

# Clinical Considerations of High Sensitivity Troponins and CVD

NEENA XAVIER, HEATHER HALLMAN, REMO GEORGE, TOSI GILFORD, ROBERT ESTES, SAMANTHA GIORDANO, KRISTLE GLASGOW, WEI LI, ANA OLIVEIRA, FLOYD JOSEPHAT, JANELLE MARIE CHIASERA

## LEARNING OBJECTIVES:

1. Describe high-sensitivity troponin clinical utility in the primary diagnosis of acute coronary syndrome (ACS)/ acute myocardial infarction in conjunction with other clinical data
2. Explain the use of high-sensitivity troponin in risk stratification of patients with ACS in terms of outcomes, adverse events, and mortality
3. Discuss other clinical scenarios that lead to elevation of high-sensitivity cardiac troponin levels.

## ABSTRACT

Cardiovascular disease (CVD) remains the number one cause of death in the United States (US). According to the American Heart Association, it causes roughly 2300 deaths per day, and one death about every 38 seconds. The introduction and generalized use of high-sensitivity cardiac troponins (hs-cTn) has the potential to improve diagnosis, which would allow for shorter times to reperfusion and better patient outcomes. Emergency departments

*Neena Xavier, The University of Alabama at Birmingham*

*Heather Hallman, The University of Alabama at Birmingham*

*Remo George, The University of Alabama at Birmingham*

*Tosi Gilford, The University of Alabama at Birmingham*

*Robert Estes, The University of Alabama at Birmingham*

*Samantha Giordano, The University of Alabama at Birmingham*

*Krystle Glasgow, The University of Alabama at Birmingham*

*Wei Li, The University of Alabama at Birmingham*

*Ana Oliveira*

*Floyd Josephat, The University of Alabama at Birmingham*

*Janelle Marie Chiasera, The University of Alabama at Birmingham*

**Address for Correspondence:** *Janelle Marie Chiasera, [chiasera@uab.edu](mailto:chiasera@uab.edu)*

in the US have established evidence-based protocols that aid providers in ruling out acute coronary syndrome or acute myocardial infarction. These protocols currently use traditional troponin assays, but are validated using high-sensitivity troponin assays. With the advent of high-sensitivity troponin assays, however, clinicians must have care in their interpretation. The myonecrosis that leads to elevations in serum troponins is not a disease-specific phenomenon, but rather is organ-specific. As such, several diseases exist other than acute myocardial infarction (AMI) that can lead to troponin elevations. It is important for providers to use these biomarkers as an adjunct to the clinical picture to determine diagnosis, management, and treatment. High-sensitivity troponin assays are also being studied to evaluate risk stratification and prognosis for CVD disorders such as procedural outcomes, transplant recipients, and chronic stable angina. The data shows mixed results in terms of applicability for risk stratification and prognosis but will likely evolve over time. Finally, the 2015 European Society of Cardiology (ESC) guidelines include an algorithm for managing acute coronary syndrome (ACS) using a 0/1-hour hs-cTn testing based on studies that demonstrated a 97% sensitivity for a 1 h testing protocol. The guidelines included 2 methods of ruling out AMI, (1) a single sample with hs-cTn levels that were undetectable and (2) a change of 6ng/L between 0 and 1 h or absolute threshold concentration > 52ng/L. In 2017, the US Food and Drug Administration cleared high-sensitivity assays for use in the United States. Continued studies are needed in the United States to determine if protocols using hs-cTn lead to early diagnosis and, subsequently, improved patient outcomes. Studies are needed to incorporate the use of hs-cTn as a better prognostic indicator for various cardiac diseases and interventions.

**ABBREVIATIONS:** ACS - acute coronary syndrome, AMI - acute myocardial infarction, BARI 2D - Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes, CABG - coronary artery bypass grafting, CAD - coronary artery disease, CKD - chronic kidney disease, CTA - coronary computed tomography angiography, CVD - cardiovascular disease, ECG - electrocardiogram, EDACS - Emergency Department Assessment of Chest Pain Score, ESC - European Society of Cardiology, ED - emergency department, hs-cTn - high-sensitivity cardiac troponin, hs-TnI - high-sensitivity troponin I, hs-TnT -

high-sensitivity troponin T, MI - myocardial infarction, m-ADAPT - 2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker, NOT - No Objective Testing, NPV - negative predictive value, NSTEMI - non-ST elevation myocardial infarction, NSTEMI ACS - non-ST-segment elevation acute coronary syndromes, PE - pulmonary embolism, ROMICAT - Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography, SPECT - single photon emission computed tomography, STEMI - ST elevation myocardial infarction, TAVI - transcatheter aortic valve implantation, TnI - troponin I, TnT - troponin T, UA - unstable angina, US - United States.

