High Sensitivity Troponin Information and Algorithm

Background on hs-TnI and diagnosis of AMI

- History, physical, ECG and cardiac biomarker testing are the gold standards for diagnosing acute coronary syndrome (ACS).
- The new troponin assay to be adopted by JPS is called Seimens Vista high sensitivity Troponin I (hs-TnI).
- This hs-TnI assay has improved analytical performance, especially at low levels, compared to the older conventional TnI assay.
- Hs-TnI assays allow for more accurate and precise troponin results at very low levels, which permits for the use of an accelerated chest pain algorithm for rapid rule-out/rule-in of AMI.
- The new hs-TnI reporting protocol will involve reporting results in ng/L (compared to the previous µg/L).
- High sensitivity troponins are not negative or positive – they will be:
  - Undetectable (below the limit of detection)^
    - <20ng/L
  - Measurable (between limit of detection but below the 99th percentile - this is termed the ‘Grey zone’)
    - >20 ng/L but <53 ng/L in Women or <78 ng/L in men
  - Above the 99th percentile (abnormal)
    - >53 ng/L in Women or >78 ng/L in men
    - These values are consistent with ACS (Type I vs Type II etc)
    - For the Seimens vista hs-TnI assay – if these values are exceeded EPIC will flag this threshold as a ‘critical value’.
    - A function of 10x the 99%ile - (>500 ng/L) Should be considered 100% specificity for AMI
- The delta (or rate of rise) of repeat troponins over 1-3 hours is important in interpreting detectable troponins. Rapidly rising OR falling troponins outside of the Delta threshold are indicative of myocardial injury even if below the 99th percentile.
  - Delta 0-15 ng/L (up OR down) – Approximately 20% of 99th%ile
  - Delta can be “down” as troponin will decrease after ACS event – still considered positive for ACS if >15ng/L change.
- Patients with non-ischemic ECGs and “grey zone” troponins at presentation will require a repeat sample.
  - Patients with stable levels (unchanging/within Delta threshold) may not have acute myocardial ischemia, but they are at higher risk for both MACE and mortality than patients with undetectable troponins.
    - These patients are in the “grey zone” – neither “rule-in” nor “rule-out” without further testing.
  - The timeframe for repeat hs-TnI will be suggested to obtain at 1 hour. When examining the literature the difference between 1hr and 2 hour pathway was shown to be non-inferior:
    - Noninferiority to 2 hr trial: At 0 and 1h (rule-out NPV 99.7%; 18% rule-in; 50% safe discharge)
    - At 0 and 2h (rule-out NPV 99.7%; 18% rule-in; 50% safe discharge)
  - Consider non-ischemic cardiac and non-cardiac causes for presentation for all patients with detectable hs troponin.
- Low-risk patients presenting after 3 hours of symptoms with non-ischemic ECGs may be “ruled-out” with a single hs troponin result below the level of detection (20ng/L) in conjunction with utilizing cardiac risk stratification.
  - These patients are at very low risk (less than 1%) of MACE (Major Adverse Cardiac Events).
Supporting literature and rationale for protocol/pathway:

- The Traditional HEART score is not validated with hs-TnI.
  - The HEART score utilizes conventional troponin assays, which will no longer apply with the adoption of the new assay.
- The Modified HEART Score “HEAR” study published this year in the Emerg Med Journal by Smith, LM et al. looked to streamline assessment of low risk chest pain patients. This study examined assessing patients without incorporating troponin results (HEAR). The aim of the study was to accurately determine ability to screen chest pain patients without using troponin measurements.
  - Sensitivity was 97.8% for HEAR score ≤1 without troponin (95%CI: 94.5%-99.4%) and 99.4% for HEAR score ≤1 with troponin (95%CI: 96.9%-100.0%)
  - NPV was 99.1% for HEAR score ≤1 without troponin (95%CI: 97.7%-99.8%) and 99.7% for HEAR score ≤1 with troponin (95%CI: 98.1%-100.0%).
    - Thusly – we can factor in utilizing the HEAR score to determine if the patient requires a screening troponin as part of the clinical assessment into the algorithm.
- Can we utilize a scoring system to apply to patients in lower risk and/or higher risk categories to determine further disposition? Additionally, can we use a rapid rule out protocol for hs-TnI?
  - The HIGH-US trial
    - Published in Circulation 2021 by Anand et al. Utilized hs-TnI with rapid rule out 0/1hr pathways. [https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.052380](https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.052380)
    - Conclusions: Implementation of an early rule-out pathway for myocardial infarction reduced length of stay and hospital admission. Although noninferiority for the safety outcome was not demonstrated at 30 days, there was no increase in cardiac events at 1 year.
    - The trial noted that adoption of this pathway would have major benefits for patients and health care providers.
  - There is a recently published piece in annals that advocates for the use of the European rapid 0/1-hour rule-out strategies utilizing the HEAR score in conjunction with the HIGH-US trial.
    - [https://www.annemergmed.com/article/S0196-0644(20)30409-1/fulltext](https://www.annemergmed.com/article/S0196-0644(20)30409-1/fulltext)
    - They reported the European Society of Cardiology 0/1-hour algorithm has a high sensitivity and specificity when applied to a diverse US population. The high-sensitivity cardiac troponin—based 0/1-hour algorithm has been mainly studied in European cohorts, with fewer data from outside the region.
    - The HIGH-US landmark study that showed that the 0/1-hour algorithm can be safely applied to patients in the United States.
  - The RACE-IT trial
    - published in Science Direct by Miller et al 2021 Utilized high sensitivity troponin I in conjunction with the HEAR score conducted at the Henry Ford Health system to determine which patients with suspected ACS and quantifiable hs-TnI values below the 99th percentile should be placed in observation for further testing or sent home.
    - See the appendix for their protocol.
      - Their values are different than the proposed values for our pathway due to a different make/model of analyzer and results.
- To assist in risk stratifying the patients that fall into the Indeterminate category with respect to the hs-Tn values we propose utilizing the HEAR aspects of the HEART score: History, ECG, Age, Risk Factors as noted to be viable by the above supporting literature.
  - See the flowsheet on the following page for advised rule out recommendations utilizing HEAR score.
- Even the most accurate troponin assay should not reassure you when the story and/or the ECG are high risk. Nothing has changed for those patients, even with an undetectable high-sensitivity troponin. Unstable angina is still a thing\textsuperscript{6}

**HEAR score**

<table>
<thead>
<tr>
<th>History</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly Suspicious</td>
<td>2</td>
</tr>
<tr>
<td>Moderately Suspicious</td>
<td>1</td>
</tr>
<tr>
<td>Slightly Suspicious</td>
<td>0</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td></td>
</tr>
<tr>
<td>Significant ST-Depression</td>
<td>2</td>
</tr>
<tr>
<td>Non-Specific Repolarization Disturbance</td>
<td>1</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>$\geq$ 65 years</td>
<td>2</td>
</tr>
<tr>
<td>45-65 years</td>
<td>1</td>
</tr>
<tr>
<td>$\leq$ 45 years</td>
<td>0</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
</tr>
<tr>
<td>$\geq$ 3 Risk Factors or History of Atherosclerotic Disease</td>
<td>2</td>
</tr>
<tr>
<td>1 or 2 Risk Factors</td>
<td>1</td>
</tr>
<tr>
<td>No Risk Factors Known</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0-8</strong></td>
</tr>
</tbody>
</table>
Proposed ACS screening and hs-TnI utilization Pathway

1. Acute Chest Pain
   - Obtain EKG
   - EKG STEMl
   - EKG No STEMl
   - HEAR Score 0
   - Consider Not Obtaining Troponin
   - HEAR score ≥ 1
   - Apply HEAR Score

2. Obtain hs-TnI
   - 0 hr hs-TnI < 20ng/L
   - Symptoms duration
     - ≥ 3 hrs
     - < 3 hrs
   - Obtain 3 hr Trop
   - HEAR Score ≥ 4
   - HEAR Score ≤ 3

3. Myocardial Injury
   - Observation Admission for 8 hr hs-TnI and AMI Risk. Consider provocative testing if indicated
   - Discharge with PCP if HEAR ≤ 3
   - HEAR Score ≥ 4
   - Obtain 1 hr hs-TnI
   - 1 hr hs-TnI < 20ng/L
   - Discharge with PCP
   - Delta < 15ng/L (up or down) but < 53ng/L Women or < 78ng/L Men
   - Delta > 15ng/L (up or down) or > 53ng/L Women or 78ng/L Men
   - Delta < 15ng/L (up or down) but < 53ng/L Women or < 78ng/L Men
   - Delta > 15ng/L (up or down) or > 53ng/L Women or 78ng/L Men

