RESEARCH

Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay

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Abstract

Background: We aimed to prospectively validate a novel 1-hour algorithm using high-sensitivity cardiac troponin T measurement for early rule-out and rule-in of acute myocardial infarction (MI).

Methods: In a multicentre study, we enrolled 1320 patients presenting to the emergency department with suspected acute MI. The high-sensitivity cardiac troponin T 1-hour algorithm, incorporating baseline values as well as absolute changes within the first hour, was validated against the final diagnosis. The final diagnosis was then adjudicated by 2 independent cardiologists using all available information, including coronary angiography, echocardiography, follow-up data and serial measurements of high-sensitivity cardiac troponin T levels.

Results: Acute MI was the final diagnosis in 17.3% of patients. With application of the high-sensitivity cardiac troponin T 1-hour algorithm, 786 (59.5%) patients were classified as "rule-out," 216 (16.4%) were classified as "rule-in" and 318 (24.1%) were classified to the "observational zone." The sensitivity and the negative predictive value for acute MI in the rule-out zone were 99.6% (95% confidence interval [CI] 97.6%–99.9%) and 99.9% (95% CI 99.3%–100%), respectively. The specificity and the positive predictive value for acute MI in the rule-in zone were 95.7% (95% CI 94.3%–96.8%) and 78.2% (95% CI 72.1%–83.6%), respectively. The 1-hour algorithm provided higher negative and positive predictive values than the standard interpretation of high-sensitivity cardiac troponin T using a single cut-off level (both $p < 0.05$). Cumulative 30-day mortality was 0.0%, 1.6% and 1.9% in patients classified in the rule-out, observational and rule-in groups, respectively ($p = 0.001$).

Interpretation: This rapid strategy incorporating high-sensitivity cardiac troponin T baseline values and absolute changes within the first hour substantially accelerated the management of suspected acute MI by allowing safe rule-out as well as accurate rule-in of acute MI in 3 out of 4 patients. **Trial registration:** ClinicalTrials.gov, NCT00470587

Acute myocardial infarction (MI) is a major cause of death and disability worldwide. As highly effective treatments are available, early and accurate detection of acute MI is crucial.[1–5] Clinical assessment, 12-lead electrocardiography (ECG) and measurement of cardiac troponin levels form the pillars for the early diagnosis of acute MI in the emergency department. Major advances have recently been achieved by the development of more sensitive cardiac troponin assays.[6–15] High-sensitivity cardiac troponin assays, which allow measure-

ment of even low concentrations of cardiac troponin with high precision, have been shown to largely overcome the sensitivity deficit of conventional cardiac troponin assays within the first hours of presentation in the diagnosis of acute MI.[6–15] These studies have consistently shown that the classic diagnostic interpretation of cardiac troponin as a dichotomous variable (troponin-negative and troponin-positive) no longer seems appropriate, because the positive predictive value for acute MI of being troponin-positive was only about 50%.[6–15] The best way to interpret and

clinically use high-sensitivity cardiac troponin levels in the early diagnosis of acute MI is still debated.[3,5,7]

In a pilot study, a novel high-sensitivity cardiac troponin T 1-hour algorithm was shown to allow accurate rule-out and rule-in of acute MI within 1 hour in up to 75% of patients.[11] This algorithm is based on 2 concepts. First, high-sensitivity cardiac troponin T is interpreted as a quantitative variable where the proportion of patients who have acute MI increases with increasing concentrations of cardiac troponin T.[6–15] Second, early absolute changes in the concentrations within 1 hour provide incremental diagnostic information when added to baseline levels, with the combination acting as a reliable surrogate for late concentrations at 3 or 6 hours.[6–15] However, many experts remained skeptical regarding the safety of the high-sensitivity cardiac troponin T 1-hour algorithm and its wider applicability.[16] Accordingly, this novel diagnostic concept has not been adopted clinically to date. Because the clinical application of this algorithm would represent a profound change in clinical practice, prospective validation in a large cohort is mandatory before it can be considered for routine clinical use. The aim of this multicentre study was to prospectively validate the high-sensitivity cardiac troponin T 1-hour algorithm in a large independent cohort.