**INDEX TERMS:** high-sensitivity troponin, acute myocardial infarction, acute coronary syndrome, protocols, chest pain, European Society of Cardiology.

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## INTRODUCTION

Heart disease remains the number one cause of death in the United States (US), accounting for 1 in every 4 deaths. The most common type of heart disease is coronary artery disease, which is the main cause of myocardial infarction (MI, commonly known as a heart attack). Every year 790,000 Americans have an acute myocardial infarction (AMI) and 73% of these events represent a first-time AMI.<sup>1</sup> The signs and symptoms of AMI have been well-described; however, not all people who experience AMI present with the same symptoms, the same severity of symptoms, or with any symptoms at all. Chest pain, one of the most frequently reported symptoms, is the second-most common cause of emergency department (ED) visits. While chest pain is a symptom frequently seen in people with AMI, the actual prevalence of AMI in people who present to the ED with chest pain is very low, approximately 13%.<sup>1</sup> Chest pain assessment, therefore, represents a major burden on healthcare systems and rapid rule-out of chest pain caused by AMI is crucial to avoid costs associated with unnecessary investigations and extended hospital stays.<sup>2</sup> The introduction and use of high-sensitivity cardiac troponin (hs-cTn) has the potential to improve AMI risk stratification and diagnosis, allowing for shorter times to reperfusion and better patient outcomes.

## ACUTE CORONARY SYNDROME, MYOCARDIAL INFARCTION DIAGNOSIS, AND CHEST PAIN PROTOCOLS

Acute coronary syndrome (ACS) is an umbrella term encompassing 3 syndromes: (1) ST elevation myocardial infarction (STEMI), (2) non-ST-segment elevation myocardial infarction (NSTEMI), and (3) unstable angina (UA).

The underlying pathology for all these syndromes is similar in that they all begin with the process of atherosclerosis, which can develop and progress for decades prior to the first presentation of a coronary event. The 3 syndromes are distinguished from one another based on symptoms, electrocardiogram (ECG) findings, and cardiac marker levels. The distinction between these syndromes is critical, because prognosis and treatment protocols vary depending on the syndrome. Unstable angina and NSTEMI are caused by a partially occlusive thrombus resulting in ischemia; however, subendocardial infarction and myocardial necrosis occurs only during NSTEMI, so cardiac marker elevations are only seen with NSTEMI and not UA. In STEMI, complete and sustained coronary occlusion occurs and perfusion to the myocardium supplied by the affected coronary artery is lost, resulting in infarction, necrosis, cardiac marker elevation, and ECG changes. The common signs and symptoms of ACS include chest pain or discomfort (may involve pressure, tightness, or fullness); pain or discomfort in one or both arms, the jaw, neck, back, or stomach; shortness of breath; indigestion; nausea; sweating; and /or feeling dizzy or lightheaded. While chest pain or discomfort is the most common symptom, the signs and symptoms can vary significantly depending on age, gender, and other medical conditions.

Emergency departments have established evidence-based protocols for risk stratification of those presenting with chest pain that aid healthcare providers in ruling out ACS or AMI, defined, as above, with either ECG changes or positive serum biomarkers suggesting myocardial necrosis. Unfortunately, these protocols continue to rely on time, approximately 6 hours post presentation; which increases the risk for complications, poor outcomes, and mortality.<sup>3,4</sup> The new high-sensitivity troponin assay can detect troponin levels sooner and at lower concentrations than the current troponin standard, providing an opportunity for earlier diagnosis and triage.

