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Outpatient versus observation/inpatient management of emergency department patients rapidly ruled-out for acute myocardial infarction: Findings from the HIGH-US study

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Outpatient versus observation/inpatient management of emergency department patients rapidly ruled-out for acute myocardial infarction: Findings from the HIGH-US study

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Background The actual Emergency Department (ED) dispositions of patients enrolled in observational studies and meeting criteria for rapid acute myocardial infarction (AMI) rule-out are unknown. Additionally, their presenting clinical profiles, cardiac testing/treatments received, and outcomes have not been reported.

Methods Patients in the HIGH-US study (29 sites) that ruled-out for AMI using a high-sensitivity cardiac troponin I 0/1-hour algorithm were evaluated. Clinical characteristics of patients having ED discharge were compared to patients placed in observation or hospital admitted (OBS/ADM). Reports of any OBS/ADM cardiac stress test (CST), cardiac catheterization (Cath) and coronary revascularization were reviewed. One year AMI/death and major adverse cardiovascular event rates were determined.

Results Of the 1,020 ruled-out AMI patients 584 (57.3%) had ED discharge. The remaining 436 (42.7%) were placed in OBS/ADM. Patients with risk factors for AMI, including personal or family history of coronary artery disease, hypertension, previous stroke or abnormal ECG were more often placed in OBS/ADM. 175 (40.1%) had a CST. Of these 32 (18.3%) were abnormal and 143 (81.7%) normal. Cath was done in 11 (34.3%) of those with abnormal and 13 (9.1%) with normal CST. Of those without an initial CST 85 (32.6%) had Cath. Overall, revascularizations were performed in 26 (6.0%) patients. One-year AMI/death rates were low/similar ($P = .553$) for the groups studied.

Conclusions Rapidly ruled-out for AMI ED patients having a higher clinician perceived risk for new or worsening coronary artery disease and placed in OBS/ADM underwent many diagnostic tests, were infrequently revascularized and had excellent outcomes. Alternate efficient strategies for these patients are needed. (Am Heart J 2021;231:6–17.)

Background

There have been algorithms published detailing the use of high sensitivity cardiac troponin (hs-cTn) measurements for the rapid rule-out of acute myocardial infarction (AMI) in Europe[1,2] and more recently in the United States (US).[3-5] These reports indicate that many (40%-60%) of the patients presenting to the Emergency Department (ED) with symptoms suspicious for AMI can have this diagnosis ruled out using a single very low baseline hs-cTn level or the combination of a low baseline measurement and a small hs-cTn delta change 1 hour later. While it is reported that these patients can be rapidly discharged from the ED there are no data available that documents outcomes based on the

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initial physician determined dispositions in different EDs in the US. Additionally, it is not known what clinical factors might be associated with emergency physicians decisions to directly ED discharge patients that have been placed in the AMI ruled out zone of the newer hs-cTn algorithms, rather than place them in observation or inpatient beds (OBS/ADM) in order to determine the presence and severity of any undiagnosed coronary artery disease (CAD) or the worsening of any preexisting CAD and how to best manage these patients.

In the High Sensitivity Cardiac Troponin I in the United States (HIGH-US) study[5] the use of a high sensitivity cardiac troponin I (hs-cTnI) rapid (0/1-hour) evaluation algorithm (using specific hs-cTnI cut points previously reported in a western European population[6]) ruled-out for AMI in 1,065 (50.4%) patients presenting to the ED with symptoms suspicious for AMI. The overall negative predictive value (NPV) was 99.7% (95% confidence interval [CI], 99.2%-99.9%) and sensitivity was 98.7% (95% CI, 96.3%-99.6%). The overall 30-day risk of post discharge AMI/death in these patients was very low (0.2%). Other studies have also reported and validated that patients with symptoms suggestive of AMI who have low initial and small absolute changes in high sensitivity cardiac troponin (hs-cTn) values with serial sampling (overall 56.6% of all patients evaluated for AMI) had similarly high NPVs (99.5%) for AMI and low 30-day rates (0.2%) for AMI/death.[7]

It has been reported that by using these rapidly ruled out AMI hs-cTnI algorithms these patients can have a rapid ED discharge, thus decreasing their length of stay (LOS) in the ED. However, given that the excellent reported outcomes are typically based on observational data that incorporates physician triage and testing decisions, a better understanding of factors that are associated with these decisions remain important to quantify before accepting that a rapid rule-out of AMI with an hs-cTn assay should result in a speedy ED discharge.

Therefore, the objectives of this report were to: (1) determine the proportion of ED dispositions (ED discharge versus OBS/ADM placement) in the subgroup of HIGH-US study patients meeting the AMI ruled out criteria using the hs-cTnI 0/1-hour algorithm ("ruled out patients") but who were managed clinically using standard of care conventional troponin assays that were the only cTn results available to the clinicians; (2) compare their various clinical presentations and profiles based on their dispositions; (3) explore the cardiac evaluations and treatments received in patients placed in OBS/ADM, and (4) to report separately for each group their 1-year AMI/all cause death and major adverse cardiovascular event (MACE) rates. MACE, for our study, was defined as the patient having an AMI, all cause death, a revascularization procedure or developed congestive heart failure.

Methods

Funding sources

The HIGH-US study was supported and funded by Siemens Healthcare Diagnostics Inc., 511 Benedict Avenue, Tarrytown, NY 10,591, USA. The authors are solely responsible for the design and conduct of this multicenter study, all study analyses, the drafting and editing of all the resulting submitted/published manuscripts and their final contents.

