



Ultrarapid Rule-out for Acute Myocardial Infarction Using the Generation 5 Cardiac Troponin T Assay: Results From the REACTION-US Study

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Study objective: We determine how well a new Food and Drug Administration–approved single cardiac troponin T (cTnT) Generation 5 baseline measurement below the level of quantification (6 ng/L) and a novel study-derived baseline and 30-minute cTnT Generation 5 algorithm might adequately exclude acute myocardial infarction in patients with suspected acute coronary syndrome in a US emergency department (ED).

Methods: Patients presenting with any symptoms suspicious for acute coronary syndrome were enrolled at a single US ED. Baseline and 30-minute blood samples were obtained and cTnT Generation 5 levels were later batch analyzed in an independent core laboratory. Acute myocardial infarction diagnosis was adjudicated by a cardiologist and an emergency physician.

Results: Of the 569 study patients, 44 (7.7%) had an acute myocardial infarction diagnosis. One hundred sixty-four patients (28.8%) had a presentation cTnT Generation 5 level less than 6 ng/L, and none of these individuals had an acute myocardial infarction (negative predictive value of 100% [95% confidence interval 97.8% to 100.0%] and sensitivity of 100% [95% confidence interval 92.0% to 100.0%]). A baseline cTnT Generation 5 value of less than 8 ng/L and a 30-minute Δ of less than 3 ng/L were present in 221 patients (41.0%), and none had acute myocardial infarction (negative predictive value of 100% [95% confidence interval 98.3% to 100.0%] and sensitivity of 100% [95% confidence interval 92.0% to 100.0%]).

Conclusion: In a single US ED, a single baseline cTnT Generation 5 measurement less than 6 mg/L and values at baseline less than 8 ng/L and a 30-minute Δ of less than 3 ng/L ruled out acute myocardial infarction in 28.8% and 41.0% of patients, respectively. Additional multicenter US studies evaluating these ultrarapid acute myocardial infarction rule-out guidelines are needed, especially to narrow the confidence intervals. [Ann Emerg Med. 2018;72:654-664.]

Please see page 655 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Despite that the incidence of acute myocardial infarction has decreased in the last 2 decades, approximately 10 million individuals present with symptoms suggestive of acute myocardial infarction in the United States annually, which is approximately 5% of all emergency department (ED) visits.¹⁻³ This figure includes only chest pain as the presenting symptom and would likely be much higher when atypical presentations are also considered. Approximately 8% of patients who receive a diagnosis of acute myocardial infarction have been reported to present without chest pain.⁴

Despite that an estimated 90% of these patients do not receive a diagnosis of an acute myocardial infarction, they are commonly admitted for further evaluation before discharge. The evaluation of these patients is time consuming and costly; in the United States, it is estimated that \$7 billion is spent annually for their evaluation.⁵ The shortest interval possible to rule out acute myocardial infarction would be very useful in helping to move patients through the ED evaluation process efficiently. Additionally, prolonged ED stays have been associated with crowding and worse outcomes.⁶

Importance

Cardiac biomarkers are essential for the diagnosis of acute myocardial infarction, along with the ECG and

Editor's Capsule Summary*What is already known on this topic*

Biomarker testing aids the evaluation of patients with potential acute myocardial ischemia.

What question this study addressed

Can a newer troponin T assay conducted immediately and again 30 minutes later exclude acute myocardial infarction in emergency department patients with suggestive symptoms?

What this study adds to our knowledge

In 569 subjects, 44 (7.7%) had acute myocardial infarction; none who tested beneath initial and Δ thresholds (change between 2 early measurements) had infarction, helping the physician safely arrive at an alternative diagnosis.

How this is relevant to clinical practice

This adds one step in early coronary ischemia evaluation, although absent knowledge on other forms of ischemia and testing, how this affects care and outcomes is uncertain.

clinical assessments. The universal definition of acute myocardial infarction requires a detection of a typical increase or decrease of the level of cardiac troponin (cTn), with a least one measurement above the 99th percentile.⁷ The current American College of Cardiology/American Heart Association guidelines recommend that cTn be measured serially during 3 to 6 hours to exclude acute myocardial infarction, but these recommendation are based on studies using older cTn assays.⁸ Newer high-sensitivity cTn (hs-cTn) assays allow earlier detection of acute myocardial infarction by measuring changes in hs-cTn during a shorter period.⁹⁻¹² Also, absolute changes in hs-cTn have been shown to have higher diagnostic utility compared with relative changes.¹³

Baseline, 1-hour rule-in, and rule-out algorithms using changes in hs-cTn have been validated in several multicenter studies. These algorithms use a baseline hs-cTn level and the absolute changes in 1 hour to divide patients into 3 groups: rule-out, observation, and rule-in. These trials show a high negative predictive value (99.1% to 100%) for excluding acute myocardial infarction.¹⁴⁻¹⁸ Non-US studies have evaluated hs-cTn levels below the level of detection at a single baseline blood test to rule out acute myocardial infarction (negative predictive value 98.8% to 100%).¹⁹⁻²⁴ Algorithms for the rapid evaluation of acute myocardial infarction (hs-cardiac troponin