The 5 widely used chest pain protocols include the HEART pathway, 2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker (m-ADAPT), the Emergency Department Assessment of Chest Pain Score (EDACS), the new Vancouver Chest Pain Rule, and the No Objective Testing (NOT) Rule.<sup>2</sup> The goal and route for each of these scores is slightly different, and overall, they can be grouped into 2 broad categories; those that seek to rule out AMI, and those that seek to rule out ACS. The former category includes 2 of the 5 protocols (m-ADAPT and EDACS) and risk stratifies patients with AMI versus those that may safely obtain further objective testing as an outpatient. The other 3 protocols (HEART, NOT Rule, and new Vancouver Chest Pain Rule) all seek to identify low-risk patients that can be discharged without further cardiac testing (rule out all ACS). Currently, all of these require the analysis of troponin at 3 and 6 hours post presentation.

The HEART pathway uses a scoring system in combination with 0 and 3-hour troponin results. The elements

that make up the HEART score are history, ECG changes, age, risk factors, and troponin level. The goal of the score is to identify a cohort of chest pain patients who could be discharged with no further cardiac testing. The scale of this score ranges from 0 to 10, with low-risk patients defined as having a score of 0 to 3 and high-risk patients defined as having a score of greater than or equal to 4. If the patient is determined to be low risk, they can be discharged home with no further evaluation.<sup>2</sup> When used with the hs-cTn assay, HEART demonstrated a sensitivity of 95% and negative predictive value (NPV) of 99.2% for ruling out ACS when reevaluated 30 days after presentation to the ED. Given the relative low sensitivity for clinicians, the study suggested use of the hs-cTn assay as part of the HEART score in Eds would adequately focus on rapid rule-out of AMI and subsequent outpatient cardiology referral.

The new Vancouver Chest Pain Rule uses an algorithm that begins with the presence/absence of elevated troponin. If there is no elevation at 0 and 2 hours, the decision tree progresses to palpable pain, age, and symptoms (specifically the radiation of pain). For example, if the pain is reproducible, then this is considered low risk. Conversely, if the pain is not reproducible, the patient is older than 50, or the pain radiates to the shoulder/jaw, then the risk of ACS is elevated and cannot be effectively ruled out. Using the hs-cTn assay, the sensitivity was found to be 98.6%, with an NPV of 99.6%. This chest pain protocol has been validated in successfully identifying patients with an extremely low risk for ACS.<sup>5</sup> However, there is one contradictory study from Singapore that shows that this rule had a lower sensitivity (78%).<sup>6</sup> The cause of this lower sensitivity is unclear; however, some considerations include cultural differences that could affect the subjective responses or differing methodologies.

The elements of the NOT Rule include age, presence of risk factors, history of previous MI, no ischemic changes on ECG, as well as no elevation of troponin levels at the 0 and 2-hour marks. The time mark begins at presentation to the ED. This score demonstrated a sensitivity of 99.3% and an NPV of 99.8% and was found to be an effective tool for rule out ACS with the hs-cTn when reevaluated 30 days after presentation to the ED.<sup>2</sup>

Other chest pain protocols in use are the m-ADAPT and EDACS. The elements in m-ADAPT are age, risk factors, aspirin use in the last 7 days, angina in last 24 hours, history of coronary artery stenosis > 50%, ECG indicative of new ischemia, and elevated troponin. Low-risk patients are defined as having 1 or fewer of those elements at 0 and 2-hour troponin checks in addition to no new ischemia on ECG. EDACS elements are age, known coronary artery disease (CAD), diaphoresis, radiating pain, pleuritic pain, gender, and pain reproduced with palpation. A low-risk patient is defined as having a score less than 16. The sensitivity for m-ADAPT for AMI when reevaluated 30 days after presentation to the emergency department was 92.8% with an NPV of 99.1%. For EDACS, the sensitivity was 92.1% with an NPV of 99.0%.<sup>2</sup> However, if this is the

first presentation of the patient, they may not know to use aspirin or be aware of the presence of coronary artery stenosis, which could affect their point value.<sup>2</sup>

Populations in Australia, New Zealand, and Canada reported a negative predictive value of  $\geq 99\%$ , with a sensitivity of  $>94\%$ .<sup>7</sup> Interestingly, a sensitivity of 94% may not be acceptable to US healthcare providers because of the high rate of malpractice lawsuits in this country. Validation studies using the hs-cTn assay are needed in the US to assess its utility in ruling out AMI in our population.

