term, or persists long term (67,69,71). As evidence of these uncertainties, the current ESC guidelines for PCI do not recommend the use of troponins after elective PCI (72). Further studies are required to resolve these uncertainties.

Recent data from the National Cardiovascular Data Registry (NCDR) show that most institutions do not routinely check troponins post-procedure. Whether this is a response to the lack of scientific consensus or to other factors is unknown. Regardless, NCDR data suggest that institutions that routinely perform and report troponin values appear to have higher post-procedure MI rates than those that do not. This disparity may be due to reporting imbalances as opposed to an actual difference in outcomes. In the absence of clear data indicating the proper clinical threshold to diagnose a MI, most troponin elevations are coded as MI. Thus, institutions that voluntarily check and report their values may be placing themselves in a disadvantaged position relative to those that do not. Although it is premature to use such data as a PCI performance measure, systematic collection of post-procedure troponin data within the NCDR may, nevertheless, be considered appropriate to determine true rates and outcomes of periprocedural troponin elevations and to create a robust dataset that will fill an important knowledge gap and facilitate the establishment of evidence-based periprocedural management.

In summary, in the era of less sensitive biomarkers, 20% of patients who had an angiographically uncomplicated PCI experienced periprocedural enzyme elevations (73). The development of newer and more sensitive troponin assays has increased the ability to detect myonecrosis so that as many as 33% of patients undergoing elective PCI have elevated troponin post-procedure, but it has created confusion as to the clinical relevance of such findings following coronary procedures. At this juncture, there are data to support the concept that detection of troponin elevations post-procedure may be associated with an increase in long-term adverse events, particularly if the pre-procedure troponin is normal or falling. The updated PCI guidelines provide a Class I, Level of Evidence: C recommendation for performing post-procedure biomarker assays (including troponin testing) when an intraprocedural angiographic complication is identified or a patient has signs or symptoms suggestive of MI during or after PCI, and give a Class IIb recommendation for post-PCI testing in all patients (62). The 2012 revision of the universal definition of MI now recommends that the threshold for defining PCI-related MI (Type 4a) in patients with a normal pre-procedure troponin level should be a troponin elevation within 48 h post-procedure of >5× ULN with either symptoms of myocardial ischemia, new ischemic ECG changes, or documented complications during the procedure (13). If elevated pre-procedure levels are stable or falling, a >20% rise above the pre-procedure level with concurrent clinical criteria is necessary to define Type 4a MI. The NACB recommended testing with the caveat that insufficient data exist to propose a specific cutoff (71). This writing group supports these recommendations for testing and defining PCI-related MI. Further, it supports the NCDR effort to obtain routine periprocedure troponin measurements in all PCI patients to establish a database from which critical questions about the utility of troponin testing peri-PCI can be evaluated. We also encourage simultaneous collection of analytical parameters of the assays used to establish a robust database from which information about true rates of elevation, relevant diagnostic thresholds, and prognostic implications—in the context of data on other clinical factors that influence prognosis—can be established. Finally, all PCI patients should receive guidelines-recommended secondary prevention, and immediate clinical care should consider the patient's overall clinical status in addition to any biomarker testing results.

5.2. Biomarkers With CABG Procedures

Because of sensitivity and lack of etiological specificity for the cause of myonecrosis, use of troponin to define perioperative MI in CABG patients is challenging. Based on data from studies using older generation assays, the NACB guidelines recommend that troponin elevation must exceed at least 5× ULN to define clinically relevant post-operative MI, with higher values associated with worse outcomes (71). However, given the variability in biomarker responses to surgery, the NACB advises that additional criteria over and above marker results are needed to define a CABG-related coronary vascular event (71). Most recently, recognizing that the threshold selection is arbitrary, the 2012 universal definition of MI document recommends that CABG-related MI be defined as a troponin elevation of >10× ULN when there is corresponding ECG (new Q waves), angiographic (occluded graft or newly occluded native vessel) or imaging (new loss of viable myocardium) evidence of MI (13). In the evolving era of highly sensitive troponin assays, no cutoff for clinically relevant post-operative MI has been defined or prospectively studied.

6. Troponins in Nonischemic Clinical Conditions

Nonischemic conditions often present with chest pain or other symptoms that create diagnostic uncertainty for the treating physician. Therefore, troponin may be ordered early in the assessment of the patient as part of the diagnostic evaluation for these conditions. Serum concentrations of cardiac troponins have been detected in many disease entities, aside from coronary and other primary cardiac conditions (71,74–77). In some cases, the mechanism of cardiac involvement is obvious (e.g., hypoxemia and secondary subendocardial ischemia from right ventricular (RV) pressure overload following a PE. In others, however, troponin release appears to represent a nonspecific "vital organ" response to systemic illness. As with any other test,

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troponin levels are only of value in nonischemic conditions when they contribute to accurate diagnosis or inform prognosis—and when such will affect treatment or clinical outcome.

Using troponin levels to estimate survival, patient appropriateness for aggressive therapy, identification of patients at risk for therapy-induced disease, and/or determination of need for prolonged inpatient monitoring have been reasonably well supported for some conditions: heart failure, PE, CKD, sepsis syndrome, chemotherapy-induced cardiomyopathy, amyloid light chain ("primary") amyloidosis, and post-cardiac transplantation monitoring, as well as following noncardiac surgery, thermal injury, and blunt cardiac trauma. Fewer data have been published on other conditions; however, enough are available to suggest that further investigation might identify value in troponin monitoring: toxins/envenomation, endocarditis, severe metabolic conditions, decompensated chronic lung disease, primary hematologic conditions, stress/catecholamine-associated myocardial dysfunction, and subarachnoid hemorrhage.

The remainder of this section will focus on 4 conditions in which a potential clinically useful role for troponin testing exists and/or for which there is substantial confusion in interpretation of clinical practice (heart failure, PE, CKD, and sepsis). Discussion of other conditions for which troponin has a potential clinical role is available in Appendix 3. In general, until further data are available on how troponin testing may clearly change patient management, unless specifically stated, it is not recommended to measure troponin levels specifically for diagnosis or prognosis in the conditions discussed in this section or Appendix 3. It is important to point out that this document, in this section and in Appendix 3, reflects prevalences and associations with outcomes that were determined with a variety of assays over several years. Many studies used troponin cutoff values other than the 99th percentile, which is currently recommended, and many used insensitive assays or older assays that were much less sensitive than current generation assays. Therefore, prevalences and strengths of association across studies may vary due to variation in these parameters and may not reflect results that would be obtained with modern assays or in the future with high-sensitivity assays.

6.1. Nonischemic Conditions With a Current or Potential Clinical Role for Troponin Measurement

6.1.1. Heart Failure

In both inpatient and outpatient heart failure populations, elevated troponin levels are common and associated with worse outcomes (Table 2). Rates and strengths of association with outcome vary widely depending on the troponin assay, assay generation, and cutoff used. These differences across studies create challenges in interpretation and generalization and will become an increasing challenge in heart failure, as seen with MI, since troponin assays continue to evolve and until there is adequate standardization across assays. In the large, multicenter ADHERE (Acute Decompensated Heart Failure Registry) National database, 81% of patients admitted with heart failure had troponin testing, and nearly 6.2% of patients had abnormal troponin test results (troponin I $\geq$1.0 μg/l or troponin T $\geq$0.1 μg/l) after excluding patients with serum creatinine $>$2.0 mg/dl (78). Hospital mortality among troponin-positive patients was 8.0%, compared with 2.7% among troponin-negative patients (adjusted odds ratio [OR]: 2.55) and was independent of an etiology of heart failure (ischemic or nonischemic). However, when a lower troponin I threshold is used (troponin I $\geq$0.4 μg/l or troponin T $\geq$0.01 μg/l), 75% of patients have detectable levels of troponin.

The key questions regarding troponins and heart failure are as follows: 1) in the evaluation and management of heart failure patients, how should troponin testing be used, if at

Table 2. Adverse Outcomes Among Heart Failure Patients With Elevated Troponin Levels

Study	Total Patients	Troponin Type	% With Elevated Troponin	Endpoint	Relative Risk
Inpatient					
Setsuta (79)	56	T	54%	Death, heart failure admit	7.0
La Vecchia (80)	34	I	29%	Death	6.9
Ishii (81)	100	T	35%	Cardiac death, heart failure admit	3.1
Taniguchi	71	T	28%	Heart failure death, heart failure admit	~3.0*
Perna 2005 (82)	184	T	32%	Death, heart failure admit	1.7
Ilva (83)	364	T	30%	Death	2.6†
Ilva (83)	364	I	51%	Death	2.0†
Outpatient					
Horwich (84)	238	I	49%	Death	1.85
Miller (85)	150	T (serial)	27%, all values elevated	Death, transplant	3.77
Sato (86)	60	T (serial)	28%, all values elevated	Cardiac death or hospital admit	7.6
Perna 2004 (87)	115	T (serial)	46%, ≥1 value elevated	Death or hospital admit	1.09
Hudson (88)	136	T	24%	Death	4.2
Lantini (42)	4,053	T	10%	Death	2.08

*Estimated from text figures. †Univariate risk; not significant in multivariate model.

all; and 2) how should clinicians respond to elevated troponin levels found in such patients? First, elevated troponin values have prognostic value in estimating future risks of death or hospitalization for heart failure patients with or without preserved ejection fractions. However, although elevated troponins have *prognostic* value in heart failure, they are poor *diagnostic* markers for an ischemic versus nonischemic etiology of heart failure or heart failure progression. For these reasons, the NACB's practice guideline on cardiac biomarker testing in heart failure gives only a Class IIb recommendation to use of troponins for risk stratification "beyond the setting of acute coronary syndromes." In addition, the guideline specifically recommends against "routine biomarker testing for the *sole* purpose of risk stratification in patients with heart failure" (89) (p. e103).