S. Meyerin DO FAAEM FACEP
References

1. Package insert for Siemens Vista.
9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7952041/ (HEAR score complete)
<table>
<thead>
<tr>
<th>Type of assay</th>
<th>Name of assay</th>
<th>Analyser</th>
<th>Manufacturer</th>
<th>Limit of blank (Lob)</th>
<th>Limit of detection (LoD)</th>
<th>99th percentile</th>
<th>10% coefficient of variation (10% CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hs-assay</td>
<td>HS-ctTNI</td>
<td>Architect</td>
<td>Abbott</td>
<td>0.7–1.3 ng/L</td>
<td>2 ng/L</td>
<td>34 ng/L</td>
<td>4.7 ng/L</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hs-assay</td>
<td>HS-ctT</td>
<td>Cobas</td>
<td>Roche</td>
<td>3 ng/L</td>
<td>5 ng/L</td>
<td>14 ng/L</td>
<td>13 ng/L</td>
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<td>POC-assay</td>
<td>cTNI-diastix</td>
<td>Pathfast</td>
<td>Mitsubishi</td>
<td>ND</td>
<td>1 ng/L</td>
<td>20 ng/L</td>
<td>3.1 ng/L</td>
</tr>
<tr>
<td>Sensitive-assay</td>
<td>cTNI-Ultra</td>
<td>Centaur</td>
<td>Siemens</td>
<td>6 ng/L</td>
<td>6 ng/L</td>
<td>40 ng/L</td>
<td>30 ng/L</td>
</tr>
<tr>
<td>Sensitive-assay</td>
<td>cTNI-Vista</td>
<td>Vista</td>
<td>Siemens</td>
<td>15 ng/L</td>
<td>20 ng/L</td>
<td>45 ng/L</td>
<td>40 ng/L</td>
</tr>
<tr>
<td>Sensitive-assay</td>
<td>cTNI-Access</td>
<td>Access</td>
<td>Beckman</td>
<td>&lt;10 ng/L</td>
<td>10 ng/L</td>
<td>40 ng/L</td>
<td>40 ng/L</td>
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<tr>
<td>Sensitive-assay</td>
<td>cTNI-Vitros</td>
<td>Vitros</td>
<td>Ortho Clinical Diagnostics (OCD)</td>
<td>7 ng/L</td>
<td>12 ng/L</td>
<td>34 ng/L</td>
<td>34 ng/L</td>
</tr>
<tr>
<td>POC-assay</td>
<td>cTNI-AQT</td>
<td>AQT</td>
<td>Radiometer</td>
<td>ND</td>
<td>9.5 ng/L</td>
<td>23 ng/L</td>
<td>27 ng/L</td>
</tr>
<tr>
<td>POC-assay</td>
<td>cTNT-AQT</td>
<td>AQT</td>
<td>Radiometer</td>
<td>ND</td>
<td>8 ng/L</td>
<td>17 ng/L</td>
<td>26 ng/L</td>
</tr>
</tbody>
</table>

ND: not declared.

Outpatient Versus Observation/Inpatient Management of Emergency Department Patients Rapidly Rulled-out for Acute Myocardial Infarction: Findings from the HIGH-US Study


Objectives
- To describe the clinical characteristics of the AMI ruled-out patients placed in observation/inpatient beds (OBS/ADM) vs. those with an ED discharge (EDD) using the HIGH-US 0/1h study algorithm.
- To describe the cardiac testing and interventions that were completed in the AMI ruled-out group placed in OBS/ADM.

Methods
- Adults (2113) presenting with suspicious AMI were enrolled (2015–2016) in 29 US medical centers. There were no exclusion criteria. The study included a final count of 2022 adults.
- Baseline and 1-hour plasma samples were analyzed using the Siemens Healthineers Atellica® IM High-Sensitivity Troponin I assay (99th percentile URL: 45.2 ng/L). AMI diagnosis was independently adjudicated by a combination of cardiologists and ED physicians using local contemporary cTn assays and clinical data.
- All cardiac stress test (CST), coronary angiogram (CA) and coronary revascularization (CR) reports for the OBS/ADM patients were analyzed.

