IMPACT OF HIGH SENSITIVITY TROPONIN ON THE EVALUATION AND TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROME
IMPACT OF HIGH SENSITIVITY TROPONIN ON THE EVALUATION AND TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROME

EMCREG-International Monograph
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Dear Colleagues,

The Emergency Medicine Cardiac Research and Education Group (EMCREG)-International was established in 1989 as an emergency medicine cardiovascular and neurovascular organization led by experts from the United States, Canada, and across the globe. We now have Steering Committee members from the US, Canada, Australia, Belgium, Brazil, France, Netherlands, New Zealand, Japan, Singapore, Sweden, and the United Kingdom. Now in our 28th year, we remain committed to provide you with the best educational programs and enduring material pieces possible. In addition to our usual Emergency Physician audience, we now reach out to our colleagues in Cardiology, Critical Care, Hospital Medicine, Laboratory Medicine, and Emergency Nursing with our EMCREG-International University of Cincinnati Office of CME accredited symposia and enduring materials.

In this EMCREG-International Monograph, Impact of High Sensitivity Troponin on the Evaluation and Treatment of Patients with Acute Coronary Syndrome, you will find a detailed discussion regarding the use of high sensitivity troponin assays in patients presenting to the hospital with ACS from multiple perspectives including Emergency Medicine, Cardiology, Hospital Medicine, Laboratory Medicine, and Emergency Nursing. High sensitivity assays for troponin have been available for clinical use in Europe for the past decade and have proved critical for the early diagnosis of acute myocardial necrosis in patients presenting to the emergency department (ED) with possible ACS and defining treatment for these patients which includes anti-platelet and anti-coagulant agents, as well as cardiologist intervention. In March 2017, high sensitivity cardiac troponin T was approved by the FDA for routine clinical use in the United States. Clearly many clinicians and laboratorians in the US have not had experience with high sensitivity troponin assays which has identified an important educational area for emphasis. This information on high sensitivity troponin becomes extremely important to emergency physicians, cardiologists, hospitalists, laboratorians, physician assistants, nurse practitioners, and emergency nurses as they routinely care for these often critically-ill patients.

The sections of this EMCREG-International Monograph emphasize the evaluation and treatment of ACS using high-sensitivity troponin assays with the integration of the multi-disciplinary team. Appropriate risk stratification of the patient with chest pain in the ED can identify the low risk patient who may be safely released from the ED Observation Unit as well as very early identification of high risk patients who will benefit from anti-coagulant treatment using agents such as heparin and low molecular weight heparin, novel antiocoagulants including Factor Xa inhibitors such as rivaroxaban, and anti-platelet agents including aspirin, clopidogrel, and ticagrelor. In this EMCREG-International Monograph, through the combined lenses of the emergency physician and cardiologist, the evidence basis for high sensitivity troponin is discussed in detail and emphasizes the use of these assays particularly when combined with a diagnostic algorithm such as the HEART score. The approach to patients with ACS confirmed by high sensitivity troponin T is extremely important for the hospitalist as care is transitioned from the ED to the in-patient setting. Clinicians must be able to understand, from the laboratory medicine perspective, the capabilities of the high sensitivity troponin assays and this Monograph has provided this expert perspective. Finally, emergency nurses, advanced practice nurses, and physician assistants are critical to the high quality care of patients with ACS and their understanding of this exciting new technology is essential.

It is our sincere hope that you will find this EMCREG-International Monograph on high sensitivity troponin useful to you in your daily practice as an emergency physician, cardiologist, hospitalist, laboratory medicine specialist, physician assistant, advanced nurse practitioner, or emergency nurse. Instructions for obtaining CME from the University of Cincinnati College of Medicine, Office of Continuing Medical Education are available at the conclusion of this EMCREG-International Monograph. Thank you very much for your interest in EMCREG-International educational initiatives and we hope you visit our website (www.emcreg.org) for future educational events and publications.

Sincerely,

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IMPACT OF HIGH SENSITIVITY TROTONIN ON THE EVALUATION AND TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROME
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<thead>
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<th>Name</th>
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<tr>
<td>Brady Bulian, MD</td>
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<tr>
<td>Robert Christenson, MD</td>
<td>Consulting, Advisory Board: Roche Diagnostics, Siemens Healthcare Diagnostics</td>
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**IMPACT OF HIGH SENSITIVITY TROPOSIN ON THE EVALUATION AND TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROME**

## EMERGENCY MEDICINE AND CARDIOLOGIST PERSPECTIVE

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IMPACT OF HIGH SENSITIVITY TROPONIN ON THE EVALUATION AND TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROME:  

EMERGENCY MEDICINE AND CARDIOLOGIST PERSPECTIVE  

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Introduction  

Between 8 and 10 million patients present to the emergency department (ED) every year with chest pain and accurately determining which of these individuals is at greatest risk for acute coronary syndrome (ACS) is critically important. Early detection and intervention for ACS improves outcomes, while missing an acute myocardial infarction (AMI) can have drastic consequences, both for the patient and provider. As a result, emergency physicians, and clinicians in general, have adopted a conservative approach to the management of chest pain patients, and a low threshold for willingness to miss an ACS case which, according to prior reports, stands at less than 1%. 1  

Millions of patients are therefore admitted to the hospital for evaluation of potential coronary artery disease (CAD) as the etiology of their chest pain, with most ultimately having a negative evaluation for ACS. 2 ,3 Short-stay chest pain and observation units have evolved over the past two decades to help streamline ED throughput and reduce resource utilization for patients with suspected ACS, particularly those at low-risk. A recent study using National Hospital Ambulatory Medical Care Survey data with visit-based propensity matching suggests that the availability of such alternatives to full-scale hospitalization may actually decrease ED release by nearly 50% of individuals who otherwise would have been sent home had observation not been an option. 4  

As might be suspected, there is also tremendous variability at the provider and institutional level in how chest pain is evaluated beyond initial assessment in the ED. While admission rates generally hover at 30-40% for patients presenting to the ED with possible ACS, studies using administrative data show that some centers perform non-invasive cardiac testing in fewer than 1% of their chest pain patients, compared to others that do so in more than half. 5 Reasons for such variability are myriad but targeted efforts to reduce it are necessary and could save the health care system as much as $3 billion annually. 5 Organizations such as the American College of Cardiology through its Chest Pain Center Accreditation Services (http://www.scpc.org/services/cpc.aspx) and the American College of Emergency Physicians through its Emergency Quality Network (E Qual) Chest Pain Learning Collaborative (https://www.acep.org/Advo-  

Troponin Based Protocols and High-Sensitivity Assays  

Development of a more efficient and expeditious method of assessment is the primary goal of cTn based chest pain risk stratification protocols, enabling delivery of the right treatment to the right patient at the right time. Earlier iterations such as the TIMI (Thrombolysis in Myocardial Infarction) and GRACE (Global Registry of Acute Coronary Events) risk scores are based on high risk patient populations with known ACS and have less clinical utility than the HEART (History, Electrocardiogram [ECG], Age, Risk factors, and Troponin) score, with the latter proving capable of reliably and safely identifying more low-risk patients in the ED setting. 6  

The HEART Pathway extends the HEART score (Table 1) from a stand-alone risk stratification tool to a full-scale clinical protocol where patient disposition and subsequent management is guided by score results (Figure 1). As shown in a recently completed, randomized controlled trial that included 282 patients, use of the HEART Pathway increased ED discharge by 21.3% (39.7% versus 18.4%; p <0.001) and reduced length of stay by 12 hours (9.9 versus 21.9 hours; p=0.013), while also decreasing objective cardiac testing at 30 days by 12.1% (68.8% versus 56.7%; p=0.048) compared to usual care. 7 Importantly, not a single patient defined as low-risk by the HEART Pathway had a major adverse cardiac event within 30 days.  

| TABLE 1 | HEART Score |
|---|---|---|---|
| **Variables** | **Points** | **Low Risk** | **Intermediate Risk** | **High Risk** |
| **HISTORY** | | | | |
| Highly suspicious | 2 | | | |
| Moderately suspicious | 1 | | | |
| Slightly suspicious | 0 | | | |
| **ECG** | | | | |
| Significant ST depression | 2 | | | |
| Nonspecific repolarization changes | 1 | | | |
| Normal | 0 | | | |
| **AGE** | | | | |
| >65 years | 2 | | | |
| 45-65 years | 1 | 0-3 | 4-6 | 7-10 |
| <45 years | 0 | | | |
| **Risk Factors** | | | | |
| ≥ 3 risk factors or history of CAD | 2 | | | |
| 1 or 2 risk factors | 1 | | | |
| No risk factors | 0 | | | |
| **Troponin** | | | | |
| >2x normal limit | 2 | | | |
| 1-2x normal limit | 1 | | | |
| ≤ normal limit | 0 | | | |

* Includes hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, positive family history, and obesity.
As shown in Figure 1, the HEART Pathway includes serial measurement of cTn over time. Serial measurement of cTn enables detection of delayed cTn release arising from an acute or hyperacute episode of myocardial necrosis, and helps to distinguish between acute and chronic elevations. Repeat cTn measurement is a cornerstone of virtually all existing troponin based protocols and pathways. Demonstration of a rise or fall in cTn on serial testing over the first 3-6 hours is currently recommended to improve specificity for diagnosis of both ACS and AMI. The amount of cTn on serial testing over the first 3-6 hours is currently recommended to improve specificity for diagnosis of both ACS and AMI. While such an approach does improve specificity of ACS and AMI compared to use of the 99th percentile alone, recent data suggest that absolute differences in cTn over time perform better diagnostically than relative ones.