Methods

Study design and population
The Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) Study, an ongoing prospective study being conducted internationally in multiple centres, is designed to advance the early diagnosis of acute MI.[8,11,13,15] Unselected patients presenting to the emergency department with nontraumatic chest pain or other symptoms suggestive of acute MI are enrolled after written, informed consent is obtained. For this analysis, 1714 patients enrolled after the initial pilot study were eligible. These patients were enrolled at 6 centres in 3 countries (Switzerland, Spain, Italy) from June 2009 to June 2013. To further increase the generalizability of the findings, the recruitment network was changed as compared with the first phase of the APACE Study:[8,11,13,15] 2 new centres were initiated, and 2 centres were closed because the local principal investigators left those centres. The onset or maximum severity of chest pain had to be within the last 12 hours before presentation. Patients with terminal kidney failure requiring dialysis were excluded. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees.

Patients with ST elevation MI (n = 58) were excluded from this analysis, because cardiac biomarkers are considered to be of limited clinical value in these patients. Among the remaining 1656 patients, samples at presentation and after 1 hour for measurement of high-sensitivity cardiac troponin T were available in 1320 patients. The most common reasons for missing values after 1 hour (n = 336) were early transfer to the catheter laboratory or coronary care unit, and diagnostic procedures around the 1-hour window that precluded blood samples being drawn at 1 hour, but did not preclude follow-up samples being drawn in the future. Baseline characteristics were similar in patients with and without a sample after 1 hour (Appendix 1, supplemental table 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.141349/-/DC1).

Routine clinical assessment
All patients underwent a clinical assessment that included medical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood test and chest radiography. Levels of cardiac troponin were measured at presentation, serially after 3 and 6 hours, and thereafter as long as clinically indicated. Timing of tests and treatment were left to the discretion of the attending physician.

Measurement of high-sensitivity cardiac troponin T
Blood samples for determination of cardiac troponin T levels were collected in serum tubes at presentation to the emergency department. Additional samples were collected after 1, 2, 3 and 6 hours. Serial sampling was discontinued when the diagnosis of acute MI was certain and treatment required transfer of the patient to the catheter laboratory or coronary care unit. After centrifugation, samples were frozen at –80°C until assayed in a blinded fashion using the Elecsys 2010 (Roche Diagnostics) in a core laboratory. The treating clinicians therefore had no access to the test results of the study samples. For high-sensitivity cardiac troponin T, limit of blank and limit of detection have been determined to be 3 ng/L and 5 ng/L, an imprecision corresponding to 10% coefficient of variation was reported at 13 ng/L and the 99th-percentile of a healthy reference population at 14 ng/L.[17]

Adjudicated final diagnosis
Adjudication of the final diagnosis was performed centrally in a core laboratory at the Universitätsspital Basel. The adjudication also included later levels of high-sensitivity cardiac troponin T to take advantage of the higher sensi-

tivity and higher overall diagnostic accuracy offered by these assays.[7–15] This allowed the additional detection of small acute MIs that would be missed by the adjudication based on conventional cardiac troponin assays. Two independent cardiologists reviewed all available medical records pertaining to the patient from the time of emergency department presentation to 90-day follow-up. Data from the medical records included patient history, physical examination, results of laboratory testing (including serial high-sensitivity cardiac troponin T levels), radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity and morphology in coronary angiography. Late samples were available for adjudication of the final diagnosis in all patients. In a minority of patients with a low pretest probability for an acute MI, serial sampling was stopped, at the discretion of the attending physician and in accordance with current guidelines from the European Society of Cardiology, once a second sample 3 hours after presentation to the emergency department was again negative.[3] In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

Acute MI was defined and cardiac troponin levels interpreted as recommended in current guidelines.[2,3,5,6] In brief, acute MI was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least 1 cardiac troponin value above the 99th percentile together with a significant rise and/or fall.[2,3,5,6] The criteria used to define rise and/or fall are described in detail in Appendix 1 (available at www.www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.141349/-/DC1).

Unstable angina was diagnosed in the following cases: patients with normal high-sensitivity cardiac troponin T levels or stable elevations not fulfilling the criteria for acute MI and typical angina at rest; patients with a deterioration of previously stable angina; cases of positive cardiac exercise testing or cardiac catheterization with coronary arteries found to have a stenosis of 70% or greater; and ambiguous cases in which follow-up information showed acute MI or a sudden unexpected cardiac death within 60 days. Further predefined diagnostic categories included cardiac disorders other than coronary artery disease (e.g., myocarditis, apical ballooning syndrome, acute heart failure, hypertensive emergency or tachyarrhythmia) and noncardiac chest pain. If acute MI was excluded in the emergency department according to the high-sensitivity cardiac troponin T assay, but no sufficient further diagnostic procedures were performed for conclusive diagnosis, symptoms were classified as of "unknown origin."