Results
- 1020 (50.4%) individuals were ruled out for AMI at 1 hour (of which 534 [57.3%] were EDD and 436 [42.7%] were placed in OBS/ADM) by contemporary clinical assessment; none had an AMI/death while in hospital. At 30 days, one AMI and one death (2 or 0.5%) had occurred. Cardiac testing was not performed in 176 (40.4%) individuals.
- The cardiac testing and/or interventions completed in some remaining patients were:
  - 175 (40.1%) had a CST with most results 143 (81.7%) normal, and 32 (18.3%) abnormal.
  - Coronary angiography was done in 11 (34.4%) with abnormal and in 13 (9.1%) with normal CST.
  - About 50% patients in each group with a CST had abnormal CA results.
- Of the 85 (19.5%) patients receiving a CA without prior CST, 47 (55.3%) were abnormal.
- Of AMI ruled-out OBS/ADM patients, 26 (6.0%) had a CR procedure (one coronary artery bypass surgery and 25 percutaneous coronary interventions).
- Also, the mean length of stay was longer in the OBS/ADM group compared to those discharged from the ED (2.0 vs. 0.6 days, p < 0.001).
- The 30-day and one-year AMI/death rates in these two groups were low and not significantly different—0.2% for 30-day and <3% for one-year.
- The HIGH-US 0/1h study algorithm—rule-out: 50.4%, NPV: 95.7%, and sensitivity: 98.7%.

Authors’ Conclusions
- "Patients in rapid hs-cTn rule-out AMI zones have very low 30-day adverse outcomes."
- "In the HIGH-US study 43% of these patients were not ED discharged by the clinicians."
- "They had more risk factors for AMI and 26 (6%) received coronary revascularization."
- "One-year AMI/all cause death rates were very low, suggesting all could be discharged."
- "Recent reports suggest these patients with new/prior CAD can be medically managed."

Significance
For patients at very low risk for AMI/death within 30 days, those with a history of CAD, stroke, hypertension, or having an abnormal ECG, or a family history of CAD were more likely placed in OBS/ADM than EDD. Decisions to place these patients in OBS/ADM could be reduced based on the excellent prognosis for these patients and the 0/1h rapid algorithm. This would lead to shorter lengths of hospital stay and fewer patients receiving CSTs, CAs, and CR procedures.

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Identification of very low-risk acute chest pain patients without troponin testing

Lane M. Smith,1 Nicklaus P. Ashburn,1 Anna C. Snaveley,2 Jason P. Stopyra,1 Kristin M. Lencio,2 Brian J. Wells,3 Brian C. Hiestrand,1 David M. Herrington3 Chadwick D. Miller,1 and Simon A. Mahler1

Abstract

Background
The HEART Pathway combines a History ECG Age Risk factor (HEAR) score and serial troponins to risk stratify patients with acute chest pain. However, it is unclear whether patients with HEAR scores of ≤1 require troponin testing. The objective of this study is to measure the major adverse cardiac event (MACE) rate among patients with ≤1 HEAR scores and determine whether serial troponin testing is needed to achieve a miss rate <1%.

Methods
A secondary analysis of the HEART Pathway Implementation Study was conducted. HEART Pathway risk assessments (HEAR scores and serial troponin testing at 0 and 3 hours) were completed by the providers on adult patients with chest pain from three US sites between November 2014 and January 2016. MACE (composite of death, myocardial infarction (MI) and coronary revascularisation) at 30 days was determined. The proportion of patients with HEAR scores of ≤1 diagnosed with MACE within 30 days was calculated. The impact of troponin testing on patients with HEAR scores of ≤1 was determined using Net Reclassification Improvement Index (NRI).

Results
Providers completed HEAR assessments on 4979 patients and HEAR scores<1 occurred in 9.0% (447/4979) of patients. Among these patients, MACE at 30 days occurred in 0.9% (4/447; 95% CI 0.2% to 2.3%) with two deaths, two MIs and 0 revascularisations. The sensitivity and negative predictive value for MACE in the HEAR ≤1 was 97.8% (95% CI 94.5% to 99.4%) and 99.1% (95% CI 97.7% to 99.8%), respectively, and were not improved by troponin testing. Troponin testing in patients with HEAR ≤1 correctly reclassified two patients diagnosed with MACE, and was elevated among seven patients without MACE yielding an NRI of 0.9% (95% CI −0.7 to 2.4%).

Conclusion
These data suggest that patients with HEAR scores of 0 and 1 represent a very low-risk group that may not require troponin testing to achieve a missed MACE rate <1%.

Trial registration number
NCT02056964
APPENDIX I

Sensitivity analysis using only cases with complete follow-up.