T [cTnT] baseline and 1-hour measurements and less than the level of detection at baseline) have been incorporated into the 2015 European Society of Cardiology guidelines.²⁵

The Roche cTnT Generation 5 assay has been approved (2017) for use in the United States. Most studies supporting a rapid cTnT algorithm for acute myocardial infarction evaluation have been completed in non-US cohorts, except for one, which included a minority of US patients (2 sites; 242/1,282, or 18.9%).¹⁸ A recent, multicenter, prospective, observational, US study, as part of a Food and Drug Administration (FDA) submission, showed that a single ED baseline cTnT Generation 5 assay level less than 6 ng/L was associated with a very low risk of acute myocardial infarction (negative predictive value 99.4%). However, the median time from ED presentation to this baseline test in this study was 5.8 hours, and the authors noted that shorter times for the initial cTnT Generation 5 test for these patients might have been associated with a deterioration of the negative predictive value.²⁶

Goals of This Investigation

The objectives of this prospective ED study were to determine the clinical usefulness of a baseline cTnT Generation 5 assay level below the FDA-approved level of quantification of 6 ng/L to rule out acute myocardial infarction, and to determine what unique cut-point values might be best suited for an optimal novel cTnT Generation 5 assay baseline and 30-minute rule-out acute myocardial infarction algorithm in a US ED population with suspected acute coronary syndrome. Additionally, we compared our results with those reported in the High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction (TRAPID-AMI) study,¹⁸ which has contributed to the European Society of Cardiology hs-cTnT acute myocardial infarction rule-out algorithm.

MATERIALS AND METHODS**Study Design, Setting, and Selection of Participants**

The Rapid Evaluation of Acute Myocardial Infarction in the United States (REACTION-US) study was a prospective convenience study (patients were screened when research coordinators were available) that enrolled ED patients with any symptoms suspicious for possible acute coronary syndrome at a single tertiary US hospital. The inclusion criteria were patients older than 21 years and presenting with any symptoms suspicious for acute coronary syndrome and who were able to comply with all aspects of the protocol and had a triage ECG completed. Exclusion criteria were ED patients with acute distress requiring immediate lifesaving interventions, cardioversion or defibrillation or thrombolytic therapy within the

previous 24 hours, ST-segment elevation myocardial infarction leading to immediate reperfusion therapy, traumatic injuries, transfers from other facilities, and patients who were pregnant or breast feeding. Study approval was obtained from the institutional review board at Henry Ford Hospital, and patients were provided written informed consent before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki and International Conference of Harmonization good clinical practice guidelines.

Subjects underwent clinical assessment by an emergency physician, which included a history; physical examination; review of all ECGs; standard blood testing, including hospital cTn measurements; and chest radiographs if needed. The timing and implementation of these tests, treatments, and dispositions were decided by the treating emergency physician.

The research coordinators, after written informed consent was obtained, asked each patient a detailed symptoms history and recorded this on a case report form. Patients were also directly asked about their medical history, but before this was entered into the case report form, it was verified by review of their electronic medical records, if available. Any appropriate additional information concerning the patients' comorbidities was recorded.

Study baseline blood samples were collected in ethylenediamine tetraacetic acid tubes within 60 minutes of the completion of the triage ECG (most often completed within 10 minutes of ED presentation). An additional blood sample was obtained at 30 minutes (SD 10 minutes) after the baseline test. Each blood tube was centrifuged to obtain plasma and was stored at -80°C (-112°F) within 1 hour of the sampling. After completion of the study, stored samples were sent to a core laboratory at the University of Maryland for independent and blinded batch measurement for cTnT Generation 5 assay. The frozen samples were thawed a single time.

The study assay used was the Roche Diagnostics Elecsys Troponin T Generation 5 assay, measured with a Roche cobas e 601 device (Roche Diagnostics, Indianapolis, IN). In Europe, the assay has 14 ng/L as the 99th percentile for both sexes, a level of detection of 5 ng/L, and an imprecision corresponding to 10% coefficient of variation at 13 ng/L.¹⁸ These values are not the same as those that have been FDA approved in the United States for the Elecsys Troponin T Generation 5 assay, which are 19 ng/L as the 99th percentile for both sexes and a level of quantification of 6 ng/L.²⁷ The level of detection is the lowest concentration of cTn when there is 95% confidence that cTn is present in the

sample, whereas the level of quantification represents the lowest cTn value at which the measurement can be reliably reported (coefficient of variation at this value is $\leq 20\%$).

Outcome Measures

Adjudication of the final diagnosis of acute myocardial infarction (type 1 or 2) was performed by a board-certified cardiologist and emergency physician working as a team, with additional review by another board-certified cardiologist in the event of disagreement. Adjudicated acute myocardial infarction was determined by following the third universal definition of myocardial infarction,⁷ using the hospital-reported contemporary cardiac troponin I (cTnI) assay values (Siemens Centaur system TnI Ultra assay on a Centaur XP analyzer; 99th percentile 40 ng/L) and all available clinical data for 30 days after ED presentation. The adjudicating physicians were blinded to the cTnT Generation 5 assay measurements.

