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The utility of risk scores when evaluating for acute myocardial infarction using high-sensitivity cardiac troponin I

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Background Risk scores including the Thrombolysis in Myocardial Infarction (TIMI) score; History, Electrocardiogram, Age, Risk Factors, and Troponin (HEART) score; and Simplified Emergency Department Assessment of Chest Pain Score (sEDACS) have been used to evaluate patients with symptoms suggestive of acute myocardial infarct (AMI). This study assessed prognostic utility of cardiac risk stratification scores when augmented with a high-sensitivity cardiac troponin-I assay (hs-cTnI).

Methods This study enrolled 2,505 suspected AMI patients at 29 hospitals in the United States from April 2015 to April 2016. Blood samples were tested for hs-cTnI on the Atellica IM TnIH Assay (Siemens Healthineers). Patients were considered low risk for death/AMI with a TIMI score = 0, HEART ≤3, sEDACS ≤15, and hs-cTnI <45 ng/L (99th percentile) at time 0 and 23 hours.

Results There were 2,336 patients included after exclusions for ST-segment elevation myocardial infarction or incomplete data. At 30 days, 283 patients (12.1%) had been diagnosed with AMI, and there were 24 (1.0%) deaths and 213 (9.1%) revascularizations. Of 298 patients with death or AMI, 258 (86.6%) had elevated hs-cTnI. The HEART score and sEDACS identified 34.5% and 36.6% of patients as low risk, respectively. This was significantly more than the 12.1% identified by the TIMI score (P < .01).

Conclusions The TIMI, HEART, and sEDACS scores all identify low-risk patients when combined with hs-cTnI measurements. The HEART score and sEDACS identified more low-risk patients compared to the TIMI score. These patients could be considered for discharge from the emergency department without further testing. (Am Heart J 2020;227:1-8.)
It is estimated that more than 8 million patients present to emergency departments (EDs) annually in the United States with symptoms suggestive of acute myocardial infarction (AMI).\(^1\) Approximately 85% of these patients are ultimately found to not have an AMI.\(^1\),\(^4\),\(^5\) However, as many as 2% of patients presenting with AMI are discharged home in error after a missed diagnosis.\(^6\) This clinical challenge has led to guidelines that call for a period of observation with further cardiac testing for patients who have symptoms suggestive of AMI but no objective evidence of myocardial ischemia.\(^7\) The cost of evaluating ED patients with possible AMI in the United States is estimated at 5-10 billion dollars annually.\(^8\) Implementation of clinical pathways for evaluation of possible AMI with structured risk stratification has been shown to reduce length of stay and increase the proportion of patients who may be safely considered for early discharge.\(^9\),\(^10\)

Risk scores have been developed to help identify low-risk patients presenting with symptoms suggestive of AMI. Three of the most commonly used risk scores are the Thrombolysis in Myocardial Infarction (TIMI); Emergency Department Assessment of Chest Pain Score (EDACS); and the History, Electrocardiogram, Age, Risk Factors and Troponins (HEART) scores. Studies validating these scores demonstrate that 20%-50% of patients evaluated for possible AMI are low risk for major adverse cardiac events (MACEs) and may be candidates for early discharge.\(^9\),\(^10\) A modified HEART score has been proposed that uses the 0/1-hour algorithm with high-sensitivity cardiac troponin-I assay (hs-cTnI) to identify a cohort of very low-risk chest pain patients.\(^17\) A simplified EDACS (sEDACS) score has also been described that uses less variables than in the original EDACS score.\(^18\)

The advent of hs-cTnI assays has further contributed to cardiac risk stratification.\(^19\) Many studies assessing the utility of cardiac risk scores in the ED involved older, conventional cTn assays. However, only a few studies have used hs-cTnI with cardiac risk scores.\(^17\),\(^20\),\(^21\) The aim of this study was to compare the prognostic utility of the TIMI, HEART, and sEDACS scores when using hs-cTnI measurements in patients evaluated for possible AMI in the ED.

### Materials and methods

We performed a secondary analysis of the of the Siemens hs-cTnI troponin trial (HIGH-US) for Food and Drug Administration clearance submission. Siemens Healthineers supported the HIGH-US study but had no role in trial design, analysis of data, preparation of the manuscript, or decision to submit for publication. The study involved 29 hospitals in the United States (urban and community facilities) in 16 different states. In this sub-study, there were 2,505 patients enrolled from April 2015 to April 2016 who were evaluated for possible AMI. Details of the study have been published elsewhere.\(^22\),\(^23\) Briefly, patients evaluated in the ED had blood samples drawn for hs-cTnI at baseline (within 90 minutes of the first clinical blood draw), 45-75 minutes, 2-3 hours, 6-9 hours, and 12-24 hours using the Atellica IM TnIH assay (Siemens Healthineers). Patients had to be 22 years of age or older and provide written informed consent to be entered in the trial. This study was reviewed and approved by the institutional review board at each participating institution. The diagnosis of AMI was determined by a panel of 5 physicians in accordance with the Third Universal Definition of AMI.\(^24\) The same panel determined if a death was cardiac or noncardiac. Use of the local contemporary cTn at each hospital was used for determination of AMI. Each reviewer was supplied with the local cTn cutoffs used and the manufacturer's package insert with recommended cutoffs for the particular cTn assay. The reviewers were blinded to the results of the hs-cTnI assay. Patients were contacted at 30 days to determine AMI and mortality. A MACE at 30 days was defined in 2 ways: MACE-1 (AMI/death) and MACE-2 (AMI/death/revascularization procedure).