Because high sensitivity cardiac troponin (hs-cTn) assays detect early, low-level cTn release, they may permit an even shorter interval between repeat cTn measurements in the ED. The recently published TRAPID-AMI (The High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction) study evaluated this approach with a 0-hour/1-hour algorithm using hs-cTnT with theoretical (but not actual) application as the sole basis for decision making in a cohort of 1,282 patients with chest pain of less than 6 hours duration. With a tri-partite approach to disposition that includes HEART score and non-adherence to directed pathways were a barrier to uptake. Reinforcing the safety and utility of such an approach while emphasizing the impact on patient care and resource utilization will clearly be important.

The Emergency Medicine Perspective

Timely evaluation of chest pain and accurate determination of the underlying cause is a critical part of Emergency Medicine practice. As hs-cTn based pathways and protocols become routinely utilized, emergency physicians will need to develop comfort in using them for decision making. Indeed, data from a stepped-wedge, cluster randomized trial of 9 Dutch EDs that implemented a “HEART care” protocol suggest that hesitancy to adopt recommended disposition and non-adherence to directed pathways were a barrier to uptake. The evidence basis for ACS evaluation in the ED remains incomplete, and that clinical application will require further study, we propose a provocative yet comprehensive algorithm that incorporates time of presentation and HEART score risk stratification within the context of the only current FDA approved hs-cTn assay available in the United States (hs-cTnT) in Figure 3. Such an algorithm may assist the emergency physician in ED disposition decisions: patients with low risk for ACS discharged to home, intermediate risk patients placed in an observation unit, and high risk patients admitted to the hospital. Ideally such an algorithm will be prospectively validated.
Although hs-cTn assays can detect increasingly low levels of cardiomyocyte injury, a positive test result should not be interpreted in isolation and caution should be exercised in assigning a diagnosis of AMI without an associated clinical suspicion for ACS. Many more individuals will have chronic elevations of hs-cTn as compared to the older assays, especially those with underlying cardiac disease. A study of an outpatient general population demonstrated that 0.7% had an elevated cTnT when using an older assay. When stored samples on the same population had hs-cTnT measured, 25% had elevated levels of hs-cTnT. Diabetes mellitus, left ventricular hypertrophy, chronic heart failure, and renal insufficiency were independently associated with an elevated hs-cTnT, underscoring the challenges when relying solely on an assay to determine diagnosis.

Likewise, in patients at moderate to high risk for ACS, negative serial cTn may be insufficient to completely exclude underlying CAD and further testing may be needed. Despite this caveat, most patients who present to the ED with chest pain or other potential angina symptoms do not have cardiac disease. Identifying these low risk individuals early during the course of evaluation is important and helps to ensure that resources are utilized appropriately. High-sensitivity troponin assays provide this capability and consequently the existence of myocardial necrosis can be safely excluded making early discharge from the ED a viable option.

The information provided by hs-cTn assays is thus a dramatic departure from what many emergency care clinicians have come to understand and incorporate in their clinical practice. Perhaps the most important point to remember when using these assays is that an elevated hs-cTn represents the likely occurrence of myocardial necrosis but does not, in and of itself, indicate a specific etiology. Though often described as falsely positive when

Figure 3: Combined Algorithm Using the High-Sensitivity Troponin T Assay with HEART Score Risk Stratification

ACS is absent, an acute hs-cTn elevation, regardless of the cause and independent of the assay used, still represents underlying myocardial injury and portends an increased risk of an adverse outcome. Even when an acute hs-cTn rise is caused by something other than CAD it is important not to minimize its significance and admission for further work-up with treatment directed towards the underlying cause is clearly indicated.

The Cardiology Perspective

Chest pain patients that do not have an elevated hs-cTn are very unlikely to benefit from aggressive therapy, be it pharmacological or interventional. Even older studies with less sensitive cTn assays did not demonstrate a benefit of aggressive pharmacologic or invasive strategies in definite ACS patients when cTn was not elevated. Perhaps only an aspirin should be given to these patients, but consideration should be given to attendant risks of aspirin therapy in patients with significant anemia or possible gastrointestinal bleeding. Although unstable angina, a high-risk CAD patient with a non-elevated cTn concentration, is a real entity, the true incidence will dramatically decrease during the transition to the era of hs-cTn. A study of an ACS population where hs-cTn was measured reported only a 7% incidence of unstable angina, which is much less than prior studies.

Numerous studies using older generation cTn assays have shown that cTn measurement assists in identifying high-risk ACS patients that benefit from anti-thrombotic, anti-platelet, and early invasive therapies. The newer hs-cTn assays will identify even more high-risk patients and these individuals will likely benefit from more aggressive therapy. A study in 2011 evaluated treatments and outcomes in patients evaluated for possible ACS before and after the introduction of a hs-cTnI assay into clinical practice. The investigators found that after implementation of the hs-cTn assay, patients with minor cTn elevation that would not have been identified by the older assay more often received cardiology referral, dual anti-platelet therapy, statin therapy, and coronary angiography. This more aggressive approach was associated with a significant decrease in mortality and AMI at 30 days. However, such potential benefits of hs-cTn will not be realized if assay appropriate 99th percentile concentrations, the cut-point at which the Third Universal Definition of Myocardial Infarction defines optimal precision for diagnosing an AMI, are not used. Based on a survey that included 276 sites participating in the ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial where only 25% reported using the 99th percentile as the AMI decision-making threshold (49% for sites using hs-cTnI assays) with many using cut-points 5-10 times higher, substantial efforts to educate the clinical and laboratory medicine community will be needed.

Patients with a Type 1 AMI, in which the primary pathology is plaque rupture or erosion, should be managed in accordance with American Heart Association/American College of Cardiology (AHA/ACC) guidelines. They should receive aggressive pharmacological therapy and an invasive strategy presuming there are no contraindications. The vast majority of patients with mild hs-cTn elevation, however, will not meet the criteria as defined in the Universal Definition of AMI. A strict application of this definition is even more
important in the era of hs-cTn. Patients must have an elevated hs-cTn above the 99th percentile with a significant rise or fall and at least one of the following: ischemic symptoms consistent with an AMI, ischemic ECG findings, or new wall motion abnormalities on imaging (such as echocardiography).

Unlike Type 1 AMI, Type 2 can be particularly problematic for the clinician. Type 2 AMI must still meet the criteria of an AMI (ischemic symptoms, ECG changes, or new wall motion abnormalities), but the mechanism of ischemia is extra-cardiac such as hypotension, hypertension, bradycardia, tachycardia, sepsis or respiratory failure. Clinically at times it can be a challenge to distinguish between Type 1 and 2 AMI, especially when there is known underlying CAD. The cornerstone of therapy in these patients remains treatment of the underlying condition. Many cardiologists would recommend aspirin and a statin in many of these patients, but there is no evidence base to support this approach. There have been no randomized trials that have shown improved outcomes in Type 2 AMI. Furthermore, these therapies should not be given in certain situations, such as in the presence of severe anemia, active gastrointestinal bleeding, or acute hepatic failure. The incidence of Type 2 AMI will likely increase with the introduction of hs-cTn. Using a hs-cTn assay, one study demonstrated that 26% of all AMIs were Type 2.