Nevertheless, it is sometimes difficult to know after initial evaluation whether patients presenting with heart failure, particularly acute decompensated heart failure with an elevated troponin test, do so as a result of unstable coronary ischemia. The 2012 universal definition of MI document cautions that troponin elevation alone is not sufficient to establish the diagnosis of MI or type of infarction or etiology of troponin elevation in heart failure (13). Thus, for patients with known coronary disease and heart failure who were previously stable or for patients with new-onset heart failure who present with an elevated troponin level, it may be useful to further evaluate for evidence of obstructive coronary disease or acute plaque rupture with functional testing or coronary angiography. For an excellent summary of the current state of troponin testing heart failure and future directions to be explored and solidified in incorporating troponin testing into heart failure management, the reader is referred to an overview published by Kociol et al. (90).

6.1.2. Pulmonary Embolism

In a 2007 meta-analysis of the prognostic value of cardiac troponins in 20 studies of acute PE (91), the rate of elevated troponin levels ranged from 10% to 77% (median 39%). Overall, elevated troponin levels were associated with short-term (up to 30 days) all-cause mortality (OR: 5.24 [95% confidence interval (CI): 3.28 to 8.38]), with similar associations for troponin I and troponin T. Of 8 studies reporting specifically on death due to PE, elevated troponin levels were highly associated with fatal PE, OR: 9.44 (95% CI: 4.14 to 21.49; $p < 0.00001$). Elevated troponin levels were also associated with nonfatal complications of PE during hospitalization, OR: 7.03 (95% CI: 2.42 to 20.43; $p = 0.0003$). A subsequent update of this meta-analysis with 5 additional studies revealed similar associations (92). Cardiac troponin elevation in PE is believed to result from pulmonary vascular obstruction and vasoconstriction that causes a sudden increase in pulmonary vascular resistance, pulmonary artery pressure, and RV afterload. RV dysfunction itself is associated with increased mortality in PE patients (93–101), and troponin elevation may be an early and reliable marker for RV dysfunction (102,103). Indeed troponin is more likely to be elevated in those with echocardiographically identified RV dysfunction (104–110). However, an elevated troponin can occur in patients without RV dysfunction. Unlike echocardiography, troponin testing is readily, cheaply, and rapidly available 24 h a day. Therefore, it might be a useful tool to identify patients with PE at higher risk of mortality and who may benefit from more aggressive treatment.

However, despite the strong associations of troponin elevation in PE with important clinical outcomes, how to respond to this prognostic information is presently unclear, and routine testing in suspected or confirmed PE is not indicated. Patients with massive PE and hemodynamic instability benefit from thrombolytic therapy, if not contraindicated, regardless of troponin elevation. Those with a relatively small PE and no RV dysfunction typically have an uncomplicated course (111,112). When RV dysfunction is present and the patient is normotensive, some advocate consideration of thrombolytic therapy (113–115), whereas others do not (116–121). Additionally, some authors would advocate surgical pulmonary embolectomy if the thrombus were centrally located (122,123). The answer to this important therapeutic question awaits the results of a large randomized trial. For now, it is clear that elevated troponin levels are not uncommon in patients with PE, and they are associated with RV dysfunction and adverse outcomes, including death. Troponin testing has no current role in the diagnosis of PE, but in the absence of hemodynamic instability, it appears to have excellent negative predictive value (NPV) for in-hospital deaths ranging from 82% to 100% (92,102,103,109,112,124). Such patients are very unlikely to benefit from aggressive treatment such as thrombolysis.

6.1.3. Chronic Kidney Disease

Although still somewhat controversial, elevated troponin levels in patients with reduced renal function (those with end-stage renal disease [ESRD] and on dialysis or those with moderate to severe renal impairment and residual renal function) are most likely not caused solely by decreased renal clearance (76,125,126). Intact troponins are large molecules; therefore, it is improbable that the kidneys are primarily responsible for their clearance from the serum. Although there are some data to suggest that residual renal function can affect troponin levels (127–129), other studies have not found this association (130–132). Diris et al. (133) have demonstrated that troponin T molecules are degraded into smaller fragments that are detected by assays and are small enough to be filtered by the kidney. These fragments might partially account for elevations of troponin T so often seen in patients with ESRD. On the other hand, elimination and half-life of troponin I after MI appears to be similar in those with normal renal function and ESRD (134).

Despite absence of a single unifying pathophysiological explanation for troponin elevation in patients with impaired renal function, the relationship with clinical outcomes is clear. In a 2005 meta-analysis (135), the rate of troponin T

positivity ranged from 12% to 66%, and 0.4% to 38% for troponin I. Elevated troponin T was significantly associated with all-cause mortality with a relative risk of 2.64 (95% CI: 2.17 to 3.20). A significant association was also demonstrated with cardiac death, with a relative risk of 2.55 (95% CI: 1.93 to 3.37). Eight subsequent studies corroborated the relationship of troponin T elevation in CKD patients with varying degrees of severity (moderate to severe impairment with residual function to ESRD on dialysis) with all-cause mortality (127,128,136–141). Because of the different assays and cutoffs, pooling of the 12 studies using troponin I was problematic; however, there was an association between elevated troponin I and all-cause mortality, relative risk 1.74 (95% CI: 1.27 to 2.38).

The NACB Laboratory Medicine Practice Guidelines (71) recommend the use of troponin for diagnosis of MI in all CKD patients (regardless of the severity of renal impairment) who have symptoms or electrocardiographic evidence of myocardial ischemia. The guidelines also advise relying on dynamic changes in troponin values of ≥20% in the 6 to 9 h after presentation to define acute MI in ESRD patients, who more frequently have chronically elevated troponin levels. The guidelines also state that troponins can be aids to risk stratification in ESRD patients and provide baseline values for comparison when there is an acute clinical change. On the basis of the relationship between troponin T levels and mortality in patients with severe renal impairment and ESRD on dialysis, the Food and Drug Administration has approved the use of troponin T for identifying CKD patients at high mortality risk. The National Kidney Foundation Disease Outcomes Quality Initiative Work Group (142) also recommends that troponin T levels be considered for risk stratification of chronic dialysis patients, but how the information should be used is still unclear. The Work Group also reinforces that the presence of a time-dependent elevation in troponin T or troponin I in the setting of ACS portends increased cardiovascular morbidity and mortality.

6.1.4. Sepsis

Detection of troponin elevations in patients with sepsis, septic shock, and the systemic inflammatory response syndrome is relatively common. The mechanism of troponin release in the absence of flow-limiting epicardial coronary atherosclerosis is uncertain but is felt to be related to the known occurrence of myocardial dysfunction in sepsis, and many possible contributors have been hypothesized and partially investigated (143–145). In a summary of studies published between 1998 and 2008 (146–155), elevated troponin I or troponin T occurred in a median 62% of patients, an interquartile range of 43% to 85%, and most elevations were modest. There was no obvious association between troponin elevation and a prior history of ischemic heart disease. Of the studies that reported outcomes, 5 found a significant association between troponin positivity and death (146,149,152–154). Only 2 studies considered the independent association of troponin with outcome (153,154), and in only 1 was it significant (153). Larger, more homogeneous studies using standardized troponin analysis are needed to clarify the role of troponin in risk stratification of septic patients.