The use of the hs-cTn assays have accelerated current chest pain protocols' ability to assist in patient risk stratification and medical decision making. The new Vancouver Chest Pain Rule and the NOT Rule, studied using the hs-cTn assays, were able to safely rule out ACS in 25% to 30% of patients within the 30-day reevaluation period. This finding suggests providers may be able to use these protocols with the hs-cTn assays to discharge patients meeting certain criteria with no further cardiac workup. The EDACS, m-ADAPT, and HEART scores effectively enabled at least 50% of patients to be discharged with plans for further outpatient objective testing. While hs-cTn assays have shown some promise in accelerating the current chest pain protocols, much more clinical judgement is needed to decide the true nature of elevated troponins due to the high sensitivity of the assay. The old paradigm of "troponin-positive" patients is likely to end with the implementation of hs-cTn because of the new assay's sensitivity. Using hs-cTn assays may allow providers to detect myocardial injury earlier and at much lower values, so there is potential to detect smaller myocardial injury that may or may not include MI or might be a result of nonischemic causes of myocardial necrosis.

## Nonischemic Causes of Myonecrosis

While great emphasis has been placed on troponins for the significant role they play in the diagnosis of AMI, care must be taken when interpreting troponin results because troponin release from cells is organ-specific, not disease-specific. As the sensitivity of the troponin assay improves (as in the case with the fifth-generation assays), more and more emphasis needs to be placed on the fact that this assay is organ-specific. If an increased troponin value is encountered in the absence of other clinical and radiological findings of ischemia, other etiologies should be explored. For example, there are many nonischemic causes of myonecrosis, including vasculitis, drug abuse, myocarditis, pulmonary embolism (PE), sepsis, renal failure, and immunoassay interference. A more complete list of diagnoses can be found in [Table 1](#).

Important comorbid conditions to consider when interpreting hs-cTn results are chronic kidney disease (CKD) (glomerular filtration rate  $< 60\text{mL}/\text{min}/1.73\text{m}^2$ ) and end-stage renal disease. CKD patients are at an increased risk of cardiovascular disease compared to those with normal renal function, and their baseline troponin

**Table 1.** List of non-ACS causes of elevated cardiac troponins

	Potential Mechanism of Action		
	Imbalance of oxygen supply and demand	Inflammation or edema	Multifactorial/unclear
List of causes	Microvascular CAD, Tachy-brady arrhythmias, aortic dissection, hypertensive crisis, cardiomyopathy, acute respiratory distress syndrome/ acute respiratory failure, pulmonary embolism, severe anemia, shock (septic, cardiogenic, or hypovolemic)	Myocarditis, rhabdomyolysis, pericarditis, defibrillator-related injury, surgery, ablation, cardiac contusion, drug-induced cardiotoxicity	Infiltrative diseases (amyloidosis, sarcoidosis), renal disease, acute neurological diseases (stroke, trauma), heart failure, stress cardiomyopathy, and vasculitis

values may be chronically elevated above the 99<sup>th</sup> percentile range. The underlying etiology of the chronic elevation of troponin remains unclear but is likely multifactorial, including ongoing myocyte necrosis due to uremia toxicity, microvascular ischemia, and decreased renal clearance.<sup>8</sup> Studies evaluating the significance of detectable cTn levels in CKD patients without AMI have shown that there is prognostic value in monitoring these levels. Different studies have shown an association with elevated levels of hs-cTn and complications such as left ventricular hypertrophy, long-term all-cause mortality, and increased serum inflammatory markers.<sup>9</sup> Although further longitudinal studies are needed, the presence of elevated hs-cTn levels in CKD patients is associated with an increased risk for underlying structural heart disease and progression to symptomatic disease. Measuring serial changes over time in CKD patients presenting with chest pain is critical to determine whether the higher values are stable, and likely due to their chronic renal condition, or rising, suggesting a more acute condition such as AMI.