After patient discharge from the hospital, follow-up by study personnel was conducted in 30 to 45 days to determine whether the patient had experienced a major adverse cardiac event: death, acute myocardial infarction, or revascularization (percutaneous coronary intervention or coronary artery bypass graft). Follow-up information was obtained from a telephone call or subsequent medical record review. If subjects or family members were not able to be reached by telephone, an electronic medical record review and death registry search were completed. If the patient's social security number was known, the Social Security Death Index was searched, but if it was unknown then Ancestry.com Michigan obituaries and a Google search were used.

Primary Data Analysis

A cTnT Generation 5 assay level of quantification cut point of 6 ng/L was used to assign patients to a ruled-out group if the level was less than 6 ng/L and a not-ruled-out group if it was greater than or equal to 6 ng/L. A novel baseline and 30-minute algorithm was derived that would have 100% negative predictive value and sensitivity for acute myocardial infarction rule-out in the largest number of patients possible who had blood tested at these 2 times. Additionally, the positive predictive value and specificity for the diagnosis of acute myocardial infarction were obtained for the not-ruled-out patients both at baseline and for the derived baseline and 30-minute algorithm. Whenever appropriate, a 95% confidence interval (CI) was calculated. A κ value was calculated for the physician agreement in the adjudication of the diagnosis of acute myocardial infarction.

RESULTS

Characteristics of Study Subjects

From May 2013 to April 2015, 1,699 patients were screened for this study but not enrolled. Reasons for nonenrollment were that 338 could not consent and have the baseline blood test completed within 1 hour of the triage ECG, 226 were impaired (substance abuse or mental health issues), 86 had been previously enrolled, 327 refused to participate, and 147 were not enrolled for other reasons. We thus enrolled 575 subjects, and 569 had suitable available data for inclusion in the analysis (4 patients had no clinically ordered cTnI measurements and 2 subjects had been enrolled twice under different identities, in which case only the first enrollment was used). Figure 1 shows the flow of the screened patients in the study.

The adjudicated final diagnosis for all patients with at least 1 contemporary cTnI level reported above the 99th percentile (116, or 20.4%) was acute myocardial infarction in 44 patients (7.7%). Of these patients, 1 had an ST-segment elevation myocardial infarction that developed after

presentation (2.3%), whereas 25 had non-ST-segment elevation acute myocardial infarction type 1 (56.8%) and 18 type 2 (40.9%). There was good interrater reliability ($\kappa=0.97$; 95% CI 0.92 to 1.00) in regard to the diagnosis of acute myocardial infarction between the adjudicating cardiologist and emergency physician, with the need for a second cardiologist review required in only 2 cases.

The baseline clinical characteristics (comorbidities, presenting vital signs, ECG analysis, and home medications) of all study patients and of those classified into the ruled-out and not-ruled-out groups after 1 hour of assessment using available cTnT Generation 5 assay measurements are shown in Table 1. Although both the ruled-out and not-ruled-out groups were identified as having many comorbidities and risk factors, the not-ruled-out group had more of these features. Patients with intermittent symptoms had their first-onset date and time recorded and the longest duration of these intermittent symptoms within this overall time frame also documented. The overall median time from onset of symptoms to ED presentation was 8.7 hours (interquartile

