Atellica IM

High-Sensitivity Troponin I (TnIH) Assay

Potential 0/1-hour Algorithm for Early Rule-in and Rule-out of Suspected Acute Myocardial Infarction[1]

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Guidelines for Suspected Acute Myocardial Infarction Diagnosis and Cardiac Troponin Testing

Due to its sensitivity and myocardial specificity, cardiac troponin (cTn) is the preferred biomarker for diagnosis of acute myocardial infarction (AMI).[2] AMI is diagnosed when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Necrosis is defined by a significant rise or fall (serial change) of cTn measured between presentation at 0 hour (h) and 1–6h later, depending on the troponin assay used.

The original AMI redefinition document specified the 99th percentile as the decision level and recommended that this should be measured with a 10% coefficient of variation (CV).[3] Due to the higher sensitivity and diagnostic accuracy for the detection of AMI at presentation, the time interval to the second cTn assessment can be shortened with the use of high-sensitivity assays. This may reduce substantially the delay to diagnosis, translating into shorter stays in the emergency department (ED) and lower costs.[4–7]

- Clinical introduction of high-sensitivity cardiac troponin (hs-cTn) assays significantly increases the number of chest pain patients presenting with values exceeding the 99th percentile as a result of causes other than AMI. This decreases specificity for AMI, complicating the appropriate triage of patients.[6,8–10]
- To assist with such triage, hs-cTn assays are useful by their ability to detect a rising or falling pattern (serial change) between 0h and 1h or 2h.[1,6]
- Absolute changes are recommended over relative changes for the assessment of patients with suspected AMI.[11] Sensitive and hs-cTn assays are not standardized; thus, absolute changes diagnostic of AMI must be determined for each assay.[12]
- Dynamic changes are not specific for AMI but are indicative of active myocardial injury with necrosis. Cardiac troponins are markers of myocardial necrosis and not just AMI.[6,11,12]
- Thus, elevations of cTn outside of an ischemic context should not be perceived as "false positive"; they reflect levels of myocardial necrosis and present a high prognostic value for morbidity and mortality.[6,12–16]

The Atellica® IM TnIH Assay is a high-sensitivity troponin I assay, with a 10% CV highest value at 6.0 ng/L, far below the 99th percentile value of 45 ng/L (combined male and female) where the CV is <4%* and its ability to detect more than 50% of healthy subjects.

Atellica IM TnIH Assay vs. ADVIA Centaur TNIH Assay

The Atellica IM TnIH Assay reagent formulation, including the three monoclonal antibodies, is the same formulation as the ADVIA Centaur® High-Sensitivity Troponin I assay (TNIH). The algorithm described below was established using the ADVIA Centaur TNIH Assay. The ADVIA Centaur TNIH Assay and the Atellica IM TnIH Assay agree analytically as shown by the following method comparison:
[y = 1.022x + 0.676 pg/mL (ng/L), r = 0.999, n = 97; range = 13.2–19.635 pg/mL (ng/L)]; ADVIA Centaur range = 0.3580–16.473 pg/mL (ng/L) and Atellica IM range = 0.2800–15.989 pg/mL (ng/L). The assay comparison was determined using the Passing-Bablock regression model in accordance with CLSI document EP09-A3.[17]

Potential 0/1h Algorithm for AMI

0/1h assessments can be recommended when hs-cTn assays with a validated algorithm are available.[1,6,18–21]

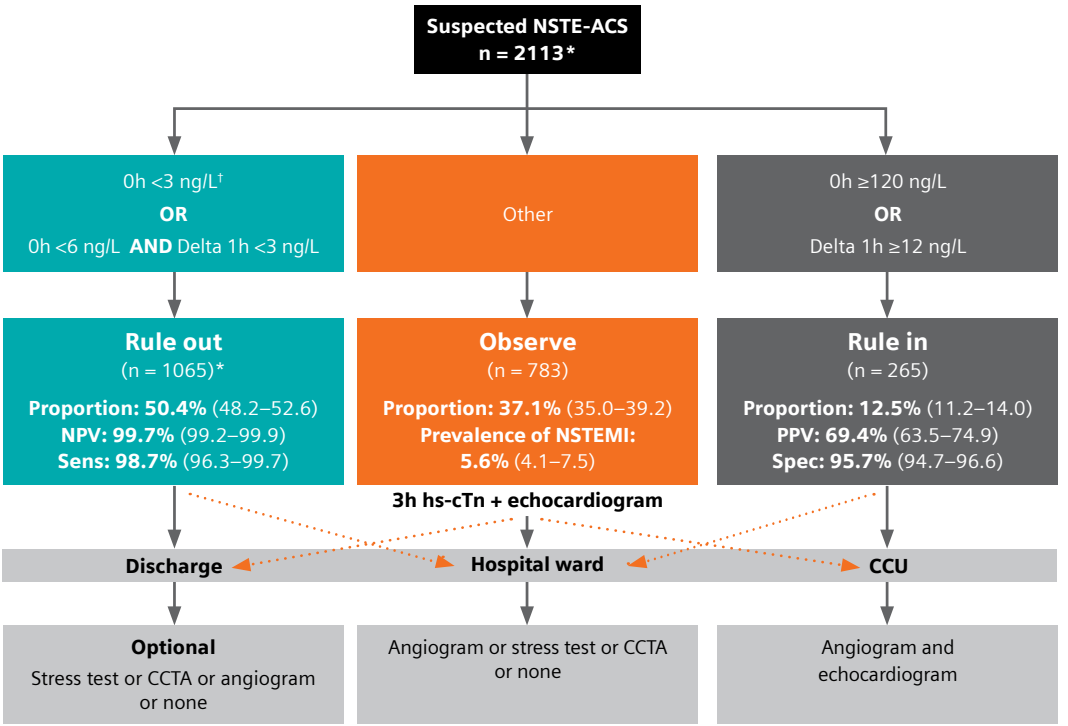
- High-sensitivity cardiac troponin is a continuous variable and the probability of AMI increases with increasing hs-cTn values.