Drug-induced myocarditis has been increasing in prevalence, likely caused by multifactorial reasons, including increased drug usage and better imaging modalities. It is important to consider patient current and previous drug use when interpreting hs-Tn results. Several classes of drugs have been implicated in inducing cardiac damage, including tricyclic antidepressants, anthracyclines, beta-2 mimetics, antimetabolites, and alkylating agents. Non-prescription drugs such as cocaine are also known to cause cardiotoxicity. The mechanisms of cardiac toxicity from these agents are varied. Anthracycline chemotherapy causes a progressive myofibrillar loss and cytoplasmic vacuolization leading to a chronic dilated cardiomyopathy. Studies have shown that the serum levels of cTnT correlate with the total cumulative dose of doxorubicin.<sup>10</sup> Other commonly used chemotherapies such as the pyrimidine antimetabolite 5-fluorouracil (5-FU), or the alkylating agent cyclophosphamide, result in a reduction in left ventricular diastolic compliance and subsequent interstitial edema.<sup>11</sup> Finally, beta-sympathomimetic agents likely cause a calcium overload leading to an imbalance of oxygen supply and demand and ultimate loss of structural integrity and cell necrosis.<sup>12</sup> Cardiac troponins are

considered the biomarkers of choice for monitoring drug-induced myocardial toxicity and can be considered a prognostic indicator for future severe and prolonged left ventricular dysfunction.<sup>13</sup>

PE causes a positive troponin level that is similar to AMI. In fact, PE is often difficult to diagnose and is included on the differential diagnosis when considering AMI. Troponin concentrations are elevated because of an increased right ventricular afterload leading to myocardial injury. Many studies have suggested using hs-cTn levels as a severity index in PE for hemodynamically stable patients.<sup>14</sup> Prospective studies are needed to determine the prognostic value of hs-cTn in intermediate- and low-risk patients diagnosed with PE.

One of the common diagnoses that clinicians fail to consider for elevated troponins is a false-positive troponin caused by immunoassay interference. Immunoassays use antibody-antigen reactions through weak hydrogen bonds and van der Waals forces.<sup>15</sup> False-positive results occur when these antibodies bind with other structurally similar molecules or if autoantibodies are formed, causing interference. The presence of heterophile antibodies in serum may lead to false-positive troponin results because of the nonspecific binding of these antibodies to the Fc-ports of the troponin assay antibodies. Heterophile antibody production may be stimulated by exposure to a variety of antigens including transfused blood, vaccinations, exposure to mice and rabbits, therapeutic use of mouse monoclonal antibodies, and some autoimmune diseases that give rise to antibodies with heterophile activity (ie, rheumatoid factor). Approximately 30% of the population has heterophile antibodies. If a false-positive value is suspected, there are several confirmatory options available. One option is to measure other cardiac biomarkers such as creatine kinase-MB and myoglobin to see if they are also elevated. If these are in the normal range, then the suspicion for false positivity increases. A number of other strategies exist to counteract interference from heterophile antibodies such as the use of pooled animal sera to remove antianimal antibodies, the use of heterophile blocking agents, and the sample being sent for testing using a different assay.<sup>16</sup>



When an increase in hs-cTn is found in a clinical setting, absent of other indicators of AMI, alternate etiologies should be explored. Although the diagnosis of AMI is strongly based on the positive presence of troponin, this lab value is only one factor as part of an entire clinical picture to diagnose coronary ischemia. It is important for a clinician to remember that troponin is a measure of specific organ damage, not specific disease state.

## TROPONIN ASSAY USE WITH RISK STRATIFICATION

Troponin assays have not only been useful in detecting AMI but have also been helpful in the assessment of adverse outcomes following coronary interventional procedures. Cardiac troponin is elevated after coronary artery bypass grafting (CABG) surgery, which is an established revascularization strategy after multivessel CAD. It is important to identify any emergent complications after CABG to undertake quick therapeutic strategies such as graft exploration, coronary angiography with or without percutaneous intervention, and intra-aortic balloon pump insertion.<sup>17</sup>

Historically, data has shown a correlation between troponin elevations and CABG-associated morbidity and mortality. Two separate prospective studies involving 290<sup>18</sup> and 1722 patients<sup>17</sup> respectively, showed that a 1000 ng/L increase in cardiac troponin T levels measured on average approximately 8 hours after surgery, correlated with a 7-fold increase in post-operative in-hospital complications such as MI, renal insufficiency, and therapies necessitating vasopressors. Beller et al have also correlated an elevated preoperative troponin level with worse outcomes following CABG.<sup>19</sup> In a comparison of prognostic performance between the hs-cTn cardiac troponin T assay and the conventional cardiac troponin T assay for predicting cardiac and cerebrovascular events post-CABG, a 2018 study linked elevated troponin values at a cutoff of 800ng/L, with worse outcomes when assessed 6 and 12 hours postoperatively.<sup>17</sup>