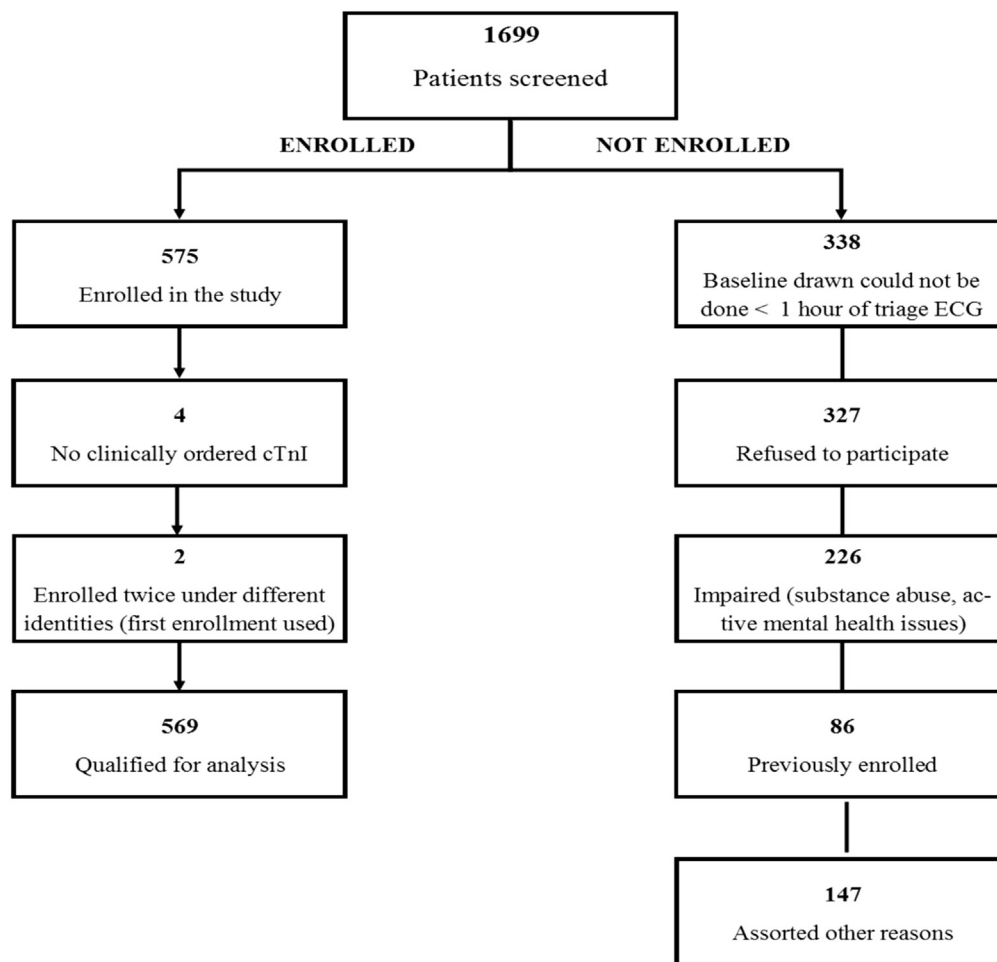


Figure 1. REACTION-US study patients screened, enrolled, and not enrolled.

Table 1. Baseline clinical characteristics for all patients and the ruled-out versus not-ruled-out groups.

Characteristic	All Patients (N=569)	Ruled Out (N=312)	Not Ruled Out (N=231)
Age (SD), median (IQR), y	55.9 (11.1), 55 (49–63)	52.9 (10.4), 53 (46–59)	59.5 (10.7), 60 (52–66)
Male sex (%)	296 (52.0)	121 (38.8)	165 (71.4)
Comorbidities (%)			
Hypertension	464 (81.5)	232 (74.4)	213 (92.2)
Diabetes	164 (28.8)	74 (23.7)	82 (35.5)
Hypercholesterolemia	286 (50.3)	135 (43.3)	139 (60.2)
Smoking	212 (37.3)	122 (39.1)	80 (34.6)
Personal history of CAD	204 (35.9)	94 (30.1)	103 (44.6)
Family history of CAD	221 (38.8)	105 (33.7)	111 (48.1)
Revascularization	140 (24.6)	60 (19.2)	75 (32.5)
PCI	129 (22.7)	56 (17.9)	68 (29.4)
CABG	31 (5.4)	9 (2.9)	22 (9.5)
Myocardial infarction	168 (29.5)	75 (24.0)	86 (37.2)
Congestive heart failure	137 (24.1)	40 (12.8)	92 (39.8)
Dialysis	30 (5.3)	0	29 (12.6)
COPD	98 (17.2)	50 (16.0)	43 (18.6)
Presenting vital signs			
Systolic BP (SD), median (IQR), mm Hg	144.8 (25.9), 143 (127–159)	143.1 (23.2), 141.5 (127–158)	146.8 (28.9), 144 (127–163)
Diastolic BP (SD), median (IQR), mm Hg	85.5 (17.5), 83 (74–96)	85.2 (16.5), 82 (74–96)	85.4 (18.7), 82 (73–97)
Pulse rate, beats/min	83.9 (19.0), 82 (70–95)	82.9 (17.6), 81 (71–92)	85.3 (20.1), 84 (69–98)
ECG findings (%)			
Atrial fibrillation tachycardia	20 (3.5)	3 (1.0)	16 (6.9)
Sinus tachycardia	75 (13.2)	32 (10.3)	39 (16.9)
Other tachycardia	10 (1.8)	6 (1.9)	4 (1.7)
Left ventricular hypertrophy	94 (16.5)	39 (12.5)	53 (22.9)
Left bundle branch block	10 (1.8)	2 (0.6)	7 (3.0)
Right bundle branch block	27 (4.7)	5 (1.6)	21 (9.1)
Paced ventricular	13 (2.3)	0	13 (5.6)
ST-segment elevation >1 mm	20 (3.5)	14 (4.5)	5 (2.2)
ST-segment depression >1 mm	25 (4.4)	5 (1.6)	19 (8.2)
T-wave inversion	169 (29.7)	68 (21.8)	100 (43.3)
Within normal limits	154 (27.1)	114 (36.5)	29 (12.6)
Home medications (%)			
Aspirin	302 (53.1)	148 (47.4)	141 (61.0)
Anticoagulant	49 (8.6)	17 (5.4)	31 (13.4)
Diuretics	142 (25.0)	56 (17.9)	78 (33.8)
ACE inhibitor	219 (38.5)	111 (35.6)	102 (44.2)
Angiotensin-receptor blocker	38 (6.7)	14 (4.5)	22 (9.5)
β -Blocker	256 (45.0)	112 (35.9)	137 (59.3)
Calcium channel blocker	145 (25.5)	58 (18.6)	80 (34.6)
Nitrate	129 (22.7)	55 (17.6)	70 (30.3)
Antiarrhythmic	14 (2.5)	5 (1.6)	9 (3.9)

CAD, Coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; BP, blood pressure; ACE, angiotensin-converting enzyme.

