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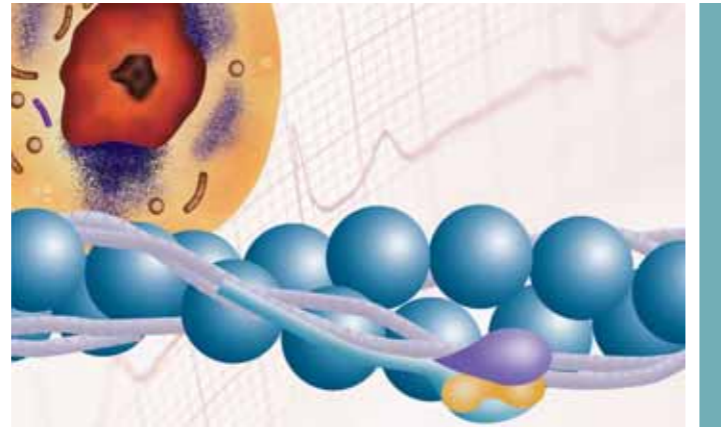
Troponin Clinical Applications

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The Evolution of Troponin



Myocardial muscle tissue

The utility of troponin has rapidly evolved since the first commercially available assays were released starting in 1997. Originally used only as an aid in the diagnosis of Acute Myocardial Infarction (AMI), troponin testing has expanded into other areas of clinical utility, including the risk stratification and prognosis of patients with acute coronary syndromes.

The expansion of the clinical utility of troponin occurred along with advances in precise imaging techniques that have a high sensitivity to detect very small infarcts. These improvements in diagnostic capabilities, coupled with a better understanding of the significance of troponin in myocardial damage, led to modifications in both the definition of a "positive troponin" and the definition of a Myocardial Infarction. Hence the clinical application of troponin in chest pain patients has changed, creating a need to better understand the critical diagnostic cutpoints reported by laboratorians and used by clinicians.

Troponin in Myocardial Infarction

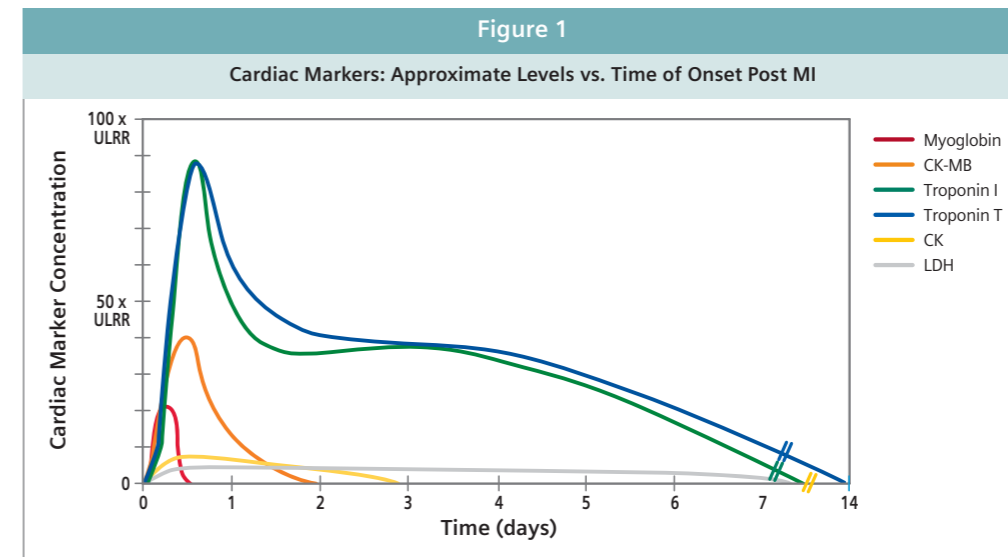
World Health Organization Definition of MI

Historically, there had been implicit agreement amongst physicians and other cardiovascular experts as to the meaning of the term "myocardial infarction". The World Health Organization (WHO) definition was widely accepted and set the standard by which physicians diagnosed MI. The 1971 WHO criteria required the presence of two of the following three features:¹