The elements of the sEDACS, HEART, and TIMI scores are shown (Tables I-II). Each element was obtained by research personnel by medical record review, patient interview, and interview of the responsible ED physician. The HEART score was modified as has been done in other trials requiring nonelevated cTn values to be considered low risk.\(^25\),\(^26\) To be considered low risk, patients needed to have an hs-cTnI <99th percentile (45 ng/L) at both presentation and 2-3 hours. A low-risk HEART score was ≤3, and a low-risk patient could have an ischemic electrocardiogram (ECG) as long as the total score was ≤3. The clinical suspicion component (low, moderate, or high) of the HEART score was based on the history and was prospectively determined by research personnel questioning the responsible physician prior to knowing

#### Table I. Components of the HEART score

<table>
<thead>
<tr>
<th>Component</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Moderate suspicion</td>
</tr>
<tr>
<td>ECG</td>
<td>ST-segment deviation 2</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;65</td>
</tr>
<tr>
<td>Cardiac risk factors*</td>
<td>≥3 or known CAD†</td>
</tr>
</tbody>
</table>

* Risk factors: hypertension, diabetes mellitus, hyperlipidemia, current tobacco abuse, and family history of CAD (first-degree relative with myocardial infarction/revascularization ≤55 years old for women and ≤45 years old for men).
† CAD: prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, or left main >50% stenosis or other vessel >70% stenosis.

**LBBB, left bundle-branch block; RBBB, right bundle-branch block; LVH, left ventricular hypertrophy; CAD, coronary artery disease.**
the cTn values and reviewing the ECG. A low-risk sEDACS score was ≤15 and required a nonischemic ECG. A simplified sEDACS was used, as some of the historical elements in the traditional EDACS score were not recorded (pain reproduced by palpation and pain worse with inspiration). A low-risk TIMI score was defined as 0 and required a nonischemic ECG, as done in prior trials. For all 3 risk scores, an ischemic ECG was defined as ST elevation ≥1 mm or ST depression ≥0.5 mm in the absence of ECG findings of left ventricular hypertrophy, left bundle-branch block, or ventricular paced rhythm. To be involved in the final analysis for the risk scores, all relevant elements of the individual scores needed to be recorded. Patients with ST-segment elevation myocardial infarction were excluded.

Statistical analysis

Baseline characteristics were compared between the patients with and without 30-day death/AMI using t tests for normally distributed numerical variables, Wilcoxon rank sum tests for non-normally distributed numerical variables, and χ² tests for categorical variables. P values < .05 were considered statistically significant.

Results

There were 2,505 individuals in the original study. After excluding the patients who had an adjudicated final diagnosis of ST-segment elevation myocardial infarction, a total of 2,336 had a known hs-cTnI status at presentation along with a known MACE status at 30 days of follow-up, which was required for this substudy. Baseline characteristics are shown in Table IV. There were 277 (11.9%) patients diagnosed with an AMI, and an additional 6 (0.3%) patients were diagnosed with an AMI within 30 days. There were 24 (1.0%) deaths at 30 days. A total of 213 (9.1%) underwent a revascularization procedure (coronary artery bypass grafting or percutaneous coronary intervention) within 30 days. Thus, the 30-day MACE-1 (death/AMI) rate was 12.8% and the 30-day MACE-2 (death/AMI/revascularization) rate was 16.8%. There were some missing risk status data. This resulted in 1,977 patients being included in the simplified EDACs analysis, 1,931 in the HEART analysis, and 1,954 in the TIMI analysis (Figure 1).