Study design and setting

The HIGH-US Food and Drug Administration (FDA) 510k study prospectively enrolled adults' ≥22 years of age who presented to the ED with any suspicion for AMI prompting the clinical ordering of a contemporary cTn test. The treating ED physicians were not aware of the study hs-cTnI measurements at the time that they evaluated the patient as these were batch analyzed later, after patient enrollment was completed. Written informed consent was obtained from all patients enrolled. The EDs consisted of 29 centers in 16 different states across the US, including both tertiary urban and suburban community hospitals. There were no patient exclusion criteria. Given the requirement for obtaining consent before enrollment generally, but not always, took place during the weekdays and so was a convenience trial. The protocol was approved by either a central or local institutional review board and enrollment occurred between April 2015 and April 2016. All enrolled patients were clinically managed by the treating physicians which included the use of contemporary FDA cleared troponin measurements and any specific institutional guidelines or protocols. Additionally, a HEART score was later calculated for each patient (research coordinators obtained the level of clinical suspicion as being low, moderate or high for AMI from the treating ED physician).[8]

Blood sample collection protocol and testing

The time points for study sample collection for analysis included a baseline (≤90 minutes from the first clinical blood collection) and a 1 hour (60 ± 15 minutes) later draw. Samples were collected in lithium heparin and serum blood tubes and sent to one of the following laboratories for testing (Siemens Healthcare Diagnostics, Tarrytown, NY; Research & Development Institute, Calabasas, CA; Baylor Scott & White Healthcare Texas A&M Health Science Center, Temple, TX; University of Maryland, Baltimore, MD; Minneapolis Medical Research Foundation, Minneapolis, MN) where measurements for hs-cTnI were performed on the Atellica IM Analyzer and ADVIA Centaur XP system. The Atellica IM hs-cTn assay is a 3-site sandwich immunoassay that uses direct chemiluminescent technology and has a measuring range of 2.5 to 25,000 ng/L, a limit of detection of 1.6 ng/L and limit of quantitation of 2.5 ng/L (20% coefficient of

variation) and a combined sex 99th percentile upper reference limit (URL) of 47 ng/L.[9] Hs-cTnI measurements run on the Atellica and ADVIA Centaur devices were similar and have been previously reported.[5]

Further details of the HIGH-US trial design including additional sample collections, sample types, preanalytical handling, and testing have been previously published.[10,11]

For patients placed in OBS/ADM all cardiac stress test (CST) reports were reviewed and entered in the database as being either normal or abnormal (indeterminate results were considered abnormal). Additionally, any coronary catheterization (Cath) and coronary revascularization procedure reports for these patients were additionally reviewed. Cath results were also entered into the database as being normal or abnormal. An abnormal Cath finding was defined as a report containing at least one quantitative stenosis ≥50% in at least one coronary artery or major branch.

AMI diagnosis adjudication

Patients clinical characteristics, ECGs, all lab values including site specific contemporary troponin measurements (each site specific assay and its 99th% value were made available), other diagnostic or therapeutic cardiovascular procedures, final patient disposition (ED discharge, observation placement or hospital admission) and all clinical information available during the 30 days after ED presentation were made available to each physician adjudicator. This included any initial narrative and discharge summary with redaction of any final hospital AMI diagnosis. At the time of this study standard of care guidelines in the US and Europe recommended a baseline and a 3- to 6-hour conventional troponin value for the evaluation of patients with symptoms suspicious for AMI. During study enrollment no FDA approved hs-cTn assays were available for clinical use.

The adjudication panel consisted of cardiologists and ED physicians with 5 physicians (at least 2 members of each specialty) assigned to each case. These individuals and the treating EM physicians were blinded to the hs-cTnI results. Adjudicators determined AMI diagnosis (type 1 or type 2) using the Third Universal Definition of Myocardial Infarction.[12] No relative or absolute threshold was prespecified for a significant rise and/or fall of cTn levels. Final diagnosis was determined by the majority adjudicator opinion.

Follow-up for adverse cardiovascular outcomes

AMI/death and MACE outcomes were recorded for up to 1 year. This information was collected by review of the patients' institutional medical records or phone call with the patient or their relative/friend or by contacting their primary care physician or cardiologist. Patients also returned for 1 year in person visit (which included an ECG). Death status was obtained by review of publicly available information which included the Social Security Death Index and obituary searches (if all other methods failed).

Primary data analysis

The clinical characteristics of patients with an ED discharge versus an OBS/ADM were compared using medians with interquartile ranges for continuous data and percentages with 95% CIs for categorical data. Stepwise logistic regression modeling was used to determine which study characteristics were significantly associated with an ED discharge versus an OBS/ADM placement. Kaplan-Meir curves were obtained to display the probability of AMI/death and MACE during the first year of follow-up for the ED discharged and OBS/ADM patients. The Kaplan-Meier curves were compared using the log-rank survival test. Lastly the overall ED discharged versus OBS/ASDM disposition rates and the CST and/or Cath/revascularization utilizations in the OBS/ADM patients were described across the participating medical centers. All analysis was performed using SAS version 9.4.