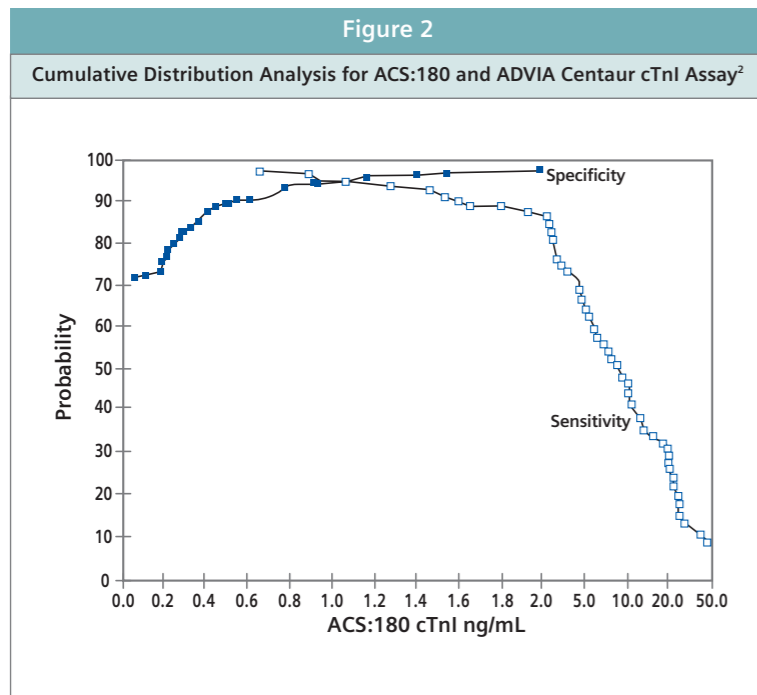
- Symptoms of myocardial ischemia (i.e continuous chest pain for 20 minutes)
- ECG changes with ST segment elevation or Q wave development
- Elevation of sensitive and specific cardiac enzymes in circulation

Prior to the commercial release of troponin assays for use in diagnostics laboratories, relatively non-specific markers of myocardial damage were used such as CK and CK-MB. The lack of specificity with these markers assisted in the delineation between patients labeled as MI and those determined to have unstable angina. Clinical studies of Troponin suggested improved cardiac specificity compared to CK or CK-MB and proved that troponin was elevated over a time period sufficient to cover the diagnostic window of MI (Figure 1).

To establish MI diagnostic cutpoints for troponin, manufacturers performed studies comparing troponin results to patient clinical diagnoses. Diagnosis of MI depended upon the standard markers available at the time (CK-MB, CK, etc.) as part of the original WHO criteria. Due to the nonspecific nature of these markers, the cutpoint chosen favored the rule-out of MI. Receiver Operator Curves (ROC) and Cumulative Distribution Analyses (CDA) were established defining the troponin value where clinical sensitivity and specificity could be maximized, and diagnostic cutpoints were established.



Chest pain patient



The CDA for the ACS:180[®] and ADVIA Centaur[®] cTnI assay is shown here. Using the appropriate statistical methods, it was determined that 1.5 ng/mL was the optimal cutpoint to differentiate MI from non-MI patients using this assay.

Troponin in Risk Stratification

In the late 1990s, the National Academy of Clinical Biochemistry (NACB) issued their “Standards of Laboratory Practice: Recommendations for the Use of Cardiac Markers” consensus statement. These recommendations stated that detection of any myocardial injury with a specific cardiac marker such as cTnI is clinically important and warrants the incorporation of a low abnormal decision limit for the optimum use of such markers in Acute Coronary Syndrome (ACS) patients. This was the first time that troponin testing had been recommended for the wider group of ACS patients and not just for MI. The NACB guidelines further recommended that a lower decision limit, or cutpoint for cardiac assays, be guided by the 97.5th percentile among healthy individuals.³

