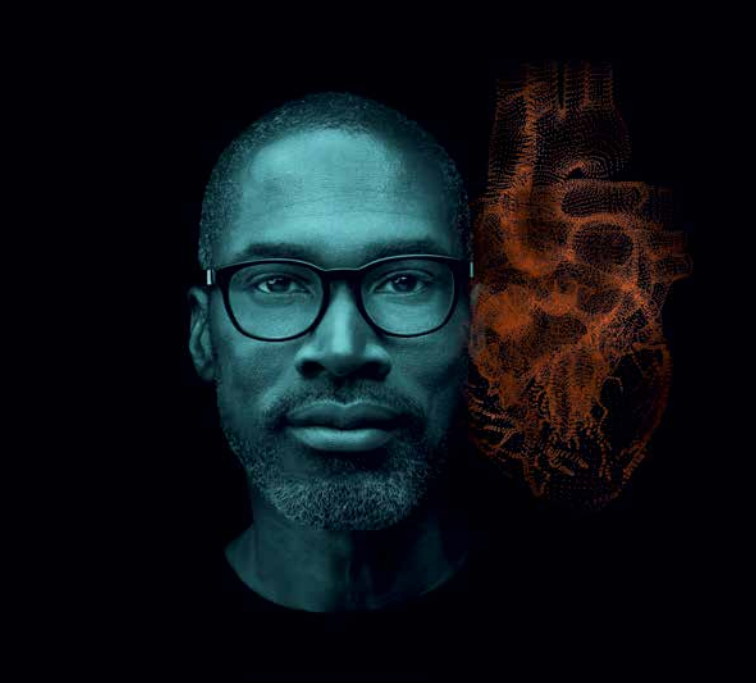


Dimension EXL LOCI TNIH Assay

High-Sensitivity Troponin I (TNIH) Assay

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

siemens-healthineers.com/troponin

SIEMENS Healthineers

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).[1] 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 1–6 h later, depending on the troponin assay used.

The original AMI redefinition document specified the 99th percentile as the decision level and recommended that it should be measured with a ≤10% coefficient of variation (CV).[2] Due to their higher sensitivity and diagnostic accuracy for the detection of AMI at presentation, the time interval to the second cTn assessment can be shortened using high-sensitivity assays. This may substantially reduce the time to diagnosis, translating into shorter stays in the emergency department (ED) and lower costs.[3-9]

- 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.[6,8-11]
- To assist with such triage, hs-cTn assays are useful in their ability to detect a rising or falling pattern (serial change) between 0 h and 1 h or 2 h.[3,8-9]
- 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.[6,9,12,13]
- Absolute changes are recommended over relative changes for the assessment of patients with suspected AMI. Sensitive and hs-cTn assays are not standardized; thus, absolute changes diagnostic of AMI must be determined using assay-specific cut-offs and changes over time.[3,6,9]
- Thus, elevations of cTn outside of an ischemic context should not be perceived as "false positive"; they reflect levels of myocardial injury and present a high prognostic value for morbidity and mortality.[6,9,13-17]

The Dimension® EXL™ LOCI® TNIH assay is a high-sensitivity cardiac troponin I assay with a 10% CV highest value of 12.0 ng/L, far below the 99th percentile values for males and females. The limit of quantitation (LoQ) is 4 ng/L. The assay reports measurable concentrations above the limit of detection (LoD) for more than 50% of healthy males and healthy females, separately.[18]

99th Percentiles for the Dimension EXL TNIH Assay

To establish the 99th percentile for the assay (Table 1), lithium-heparin specimens were collected from apparently healthy individuals from the United States who ranged from 22–91 years of age. The 99th percentile values were determined using the nonparametric statistical method described in CLSI EP28-A3c.[19]

Table 1. Dimension EXL TNIH assay 99th percentile values for males, females, and sexes combined.