Results

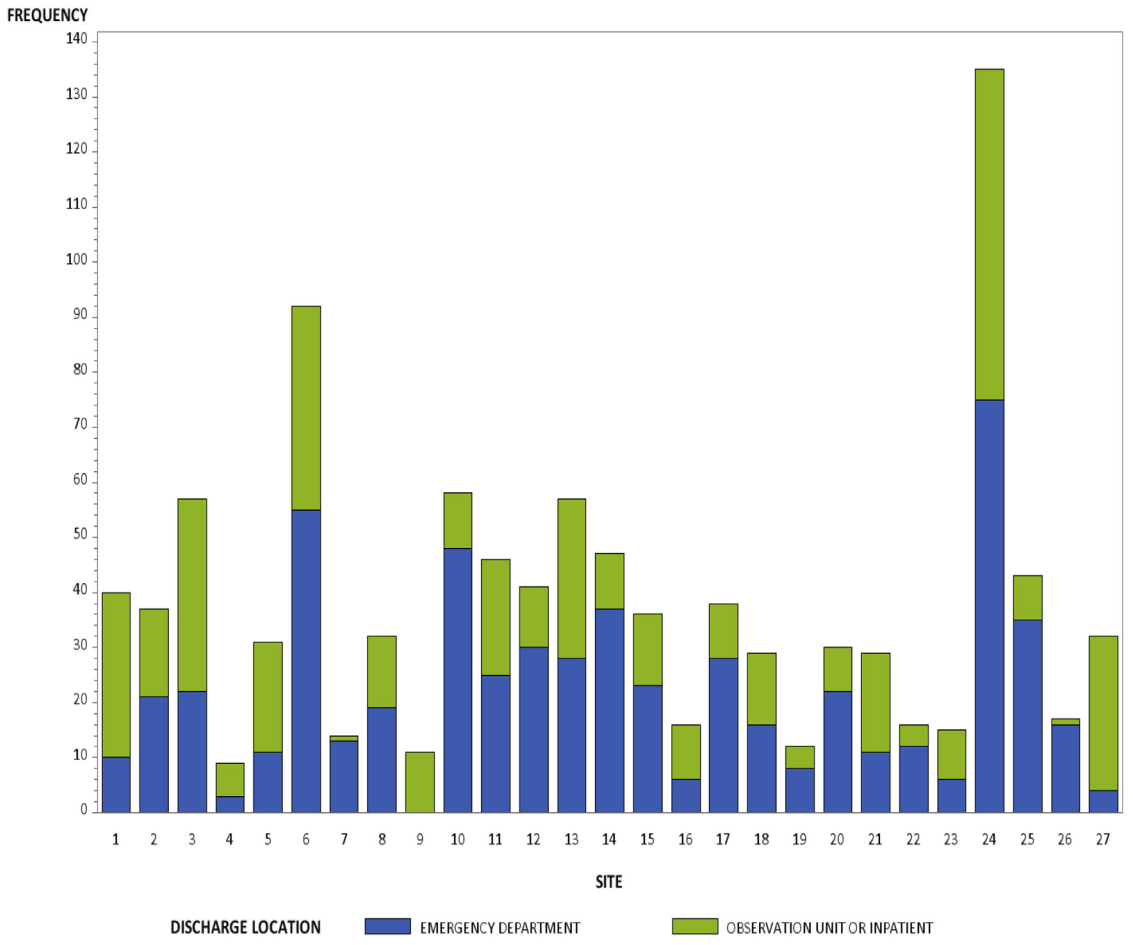
Dispositions for AMI ruled out patients

A total of 2,505 patients were enrolled in the HIGH-US Study and 2,113 qualified for the assessment of the hs-cTnI 0/1-hour AMI rule-out algorithm. Of these 2,037 had a recorded final disposition other than signed out against medical advice (76 subjects). Additionally 15 patients were adjudicated as having a ST-segment elevation AMI and were excluded from the analyses, leaving 2,022 for the population studied. Of these 1,020 (50.4%) met the AMI ruled out criteria using the hs-cTnI 0/1-hour algorithm values (67% with a baseline hs-cTnI <3 ng/L and 33% with a baseline <6 ng/L and a delta baseline 1 hour change of <3 ng/L[5]). Five hundred and eight four (57.3%) patients had an ED discharge and 436 (42.7%) were placed in OBS/ADM. The frequency of patients having an ED discharge rather than being placed in OBS/ADM varied significantly (0.0%-94.1%) among 27 (2 centers had no patients eligible for analysis, 1 enrolled 2, the other 5 patients) of the medical centers (Figure 1). In most EDs most placed in the hs-cTnI AMI ruled-out zone patients had an ED discharge, while in a few centers most were placed in OBS/ADM.

Patient clinical characteristics

A comparison of the clinical characteristics and initial ECG findings of patients with an ED discharge versus OBS/ADM disposition are shown in Table I. Patients placed in OBS/ADM were older and had more traditional risk factors for AMI including a personal history of CAD, a family history of CAD, stroke and no heart failure (HF) hospitalization with worse renal function

Figure 1



Dispositions of AMI ruled out patients by participating medical center. *AMI,* acute myocardial infarction.

and with fewer having a normal ECG. The HEART score was overall lower in ED discharged patients compared to those placed in OBS/ADMI (median 3.0, interquartile range [IQR] 3.0-4.0 versus 4.0, IQR 3.0-5.0 respectively) and more often low (0-3) and less often moderate (4-6) or high (>7) when divided into specific ranges. The higher of the baseline and 1-hour hs-cTnI values in each group were very low but different in the ED discharged (median 2.0 ng/L, IQR 1.1-3.5) and OBS/ADM (median 2.9 ng/L, IQR 1.8-4.3) groups. No patients with an ED discharge had an adjudicated AMI final diagnosis while 3 (0.7%) of those placed in OBS/ADM hs-cTnI algorithm zone did. In these 3 patients at least 1 of the contemporary troponins was >99th percentile in the ED while the hs-cTnI results were not. Why at least one of the contemporary troponin results was above the 99th percentile while none of a serial hs-cTnI results in these 3 patients is not clear. Two were admitted to the hospital (1 had an adjudicated type 1, another a type 2 AMI) while the third patient was seen by cardiology in the ED and after a cardiac stress test was performed had an ED discharge A multivariate logistic regression analysis of the clinical parameters in Table I was performed. The significant factors associated with being placed in OBS/ADM are shown in Table II. These included a personal history of CAD, a family history of CAD, history of hypertension, previous stroke, no history of HF hospitalization or the patient had an abnormal ECG.

Patient evaluations, treatments and outcomes

ED discharged patients had a shorter hospital LOS (median 12 hours, IQR 12-12) than those patients placed in OBS/ADM (median 24 hours, IQR 24-48).

No deaths or AMIs occurred in the 436 patients rapidly ruled-out for AMI while they were in the hospital. Around 175 (40.1%) of OBS/ADM patients received a CST. The types of CST performed were 24 (13.7%) had exercise stress testing without imaging, 82 (46.9%)