In addition to mortality, troponin elevation in sepsis may also be associated with impaired LV function, which commonly occurs in septic patients (~50% of patients with severe sepsis and septic shock) (143,144). In summation, elevated troponin levels appear to be a potential marker for poor LV function in septic patients. More studies corroborating the association and how this mediates the association with mortality and, specifically, how tailored treatments might modify sepsis-related LV dysfunction and mortality are needed. At present, however, *routine troponin testing in septic patients is not recommended.*

6.1.5. Chemotherapy-Associated Cardiac Toxicity

Expert panels have identified troponin as the preferred biomarker to detect drug-induced cardiac injury (156). The ability of high-dose chemotherapy (including anthracyclines, cyclophosphamide, and perhaps platinum-based agents) to induce both transient (early) and permanent LV systolic dysfunction, diastolic dysfunction, and arrhythmias is well established. Several studies of troponin testing in patients treated with these chemotherapeutic agents revealed findings worth noting: 1) troponin positivity at almost any level, and at almost any time during multicycle chemotherapy regimens, identifies patients with a significantly increased risk of permanent or more severe reduction in LV systolic function (157,158) and/or premature death (159); 2) the magnitude and frequency of troponin elevations correlate with cumulative drug dose, including from earlier courses/regimens (160); 3) following an early chemotherapy-induced reduction in LV ejection fraction (LVEF), patients without elevated troponin tend to show significant or total recovery of LV function over time (157,161); 4) lower-level troponin elevation may be associated primarily with changes in diastolic ventricular performance (162,163); and 5) the NPV of a normal troponin level is very powerful when patients are sufficiently stratified (164). Finally, results from a randomized trial of 473 patients who had an elevated troponin level within 72 h after high-dose chemotherapy suggested that administration of enalapril (2.5 mg daily started 1 month after the last dose of chemotherapy and increased in 3 subsequent steps to 20 mg daily for 1 year of treatment) may dramatically reduce the risk of developing LV dysfunction at 1 year (hazard ratio: 0.015 vs. placebo; no patients in enalapril group vs. 25 patients in the control group developed an absolute decrease in ejection fraction of 10% or more from baseline). These results suggest a role for troponin testing in guiding adjuvant therapy (165). On the basis of these data, troponin appears to be a useful tool in detecting cardiac toxicity and stratifying risk for the severity of ventricular dysfunction. If confirmed in additional, well-done randomized

clinical trials, use of angiotensin-converting enzyme inhibitors may prove useful in preventing cardiotoxic effects of some chemotherapy.

Observational studies limited to children were less likely to document troponin elevations during anthracycline chemotherapy (166) or, when troponin was elevated, found no relation to systolic function (167). Other studies did correlate LV dilation to troponin elevation, at least in the short term (168). A key question in this population, as to whether troponin can predict long-term cardiovascular mortality, remains unanswered.

6.1.6. Assessing Cardiotoxicity in Drug Development

Just as troponin is a marker for anthracycline cardiotoxicity in clinical practice, another area of intense interest in which troponin testing may be of value is monitoring for cardiotoxicity during the early phases of new drug development. Similar advantages of sensitivity and cardiac specificity are of value in this arena just as in clinical care. Similar considerations for population variation, definition of normal levels and relevant incremental changes (particularly with high-sensitivity troponin assays), and the lack of etiological specificity are operative in using troponin as a biomarker of cardiotoxicity in early drug development. The Cardiac Safety Research Consortium produced a white paper on this topic (169).

7. Other Nonischemic Conditions in Which Interpretation Creates Clinical Uncertainty

Troponin elevation has been reported to occur in a number of other nonischemic clinical conditions (170). In some conditions, there is a clear association of troponin elevation with adverse outcomes; in others, the relationship is less clear. In none of these conditions is there yet a clear or potential clinical indication for the use of troponin testing for diagnosis, risk stratification, disease state monitoring, or to tailor treatment. Because myocarditis and myopericarditis may be major contributors to nonischemic elevation of troponin in patients who present for acute evaluation of chest pain, they are discussed in this section. Other nonischemic conditions that may confound interpretation in the clinical setting are discussed briefly in Appendix 4. The literature discussed in this section and in Appendix 4 reflects prevalences and associations with outcomes that were determined with a variety of assays over several years. Many studies used troponin cutoff values other than the 99th percentile, which is currently recommended, and many used less sensitive or older assays that were much less sensitive than current generation assays. Therefore, prevalences and strengths of association across studies may vary due to variation in these parameters and may not reflect results that would be obtained with modern assays or in the future with high-sensitivity assays.

7.1. Infection and Myocarditis

Many infectious and toxic agents have been linked to myocardial inflammation and dysfunction (171,172), but information on serum troponin levels is scant. In the Myocarditis Treatment Trial (173), 34% of patients with biopsy-proven active myocardial inflammation had elevated troponin (>3.1 ng/ml) compared with only 11% with systolic heart failure but negative endomyocardial biopsies (174). Although not linked to prognosis or response to therapy, it was noted that elevated troponin levels were much more common among patients with ≤1 month of heart failure symptoms, suggesting it could have a role in determining the chronicity of individual patients' myocarditis. Additionally, 4.4% of enrolled patients had demonstrable anti-hepatitis C virus antibodies (of those, 30% demonstrated elevated troponin I and 48%, elevated troponin T), which was also possibly consistent with troponin identifying active inflammation and myocyte necrosis (175). Other randomized trials studying treatment for myocarditis/acute cardiomyopathy have not published troponin data from their populations (176).

Human immunodeficiency virus (HIV) may involve the heart in a number of ways. Between 9% to 34% of HIV-positive individuals will have demonstrable cardiac abnormalities. Present estimates suggest that troponin elevation is nonspecific in this population, and it roughly parallels the increased incidence of coronary events associated with HIV complications that impair coronary blood flow (drug-related hypercoagulability, endothelial dysfunction, and vasculitis) (177).

Reviews on Lyme carditis did not identify troponin data linked to diagnosis, treatment, or outcome (178,179). A series of 91 children with dengue hemorrhagic fever or dengue shock syndrome found no patients with troponin T elevation, despite demonstrating that 36% of victims had significant acute reductions in LVEF over the course of the illness (180). Troponin T levels were not statistically different between *Plasmodium falciparum*–infected patients with uncomplicated malaria and those with clinical cardiac involvement (181). Of those 540,824 military personnel who received smallpox vaccinations, 67 developed myopericarditis, and 81.6% of these personnel showed a significant troponin I elevation (mean 14.1 ng/ml), occurring an average of 10 days post-immunization; 96% had fully recovered after 32 weeks, with normalized troponin I levels. Because samples were drawn on only vaccine recipients manifesting symptoms, and with the total recovery rate so high, this study suggested no prognostic value of troponin levels in this setting (182). In 2 small series, snake bites resulted in troponin elevation in 2 of 24 patients (183), but none of another 7 victims showed troponin elevation (184). Reports of other envenomations (e.g., jellyfish and scorpions) have demonstrated troponin elevations in as many as 20% of victims (185). No long-term outcomes have thus far been linked to troponin status in envenomations.

Acute rheumatic fever—always assumed to be a pancarditis based on demonstration of intramyocardial Aschoff bodies—manifests minimal if any troponin abnormalities (186–190). Thus, to date, there appears to be no value in measuring or following troponin in patients with acute rheumatic fever, with or without obvious acute carditis.

7.2. Myopericarditis

Cardiac troponin I elevation has been documented in 22% to 71% of patients with clinical pericarditis; positive levels ranged from 0.5 ng/ml to >50 ng/ml (191,192). One study suggested that troponin I elevation was much more common among patients with idiopathic pericarditis than among those with a demonstrable cause of peri/myocardial inflammation (193). Overall, with follow-up as long as 31 months, in multivariable analyses, troponin I positivity was not predictive of any clinically relevant outcomes (symptom recurrence, hospital readmission, tamponade, constriction, or ventricular dysfunction) (193). Deaths in these studies were too infrequent to determine any relationship with troponin I levels (194), which in turn do not appear to add power to existing risk models (192).

8. Summary and Overview of Recommendations

Most current assays for cardiac troponin are robust with respect to both sensitivity and analytic performance around the lower limits of detectability. With rare exception, these assays are able to selectively detect cardiac troponin to the exclusion of troponin from other tissues. Therefore, the premise moving forward is that the values obtained are in fact accurate and do reflect a release of troponin from myocytes into the systemic circulation. Table 3 summarizes answers to some of the frequent questions regarding the use of troponin in the clinical setting.

The challenge is how to calculate the specificity of troponin elevation for ACS and apply this to clinical decision making. Specificity requires both a clinical definition and an existing "gold standard" as a basis to compare the results of a test. The point of this paper is to provide the framework for clinicians to interpret the results of troponin testing in a useful mechanism-based construct. The first distinction to be made is that elevated troponin in and of itself does not indicate MI; rather, it is a sensitive and specific determinant of myocardial necrosis that is nonspecific relative to the etiology of that necrosis. The current diagnosis of MI is limited to a specific clinical condition in which myocytes are compromised by ischemia (see Fig. 1), whether that is related to acute plaque rupture (Type 1), other ischemic etiologies (Type 2), or regional or global insults related to revascularization procedures (Types 4a and 5) (see Fig. 2). As a further point of distinction, MI is not synonymous with ACS (plaque disruption with thrombosis), since ischemia can occur via a number of other mechanisms, including the most common coronary insufficiency resulting from fixed (stable) lesions and increased demand.

As troponin assays become more sensitive, there will be an increasing number of conditions discovered that result in low-level troponin elevations. It has been shown in population-based studies that with high-sensitivity assays, even a proportion of apparently healthy, normal population distributions will have detectable troponin levels, and a small proportion of apparently healthy individuals will have elevations above the 99th percentile. In that context, there will need to be a renewed reliance on the diagnostic model that was put forward by the World Health Organization in 1979, which required both ECG *as well as* the clinical components and biomarkers of necrosis to make a diagnosis of MI. This concept is addressed in Section 2, where the argument is made that the diagnosis of MI follows a Bayesian model, and as such, an important consideration in

Table 3. Frequently Asked Questions Regarding the Use of Troponin in the Clinical Setting

What does an elevated troponin level mean?