Sample Type	Sex	n	99th Percentile (ng/L or pg/mL)	90% CI* (ng/L or pg/mL)
Heparin plasma	Female	1017	51.4	35.6–109.2
	Male	1003	76.2	42.3–117.0
	Combined	**2020**	**60.4**	**43.2–81.3**

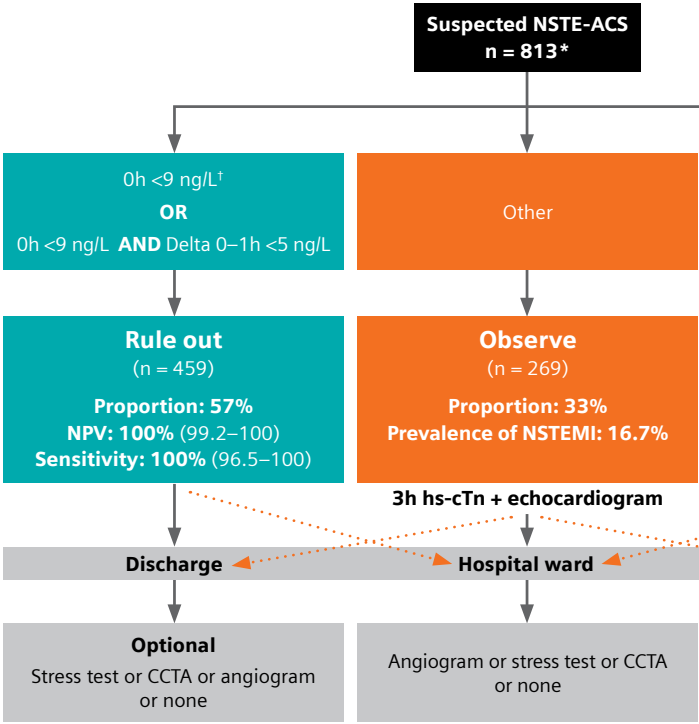
**CI: confidence interval.*

Note: data for serum specimens are also available, see assay-specific Instructions for Use.

Potential 0/1 h Algorithm for AMI

Current guidelines advocate the use of hs-cTn assays and assay-specific European Society of Cardiology (ESC) 0/1 h hs-cTnT/I algorithms with a class I recommendation. Clinical practice guidelines and expert committees indicate that the clinical performance of new hs-cTn assays, including their optimal, assay-specific triage cutoffs, needs to be evaluated in large prospective clinical studies.[9,22,23] This has been done for the LOCI High Sensitivity Troponin I assay (TNIH) on the Dimension EXL system.[3]

0/1 h assessments can be recommended when hs-cTn assays with a validated algorithm are available.[3,6,8,9] High-sensitivity cTn is a continuous variable, and the probability of AMI increases with increasing hs-cTn values.



NPV: Negative predictive value
PPV: Positive predictive value
CCTA: Coronary Computed Tomography Angiography

The cutoff levels and delta in the 0/1 h algorithm provided in this document were determined using the Dimension EXL TNIH assay with the Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) cohort in a derivation-validation study.[3] The derivation study established the rule-in, rule-out, and delta decisional cutoff parameters, while the validation study confirmed the clinical performances.

Early absolute changes in cTn levels within 1 h can be used as surrogates for absolute changes over 3 h or 6 h and provide incremental diagnostic value to the cTn assessment at presentation.[9]

The algorithm described above was established using the LOCI High Sensitivity Troponin I (TNIH) assay on the Dimension EXL system.

Patients with terminal renal failure or on chronic dialysis were excluded from the APACE derivation and validation studies.[1] To ensure the best possible clinical use, assay-specific, optimal cutoff levels, which are higher in patients with renal dysfunction, should be used.[20]

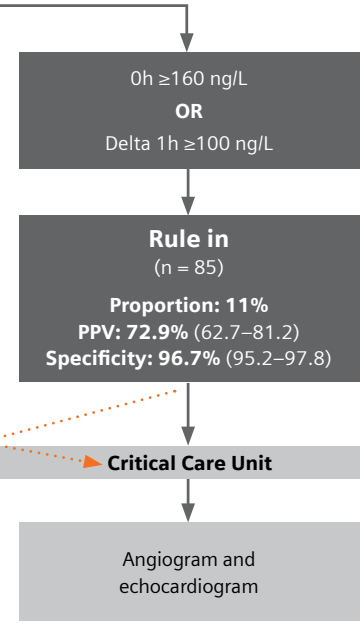


Figure 1. Potential Dimension EXL High-Sensitivity Troponin I assay 0/1 h algorithm. This algorithm uses the high-sensitivity cardiac troponin I assays in the APACE overall cohort.[1]
For additional information regarding the APACE cohort and the adjudication process, refer to the publication by Luca Koechlin et al.[3]