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>HEAR 0 (95% CI)</th>
<th>HEAR ≤ 1 (95% CI)</th>
<th>HEAR ≤ 1 + Troponin (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>99.4% (96.8-100.0%)</td>
<td>97.7% (94.2-99.4%)</td>
<td>99.4% (96.7-100.0%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>2.2% (1.7-2.7%)</td>
<td>11.5% (10.4-12.7%)</td>
<td>9.0% (7.9-10.3%)</td>
</tr>
<tr>
<td>PPV</td>
<td>5.3% (4.6-6.2%)</td>
<td>5.8% (5.0-6.7%)</td>
<td>6.5% (5.5-7.5%)</td>
</tr>
<tr>
<td>NPV</td>
<td>98.5% (92.1-100.0%)</td>
<td>98.9% (97.2-99.7%)</td>
<td>99.6% (97.7-100.0%)</td>
</tr>
<tr>
<td>+LR</td>
<td>1.016 (1.003-1.029)</td>
<td>1.104 (1.075-1.133)</td>
<td>1.092 (1.074-1.110)</td>
</tr>
<tr>
<td>-LR</td>
<td>0.268 (0.037-1.922)</td>
<td>0.202 (0.076-0.535)</td>
<td>0.066 (0.009-0.471)</td>
</tr>
</tbody>
</table>

APPENDIX II

Key differences in the HEART Score and HEART Pathway assessment

<table>
<thead>
<tr>
<th>Feature</th>
<th>HEART score</th>
<th>HEART Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uses serial troponin measurements</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Must have negative troponin to be low-risk</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Must have non-ischemic ECG to be low-risk</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Uses objective history and ECG criteria</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Calculates scores using a CDS tool algorithm</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Must have no history of CAD, MI, or revascularization to be low-risk</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease, MI indicates myocardial infarction, CDS indicates clinical support, and ECG indicates electrocardiogram.

RACE-IT pathway schematic
HFHS Guideline for hs-cTnI Testing in Emergency Department Patients with Suspected Myocardial Infarction

**INITIAL hs-cTnI <4 ng/L**
- **NSTEMI CAN BE RULED OUT**
- **CONSIDER ALTERNATIVE DIAGNOSES**
- Provide return precautions AND follow up with PCP

**FURTHER TROPININ TESTING SHOULD BE CONSIDERED IN PATIENTS WITH SHORT DURATION OF SYMPTOMS (~3 HOURS PRIOR TO TROPININ TESTING).**

**INITIAL hs-cTnI =4 ng/L**
- **PERFORM 1 HOUR TROPININ**
- **1 HOUR REPEAT ≤7 ng/L**
- **NSTEMI HAS BEEN RULED OUT**
- **CONSIDER ALTERNATIVE DIAGNOSES**
- Provide return precautions AND follow up with PCP

**IF 1 HOUR INCREASE ('DELTA') ≥4 ng/L PROCEED TO ORANGE (SECOND) COLUMN**

**INITIAL hs-cTnI ≥5 but ≤18 ng/L**
- **REPEAT troponins at 1 HOUR AND 3 HOUR**
- **ALL VALUES REMAIN ≤18 ng/L**
- **NSTEMI HAS BEEN RULED OUT**
- **CONSIDER ALTERNATIVE DIAGNOSES**

**HEAR 23** Provide return precautions and F/U with PCP

**Hear 24** Consider observation placement for further evaluations

**hs-cTnI >99th percentile (≥18 ng/L) AT ANY TIME**
- AMI (NSTEMI type 1 or type 2) or acute cardiac injury diagnosis requires at least 1 hs-cTnI value >99th percentile (≥18 ng/L) with a typical rise and/or fall in the hs-cTnI measurements and should be supported by at least 1 of the following:
  - clinical ischemic symptoms
  - ECG findings
  - cardiac imaging results.

Although NSTEMI can be diagnosed at any level >99th percentile >18 ng/L, levels ≥100 ng/L have been designated as the “CRITICAL VALUE” for HFHS which will trigger lab notification to the treating physician.

Increase/decrease in troponin from initial value by ≥15 ng/L (aka 'delta ≥ 15ng/L') at 1 hour:
- Increases likelihood of myocardial infarction/ adverse cardiovascular events and should be considered for telemetry monitoring and cardiology evaluation.
- **Is not an absolute cutoff** and should be interpreted in context of patient’s comorbid conditions and presenting symptoms.