

Simplified Predictive Instrument to Rule Out Acute Coronary Syndromes in a High-Risk Population

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Background—It is unclear whether diagnostic protocols based on cardiac markers to identify low-risk chest pain patients suitable for early release from the emergency department can be applied to patients older than 65 years or with traditional cardiac risk factors.

Methods and Results—In a single-center retrospective study of 231 consecutive patients with high-risk factor burden in which a first cardiac troponin (cTn) level was measured in the emergency department and a second cTn sample was drawn 4 to 14 hours later, we compared the performance of a modified 2-Hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Using Contemporary Troponins as the Only Biomarker (ADAPT) rule to a new risk classification scheme that identifies patients as low risk if they have no known coronary artery disease, a nonischemic electrocardiogram, and 2 cTn levels below the assay's limit of detection. Demographic and outcome data were abstracted through chart review. The median age of our population was 64 years, and 75% had Thrombosis In Myocardial Infarction risk score ≥ 2 . Using our risk classification rule, 53 (23%) patients were low risk with a negative predictive value for 30-day cardiac events of 98%. Applying a modified ADAPT rule to our cohort, 18 (8%) patients were identified as low risk with a negative predictive value of 100%. In a sensitivity analysis, the negative predictive value of our risk algorithm did not change when we relied only on undetectable baseline cTn and eliminated the second cTn assessment.

Conclusions—If confirmed in prospective studies, this less-restrictive risk classification strategy could be used to safely identify chest pain patients with more traditional cardiac risk factors for early emergency department release. (*J Am Heart Assoc.* 2015;4:e002351 doi: 10.1161/JAHA.115.002351)

Key Words: acute coronary syndromes • chest pain • coronary disease • emergency department • risk classification

A minority of the 8 million patients who present each year to US emergency departments (EDs) with chest pain will be diagnosed with acute coronary syndromes (ACS).¹ The purpose of the initial evaluation of these patients is to distinguish between those with and those without immediately life-threatening conditions.

Although not yet available in the United States, high-sensitivity cardiac troponin (hs-cTn) assays have made it possible to rule out acute myocardial infarction (MI) rapidly on ED arrival.^{2–5} Despite the increased sensitivity of cTn assays,

there are still cases of biomarker-negative ACS,⁶ and many patients without acute MI are observed or admitted for stress testing for additional risk stratification after initial exclusion of MI. For that reason, cTn assays have been combined with the electrocardiogram (ECG) and clinical parameters to create accelerated diagnostic protocols (ADPs) that seek to identify patients for whom early discharge without further testing is safe.

One of the most evaluated ADPs is the rule studied in the 2-Hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Using Contemporary Troponins as the Only Biomarker (ADAPT) trial. The ADAPT study showed that patients with a Thrombosis In Myocardial Infarction (TIMI) risk score (TRS) of 0, without ischemic ECG changes, and with sensitive cTn assays below the 99th percentile on 2 assessments 2 hours apart were at only a 0.3% risk of 30-day major cardiac events.⁷ The ADAPT rule identified 20% of patients as low risk and potentially appropriate for ED discharge.

Because the ADAPT study enrolled relatively young patients (mean age 60) with few cardiac risk factors (TRS ≤ 1 in 44% of patients), it is unclear whether the ADAPT rule will be effective in older cohorts and/or those with more traditional cardiac risk factors and, if it is, whether it would identify a substantial number of patients at low risk.

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Thus, we tested a simple risk stratification strategy in a cohort of patients with multiple cardiac risk factors. We hypothesized that patients older than 65 years and/or with traditional cardiac risk factors would have 30-day event rates that were similar to those of patients identified as low risk by ADAPT if they had conventional cTn levels below the limit of detection (LOD) of the assay on presentation and 4 to 14 hours later, no clear ischemic changes on ECG at presentation and no history of coronary artery disease (CAD). We used the LOD of the assay rather than the 99th percentile (as used in ADAPT) to augment the sensitivity of the cTn component of the rule and to offset the reduction in sensitivity that would come from including as low risk patients with traditional cardiac risk factors and concerning chest pain histories. As proof-of-concept for our risk classification scheme, we retrospectively applied it to our cohort and compared its performance to a modified ADAPT rule.

Methods

Study Design and Setting

We performed a single-center, retrospective cohort study to assess operating characteristics of a simple risk stratification strategy that consisted of (1) no known history of CAD, (2) a nonischemic ECG on presentation, and (3) cTn levels below the LOD of the assay at presentation and 4 to 14 hours later. The study was performed at the Durham Veterans Affairs Medical Center (VAMC), a 271-bed tertiary care hospital in Durham, NC, serving 200 000 patients. The research protocol was approved by the Durham VAMC institutional review board with a waiver of informed consent and Health Insurance Portability and Accountability Act of 1996 authorization.

