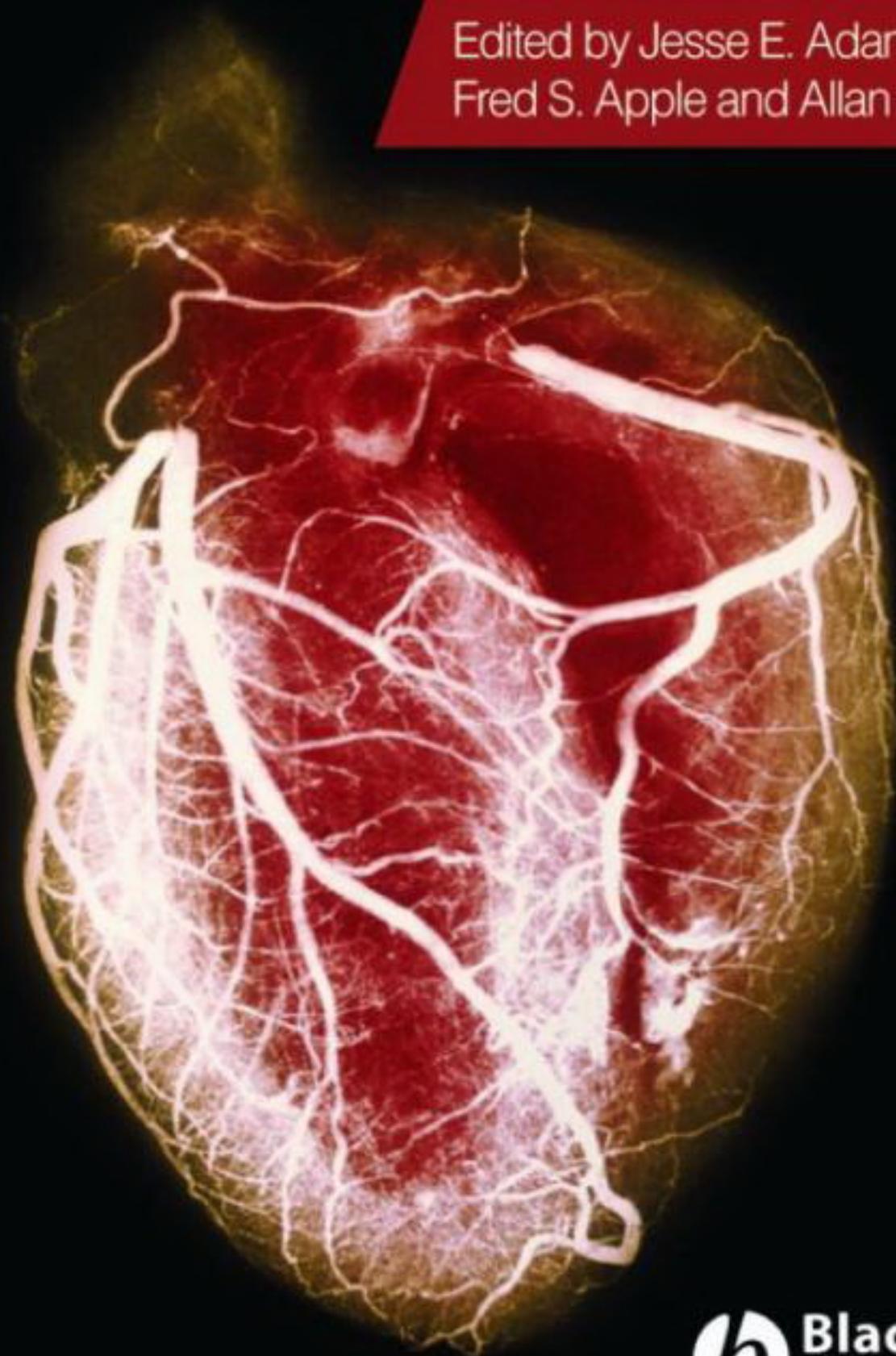


# Markers in Cardiology

## A Case-Oriented Approach

Edited by Jesse E. Adams,  
Fred S. Apple and Allan S. Jaffe



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APPROACH

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## A CASE-ORIENTED APPROACH

EDITED BY

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# Preface

There is only one good, knowledge, and one evil, ignorance.