Numeric data are presented as mean (SD) and median (IQR) values. Categorical data are presented as frequency (%) measurements.

range [IQR] 2.3 to 41.5 hours), whereas the median time for longest duration of symptoms to ED presentation was 3.4 hours (IQR 1.4 to 11.3 hours). For acute myocardial infarction patients, the median time from symptom onset to presentation was 10.9 hours (IQR 1.9 to 472.6 hours). There were 13 (29.5%) and 6 (13.6%) patients whose symptoms started within 2 hours and 1 hour before arrival, respectively. Thirty patients (5.3%) were receiving dialysis when enrolled.

Main Results

When the 164 enrolled patients (28.8%) with a baseline cTnT Generation 5 assay level of less than 6 ng/L were adjudicated, no patient had an acute myocardial infarction, resulting in a negative predictive value of 100% (95% CI 97.8% to 100.0%) and a sensitivity of 100% (95% CI 92.0% to 100.0%) (Figure 2). Two of these patients had a major adverse cardiac event (one noncardiac death and one acute myocardial infarction) within the 30-day

follow-up period, resulting in a negative predictive value of 98.8% (95% CI 95.7% to 99.9%) and sensitivity of 87.5% (95% CI 61.7% to 98.5%). In the not-ruled-out group of 405 patients (71.2%), 44 had an acute myocardial infarction, with a resulting positive predictive value of 10.9% (95% CI 8.0% to 14.3%) and specificity of 31.2% (95% CI 27.3% to 35.4%).

We determined that the use of a baseline cTnT Generation 5 assay value of less than 8 ng/L with a 30-minute Δ of less than 3 ng/L missed no acute myocardial infarctions and that these measurements were available for 221 (41.0%) of all study subjects (Figure 3). This resulted in a negative predictive value of 100% (95% CI 98.3% to 100.0%) and sensitivity of 100% (95% CI 92.0% to 100.0%) for acute myocardial infarction. One of these patients had a major adverse cardiac event (a noncardiac death) within the 30-day follow-up window, resulting in a negative predictive value of 99.5% (95% CI 97.5% to 100.0%) and sensitivity of 93.3% (95% CI 68.0% to 99.8%). In the not-ruled-out group of 318 patients (59.0%), 44 had an acute myocardial infarction, with a resulting positive predictive value of 13.8% (95% CI 10.2% to 18.1%) and specificity of 44.6% (95% CI 40.2% to 49.2%).

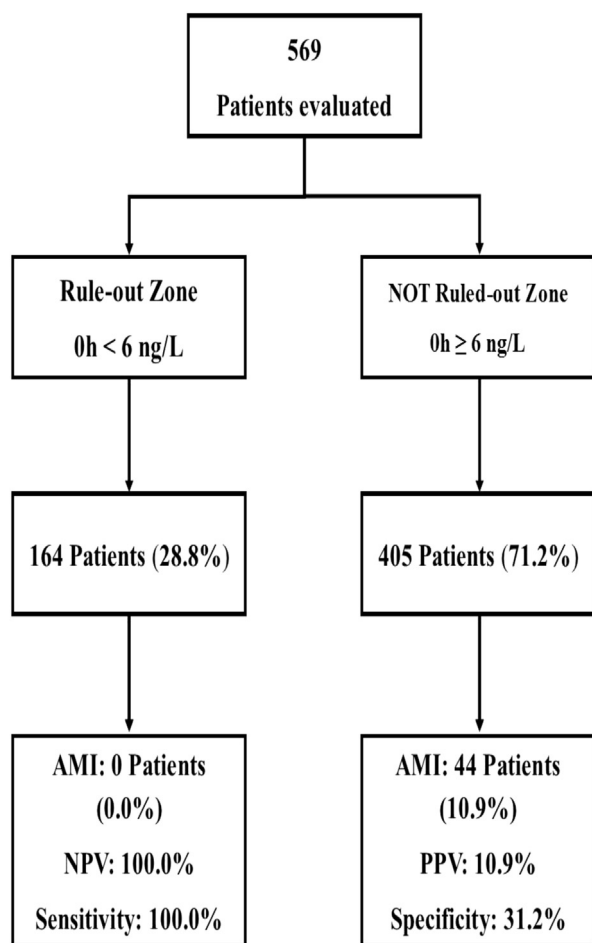


Figure 2. Baseline cTnT Generation 5 assay level less than 6 ng/L for the rule-out of acute myocardial infarction. AMI, acute myocardial infarction; NPV, negative predictive value; PPV, positive predictive value.

