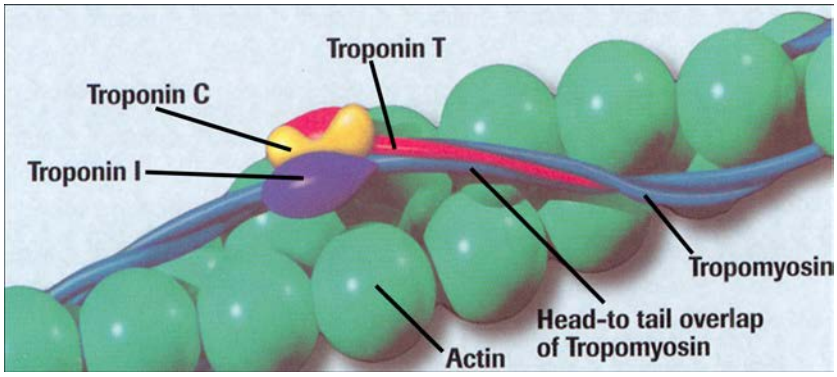
Increasingly Sensitive Assays for Cardiac Troponins:

One Step Back and Two Steps Forward?



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Internal Medicine Grand Rounds

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Research Interests

My research interests include enhancing diagnosis, phenotype characterization and risk assessment in cardiovascular disease, with a particular focus on cardiovascular biomarkers. Recent work has focused on novel applications of highly sensitive assays for cardiac troponins, which will be the focus of this Grand Rounds.

Purpose and Overview

The current indications for measurement of cardiac troponins T and I primarily focus on diagnosis and risk stratification in patients with suspected myocardial infarction. Recently, highly sensitive (hs) assays for cTnT and cTnI have been developed that can detect troponin concentrations ~10-fold lower than is possible with assays currently available for clinical use in the U.S. These assays improve sensitivity for the detection of MI, particularly early after symptom onset, at a cost of decreased specificity. Importantly, the ability to detect very low circulating troponin levels with these hs assays has opened the door for many additional potential applications for troponin measurement, both for clinical and for research purposes. The Grand Rounds today will review the current status and challenges with standard troponin assays, the implications of incorporating highly sensitivity assays for MI evaluation, and potential new indications for hs-troponin testing outside of the "rule out MI" setting.

Objectives

1. Highlight challenges with interpretation of troponin assays in contemporary clinical use.
2. Critically evaluate evidence regarding new, highly sensitive troponin assays for evaluation of patients with chest pain and suspected acute coronary syndromes.
3. Discuss novel applications for highly sensitive troponin assays, including risk assessment among patients with chronic cardiovascular conditions and screening for cardiovascular disease in apparently healthy individuals.

Biochemistry 101

Cardiac troponins (cTnT) and I (cTnI) are components of the myofibrillar contractile apparatus of cardiomyocytes. cTnT has a molecular weight of ~35kDa and cTnI of ~23 kDA. These low molecular weight proteins are released into the circulation following damage to cardiac myocytes by ischemia, infarction, trauma, toxic damage or inflammation.[1] The current generation immunoassays for cTnT and cTnI can detect concentrations in the peripheral blood reflecting < 1 gm of myocardial tissue necrosis. cTn can be detected in circulating blood as early as 2-3 hours after the onset of myocardial ischemia (and almost always by 6 hours), peaks at approximately 24 hours and may remain elevated for 10 days or longer after infarction. cTnT and cTnI have near absolute cardiac specificity, as adult skeletal muscle does not express the cardiac isoform of TnT or TnI, except under rare circumstances. Recently, several case series have demonstrated that some individuals with severe skeletal myopathies, including dermatomyositis and polymyositis, may have markedly elevated cTnT with normal cTnI, in the absence of any evidence of cardiac involvement. Re-expression of a fetal isoform of cTnT in skeletal muscle has been suggested in these individuals.[2]

Troponin measurement to "Rule out MI"—Where are we now?

Evaluation for acute coronary syndrome (ACS) accounts for over 1 million emergency room visits each year in the U.S. Troponins are currently considered the preferred biochemical markers of myocardial necrosis in patients with suspected ACS, due to their high sensitivity and nearly absolute cardiac specificity.[3] The *Universal Definition of MI*, negotiated by consensus by cardiologists representing the American College of Cardiology and the European Society of Cardiology, defines MI using troponin elevation and "clinical context," by which elevated troponin must be accompanied by symptoms or signs of ischemia to be classified as MI.[3] (Table)

Table. Third Universal Definition of MI

Detection of rise and/or fall of cardiac biomarkers (preferably cardiac troponin (cTn)) with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:
• Symptoms of ischemia;
• New significant ST-T changes or new left bundle branch block (LBBB);
• Development of pathological Q waves in the ECG;
• Imaging evidence of new loss of viable myocardium;
• Identification of an intracoronary thrombus by angiography

The Universal Definition subcategorizes five types of MI. Type 1 MIs represent spontaneous MI due to atherosclerotic plaque rupture or ulceration, with resulting coronary thrombus obstructing blood flow. Type 2 MIs are secondary MIs in which myocardial necrosis occurs when a condition other than CAD contributes to increased myocardial oxygen demand or decreased myocardial blood flow. Plaque rupture or fissuring is usually not present in type 2 MI, but underlying coronary artery disease may be present. MIs in the setting of severe anemia, atrial

arrhythmias, hypertensive emergencies, and critical medical or surgical illness may all meet criteria for type 2 MI. Type 3 MI represents sudden cardiac death, whereas type 4(PCI) and 5 (CABG) represent periprocedural MI.

Assays for cTnT are produced by only a single manufacturer, whereas many different manufacturers produce assays for cTnI, each using different proprietary antibody pairs. Thus the MI detection limits are specific for each assay. The decision limit for MI is set by consensus at the 99th percentile value of a "healthy normal population." It should be noted that this cutpoint has typically been defined by the assay manufacturers and not via rigorous scientific investigation. Moreover, the "in house" studies typically performed by the manufacturers to generate the normal reference ranges for the assays have not included sufficient numbers of patients to accurately define the 99th percentile value. These methodological weaknesses had modest impact when troponin assays were less sensitive, and could not detect values below the 99th percentile value. However, with more sensitive assays, that can detect levels well below the 99th percentile range, defining accurately the distribution of troponin levels in the population becomes critical to avoid misclassification of MI events.

Use of cTn in place of CK-MB resulted in a substantial increase in the frequency of MI diagnosis, with a significant proportion of individuals who were formerly diagnosed with unstable angina subsequently diagnosed with MI.[4] Kavsak et al. observed a relative increase of 84% in MI diagnosis in patients admitted for a clinical suspicion of unstable angina with normal CK-MB levels following the introduction of routine troponin testing.[5] In patients with a lower index of suspicion for ACS, an even greater proportional increase in MI incidence occurred.[5] Patients diagnosed with MI by troponin criteria, who would not have been diagnosed using the old CKMB criteria, were clearly at higher risk for adverse events compared to patients with undetectable troponin levels.[4] Similar findings have been observed when more sensitive troponin assays were compared with less sensitive assays. Improvement in assay sensitivity has resulted in more MIs (vs. unstable angina) being diagnosed, with the individuals newly diagnosed demonstrated to be at higher risk for adverse events than those without evidence of myocardial necrosis.