Follow-up

After hospital discharge, patients were contacted after 3, 12 and 24 months by telephone or in written form. Information regarding death was obtained from the national registry on mortality, the hospital's diagnosis registry and the family physician's records.

Description of the algorithm

The 1-hour algorithm for rapid rule-in and rule-out of acute MI has been described previously.[11] In brief, the algorithm incorporates both baseline high-sensitivity cardiac troponin T levels and absolute changes in the levels within the first hour. Selection of these 2 parameters was based on the previously published very high diagnostic accuracy of their combination.[14,18] For rule-out of acute MI, the criterion was defined as a baseline high-sensitivity cardiac troponin T level of less than 12 ng/L *and* an absolute change within the first hour of less than 3 ng/L. For rule-in of acute MI, the criterion was defined as either a baseline high-sensitivity cardiac troponin T value of 52 ng/L or greater, *or* an absolute change within the first hour of 5 ng/L or greater. Patients fulfilling neither of the above criteria for rule-in or rule-out were classified in a third group called "observational zone."

Statistical analysis

Continuous variables are presented as means ± standard deviations, or as medians and interquartile ranges; categorical variables are presented as numbers and percentages. Differences in baseline characteristics between patients with and without acute MI were assessed using the Mann–Whitney test for continuous variables and the Pearson χ^2 test for categorical variables. Receiver operating characteristic (ROC) curves were constructed to assess the diagnostic accuracy for the diagnosis of acute MI for high-sensitivity cardiac troponin T levels at presentation and the combination with absolute changes in levels within the first hour and within the first 2 hours after presentation. The comparison of areas under the ROC curves was performed as recommended by DeLong and colleagues.[19] Mortality during 30 days and 2 years of follow-up according to the classification provided by the algorithm was plotted in Kaplan–Meier curves, and the log-rank test was used to assess differences in mortality between groups.

In calculating the sample size, we aimed to document the achievable estimation precision for the negative and positive predictive values.

Assuming a negative predictive value of 99.7% for acute MI in the rule-out group, 60% of patients ruled-out and a dropout rate of up to 25% of patients due to missing 1-hour samples, enrolment of at least 1500 patients will result in 600 patients in the rule-out group with analyzable data and a lower boundary of the 1-sided 95% confidence interval (CI) of the negative predictive value of 99.0%

All hypothesis testing was 2-tailed, and p values < 0.05 were considered significant. All statistical analyses were performed using SPSS for Windows 19.0 (SPSS Inc.) and MedCalc 9.6.4.0 (MedCalc Software).

Results

Characteristics of patients
Among the 1320 patients who presented to the emergency department with acute chest pain

(Table 1), the adjudicated final diagnosis was acute MI in 229 patients (17.3%), unstable angina in 109 (8.3%), cardiac symptoms of origin other than coronary artery disease in 194 (14.7%), noncardiac symptoms in 732 (55.5%) and symptoms of unknown origin in 56 (4.2%).

Diagnostic performance of the algorithm
With application of the high-sensitivity cardiac troponin T 1-hour algorithm, 786 (59.5%) patients were classified as "rule-out," 216 (16.4%) were classified as "rule-in" and 318 (24.1%) were classified in the "observational zone" (Figure 1). The sensitivity and the negative predictive value for acute MI in the "rule-out" zone were 99.6% (95% CI 97.6%–99.9%) and 99.9% (95% CI 99.3%–100%), respectively. The negative predictive value was comparable in various subgroups, including patients who presented early after the onset of chest pain (Appendix 1). The algorithm

Table 1: Baseline characteristics of patients presenting to the emergency department with acute chest pain

Characteristic	Group; no. (%) of patients*			
	Total $n = 1320$	Acute MI $n = 229$	Other† $n = 1091$	p value
Age, median (IQR), yr	60 (49–73)	70 (58–80)	58 (47–70)	< 0.001
Sex, male	915 (69.3)	175 (76.4)	740 (67.8)	0.01
Risk factors				
Hypertension	770 (58.3)	171 (74.7)	599 (55.0)	< 0.001
Hypercholesterolemia	658 (49.8)	158 (69.0)	500 (45.8)	< 0.001
Diabetes	218 (16.5)	59 (25.8)	159 (14.6)	
Current smoking	345 (26.1)	52 (22.7)	293 (26.9)	0.2
History of smoking	501 (38.0)	103 (45.0)	398 (36.5)	0.01
History				
Coronary artery disease	440 (33.3)	106 (46.3)	334 (30.6)	< 0.001
Previous MI	305 (23.1)	77 (33.6)	228 (20.9)	< 0.001
Previous revascularization	372 (28.2)	88 (38.4)	284 (26.0)	< 0.001
Creatinine clearance, median (IQR), mL/min/m²	85 (70–101)	75 (56–94)	87 (73–103)	< 0.001
Creatinine clearance < 50 mL/min/ m²	108 (8.2)	45 (19.7)	63 (5.8)	< 0.001
ECG findings				
Left bundle branch block	35 (2.7)	11 (4.8)	24 (2.2)	0.02
ST segment elevation	24 (1.8)	6 (2.6)	18 (1.6)	0.3
ST segment depression	119 (9.0)	62 (27.1)	57 (5.2)	< 0.001
T wave inversion	108 (8.2)	27 (11.8)	81 (7.4)	0.02
No significant abnormalities	1034 (78.3)	123 (53.7)	911 (83.5)	< 0.001