For the Cardiologist, it is critical to realize that the increased sensitivity of hs-cTn assays to detect myocardial injury comes at the price of decreased specificity for establishing a diagnosis of true AMI. There will be an increasing number of individuals with an elevated hs-cTn of unclear etiology. If the blood cTn level does not change over time, these elevations may come from a newly diagnosed yet chronic condition. These elevations may also represent an acute but non-CAD based condition causing myocardial damage such as myocarditis or pulmonary embolism. Many of these patients can be evaluated in an observation unit if their clinical condition does not require hospital admission. Increasingly in the future, hs-cTn will be measured in the outpatient setting to track cardiac damage resulting from potentially cardiotoxic chemotherapeutic agents in cancer patients, to more accurately determine stroke risk in atrial fibrillation patients, and to improve risk modeling for heart failure development in patients with CAD or hypertension to name just a few potential diagnoses impacted by this new technology. Once this approach becomes routine, emergency physicians will have greater access to baseline hs-cTn concentrations, helping to distinguish acute from chronic elevations. Inevitably though, for some patients in whom an alternative etiology cannot be established on initial assessment, further investigation for CAD may be warranted.

Conclusions

The introduction of a hs-cTn assay in the United States will improve the management of chest pain patients with suspected ACS. Low-risk patients can be more efficiently identified and discharged from the ED without need for excessive resource utilization, and more high-risk ACS patients will be identified with the opportunity for improved outcomes through application of more aggressive, evidence-based therapies. When combined with multidisciplinary care pathways that are based on objective risk stratification using hs-cTn as a cornerstone, implementation of a comprehensive treatment strategy that is clinically efficacious and cost effective may be achievable.

References

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Introduction

Chest pain is the second most common reason for non-traumatic emergency department (ED) visits in the United States (US) accounting for 5-10% of all presentations. Most patients presenting with chest pain (75-85%) will not be diagnosed with acute myocardial infarction (AMI), yet many are admitted to the hospital for observation and several more hours of testing. In 2010, 295,000 Americans aged 45-64 were hospitalized for nonspecific chest pain. For the Hospitalist, this translates into one of the most common reasons for hospital admission.

Appropriate and early diagnosis of AMI is essential to patient survival and yet can be one of the more vexing challenges for clinicians. With a high sensitivity cardiac troponin (hs-cTn) now available in the US, the acute evaluation of chest pain will undergo significant changes. The benefits of the availability of hs-cTn troponin have significant potential to improve outcomes and reduce unnecessary care for patients and costs to the health care system.

Anticipated Changes in Hospital Medicine Clinical Practice

More Rapid Rule-Out of Acute Myocardial Infarction (AMI)

The current approach to evaluating patients for possible acute coronary syndrome (ACS) in the US is to obtain serial cardiac troponins at intervals of 3 to 6 hours. A more efficient ED evaluation and discharge process has the potential for improving care with substantial cost savings. High sensitivity troponin assays allow clinicians to rule-out AMI more rapidly, reducing time spent in the ED and the number of hospital admissions with associated decrease in health care costs.

Most current troponin assays in the US are 4th generation. In other parts of the world, 5th generation hs-cTnT assays have been available for several years and were given preference over 4th generation assays by the European Society of Cardiology in the 2015 Acute Coronary System (ACS) Guideline. The hs-cTnT assays detect myocardial cell necrosis using the same protein that the current sensitivity assays detect, just at much lower concentrations. Studies of protocols combining troponin levels and clinical assessment have evaluated the effectiveness of a single baseline hs-cTnT measurement or accelerated intervals for serial troponins. The primary goal is to identify protocols with a negative predictive value (NPV) of 99.5% or greater for detecting AMI at 30 days. A secondary goal is identifying a large proportion of patients that can safely and rapidly be discharged from the ED or observation unit for outpatient follow up. From the perspective of a Hospitalist, the most notable trials are discussed below and compared in Table 1.

Single High Sensitivity Troponin Strategies – Several studies have sought to rule-out AMI with a single baseline measurement of hs-cTnT at the time of presentation. A collaborative meta-analysis with data from 11 studies and 9,240 patients estimated the ability of a single high sensitivity cardiac troponin T (hs-cTnT) measurement less than 5 ng/L and a non-ischemic electrocardiogram (ECG) to rule-out AMI in adults presenting to the ED with chest pain. This strategy identified 31% of patients as low risk, with a 99.3% pooled NPV for AMI or 30-day major adverse cardiac events (MACE). It was suggested that a single baseline measurement of hs-cTnT could rule out AMI, with one caveat - half of the patients with a negative hs-cTnT who went on to develop an AMI had presented within 3 hours of symptom onset. Thus, single hs-cTnT strategies should be avoided in patients presenting within 3 hours of symptom onset.

Accelerated Diagnostic Protocols and Serial Troponins

Accelerated Diagnostic Protocols (ADPs) combine serial hs-cTnT, the 12-lead ECG and clinical risk scores. Multiple ADPs have been implemented using serial troponin testing at 1 hour, 2 hours and 3 hours from presentation; several of these ADPs have been validated in subsequent trials. A 1-hour protocol that effectively ruled out AMI in 60% of patients was validated in 2015 and is highlighted in Figure 1. Several 2-hour ADPs, including those implemented in the ASPECT trial in 2011 and the ADAPT trial in 2012 and subsequently validated in the APACE trial in 2013, suggest that approximately 40% of patients presenting to the ED with chest pain can be safely ruled out and discharged directly home from the ED using a 2-hour protocol. A cost-effectiveness analysis based on the ADAPT trial has been performed and demonstrated an average cost reduction of $490 per patient when compared with standard care. Overnight stays decreased by up to 43% and total length of stay was reduced by 13.6 hours.

<table>
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<td>&lt;5</td>
<td>Non-ischemic ECG</td>
<td>99.7%</td>
<td>40%</td>
</tr>
<tr>
<td>0 and 1 hour measurement</td>
<td>Rechlin (2015)</td>
<td>1320</td>
<td>0 h &lt; 12 and 1 h ≤ 3</td>
<td>None</td>
<td>99.9%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>Cullen (2013)</td>
<td>909</td>
<td>0 h &lt; 26.2** and 2 h &lt; 26.2**</td>
<td>TIMI ≤ 1</td>
<td>99.7%</td>
<td>23%</td>
</tr>
</tbody>
</table>

* – negative predictive value for myocardial infarction at 30 days
** – 26.2 ng/L is the 99th percentile URL for hs-cTnI, comparable to 14 ng/L for hs-cTnT
Earlier Diagnosis of Non-ST-Elevation Myocardial Infarction

Another important impact that hs-cTn assays will have on clinical practice is the more rapid diagnosis of non ST segment elevation myocardial infarction (NSTEMI), which will allow treatment to be initiated or intensified earlier in the disease process. The hs-cTn assay detects troponin in the bloodstream at an earlier point in the disease process, between 90 and 180 minutes from event onset.6 An analytical validation of the hs-cTn assay has been performed and demonstrated significantly shorter time to diagnosis of NSTEMI, 72 minutes vs. 247 minutes (P < 0.01), compared with the currently used 4th generation assay.20 This dramatic improvement in diagnostic timing by almost 3 hours could allow treatment initiation or intensification to occur much earlier in the disease process, including dual-antiplatelet therapy (DAPT), anticoagulation administration and invasive coronary intervention.

Not only will NSTEMI be diagnosed sooner, it will also be diagnosed at an increased rate. Studies have noted a 4% absolute and 20% relative increase in the diagnosis of NSTEMI using hs-cTn.3,6 This increased rate of diagnosis of NSTEMI has been associated with a reciprocal decrease in unstable angina (UA) diagnoses, as cardiomyocyte necrosis is detected with far greater sensitivity. This is a clinically important distinction because patients with UA, compared with those with NSTEMI, have been found to derive less benefit from intensification of medical therapy including DAPT, anticoagulant therapy, and invasive therapies. These patients also have lower mortality rates than patients with NSTEMI.7,15

As the rate of diagnosis of NSTEMI increases and becomes more exact, this will presumably lead to more aggressive and appropriate treatment, allocation of resources, and outcomes. Cardiac biomarker testing has become more and more sensitive over the last couple of decades. This associated improvement in diagnosing and treating small NSTEMIs, which previously would have been biomarker negative and thus considered UA, has led to improved outcomes. Lowering the diagnostic threshold of troponin from 0.20 ng/mL to 0.05 ng/mL increased detection of MI by 29% and was associated with a lower risk of death and recurrent MI (from 39% to 21%) at one year. It was also noted that more patients were referred to a Cardiologist (74% vs 44%), received DAPT (58% vs 27%), and underwent coronary angiography (46% vs 20%; P < 0.001 for all comparisons).21 Therefore it could be anticipated that Cardiologists might see an increase in requests for consultation and catheterization.