—Socrates

Knowledge is power.

—Sir Francis Bacon, *Meditationes Sacrae, De Haeresibus*

Everything should be made as simple as possible, but not simpler.

—Albert Einstein

The application of biomarkers has revolutionized the practice of cardiology, allowing more facile and accurate diagnoses. Increasingly sensitive assays and utilization of markers in combination have furthered the field in the last decade, but with this increased sophistication has also come increased frustration on the part of some clinicians. Some feel that low levels of troponins, for example, that do not appear to correlate with anatomic data obtained during cardiac catheterization, for example, represent “trash” troponin results. This point of view is indicative of the frustrations that many clinicians find in attempting to properly interpret biomarker values. It is necessary to properly understand these assays and how they intercalate with other diagnostic modalities to properly facilitate patient care. Although clinicians would prefer easy answers, the reality is that biomarker values are only as good as those interpreting them in the context of the clinical situation. Elevations can be associated with acute disease or more chronic abnormalities and there are substantial issues with how the markers are measured and differences related to patient presentation and underlying demographics that often can explain elevations or their lack. The idea of not chasing biomarker abnormalities when we know they most often have prognostic implications is unwise. The real question is how to do these evaluations in the best way so we can provide the appropriate care for our patients and not waste our valuable time and resources inappropriately. Thus, perhaps the term “the smart chasing of biomarker abnormalities” might be considered.

In thinking about how we might best help with this, we decided that developing a book of cases that would represent real world patient problems with potential explanations for values of troponins, natriuretic peptides, and other analytes might be a helpful adjunct to clinicians who are often busy and find it difficult to stay up with all the details of the literature. The cases by a highly distinguished group of clinician investigators are presented as an attempt to provide a roadmap with which to consider the various clinical presentations in which BNP and troponin may be useful. Obviously, every nuance cannot be

covered. On the other hand, if we can provide guidance and help only a small percentage of clinicians who use the book to learn how best to treat patients, we believe we will have made a contribution.

We would like to know if this approach is useful. Therefore, we would very much appreciate your feedback and cases from those of you who are interested so that when and if we redo this book, it will become even more helpful to those of you who smartly chase these biomarker abnormalities. In the long run, it is our goal to help translate the science of our field into practical patient care.

Jesse Adams, MD, FACC

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PART 1

---

# **Cardiac troponins**

# Basics of cardiac troponin: practical aspects of assays, potential analytical confounders, and clinical interpretation

**Fred S. Apple**

## Case 1

Following an episode of shortness of breath and fainting, a 79-year-old woman is driven to the emergency department by her family. She has a history of rheumatoid arthritis and coronary artery disease, with limited physical activity. Her initial electrocardiogram (ECG) showed mild, nonspecific changes, including T waves. To assist in her differential, serial cardiac troponin (cTn) values were obtained. While the clinician did not expect the patient to have a myocardial infarction (MI), her substantial increase in cTnI (based on a first-generation assay that is no longer on the marketplace) was at odds with (a) neither a rising or falling pattern found on subsequent values and (b) normal and unchanging total creatine kinase (CK) and creatine kinase-MB (CK-MB) values. Following clinician contact with the laboratory, reanalysis of the specimens using a second-generation cTnI assay by the same manufacturer and a third-generation cTnT assay demonstrated no detectable cTn, and the laboratory results were corrected in the medical record. Follow-up studies by the laboratory revealed the presence of a heterophile-interfering antibody, which once removed (Scantibody tubes) resulted in normal cTnI values by the original assay.

<i>Time (h)</i>	<i>Total CK</i>	<i>CK-MB</i>	<i>cTnI 1st</i>	<i>cTnI 2nd</i>	<i>cTnT</i>
0	25	1.5	20.8	<0.025	<0.01
6	29	1.4	23.0	<0.25	<0.01
15	28	1.3	24.8	<0.025	<0.01

All units ng/mL.

1st, initial, first-generation assay; 2nd, second-generation assay.