Table I. Characteristics of AMI ruled out patients by final disposition

Patient characteristics	ED Discharge ($n = 584$)	Observation/hospital discharge ($n = 436$)
Age, median (IQR), y	52.0 (44.0-59.0)	55.0 (49.0-62.5)
Male sex, percent (95% CI)	43.8 (39.8-48.0)	49.3 (44.5-54.1)
Race, percent (95% CI) White	59.8 (55.7-63.8)	63.3 (58.6-67.8)
Black	36.5 (32.6-40.5)	33.5 (29.1-38.1)
Other or Multiple	3.8 (2.4-5.7)	3.2 (1.8-5.3)
Hispanic or Latino, percent (95% CI)	9.6 (7.3-12.3)	6.7 (4.5-9.5)
Symptom onset to first blood draw, median (IQR), h	6.9 (3.4-25.7)	7.8 (3.6-25.6)
First draw within 3 h of onset, percent (95% CI) h	19.3 (16.2-22.8)	16.5 (13.1-20.3)
AMI risk factors, percent (95% CI)		
Hypertension	50.4 (46.3-54.6)	71.8 (67.3 – 76.0)
Dyslipidemia	27.9 (24.2-31.8)	45.3 (40.4 – 50.2)
Diabetes mellitus	19.1 (16.0-22.5)	30.0 (25.7 – 34.5)
Current smoker	26.5 (23.0-30.3)	26.4 (22.3-30.8)
Former smoker	22.9 (19.6-26.6)	32.3 (28.0-37.0)
Never smoked	50.5 (46.4-54.6)	41.3 (36.6-46.1)
Coronary artery disease	16.1 (13.1-19.3)	41.0 (36.3-45.8)
Previous myocardial infarction	7.2 (5.2-9.6)	23.0 (19.1-27.4)
Previous coronary revascularization	10.5 (8.1-13.4)	31.1 (26.7-35.8)
Peripheral artery disease	1.4 (0.6-2.8)	3.0 (1.6-5.2)
Previous stroke	4.0 (2.6-6.0)	13.7 (10.5-17.4)
Renal dialysis	0.2 (0.0-1.0)	0.0 (0 0-0.9)
Heart failure hospitalizations	7.0 (5.0-9.4)	11.4 (8.5-14.8)
Family history of coronary artery disease	42.8 (38.5-47.1)	52.8 (47.8-57.8)
CKD-EPI eGFR <60 mL/min per 3.73 m^2	5.7 (4.0-8.0)	9.7 (7.0-12.8)
Creatinine, median (IQR), mg/dL	0.8 (0.7-1.0)	0.9 (0.7-1.0)
Body mass index, median (IQR), kg/m^2	29.7 (25.9-34.6)	30.4 (26.4-35.2)
ECG findings, percent (95% CI)		
Left bundle branch block	0.5 (0.1-1.5)	0.9 (0.2-2.3)
ST-segment depression ≥0.5 mm	2.1 (1.1-3.6)	3.0 (1.6-5.1)
T-Wave inversion	3.8 (2.4-5.7)	6.2 (4.1-8.9)
Normal ECG	51.7 (47.6-55.8)	36.5 (31.9-41.2)
HEART score (95% CI)		
0–3	7070.5 (66.5-74.2)	35.0 (30.4-39.7)
4–6	66.5 29.2 (25.4-33.1)	063.8 (59.1-68.4)
>7	0.4 (0.0-1.3))	1.2 (0.4-2.7)
AMI final diagnosis	0.0 (0.0-0.6)	0.7 (0.1-2.0)

AMI, acute myocardial infarction; *CI,* confidence interval; Categorical data is given as Frequency (Percent of Total) and numerical data is given as Median (Interquartile Range).

Table II. Clinical variables associated with an observation/inpatient disposition for AMI ruled out patients

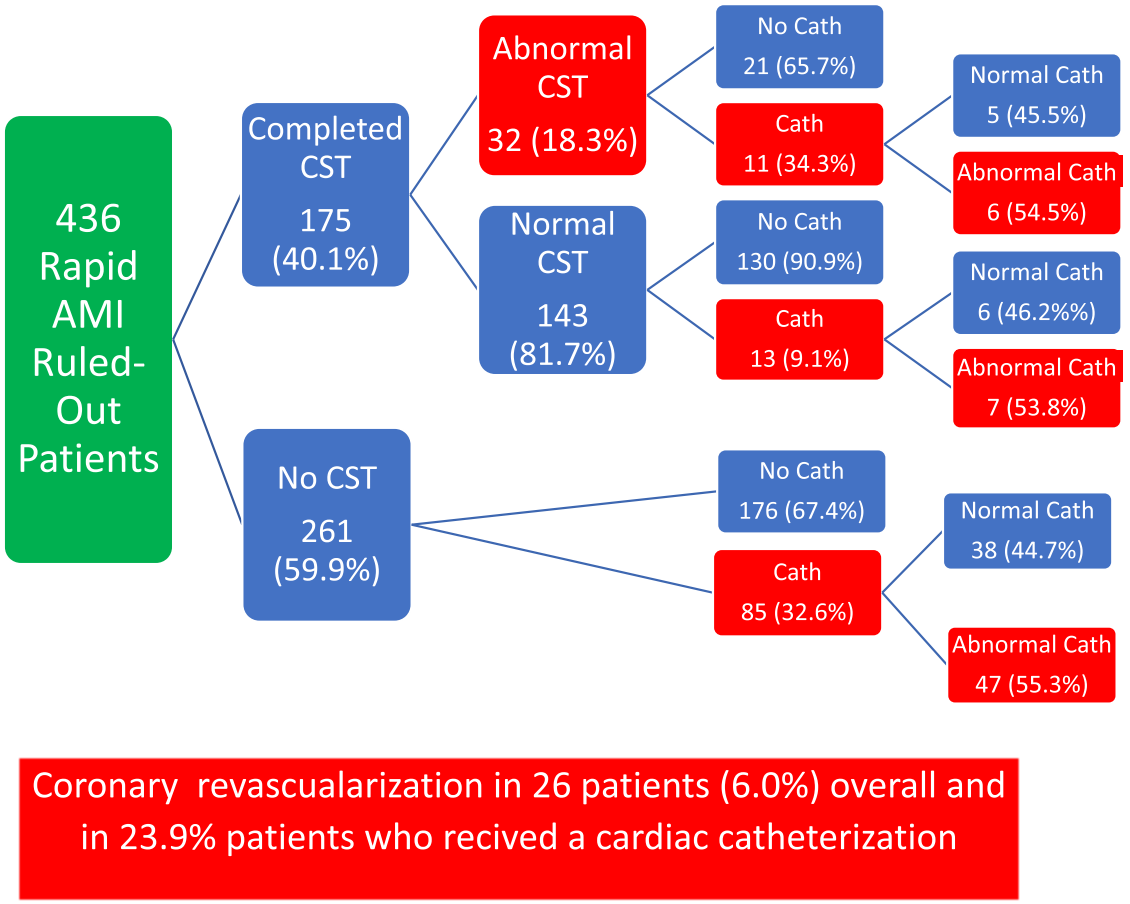
Variable	Odds ratio estimate	Odds ratio 95% confidence limits	
History of coronary artery disease	2.940	1.999	4.325
History of previous stroke	2.742	1.460	5.148
No prior heart failure hospitalization	2.022	1.121	3.647
History of hypertension	1.895	1.361	2.638
Abnormal ECG	1.766	1.292	2.413
Family history of coronary artery disease	1.399	1.024	1.912

nuclear myocardial imaging perfusion with pharmacologic stressor, 32 (18.3%) nuclear myocardial imaging perfusion with exercise stressor, 13 (7.4%) echocardiography with pharmacologic stressing, and 25 (1.4%) echocardiology with exercise stress testing.