Essential Roles for the Hospitalist

Hospitalists will play important roles in building collaborative systems to incorporate this new assay and maximize its benefits. Three important areas of opportunity include 1) leading interdisciplinary work to establish local best practices; 2) developing pathways and protocols supported by the electronic health medical record; and 3) ensuring safe transitions of care from the Emergency Physician to the Cardiologist.

Interdisciplinary Role of the Hospitalist

Prior to incorporating this new assay, it will be paramount to prepare locally. The Hospitalist can serve as a leader or key collaborator in assembling the interdisciplinary team (Figure 2). The team, at its minimum, should include representation from Laboratory Science, Nursing, Primary Care, Hospital Medicine, Emergency Medicine, Cardiology and Information Technology.

Local laboratories should guide the decision of what hs-cTnT level to consider positive based on the reference population with attention to sex-specific differences.21,22 Through discussions with Emergency Medicine, Hospital Medicine and Cardiology, the appropriate positivity thresholds should be decided upon and may vary by situation. Teams need to consider whether to use absolute or relative changes in hs-cTn. The literature remains unsettled on the appropriate approach; however, absolute measurement changes may outperform relative measurement changes in diagnostic accuracy for Type 1 AMI caused by plaque rupture.15 Laboratory Science should aid in developing the needed educational materials for clinicians to ensure an understanding of the properties and appropriate applications of the assay. Inpatient and ED nurses can help to ensure protocols are realistic and practical. Nursing also has strong roots and strengths in patient education and is an essential partner in creating patient education scripting and informational materials. Nurse care coordinators can aid with creating transition plans for the increased number of patients discharged from the ED and Observation Unit.

Teams can anticipate a decrease in numbers of admission requests for ‘chest pain - rule out,’ as many of these patients will now be discharged from the ED for further evaluation as an outpatient. Primary Care will need guidance from the interdisciplinary team in determining appropriate outpatient evaluation.

Hospitalists should anticipate an increase in hospital admissions for patients with a positive troponin. Admissions for Type 1 NSTEMI (plaque rupture) have been noted to increase by 4% with implementation of hs-cTn assays.22 Moreover, a 2-fold increase in the diagnosis of Type 2 MI (supply-demand mismatch) has also been observed. Consideration of the clinical context in the setting of elevated hs-cTn will be crucial. Patients with minor hs-cTn elevations not attributable to Type 1 AMI have been found to have mortality

FIGURE 1 Performance of The High-Sensitivity Cardiac Troponin T (hs-cTnT) 1-Hour Algorithm For Rapid Diagnosis Of Acute Myocardial Infarction (AMI) In Patients Presenting With Acute Chest Pain

Adapted from Reichlin et al.16

<table>
<thead>
<tr>
<th>Rule Out</th>
<th>Observation</th>
<th>Rule In</th>
</tr>
</thead>
<tbody>
<tr>
<td>60% of patients</td>
<td>24% of patients</td>
<td>16% of patients</td>
</tr>
<tr>
<td>NPV 99.9% for MI at 30 days</td>
<td>Prevalence of AMI 18.6%</td>
<td>PPV 78.2% for AMI</td>
</tr>
<tr>
<td>30-day mortality: 0.0%</td>
<td>30-day mortality: 1.6%</td>
<td>30-day mortality: 1.9%</td>
</tr>
<tr>
<td>2-year mortality: 1.1%</td>
<td>2-year mortality: 16.5%</td>
<td>2-year mortality: 13.4%</td>
</tr>
</tbody>
</table>

Baseline hs-cTnT < 12 ng/L & 1-hour hs-cTnT Δ < 3 ng/L
Baseline hs-cTnT 12-51 ng/L & 1-hour hs-cTnT Δ 3-4 ng/L
Baseline hs-cTnT ≥ 52 ng/L & 1-hour hs-cTnT Δ ≥ 5 ng/L

Baseline hs-cTnT < 12 ng/L & 1-hour hs-cTnT Δ < 3 ng/L
Baseline hs-cTnT 12-51 ng/L & 1-hour hs-cTnT Δ 3-4 ng/L
Baseline hs-cTnT ≥ 52 ng/L & 1-hour hs-cTnT Δ ≥ 5 ng/L

Rule Out 60% of patients
Observation 24% of patients
Rule In 16% of patients

NPV 99.9% for MI at 30 days
Prevalence of AMI 18.6%
PPV 78.2% for AMI

2-year mortality: 0.0%
2-year mortality: 1.1%
2-year mortality: 1.9%

30-day mortality: 0.0%
30-day mortality: 1.6%
30-day mortality: 1.9%

Prevalence of AMI 18.6%
2-year mortality: 16.5%
2-year mortality: 13.4%

1-hour hs-cTnT /uni0394 < 3 ng/L
1-hour hs-cTnT /uni0394 ≥ 3 ng/L

Baseline hs-cTnT < 0.05 ng/mL increased detection of MI by 29% and was associated with
rates comparable to those with Type 1 AMI. Therefore, Hospitalists need to remain vigilant with these patients and focus on risk factor modification.

Emergency Medicine, through collaboration with the interdisciplinary team, should determine which protocol (0 hour, 1 hour, 2 hour, 3 hour) to adopt in the local institution for rapid rule-out and discharge of the many low risk patients, who comprise up to 60% in some trials. The EDs can anticipate more direct discharges and fewer admissions for patients presenting with chest pain. Staff will need to be trained on the new protocol and appropriate planning for patients released home from the ED. Hospitalists should aid in these decisions to support the protocol development given the change in type and distribution of admissions and ED discharges.

The team should anticipate an increase in consultations to Cardiology for NSTEMI and possibly an increased demand for coronary angiography. Cardiologists will continue to be relied upon as the experts regarding interpretation of positive troponin measurements and optimization of treatment pathways for those diagnosed with AMI. In settings where Cardiology has less availability, there will be increased focus on Hospitalists collaborating with Cardiology to assure evaluation and treatment are initiated and escalation of care is appropriately activated.

As protocols are created through this collaborative work, Information Technology should identify and aid with development of order-sets and templated documentation options.

**Incorporating Protocols into the Electronic Health Record**

Leveraging the functionality of the electronic health record (EHR) will assist in implementation and tracking of new protocols. At many institutions, Hospitalists are centrally linked with EHR applications and improvements. Hospitalists will likely play an important role in translating protocols into clinical EHR workflow. An order-set entered by the ED physician that automatically includes hs-cTn measurements at predefined and agreed upon time intervals has been proposed. It is further recommended though that the EHR should not limit the ordering of cardiac troponin testing to only the order-set, as there are situations other than AMI in which troponin can provide useful diagnostic or prognostic information.

With the new analytical changes from the 4th generation to the 5th generation high-sensitivity assays, providers may initially struggle to interpret the assay measurements. One study found that providers largely ignored a Best Practices Alert (BPA) aimed at reducing excessive cardiac troponin testing, finding that providers would override the alert 97% of the time. It is therefore important to minimize BPAs and maximize other methods of educating clinicians. The EHR should be leveraged to provide a smooth transition into the adoption of this new assay by properly displaying result interpretation. Table 2 provides an example EHR display based on a validated 1-hour ADP, with both negative and positive results for comparison. Following implementation of the new assay into clinical practice, prospective monitoring of outcomes through EHR-driven data tracking and collaboration with clinicians will help determine if the positivity thresholds are set appropriately and whether the assay is achieving the desired benefits.

**Ensuring Safe Transitions**

As the constant thread for inpatients, Hospitalists are uniquely qualified to aid in ensuring safe transitions. Risk of medical errors during a care transition stems from poor communication from provider to provider, poor communication among providers and nursing, and inaccuracy of medication reconciliation. Hospitalists accepting, transferring or discharging a patient need to ensure adherence to treatment guidelines, including loading with DAPT, initiation of anticoagulation, administration of high-intensity statin, beta-blockade (if not contraindicated) and consultation with a Cardiologist for determination of interventional approaches. Hospitalists in community hospitals or smaller rural critical access hospitals should be prepared to initiate or intensify treatments themselves as often a Cardiologist is not immediately available.
At hospital discharge, the plan should be directly communicated to the outpatient provider to ensure therapy is continued in the ambulatory setting, including DAPT for 12 months and high-intensity statin and cardiac rehabilitation, among other guideline-directed therapies. Optimizing a safe transition out of the hospital should also include securing early follow up with Primary Care Providers and Cardiology.