Expedited Protocols for Excluding MI

With conventional clinical assays, serial troponin measurements are needed to fully exclude MI, since a single test for cTn has only ~ 70-85% sensitivity and thus may miss up to 25% of MIs.[6, 7] For patients presenting within 3 hours of symptom onset, the sensitivity of a single troponin measurement is only 50-60% using standard assays.[6, 7] It should be noted that relatively few individuals present this early after symptom onset. If > 9 hours have elapsed since the last episode of chest pain, a single normal (undetectable) troponin level can reliably exclude MI.

Although the period of monitoring with serial troponin measurement had typically lasted 6-9 hours, shorter durations of monitoring appear to be appropriate among individuals with a low probability of MI who are also at low risk for complications. An innovative approach proposed by Than et al in the ADAPT study incorporated assessment of pre-test probability for MI and risk

for complications using the TIMI risk score, together with ECG findings and 0 and 2 hour measurement of cTnI.[8] Low risk was defined prospectively as a TIMI Risk Score of 0, no ischemic ECG changes, and a cTnI below the MI detection threshold. They identified 20% of 1975 patients presenting with suspected ACS to be at low risk with this algorithm. Only 1 individual had an adverse event in the low risk group, yielding a NPV of 99.7%. This expedited algorithm may allow rapid discharge of a meaningful proportion of individuals from the ED without additional testing.

Such "low probability, low risk" individuals comprise a large proportion of individuals monitored in chest pain observation units such as 2SS at PMH, where the rule in rate for MI is well below 5%. We have shortened the standard troponin "rule out MI" protocol on 2SS to 3 hours based on internal data (unpublished) showing extremely high negative predictive value with serial negative cTnT at 0 and 3 hours. As will be described below, with higher sensitivity assays, it may be possible to shorten the "rule out MI" observation period even further in some individuals.

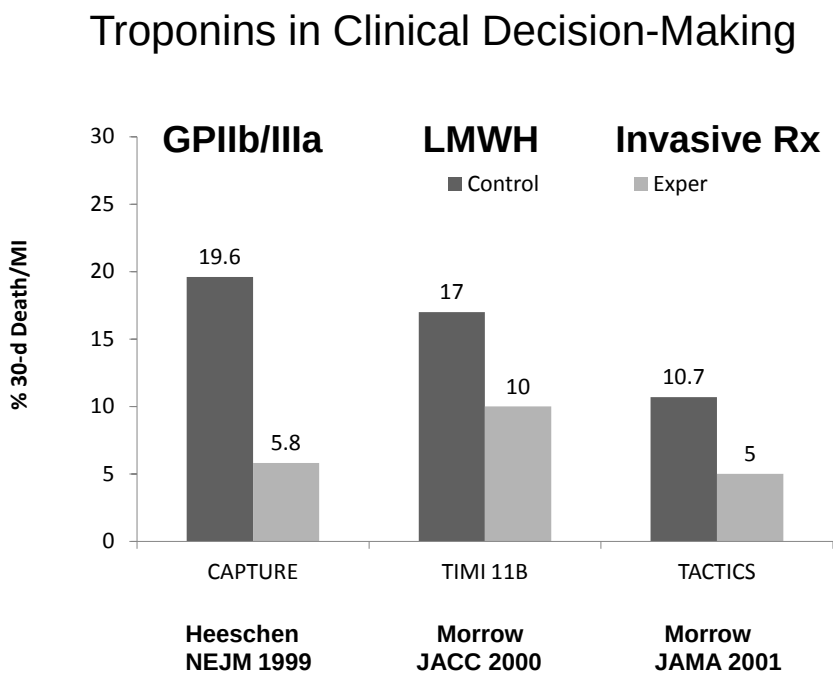
Diagnostic criteria for MI require not only a troponin value above the 99th percentile detection threshold, but also either a rise or a fall in levels over serial measurements. Observation of a rise and/or fall in cTn level in the appropriate time-frame increases the diagnostic specificity for MI. However, clear criteria for what defines a rise and fall have not been established.

Troponin measurement for Risk Stratification and Therapeutic Decision Making in Patients with Suspected ACS

Beyond their diagnostic role, troponins have a clear role in risk assessment for patients with suspected ACS. For example, Lindahl et al. described that the risk of cardiac events (death or non fatal MI) in five months following an initial event of unstable coronary artery disease was 4.3%, 10.5%, and 16.1% with cTnT levels < 0.06 µg/L, 0.06-0.18 µg/L, and > 0.18 µg/L respectively.[9] In a meta-analysis of 21 ACS studies involving 18,982 patients, the odds ratio for death or MI was 3.44 (95% CI 2.94 to 4.03, $p < 0.00001$) for patients with elevated compared to normal cTn.[10] Importantly, associations between troponin and outcome extend to even very minor elevations in levels.[11]

Beyond simple risk assessment, troponins also provide insight into underlying coronary artery morphological abnormalities. Severe coronary stenosis, 3-vessel disease, left main stenosis, complex plaque and visible thrombus have been more frequently seen during coronary angiography in patients with non-ST segment elevation ACS when elevated cTn is detected.[12] In the TACTICS-TIMI 18 Study, which enrolled patients with a very high probability of ACS, those with detectable cTn were more likely to have severe obstruction in the culprit coronary artery, visible intracoronary thrombus and abnormalities in microvascular perfusion, indicative of downstream embolism of platelet-thrombus to the coronary microcirculation.[13] Among patients with suspected ACS, even when coronary angiography reveals no significant CAD, elevated cTn is associated with a higher risk for death or re-infarction.[14]

These pathophysiological observations have been translated to facilitate therapeutic decision-making, as clinical trials have demonstrated significant benefit of aggressive antiplatelet and antithrombotic therapies, as well as percutaneous coronary interventions, in patients with elevated cTn levels. (Figure)



Multiple studies have shown that elevated cTn helps to identify patients with ACS who benefit from antiplatelet therapy with glycoprotein (GP) IIb/IIIa inhibitors. In contrast no benefit has been observed for GP IIb/IIIa inhibitors among patients with normal troponin levels.[15, 16] The FRISC study group reported that elevated cTnT identified a subgroup of patients with unstable coronary disease in whom more aggressive anti-thrombotic treatment is beneficial. In patients with a cTnT level ≥ 0.1 µg/L, administration of dalteparin reduced short-term incidence of death or MI from 6.0% to 2.5% ($p < 0.05$) compared to an insignificant reduction ($p = 0.12$) in patients with cTnT < 0.1 µg/L.[17] Similar findings were reported by Morrow et al. using cTnI for identification of patients benefitting from enoxaparin for unstable angina.[18] Most importantly, an early invasive strategy with routine coronary angiography and revascularization has shown substantial benefit in patients with elevated troponin levels after non-ST segment elevation ACS, compared to little or no benefit among patients with normal troponin levels.[11, 19]