ECG = electrocardiography, IQR = interquartile range, MI = myocardial infarction.
*Unless stated otherwise.
†Unstable angina, cardiac symptoms of origin other than coronary artery disease, noncardiac symptoms and symptoms of unknown origin.

missed only 1 patient, an older woman who was a current smoker and had hypertension and dyslipidemia and who presented early with a small acute MI. Her initial high-sensitivity cardiac troponin T level was 10 ng/L, rose to 12 ng/L after 1 hour and later reached a peak of 17 ng/L.

For the rule-in zone, specificity and positive predictive value for acute MI were 95.7% (95% CI 94.3%–96.8%) and 78.2% (95% CI 72.1%–83.6%), respectively (Figure 1). Of 229 patients with acute MI, 169 (73.8%) were ruled-in after 1 hour. The final adjudicated diagnosis of the ruled-in patients with a diagnosis other than acute MI (n = 47) were cardiac arrhythmia (n = 17), myocarditis (n = 6), pulmonary embolism (n = 5), acute heart failure (n = 3), Takotsubo cardiomyopathy (n = 3), unstable angina (n = 1), hypertensive crisis (n = 1) and noncardiac chest pain (n = 11). Taken together, the algorithm allowed for a definite diagnosis after 1 hour in 75.9% of patients (either rule-in or rule-out). The remaining 318 (24.1%) patients were classified in the "observational zone," and 59 of these patients were finally classified as having acute MI, reflecting a prevalence of acute MI of 18.6% in the observational zone group.

Comparison with standard of care (classic interpretation of cardiac troponin)

A single cut-off value for high-sensitivity cardiac troponin T (14 ng/L) at presentation resulted in a sensitivity and negative predictive value of 92.1% (95% CI 88.4%–95.3%) and 98.1% (95% CI 96.5%–98.6%), and a specificity and positive predictive value of 79.4% (95% CI 76.3%–81.3%) and 48.4% (95% CI 43.3%–53.3%), respectively. Measures for diagnostic accuracy of different cut-off points of high-sensitivity cardiac troponin T are shown in Table 2.

Comparison with standard of care (cardiac troponin T and ECG)

Combining the classic interpretation of cardiac troponin with ischemic ECG findings (ST elevation, ST depression, T inversion and complete left bundle branch block), the combination of both a normal high-sensitivity cardiac troponin T level and no ischemic ECG findings at presentation had a sensitivity and negative predictive value of 95.2% (95% CI 91.6%–97.6%) and 98.6% (95% CI 97.5%–99.3%), respectively. "Rule-in" defined as either one (or both) being positive had a specificity and positive predictive value of 69.8% (95% CI 67.0%–73.0%) and 39.9% (95% CI 35.7%–44.1%), respectively.