## Case 2

The patient presents with a chief complaint of “I have a pain in my chest that hurts very bad.” He is a diabetic with a history of atypical chest pain over the past 3 months. He now presents with ischemic symptoms, chest pain, shoulder

pain, aching jaw, and nausea. His ECG demonstrates an ST-segment elevation acute MI. His initial cTnT value is increased above the 99th percentile reference cutoff ( $>0.01$  ng/mL) at  $0.013$  ng/mL and increases to  $0.073$  ng/mL over the next 4 hours. He is immediately transferred, following medical therapy, to the catheterization laboratory, where a stent is successfully placed.

<i>Time (h)</i>	<i>Initial cTnT</i>	<i>Serum cTnT</i>	<i>Plasma cTnT</i>
0, presentation	0.013	0.013	0.010
4	0.073	0.073	0.022
8	0.025	0.133	0.025
12	0.293	0.763	0.293

All units ng/mL.

However, the laboratory findings after the initial rising cTnT over the first two samples (0h and 4h), followed by a subsequent decrease on the 8h sample, were quite perplexing to both the attending cardiologist and the pathologist in the laboratory, since the patient was diagnosed with an acute, evolving ST-segment elevation MI. At 12 hours, the cTnT value again demonstrated an increasing value. An astute laboratory medicine resident reviewing the case recollected a paper that demonstrated the potential of lower cTnT results in heparin-plasma specimens (green top tubes) versus serum (red top tubes). Further investigation did reveal that the 0h and 4h specimens were serum and that the 8h and 12h specimens were heparin plasma, and both plasma samples had analytically false low values. When waste serum specimens, drawn for other chemistries, were located in the laboratory refrigerator for the same 8h and 12h draw times and reanalyzed, both showed substantially higher and rising cTnT concentrations at  $0.133$  and  $0.763$  ng/mL as expected. Since July 2006, the cTnT assay by Roche, now a fourth-generation assay, has been reformulated and currently does not show any significant difference between serum and heparin plasma, allowing for a laboratory to use mix and matched specimen types. However, as cTnI assays have also been shown to demonstrate either a constant or random lower heparin-plasma cTnI lower bias, it is recommended to use only one specimen type for an individual patient when ruling in or out an acute MI.

### Case 3

A 64-year-old male is found unresponsive at home by his wife while he was sitting and apparently watching a football game on a Sunday afternoon at 2:30 p.m. 911 was called after she was unable to arouse him. Emergency medical services arrive within 15 minutes and upon examination his ECG demonstrates an ST-segment depression and T waves. He is transported on 100% oxygen to the hospital, and is now awake but disoriented, but

complaining of severe chest pain and left shoulder pain. His ECG remains unchanged and his 0h presenting cTnI concentration performed at the bedside using a point-of-care (POC) assay (15-min turnaround time) is within normal limits: less than the 99th percentile cutoff of 0.04 ng/mL. During the course of the patient's treatment in the emergency department, a second POC cTnI at 3 hours is also normal. However, a call from the central laboratory at this time reports that the initial plasma sample (0h) when reanalyzed per protocol in the central laboratory reflects an increased value of 0.07 ng/mL (central laboratory 99th percentile cutoff 0.025 ng/mL). Based on this discrepant finding, the patient is immediately transferred to a telemetry unit and the diagnosis of a non-ST-segment elevation MI is made. Further investigation of two additional serial cTnI samples shows a rising pattern by both the POC and central laboratory assays, but reveals that the POC assay's poor low-end analytical sensitivity was not able to detect the early increase in cTnI until 8h versus 0h for the second-generation central laboratory cTnI assay. Further it was found that there was a poor correlation between the two different assays. This case demonstrates the importance of understanding the limitations of first-generation versus second-generation assays, irrespective of whether they are POC or central laboratory platforms. The first-generation assays are not as analytically sensitive nor as precise as the newer generation troponin assays. Therefore, different clinical impressions based on the troponin assay used can confuse the clinician caring for a patient. One needs to know the assay and understand that not all assays are created equal.

<i>Time (h)</i>	<i>POC cTnI</i>	<i>Central laboratory cTnI</i>
0, presentation	<0.04	0.07
3	<0.04	0.18
8	0.09	0.37
12	0.33	1.05

All units ng/mL.