- Elevated troponin is a sensitive and specific indication of cardiac myonecrosis, with troponin release from myocytes into the systemic circulation.
- In and of itself, elevated troponin does not indicate MI (myonecrosis due to ischemia); rather, it is nonspecific relative to the etiology of cardiac myonecrosis.
- Troponin elevation occurs in many nonischemic clinical conditions. As assays become more sensitive, more conditions that result in low-level troponin elevations will be identified.

When should a troponin level be obtained?

- Because it is not specific for MI, troponin evaluation should be performed only if clinically indicated for suspected MI.
- An elevated troponin level must always be interpreted in the context of the clinical presentation and pre-test likelihood that it represents MI.
- Troponin is recommended for diagnosis of MI in CKD patients with symptoms of MI (regardless of the severity of renal impairment). Dynamic changes in troponin values of ≥20% over 6 to 9 h should be used to define acute MI in ESRD patients.
- In the absence of specific interventions based on the results, routine troponin testing is not recommended for nonischemic clinical conditions except:
  - FDA-approved troponin testing for prognosis in CKD patients.
  - Treatment of patients undergoing chemotherapy who have drug-induced cardiac injury.

What is the prognostic significance of an elevated troponin level?

- Troponin elevation imparts a worse prognosis, irrespective of the underlying etiology.
- For patients with non-ST-segment elevation ACS, global risk assessment rather than any single risk marker, best informs prognosis and is preferred to guide therapeutic decisions.

ACS = acute coronary syndrome; CKD = chronic kidney disease; ESRD = end-stage renal disease; FDA = Food and Drug Administration; MI = myocardial infarction.

using these tests should be a pre-test probability assessment that will influence the post-test interpretation of the result. That model is best developed for the acute coronary syndromes, including MI.

Even when troponin elevation is not thought to be diagnostic for MI, there remains an imperative to determine the true etiology because in most cases, the result will provide some prognostic information. Because for most etiologies, little is known about specifically what to do clinically to manage patients in these settings, routine testing is not indicated.

From a clinician's perspective, the first priority is to understand when (and why) to order (or not order) a troponin test. The best value of troponin testing remains in the diagnosis of MI. Therefore, in the setting of symptoms suggestive of ischemia and a nondiagnostic ECG, serial troponin testing is invaluable and has high sensitivity and specificity (see discussion of Bayes' Theorem in Section 2.2), especially when temporal changes in troponin level are considered. Even in the setting of MI, it is important to understand the clinical context as treatment may vary considerably (e.g., between Type 1 and Type 2 MI). Therefore, it is crucial that the correct assignment is made according to the 2012 Universal Definition of Myocardial Infarction (13) and that the patient is treated accordingly.

It must be remembered that the sensitivity and specificity of troponin are for myocardial necrosis and not for infarction. Therefore, it is incumbent upon the clinician to attempt to ascertain the reason for an elevation as in most cases it provides important prognostic information and, in some cases, will guide therapy. Myocardial necrosis is a laboratory diagnosis that does not imply an etiology, whereas MI is a clinical diagnosis. As troponin assays become increasingly sensitive, understanding the clinical scenario will become increasingly important in deciding who to test, and integration of clinical data along with laboratory data will become even more crucial to the diagnosis resulting from testing.

ACCF Staff List

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Key Words: ACCF Expert Consensus Documents ■ acute myocardial infarction ■ clinical practice ■ consensus ■ diagnosis ■ heart failure ■ risk stratification ■ troponin.

APPENDIX 1. RELEVANT AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES: 2012 ACCF EXPERT CONSENSUS DOCUMENT ON THE PRACTICAL CLINICAL CONSIDERATIONS IN THE INTERPRETATION OF TROPONIN ELEVATIONS

Committee Member	Employer/Title	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
Robert L. Jesse (Co-Chair)	• Veterans Health Administration; Medical College of Virginia/Virginia Commonwealth University	None	None	None	None	None	None
L. Kristin Newby (Co-Chair)	Duke University Medical Center—Professor of Medicine, Division of Cardiovascular Medicine	• Amgen • AstraZeneca Biovascular • CV Therapeutics • Merck • Schering Plough	None	None	• AstraZeneca • BG Medicine • diaDexus* • GlaxoSmithKline* • Merck • NIH* • Schering Plough	None	None
Joseph D. Babb	East Carolina University—Professor of Medicine; Director Cardiac Cath Lab	None	None	None	None	None	None
Robert H. Christenson	University of Maryland School of Medicine—Professor of Pathology; Professor of Medical & Research Technology; Director, Rapid Response Labs	• Inverness Medical • Response Biomedical • Biosite Diagnostics • Siemens Medical Diagnostics • Instrumentation Laboratories	• Abbott Diagnostics	• Response Biomedical	• Inverness Diagnostics* • Roche Diagnostics* • Siemens Medical Diagnostics*	None	None
Thomas M. De Fer	Washington University School of Medicine—Clerkship Director	None	None	None	None	None	None
George A. Diamond	Cedars-Sinai Medical Center—Senior Research Scientist, Emeritus	None	• Merck Schering-Plough*	None	None	None	None
Francis M. Fesmire	Director—Heart Stroke Center	• Abbott	None	None	None	None	• Plaintiff's attorney, acute coronary syndrome, 2010
Stephen A. Geraci	University of Mississippi School of Medicine—Professor, Internal Medicine	None	None	None	None	None	None
Bernard J. Gersh	Mayo Clinic—Professor of Medicine	• Abbott Laboratories • Amorcyte • AstraZeneca • Boston Scientific • Bristol-Myers Squibb • CV Therapeutics	None	None	None	• Amorcyten (DSMB)	None
Greg C. Larsen	Portland Veteran Affairs Medical Center Cardiology Division—Chief Cardiology Section; Oregon Health and Science University—Associate Professor of Medicine	None	None	None	None	None	None

Committee Member	Employer/Title	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
Sanjay Kaul	Cedars-Sinai Medical Center—Director, Cardiology Medical Center Fellowship Training Program	• FDA Cardiorenal Advisory Panel • Hoffman La Roche • Novo Nordisk	None	None	• Hoffman La Roche*	None	None
Charles R. McKay	Harbor-University of California, Los Angeles Medical Center—Professor of Medicine	None	None	None	• Colorado Prevention Center	None	None
George J. Philippides	Boston University—Associate Professor of Medicine; Clinical Director, Cardiovascular Section	None	None	None	None	None	None
William S. Weintraub	Christiana Care Health System—Section Chief, Cardiology	• AstraZeneca* • Bayer* • Cardionet • Eli Lilly • Pfizer • sanofi-aventis • Shionogi	None	None	• Abbott* • AstraZeneca* • Bristol-Myers Squibb* • Otsuka* • sanofi-aventis	None	• Defendant, aprotinin, 2004 • Defendant, quetiapine and diabetes, 2008 • Defendant, Celebrex (Pfizer), 2008

This table represents the relationships of committee members with industry and other entities that were reported by authors to be relevant to this document up to 24 months before beginning of the writing effort September 2009. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

*Significant relationship.

DSMB = Data and Safety Monitoring Board; FDA = Food and Drug Administration.

APPENDIX 2. RELEVANT PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES: 2012 ACCF EXPERT CONSENSUS DOCUMENT ON THE PRACTICAL CLINICAL CONSIDERATIONS IN THE INTERPRETATION OF TROPONIN ELEVATIONS

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
Wyatt Decker	Organizational Reviewer—HFSA	None	None	None	None	None	None
Gregory J. Dehmer	Official Reviewer—ACCF Board of Trustees	• American Medical Foundation*	None	None	• C-PORT Elective Trial, Member (DSMB) • IP005 Percutaneous Valve Study (DSMB)	• SCAI, Past President	None
Deborah B. Diercks	Organizational Reviewer—HFSA	• Abbott Cardiovascular • AstraZeneca • Daiichi Sankyo	None	None	• Beckman Coulter† • Nanosphere†	• Society of Chest Pain Centers and Providers	None
Timothy J. Gardner	Official Reviewer—ACCF Task Force on CECD	None	None	None	None	None	None
M. Eugene Sherman	Official Reviewer—AACC Board of Governors	None	• Abbott Laboratories • Eli Lilly • Schering-Plough	• ABIO–Arca-Biopharm* • Colorado Heart Institute*	None	None	None
Jun R. Chiong	Organizational Reviewer—ACCP	• Roche Diagnostics	None	None	None	None	None
Richard Hoffman	Organizational Reviewer—ACP	None	None	None	None	None	None