Comparison of 1 hour versus other time points

The area under the curve for the combination of high-sensitivity cardiac troponin T at presentation with 1-hour absolute change (0.96, 95% CI 0.95–0.97) was significantly higher as compared with the area under the curve of high-sensitivity
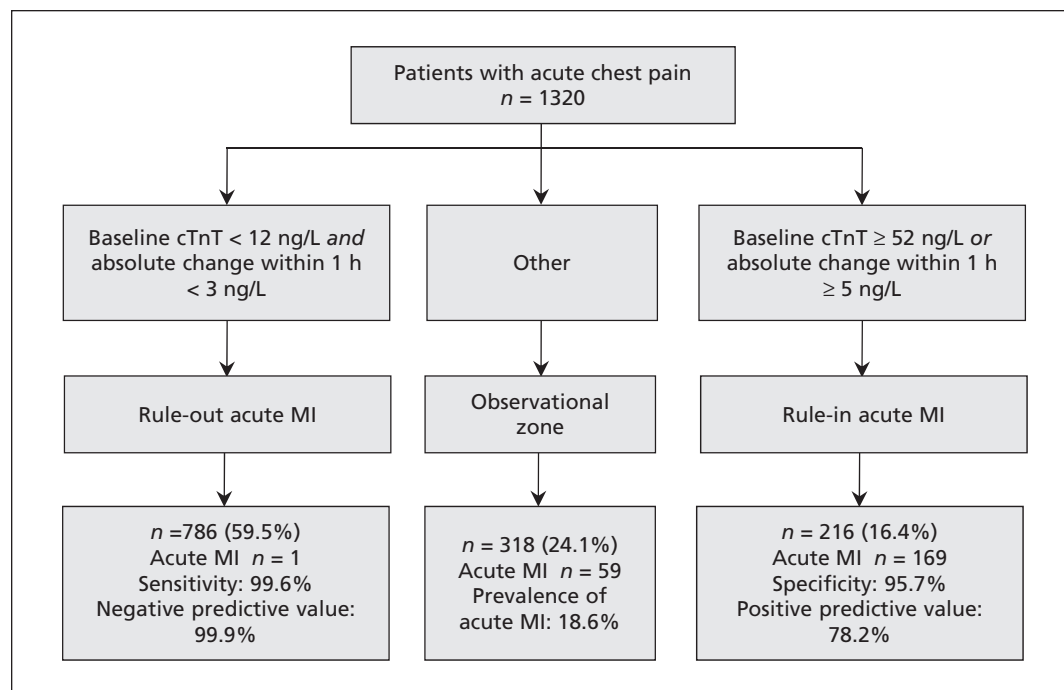

Figure 1: Performance of the high-sensitivity cardiac troponin T (cTnT) 1-hour algorithm for rapid diagnosis of acute myocardial infarction (MI).

cardiac troponin T at presentation alone (0.93, 95% CI 0.92–0.95), and comparable to the combination of high-sensitivity cardiac troponin T at presentation with 2-hour absolute change (0.96, 95% CI 0.95–0.97).

Prognostic performance of the 1-hour algorithm for mortality

The mean duration of follow-up was 24.4 ± 10.1 months. There were 9 deaths within 30 days (0.7%) and 74 deaths within 24 months (5.6%). Mortality was significantly associated with the categories "rule-out," "observational zone" and "rule-in" as classified by the high-sensitivity cardiac troponin T 1-hour algorithm (Figure 2A). Cumulative 30-day mortality was 0.0%, 1.6% and 1.9% in patients classified as "rule-out," "observational zone" and "rule-in," respectively (log-rank $p = 0.001$). This pattern continued to a follow-up of 2 years with cumulative all-cause mortality of 1.1%, 16.5% and 13.4% in patients classified as "rule-out," "observational zone" and "rule-in," respectively (log-rank $p < 0.001$) (Figure 2B).

Interpretation

This international multicentre study, performed to prospectively validate the high-sensitivity cardiac troponin T 1-hour algorithm for rapid rule-out and rule-in of acute MI, had 6 major findings.

First, the negative predictive value for acute MI in the rule-out zone defined only by high-sensitivity cardiac troponin T levels at presentation and the absolute change within 1 hour was 99.9%. Overall, 59.5% of all patients could be assigned to the rule-out category. Although the achieved negative predictive value is extremely high, it is important to stress that the high-sensitivity cardiac troponin T 1-hour algorithm should always be used in conjunction with full clinical assessment, including patient history and examination, and 12-lead ECG.

Second, the positive predictive value for acute MI in the rule-in zone was 78.2%. Many of the patients in the rule-in zone with a diagnosis other than acute MI did have conditions that usually still require coronary angiography for accurate diagnosis, including Takotsubo cardiomyopathy, myocarditis and unstable angina.[2,3] Therefore, the immediate clinical consequence of being assigned the rule-in zone would be urgent coronary angiography, unless clinical assessment would indicate another obvious condition associated with acute cardiomyocyte damage (e.g., heart failure, tachyarrhythmia or hypertensive crisis).[2,3] The rule-in zone of this algorithm is more precisely defined in the 2011 European Society of Cardiology algorithm.[3] Because the rule-in of acute MI in patients with mild elevations in high-sensitivity cardiac troponin is often challenging for clinicians,[5,6] it is a key advantage of this 1-hour algorithm to provide more detailed guidance in this difficult setting.