There is no cutoff value for troponin concentration below which it could be considered harmless.[11, 20] A continuous relationship between cTn levels and mortality has been shown.[12, 21] However, the association between cTn levels and the risk of recurrent non-fatal myocardial infarction is a threshold function where ANY detectable level is associated with a significant increase in the risk for nonfatal recurrent ischemic events.[11] Importantly, the benefit from aggressive revascularization strategies appears to be greater among patients with low-level troponin elevation than among those with high-level troponin elevation.[11] This could be because

patients with very high cTn levels have sustained significant irreversible myocardial damage while those with lower-level elevations have salvageable myocardium but high-risk coronary anatomy.

In summary, in patients with ACS, troponins represented a paradigm for biomarker-guided personalized medicine, whereby a biomarker provides not only diagnostic and prognostic information, but pathophysiological information that can be exploited to guide specific clinical decisions. This is reflected in the American College of Cardiology/American Heart Association guidelines for Management of Unstable Angina and NSTEMI, which recommend that patients with suspected ACS and elevated troponins be treated with an early invasive strategy.[22]

The Specificity Problem

While troponins are almost exclusively specific for myocardial injury, they are not specific for an acute ischemic mechanism of injury.[1, 23] Any condition–acute or chronic--that causes injury to cardiomyocytes may lead to measurable increases in circulating troponins. Among the most important of these are heart failure, pulmonary embolism, renal failure, and sepsis.[1, 23] Recently, it has also been demonstrated that *chronic* cardiac conditions may lead to persistent low level release of cardiac troponins.[24-26] In each of these non-ACS disease states, elevated troponins mark individuals at high risk for death and complications. However, many of these conditions may confound the diagnosis of MI, particularly among complex hospitalized patients. Pulmonary embolism is a particularly important differential diagnosis to consider: low level troponin elevation in a patient with chest symptoms and nondiagnostic ECG changes may well be caused by PE rather than MI.

Tom Wallace, while he was a UTSW Chief Resident, performed a study evaluating determinants of detectable cTnT in the general population, using the Dallas Heart Study as the test cohort.[27] The cTnT assay used for the study was the same assay as is currently used at all of the UTSW-affiliated hospitals. In this study, which evaluated asymptomatic subjects representing the population of Dallas ages 30-65, 0.7% of the general population had detectable levels of cTnT ($\geq$ 0.01 µg/L). A specific adverse phenotype was observed among individuals with detectable cTnT, with four factors independently contributing to elevated cTnT —left ventricular (LV) hypertrophy (LVH), LV systolic dysfunction or evidence of heart failure, diabetes, and chronic kidney disease (CKD). (Figure, next page, left panel)

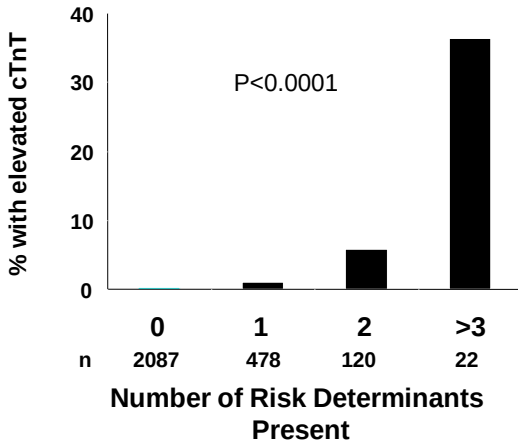
Of note, prior MI and coronary calcium (a measure of the burden of coronary atherosclerosis) did not associate independently with cTnT. These data suggested that either structural heart disease, or major determinants of structural heart disease (diabetes and CKD) explain most cases of chronically elevated cTnT in asymptomatic individuals. Moreover, individuals with multiple of these determinants have a high probability of chronically elevated cTnT. (Figure, next page, right panel) For example, a person with diabetes, mild to moderate CKD, and LVH may have a >30% probability of measurable cTnT in daily life; determining whether an elevated cTnT in such an individual is due to MI or represents chronic elevation may prove very challenging.

Troponin Elevation in the General Population

The Dallas Heart Study

0.7% prevalence of cTnT > 0.01 mg/L

Risk Determinant	Odds Ratio
Diabetes	**4.6**
LV Hypertrophy	**5.4**
Congestive Heart Failure	**5.3**
Chronic Kidney Disease	**20.4**



An elegant study by Alcalai et al. evaluated the frequency of non-ACS cTn elevations in the hospital setting.[28] They evaluated all elevated cTn values over a one year period in their hospital, and adjudicated a final diagnosis using all available records. Only about half of the elevated cTn measurements were due to MI; when complex patients were evaluated (older patients, those with CKD), the proportion due to MI was even lower (Table).

Positive Predictive Value for the Diagnosis of ACS in Different Patient Profiles

Patient Profile	Troponin Levels: Any Positive Result	0.1-1.0 ng/mL	>1.0 ng/mL
All patients	**56 (52-60)**	**48 (43-53)**	**76 (69-82)**
Age < 70 y and creatinine < 1.13 mg/dL	**78 (72-84)**	**73 (65-80)**	**89 (79-95)**
Age < 70 y and creatinine ≥ 1.13 mg/dL	**44 (35-55)**	**40 (29-52)**	**59 (36-79)**
Age > 70 y and creatinine < 1.13 mg/dL	**52 (42-63)**	**42 (31-54)**	**90 (68-99)**
Age > 70 y and creatinine ≥ 1.13 mg/dL	**37 (29-45)**	**27 (20-37)**	**59 (43-73)**

Alcalai et al. *Arch Intern Med.* 2007;167:276-81.

Unfortunately, the prognosis of these non-ACS cTn elevations is actually worse than cTn elevations from ACS, with 2-year mortality more than double in the non-ACS group compared

with the ACS group.[28] Thus, while we often trivialize non-ACS elevations using terms like troponinemia or troponinosis, these elevations carry important prognostic significance.

Few data are available to help clinicians sort out which cTn elevations are due to MI vs. other causes. Higher elevations are more commonly due to MI; moreover, observation of a larger rise and/or fall in cTn level over a 3-6 hour time period improves the diagnostic specificity for MI. However, clear criteria for what defines a rise and fall have not been established.