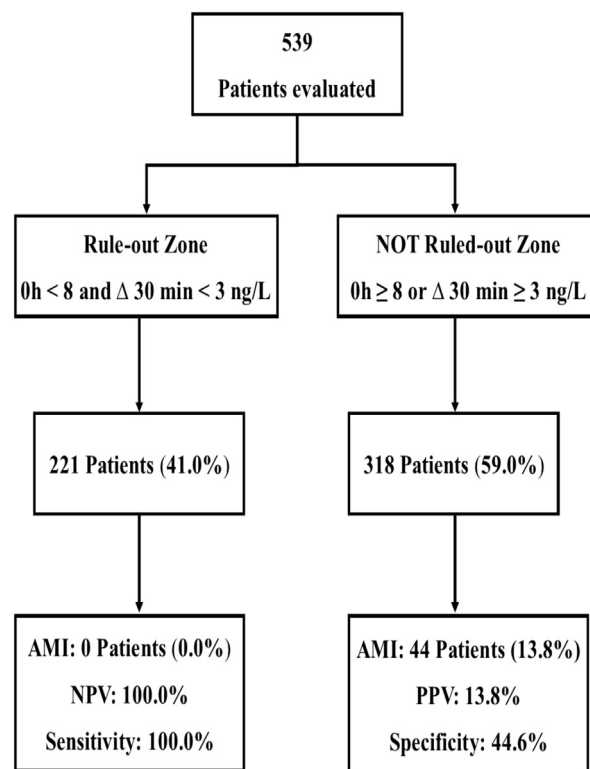


Figure 3. cTnT Generation 5 assay 0-hour and 30-minute algorithm for the rule-out of acute myocardial infarction using values at baseline less than 8 ng/L and a Δ value less than 3 ng/L.

Table 2. Major adverse cardiovascular events at 30 days for each ultrarapid acute myocardial infarction rule-out algorithm.

	Total Patients, No. (%) (95% CI)	Total MACE, No. (%) (95% CI)	Death		AMI, No. (%) (95% CI)	PCI or CABG, No. (%) (95% CI)
			CV, No. (%) (95% CI)	Non-CV, No. (%) (95% CI)		
LoQ algorithm (n = 569)						
Ruled out	164 (28.8) (25.1–32.7)	2 (1.2) (0.1–4.3)	0 (0.0–2.2)	1 (0.6) (0.0–3.4)	1 (0.6) (0.0–3.4)	0 (0.0–2.2)
Not ruled out	405 (71.2) (67.3–74.9)	14 (3.5) (1.9–5.7)	4 (1.0) (0.3–2.5)	2 (0.5) (0.1–1.8)	7 (1.7) (0.7–3.5)	4 (1.0) (0.3–2.5)
Baseline/30-min algorithm (n = 539)						
Ruled out	221 (41.0) (36.8–45.3)	1 (0.5) (0.0–2.5)	0 (0.0–1.7)	1 (0.5) (0.0–2.5)	0 (0.0–1.7)	0 (9.9–1.7)
Not ruled out	318 (59.0) (54.7–63.2)	14 (4.4) (2.4–7.3)	4 (1.3) (0.3–3.2)	2 (0.6) (0.1–2.3)	7 (2.2) (0.9–4.5)	4 (1.3) (0.3–3.2)

MACE, Major adverse cardiac event; CV, cardiovascular; LoQ, level of quantification.

Overall, of all study patients, 109 were not able to be contacted by telephone for the 30-day follow-up. All patients had their electronic medical records reviewed. Of the individuals not able to be contacted by telephone, 2 had a cardiac death confirmed by hospital readmission. Another 77 had no Henry Ford Health System visits or testing conducted within this period, and so they could have been considered as lost to follow-up. However, in a later follow-up at 12 to 18 months only 14 of these 77 patients (overall 14/569, or 0.02%) remained as lost to follow-up and possibly having had an unrecognized major adverse cardiac event. The 30-day major adverse cardiac event rates for each algorithm are summarized in Table 2, showing that very few patients in our ultrarapid rule-out acute myocardial infarction groupings had an event.

The overall ED ultrarapid acute myocardial infarction rule-out results are summarized in Figure 4, which shows that the percentages of patients in the ED with suspected acute coronary syndrome that could be ruled out increased from 28.8% with a single baseline cTnT Generation 5 assay level of less than 6 ng/L to 41.0% with a novel baseline and 30-minute algorithm. The positive predictive values and specificities for the rule-in of acute myocardial infarction in the not-ruled-in patients remained poor during these same periods.

LIMITATIONS

The REACTION-US trial involved a single urban center, and so our results will require validation in a prospective multicenter US trial using our cut points used for decisionmaking and ensuring the enrollment of additional early presenters (within 2 to 3 hours of symptom

onset). Larger numbers of patients studied will be needed to narrow the CIs to less than 1% for our reported negative predictive values and sensitivities for both the baseline and the 30-minute algorithms. Our data were obtained in an observational diagnostic study in which the cTnT Generation 5 assay results were compared with an adjudicated acute myocardial infarction diagnosis that relied on the use of a contemporary cTnI assay. Perhaps had the adjudicating physicians used the cTnT Generation 5 assay results to determine the presence of acute myocardial infarction, the results would have been different.