Many studies have looked at other procedure-related elevations in cardiac troponin. This increase can be the result of periprocedural myocardial injury from a variety of conditions including side chain occlusions, distal embolization, prolonged or multiple balloon inflation, coronary dissection with diminished flow, and microthrombi preventing reflow.<sup>20</sup> Outcome measures in the setting of percutaneous coronary interventions have demonstrated that procedural elevation of hs-cTn values (3 to 5 times the upper normal limit) correlates proportionately with the extent of postprocedural myocardial injury.<sup>20-22</sup> However, the significance of this elevation at lower values, correlating with smaller amount of cellular damage, is not usually apparent clinically or angiographically and thus require more research to assess the clinical significance and possible interventions at these levels of assay

sensitivity.<sup>21,23,24</sup> Similar results have been shown to be associated with postprocedural elevated cardiac troponin levels involving transcatheter aortic valve implantation (TAVI) in patients with inoperable severe aortic stenosis. At elevated baseline cardiac troponin levels, there appeared to be a correlation with post-TAVI outcomes including AMI, stroke, and death; however, these effects were not apparent at lower levels.<sup>25-29</sup>

Troponin levels have been used, with mixed results, to evaluate outcomes in heart transplant recipients who received hearts from donors with elevated troponin. Earlier studies demonstrated that there was an increased risk to the recipient with elevated donor Tnl or TnT levels in the form of decreased left ventricular ejection fraction and primary graft failure.<sup>30,31</sup> However, later studies with much larger sample sizes, including one recent study with 11,000 subjects, have not been able to demonstrate this relationship, and have concluded that elevated donor troponin levels were not associated with primary graft dysfunction or increased mortality.<sup>32-36</sup>

Goldstein et al looked at the relationship between baseline troponin levels and patients with long-term medically managed non-ST-segment elevation acute coronary syndromes (NSTEMI ACS) patients, receiving antiplatelet therapy.<sup>37</sup> A total of 6763 randomized medically managed NSTEMI ACS patients in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) study were tracked using their peak troponin/upper limit of normal ratio measured within 48 hours of the onset of ACS. They were monitored for up to 30-months for myocardial infarction, stroke, cardiovascular death, and all-cause death. The results showed that among medically managed NSTEMI ACS patients, there was a proportional relationship between increasing peak troponin and long-term ischemic events, and that troponin levels in these patients could be a predictor of prognostic outcomes.

Recent studies have looked at cardiovascular risk in patients with stable ischemic disease and hs-cTn concentrations, independent of conventional risk markers. Omland et al conducted a 5-year post-hoc analysis of stable ischemic heart disease patients enrolled in the Prevention of Events with Angiotensin-Converting Enzyme Therapy (PEACE) trial, and showed that elevated baseline hs-cTn levels correlated independently with risk of death from cardiovascular diseases and heart failure, but were not associated with increased risk of AMI.<sup>38</sup> Another study demonstrated that even very low levels of troponin are associated with increased risk of cardiovascular disease and death in women with diabetes who have never had ischemic heart disease.<sup>35</sup> Results from the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial involving 2277 patients with both stable ischemic heart diseases and diabetes mellitus have further strengthened the theory that elevated hs-cTn values are associated with increased risk of cardiovascular events among patients with stable ischemic heart

disease.<sup>39</sup> Approximately 40% of the patients in BARI 2D study were found to have increased hs-cTn values ( $\geq 14$  ng/L) compared to baseline detectable levels ( $\geq 3$  ng/L), which directly correlated with risk of death from cardiovascular causes, AMI, or stroke, with or without adjusting for other risk factors.