The cutoff levels and delta within the 0/1h algorithm provided in this document were determined using the ADVIA Centaur TNIH assay with the "Advantageous Predictors of Acute Coronary Syndrome Evaluation" (APACE) cohort in a derivation-validation study.[1] The derivation study established the rule-in, rule-out, and delta decisional cutoff parameters.

Validation of the 0/1h algorithm with two additional cohorts, one in Scotland "High-Sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome" (High-STEACS) and one in the U.S. "High-Sensitivity Cardiac Troponin I Assays in the United States" (HIGH-US) align with the latest guidelines and confirm the APACE algorithm validation published in 2018.[21,22]

- Early absolute changes of the levels within 1h can be used as surrogates for absolute changes over 3h or 6h and provide incremental diagnostic value to the cardiac troponin assessment at presentation.[18]

**High-Sensitivity Cardiac Troponin I and T Assay Analytical Characteristics Designated by Manufacturer; IFCC Committee on Clinical Applications of Cardiac Bio-Markers (C-CB) v122019.*



NPV: Negative predictive value
PPV: Positive predictive value

Figure 1. Potential Atellica IM High-Sensitivity Troponin I Assay 0/1h algorithm. This algorithm uses the "High-Sensitivity Cardiac Troponin I Assays in the United States" (HIGH-US) cohort validation study[22] (which was based on the algorithm established in a derivation-validation study with the "Advantageous Predictors of Acute Coronary Syndrome Evaluation" [APACE] cohort).[1] For additional information regarding the APACE cohort and the adjudication process please refer to the publication by Boeddinghaus et al.[1]

**Clinical performance of the Atellica IM TnIH Assay (using HIGH-US cohort).[2]*
†If chest pain onset >3h before presentation to the ED

"If myocardial ischemia is present clinically or detected by ECG changes together with myocardial injury, manifested by a rising and/or falling pattern of cardiac troponin values, a diagnosis of acute MI is appropriate. If myocardial ischemia is not present clinically, then elevated cardiac troponin levels may be indicative of acute myocardial injury if the pattern of values is rising and/or falling, or related to more chronic ongoing injury if the pattern is unchanging."[6]

Patients with terminal renal failure or on chronic dialysis were excluded from the APACE derivation and validation studies,[1] while the HIGH-US cohort did not exclude patients with renal dysfunction. To ensure the best possible clinical use, assay-specific optimal cutoff levels, which are higher in patients with renal dysfunction, should be used.[18]

The accuracy for the early rule-out or rule-in of AMI with either a 0/1h or 0/2 to 3h novel hs-cTnI algorithm based on the APACE study was validated in a separate more diverse ED population (n = 2113) that also included renal dysfunction patients. Results were similar to those of the APACE study, allowing greater confidence that ED patients can be equivalently evaluated with either a 0/1h or 0/2 to 0/3h algorithm. The rule-out zone hs-cTnI cut points of these algorithms additionally accurately predict the low-prevalence 30-day outcomes of all-cause mortality and AMI, regardless of any ECG changes or the use of any clinical risk stratification tools.[21]

Elevations of Cardiac Troponin Values Due to Myocardial Injury[6]

Myocardial injury related to acute myocardial ischemia

Atherosclerotic plaque disruption with thrombosis.

Myocardial injury related to acute myocardial ischemia because of oxygen supply/demand imbalance

Reduced myocardial perfusion, e.g.,

- Coronary artery spasm, microvascular dysfunction
- Coronary embolism
- Coronary artery dissection
- Sustained bradyarrhythmia
- Hypotension or shock
- Respiratory failure
- Severe anemia

Increased myocardial oxygen demand, e.g.,

- Sustained tachyarrhythmia
- Severe hypertension with or without left ventricular hypertrophy

Other causes of myocardial injury

Cardiac conditions, e.g.,

- Heart failure
- Myocarditis
- Cardiomyopathy (any type)
- Takotsubo syndrome
- Coronary revascularization procedure
- Cardiac procedure other than revascularization
- Catheter ablation
- Defibrillator shocks
- Cardiac contusion

Systemic conditions, e.g.,

- Sepsis, infectious disease
- Chronic kidney disease
- Stroke, subarachnoid hemorrhage
- Pulmonary embolism, pulmonary hypertension
- Infiltrative diseases, e.g., amyloidosis, sarcoidosis
- Chemotherapeutic agents
- Critically ill patients
- Strenuous exercise

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