Approach to the Patient with Non-ACS Elevations in cTn

Troponin elevation, while specific for myocardial injury, is not specific for an ischemic mechanism and thus must be interpreted within the clinical context in which it is measured. In patients with a high clinical suspicion for ACS, troponin elevation provides powerful risk stratification information and can be used to guide therapeutic decision making. While non-ACS elevations in cTn may be due to type 2 MI (I.e. due to hemodynamic stress without plaque rupture), more commonly they represent acute cardiac injury from other causes (I.e. acute medical illness, heart failure, PE) or are chronic elevations associated with structural heart disease or CKD. Few data are available to guide management of patients with troponin elevation when the cause is not from ACS. A prudent approach utilizing clinical judgment, judicious testing, control of any hemodynamic derangements, and observation is reasonable in most circumstances. Data on elevated cTn in conditions such as congestive heart failure, pulmonary embolism, sepsis, renal failure and cardiac trauma is still evolving. There is evidence to suggest that elevated cTn in these patients indicates a high risk for complications, but it is not yet clear how this information should be used to alter the diagnostic or therapeutic approach. There is also a real possibility of misdiagnosis of these patients as having ACS, leading to inappropriate therapy for ACS and delays in delays in treatment of the precipitating cause.

Based upon the available evidence, it can be concluded that finding elevated cTn is rare in a healthy subject using assays currently available in the U.S. Therefore, any unexplained elevation of cTn should prompt additional evaluation and risk factor modification for cardiovascular disease. The evaluation and management should include detailed history, physical examination, standard laboratory testing, and an ECG. Given the strong association between cTn elevation and cardiac structural and functional abnormalities, an echocardiogram would also seem prudent. The diagnosis of pulmonary embolism should be considered and further testing should be performed as indicated by the clinical presentation.

When elevated cTn levels are found in patients hospitalized for non-cardiac reasons, or in post-operative patients without signs or symptoms of ischemia, treatment should be directed towards the primary disease. Additional cardiac evaluation should include ECG and often an echocardiogram. If the underlying condition would permit, therapy with aspirin and beta-blockers may be initiated. A noninvasive evaluation for ischemia may be considered in selected high risk individuals once the patient has fully recovered from noncardiac illness or surgery**. *Importantly, if detection of elevated cTn would not change clinical management, cTn levels should not be drawn as the test results may lead to confusion and inappropriate treatment.***

HIGHLY SENSITIVE TROPONIN ASSAYS

Given the important information that is provided by the detection of low levels of troponin, interest has focused on using higher sensitivity assays to detect even lower concentrations of this biomarker. Recently, a highly sensitive assay for troponin T (hs-cTnT) has been developed and commercialized (although not yet approved by the US FDA). This assay can detect levels of cTnT approximately 10-fold lower than the current 4th generation cTnT assay in use at UTSW/PMH and throughout the U.S. (Table)

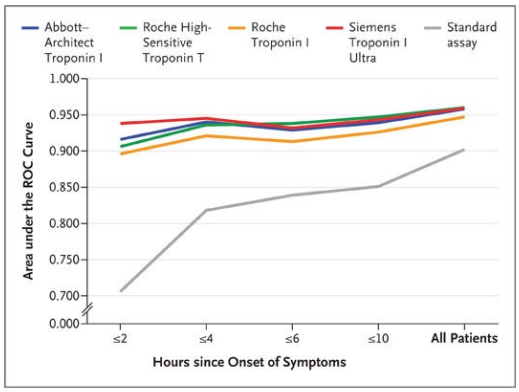
Table. Comparison of Conventional and Highly Sensitive cTnT Assays

	Conventional cTnT assay	Highly sensitivity cTnT assay
99th percentile in a healthy population	0.01µg/ L	0.014 µg/ L
10% coefficient of variation	0.03 µg/ L	0.012 µg/ L
Lower limit of detection	0.01µg/ L	0.003 µg/ L

Are the hs-cTn Assays Really an Advance in MI Diagnosis?

Several recent studies have evaluated the performance of highly sensitive troponin assays for MI detection in the emergency room.[6, 7] These studies demonstrated improved discrimination of MI events with the more sensitive assays, particularly in the early hours after symptom onset, in populations selected based on a relatively high probability of ACS. (Figure)

hs-cTn Assays for MI Diagnosis



Parameter	cTnT	hs-cTnT
Sens	83	95
Spec	95	80
NPV	97	99
PPV	72	50

cTnT threshold=0.01 µg/l
hs-cTnT threshold=0.014

Reichlin, NEJM 2009; 361:858-867

The improvement in the area under the ROC curve was due to the improved sensitivity of the new assays, which overcame worsening in specificity. These findings have been met with considerable enthusiasm, and the hs-cTnT assay is now in wide use for MI "rule out" in many parts of the world, including Europe, where it has largely replaced standard assays. Despite the apparently favorable findings of these studies, however, there are several concerns.

Although the negative predictive values of the more sensitive assays are evident from these studies, with the consequence that more patients may be able to be sent home sooner, the decrement in the positive predictive value has concerning implications for cardiologists. Few topics cause more consternation among cardiologists than the "troponin consult," which is a consult to a cardiologist to provide interpretation of an abnormal troponin value in a patient without evidence of acute ischemia These consults are challenging because even when the various potential causes of myocardial injury are considered, frequently no clear attributable cause can be found for the troponin increase. Moreover, the consulting cardiologist often perceives such consults as an explicit transfer of medico-legal liability from another provider [i.e., the emergency department (ED) or the primary-care team] to the cardiologist.

At least 60%–70% of individuals presenting to an ED with chest symptoms on a daily basis will have measurable troponin concentrations with the new highly sensitive assays, as will be discussed below. Moreover, among patients observed in a chest pain unit, it will be common for troponin concentrations to be above the MI detection threshold chronically, because such patients typically have either known cardiovascular disease or multiple risk factors. For example, in a study of chest pain patients by Januzzi et al., 16.4% of patients had cTnT values ≥13 ng/L, despite an MI rate of only 2.1%.[29] These observations highlight the need for a paradigm shift regarding the interpretation of troponin values. Whereas troponin results have classically been interpreted solely as dichotomous tests (positive/negative), there may now be a rationale to consider interpretation on a continuous scale.

Bayesian principles need to be considered when interpreting the highly sensitive troponin assays for MI detection. In the typical chest pain observation unit in the US (like 2SS at PMH), which does not admit individuals with clear or probable ACS, the probability of MI is low, typically <5%. With such a low pretest probability of MI, the balance between detecting an MI that would have been missed with a standard assay vs. detecting myocardial injury due to something other than MI will tip markedly toward increased "false positives" (Table).