**Clinical performance of the high-sensitivity cardiac troponin I on the Dimension EXL system (using the APACE overall cohort).[3]*
†If chest pain onset >3 h 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."[6,9]

Elevations of Cardiac Troponin Values Due to Myocardial Injury[6,22]

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

References:

1. Morrow DA, Cannon CP, Jesse RL, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Clin Chem. 2007;53:552-74.
2. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. Eur Heart J. 2000;21:1502-13.
3. Koechlin L, Boeddinghaus J, Lopez-Ayala P, et al. Diagnostic discrimination of a novel high-sensitivity cardiac troponin I assay and derivation/validation of an assay-specific 0/1h-algorithm. Am Heart J. 2023;255;58-70. doi: https://doi.org/10.1016/j.ahj.2022.10.007
4. Apple FS, Collinson PO. Analytical characteristics of high-sensitivity cardiac troponin assays. Clin Chem. 2012;58:54-61.
5. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting without Persistent ST-segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2999-3054.
6. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. Eur Heart J. 2018;00:1-33.
7. Twerenbold R, Boeddighaus J, Mueller C. Update on high-sensitivity cardiac troponin in patients with suspected myocardial infarction. Eur Heart J. Suppl 2018;(Supplement G):G2-G10.
8. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:267-315.
9. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2020;00:1-79.
10. Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med. 2009;361:868-77.
11. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009;361:858-67.
12. Wu AH, Lu QA, Todd J, Moecks J, Wians F. Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. Clin Chem. 2009;55:52-8.
13. Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation. 2011;124:136-45.
14. Jaffe AS, Moeckel M, Giannitsis E, et al. In search for the Holy Grail: suggestions for studies to define delta changes to diagnose or exclude acute myocardial infarction: a position paper from the Study Group on Biomarkers of the Acute Cardiovascular Care Association. Eur Heart J - Acute Cardiovasc Care. 2014;3:313-6.
15. Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: the present and the future. J Am Coll Cardiol. 2006;48:1-11.
16. Scharnhorst V, Krasznai K, van 't Veer M, Michels RH. Variation of cardiac troponin I and T measured with sensitive assays in emergency department patients with noncardiac chest pain. Clin Chem. 2012;58:1208-14.
17. Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J. 2012;33:2252-7.
18. High-sensitivity cardiac troponin I and T assay analytical characteristics designated by manufacturer. IFCC Committee on Clinical Applications of Cardiac Biomarkers (C-CB). v042021.
19. Clinical and Laboratory Standards Institute. CLSI document EP28-A3c: Defining, establishing, and verifying reference intervals in the clinical laboratory. Approved guideline—third edition. CLSI, Wayne, PA. 2010.

(continued on next page)

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

References *(continued from previous page)*:

20. Miller-Hodges E, Anand A, Shah ASV, et al. High-sensitivity cardiac troponin and the risk stratification of patients with renal impairment presenting with suspected acute coronary syndrome. Circulation. 2018;137:425-35.
21. Stepinska J, Lettino M, Ahrens I, et al. Diagnosis and risk stratification of chest pain patients in the emergency department: focus on acute coronary syndromes. A position paper of the Acute Cardiovascular Care Association. Eur Heart J - Acute Cardiovasc Care. 2020 Feb;9(1):76-89.
22. Twerenbold R, Boeddinghaus J, Nestelberger T, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. J Am Coll Cardiol. 2017;70:996-1012.
23. Lopez-Ayala P, Boeddinghaus J, Koechlin L, et al. Early rule-out strategies in the emergency department utilizing high-sensitivity cardiac troponin assays. Clin Chem. 2021;67:114-23. doi: 101093/clinchem/hvaa226.

Siemens Healthineers Headquarters
Siemens Healthcare GmbH
Henkestr. 127
91052 Erlangen, Germany
Phone: +49 9131 84-0
siemens-healthineers.com

Published by
Siemens Healthcare Diagnostics Inc.
Laboratory Diagnostics
511 Benedict Avenue
Tarrytown, NY 10591-5005
USA
Phone: +1 914-631-8000

Published by Siemens Healthcare Diagnostics Inc.
30-23-DX-2437-76 · HOOD05162003331062 · 03-2023