To better risk stratify and to increase diagnostic accuracy in patients with acute coronary syndromes, many authors have suggested combining troponin values with imaging modalities such as single photon emission computed tomography (SPECT) imaging, and coronary computed tomography angiography (CTA). Compelling results in support of this combination approach were obtained from 2 observational cohort studies: The Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT) I and II trials.<sup>40,41</sup> In the ROMICAT I trial,<sup>40</sup> patients admitted to the ED underwent high-sensitivity troponin T (hs-TnT) measurements, SPECT myocardial perfusion imaging, and 64-slice CTA. In the ROMICAT II trial, patients presenting to the ED underwent high-sensitivity troponin I (hs-TnI) measurements, along with CTA imaging for traditional (no CAD, nonobstructive CAD,  $\geq 50\%$  stenosis) and advanced features of CAD ( $\geq 50\%$  stenosis, high-risk plaque features). The results from these studies indicated that hs-TnT levels had good discriminatory ability for prediction of abnormal SPECT-MPI. Both reversible myocardial ischemia and the extent of coronary atherosclerosis detected by the imaging studies independently and incrementally predicted the measured hs-TnT levels. Also, the combined hs-TnI and advanced coronary CTA assessments showed improved risk stratification accuracy for ACS as compared to conventional troponin/traditional coronary CTA. Of note, the Medicare reimbursement rates for troponin testing averaged \$13 in 2018, compared to that of myocardial SPECT imaging and CTA which amounted to \$1202 and \$252, respectively, without factoring in the associated Medicare physician fee schedules. The additional cost involved with these imaging modalities may be a factor that plays a role in the decision making process for some patients.<sup>42</sup>

Cardiac troponin values have become part of routine use for risk stratification across a spectrum of heart-related issues in the ED, as well as in routine clinical practice. Just as described in the introduction article, the full impact of hs-cTn for its clinical use will be seen in the years to come.

## EUROPEAN GUIDELINES FOR HIGH-SENSITIVITY TROPONIN

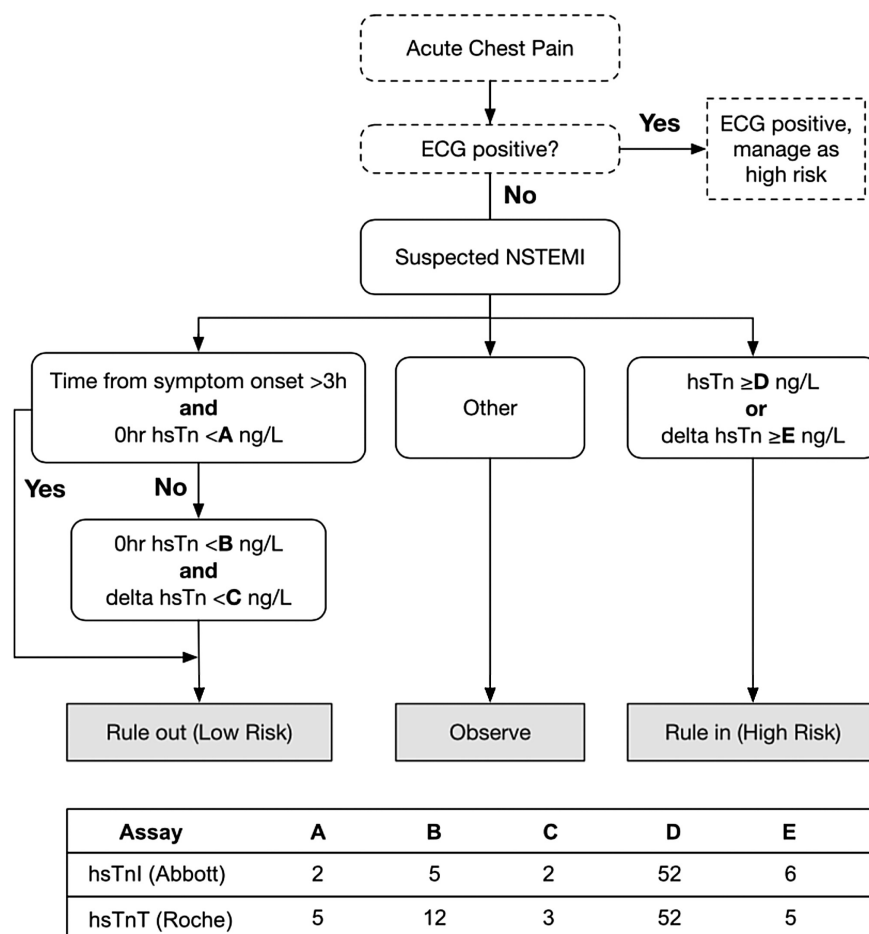
In 2012, the International Federation of Clinical Biochemistry established criteria to define an hs-cTn assay. To be classified as a high-sensitivity assay, it must have a coefficient of variation of 10% or less at the 99th percentile and be able to detect cTn in at least 50% of the reference population.<sup>43</sup> The utility of the high-sensitivity assay in ruling out ACS according to the initial values of cTn was