Thirty-two (18.3%) CSTs were abnormal and 143 (81.7%) normal. For patients who had a CST Cath was done in 11 (34.3%) of those with abnormal and 13 (9.1%) of patients with a normal CST result. Of those without an initial CST, 85 (32.6%) had Cath and of these 47 (55.3%) were abnormal. Overall, Cath was completed in 109 (23.6%) and revascularization was performed in 26 (6.0%) patients (25 percutaneous coronary interventions and 1 coronary artery bypass surgery). A consort diagram detailing the overall cardiac testing and resulting therapeutic interventions for the OBS/ADM patients is shown in Figure 2. In these patients there did not appear to be any uniform approach to the ordering of CSTs and specific medical actions, including Cath, if the CSTs were reported as being normal or abnormal.

The frequency of cardiac testing (no CST, CST only, Cath only, both CST and Cath) for patients with

Figure 2



Cardiac evaluations and interventions for patients placed in OBS/ADM.

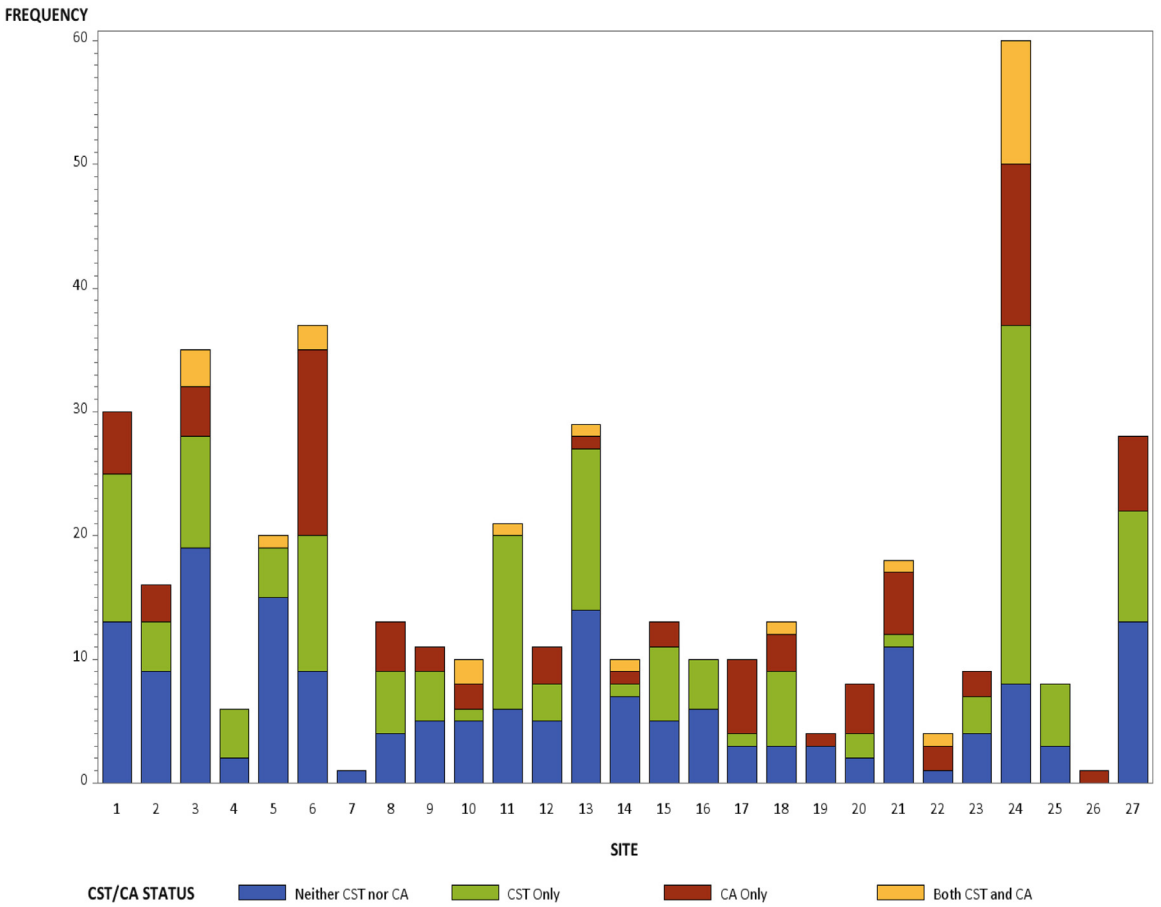
OBS/ADM placement was different when compared across the 27 participating medical centers for this analysis (Figure 3).

The 1 year AMI/death rates were very low for both groups (2.4% for ED discharged, 2.9% for OBS/ADM) and were not significantly different ($P = .553$) between the groups (Figure 4). At 1-year after ED presentation there were 3 AMIs and 9 deaths in the ED discharged patients and 7 AMIs and 6 deaths in those placed in OBS/ADM. The first AMI and deaths occurred at 69 and 7 days and in 40 and 21 days respectively after enrollment in the ED discharge and OBS/ADM groups. The 1 year MACE rates were higher in both groups (5.9% for ED discharge, 18.5% for OBS/ADM) and were significantly different ($P < .001$) between the 2 groups (Figure 5).

Discussion

We have previously reported from the HIGH-US study that many ED patients presenting with symptoms suspicious for AMI can be rapidly ruled out using a 0/1-hour hs-cTnI algorithm.[5] We detail in this report the clinical characteristics, dispositions, further assessments and interventions for 1,022 of these individuals who were rapidly ruled-out using the 0/1 hs-cTnI algorithm and compared their clinically determined ED dispositions during the study period. There are several important findings. First, ED disposition of these patients was quite different among the participating medical centers, perhaps based on the population served, the different local troponin assays or use of various institution protocols. Second, there were differences in the clinical characteristics between ED discharged patients compared to those placed in OBS/ADM. The latter were older and had more traditional risk factors for AMI. Third, despite having more of these risk factors and comorbities the OBS/ADM patients had similarly low AMI/death adverse outcomes 365 days after ED enrollment. The OBS/ADM patients had many noninvasive and invasive procedures ordered and completed but this ultimately resulted in