**Conclusion**

The hs-cTn assay is now available in the United States. Implementation of this hs-cTn assay will lead to more rapid rule-out of AMI with associated cost savings and earlier diagnosis. As leaders within a hospital system, it is essential that Hospitalists collaborate with their colleagues in Emergency Medicine, Laboratory Science, Nursing, Cardiology, Information Technology and Primary Care to ensure patients with an elevated hs-cTn receive proper care in the hospital and experience safe care transitions throughout their stay and eventually when discharged home.

**References**


IMPACT OF HIGH SENSITIVITY TROPONIN ON THE EVALUATION AND TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROME:

LABORATORY MEDICINE PERSPECTIVE

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Background

For over 60 years, biochemical markers have been utilized for diagnosis, risk assessment, and management of patients suspected of having the acute coronary syndromes, a spectrum of diseases ranging from unstable angina and no irreversible cardiac damage through ST elevation myocardial infarction (MI) and large areas of myocardial necrosis. Figure 1 displays the evolution of cardiac biomarkers, beginning in 1954 with Dr. Arthur Karmen’s discovery that aspartate aminotransferase increased in the period immediately after an acute MI and continuing through the cardiac troponin (cTn) era and availability of high-sensitivity assays. In the 1970’s and 1980’s, rapid, automated, and accurate laboratory testing for the “cardiac selective” biomarker MB isoenzyme of creatine kinase (CK-MB) was developed. At the time, CK-MB revolutionized the management of patients with acute cardiac events.1 Myoglobin, albeit a ‘non-specific’ cardiac marker, was widely utilized as an early marker of myocardial injury, typically in combination with CK-MB. During the last decade of the 20th century, evidence for cTnT and cTnI indicated superior cardiac tissue specificity, as well as high diagnostic accuracy. These data were so compelling that cTn was fast becoming the standard biomarker for diagnosis, risk stratification and management of patients with acute myocardial infarction (AMI). In 1999, a Global Task Force of experts was assembled and promulgated the consensus recommendation that cTn is the sole biomarker required for diagnosis of MI (Table 1)². This universal definition for cTn has been consistent through the second and third Global Task force meetings conducted in 2007 ³ and 2012 ⁴. Furthermore, evidence-based guidelines from professional societies, including the National Academy of Clinical Biochemistry (NACB) ⁵, the European Society of Cardiology ⁶ and the 2014 American Heart Association/American College of Cardiology Foundation (AHA/ACCF) ⁷, are unanimous in Class I recommendations that cTnT or cTnI should be the sole biomarker utilized for MI diagnosis and risk stratification, as supported by a level of evidence A. The most recent AHA/ACCF guidelines recommend against utilization of CK-MB and/or myoglobin for MI diagnosis in a Class III endorsement supported by a level of evidence A, stating that these biomarkers have “no benefit” with availability of cTnT or cTnI ⁸.

The uptake of and compliance with guidelines in medicine is slow and far from ubiquitous. In the context of cTn for use in MI diagnosis and risk assessment, despite the unanimous, worldwide recommendations and expert guidance about use of cTn, a recent retrospective analysis of routine cardiac marker protocols collected from 824 US hospitals participating in Chest Pain Center Accreditation through the Society of Cardiovascular Patient Care (SCPC) from 2009-2014 showed that only 49% of accredited institutions used cTn as the sole marker ⁹. This same theme was seen in the CARMAGUE study that surveyed 442 North American and European Union medical centers in 2013–2014, which showed that 40% of institutions were using a biomarker in addition to cTn ². Although compliance is well below ideal, use of cTn-only protocols did increase more than 2.6-fold from 2009 to 2014 in the SCPC study, and use of cTn alone also increased in the worldwide survey.

Clearly, cTn is the preferred biomarker for diagnosis of AMI and risk assessment of acute coronary syndrome (ACS) patients. As medicine enters the high-sensitivity cTn (hs-cTn) era, it is expected that the superior performance of cTnT or cTnI ².

Criteria for diagnosis of acute myocardial infarction are:

Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following:

- Symptoms of ischemia
- New or presumed new significant ST-segment –T wave changes or new left bundle branch block.
- Development of pathological Q waves in the Electrocardiogram.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.

TABLE 1 The Term Acute Myocardial Infarction Should Be Used When There Is Evidence Of Myocardial Necrosis In A Clinical Setting Consistent With Acute Myocardial Ischemia. Under These Conditions The Biomarker Criteria Are As Follows ²

<table>
<thead>
<tr>
<th>Criteria for diagnosis of acute myocardial infarction are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following:</td>
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</tr>
<tr>
<td>• Identification of an intracoronary thrombus by angiography or autopsy.</td>
</tr>
</tbody>
</table>

FIGURE 1 Timeline of Biochemical Biomarkers Used For Diagnosis of Myocardial Infarction, Risk Assessment and For Guiding Management of Patients Suspected of Acute Coronary Syndrome


AST in MI LD & CK isoenzymes Electrophoresis CK & LD CK-MB in MI CK-MB RIA WHO criteria MI cTnT/cTnI risk stratification cTnT risk in MI cTnI risk in MI Hs-cTnT cleared by US FDA

Hs-cTnT cleared by US FDA

1 WHO = World Health Organization; MI = Myocardial Infarction; CK = Creatine Kinase; LD = Lactic Dehydrogenase; AST = Aspartate aminotransferase
2 hs-cTnT cleared by US FDA
3 hs-cTnT cleared by US FDA
4 WHO = World Health Organization; MI = Myocardial Infarction; CK = Creatine Kinase; LD = Lactic Dehydrogenase; AST = Aspartate aminotransferase
5 Hs-cTnT cleared by US FDA
6 WHO = World Health Organization; MI = Myocardial Infarction; CK = Creatine Kinase; LD = Lactic Dehydrogenase; AST = Aspartate aminotransferase
7 hs-cTnT cleared by US FDA
8 WHO = World Health Organization; MI = Myocardial Infarction; CK = Creatine Kinase; LD = Lactic Dehydrogenase; AST = Aspartate aminotransferase
9 hs-cTnT cleared by US FDA
10 WHO = World Health Organization; MI = Myocardial Infarction; CK = Creatine Kinase; LD = Lactic Dehydrogenase; AST = Aspartate aminotransferase
of these assays will incentivize use as the sole biomarker. The purpose of this contribution is to explain the laboratory-based information that is critical for understanding and successfully implementing patient testing with hs-cTn assays.

**What are High-Sensitivity Cardiac Troponin Assays?**

In general, there are two types of cTn assays, listed in Table 2, that are relevant for discussion. The first are coined contemporary cTn assays; these are also referred to as laboratory quality cTn assays to distinguish them from early generation tests having inferior analytic performance. The second type of tests are hs-cTn assays, which according to the International Federation for Clinical Chemistry and Laboratory Medicine (IFCC) Task Force on Clinical Applications of Cardiac Bio-Markers, must meet two criteria. One criterion needed for designating a cTn assay as “high-sensitivity” is that total imprecision (reproducibility), as calculated from the Clinical Laboratory Standards Institute (CLSI) document EP05-A3, at the 99th percentile of a normal healthy population must be less than a Coefficient of Variation (CV) of 10 \(^\text{a}\). The second criterion is that at least 50% of samples from healthy individuals must have detectable levels, meaning concentrations exceeding the assay’s limit of detection determined as specified by CLSI document EP17. It is important to understand that the term “high-sensitivity” addresses an assay’s characteristics and does not refer to a difference in the forms of cardiac troponin (I or T) being measured. Although the initial definition of hs-cTn assays did not distinguish between male and female normal populations, it has been documented that healthy populations of the two sexes have different values, and hs-cTn assays will have sex-specific 99th percentile upper reference limits for normal healthy individuals (Table 2). For this reason, the high-sensitivity definition has been expanded such that the high-sensitivity assay must detect >50% of cTn values for both the female and male cohorts of normal healthy reference groups individually.

It is noteworthy that these criteria for high-sensitivity assays apply to both central laboratory and Point of Care (POC) assays. When implementing a hs-cTn assay in institutions that also have POC cTn measurements available, Emergency Medicine, Cardiology and Laboratory Medicine stakeholders will need to characterize the relationship between the assays.