Participants

Data were abstracted through chart review from 246 consecutive patient care episodes involving 231 individual patients between January 1, 2012, and December 31, 2012, during which a first cTn sample was drawn in the ED and a second cTn sample was drawn 4 to 14 hours later. Only a patient's first presentation was included for analysis; 15 patient care episodes were repeat presentations and were excluded. The Durham VAMC uses a Siemens Dimension VISTA cTnI assay, which has a lower LOD of 0.015 ng/mL. The upper limit of normal (99th percentile) is 0.045 ng/mL, and the % cardiovascular at the 99th percentile is 10%.

Data were collected retrospectively by using the VAMC Computerized Patient Record System. Demographic data, including the presence or absence of CAD and data related to the patient's presenting chest pain episode, were collected through manual chart review from solely the ED documenta-

tion, to better approximate the conditions under which this risk stratification scheme would be used. Specific demographic data collected included preexisting CAD, age, family history of premature CAD, hypertension (taking antihypertensive medications or having a diagnosis of hypertension), hyperlipidemia (taking a statin or having a diagnosis of hyperlipidemia), active tobacco abuse, diabetes mellitus, obesity (body mass index >30 kg/m²), and current aspirin use. Variables related to patient presentation included cTnI value at presentation and 4 to 14 hours later, ECG at presentation (scored as clearly ischemic, indeterminate, and normal), and chest pain history (scored as clearly consistent with angina, somewhat consistent with angina, and inconsistent with angina). Follow-up data (including MI, death, cause of death, percutaneous coronary intervention, coronary artery bypass graft surgery, and stress testing) were collected at 30 days and 6 months through review of patient notes within the VAMC medical record. The VAMC's computerized records system has $>98\%$ sensitivity for recording death, compared with the National Death Index.⁸ For all patients without a 30-day event on VAMC records, notes from subsequent visits were reviewed to identify any events that were treated at a facility outside the VA within 30 days after the index visit. This was a retrospective analysis of data collected in the context of routine clinical care. Treating physicians were given no guidance regarding care of the patients and no assistance in determining risk of ACS.

Index Tests

The prespecified risk classification strategy we investigated consisted of (1) no known history of CAD before presentation, (2) a nonischemic ECG, and (3) 2 cTn levels below the LOD (0.015 ng/mL) of the assay (at baseline and at 4 to 14 hours). For a patient to be classified as low risk, all 3 criteria had to be negative. History of CAD was defined as prior MI, prior percutaneous intervention or coronary artery bypass graft surgery, or typical symptoms with positive noninvasive testing or invasive imaging for CAD; if none of these findings were documented in the ED provider's note, the patient was classified as not having known CAD. A nonischemic ECG was defined by the absence of ST-segment depression or elevation of ≥ 0.5 mV in ≥ 2 contiguous leads; prior ECGs were not reviewed. The ADAPT rule was applied to our cohort as described,⁷ but first and second cTn values were used, regardless of the time they were collected. For use in the ADAPT algorithm, a negative troponin was defined as <0.05 ng/mL, the 99th percentile for the assay. In addition to testing these schema, we performed a sensitivity analysis to determine the potential applicability of our risk stratification strategy to an ADP. In the sensitivity analysis, rather than testing a strategy that involved cTn samples drawn at

presentation and 4 to 14 hours later, our strategy involved only (1) no known history of CAD before presentation, (2) a normal ECG, and (3) presentation cTn level below the LOD of the assay.

Reference Standard

The primary end point was a composite of major adverse cardiac events that occurred within 30 days of ED presentation. Adverse events included death (unless there was a clear noncardiac cause), any revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery), or acute MI. Acute MI was defined consistent with the Third Universal Definition of MI,⁹ requiring evidence of myocardial necrosis along with clinical evidence of myocardial ischemia. Consistent with the Third Universal Definition of MI, necrosis was defined as ≥ 1 cTn value above the 99th percentile (0.05 ng/mL) with evidence of a rising and/or falling pattern (Δ cTn $>20\%$); clinical evidence of myocardial ischemia was defined as a typical or atypical chest pain syndrome, potentially ischemic ECG changes (either on presentation or later), evidence of myocardial ischemia on stress testing, hemodynamically significant coronary artery stenosis, or a revascularization procedure. A true positive stress test was defined as a positive stress test followed by cardiac catheterization revealing significant CAD.