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
Allan S. Jaffe	Organizational Reviewer—AACC	• Beckman Coulter • Critical Diagnostics • Inverness • Ortho Diagnostics • Pfizer • Siemens • Singulex • Tethys Bioscience	None	None	None	None	None
Josh Kosowsky	Organizational Reviewer—HFSA	None	None	None	None	None	• Defendant, appropriateness of guidelines for chest pain, 2010
Michael S. Lee	Organizational Reviewer—SCAI	• Daiichi Sankyo • Novartis	• Bristol-Myers Squibb* • BSCI* • Schering-Plough*	None	None	None	None
Lia S. Logio	Organizational Reviewer—ACP	None	None	None	None	None	None
David A. Morrow	Organizational Reviewer—AHA	• AstraZeneca* • Beckman Coulter • Boehringer Ingelheim • CardioKinetix • Critical Diagnostics • CV Therapeutics • Daiichi Sankyo • Eli Lilly • Genentech • Gilead • Ikaria • Menarini • Novartis • Roche Diagnostics • sanofi-aventis • Schering-Plough Research Institute • Siemens Medical Solutions	None	None	• AstraZeneca* • Beckman Coulter* • CV Therapeutics* • Daiichi Sankyo* • Eli Lilly* • GlaxoSmithKline* • Merck* • Nanosphere* • Novartis* • Roche Diagnostics* • sanofi-aventis* • Schering-Plough* • Siemens Medical Solutions* • Singulex*	None	None
Paul Sorajja	Organizational Reviewer—SCAI	None	None	None	None	None	None
Alan Wu	Organizational Reviewer—AACC	None	None	None	None	• Beckman Instruments • Response Biomedical	
Jeffrey L. Anderson	Content Reviewer—ACCF Unstable Angina Guideline	• BSCI/sanofi	None	None	• AstraZeneca (DSMB) • Gilead Pharma (DSMB) • Hamilton Health Sciences University (DSMB) • Harvard (DSMB) • NIH (DSMB) • Toshiba	• Deseret Foundation, Intermountain Healthcare • NIH	• Defendant, management of cardiopulmonary arrest post-op, 2010 • Defendant, stroke after ablation for AF, 2010

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
James A. de Lemos	Content Reviewer—ACCF Task Force on CECD	• Johnson & Johnson • Tethys	• Bristol-Myers Squibb/ sanofi-aventis partnership*	None	• Bristol-Myers Squibb (DSMB) • Roche Diagnostics*	• AstraZeneca* • Daiichi Sankyo	None
Robert A. Guyton	Content Reviewer—ACCF CABG Guideline	None	None	None	• Edwards Lifesciences • NIH	None	None
Richard J. Kovacs	Content Reviewer—ACCF	• Abbott Laboratories • Biomedical Systems • Cook* • ECG Scanning and Medical Services* • Eli Lilly* • Endocyte • Essentialis • XenoPort	None	None	None	None	None
Frederick G. Kushner	Content Reviewer—ACCF STEMI Guideline	• FDA	None	• Bristol-Myers Squibb Merck • Roche Holding*	• Daiichi Sankyo • Hoffmann La Roche • NIH • Novartis	• FDA Science Board	None
David Lanfear	Content Reviewer—ACCF Heart Failure and Transplant Committee	• Thoratec	None	None	• sanofi-aventis* • Johnson & Johnson*	• HFSA	None
John F. Robb	Content Reviewer—ACCF	None	None	None	None	None	None
Sidney C. Smith, Jr.	Content Reviewer—ACCF PCI Guideline	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

*Significant relationship. †No financial benefit.

AACC = American Association for Clinical Chemistry; ACCF = American College of Cardiology Foundation; ACCP = American College of Chest Physicians; ACP = American College of Physicians; AF = atrial fibrillation; AHA = American Heart Association; CABG = coronary artery bypass graft surgery; CECD = Clinical Expert Consensus Documents; DSMB = Data and Safety Monitoring Board; FDA = Food and Drug Administration; HFSA = Heart Failure Society of America; NIH = National Institutes of Health; PCI = percutaneous coronary intervention; SCAI = Society for Cardiovascular Angiography and Interventions; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

Appendix 3. Additional Nonischemic Syndromes in Which Troponin Testing May Have Potential Clinical Application

1.1. Amyloidosis

Serum troponin I has become an integral part of disease staging in amyloid light chain (primary or systemic light chain) amyloidosis, where cardiac involvement is seen in up to 90% of cases (195). It is a powerful predictor of overall life expectancy (196), with median survival differing from 22 months (troponin-negative) to 7 months (troponin-positive). In another observation of patients too ill/advanced for consideration for bone marrow or cardiac transplantation who were treated with oral melphalan and dexamethasone, patients with a troponin I level <0.12 ng/ml had a median survival of 38 months versus 23 months when troponin I was >0.12 ng/ml (197). Amyloid can infiltrate both the interstitium and the vasculature, though epicardial obstructive lesions from amyloid arteriopathy or accompanying atherosclerosis are not consistent findings in this disorder (198). Troponin T elevation has correlated well with cardiac involvement (defined by extracardiac biopsy-proven amyloidosis plus echocardiographic/ECG findings consistent with cardiac involvement) (199). When combined in a model with NT-proBNP, troponin I appears to be more accurate than troponin T in predicting outcome in this disease (200). Patients with transthyretin amyloidosis have a much lower rate of cardiac involvement as defined by troponin elevation (troponin T positive: 10%; troponin I positive: 21%), which in turn does not correlate with echocardiographic myocardial abnormalities (201).

Stem cell transplantation has offered new hope for prolonged survival in amyloid light chain amyloidosis, but survival is heavily influenced by treatment-associated mortality (up to 25%). Furthermore, troponin elevation also appears to be associated with post-transplant survival. In 1 series, patients with troponin T levels <0.06 ng/ml had 7% 100-day mortality compared with 28% among those with troponin T levels ≥0.06 ng/ml (202). When troponin T was >0.035 ng/ml (14% of patients), median post-transplant survival was 26 months, compared with >66 months if troponin T was <0.035 ng/ml. In another study, when both troponin I and NT-proBNP were elevated, the hazard ratio for overall mortality was 3.2 (200). Thus, the role of troponin in predicting outcomes in several situations in amyloid light chain amyloidosis is well supported.

1.2. Cardiac Transplant Monitoring

Several studies have identified early and significant elevations in both troponin T (203,204) and I (205) after cardiac transplantation, which typically normalizes within 3 months post-transplantation and does not predict long-term graft survival or subsequent coronary vasculopathy, but this may be related to cold storage time and/or ischemic period (205).

Troponin has been studied as a biomarker of significant rejection in asymptomatic patients without renal failure or active CMV infection (206). Three such studies failed to identify diagnostic correlation with biopsy-proven rejection (207–209). However, another showed good correlation between increasing mean troponin T levels and higher grades of rejection (210). In other studies defining significant rejection as the International Society for Heart & Lung Transplantation grade >3A, troponin elevation appeared predictive of a high-grade rejection, particularly in male recipients under 60 years of age and with female donors older than 33 years of age (211–213). Although sensitivity was still unacceptably low, importantly, troponin T below the study cutoff carried powerful NPV (from 95% to 99.5%) for the absence of rejection grade ≥3B.

Separately, studies have evaluated whether later (>1 to 3 months post-transplant) troponin elevations predict development of graft vasculopathy, a major cause of graft failure more than 1 year post-transplant. Three small prospective observational studies (204,214,215), over 36 to 69 months (mean) observation, noted a markedly higher incidence and severity of graft vasculopathy when troponin levels remained measurable after the first 1 to 3 months post-transplant. Although associations were strong in these studies, data are insufficient to recommend that troponin monitoring replace coronary angiography or other ischemia testing at this time.

1.3. Blunt Cardiac Injury

Major trauma can lead to cardiac injury by a variety of mechanisms: direct cardiac impact or compression, deceleration, hydraulic ram effect (following abdominal and lower extremity trauma), hypotension, hypoxia, anemia, and catecholamine storm (resulting in high oxygen demand and possible coronary spasm) (216,217), as well as via systemic inflammatory response associated with critical illness (218). Although transesophageal echocardiography appears to provide the most reliable information on regional and global LV function, valve disruption, traumatic ventricular septal defect, hemopericardium and tamponade, free-wall rupture, some coronary artery lacerations/dissections/thrombosis, and aortic transection/dissection/rupture/intramural hematoma, less invasive methods have been sought that would identify patients requiring additional evaluation and observation, particularly in the absence of gross post-traumatic cardiac abnormalities identified by imaging. The use of older biomarkers was confounded by their presence in other nonmyocardial sites (diaphragm, small intestine, uterus, prostate, and skeletal muscle) frequently injured in major trauma. As troponin T can be re-expressed in skeletal muscle that regenerates after injury, studies of this protein, particularly those using early-generation assays, are of unclear value. Recent focus has been on troponin I and its use in predicting late, clinically relevant cardiac complications (arrhythmias, late rupture, and delayed ventricular septal

defect) after blunt chest injury and associated major trauma (219,220).