Figure 3



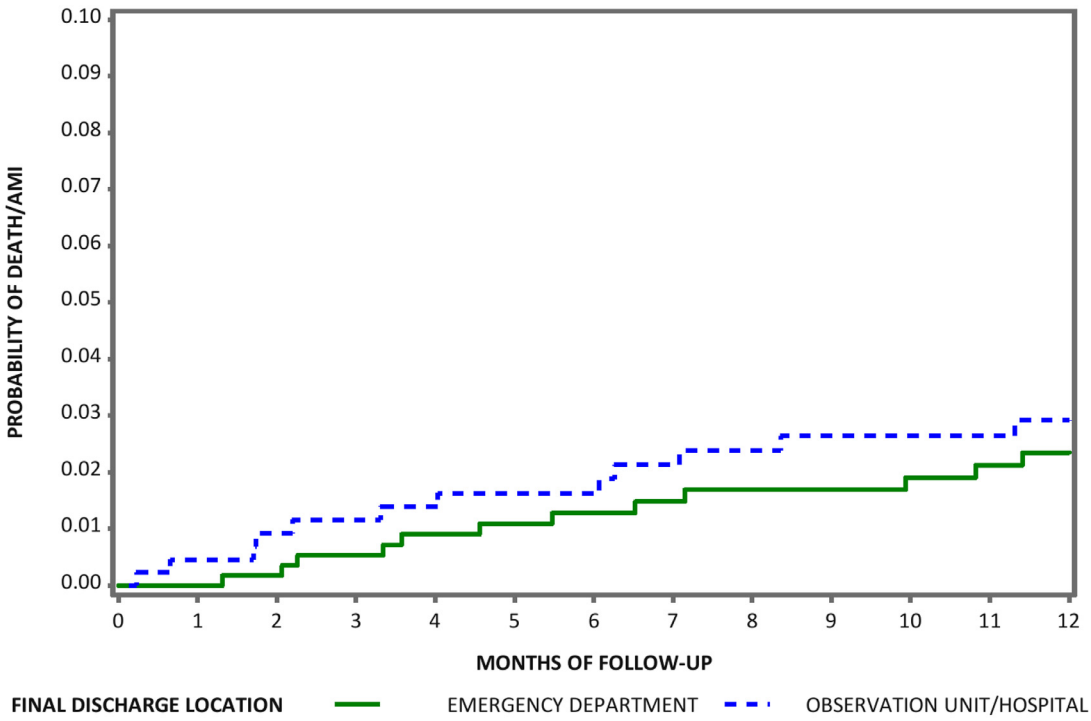
Cardiac testing in the AMI ruled out patients by participating medical center. *AMI,* acute myocardial infarction.

relatively few revascularizations procedures performed during their hospital stays. Which, if any, further cardiac testing/treatments the ED discharged patients had on an outpatient basis was not collected in the HIGH-US study.

ED physicians, when evaluating patients for possible AMI, often use an accepted risk stratification score such as the HEART score[13] and/or their own clinical judgment to decide which patients ruled out for AMI using troponin measurements can have an ED discharge and which others require further evaluations in OBS/ADM. Our reported HEART scores were independently calculated after research personal determined if the treating physician thought that the presenting symptoms were of low, moderate or high suspicion for AMI. We do not know if, or to what extent, a treating ED physician determined HEART score might have played in their ED disposition decision making during the study period. Consistent with having increased traditional cardiac risk factors for AMI those patients rapidly ruled out for AMI patients placed in OBS/ADM had higher overall HEART scores with more patients having scores in the 4 to 6 and >7 range as compared to those with an ED discharge. However, as shown in Table I, about one-third of patients with an ED discharge and two-thirds of those placed in OBS/ADM had a HEART score of ≥4, suggesting that the score alone was not well associated with determining ED dispositions.

The clinical parameters independently most associated with the decision to place patients in OBS/ADM were a personal history of CAD, a family history of CAD, a history of hypertension, prior stroke, no hospitalization for HF, and the patient having an abnormal ECG. The odds ratios for both prior revascularization and prior MI did not encompass 1.0 (but indicated that a patient had a personal history of CAD) and so were not included in Table II. It is not clear why the variable "no history of HF hospitalization" was associated with a decision to place a patient in OBS/ADM. This may have been a random result given the number of parameters placed in the regression analysis or that patients with prior admissions for

Figure 4



Number at risk, 0/1-hour ruled out for AMI		
	ED Disch	OBS/ADM
Zero month	584	436
12 months	249	196

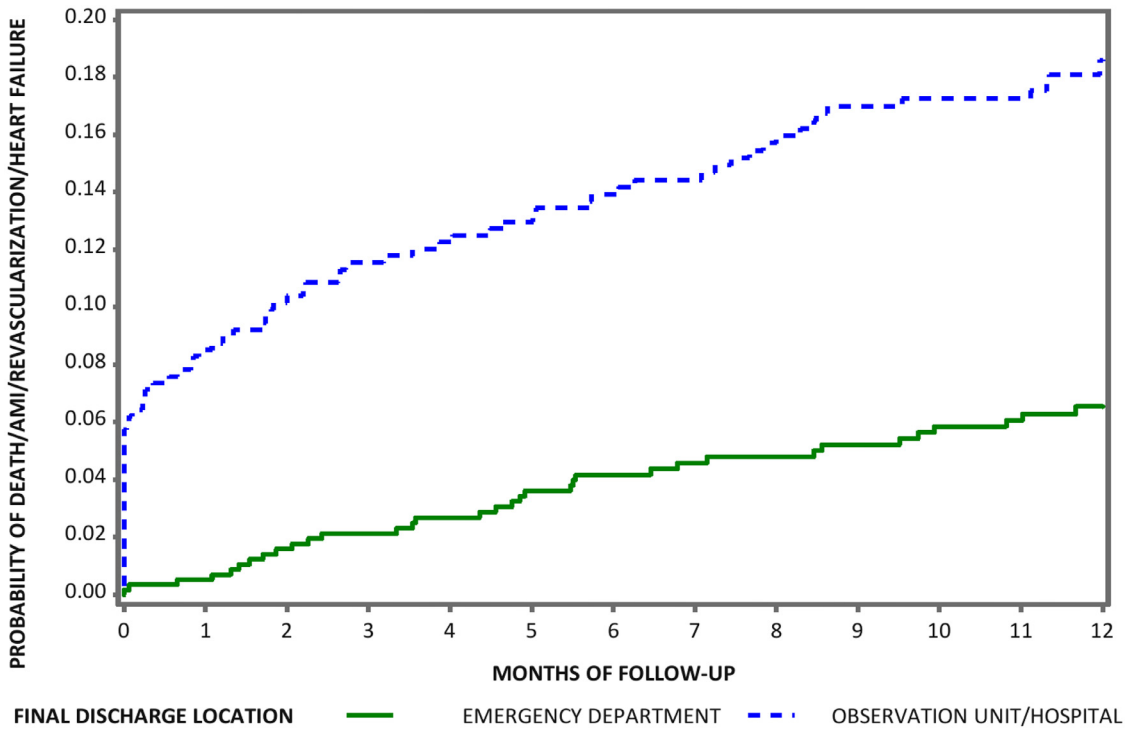
One-year Kaplan-Meir plots for AMI/death in AMI ruled out patients having EDD versus OBS/ADM placement (*P*= .553). *AMI,* acute myocardial infarction.