**The 99th percentile of Normal Healthy Individuals: The Universally Recommended Decision Point for Both Contemporary and High-Sensitivity Cardiac Troponin Assays**

The ideal practice for defining a biomarker’s decision point is to construct a Receiver Operator Characteristics (ROC) curve where diagnostic sensitivity is plotted on the y-axis versus [1-specificity] on the x-axis for a population of patients, all having signs and symptoms suggestive of the condition of interest. An independent “gold standard”, such as a biopsy, is used for determination of which subjects in the population have the disease (positives) and which do not (negatives). The ROC curve can be used to determine diagnostic performance of the biomarker, as well as the decision point that minimizes the number of false positive and false negative values for the population of interest.

The cardiac biomarker cTn (and many other biomarkers) have no truly objective “gold standard” for diagnosis of MI. Typically for such biomarkers, the upper 97.5th percentile of normal individuals is defined as the upper cutpoint. For cTn, the first Global Task Force group specified the 99th percentile of normal healthy individuals as the consensus decision point, presumably because use of the traditional 97.5th percentile would have potentiated a 2.5% incidence of falsely positive results which would likely overwhelm the healthcare system. In the years since publication of the first Global Task Force guidance in 2000, outcome studies have been conducted in the Emergency Medicine setting which have shown evidence that use of the 99th percentile consensus-based decision point versus a more elevated cTn cutpoint is linked to improved health outcomes. Along with the Global Task guidance, these data helped lead to universal acceptance of the cTn concentration corresponding to the 99th percentile as the decision point in evidence-based guidelines developed by Cardiology and Laboratory Medicine professional associations worldwide.

As noted earlier, even years after dissemination of evidence-based guidelines there is usually only modest adaptation and compliance. Despite universal endorsement of the 99th percentile cutoff, and also outcome studies demonstrating significant health benefit, only 33% to ~50%.
of institutions use the 99th percentile. This is more than 15 years after the 99th percentile was first recommended. The fact that between 40 and 66% of institutions do not use the 99th percentile cutoff must be addressed and improved with adaptation of hs-cTn assays to achieve maximum benefit from this innovation.16

A major element that is challenging for adaptation of the 99th percentile cutoff is defining criteria for the subjects comprising the normal control population. Although performance of imaging studies for all potential subjects would be ideal, the expense would be burdensome. Also, questions arise such as whether individuals over 50 years who are administered certain medications such as a statin drug should be excluded from normal values studies, even though a substantial proportion of a healthy population takes such medications. This and other questions are critically important because the use of different criteria for normality has led to 99th percentile cutoff values that are not numerically equivalent 13,18,19 and, most importantly, that are not biologically equivalent 19. To assist in resolving these issues, the academy of the American Association for Clinical Chemistry (AACC) and IFCC have collaborated in developing criteria for defining normal populations for use in determining the 99th percentile 20. For populations used for defining the 99th percentile, the AACC has assembled cohort samples in a universal sample bank of documented normal individuals, which has over 350 men and 350 women. This resource can be accessed by any interested parties, including manufacturers, academics, or regulators 20.

The universally recommended 99th percentile decision point holds regardless of whether the assay is classified as a contemporary, earlier generation test, or a hs-cTn assay. It is noteworthy that there is an important distinction between contemporary and high-sensitivity assays regarding the 99th percentile. Although there is no difference between men and women with contemporary, earlier generation assays because of inadequate sensitivity 10,22, there are abundant data demonstrating that the 99th percentile differs between the sexes for hs-cTn with women having lower values compared to men 10,22. Sex-specific 99th percentile cutoffs will be determined for virtually all hs-cTn assays, as well as a 99th percentile cutoff for the overall population. For example, the Instructions for Use or package insert for the FDA-cleared hs-cTnT assay lists cutoffs of 14 ng/L for women and 22 ng/mL for men; the 99th percentile cutoff for the overall population is listed as 19 ng/L.

Although the use of sex-specific cutoffs has been recommended 18, the practice of utilizing them for interpreting hs-cTn results has varied in non-United States institutions. Some practitioners have reported that even though the 99th percentile is different for normal men and women, the area under the ROC curve for acute MI using an overall cutoff of 19 ng/L is virtually identical for the sexes with the 5th generation hs-cTnT assay. The rationale for this equivalence is based on the finding that cTn increases with age, and that women are, in general, older than men when they present with signs and symptoms of AMI. Stakeholders at each institution will need to work together in determining the most appropriate 99th percentile cutoffs for evaluation of their local population, and whether to use sex-specific cutoffs or the overall 99th percentile.

Benefits of Availability of High-sensitivity Cardiac Troponin Assays

Some of the benefits conferred by the superior analytical characteristics of hs-cTn assays are noted in the text which follows. For a more comprehensive discussion of these points and other recommendations regarding hs-cTn assays, please see Analytical Recommendations for the Use of Cardiac Troponin in Coronary Artery Disease: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry. 23.

Integer values (units of ng/L) reported for high-sensitivity cTn assays

Results of contemporary and earlier generation cTn assays were reported in units of ng/mL, causing results to appear as decimal values on patient and other documents. The recommendation of the AACC Academy and IFCC Task Force Consensus Guidelines 23 are to report hs-cTn results in units of ng/L, so that all results will be reported as whole number values. For example, a value of 0.07 ng/mL for a contemporary cTn assay will have value of 0.07 ng/L for a high-sensitivity test. Reporting high-sensitivity results as whole numbers will facilitate interpretation and allow differentiation of whether an assay is high-sensitivity, a contemporary, or earlier generation test. It is believed that expressing results as whole numbers, rather than as decimals as is recommended with contemporary and earlier generation cTn assays, will reduce error when interpreting cTn results 10.

Improved measurement precision in the critical concentration range

Compared to contemporary and earlier generation assays, hs-cTn assays have superior measurement precision with a far smaller 95% confidence interval around each temporal measurement at concentrations both near the 99th percentile cutoff and at lower values. For this reason, overlap between temporal samples is greatly reduced and aids in earlier recognition that timed samples either have no or a small absolute change versus showing a rising and/or falling temporal pattern. Thus, improved precision associated with hs-cTn assays allows early detection of a rise and/or fall in cardiac troponin in early samples with greater certainty.

Quality monitoring at critical cardiac troponin levels

Accurate and precise measurement in the region of the 99th percentile cutoff is arguably the most important aspect of any cTn quantification method. However, Quality Control monitoring of cTn measurement is typically done at concentrations that are many fold higher than the 99th percentile. This is because measurements with contemporary and earlier generation cTn assays were very imprecise at or below the 99th percentile, and therefore monitoring was not conducive to indicating actual assay performance. As a result, with contemporary and earlier generation cTn assays, laboratorians were blinded to performance of important assay characteristics, including precision and bias, in a most clinically relevant measurement region. On the other hand, hs-cTn assays have better precision at low values in the region of the 99th percentile so it is possible to effectively monitor the assay characteristics and assure more reliable patient data. Also, use of hs-cTn assays and quality monitoring should facilitate the harmonizing of cTn values within institutions, between affiliated medical centers and within health systems using the same high-sensitivity assay.

Decreased time to MI diagnosis

The 2007 NACB Guidelines recommend sampling at presentation and then 6 to 9 hours later 3. As the use of more sensitive contemporary cTn assays has become more prevalent in the US over the past decade, the time from symptom onset to a positive cTn result has decreased, which has enabled earlier strategies for ruling-out AMI. This is reflected in the United States based 2014 AHA/ACC non-ST elevation MI guidelines, which recommend sampling at presentation and then 3 to 6 hours later 7. No high-sensitivity assays were available in the United States until early 2017. However, Europe
and the rest of the world have had access to hs-cTn assays starting in 2009. In 2011, the European Society of Cardiology contracted the recommended sampling timing for rule-out MI to presentation and then 3 hours later.

Availability of hs-TnT and hs-Tnl assays in countries other than the United States has allowed investigation into the development and effectiveness of alternative sampling strategies and algorithms. Several of these algorithms have been validated for very early rule-out, diagnosis and risk stratification of suspected AMI patients. Specifically, strategies in which sampling was done at patient presentation and one hour later were determined to safely help diagnose and manage patients with suspected MI. Several of these 1-hour algorithms are advocated and discussed in the 2015 European Guidelines for non-ST elevation MI.