### Discussion of Cases 1, 2, and 3

A European Society of Cardiology/American College of Cardiology (ESC/ACC) consensus conference along with the AHA (American Heart Association)/ACC guidelines for differentiating acute MI and unstable angina codified the role of cTn monitoring by advocating that (a) the diagnosis of MI and (b) establishing a high-risk profile (evidence of myocardial injury) are based on increases of cTnI or cTnT in the appropriate clinical setting [1–3]. These guidelines are also supported by parallel statements by the IFCC Committee on Standardization of Markers of Cardiac Damage (C-SMCD) [4]. The guidelines recognized the reality that neither the clinical presentation nor the ECG had adequate clinical sensitivity and specificity for detecting MI without

the use of biomarkers. The guidelines do not suggest that all increases of these biomarkers should elicit a diagnosis of acute MI or high-risk profile—only those associated with the appropriate clinical and ECG findings. When cTn increases not due to acute ischemia, the clinician is obligated to search for another etiology for the elevation (see Chapter 8). Overall, the goal of both laboratorians and clinicians is to establish acceptable, uniform criteria for all cTn assays so that they can be objectively evaluated for their analytical qualities [5] and clinical performance [2, 3].

The first investigators to develop an assay (radioimmunoassay) to measure cTn using polyclonal anti-cTnI antibodies were Cummins *et al.* [6]. While the assay showed approximately 2% cross-reactivity with skeletal TnI, it still had excellent clinical specificity for cardiac muscle injury. However, the assay was never developed for commercial use. The first monoclonal, anti-cTnI antibody-based immunoassay was described by Bodor *et al.* [7]. This assay has <0.1% cross-reactivity with skeletal TnI, but it was not suited for clinical use because of the lengthy assay time. Over the past 15 years, numerous manufacturers have described the development of monoclonal antibody-based diagnostic immunoassays for the measurement of cTnI and cTnT in serum [8, 9]. Assay times range from 5 to 30 minutes. Table 1.1 shows that over a dozen assays have been cleared by the Food and Drug Administration (FDA) for patient testing within the United States on central laboratory and POC-testing platforms.

**Table 1.1** FDA-cleared cTn assays.

Assay	LLD	99th	WHO-ROC	10% CV*
Abbott ARCH	0.009	0.012	0.3	0.032
Abbott AxSYM ADV	0.02	0.04	0.4	0.16
Abbott i-STAT <sup>†</sup>	0.02	0.08 (WB)	ND	0.1
Bayer Centaur	0.02	0.1	1.0	0.35
Bayer Ultra	0.006	0.04	0.9	0.03
Beckman Accu	0.01	0.04	0.5	0.06
Biosite Triage <sup>†</sup>	0.05	<0.05	0.4	NA
bioMerieux Vds	0.001	0.01	0.16	0.11
Dade RxL	0.04	0.07	0.6–1.5	0.14
Dade CS <sup>†</sup>	0.03	0.07	0.6–1.5	0.06
DPC Immulite	0.1	0.2	1.0	0.6
MKI Pathfast	0.006	0.01	0.06	0.06
Ortho Vitros ES	0.012	0.032	0.12	0.053
Response <sup>†</sup>	0.03	<0.03 (WB)	ND	0.21
Roche Elecsys	0.01	<0.01	0.03	0.03
Roche Reader <sup>†</sup>	0.05	<0.05 (WB)	0.1	ND
Tosoh AIA	0.06	0.06	0.31–0.64	0.06

LLD, lower limit of detection; 99th, percentile reference limit; ROC, receiver operator characteristic curve optimized cutoff; 10% CV, lowest concentration to provide a total imprecision of 10%.

\*Per manufacturer.

<sup>†</sup>POC assay. Adapted from Ref. [8].

In addition to these quantitative assays, several assays have been FDA cleared for the qualitative determination of cTnI and cTnT. Over 50% of the assays are newer second-, third-, or fourth-generation assays that have improved low-end analytical sensitivity, without analytical interferences that have plagued first-generation assays.