HF often have chronically elevated troponins and thus are adjudicated as having chronic cardiac injury. If patients did not have any elevated contemporary troponin value, then the ED clinicians may have chosen to place the patient in OBS/ADM to have further cardiac testing completed. Many of the 436 OBS/ADM AMI ruled out patients underwent further evaluations to determine the presence and severity of CAD or its progression if already known to be present and what should be done regarding its management. Our study demonstrates, like previous ones,[14] that traditional risk factors for AMI contribute very little to prognosis above and beyond high sensitivity cardiac troponin values when rapidly ruled out for AMI patients are being evaluated in the ED. We also report that in study patients with very low hs-cTnI measurements a calculated HEART score was not useful for predicting clinical outcomes.

Additional cardiac stress testing among these 436 AMI ruled out patients placed in OBS/ADM was quite frequent. Overall only 26 (6.0%) patients received a cardiac revascularization procedure, not because a new AMI diagnosis had been made, but rather because the treating ED clinicians thought that there might be further cardiac testing needed to detect new underlying CAD or they were suspicious that any preexisting CAD might have progressed and these concerns might require urgent invasive intervention to prevent future adverse outcomes and/or to potentially treat ongoing symptoms. There was significant heterogeneity between participating sites regarding the use of further cardiac diagnostic testing and the choice of an initial noninvasive or invasive strategy for treatment of CAD, perhaps based on different institution protocols or individual practitioners' practice patterns.

We have previously reported that the overall 30-day AMI/death rates for rapidly ruled out AMI patients were very low (0.2%) and now report that these adverse outcomes at 1 year in the ED discharged and OBS/ADM

Figure 5



Number at risk, 0/1-hour ruled out for MACE		
	ED Disch	OBS/ADM
Zero month	584	436
12 months	242	161

One-year Kaplan-Meir plots for MACE in AMI ruled out AMI patients having ED Disch versus OBS/ADM placement ($P < .001$). *AMI,* acute myocardial infarction; *ED,* emergency department; *MACE,* major adverse cardiovascular event.

placed individuals were also low (2.4% and 2.9%, respectively) and not significantly different. In a large multicenter European study of 4,368 patients rapidly ruled out for AMI using hs-cTn algorithms using hs-cTn values in the rule-out zones overall (there was no reporting of ED patient dispositions) there were similarly very low 30-day and low 1-year AMI/all cause death rates reported (0.5% and 1.7% for hs-cTnT, respectively and 0.6% and 2.1% for hs-cTnI, respectively ([15], online data).

A recent US study of 79,040 patients who were ruled out for acute coronary syndrome (AMI and unstable angina) in the ED, of which 16,164 (20.5%) received noninvasive cardiac testing (NIT) within 72 hours of the ED visit, there was minimal improvement in absolute 30 day adverse outcomes (AMI/death) rates in these patients when compared to those who did not receive NIT (both groups <1%). Furthermore, to prevent 1 death or 1 AMI in this 30-day period by using NIT within 72 hours of the ED visit the number of patients needed to treat was 500 and 330 respectfully. The authors concluded that the clinical strategy of early NIT after patients had been ruled out for AMI in the ED may not be optimal for most of these patients, given the large numbers needed to treat.[16] These results support our hypothesis that ED patients rapidly ruled out for AMI using hs-cTnI could be safely ED discharged with close outpatient follow-up.

Our results raise 2 fundamental questions: (1) did the 26 revascularization procedures performed on an urgent basis in the OBS/ADM in patients enrolled in the HIGH-US study contribute to their low death/AMI rates in the ensuing 30 and 365-days after ED presentation and (2) if not, what might be an alternative management plan for this rapidly AMI ruled out by hs-cTnI patient population.

The recently reported results of the International Study of Comparative Health Effectiveness with Medical and invasive Approaches (ISCHEMIA) trial[17] might help to

answer these questions. This international study showed that patients having stable and possibly cardiac related symptoms with inducible moderate or severe cardiac ischemia during stress testing (ie, traditionally identifying patients with significant CAD requiring invasive intervention) had no difference in death from cardiovascular causes, myocardial infarction, resuscitated cardiac arrest or hospitalization for unstable angina or heart failure rates in the following 3.2 years whether they received cardiac revascularization or optimal medical therapy alone (taking medicines and making lifestyle changes) and subsequent Cath if the medical therapy failed.[18]

An alternative treatment pathway might be to have the patients without known CAD to first receive a coronary tomographic coronary angiogram (CTCA) while in the ED or after a follow-up visit as an outpatient, understanding that not all patients (those with arrythmias, chronic or acute renal injury etc.) are candidates for CTCA. If significant CAD is seen on the ED study and the patient's symptoms are stable, then medical therapy for CAD could be initiated and the patients might have an ED discharge with close outpatient follow-up. Additionally, recent evidence suggests that plaque characterization that can be easily obtained in an automated manner may be particularly powerful for identifying stable patients at highest risk for a subsequent AMI.[19] For stable patients with known preexisting CAD but who have ruled out for AMI using hs-cTnI further optimization of medical therapy might be initiated and the patient discharged directly home, also with close outpatient follow-up

A strategy[20] utilizing outpatient management of patients with stable chest pain with CTCA versus "usual care" (including cardiac stress testing for possible CAD) has been associated with a lower risk for AMI and cardiac death over 5 years, likely driven by the initiation of more preventative medical treatment and not more coronary artery revascularizations.