Table. Estimated proportion of false positive MI diagnoses with hs-assay

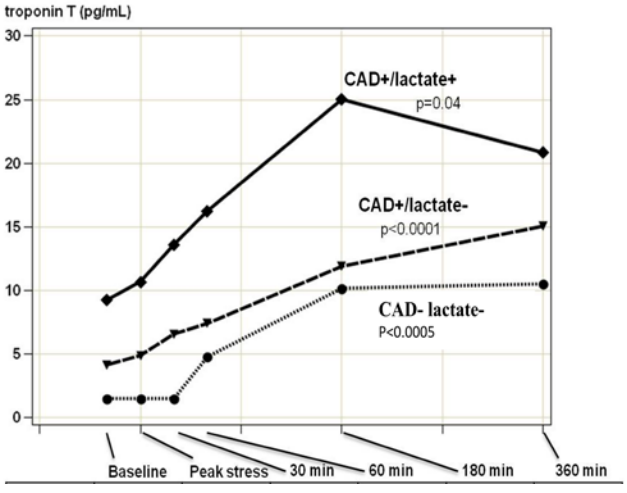
MI probability	**Positive tests with standard assay (per 1000 patients)**	**Positive tests with hs assay (per 1000 patients)**	**Additional positive tests meeting MI definition (per 1000 patients)**	**Additional positive tests not meeting MI definition (per 1000 patients)**
17%	199	328	21	108
10%	146	275	12	117
5%	108	237	8	121
3%	93	222	3	126

Thus, appropriate interpretation of troponin results with the highly sensitive assays will necessarily require a shift back to a global assessment of the clinical probability of myocardial ischemia that is inherently more demanding than simply interpreting troponin results as positive or negative. Additionally, it is likely that some ED providers will be uncomfortable managing the patient with a detectable troponin value that is below the MI-decision limit. If such individuals are routinely referred for cardiology consultation and/or additional testing, the indirect costs (and potential harms excess testing) associated with the highly sensitive assays may be substantial.

There are, of course, also potential advantages of the highly sensitive assays in the ED setting. Improved precision of these assays at the MI-detection threshold should improve MI classification. Although most of the detectable troponin values below the 99th percentile value will represent "baseline" concentrations reflective of chronic injury, concentrations in this interval may identify an adverse prognosis in patients with ACS,[20] and this information may improve risk assessment in the ED. Prospective studies are needed in chest pain populations at lower risk to determine whether detectable concentrations of troponin below the MI threshold identify individuals at increased risk for short-term adverse events and whether cost-effective strategies for additional evaluation can be defined. Finally, it is also possible that serial increases in troponin concentrations with values that remain below the MI-detection threshold will help to identify acute coronary ischemia earlier, prompting earlier intervention and preventing additional myocardial injury. This hypothesis, however, although attractive, has yet to be proved.

Can very low levels accurately discriminate unstable angina or reversible ischemia?

Although troponin elevation above thresholds of detection using current generation assays has become synonymous with "myonecrosis," it is less clear whether very low levels of troponin detected with more sensitive assays may result from ischemia without necrosis. To address this question, Aslan Turer from UTSW quantified myocardial release of cTnT using the new hs-cTnT assay during induced ischemia in a controlled human model, and correlated release with objective indicators of ischemia.[30] (Figure)



Turer et al. JACC 2011;57:2398-405

Figure: changes in peripheral cTnT concentrations following rapid atrial pacing in humans. Lactate elution is considered the gold standard for confirming ischemia.

Following rapid atrial pacing, circulating concentrations of cTnT detected by the hs assay were noted to increase both in patients with and those without biochemical or angiographic correlates of coronary ischemia. Although the absolute magnitude of increase was greatest in those without ischemia, relative increases were similar across groups, and a significant proportion of patients without markers of ischemia (e.g. those with no angiographic CAD and no evidence of cardiac ischemia by lactate elution) still had large relative increases in their cTnT levels. Sabatine et al measured cTnI with a novel hs-assay in 120 individuals undergoing stress-perfusion imaging, with measurements performed before, immediately after and 2 ad 4 hours after exercise induced stress. Transient, very low level release of cTnI was detected among individuals with ischemia (with greater increases in those with more severe ischemia) with no increase in those without ischemia. The changes seen were small, however, and were not able to accurately discriminate reversible ischemia.[31]

In aggregate, these findings suggest that reversible ischemia, without necrosis, may result in release of very small amounts of cardiac troponins, measurable with the hs-assay. They do not, however, suggest that cTn will be useful clinically to diagnose reversible ischemia. The poor diagnostic value for the hs-cTnT assay for unstable angina was confirmed by Reichlin et al, who reported AUCs of only 0.6-0.7 for diagnosis of unstable angina (compared with AUCs 0.9-0.95 for MI diagnosis). [32]

Potential Strategies to Maximize Strengths and Minimize Weaknesses of the hs-cTn Assays

Serial Measurements in cTn to improve specificity

Although it has been recommended that dynamic changes in troponin concentrations over short periods of time may be useful for distinguishing ischemia from other causes of troponin elevation, [29] few data are available to support this recommendation. Indeed, current recommendations focus on *relative* changes in cTn over serial follow-up as the preferred method to document a rising cTn levels. However, as described above in the Turer study, substantial *relative* increases are common even among individuals without evidence of ischemia or infarction. For example, 3 of the 5 patients without CAD in Turer's study had a tripling of their baseline cTnT levels with pacing, which was similar to the proportion seen in patients with CAD.[31]

Recent data suggest that a superior strategy is to evaluate *absolute* changes in cTn concentrations over time, which demonstrate much greater specificity than even large *relative* changes. With the hs-assays, it is possible to have a large relative change in cTn despite a very small absolute increase. Such small absolute changes do not demonstrate specificity for MI. Reichlin et al compared absolute and relative changes over a 1 and 2 hour period and demonstrated markedly greater specificity and PPV for absolute compared with relative increases.[32] (Table, next page)

Table. Operating Characteristics for Change in cTnT over 1 or 2 hours

hs-cTnT	AUC	ROC cutpoint	Sens	Spec	PPV	NPV
1 hour						
Absolute Δ	0.93	0.004	84	93	66	97
Relative Δ	0.66	17%	57	74	27	91
2 hour						
Absolute Δ	0.95	0.007	89	93	64	98
Relative Δ	0.76	30%	64	84	35	94

Reichlin T et al. Circulation 2011;124:136-145

These data provide clear evidence that when assessing change in cTn over time, clinicians should focus on absolute rather than relative changes. In summary, higher troponin values at the time of presentation, and greater absolute changes in troponin over 1-2 hours of follow-up, increase the probability of MI as the final diagnosis.