Table 2: Diagnostic accuracy of different cut-off points of absolute high-sensitivity cardiac troponin T levels at baseline and changes within the first hour

Cut-off point, ng/L	% (95% CI)			
	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Baseline				
5	99.6 (97.6–100.0)	37.9 (35.0–40.9)	25.4 (22.6–28.4)	99.8 (98.7–100.0)
10	94.4 (90.6–97.0)	70.0 (67.2–72.7)	40.0 (35.9–44.2)	98.3 (97.1–99.1)
14	92.1 (88.4–95.3)	79.4 (76.3–81.3)	48.4 (43.3–53.3)	98.1 (96.5–98.6)
20	80.1 (74.3–85.0)	89.0 (87.0–90.8)	60.7 (54.9–66.2)	95.5 (94.0–96.7)
50	50.2 (43.6–56.8)	97.6 (96.5–98.4)	81.7 (74.3–87.7)	90.2 (88.4–91.9)
100	29.0 (23.2–35.3)	99.3 (98.6–99.7)	89.3 (80.0–95.3)	86.8 (84.8–88.7)
Within 1 hour				
1	84.4 (79.1–88.8)	84.9 (82.6–86.9)	54.2 (48.9–59.4)	96.2 (94.8–97.4)
3	70.1 (63.8–76.0)	95.7 (94.3–96.8)	77.5 (71.2–83.0)	93.8 (92.2–95.1)
5	59.3 (52.7–65.7)	97.3 (96.1–98.1)	82.0 (75.4–87.5)	91.8 (90.1–93.4)
10	42.4 (36.0–49.1)	98.2 (97.2–98.9)	83.1 (75.0–89.3)	88.9 (87.0–90.7)
15	35.9 (29.7–42.5)	98.5 (97.6–99.2)	83.8 (75.0–90.5)	87.9 (85.9–89.7)
25	25.5 (20.0–31.7)	99.2 (98.4–99.6)	86.8 (76.3–93.8)	86.3 (84.2–88.1)

Note: CI = confidence interval.

Third, accordingly, the negative predictive value, but particularly also the positive predictive value, of the high-sensitivity cardiac troponin T 1-hour algorithm is significantly higher than that achieved by the current standard of care (classic interpretation of high-sensitivity cardiac troponin T with or without ECG findings).

Fourth, our data confirm the selection of the 1-hour time point, as the diagnostic accuracy for high-sensitivity cardiac troponin T and its changes were higher at 1 hour than at presentation only and comparable to that of the 2-hour time point. It is important to highlight that the 1-hour time point did not provide a definite answer in all patients (about 24.1% remained in the observational group). Accordingly, later time points (e.g., 3 or 6 h) still remain necessary in some patients.

Fifth, the 1-hour algorithm overall assigned 75.9% of patients a definite process (either rule-out or rule-in). Thereby, the high-sensitivity cardiac troponin T 1-hour algorithm was even more effective in the early triage of patients with acute chest pain than, for example, the recently developed accelerated diagnostic protocol combining the Thrombolysis in Myocardial Infarction Score with high-sensitivity cardiac troponin levels at baseline and 2 hours, or the dual-marker approach combining high-sensitivity cardiac troponin with copeptin, which assign 20%–40% of patients for rapid rule-out.[20–27] This difference is at least partly explained by the fact that the latter approaches exclusively select patients for rule-out, but do not provide guidance for rule-in.

Sixth, cumulative 30-day mortality was 0.0% in patients assigned the rule-out zone, further documenting the safety of this approach and the suitability of many of these patients for early discharge.