One such algorithm involves utilizing hs-cTnT measurements in serial samples collected at presentation and one hour later in patients suspected of having AMI who present within 12 hours of symptoms onset. The algorithm was first tested in the APACE study (n=872), and then validated in a prospective study (n=1320) and in the TRAPID AMI trial (n=1282). Figure 2 Panel A shows that the patients clinically suspected of having AMI were stratified into the following three groups based on their initial hs-cTnT value and the absolute change between presentation to 1-hour: (1) rule-out AMI, (2) observation and (3) rule-in AMI. Figure 2 Panel A shows that the algorithm had high diagnostic sensitivity, and a negative predictive value for ruling-out AMI of 99.1%. Further, AMI could either be ruled-out or ruled-in using the algorithm for 77.8% of subjects. The patients with intermediate initial and 1-hour absolute change in hs-cTnT values comprised 22.2% of the population; these individuals were held for observation. Figure 2 Panel B displays the 30-day mortality in each group; mortality was 0.1% in the rule-out group. Therefore the hs-cTnT 0-hour/1-hour algorithm performed well for early and safe rule-out and rule-in of acute MI.

### Summary Tips on Implementation of High-Sensitivity cTn Assays

Successful implementation of a hs-cTn assay must be a coordinated collaboration that includes all stakeholders including Laboratory Medicine, Emergency Medicine, Cardiology, Nursing, Information Technology, Administration and any other area of the medical center which utilizes cTn measurements. Medical centers should provide information and education to users through a number of approaches which includes key literature, case studies and presentations, and abundant opportunities to ask questions. Communications should include specifying the category of cTn assay in current use and any changes to the test, as this may involve a difference that is critical for interpretation of analytical and clinical performance. One resource that may help set expectations for differences during a change in cTn assays is the ASSESS study which examined the comparison of 13 cTn methods that included contemporary, high-sensitivity and earlier generation assays in a common cohort of patient samples. Another resource is the expert consensus document previously mentioned.

One recommendation that may be useful for facilitating the transition to the new cTn assay is to provide clear communication to users about the differences between the old and new assays, including any changes in measurement units. This can help ensure that users are informed about the potential impact on their diagnostic and clinical decision-making processes.
References


IMPACT OF HIGH SENSITIVITY TROPONIN ON THE EVALUATION AND TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROME:

NURSING PERSPECTIVE

Kay S. Melching, MSA, RN, AACC, CPHQ
Columbus, OH

Introduction

The management of high sensitivity cardiac troponin T and I (hs-cTnT and hs-cTnI) assays starts in the Emergency Department (ED) as the first point of entry into the health care system for most patients with signs and symptoms of acute coronary syndrome (ACS). To maximize efficiency and improve quality outcomes, changes are required to make full use of the hs-cTn assays. The nurse plays a pivotal role as the first professional of the health care team to assess the patient.

The ED nurse’s role in the impact of hs-cTn in the evaluation and treatment of patients with ACS will be based on hard-wired processes, evidence-based protocols, staff education, and metrics to validate success. Education should extend beyond the ED doors to emergency medical services (EMS) as a health care and business partner. Use of hs-cTn testing can have a positive influence on health care practice by accelerating diagnosis and potentially improving patient outcomes. However, there is potential for confusion and increased workload if the introduction of troponin testing is not managed correctly.

Pre-analytical Phase

A multidisciplinary team comprised of a Cardiologist, Emergency Medicine physician, front line ED staff, laboratory process improvement specialist, EMS, and management should review current processes, flowchart new processes, standardize order sets, and update education needs and policies. Successfully identifying the patient who presents with signs and symptoms of ACS at the point of entry in the ED or in the field by the EMS begins the cascade of efficient and quality care. If the patient’s ACS presentation is missed, treatment will be delayed along the entire continuum of care. Chest pain is the second most frequent presenting complaint and represents approximately 7.1% of all patients arriving to EDs across the United States. These data do not include those patients who present with non-typical signs and symptoms, which are more predominant in the elderly, diabetics, and women. Chest pain is also the second leading hospital discharge diagnosis.

Triage training for emergency nurses should include identifying patients who should begin the treatment pathway for ACS. Non-ST segment elevation myocardial infarction (NSTEMI) most commonly presents as a pressure-type chest pain that typically occurs at rest or with minimal exertion. The pain most frequently starts in the retrosternal area and can radiate to either or both arms, the neck, or the jaw, but may also occur in these areas without the typical chest pain. Patients with NSTEMI may also present with diaphoresis, dyspnea, nausea, abdominal pain, dyspnea or syncope. A nose to navel approach is inclusive enough to ensure atypical signs and symptoms are recognized.

When EDs use immediate bedding for patients until all beds are full, all nurs-
be determined for the patient’s symptoms. Any escalation in symptoms also warrants a repeat ECG. An ECG is a non-invasive, relatively inexpensive test that requires little human resources and can be diagnostic. A nurse-driven protocol should be in place for a repeat ECG at the nurse’s discretion based on the patient’s signs and symptoms.

**Post-analytical Phase**

The facility can expect more patients to “rule out” than to “rule in” to the ACS pathway. Patients with negative hs-cTn and who are at extremely low risk for an ACS event can be safely discharged home from the ED with follow up. This allows a unique opportunity for the nurse to have a teachable moment with the patient upon discharge regarding preventive risk factors, lifestyle modifications, and signs and symptoms of ACS.

The importance of developing metrics to measure, analyze, and improve performance is crucial to establishing baseline performance and setting improvement goals (Table 1). Demonstration of success, financial benchmarks and quality measures can only be accomplished through metrics. To validate the success of implementation of new processes and the use of a hs-cTn assay, nursing management must have baseline data. Metrics may be collected monthly at the beginning to establish whether new process changes are becoming hard-wired or need to be re-evaluated. Metrics should also be shared with front-line staff who largely carry the responsibility for implementing processes. This will reinforce positive behaviors and engage staff.

**Conclusion**

The hs-cTn assay will drive process changes and should not be implemented until the multidisciplinary team has finished its analysis and provided education to the staff and physicians. Increased troponin levels cannot be used in isolation to diagnose or rule out heart damage. A physical exam, clinical history, risk stratification tool and ECG are all part of the collective tools used for diagnosis. An investment in staff education regarding ACS, troponin utility, new policies, procedures and processes will allow for a successful introduction of a hs-cTn protocol.

The use of a hs-cTn assay in the healthcare environment has the potential to increase efficiency and improve patient outcomes and patient satisfaction. Hospitals have the potential to gain due to improved throughput, decreased length of stay and decreased mortality, which translate into cost savings.

**References**


3. U.S. Department of Health and Human Services • Centers for Disease Control and Prevention • National Center for Health Statistics National Hospital Ambulatory Medical Care Survey: 2013 Emergency Department Summary


**TABLE 1**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Rationale</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Median time from ED arrival to disposition decision.</td>
<td>hs-cTn should lead to faster diagnosis and disposition from ED.</td>
<td>Arrival time should be clearly defined by each facility. Bed request is used versus bed placement to determine disposition time due to the variables that occur on the inpatient side.</td>
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<tr>
<td>Median time from ED arrival to ED departure for discharged ED patients.</td>
<td>hs-cTn should lead to faster diagnosis and disposition from ED.</td>
<td>Time of arrival to ED is used when standardized protocols are in place versus order to result. Additional metrics may be needed to validate on the inpatient side, such as: length of stay, adherence to guideline based medications, mortality, etc.</td>
</tr>
<tr>
<td>Median time from ED arrival to first positive troponin for patients presenting with signs and symptoms of ACS.</td>
<td>Positive troponin can translate into earlier diagnosis of Non-STE ACS, allowing for immediate implementation of guideline recommended medications. On boarding of guideline-based medications may result in improved patient outcomes.</td>
<td></td>
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<tr>
<td>Number of patients who left without being seen (LWBS) by an emergency provider or before completing treatment.</td>
<td>hs-cTn should lead to faster diagnosis and decompress ED allowing additional volumes.</td>
<td>Calculate recovered revenue from decrease in LWBS.</td>
</tr>
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<td>Number of patients diagnosed with NSTEMI.</td>
<td>hs-cTn may identify more patients with myocardial cell damage.</td>
<td>Associate increase in patient volumes and NSTEMI coding with revenue.</td>
</tr>
<tr>
<td>Number of patients presenting with signs and symptoms of ACS who are discharged from the ED for follow up (does not include patients with another cause for their pain).</td>
<td>hs-cTn may &quot;rule out&quot; low risk patients presenting with signs and symptoms of ACS who can be safely discharged from the ED for follow up.</td>
<td>Associate cost savings regarding patient with ED visit versus if the patient would have been admitted or placed in observation status. Consider calculating additional revenue an inpatient bed provides when a patient has a higher case mix index other than chest pain.</td>
</tr>
<tr>
<td>Patient satisfaction.</td>
<td>Patient satisfaction could potentially increase when hs-cTn contributes to decrease length of stay in ED.</td>
<td>Associate increase in patient volumes and NSTEMI coding with revenue.</td>
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Continuing Medical Education Post-Test: IMPACT OF HIGH SENSITIVITY TROPONIN ON THE EVALUATION AND TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROME

Based on the information presented in this monograph, please choose one correct response for each of the following questions or statements. Record your answers on the answer sheet on found on the last page. To receive Category I credit, complete the post-test and record your responses on the following answer sheet and complete the evaluation. CME can be returned by E-mail, Fax or Mail using the included return envelope. Please return the CME no later than September 1, 2018. A passing grade of 80% is needed to receive credit.