All 3 risk scores with nonelevated serial hs-cTnI values had high sensitivities (97.9%-100%) for MACE-1 (Table V). The sensitivity of the TIMI score for MACE-1 (100%) was significantly higher than that for sEDACS (97.6%, P = .041), with no significant difference between sensitivities for sEDACS and HEART (P = .545). However, although the TIMI score identified 100% of patients at risk for AMI/death at 30 days, both the sEDACS and HEART score identified significantly more patients as low risk. The HEART score and sEDACS identified 34.5% (95% CI 32.4-36.7) and 36.6% (95% CI 34.4-38.7) of patients as low risk for MACE-1, respectively. This was significantly more than the 12.1% (95% CI 10.7-13.7) identified as low risk by the TIMI score (P < .01). There was no significant difference between the HEART score and sEDACS for identifying patients as low risk for MACE-1 (P = .19). The characteristics of the 6 patients that were incorrectly identified as low risk by sEDACS or HEART are shown (Table VI). None of these 6 patients had an ischemic ECG at presentation, an AMI at 30 days, or a revascularization procedure within 30 days. Of the 298 patients that suffered death or AMI within 30 days, 258 (86.6%) had an elevated hs-cTnI at either presentation or 2-3 hours. Thus, although serial hs-cTnI measurements identified the majority of patients at risk for 30-day death/AMI, the integration of risk scores was able to identify 34 (11.4%-40 (13.4%) additional low-risk patients.

When the risk scores were evaluated in patients who would have not met the rapid rule-out protocol as used in the HIGH-US study (hs-cTnI ≥5 ng/L), similar findings were observed. The TIMI score again demonstrated 100% sensitivity for both MACE-1 and MACE-2 at 30 days; however, it only characterized an additional 55 patients (5.2%) as being low risk. The sEDACS and HEART scores identified greater numbers of patients as low risk (21.4%...
and 18.1%, respectively); however, both scores demonstrated diminished sensitivity for adverse outcomes when the very low troponin population was excluded. The sEDACS score had 98.0% sensitivity for MACE-1 (95% CI 95.4%-99.4%) and 95.8% (95% CI 92.9%-97.7%) for MACE-2. The HEART score fared similarly with sensitivity for MACE-1 of 98.8% (95% CI 96.4%-99.8%) and for MACE-2 of 96.9% (94.3%-98.6%). (Table VII)

Discussion

The main finding of this study was that when evaluating patients with possible AMI, all 3 of the risk scores (sEDACS, TIMI, and HEART) when combined with serial hs-cTnI over 2-3 hours identified patients who were at low risk for 30-day AMI or death. This suggests that these patients could be considered for early discharge from the ED without stress testing or cardiac imaging, such as coronary computed tomography angiography (CCTA). The rate for death or AMI at 30 days was 0%-0.83%. This is within the generally accepted 30-day missed MACE rate of <1% in such patients.28 When adding revascularization to death or AMI, the MACE rate ranged from 0.42% to 3.3% for the 3 risk scores. However, to include revascularization as a MACE in a low-risk population with normal serial hs-cTnI values is controversial. Urgent revascularization has been considered a MACE in studies of patients with definite AMI as a surrogate for unstable angina. Although all 3 scores identified patients as low risk for 30-day MACE-1, the TIMI identified significantly less (12.1%) when compared to either sEDACS (36.6%) or HEART (34.5%). When patients who presented with hs-cTnI between 5 and 45 ng/L were evaluated, eliminating patients who would be considered for discharge based on very low presenting hs-cTnI alone, the sensitivity for risk scores combined with the hs-cTnI was notably diminished.
resulting in unacceptably high 30-day adverse event rates. The sEDACS, HEART, and TIMI scores incorrectly identified 6, 4, and 0 patients as low risk, respectively. But this may have been the play of chance, as there were no significant differences in the sensitivities for death/AMI at 30 days. In the 10 patients with missing 30-day MACE data, there were no significant differences in patient characteristics compared to the 2,336 patients evaluated in the study. The TIMI score was originally derived from and prospectively validated in a patient population with definite AMI. On the other hand, the sEDACS and HEART scores were studied in patient

Table V. Thirty-day outcomes in patients designated low risk by score

<table>
<thead>
<tr>
<th>Risk score</th>
<th>Sensitivity for MACE-1 (95% CI)</th>
<th>Incidence of MACE-1</th>
<th>Sensitivity for MACE-2 (95% CI)</th>
<th>Incidence of MACE-2</th>
<th>Total number low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>sEDACS</td>
<td>97.6 (94.9-99.1)</td>
<td>6/723 (0.83%)</td>
<td>92.9 (89.7-95.4)</td>
<td>24/723 (3.22%)</td>
<td>723/1977 (36.6%)</td>
</tr>
<tr>
<td>HEART</td>
<td>98.8 (96.4-99.7)</td>
<td>3/667 (0.45%)</td>
<td>96.6 (94.1-98.3)</td>
<td>11/667 (1.65%)</td>
<td>667/1931 (34.5%)</td>
</tr>
<tr>
<td>TIMI</td>
<td>100 (98.5-100)</td>
<td>0/237 (0%)</td>
<td>99.7 (98.4-100)</td>
<td>1/237 (0.42%)</td>
<td>237/1954 (12.1%)</td>
</tr>
</tbody>
</table>

MACE-1 = acute myocardial infarction or death within 30 days. MACE-2 = acute myocardial infarction, death, or revascularization within 30 days.