first introduced in the European Society of Cardiology (ESC) 2011 guidelines and reaffirmed in the most recent 2015 guidelines.<sup>43</sup> The 2015 guidelines included an algorithm for managing ACS using 0/1-hour hs-cTn testing. The guidelines included 2 methods of ruling out AMI, (1) a single sample with hs-cTn levels that were undetectable and/or (2) a change of 6ng/L between 0 and 1 hour or absolute threshold concentration  $> 52$ ng/L. A modified 0/1-hour algorithm using hs-cTn was presented by Pickering et al in 2017 (Figure 1).<sup>7</sup> These recommendations have been implemented in the United Kingdom, Australia, Scotland, and other European countries. Implementing a similar 1-hour rule-out in the United States may drastically decrease overcrowding and wait times in emergency rooms. However, the approximately 97% clinical sensitivity of the hs-cTn protocol demonstrated by Pickering et al may not be accepted in the United States given our higher rate of malpractice.<sup>44</sup>

In 2014, the National Institute for Health and Care Excellence recommended the use of hs-cTn. However, as of July 2018, the only assay cleared by the US Food and Drug Administration is the Roche Elecsys Troponin T Gen 5 Stat.<sup>3</sup> According to the European labels for the assay, the test achieves a less than 10% coefficient of variation at the 99<sup>th</sup> percentile of 19ng/L overall with a limit of detection of 5ng/L.<sup>45</sup> The assay also provides results in 9 minutes, shortening the time to diagnosis by almost 3 hours when compared with Roche's conventional TnT assay. Companies with high-sensitivity troponin tests that are not yet approved in the United States include Siemens, Abbott, and Beckman Coulter. As these new assays are cleared for use, it will become important to be familiar with assay specifics as it relates to AMI.<sup>4</sup>

Another major change with the clearance of the new hs-cTn assays is the recommendation for the use of gender-specific cutoffs. Research has shown that women who have heart disease or had an MI do worse than men even though the therapies developed are gender neutral. One reason may be that women are not as rapidly detected and treated as men. In almost all the studies with hs-cTn, there are substantial differences in the normal ranges between men and women, with men carrying much higher levels. Therefore, the hs-cTn assays identify gender-specific cutoffs with values 50% lower for women.<sup>46</sup> There have been several studies examining the benefits of using age- and gender-specific cutoffs for diagnosis and prognosis of AMI, but results have been conflicting and the clinical utility of gender-specific reference intervals and cutoffs remains uncertain.<sup>47</sup>

Several studies have validated the ESC algorithm with respect to the ABBOTT assay.<sup>7</sup> Other studies have concluded that a single hs-cTnI measurement at presentation that is below the lower limit rules out acute myocardial injury regardless of other findings with a sensitivity of 100% in men.<sup>46</sup> Patients have a high likelihood for non-ST elevation myocardial infarction (NSTEMI) if the hs-cTn concentration at presentation is even slightly elevated. However, in women, the NPV and sensitivity for AMI was



**Figure 1.** Modified European Society for Cardiology Guidelines Flow Chart for Risk Stratification<sup>7</sup>

lower at 98.3%, but if normal ECG was added the NPV improved to 99.3%. An early rule-out of AMI decreased wait times and facilitated early discharge of patients without ACS and subsequently decreased the healthcare burden.<sup>4</sup>

## FUTURE DIRECTIONS/CONCLUSIONS

The introduction of testing for myonecrosis in the emergency setting for diagnosis of ACS was a groundbreaking milestone in our approach to triaging and treating patients with chest pain. Guidelines abroad now recommend the use of hs-cTn to assist with diagnosis and risk stratification that can occur at earlier timeframes and for alternative etiologies for increased troponin levels.

Continued studies are needed in the United States to determine if protocols using hs-cTn lead to early diagnosis and, subsequently improved patient outcomes. In addition, studies are needed to incorporate the use of hs-cTn as a better prognostic indicator for various cardiac diseases and interventions. In the past, clinicians have been taught that troponin-positive results or ECG changes meant activation of the cardiac catheterization lab to patients and clinicians. With the integration of hs-cTn, a new mantra may be coming in medical education.

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