1. Therapies that have been shown to improve outcomes in Type 2 AMI include:
   A. Aspirin
   B. Beta-blocker
   C. Percutaneous coronary intervention
   D. All of the above
   E. None of the above

2. Which of the following statements are true?
   A. The hs-cTn assay will allow exclusion of AMI more rapidly
   B. All hs-cTn assays will give the same value on a patient’s blood specimen
   C. The use of hs-cTn assays will lead to a decrease in the incidence of unstable angina
   D. All of the above
   E. A and C only

3. Compared to contemporary troponin assays, high-sensitivity assays have:
   A. Increased specificity but decreased sensitivity for AMI
   B. Increased sensitivity but decreased specificity for AMI
   C. Increased sensitivity and specificity for AMI
   D. Decreased sensitivity and specificity for AMI
   E. None of the above

4. Which of the following is consistent with current, guideline based high-sensitivity troponin T (hs-cTnT) chest pain rule-out protocol?
   A. Measure hs-cTnT at 0 and 1 hour. AMI can be excluded if both values are below the 99th percentile (14 ng/L).
   B. Measure hs-cTnT at 0 and 1 hour. AMI can be excluded if the first hs-cTnT is 8 ng/L and the second is 10 ng/L.
   C. Measure hs-cTnT at 0 and 1 hour. The patient will rule-in for AMI if the first hs-cTnT is 50 ng/L and the second hs-cTnT is 54 ng/L.
   D. Measure hs-cTnT at 0 and 1 hour. The patient will rule-in for AMI if the first hs-cTnT is 52 ng/L and the second is 56 ng/L.
   E. Measure hs-cTnT at 0 and 1 hour. AMI can be excluded if the first hs-cTnT is 7 ng/L and the second hs-cTnT is 11 ng/L

5. The HEART score includes all of the following variables, except:
   A. Age
   B. NT-pro BNP results (heart failure)
   C. History
   D. Risk factors
   E. Electrocardiographic findings

6. Which of the following is true regarding the 99th percentile for troponin assays
   A. It is routinely utilized at all hospitals as the threshold for establishing a diagnosis of AMI.
   B. It should only be used with high-sensitivity assays.
   C. It is the established threshold for AMI according to the Third Universal Definition of Myocardial Infarction.
   D. It is represented by a single value that is applicable to all assays.
   E. It is just a laboratory matter and should not impact clinical care

7. The HEART Pathway involves which of the following?
   A. Directed intervention and disposition solely based upon troponin results.
   B. Single troponin measurement as a routine practice.
   C. Early admission for low-risk patients with negative serial troponins.
   D. Placement in observation status or in-patient admission for high-risk patients with negative troponins.
   E. Discharge home for low-risk patients with a positive troponin.

8. From a cardiology perspective, low risk patients with negative high sensitivity troponins should:
   A. All be admitted to telemetry for further work-up.
   B. Potentially receive aspirin as secondary preventative therapy provided they are at low-risk for complications such as GI bleed.
   C. Receive aggressive pharmacological therapy inclusive of beta-blockers for all.
   D. Be referred for outpatient evaluation by an interventional cardiologist.
   E. Undergo routine cardiac computed tomographic angiography (CCTA) to be sure there is not underlying CAD.

9. How has implementation of high-sensitivity troponin testing affected the number of admissions for Type 1 NSTEMI (plaque rupture)?
   A. Decrease by 8%
   B. No change
   C. Increase by 4%
   D. Increase by 8%

(Continued Next page)
10. Hospitalists can anticipate the following change to their clinical practice after implementation of a high-sensitivity assay-based protocol?
   A. Increased number of admissions to ‘rule-out AMI.’
   B. Fewer admissions to ‘rule-out AMI’

11. Which diagnostic protocol(s) tested in prospective trials achieved ‘ED rule-out’ in > 25% while maintaining a NPV > 99.5% for MI at 30 days?
   A. Single baseline troponin measurement plus clinical risk assessment and ECG
   B. 0 hour and 1 hour troponin measurements
   C. 0 hour and 2 hour troponin measurements plus clinical risk assessment and ECG
   D. All of the above

12. In the 2015 validation study of a 1-hour diagnostic protocol by Reichlin et al mortality rates were similar between those patients assigned to ‘observation’ and those patients who were ‘ruled in,’ suggesting that even in the absence of a Type 1 NSTE-MI an elevated hs-cTn warrants appropriate medical attention
   A. True
   B. False

13. Ordering of hs-cTn should be limited to Ordersets through use of a Best Practices Alert.
   A. True
   B. False

14. Which service is best positioned to serve as leaders of the interdisciplinary team regarding implementation of hs-cTn assay-based protocols?
   A. Emergency Medicine
   B. Hospital Medicine
   C. Cardiology
   D. Primary Care

15. Which of the following statements regarding cardiac troponin is FALSE?
   A. According to the ‘Third Universal Definition of Myocardial Infarction’, cardiac troponin is the preferred biochemical marker for myocardial infarction diagnosis.
   B. Cardiac troponin can be elevated in renal failure patients without myocardial infarction.
   C. High sensitivity cardiac troponin assays will detect myocardial infarction later after symptom onset than earlier generation assays.
   D. High-sensitivity troponin assays are defined by their ability to validly detect troponin in ≥50% of a normal reference population.

16. Which of the following meets the current criteria for the diagnosis of myocardial infarction according to Third Universal Definition of Myocardial Infarction?
   A. A single cardiac troponin value exceeding the 99th percentile of the upper reference limit.
   B. Serial measurement with a contemporary cardiac troponin assay demonstrating a rising/and or falling pattern with presumed new significant ST-segment-T wave changes.
   C. Significant new ST-segment changes and a cardiac troponin value exceeding the 99th percentile with signs and symptoms of cardiac ischemia.
   D. Signs and symptoms of ischemia and detection of a rise and/or fall of cardiac troponin with at least one value above the 99th percentile upper reference limit.

17. According to recent guidelines, which of the following regarding use of biomarkers for diagnosis of myocardial infarction is FALSE:
   A. Cardiac troponin is the preferred biomarker for diagnosis of myocardial infarction.
   B. CK-MB and myoglobin provide added information to contemporary generation cardiac troponin assays for myocardial infarction diagnosis.
   C. The 99th percentile of a normal healthy population is the recommended cutpoint for both contemporary generation cardiac troponin assays and high sensitivity cardiac troponin assays.
   D. Cardiac troponin can be elevated above the 99th percentile cutpoint in conditions other than acute myocardial infarction.
After you have read the monograph, carefully record your answers by circling the appropriate letter for each question on the CME ANSWER SHEET on this page and complete the evaluation questionnaire.

CME expiration date September 1, 2018

Return the answer sheet to:
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OR EMAIL TO: support@emcreg.org

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1. On a scale of 1 to 5, with 1 being highly satisfied and 5 being highly dissatisfied, please rate this program with respect to:

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<td>Content of monograph:</td>
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2. What topics would be of interest to you for future CME programs?
________________________________________________________________________

3. Was there commercial or promotional bias in this monograph? □ YES □ NO
   If YES, please explain:
________________________________________________________________________

4. How long did it take for you to complete this monograph? _________________

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COMPLIMENTARY CME MONOGRAPH

AUGUST 2017

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