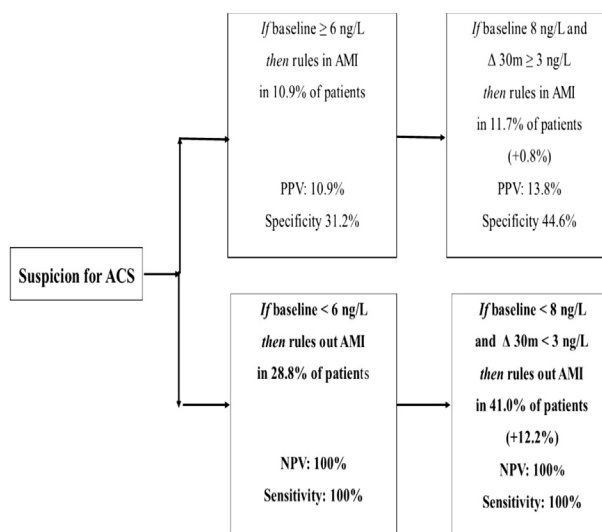


Figure 4. ED rule-out acute myocardial infarction assessments showing increasing percentages from baseline to 30 minutes. Rule-in rates in the not-ruled-out groups remained low during this same time.

We had 1,699 patients screened for study enrollment and 575 of these were enrolled (33.9%), so there may have been some patient selection bias. However, once consent was obtained and patients were enrolled, our rate of patients unqualified for inclusion in the analysis was very low (6 of 575; 1.0%) compared with that of the TRAPID-AMI trial (176 of 1,458; 12.1%).¹⁸ Last, because we excluded patients with life-threatening illness, cardioversion or defibrillation within 24 hours of presentation, ST-segment elevation myocardial infarction patients requiring immediate reperfusion, or those who were pregnant or breast feeding, we do not know how any of our analyses would have changed had these patients been included.

DISCUSSION

There have been articles published describing the use of hs-cTnT and hs-cTnI in the ED to rule out or rule in acute myocardial infarction, using the baseline and 1-hour Δ values, and for using a single baseline value less than level of detection for its rule-out. These recommendations were published in the 2015 European Society of Cardiology guidelines for the rapid assessment of patients with suspected non-ST-segment elevation acute myocardial infarction.²⁵ However, these recommendations have not been incorporated in any of the current US cardiology (American College of Cardiology/American Heart Association) or emergency medicine (American College of Emergency Physicians) guidelines.

The TRAPID-AMI trial evaluating hs-cTnT was mostly a non-US study that had only 2 participating US sites. The previous Advantageous Predictors of Acute Coronary Syndromes Evaluation study results (validated by TRAPID-AMI) enrolled only European patients. Additionally, to enrich the study population with early onset of symptoms, enrollment was limited to subjects with chest pain onset less than 6 hours in TRAPID-AMI. Last, patients with renal failure requiring dialysis and those with acute myocardial infarction or coronary artery bypass graft within the previous 3 weeks and 1 month, respectively, were excluded.

Because the cTnT Generation 5 assay was approved in 2017 by the FDA for use in the United States for aid in the diagnosis of acute myocardial infarction, it is important that US studies be completed to determine how to best incorporate these cTnT measurements for the rapid assessment for acute myocardial infarction in the ED. In the United States, the measurement of cTn levels is widely ordered (14% of all ED patients²⁸) and so cTnT Generation 5 assay studies should reflect this clinical practice before any guidelines are adopted for emergency medicine clinician use. Our study enrollment was open to patients with any

symptoms (not only chest pain) that were suspicious for acute myocardial infarction and without limitation on the length of onset of these complaints. Additionally, patients requiring dialysis or with acute myocardial infarction within 3 weeks or coronary artery bypass graft within 1 month of enrollment were included. All of our 30 study subjects (5.0%) who were receiving dialysis were assigned to the not-ruled-out acute myocardial infarction group for both algorithms. To our knowledge, the use of cTnT Generation 5 assay measurements has not previously been reported in a study evaluating its use in a US ED setting for rapid assessment for acute myocardial infarction.

The REACTION-US median times from symptom onset to ED presentation were much longer than those in TRAPID-AMI (8.7 hours [IQR 2.3 to 41.5] versus 1.8 hours [IQR 1.0 to 2.9]) because the TRAPID-AMI trial by design enrolled only patients with chest pain of 6 hours' duration or less, whereas the REACTION-US trial was a more practical study, enrolling all comers with suspected acute coronary syndrome and documenting the start of any intermittent symptoms, not simply the duration of the longest symptom. However, 13 of 44 patients (29.5%) with acute myocardial infarction were early presenters, coming to the ED less than 2 hours after symptom onset. Patients with a primary complaint that was not chest pain (85, or 14.9%) were enrolled in REACTION-US, whereas all TRAPID-AMI subjects had chest pain at presentation. REACTION-US enrolled 30 patients (5%) who were receiving dialysis, whereas TRAPID-AMI excluded all of these individuals.