Rapid ROMI protocols with the hs-assays

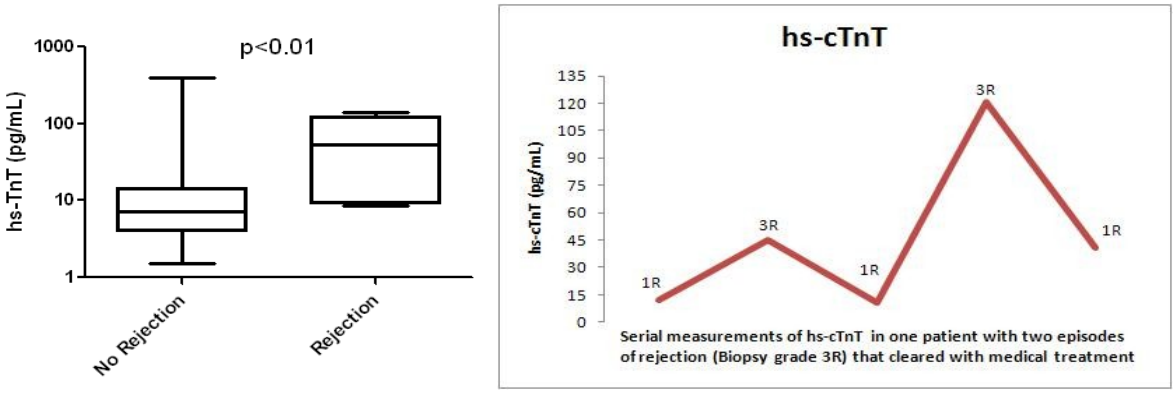
One strategy to maximize advantages of the lower detection range of the hs-assays is to focus not on the 99th percentile value (the MI detection threshold) but rather on the other end of the distribution of troponin values—those individuals below the detection range of the hs-assay. In one study of 703 patients from the UK, 19% were ultimately determined to have MI. Among the 28% of individuals with cTnT below the 3 pg/mL detection threshold, none had an MI (NPV 100%).[33] These preliminary findings suggest that serial troponin monitoring may not be necessary for the subset of individuals with undetectable cTnT using an hs-assay.

Reichlin et al created an hs-cTnT algorithm incorporating baseline values as well as absolute changes over a one hour follow-up period.[34] After applying the hs-cTnT algorithm developed in a derivation cohort to a validation cohort, 259 patients (60%) could be classified within 1 hour as "rule-out," 76 patients (17%) as "rule-in," and 101 patients (23%) as in an "observational zone." This resulted in sensitivity and negative predictive value of 100% for rule-out, specificity and positive predictive value of 97% and 84%, respectively, for rule-in, and a prevalence of AMI of 8% in the observational zone group. 30-day survival was 99.8% in the “rule out” group. This simple one-hour algorithm allowed a safe rule-out or accurate rule-in of AMI in 77% of unselected patients with acute chest pain. If validated, this algorithm, or a similar one, may help to address some of the important challenges limiting application and interpretation of the hs-cTn assays for MI rule out in the U.S.

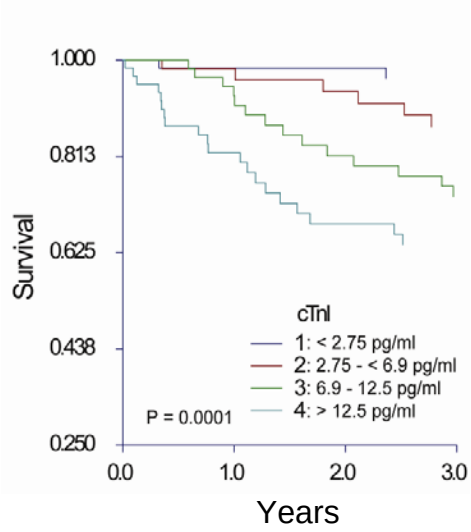
Chronic Cardiovascular Disease Risk Assessment: A better use of the hs-assays?

The ability to detect concentrations of circulating troponin in the pg/mL range has expanded the potential applications of troponin testing in new directions, including in the ambulatory setting. For example, using a research version of the hs-cTnT assay, investigators from the Valsartan Heart Failure Trial (Val-HeFT) trial demonstrated cTnT to be detectable at very low concentrations in nearly 100% of outpatients with stable chronic heart failure; moreover, increasing concentrations of cTnT, still well below the detection limit of standard cTnT assays, were associated with progressively higher rates of death and heart failure progression.[35] We investigated the hs-cTnT assay among 3594 individuals with chronic coronary artery disease and preserved LV function enrolled in the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial.[36] Approximately 98% of these individuals had measurable levels of cTnT with the hs-assay. Dose dependent associations were observed between low levels of cTnT and the subsequent risk for death and heart failure, at levels well below the detection threshold for the standard assay. These associations were independent of standard risk predictors including NT-proBNP. Of particular interest, although this was a study of patients with CAD, cTnT did not identify risk for MI, but rather was specifically associated with heart failure and CVD death. This finding complemented the earlier Dallas Heart Study observation linking cTnT in asymptomatic individuals not to CAD but rather to LV structure and function.

Monitoring for subclinical cardiac injury may be of value in disease states beyond ambulatory heart failure and CAD. Adrian Dyer, a pediatric cardiology fellow at Children's Hospital in Dallas, recently reported preliminary findings using the hs-cTnT assay to screen pediatric heart transplant recipients for cardiac rejection.[37] Biopsy-proven cellular rejection episodes were associated with increased levels of cTnT (Figure, panel A), with an area under the ROC curve for diagnosis of rejection of 0.89 (95% CI 0.78-0.99). Notably, among the small number of children with serial blood samples available, cTnT was seen to rise during episodes of rejection and then fall after effective immunosuppressive therapy (Figure, panel B); this pilot observation suggests the possibility that serial cTnT monitoring might prove useful to screen for cellular rejection. Given the costs and morbidity associated with routine endomyocardial biopsy, the current strategy used to screen for rejection, a simple biomarker-based strategy would be of considerable value.



Mariella Velez-Martinez, Kelly Chin, and other investigators from the Pulmonary Hypertension section have explored the potential role of a novel hs-cTnI assay for risk assessment and chronic disease monitoring among patients with pulmonary hypertension. In preliminary findings, they have found that almost all individuals with PH have measurable cTnI with the hs-assay. Major determinants of higher cTnI levels in the PH population included higher PA pressures, lower right ventricular ejection fraction and lower cardiac index. An > 4-fold gradient of risk for death or transplant was observed across higher levels of cTnI, even at values well below the level of detection with standard cTn assays. (Figure)

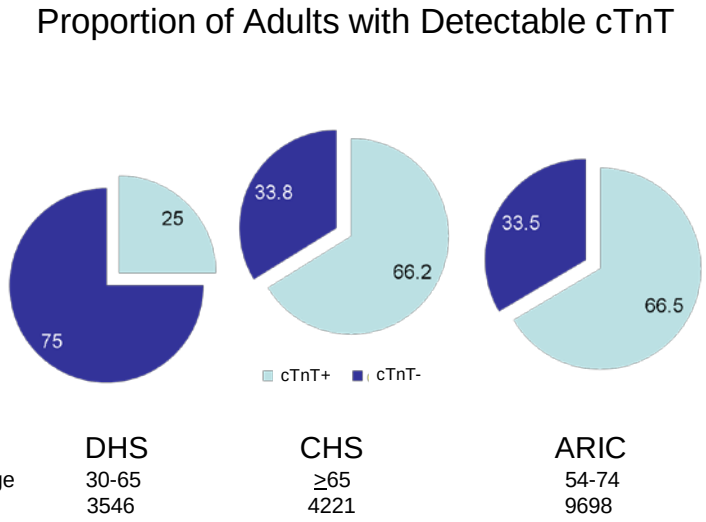


Higher cTnI remained associated with death or transplant independent of known prognostic markers in PAH, including age, sex, race, creatinine, 6 minute walk distance and WHO disease classification group. These preliminary findings suggest a potential role for measuring cTnI with an hs-assay to enhance risk assessment in PAH. Therapies for PAH are both costly and associated with significant risks and morbidity. Simple tools that can be used to target therapy to high risk patients may improve the risk/benefit and cost/benefit of existing and emerging treatments.