Overall, as might be expected, troponin elevations in trauma patients are more likely in patients with thoracic injuries compared with nonthoracic injuries (221); however, there has been poor correlation of troponin T or I elevation with echocardiographic evidence of contusion, ECG changes, or arrhythmias (222). That said, progressively higher levels of troponin elevation have been associated with increasing mortality (223). Perhaps most importantly, several studies of troponin I suggest that it has excellent NPV for contusion and adverse clinical outcomes when levels are normal after major trauma (224–228). Particularly when serial testing within 24 h is used and when low troponin levels are combined with negative ECG assessment, the NPV of low troponin levels for subsequent clinical cardiac events after trauma is reported to be 98% to 100%. The PPV of troponin in this setting is not established, and as with elevated troponins in other settings, interpretation must be made considering clinical context and alternative diagnoses. These data suggest potential roles for troponin I measurement in blunt chest trauma.

1.4. Noncardiac Surgery

The use of troponin to predict short- and long-term adverse cardiovascular outcomes/mortality following noncardiac surgery has been studied since the assays became available (229). The "2007 ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery" (230) reviewed several studies in which troponin I elevation on post-operative days 1, 2, and 3 was associated with increased mortality regardless of whether it was due to "myocardial damage" (cardiac troponin [cTn] elevation in absence of ischemic symptoms or ECG changes) or frank MI. Although this predictive value has been observed in other studies, no data are available to direct changes in treatment based on troponin elevation that would alter the observed outcomes. As such, routine troponin sampling (surveillance) in asymptomatic patients without ischemic ECG changes or hemodynamic instability is not recommended by the present guidelines.

In the noncardiac perioperative surgical setting, troponin elevation is most likely to occur in the early post-operative timeframe, and it has been correlated with higher circulating catecholamine levels (231). Strong positive associations have been reported for troponin elevations with 1-year and 4-year all-cause mortality (232,233) and 6-month major adverse cardiovascular events in general surgical patients (234), longer length of stay and in-hospital mortality in critically ill surgical patients (235), and a 6-month incidence of death and MI in vascular surgery patients (236).

Although the clinical role of post-operative troponin measurement still requires further definition, particularly in nonvascular surgery settings, the correlation of troponin elevation with a number of negative outcomes, along with a fairly powerful NPV of normal concentrations, suggests a future role in this setting.

1.5. Thermal Injury

Animal models suggest troponin elevations parallel myocardial dysfunction following burn injury (237). In small series, modest cardiac troponin I elevations have been found in almost all patients with significant (>15% total body surface area) burn injuries, with peak levels higher and earlier with more severe/extensive burns (238,239). Troponin elevation in the setting of severe burns appears to be related to systemic stress (wound infection, tachycardia, and systemic inflammation) but exclusive of findings of ACS or myocardial ischemia. Whether the timing or magnitude of troponin elevation in burn patients will offer additional prognostic information is yet to be determined, though the high incidence of secondary cardiovascular mortality (6.8%) (239) in burn patients identifies this as a worthwhile setting for further investigation.

Appendix 4. Other Nonischemic Conditions in Which Interpretation of Troponin Testing Has Created Clinical Uncertainty

1.1. Subarachnoid Hemorrhage

Multiple studies were published in the past 10 years documenting troponin elevation in stroke and subarachnoid hemorrhage (SAH). Neurocardiogenic abnormalities have been best described in SAH, but they are now being better characterized in ischemic and hemorrhagic strokes. Abnormalities run the gamut from ECG changes (240,241) and arrhythmias to blood pressure changes and myocardial injury and dysfunction (242). In the absence of a typical thrombotic MI, elevated troponin levels are presumed to signify myocardial injury related to these pathophysiological mechanisms.

Rates of troponin elevation in SAH patients range from 13% to 68%, (243,244), and they generally appear to be related to SAH severity. However, in the largest cohort studies, an association with worse clinical outcomes was not unequivocally demonstrated (243,245). It is postulated that myocardial damage in SAH is most likely caused by excess sympathetic stimulation rather than a global ischemia or focal ischemia, due to flow-limiting coronary atherosclerotic lesions (242,246). However, in patients with significant CAD, the co-occurrence of an acute MI must be ruled out. LV global dysfunction and regional wall motion abnormalities (often reversible) have been described with SAH and likened to takotsubo cardiomyopathy, with which it may share a common pathophysiology (i.e., massive catecholamine release) (247). Elevated troponin may be a useful marker of neurocardiogenic injury and possibly of an increased risk of cerebral vasospasm and mortality (248). Being able to identify patients at a greater risk of mortality could allow for timelier and more specific treatments, such

as alpha and beta blockade, but formal testing of this hypothesis has not been undertaken.

1.2. Stroke

The mechanism of troponin release in stroke patients is less understood, and the incidence of troponin elevation outside of the co-occurrence of ACS is uncertain. Due to shared risk factors, CAD is more common in these patients and is the main cause of long-term mortality (249). Therefore, the possibility of a coexistent MI must be excluded with care. Here, too, the catecholamine hypothesis has been made, and increased catecholamine levels have been reported in stroke (250). One small study has suggested a possible benefit of beta blockers in patients with stroke, but further study is needed (251). Several studies have shown an association between stroke severity and elevated troponin (252–255), and within studies reporting on relationships of troponin elevation with mortality and disability in stroke patients, there appears to be a modest increase in mortality in cTn-positive stroke patients and possibly those with longer-term disability (253,255–260). Given the many shared risk factors, troponin-positive stroke patients should be more carefully screened for CAD, with special consideration for noninvasive functional testing when recovered from stroke or more urgent invasive assessment—if clinical signs or symptoms suggest ongoing cardiac ischemia and neurological condition will allow.

1.3. Endocarditis

There are surprisingly few data available on troponin concentrations in endocardial infections. Three small studies (261–263) have reported on 128 total patients. Purcell et al. (259) identified troponin-positive patients as more likely to suffer an event (death, abscess, or central nervous system event) both collectively and individually, but this study was retrospective and included only patients who had a troponin drawn for some clinical reason (including worsening LV function) . In a smaller study, Watkin et al. (258) found troponin-positive patients were not more likely to require valve replacement, have perivalvular extension, or suffer other major complications over 2 years. However, Tsenovoy et al. (263) found an incidence of in-hospital mortality plus the need—by Duke criteria—for valve replacement of 51% when cTnI exceeded 0.4 ng/ml at the time of diagnosis, compared with 15% when TnI was below this level. Although logical to expect higher complication rates with evidence of more myocyte necrosis, insufficient data are available to conclude that evaluation or treatment should be changed based solely on troponin levels in endocarditis.

1.4. Cardiac Tumors and Systemic Malignancies

Tumors metastatic to the heart and pericardium are at least 10 times as common as primary cardiac tumors. Any tumor has the possibility of causing serum troponin elevations, either through direct invasion (laryngeal carcinoma), coronary embolization of tumor fragments or associated thrombus (myxomas), or by creating a systemic prothrombotic environment leading to coronary thrombosis and ischemia (lymphoma). Although individual case reports occasionally note low-level troponin elevations (264), relevant reviews have failed to provide information on the frequency of troponin elevation, or whether it could be used in any diagnostic or prognostic way for cardiac tumors (265–271). Reviews of specific tumor types (mesenchymal [272], fibromas [273], and primary sarcomas [274]) also excluded comments on troponin from both diagnosis and management discussions. In addition, troponin data are also unavailable in reviews of pericardial tumors (275), tumor-like conditions (276), and lymphangioleiomyomatosis (277). Although Kaposi sarcoma can involve the heart in 15% to 18% of cases at autopsy, it is usually asymptomatic and has not been reported to be associated with troponin elevation (278). Sporadic case publications report troponin elevation in patients without other evidence of cardiac disease with, for example, uterine leiomyosarcoma (279) and alveolar rhabdomyosarcoma (280).

Carcinoid heart disease, reported to complicate up to 70% of cases of carcinoid syndrome, is the presenting symptom in 20% of patients (281). Right heart valvulopathy, pericardial effusions and constriction, and restrictive-physiology cardiomyopathy patterns may be seen. In a study of 20 patients with metastatic carcinoid disease without heart failure, neither troponin I nor troponin T was detectable regardless of symptoms, echocardiographic findings, or urinary concentrations of tumor metabolites (282).

1.5. Hematologic Conditions

In addition to cardiac complications of cancer treatment, other hematologic disorders can involve the heart and elevate troponin (202) via endomyocardial damage (and thromboembolism) from hypereosinophilic syndrome (283), or via micro- or macrovascular obstruction from thrombotic thrombocytopenic purpura (284) and thrombotic microangiopathy (285). In patients with transfusion-dependent diseases such as major thalassemia, troponin I has not been identified as predictive of progressive iron overload or echocardiographic abnormalities (286). Troponin elevations appear infrequent in patients with sickle cell crisis (287,288) and may represent consequences of pulmonary hypertension associated with acute chest syndrome (289), though frank MI has been reported (290).