Two major hurdles are present that limit the ease for switching from one cTnI assay to another. Assay concentrations fail to agree because (1) there is currently no primary reference cTnI material available for manufacturers to use for standardizing their assays and (2) different epitopes are recognized by the different antibodies used on individual platforms. An effort has been underway for the past 3 years by the AACC Subcommittee on Standardization of Cardiac Troponin I to prepare a primary reference material [10, 11]. In collaboration with the National Institute for Standards and Technology (NIST), a reference material, a cTnT–cTnI–cTnC ternary complex, has been identified (SRM 2921). Working with NIST and the *in vitro* diagnostic industries, preliminary round-robin studies have demonstrated that while standardization of assays remains elusive, harmonization of cTnI concentrations by different assays has been narrowed from a 20-fold difference to a 2- to 3-fold difference [11].

cTnI is present in the circulation in three forms: (1) free, (2) bound as a two-unit binary complex (cTnI–cTnC), and (3) bound as a three-unit ternary complex (cTnT–cTnI–cTnC). In addition, there are potentially several additional forms that also exist for these three forms, representing N- and C-terminal degradation forms, oxidation and reduction forms, and phosphorylated forms [12]. Therefore, different assays do not produce equivalent concentration results, and comparisons of absolute cTnI and cTnT concentrations in clinical studies cannot and should not be made because not all assays measure the different forms with equal molarity (Case 3). Comparisons between assay systems must view changes as relative to each assay's respective upper reference limit. Users must understand the analytical characteristics of each troponin assay prior to clinical implementation.

There is only one cTnT assay in the marketplace, currently a fourth generation, due to intellectual property rights owned by Roche. Several adaptations of the cTnT immunoassay kit marketed by Roche Diagnostics (Indianapolis, IN) have been described. Two monoclonal anti-cTnT antibodies are used in the second- through fourth-generation assays. Skeletal muscle TnT is no longer a potential interferent, as was found in the first-generation ELISA cTnT assay [13]. In contrast to cTnI, no standardization bias exists for cTnT because the same antibodies (M11, M7) are used in both the central laboratory and POC quantitative and POC qualitative assay systems. The fourth-generation assay is no longer prone to interference due to heparin, as found in green top sample collection tubes, which previously was shown to cause assay-decreased cTnT and assay-dependent cTnI values when compared to serum [14].

Surveys on cTn use have been carried out, but the data in the peer-reviewed literature are minimal. The distribution of cTn assays used as reported over the

**Table 1.2** Quality specifications—cTn assays.

A.	Analytical factors
1.	Antibody specificity—recognize epitopes in stable part of molecule and equimolar for all forms
2.	Influence of anticoagulants
3.	Calibrate against natural form of molecule
4.	Define type of material useful for dilutions
5.	Demonstrate recovery and linearity of method
6.	Describe detection limit and imprecision (10% CV)
7.	Address inferents, i.e., rheumatoid factors, heterophile antibodies
B.	Preanalytical factors
1.	Storage time and temperature conditions
2.	Centrifugation effects—gel separators
3.	Serum-plasma-WB correlations

past several years by the College of American Pathologists surveys accounted for approximately 85% of cTnI assays (11 vendors) and 15% cTnT assays (1 vendor). Approximately 10–15% of all users utilize POC-testing assays.

In 2001, the IFCC C-SMCD established recommended quality specifications for cTn assays [5]. The objectives were intended for use by the manufacturers of commercial assays and by clinical laboratories utilizing troponin assays. The overall goal was to attempt to establish uniform criteria in order that all assays could objectively be evaluated for their analytical qualities and clinical performance. Both analytical and preanalytical factors were addressed as shown in Table 1.2. First, an adequate description of the analytical principles, method design, and assay components needs to be made. This includes the following recommendations. Antibody specificity as to what epitope locations are identified needs to be delineated. Epitopes located on the stable part of the cTnI molecule should be a priority. Further, assays need to clarify whether different cTn forms (i.e., binary versus ternary complex) are recognized in an equimolar fashion by the antibodies used in the assay. Specific relative responses need to be described for the following cTnI forms: free cTnI, the cTnI–cTnC binary complex, the cTnT–cTnI–cTnC ternary complex, and oxidized, reduced, and phosphorylated isoforms of the three cTnI forms [15]. Further, the effects of different anticoagulants on binding of cTnI need to be addressed (Case 2) [14]. Second, the source of material used to calibrate cTn assays, specifically for cTnI, should be reported. Currently, a cTnI standardization subcommittee of the AACC is recommending the use of SRD 2921 as a primary reference material that will assist in at least harmonizing cTnI concentrations across different assays, providing traceability [11]. Because antibody differences will always be present in different assays, complete standardization will never be possible for cTnI. For cTnT however, as there is only one assay manufacturer (Roche Diagnostics), standardizing between assay generations has been consistent. Third, assays need to describe minimal detection limits and total imprecision at the 99th percentile reference cutoff, as well as potential interferent, such

as rheumatoid factors, heterophile antibodies, human antimouse antibodies (Case 1). Preanalytical factors that should be described include effect of storage time and temperature, effect of glass versus plastic tubes and gel separator tubes, and influence of anticoagulants and whole blood measurements. As more assay systems are devised for POC testing, the same rigors applied to the central laboratory methodologies need to be adhered to by the POC-testing systems.