Measuring cTn in apparently healthy adults: a potential use that maximizes the advantages of the hs-assays?

Population screening with cardiac troponins had previously been thought to be impractical, given the very low prevalence of detectable troponin in the general population with standard assays. However, the Wallace et al. paper from the Dallas Heart Study described above provided a proof in principle that if more sensitive assays became available, cTn might be a very interesting marker to consider for population screening.[27] With the development of the hs-cTnT assay, exploration of cTnT as a potential screening tool to identify asymptomatic individuals who are at risk for cardiovascular disease has been performed. In the Dallas Heart Study, cTnT was measured with both standard and highly sensitive assays in 3593 adults between 30 and 65 years of age.[38] The prevalence of detectable cTnT (≥3 ng/L) with the highly sensitive assay was

25%, compared with 0.7% for the standard assay. In the Cardiovascular Health Study,[39] which studied 4221 adults ≥65 years of age, and the Atherosclerosis Risk in Communities Study, which included 9698 participants between 54 and 74 years of age,[40] the prevalence of detectable cTnT with the hs-cTnT assay was 66.2% and 66.5%, respectively. (Figure)



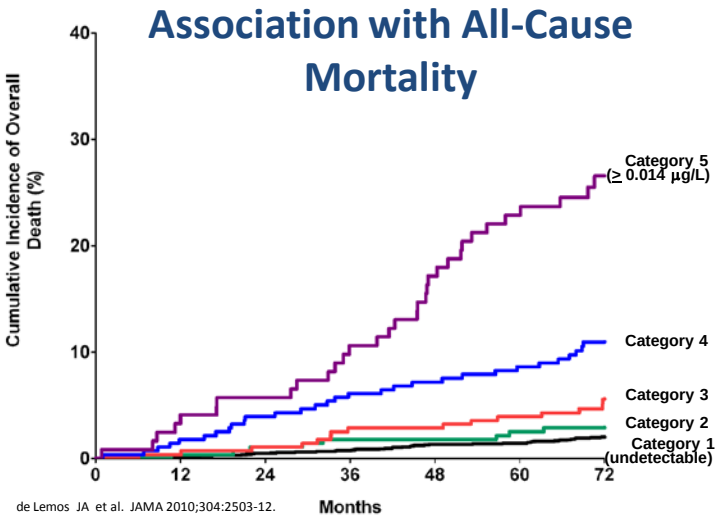
Concentrations of cTnT in the population were higher among older individuals, males, and African Americans. A clear adverse cardiovascular phenotype associated with higher cTnT concentrations, with measures of structural heart disease including left ventricular hypertrophy, left ventricular systolic dysfunction, as well as chronic kidney disease, increasing markedly across categories of higher cTnT concentrations.[38] Independent determinants of detectable cTnT in the DHS are shown in the Table.

Table. Independent Determinants of cTnT in the Dallas Heart Study

Male sex	LV mass
Age	LV EDV
Diabetes	LV Wall Thickness
Black Race	eGFR
Hypertension	History of Heart Failure

Of interest is that prior MI, angina and coronary calcium were not independently associated with detectable cTnT. This finding provides mechanistic support for the observations from the PEACE trial, which found cTnT to be associated strongly with death and heart failure events but not with myocardial infarction.[36]

In each of the three studies, higher cTnT associated robustly with all-cause and CVD mortality. Mortality by cTnT categories in the DHS is show in the Figure.



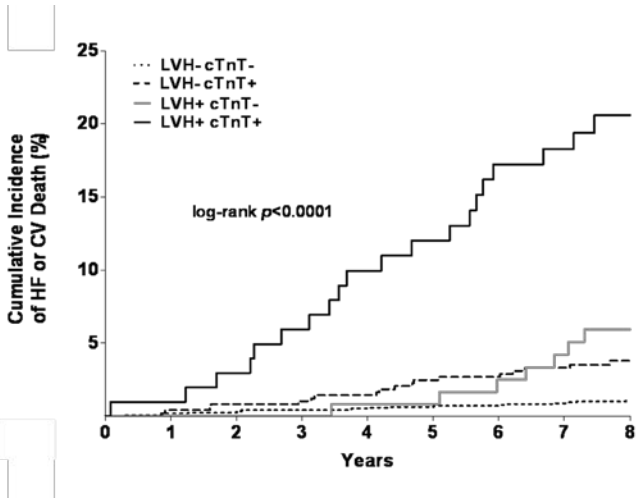
Similar graded associations across cTnT categories were seen with regard to incident heart failure in all three studies. Although an independent association with coronary heart disease events was observed in ARIC, this association was considerably weaker than the associations seen for death and heart failure events.[40]

In each of the studies, associations of cTnT with death and heart failure remained significant after adjustment for traditional risk factors, as well as for renal function and concentrations of NT-proBNP and hs-CRP. The addition of cTnT augmented the performance of traditional risk-prediction models, such as the Framingham Risk Score, improving metrics of discrimination and risk classification. When cTnT was compared directly with NT-proBNP and hs-CRP, cTnT performed at least as well as NT-proBNP and clearly outperformed hs-CRP. [38-40]

Does chronic cardiac injury, as measured with the hs-cTnT assay, identify a malignant phenotype of LVH?

Ian Neeland, a cardiology research fellow working in the DHS, has identified robust interactions between cardiac injury and LVH.[41] Individuals with LVH and cardiac injury (cTnT+) were > 20-fold more likely to develop death or heart failure over follow-up than those without LVH or detectable cTnT (Figure, next page); after adjustment for other risk markers for heart failure, the hazard ratio in the LVH+ cTnT+ group was still 6.2 (95% CI 2.8, 13.7) compared with the LVH- cTnI- group.

Although high risk phenotypes with LVH and biomarker elevation were observed in fewer than 6% of the general population without HF at baseline, this subgroup represented ~40% of heart failure or CV deaths that occurred during follow-up.