1.6. Neuromuscular and Myopathic Conditions

Congenital myopathies and muscular dystrophies can affect the heart, but any value in measuring serum troponin remains unclear (291). In a retrospective database study, Finsterer et al. (292) observed that among 1,408 abnormal troponin T levels identified at a single center over a 1-year period, 6.3% of positive patients carried a primary neuromuscular diagnosis and no other obvious cause of troponin positivity. Both troponin T and troponin I were measured in 129 known carriers of muscular dystrophies (293) who are

known to be at increased risk of chronic heart failure compared with the general population. Only 2 patients had mild troponin T elevation (0.04 ng/ml and 0.16 ng/ml), and they had no significant cardiac structural abnormalities. No patients had troponin I >0.4 ng/ml, despite the fact that more than 5% of the cohort suffered from frank dilated cardiomyopathy and another 18% had otherwise unexplained LV dilation (293). Hence, in these conditions, troponin surveillance does not appear to identify patients at risk for, or with, associated cardiomyopathy.

1.7. Autoimmune and Connective Tissue Diseases

This broad group of disorders can affect the heart in many ways: epicardial or small-vessel vasculitis with obstruction or spasm; serositis (pericarditis), granulomas, noninfectious myocarditis, and/or through the development of pulmonary arterial hypertension (294). However, data on the value of troponin measurement are sparse. Yasutake et al. (295) found troponin T was not elevated among any of the 27 patients with documented cardiac sarcoidosis, whereas atrial and BNP elevations were associated with demonstrable cardiac abnormalities. In another observation, 40 women with systemic sclerosis had significantly higher levels of ischemia-modified albumin and NT-proBNP, but they had identical levels of troponin T (<0.01 ng/ml) with 40 age-matched healthy controls (296). One observational study of patients with inclusion body myositis found that 62% of the 42 consecutive patients demonstrated troponin T elevation (>0.05 ng/ml), which remained abnormal for a mean follow-up of 17 months; no other evidence of myocardial damage or dysfunction was found in these patients (297). Several papers on polymyositis/dermatomyositis, in which Tc-99 pyrophosphate scans show cardiac abnormalities in 57% and autopsy studies show myocardial involvement in about one-third of patients (298), are available; troponin T elevations have been noted in case series (27%) (299) and case reports (300). Kiely et al. (301) found troponin I levels normal and not different from normal controls in 16 patients with inflammatory muscle disease. In no reports have troponin levels been linked to specific, clinical cardiac involvement or outcomes. No troponin data are available on other autoimmune diseases that affect the heart, including Wegener's granulomatosis (which can cause pericarditis and coronary arteritis) (302) or giant cell myocarditis (303).

1.8. Arrhythmia Treatments and Resuscitation

Endocardial lead implantation, whether for antibradycardia pacemakers (304) or transvenous cardioverter-defibrillators (305), typically results in low-level myocardial injury (troponin T and troponin I <1.5 ng/ml) through mechanical trauma related to the types and diameters of leads used; control patients who only undergo generator replacement have no troponin release. Repeated discharges during internal defibrillator implantation/testing demonstrate troponin elevations in 40% to 90% of patients, although the data conflict as to whether number of shocks and/or delivered energy level correlate with peak levels or percent positive samples among patients (306–308). In neither circumstance have observed serum troponin levels been correlated with later events.

Troponin elevation is far less frequent after elective external cardioversion/defibrillation. In a study of 40 patients receiving a mean cumulative delivered energy of 250 ± 150 J, no elevations of troponin T were noted 6, 12, or 24 h after treatment (309). Thirteen patients receiving up to 1,000 J cumulative energy also showed no troponin T elevation at 8 or 18 h following shock delivery (310). Lund identified only 1 case of 72 elective cardioversion attempts for atrial flutter or fibrillation (cumulative energy 408 ± 318 J, range 50 J to 1,280 J) where troponin T exceeded the normal range, despite 6 samples being measured over the succeeding 24 h (311). In comparing newer biphasic with traditional monophasic techniques, none of 141 patients divided between monophasic and biphasic shocks showed any troponin I elevation (all <0.03 ng/ml) at 3 to 7 h after treatment (312). Another comparison involving 48 atrial fibrillation patients noted a mean increase in troponin I at 24 h post-shock in patients undergoing monophasic cardioversion (with no such increase in patients receiving biphasic shocks); however, the former cohort received on average twice the delivered cumulative energy (348 J vs. 188 J mean), and troponin I data was driven primarily by 2 outliers (troponin I 4.1 and 1.6) without whom the groups might not have showed statistical difference (313). Thus, the literature does not support significant troponin elevation 6 to 24 h after elective external cardioversion/defibrillation for supraventricular arrhythmias. In a somewhat related setting, electrical weapon discharge (TASER) does not appear to result in troponin I elevation among healthy adult volunteers with a typical distribution of cardiac risk factors (314).

Endocardial radiofrequency ablations have been well documented to elevate troponin I within 24 h of the procedure in 54% to 100% of cases (315,316), with the frequency and magnitude of elevations roughly proportional to the delivered energy, duration of application, number of applications, and perhaps, the endocardial location of treatment (317–320). Similar elevations in troponin T have also been demonstrated, but correlation to specific parameters of the electrophysiological procedure is less consistent (321,322). In all of these studies, patients suffered no complications requiring further intervention. Interestingly, 1 study suggested cryoablation was associated with less myocardial injury (lower peak troponin levels) than radiofrequency techniques treating similar arrhythmias (323). No correlation between troponin release and long-term adverse outcomes has been documented, but these data do show that periprocedural troponin elevation is expected after ablation procedures and does not represent an additional cardiac event.

Only 1 report is available on troponin levels following successful cardiopulmonary resuscitation where electrical therapy was not employed. This small cohort of 8 patients—

selected because of their absence of pre-existing cardiovascular disease, major chest trauma, or septic shock—demonstrated troponin I elevations, most of which had returned to normal within 30 h of return of spontaneous circulation (324). These findings could be helpful in separating true MI (in which troponin I would typically be elevated for several days) as the precipitating event from myonecrosis strictly caused by cessation of systemic circulation and resuscitative efforts.

1.9. Metabolic Disorders

Ketoacidosis in Type 1 diabetes can result in minor troponin I elevations in 10% of patients (325) with a mean level ~12% above that of healthy volunteers and greater elevations possibly related to the severity of acidosis (pH <7.0) (326). Almost all elevated levels in these studies returned to normal within 24 h of treatment initiation, thus, demonstrating different release kinetics than that apparent in acute MI. In an important retrospective study of 96 adults without evidence of ACS and who had troponin I drawn when presenting with diabetic ketoacidosis, 2-year mortality was significantly higher among the 26 patients with elevated troponin levels (50% vs. 27%), as were all major cardiac events. Kaplan-Meier analysis and Cox proportional hazard models identified troponin I elevation as a predictor of mortality independent of ketoacidosis severity or underlying cardiovascular disease (327). Should this predictive association be confirmed in prospective observational studies, troponin I could become an important prognostic tool among the growing diabetic population.

Although case reports have suggested that patients with moderate to severe hypothyroidism may have troponin I elevation accompanying chest pain in the absence of coronary disease (328,329), 52 consecutive asymptomatic patients with significant hypothyroidism (mean TSH >25 mU/l) had no troponin I elevation on routine sampling. The importance of these findings remains to be determined (330).

1.10. Chronic Obstructive Lung Disease

Interpretation of cardiac biomarker abnormalities has always been difficult in patients with advanced/decompensated chronic lung disease: risk factors for chronic obstructive pulmonary disease are similar to those for coronary disease, and the 2 are often present concurrently; atypical chest pain can be due to either, or both, conditions; hypoxemia and/or respiratory acidosis can induce secondary myocardial ischemia, whereas secondary pulmonary hypertension can result in RV hypertrophy, dilation, and subendocardial demand-induced ischemia; chest hyperinflation and anatomic shift in cardiac orientation can result in ECG changes in the absence of actual cardiac pathology. Although far more specific for cardiac injury than CK-MB or other markers that can be elevated from hypertrophied diaphragmatic sources, in the absence of diagnostic ischemic ECG changes, interpretation of elevated troponin in a given patient can remain perplexing. However, some studies do suggest that an elevated troponin level in the setting of chronic obstructive pulmonary disease exacerbation is independently associated with in-hospital and 2-year mortality (331,332). Further study is needed to clearly define the role of troponin testing for this large population.

1.11. Autonomically Mediated Disorders

Several clinical scenarios can lead to acute changes in autonomic input to the heart, causing troponin release and ventricular dysfunction. Stress (takotsubo) cardiomyopathy, which typically occurs after sudden and extreme emotional duress, can mimic acute MI with ECG changes of significant myocardial ischemia or injury and marked hypo/a/dyskinesis of the mid and apical left ventricle (although other patterns have been reported). It is accompanied by a much more modest and less protracted elevation in troponin than seen in acute infarctions of comparable ECG distributions. In the vast majority of cases, troponin normalizes in 3 to 4 days, and the left ventricle appears to recover fully within days or weeks (333,334). Profound sympathetic outflow in response to mental stress has been documented (335), supporting this connection. Interestingly, several case reports of patients with pheochromocytoma have also documented transient ventricular "ballooning" (336) including some with documented elevations of cTnI (337). Whether the more protracted heightened sympathetic outflow demonstrated in patients with nontraumatic SAH (338), in which profound T-wave inversions are often observed, produces similar ventricular stunning and troponin release has not yet been demonstrated.