Both studies had a generally lower incidence of baseline cardiac risk factors and comorbidities in patients who were not ruled out for acute myocardial infarction (see [Table 1](#) for REACTION-US results). This is important because some of the ruled-out patients may be candidates for discharge with outpatient follow-up if a cardiac risk score, such as the History, ECG, Age, Risk Factors and Troponin,²⁹ is low. Recently, this approach using 5 different accelerated diagnostic pathways was retrospectively analyzed in an Australian ED patient population with a low acute myocardial infarction and acute coronary syndrome prevalence. Patients presenting with symptoms suggestive of acute coronary syndrome but with 0- and 2-hour high-sensitivity troponin I (Beckman Access high sensitivity I) measurements below the 99th percentile were evaluated with the History, ECG, Age, Risk Factors and Troponin; modified accelerated diagnostic protocol to assess patients with chest pain symptoms using troponin as the only biomarker; Emergency Department Assessment of Chest Pain Score; the New Vancouver Chest Pain Rule; and the No Objective Testing Rule pathways. The study showed that one third of patients could be safely

discharged with no further testing with the New Vancouver Chest Pain Rule or No Objective Testing Rule pathways, whereas half of patients could be rapidly referred for objective cardiac testing with the Emergency Department Assessment of Chest Pain Scores, modified accelerated diagnostic protocol to assess patients with chest pain symptoms using troponin as the only biomarker, or History, ECG, Age, Risk Factors and Troponin pathways.³⁰

REACTION-US results concerning the use of cTnT Generation 5 assay levels below the FDA-approved level of quantification (6 ng/L) at baseline blood testing in the ED to rule out acute myocardial infarction had a negative predictive value and sensitivity of 100%. In a TRAPID-AMI substudy, Body et al²⁴ reported that 560 patients (43.7%) had a baseline hs-cTnT level less than 5 ng/L (European level of detection) and that 4 (0.7%) of these individuals had an acute myocardial infarction (sensitivity 98.1%). Also, of the 471 subjects (36.7%) who had baseline hs-cTnT levels less than 5 mg/L without ischemic changes on their initial ED ECG, only 2 had an adjudicated acute myocardial infarction. This latter group had a probability of acute myocardial infarction of 0.4%, with a negative predictive value of 99.6% and sensitivity of 99.1%. In REACTION-US, 164 patients (28.8%) had a baseline cTnT Generation 5 assay level less than 6 ng/L, and of these, none had an acute myocardial infarction, irrespective of the presence of any ischemic ECG changes. It is unclear why there were lower percentages of patients with cTnT Generation 5 assay baseline values less than the level of quantification in the REACTION-US trial and that none had an acute myocardial infarction. Perhaps if we had had higher numbers of subjects enrolled in our study, we might have had results similar to those reported by Body et al.²⁴ Regardless, it appears that baseline newer cTnT assays reporting values less than the level of quantification or less than the level of detection indicate a very low likelihood of acute myocardial infarction diagnosis in ED populations in the United States and elsewhere.

We determined that the optimal cut-point values to rule out all acute myocardial infarctions with 0-hour and 30-minute cTnT Generation 5 assay measurements were a baseline level less than 8 ng/L, with a Δ at 30 minutes of less than 3 ng/L. This was observed in 221 of the 539 study patients (41.1%), or an additional 12.2% of patients to those individuals ruled out at baseline (Figure 4).

The total major adverse cardiac events for the level of quantification algorithm were 2 (1.2%), one acute myocardial infarction and one noncardiovascular death; and for the baseline and 30-minute algorithm, 1 (0.5%) (1 noncardiovascular death). These major adverse cardiac

event rates are very low and need to be evaluated in further studies with larger patient enrollments.

In both of these cTnT Generation 5 assay ultrarapid rule-out acute myocardial infarction protocols, the positive predictive value and specificity for acute myocardial infarction in the not-ruled-out group (REACTION-US) and ruled-in group (TRAPID-AMI) were too low to act on (administering systemic anticoagulation, for example) this early in the ED care. The very low reported values in the REACTION-US trial can be explained because we combined the observation and the rule-in zones reported in previous studies into a non-ruled-out group and also because we included dialysis patients. These not-ruled-out patients will require additional serial cTnT Generation 5 assay measurements (and possibly other testing) over time to determine which ones have a typical increase or decrease and can receive a diagnosis of acute myocardial infarction.

The REACTION-US study has shown that in a single urban center following US cTn ordering patterns (including dialysis patients and those without chest pain as a primary complaint), the use of a single baseline cTnT Generation 5 assay measurement of less than 6 ng/L to rule out acute myocardial infarction performed better in the United States compared with using a value less than 5 ng/L, as reported in the TRAPID-AMI multinational study. Additionally, when cTnT Generation 5 assay values at baseline less than 8 ng/L and a Δ 30-minute value less than 3 ng/L were used to rule out acute myocardial infarction, there were also no missed cases. Further multicenter trials are needed to determine whether a baseline cTnT Generation 5 assay value less than 6 ng/L and a novel baseline and 30-minute algorithm are appropriate for use in the United States and whether any alternative cTnT Generation 5 assay-directed options might be more useful.

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