An international group of physicians (TIMI [Thrombolytics in Myocardial Infarction]) conducted a study which expanded on the NACB guideline recommendation using the 97.5th percentile of normal as a decision limit in ACS patients. In this study, the outcomes of patients with unstable angina (UA) and Non-ST Elevated MI (NSTEMI), as defined by electrocardiographic (EKG) profiles, were assessed for negative clinical events in the first 43 days after admission into the study with symptoms of chest pain.⁴



Risk stratification is applicable only to patients that are diagnosed with unstable angina or NSTEMI and are having chest pain.

The authors concluded that UA/NSTEMI patients with cTnI ≥ 0.10 ng/mL, using the ACS:180 cTnI assay, had a 3 to 4-fold increased risk (odds ratio) of a coronary event occurring compared to those patients with values < 0.10 ng/mL. This additional indication for use of cTnI at cutpoints approximately 10-fold lower than previously used was initially called “Risk Stratification of Acute Coronary Syndromes”. The data from this study provided Siemens Diagnostics with FDA clearance for risk stratification of patients with non-ST segment elevation acute coronary syndromes (Table 1).

The risk stratification concept is used to estimate the probability of the patient having a major cardiac event in the next 30-60 days. Risk stratification is applicable only to patients that are diagnosed with unstable angina or NSTEMI and are having chest pain. Risk stratification is based on serial testing over the first 24 hours after the onset of chest pain or admission to the hospital.

Table 1: Data Yielding Siemens Diagnostics ACS:180 cTnI Assay FDA Clearance for Risk Stratification			
Clinical outcomes at 43 days among all substudy patients stratified by cTnI results (0-24 h after enrollment)			
Outcome at 43 days	Positive, % (n = 444)	Negative, % (n = 237)	P
Death	5.4	2.5	0.08
MI	10.4	3.0	0.0004
Death or Nonfatal MI	13.7	4.2	<0.0001
Composite Endpoint	26.1	12.2	0.00002

“Positive” and “negative” refer to cTnI results from the first 24 h after enrollment for each of the assays, with positive cTnI concentrations being $(\geq) 0.1$ ug/L.

Composite endpoint: death, MI or urgent revascularization.

Troponin in the Redefinition of Myocardial Infarction

In 2000, a joint committee of the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) convened to reevaluate MI as previously defined by the World Health Organization. In light of advances in precise imaging techniques and the availability of a more sensitive and specific cardiac biomarker (troponin), the committee recommended a new definition of Myocardial Infarction.

elevation of troponin above the upper limit of the reference population would now be defined as MI. The ESC/ACC stipulated that troponin assays have an acceptable precision at the 99th percentile and defined this as $\leq 10\%$.

Troponin Assays and the Redefinition of MI

The ESC/ACC consensus document defines MI as any amount of myocardial necrosis caused by ischemia. The committee indicated that the preferred biomarker for myocardial damage is cardiac troponin, as it has nearly absolute myocardial tissue specificity, high sensitivity, and identifies even microscopic zones of myocardial necrosis.⁵