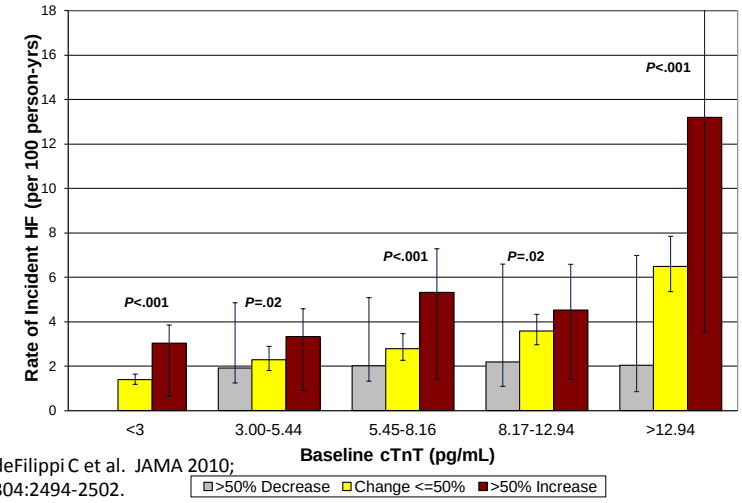


African-Americans are more likely than other race/ethnic groups to have hypertension as an antecedent to clinical heart failure [42] and 2-3 times more likely to have LVH compared with Caucasians.[43] In the DHS, African-American men had the highest probability of any race/sex group of LVH with detectable cardiac injury. Moreover, the majority of the adverse events in African American men occurred among individuals with both LVH and detectable cTnT.[41] These findings suggest that subclinical cardiac injury may be a mechanism underpinning the disproportionate burden of heart failure and CV death among African Americans.

Is the risk associated with chronic cardiac injury modifiable?

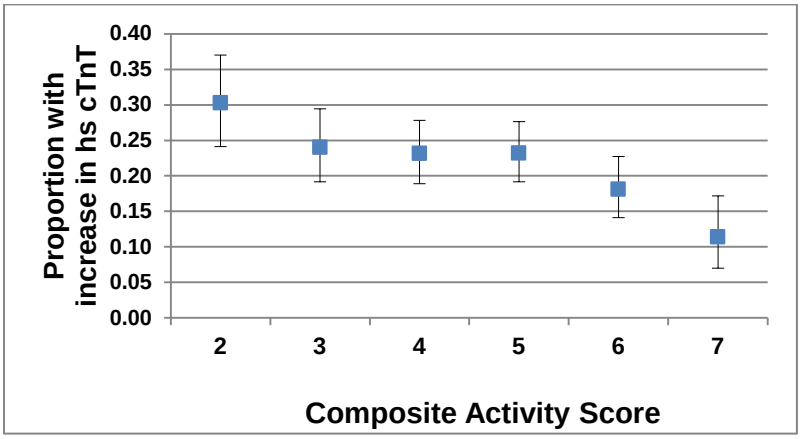
In the CHS, a second measurement of cTnT was performed 2–3 years after the baseline measurement in approximately two-thirds of the cohort. Regardless of the baseline cTnT concentration, an increase in cTnT by ≥50% was associated with a subsequent increased risk of death and heart failure, whereas a decrease by ≥50% was associated with lower risk. [39] (Figure)

Change in cTnT level from baseline to follow-up
Association with new-onset heart failure



deFilippi C et al. JAMA 2010; 304:2494-2502.

This association remained robust after accounting for potential confounders in multivariable analyses. These observations are important because they suggest that risk reflected by higher cTnT concentrations may be modifiable. To date, only limited data are available regarding the factors that might favorably modify cTn levels over time. Among elderly individuals enrolled in the CHS, a dose dependent association was seen between higher levels of baseline physical activity and fitness and a lower probability of cTnT increase over follow-up.[44] (Figure)



In the ARIC study, higher hemoglobin A1c levels (even below the diagnostic range for diabetes) associated with higher cTnT levels measured years later.[45] These data provide preliminary support for the hypothesis that increased physical activity and fitness and better glycemic control may prevent or modify cardiac injury, and help to prevent heart failure development in the future.

Next Steps in the Transition of Troponin Testing to the Physician's Office

In aggregate, these results from large population-based studies suggest that the chronic release of very low concentrations of cardiac troponins is common among asymptomatic adults. When detected, low levels of troponin identify individuals who may have unrecognized structural heart disease and a disproportionately high risk of heart failure and cardiovascular death. Although these early findings offer promise that highly sensitive troponin assays may provide a relatively inexpensive tool for office-based screening, more work needs to be done before routine testing can be recommended. First, it will be necessary to identify lifestyle factors or drug treatments that can modify the risk associated with low-level increases in troponins; ideally, such treatments would also reduce the troponin concentration so that serial testing could be used to monitor the effectiveness of the intervention. Additionally, studies with longer follow-up times will be necessary to determine whether all detectable troponin values are associated with risk or whether there is a “normal” threshold below which cTnT concentrations carry minimal risk. Whether such thresholds vary with age, sex, and other clinical characteristics will also need to be clarified, along with the influence of transient acute medical conditions that may or may not carry the same link with long-term risk.

It is unlikely that a uniform therapeutic response will be appropriate for all individuals with detectable concentrations of cTn. Although structural heart disease and chronic kidney disease appear to explain some of the variation in troponin concentration in the population, many other known and unknown factors contribute as well. In the ambulatory setting, troponins may function as relatively nonspecific markers of “end-organ damage,” with concentrations reflecting the final common pathway of multiple different pathways to chronic cardiac injury. The absence of a specific biological pathway leading to troponin release may hinder the use of troponins as a trigger for a particular treatment response in this setting. A more likely algorithm would be for the troponin value to prompt additional testing, likely with cardiovascular imaging (focusing on structural heart disease rather than atherosclerosis), to identify the source of chronic cardiac injury and to target therapy based on the presumed mechanism of injury. With advances in ultrasound technology, it may soon be possible to perform a handheld echocardiogram in a physician's office as a response to a “positive” result for a highly sensitive troponin assay.[46] Although a troponin measurement is inexpensive, the impact and cost of downstream testing, particularly cardiovascular imaging, will need to be assessed prior to implementation of a screening strategy.[47]

Conclusions:

It is clear that the highly sensitive troponin assays will present new challenges in the ED and at the interface between the ED and the cardiology consultant. The adoption of highly sensitive assays for MI detection should be accompanied by the development of algorithms for interpreting detectable troponin values that are below the MI threshold, together with recommendations for additional testing and referral for patients with an increased cardiac troponin concentration and a low clinical suspicion for acute coronary syndrome. In contrast, the application of highly sensitive troponin assays in the ambulatory setting appears to be an attractive approach to enhance primary and secondary prevention, with fewer negative implications. In this setting, the detection of very low troponin concentrations identifies risk not captured with other tools. It is hoped that future studies will clarify the clinical value and identify the best approach to incorporating these assays for population screening.

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