While clinicians and laboratorians continue to publish guidelines supporting TATs of <60 minutes for cardiac biomarkers, the largest TAT study published to date has demonstrated that TAT expectations are not being met in a large proportion of hospitals. A CAP Q-probe survey study of 7020 cTn and 4368 CK-MB determinations in 159 hospitals demonstrated that the median and 90th percentile TAT for troponin and CK-MB were as follows: 74.5, 129, 82, 131 minutes, respectively [16]. Less than 25% of the hospitals were able to meet the <60-minute TAT, representing the biomarker order-to-report time. Unfortunately, a separate subanalysis of just POC-testing systems was not reported. However, preliminary data have shown that implementation of POC cTn testing can decrease TATs to <30 minutes in cardiology critical care and short-stay units [17]. These data highlight the continued need for laboratory services and health-care providers to work together to develop better processes to meet a <60-minute TAT as requested by physicians.

Defining the 99th percentile of a reference group for cTn assays should be determined in each local laboratory by internal studies using the specific assay used in clinical practice or accept the validation provided in the peer-reviewed literature [18]. Further, acceptable imprecision (coefficient of variation, % CV) of each cTn assay has been defined as  $\leq 10\%$  CV at the 99th percentile reference limit [19]. Unfortunately, the majority of laboratories do not have the resources to perform adequately powered reference-range studies nor the ability to carry out National Committee for Clinical Laboratory Standards (NCCLS) protocols to establish total imprecision criteria for every cTn assay in the marketplace. However, newer generation assays are now starting to meet these imprecision goals. Therefore, clinical laboratories need to rely upon the peer-reviewed published literature to assist in establishing local reference limits. Numerous reference studies have been carried out for specific cTn assays. When reviewing these studies, caution must be taken when comparing the findings reported in the manufacturer's FDA-cleared package inserts, with the findings reported in journals because of differences in total sample size, distributions by gender and ethnicity, age ranges, and the statistic used to calculate the 99th percentile given. To date, very few *in vitro* diagnostic companies have published their 99th percentile cutoffs in their package inserts. There is no established guideline set by the FDA to mandate a consistent evaluation of the 99th percentile reference limit for cTn. The largest and most diverse reported reference range study to date shows plasma (heparin) 99th percentile reference limits for eight cTn assays (seven cTnI and one cTnT; [18]). These studies were performed in 696 healthy adults (age range 18–84 yr) stratified by gender and ethnicity.

The data, while generally in agreement with information provided by personal communication by the manufacturer, demonstrate several issues. First, two cTnI assays show a 1.2- to 2.5-fold higher 99th percentile for males versus females. Second, two cTnI assays demonstrated a 1.1- to 2.8-fold higher 99th percentile for African Americans versus Caucasians. Third, there was a 13-fold difference between the lowest versus the highest measured cTnI 99th percentile limit. The lack of cTn assay standardization (there is no primary reference material available) and the differences in antibody epitope recognition between assays (different assays use different antibodies) give rise to substantially discrepant concentrations. What is generally recognized, though, as long as one understands the characteristics of an individual assay and does not attempt to compare absolute concentrations between different assays, clinical interpretation should be acceptable for all assays.