Our findings extend and corroborate previous work with high-sensitivity cardiac troponin[6–15] as well as recent pilot data obtained for the 1-hour algorithm.[11] We found that safe rule-out and accurate rule-in was feasible much more rapidly than suggested in current guidelines from the American College of Cardiology Foundation and American Heart Association,[2] and the European Society of Cardiology[3] in 3 out of 4 patients presenting to the emergency department with suspected acute MI. The performance of the high-sensitivity cardiac troponin T 1-hour algorithm in this validation cohort was very similar to that found in the pilot study (negative predictive value 100%, positive predictive value 80%).[11] The findings of this study now provide an important prospective validation of the hypothesis raised in the initial pilot data. Whereas the pilot study[12] derived among multiple possible options the best
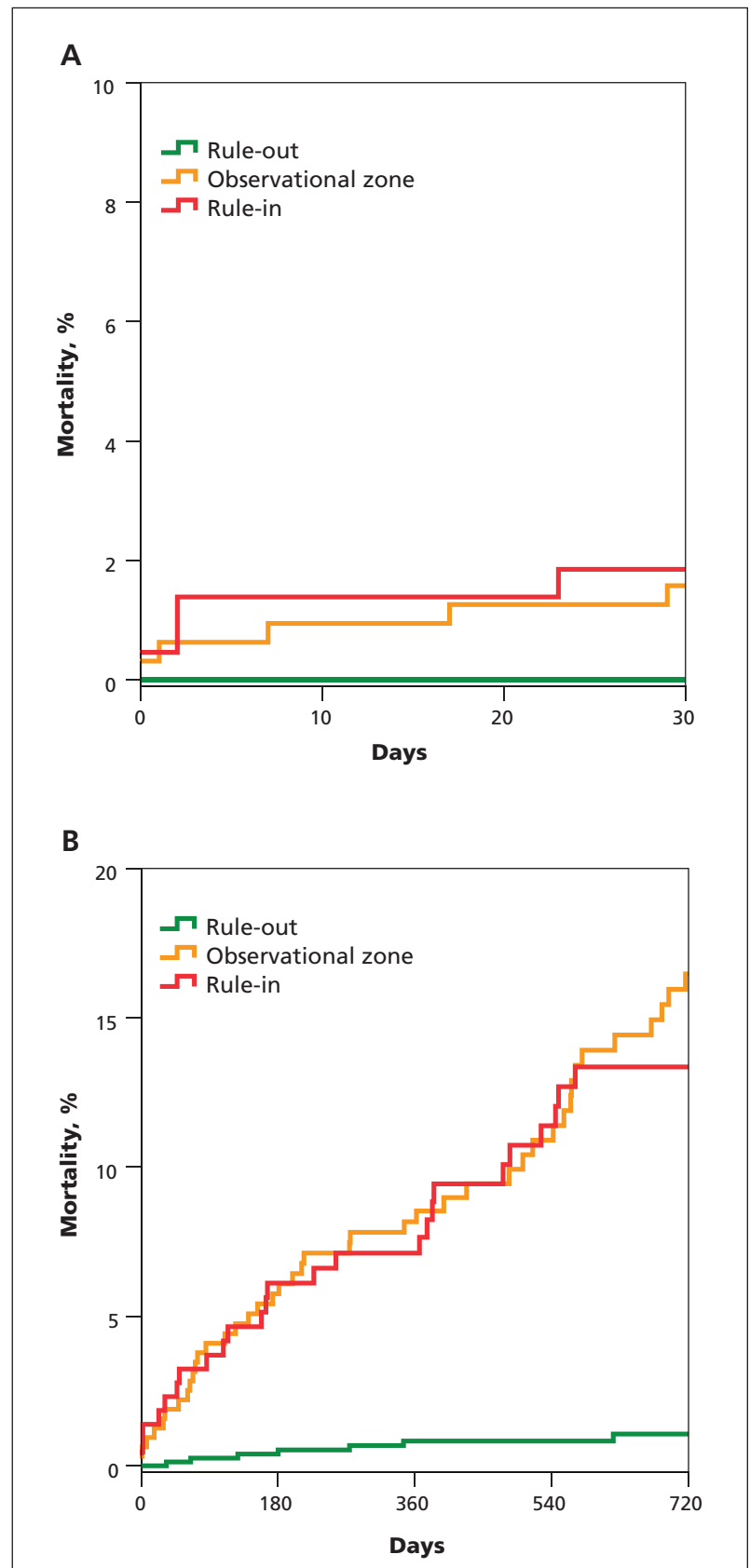

Figure 2: Kaplan–Meier curves showing cumulative mortality within 30 days (A) and 2 years (B) of follow-up according to the classification into "rule-out" (*n* = 786), "observational zone" (*n* = 318) and "rule-in" (*n* = 216) as determined by the high-sensitivity cardiac troponin T 1-hour algorithm.

high-sensitivity cardiac troponin T algorithm, the achievement of this validation study was to transfer this innovative approach from the research setting into the centre of clinical practice. Furthermore, the TRAPID-AMI (High-Sensitivity Cardiac Troponin T Assay for Rapid Rule Out of Acute Myocardial Infarction) study, which was specifically designed to externally validate the performance of the algorithm, has recently been completed. Preliminary results have been presented at the European Society of Cardiology Congress 2014 in Barcelona, Spain, and confirmed the excellent performance of the 1-hour algorithm in an independent cohort.[28]

Due to the poor harmonization among different cardiac troponin assays,[3,6,12] the results of this study cannot be directly extrapolated to other assays. Several ongoing studies are currently developing similar assay-specific 1-hour algorithms with other sensitive and high-sensitivity cardiac troponin assays. As some of these assays have been shown to have similar diagnostic accuracy at presentation as high-sensitivity cardiac troponin T,[6–15] it is likely that they will achieve a similar overall performance.