1.12. Pregnancy and Related Conditions

Although ACS is exceedingly uncommon in pregnant women, the increasing prevalence of diabetes, hypertension, and other cardiovascular diseases at younger ages makes interpretation of troponin values increasingly important in these patients. Two studies have suggested that troponin I is not increased as a consequence of normal labor and delivery (339), including Cesarean delivery (340). A third observation (341) found that 81% of 26 patients who had no history of hypertensive, endocrinologic, or cardiovascular disease history and underwent elective Cesarean section showed ischemic ECG changes on continuous ST-segment monitoring, whereas 2 patients (7.7%) exceeded their laboratory cutoff for abnormal troponin I, 12 h post-operatively: All patients received oxytocin immediately after fetal delivery, and most equivalent average doses of ephedrine for transient hypotension, but neither drug administration nor tachycardia/blood pressure changes correlated with ischemic ECG abnormalities. Most patients complained of chest pain, with 42% requiring opioids for relief. As no further cardiovascular evaluation or long-term follow-up was performed, the meaning of troponin elevation in this setting is unclear. Intravenous tocolytic therapy with fenoterol and verapamil raised the mean troponin T level of 20 otherwise healthy women from normal pre-treatment levels (0.08 ng/ml) to

statistically higher, abnormal levels (0.35 ng/ml mean) by the third day of treatment (342); again, no additional cardiac evaluation was done in this study, but the young age (24.4 ± 1.2 years) and absent history of cardiac/coronary equivalent disorders makes underlying primary heart disease unlikely in this study population. Complicated pregnancies may be more likely to demonstrate troponin elevations. Troponin I randomly sampled between 35 to 38 weeks gestation was higher in 20 women with gestational hypertension than in 43 pregnant women without hypertension (0.09 vs. 0.03 ng/ml) and higher still (0.16 ng/ml) among 6 with pre-eclampsia (hypertension accompanied by proteinuria) (343). Contrasting with these findings, troponin I levels were identical between pre-eclamptic (0.008 ng/ml) and normal (0.01 ng/ml) pregnant patients in another study (344). Of note, magnesium sulfate treatment may reduce troponin I release in pre-eclamptic patients (345). Peripartum cardiomyopathy may also be associated with troponin elevation. In 1 study nearly 31% (33/106) of women with peripartum cardiomyopathy had elevated troponin T levels measured within 2 weeks of onset of symptoms (346). Troponin elevation was correlated with LVEF in follow-up; women with levels >0.04 ng/ml had lower ejection fractions at 6-month follow-up than women whose initial levels were ≤0.04 ng/ml (group means, 35.4% vs. 50.2%, respectively). Using 0.04 ng/ml as a cutpoint, the troponin T level predicted persistent LV dysfunction with a sensitivity of 55% and a specificity of 91%.

1.13. Strenuous Exercise

In the absence of obstructive coronary disease or demonstrable ischemia, the question of whether extreme exercise (marathons, triathlons, mountain bicycle races, ultraendurance events) is associated with myocardial injury, or whether troponin elevations should prompt further coronary work up, remains controversial. Two studies (total N = 29) measured troponin T and/or troponin I after extreme exercise and found no elevations (347,348), whereas a third found no elevations in an additional 8 patients who performed 2 separate protracted treadmill protocols (349). Conflicting data are found in other studies, including 1 of 30 participants of the 2005 Boston Marathon, which showed a cohort increase in troponin T from <0.01 to 0.03 ng/dl, with 7 of 30 exceeding 0.05 ng/dl and 2/30 above 0.10 ng/dl (350). One-third of 38 studied participants in a mountain bicycling ultramarathon demonstrated increases in troponin I from <0.05 ng/ml to 0.90 to 4.9 ng/ml immediately post-race (351), whereas 20% of 45 runners in the 1995 Boston Marathon had increases in both troponin T and troponin I compared with pre-race levels, with absolute concentrations remaining within the normal range; in this latter study, 1-year clinical follow-up showed no cardiac events or symptoms in the troponin-positive group (352). In all studies that included multiple samplings, elevated troponin levels generally returned to normal within 24 h. Two additional observations suggested that less conditioning was associated with a greater likelihood of troponin elevation (40% of 60 in 2 cohorts of marathon runners, troponin T >0.03 ng/ml (353,354); 11% of 36 Alpine marathoners, troponin T 0.11 ng/ml to 0.20 ng/ml) (353). All the above studies excluded patients with known cardiovascular disease, cardiac symptoms, or other historical risk factors for ischemic heart disease. Long-term follow-up was not performed in most studies to determine whether these small troponin elevations after extraordinary physical stress predicted any incremental risk for future cardiac events. Shave et al. (355) concluded that troponin elevation occurs in 8% to 100% of subjects tested after extreme exertion and was generally mild and related to baseline physical conditioning, type and duration of exertion, timing of testing, and assay threshold. They concluded that in the absence of consistent effects on cardiac function or documented long-term complications, routine testing was not recommended for individuals without post-exercise complaints that might be reflective of myocardial ischemia (e.g., chest pain or unexplained dyspnea).

1.14. Rhabdomyolysis

Few studies examining troponin levels in patients with rhabdomyolysis are available, but those published suggest that new-generation assays for both troponin T and troponin I are cardiac specific; that elevations are independent of total CK release in the absence of renal failure; and that patients with troponin elevations are sicker, suffered an insult/complication that could have induced myocardial injury independent of the skeletal muscle necrosis itself, and were more likely to have ECG changes, echocardiographic abnormalities, or both (356–359). Although data are too few to draw conclusions, the frequency of potential cardiac insults and ECG/echocardiogram abnormalities suggests that cTn elevation more likely represents separate cardiac injury than laboratory abnormalities or "false-positive" samples from massive skeletal muscle necrosis. Whether cTn elevation in patients with rhabdomyolysis should initiate further cardiac evaluation is yet to be determined.

1.15. Aortic Dissection

Nontraumatic thoracic aortic dissection is a rare but life-threatening condition with an incidence of 3 cases per 100,000 people per year in the United States. Approximately 70% of patients have hypertension. Other disorders that may be associated with aortic dissection are connective tissue disorders, bicuspid aortic valve, coarctation of the aorta, and pregnancy. Almost 50% of patients have acute ECG changes diagnostic or suggestive of injury or ischemia (360). In a cohort of 119 consecutive patients admitted for acute aortic dissection of the ascending aorta (Type A), and 28 (23.5%) had elevated troponin I levels. Of these patients, 14% had ST-segment elevation, 14% had ST-segment depression, and 36% had T-wave inversions. Patients with elevated troponin had a 4-fold higher risk of death com-

pared with patients with a normal troponin level. However, after controlling for age, stroke, ST-segment elevation, tamponade, catecholamine infusion and renal failure in a multivariate model, this association disappeared. Though ascending aortic dissection may rarely involve the ostium of the coronary arteries, the major mechanism of troponin elevations is thought to be due to hemodynamic stresses and instability.

Appendix 5. Abbreviation List

ACS = acute coronary syndrome

ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy

ADHERE = Acute Decompensated Heart Failure Registry

NT-proBNP = N-terminal pro-brain natriuretic peptide

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CKD = chronic kidney disease

CK-MB = creatine kinase-MB

CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events

ECD = expert consensus document

ECG = electrocardiogram

ESC = European Society of Cardiology

ESRD = end-stage renal disease

FRISC II = Fragmin and Fast Revascularization during Instability in Coronary artery disease

GUSTO IV = Global Use of Strategies to Open Occluded Coronary Arteries

HIV = human immunodeficiency virus

ICTUS = Invasive versus Conservative Treatment in Unstable Coronary Syndromes

LV = left ventricular

MI = myocardial infarction

MORGAM = Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA), Risk, Genetics, Archiving, and Monograph

NACB = National Academy of Clinical Biochemistry

NCDR = National Cardiovascular Data Registry

NPV = negative predictive value

PEACE = Prevention of Events with Angiotensin Converting Enzyme Inhibition

PCI = percutaneous coronary intervention

PPV = positive predictive value

PE = pulmonary embolism

RV = right ventricular

SAH = subarachnoid hemorrhage

TACTICS–TIMI 18 = Treat Angina with Aggrastat and Determine Cost of Therapy with Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18

ULN = upper limit of normal

Val-Heft = Valsartan Heart Failure

Vanquish = Veterans Affairs Non–Q-Wave Infarction Strategies In-Hospital

VINO = Value of First Day Angiography/Angioplasty in Evolving Non–ST-Segment Elevation Myocardial Infarction