Operationalizing the 2000 ESC/ACC redefinition of MI consensus document, which is predicated on cTn monitoring, has already substantially impacted the rate of defining MI in day-to-day clinical practice, in the emergency department, in epidemiology, in clinical trials, in society, and in public policy [3]. To quote Harvey D. White, DSc (cardiologist from New Zealand), "Things ain't what they used to be" [20]. Characteristics used to define a disease in one county may be interpreted differently by clinicians in another nation, thus possibly rendering comparison of cardiac disease between countries difficult but not impossible. In this light, a statement cosponsored by the AHA, the World Heart Federation Councils on Epidemiology and Prevention, the Center for Disease Control and Prevention, and the National Heart, Lung, and Blood Institute recently published a case definition for acute coronary heart disease (CHD) in epidemiology and clinical research studies [3]. This statement was based on a systematic review of evolving diagnostic strategies, with the goal of developing standards for population studies of CHD. The definition of CHD cases was deemed dependent on symptoms, signs, ECG, and/or autopsy findings and biomarkers. Cardiac biomarkers, measures of myocardial necrosis, were prioritized for use as follows: cTn > CK-MB mass > CK-MB activity > CK. An adequate set of biomarkers was determined to be at least two measurements of the same biomarker at least 6 hours apart (similar to the preestablished ESC/ACC consensus [2]). A diagnostic biomarker was, at least, one positive biomarker in an adequate set showing a rising or falling pattern in the setting of clinical ischemia and the absence of noncardiac causes of biomarker elevation. An equivocal biomarker was when only one available measurement was positive, but not in the clinical setting of ischemia or in the presence of nonischemia causes. A positive biomarker was defined as exceeding the 99th percentile or the lowest concentration at which a 10% CV can be demonstrated.

For clinical trials, to avoid the confusion of multiple centers using multiple assays, several approaches are recommended for utilizing cTn testing [8, 21]. First, analyze all samples from trial centers in a core, central laboratory with a precise, well-defined assay. Second, provide all trial centers with the same

well-defined assays. Third, uniformly define each center's assays by using the 10% CV concentration (assay dependent), thus not relying on local laboratory criteria and troponin cutoffs. Fourth, use a multiple (two- to threefold) of the 10% CV cutoff value. Fifth, if trials decide to use cutoff values defined in earlier studies, the degree of variability should be reported. However, since these earlier recommendations, the Global Task Force for defining MI has superseded the 10% CV value, and now, along with laboratory and emergency medicine organizations, 100% endorse the use of the 99th percentile reference cutoff. The revision from the 10% CV to the 99th percentile cutoff was supported by two studies that showed that imprecision at the 99th percentile did not significantly impact the diagnostic use or risk stratification assessment of patients presenting with clinical symptoms suggestive of acute coronary syndrome (ACS) [22, 23].

The advances in diagnostic technology in the development of improved low-end analytical detection of cTn have begun to impact the prevalence of acute MI detection. Accumulating data suggest that the more sensitive cTn tests result in greater rates of MI diagnosis and greater rates of cTn positivity compared to other markers [3, 24]. Milder and smaller degrees of myocardial injury will be detected. Clinical cases that were earlier classified as unstable angina will be given a diagnosis of MI (due to an increased cTn), and now procedure-related troponin increases, i.e., following angioplasty, will be labeled as an MI. The importance of small troponin increases even within the 99th percentile reference range has been confirmed by their association with a poor prognosis [24, 25]. Based on several studies that compared CK-MB and cTn assays in ACS patients, a substantial increase in rate of MIs ranging from 12 to 127% was detected [3]. In one of the studies by Lin *et al.*, a subset (5%) of cTnI-negative, but CK-MB-positive patients revealed the potentially underlying false-positive MI rate when using CK-MB as a standard for MI detection [24]. This was likely due to release of CK-MB from skeletal muscle in the absence of myocardial injury. Further, a subset (12%) of cTnI-positive, CK-MB-negative patients demonstrated a subset of patients diagnosed as having had an MI that would not have been detected without cTn monitoring. These data support the implementation of cTn in place of, not in combination with, CK-MB.

Thus, the quality of cTn assays is improving with release of second-, third-, and fourth-generation immunoassays. Manufacturers are working more closely with clinical and laboratory investigators to appropriately validate the analytical qualities of new assays. Implementation of these new assays into clinical trials will be crucial for establishing an appropriate evidence-based literature. As cTn assay implementation grows and lower analytical cutoffs are implemented for detection of myocardial injury, diagnosis of MI, and risk stratification, patient care and management will be impacted across society.

Several factors have been identified for being responsible for both analytical false-positive cTn findings without the presence of myocardial injury [26] and false-negative findings when myocardial injury was present [27]. Common