The medical implications of accelerated rule-in include more rapid initiation of antiplatelet, anticoagulant and anti-ischemic medication, as well as more rapid transfer to coronary angiography and, if feasible, coronary revascularization.[2,3] The medical implications of accelerated rule-out include more rapid relief of patient anxiety and more rapid identification of an alternative cause of acute chest pain without the need for continued rhythm monitoring. The clinical application of the high-sensitivity cardiac troponin T 1-hour algorithm may also lead to substantial economic benefits. It will help to correct the disproportional and inappropriate use of resources in the emergency department.[4,6,29] We hypothesize that the algorithm has the potential to reduce the time to discharge from the emergency department by about 50%. Of course, this hypothesis needs to be tested in dedicated cost-effectiveness studies.

Although the clinical application of the high-sensitivity cardiac troponin T 1-hour algorithm will profoundly affect the management of about 75% of patients, it will not affect or will only marginally affect the management of the 25% of patients assigned the observational zone. Given that the short- and long-term prognosis of the patients in the observational zone is similar to that observed in patients with acute MI, these patients require attention. The optimal management of patients assigned to the observational zone likely will be highly individualized. It may include coronary angiography in patients with a high clinical suspicion of acute MI, coronary CT angiography in patients with low-to-intermediate likelihood for acute MI, a third high-sensitivity cardiac troponin sample at 3 or 6 hours in many patients, or no further immediate diagnostic testing when complete clinical evaluation has established a different final diagnosis (e.g., rapid atrial fibrillation or hypertensive crisis).[2,3,6]

It might be possible to further simplify the rule-out process in patients with very low (undetectable) high-sensitivity cardiac troponin levels.[30–32] Recent evidence from 3 large studies indicated a very high negative predictive value for acute MI in patients with very low (undetectable) high-sensitivity cardiac troponin levels even without any serial sampling.[30–32]

Limitations

Potential limitations of the present study merit consideration. First, the comparison against a gold standard diagnosis adjudicated by 2 independent cardiologists according to a universal definition of acute MI is a very stringent methodology for this research objective. Although the universal definition of acute MI is the undisputed reference to use, it may create an incorporation bias in favour of all elements that are used in it, most importantly cardiac troponin levels.[33] This inherent incorporation bias also affects this study, as well as all previous and future studies in this setting,[7–27] and may have led to an overestimation of the diagnostic accuracy of the proposed algorithm.[33]

Second, our study involved patients presenting to the emergency department with symptoms suggestive of acute MI. Additional studies, for example, involving patients presenting to a general practitioner, are required to learn whether this algorithm would also be safe and effective in patients with lower pretest probability.

Third, the data presented were obtained in a blinded diagnostic study; studies are warranted to apply the algorithm prospectively for clinical decision-making and to assess its cost-effectiveness. Although a randomized controlled trial (RCT) would provide additional insights, it would also be associated with several limitations due to its open design, the definition of "standard of care" in the control group and selection bias. Based on our previous experience conducting an RCT in this setting,[26] we expect that the percentage of patients declining participation in an RCT would be much higher than the percentage of patients currently declining participation in this diagnostic study. Thereby, the generalizability of the data of any future RCT may be limited by substantial challenges to obtain informed patient consent and the possible resulting bias regarding the characteristics of patients finally enrolled. In a previous study,

this effect was so large that the observed event rate was only half the expected rate.[26]

Fourth, one quarter of the cohort had to be excluded from the analysis because of missing values after 1 hour. Even though baseline characteristics were similar in patients with and without a sample after 1 hour (Appendix 1, supplemental table 1), we cannot exclude a selection bias.

Fifth, we used one specific high-sensitivity cardiac troponin assay for validation of the algorithm. Different sensitive and highly sensitive assays vary considerably with regard to the amount of patients detected with elevated troponin levels. We hypothesize that similar algorithms can be developed for other high-sensitivity cardiac troponin assays,[34] but this first requires similar derivation and validation in patients with chest pain.

Conclusion

This rapid strategy incorporating high-sensitivity cardiac troponin T baseline values and absolute changes within the first hour substantially accelerated the management of suspected acute MI by allowing safe rule-out as well as accurate rule-in of acute MI in 3 out of 4 patients.

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