The 1 year MACE rates were significantly higher in the OBS/ADM patients when compared to the ED discharged group. The initial steep rise in the MACE outcomes in this rapidly AMI ruled-out group was because the revascularization procedures performed while patients were in OBS/ADM were included in the MACE analyses. Our results suggest that the revascularization procedures urgently performed while patients were in the hospital might have been replaced by initiating or optimizing medical cardiovascular care and an early ED discharge, with close outpatient follow-up. Additionally, the OBS/ADM group had much more additional comorbidity and risk factors for AMI than the ED discharged patients and this likely explains their continued higher MACE rates over the ensuing 1 year. We believe that the goals of a safe ED discharge for these rapidly AMI ruled-out patients are low 30-day and 1-year AMI/death rates while providing appropriate ED medical therapies and close follow-up. This strategy provides for careful control of patients' comorbidities and any underlying CAD, thus minimizing their MACE rates over the ensuing 365 days.

It has been recently reported that the use of rapid high-sensitivity troponin assays to rapidly rule-out AMI and thus to allow more patients to be discharged directly from the ED rather than to be hospitalized for further evaluations may not satisfy the medical care needs of patients, as they often may not know, and it is often not adequately discussed with them, what their future health status could be.[21] This emphasizes that the ED evaluation cannot be considered complete with an accelerated AMI rule-out algorithm without a minimum of provider reassurance or having further evaluations completed as needed. If this is not done then significant ED recidivism could result, potentially negating the benefit of the initial rapid AMI rule-out evaluation using hs-cTn assays.

Limitations

One, we are unable to report a detailed cost effectiveness analysis of ED discharged versus OBS/ADM for rapidly AMI ruled-out patients. However, the median LOS was a day half longer in the OBS/ADM patients and the costs of placing a patient in OBS/ADM, even for a relatively short time period, are higher. Given the chronic overcrowding of EDs and hospitals (especially observation units) any increased number of early ED discharged patients ruled-out for AMI would be helpful in providing more efficient ED care. In addition, there were likely substantial additional costs incurred for the urgent 175 CSTs, 109 Cath studies and the 26 coronary revascularization procedures performed that resulted after patients were placed in OBS/ADM. Given the absence of a difference in the adverse 1-year events between the 2 groups, combined with a recent understanding of limited efficacy of coronary revascularization to reduce future AMI/death in the absence of an AMI, it would be difficult to demonstrate meaningful cost-effectiveness for these additional urgent evaluations and invasive treatments that were associated with the OBS/ADM approach in patients rapidly ruled out for AMI using a hs-cTnI algorithm.

Two, if hs-cTnI and not a variety of contemporary troponin assays had been used to adjudicate for AMI diagnosis, the NPV and sensitivity of the ruled-out zone patients and the PPV and number of ruled-in AMIs of the hs-cTnI algorithm zone may have been different. The adjudicated reclassification of AMI or cardiac injury using an hs-cTnI value below the diagnostic threshold of a standard care contemporary assay has been reported to occur in 17% of patients.[22] However, in that report there was no increase in the primary outcome of AMI or cardiovascular death within 1 year in those patients that had a reclassified AMI diagnosis.

Three, there was a possible time draw bias increasing both the NPVs and the positive predictive values (PPVs) in the study as the hs-cTnI specimens were draw approximately 40 minutes after the standard of care (SOC) blood samples were obtained, as written informed consent was required before any patient could be enrolled. Therefore, the excellent prognosis seen in the AMI ruled-out patients' needs to be considered in the context of this later blood draw.

Four, patient enrollments were not consecutive in time at any site and enrollment periods varied at each participating medical center. Whether the results might have been different if consecutive patient enrollment was accomplished is not known.

Five, 5% of enrolled patients did not have an adequate baseline blood sample drawn (no baseline hs-cTnI value), potentially leading to a bias for patients where blood collection is challenging.

Six, for the ED discharged group we do not know if any cardiac medications were prescribed at ED discharge or later during the follow-up period nor do we know if any outpatient cardiac testing was completed during this time. These variables will require attention in future clinical study designs.

Lastly, this report is a retrospective post-hoc analysis looking at the characteristics of patients meeting the rule-out criteria of the rapid 0/1 h hs-cTnI algorithm. The hs-cTnI algorithm was not used as part of the patient's clinical care, including the decision for ED discharge versus OBD/ADM placement. The HIGH-US trial did not have an interventional component to it.

Conclusions

Our observational findings from the HIGH-US multicenter study suggest that most patients presenting to the ED with symptoms suspicious for AMI but meeting the rapid rule-out AMI criteria using an hs-cTnI 0/1-hour algorithm might be managed as outpatients. There was wide variation between medical centers for placing patients in OBS/ADM and for any subsequent cardiovascular testing that they received. We provide a quantifiable estimate of the increased proportion of AMI ruled-out patients using hs-cTnI who might have an ED discharge, including those with clinical cardiac risk factors traditionally felt to be at higher risk for CAD. The very important issue of how to optimally and consistently manage patients rapidly ruled-out for AMI using the newer hs-cTnI algorithm requires further prospective clinical trials to validate our results and recommendations determined from the HIGH-US study.

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Author contributions

RMN: Helped conceive and design the study, acquired results at his institution, analyzed the results and wrote the paper with CRD; RHC: Helped conceive and design the study, acquired results at his institution, helped to analyze the results and contributed to the writing of the

manuscript; GD: Responsible for the statistical analyses of the results of the study; FRS: Helped conceive and design the study, acquired results at his institution, helped to analyze the results and contributed to the writing of the manuscript; AJS: Helped conceive and design the study, acquired results at his institution, helped to analyze the results and contributed to the writing of the manuscript; AL: Helped conceive and design the study, acquired results at his institution, helped to analyze the results and contributed to the writing of the manuscript; WFP: Helped to analyze the results and contributed to the writing of the manuscript; CRD: Helped conceive and design the study, acquired results at his institution, analyzed the results and wrote the paper with RMN. All authors made substantial contributions to study and were involved in drafting the manuscript and critically revising it for intellectual content and accuracy. All authors have approved the final version of the manuscript submitted for publication.

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