Table VI. Patients incorrectly characterized as low risk by HEART/sEDACS scores with outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Chief complaint</th>
<th>TIMI</th>
<th>HEART</th>
<th>sEDACS</th>
<th>Time (h)</th>
<th>hs-cTnI (ng/L)</th>
<th>AMI at presentation</th>
<th>30-d death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>Female</td>
<td>Chest pain</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>Female</td>
<td>Dyspnea</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>7</td>
<td>14</td>
<td>28</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>Male</td>
<td>Chest pain</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>24</td>
<td>37</td>
<td>*</td>
<td>1169</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>Male</td>
<td>Fatigue</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>22</td>
<td>25</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>Male</td>
<td>Other</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>32</td>
<td>32</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>Female</td>
<td>Chest pain</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>22</td>
<td>22</td>
<td>19</td>
<td>*</td>
</tr>
</tbody>
</table>

* Data not collected.
populations where the diagnosis of AMI was uncertain, and it should not be surprising that the TIMI score does not perform as well in this group. When applied to patients with undifferentiated chest pain in the ED, the TIMI score has not performed well, with poor prognostic ability to predict MACE at 30 days.\(^{29,30}\) In a meta-analysis of more than 17,000 patients, it was shown that the TIMI score was not sensitive enough to assist in the disposition of patients evaluated for possible AMI in the ED.\(^{31}\)

Both the sEDACS and HEART scores performed well in identifying more than one third of the patients as low risk. The clinical suspicion for AMI based on the history of the patient is an integral part of the HEART score. One aspect of our study that distinguishes it from others is that research personnel prospectively asked the responsible ED physician what their clinical suspicion was based on the presenting history. Other studies of the HEART score have used retrospective medical record review or patient disposition to determine the degree of clinical suspicion.\(^{32,33}\) Our study is more representative of how the HEART score would be used in clinical practice. Although the sEDACS and HEART scores performed similarly in this study, the bedside calculation of the HEART score is easier than the sEDACS, which may make it more practical to use.

A tremendous amount of time and effort is spent on stress testing and cardiac imaging on patients that are evaluated for possible AMI in the ED. Much of this is done because cardiology professional societies recommend this testing before or within 72 hours of hospital discharge.\(^{34,35}\) These recommendations have become standard practice in many institutions even though there is no evidence that such a strategy improves clinical outcomes. In fact, when such tests are applied to a low-risk population with a low pretest probability for coronary artery disease, false-positive test results become more likely. One study of low-risk patients in an observation unit showed that 69% of all positive stress test results were false-positives.\(^{36}\) In another study in an observation unit, there were 838 patients evaluated and 873 stress tests or CCTAs performed. There were 54 (6%) patients with positive test results, and of these, 8 had a HEART score ≤ 3. Of these 8, all were considered false-positives: 5 had nonobstructive disease at coronary angiography, and 3 were considered false-positives after cardiology consultation.\(^{35}\)

Cardiac testing of all low-risk patients is not only costly but potentially can be harmful. Estimates are that a dose of 10 mSv may be associated with a ~1 chance in 2,000 of a fatal cancer, which may be clinically relevant if a large population receives medical radiation exposure.\(^{37}\) Radiation exposures for cardiac procedures have been estimated to be 15 mSv for percutaneous coronary intervention and 11.4 mSv for stress nuclear testing.\(^{38}\) A randomized trial of CCTA in the ED demonstrated that those randomized to CCTA had a 3 times greater chance of having a revascularization procedure.\(^{39}\) Not only does percutaneous coronary intervention expose low-risk patients to radiation, but evidence also suggests that these interventions do not appear to improve outcomes in this patient population.\(^{40}\)

**Limitations**

We had to use a simplified EDACS instead of a traditional EDACS because not all of the historical features for the traditional score were collected by research personnel. If information on the full EDACS were obtained, the results may have been different. There were some missing data used in the calculation of the risk scores. The hs-cTnI values were not known to clinicians, and the risk scores were retrospectively applied. These findings would need to be prospectively validated. Adverse events at 30 days were not adjudicated but were patient reported. For the 3 scores, there were missing data in 15%-17% of the cases which may have affected the results.

**Conclusions**

When evaluating patients in the ED with possible AMI, the TIMI, sEDACS, and HEART scores, when combined with serial hs-cTnI testing over 2-3 hours, identified a cohort at low risk for AMI/death at 30 days who could be considered for early discharge without any further cardiac testing. Of these scores, the TIMI identified significantly fewer low-risk patients. With the advent of hs-TnI assays, the incremental value of existing risk scores appears to be reduced, with most prognostic power tied to presenting hs-TnI levels.
References