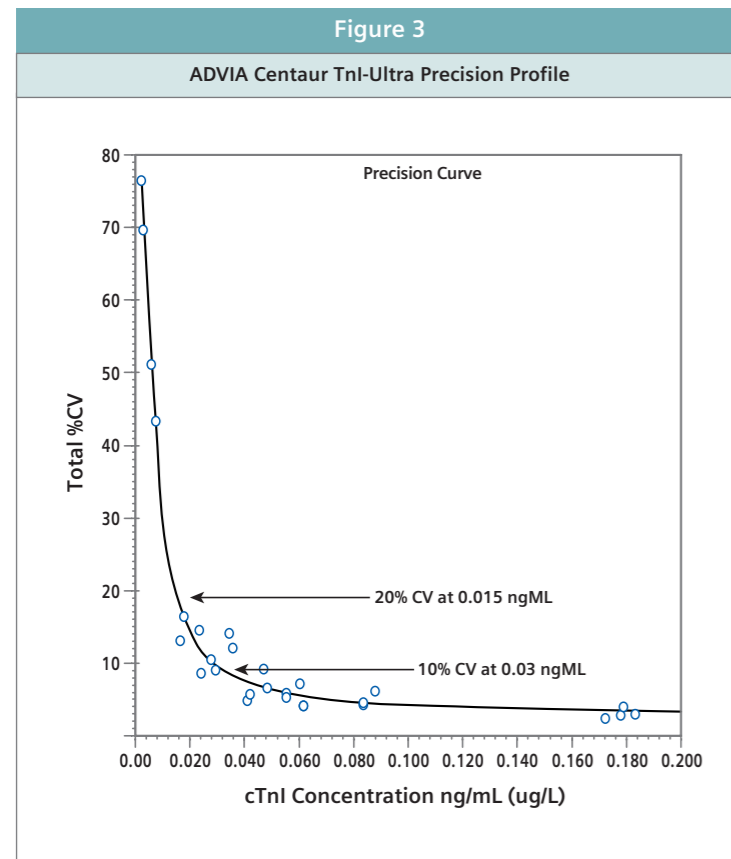
When the ESC/ACC consensus document was published, no manufacturer’s troponin assay met the guidelines for precision at the 99th percentile. In fact, most troponin assays had a 20-35% CV at this critical decision point. This lack of precision posed a problem for clinicians who adopted the 99th percentile diagnostic cutpoint for MI, as repeat or serial samples often did not match. This created a lack of confidence in laboratory test results.

The ESC/ACC committee defined an increased value for cardiac troponin as a measurement exceeding the 99th percentile of a reference control group of “normal” or non-diseased individuals. This meant that any positive

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Since the publication of the ESC/ACC consensus document on the redefinition of MI, Siemens has been developing a high precision, high sensitivity troponin assay designed to meet the ESC/ACC guidelines on the ADVIA Centaur and ADVIA IMS*. The assay is also available on the ADVIA Centaur CP.

The reference range for the ADVIA Centaur TnI-Ultra assay was established by measuring circulating Troponin I levels in 1845 samples from 648 apparently health individuals. Statistical analysis of the data showed a 99th percentile of 0.04 ng/mL and a 10% CV at 0.03 ng/mL. This is a 10-fold improvement in precision versus the ADVIA Centaur cTnI assay and many of the other Troponin assays on the market today* (Figure 3).



The TnI-Ultra assay is the first “fully-automated” troponin assay that meets the ESC/ACC guidelines for precision at the 99th percentile.



Patient recuperating from Myocardial Infarction

Improvements in low-end precision were precipitated by a novel change in the architecture of the ADVIA Centaur TnI-Ultra assay. These events have also led to an improvement in the analytical sensitivity of the assay. The ADVIA Centaur TnI-Ultra assay has a mean detectable concentration of 0.006 ng/mL in comparison to 0.03 ng/mL with the ADVIA Centaur cTnI Assay. (Table 2)

While the results of the TnI-Ultra assay should be interpreted in light of all relevant clinical information, including physical examination, ECG results, and medical history, the improved precision and analytical sensitivity of this new generation troponin assay are expected to confer greater confidence for the laboratorian in troponin reporting and for the physician in clinical decision-making.

Table 2: Assay Characteristic ADVIA Centaur TnI-Ultra ADVIA Centaur cTnI Benefit			
Assay Characteristic	ADVIA Centaur TnI-Ultra	ADVIA Centaur cTnI	Benefit
10% CV Value	0.03 ng/mL	0.33 ng/mL	10 fold improvement in precision
99th Percentile	0.04 ng/mL	0.07 ng/mL	Nearly 50% lower values
Minimum Detectable Concentration	0.006 ng/mL	0.03 ng/mL	5 times more sensitive
WHO Cutpoint	0.78 ng/mL	0.9 ng/mL	

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