Statistical Analysis

Baseline characteristics of the patients were analyzed with the use of conventional descriptive statistics. Age was recorded as a continuous variable; median and SD are reported. All other characteristics were recorded as categorical variables, and the raw percentages of patients with and without the characteristic are reported. Sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) were also calculated for each test. Sensitivity was calculated by dividing the number of patients with true-positive tests by the total number of patients with a cardiovascular event at 30 days; specificity was calculated by dividing the number of patients with true-negative tests by the total number of patients without a cardiovascular event at 30 days. NPV was calculated by dividing the number of patients with true-negative tests from the total number of patients identified as low risk; PPV was calculated by dividing the number of patients with true-positive tests from the total number of patients identified as high risk. The CIs for diagnostic test performance indices were calculated by using the exact method.¹⁰ The comparison of risk classification by ADAPT versus our new classification strategy in those who received a cardiac testing procedure was performed by using Fisher's exact test. All statistical

analysis was performed by using SAS version 9.2 (SAS Institute).

Results

Patient Characteristics

Two hundred thirty-one patients were studied, of whom 95% were men. They had high rates of preexisting cardiovascular risk factors, and 52% had known CAD at the time of ED presentation (Table 1).

Consistent with their advanced age and cardiovascular risk factors, the patients tended to have high TRS; only 10% (n=23) had TRS of 0, and 25% (n=58) had TRS ≤ 1 (Figure 1).

A total of 47 (20%) patients had a cardiovascular event in the 30 days after their ED visit; 18 events were revascularization alone, 13 were MI alone, 9 were both, 2 were fatal MIs, and 5 were other cardiovascular deaths. The ADAPT rule (modified to incorporate cTnI on presentation and at 4 to 14 hours, rather than on presentation and at 2 hours) identified 7.8% (n=18) of patients as low risk, and our classification strategy (no CAD, a nonischemic ECG, and 2 cTnI determinations below LOD) identified 22.9% (n=53) of patients as low risk.

Diagnostic Performance

Table 2 describes the performance of our expanded classification strategy and the modified ADAPT rule for predicting 30-day events in our cohort. Of the 47 patients who developed a cardiovascular event, 46 (sensitivity 98%, 95% CI 89% to 100%) were correctly identified as high risk based on our classification scheme. Further, the classification scheme identified 53 patients as low risk, of whom 52 did not have

Table 1. Baseline Characteristics of the Cohort by Low and High Risk of cardiovascular Disease

Characteristic	Overall (N=231)	Low Risk* (n=53)	High Risk* (n=178)
Age, y	66 \pm 10.4	62 \pm 8.7	67 \pm 10.7
History of CAD	120 (52%)	0 (0%)	120 (67%)
Diabetes	105 (45%)	17 (32%)	88 (49%)
Hypertension	208 (90%)	44 (83%)	164 (92%)
Hyperlipidemia	166 (72%)	29 (55%)	137 (76%)
Smoking	51 (22%)	14 (26%)	37 (21%)
Obesity [†]	100 (43%)	20 (38%)	80 (45%)

BMI indicates body mass index; CAD, coronary artery disease; cTn, cardiac troponin; LOD, limit of detection.

*Low risk is defined as (1) no known history of CAD, (2) a nonischemic ECG on presentation, and (3) cTn levels below the LOD of the assay at presentation and 4 to 14 hours later. High risk is defined as either (1) known history of CAD, (2) ischemic ECG on presentation, or (3) cTn level above the LOD of the assay either at presentation or 4–14 hours later.

[†]Obesity is defined as BMI >30 mg/kg².

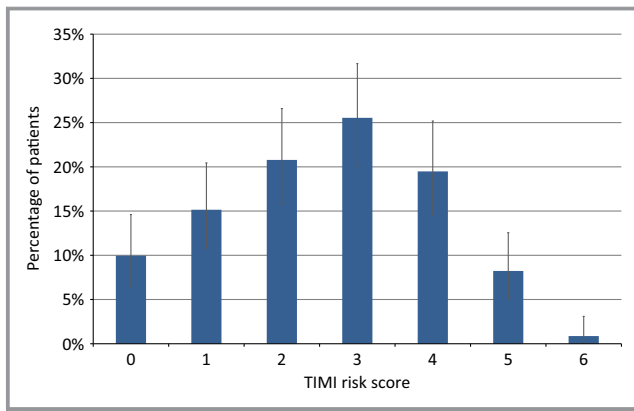


Figure 1. Median TIMI risk score in the cohort was 3; 25% of patients had a TIMI risk score of 0 or 1. Shown is percentage of patients at each TRS strata; error bars represent 95% CI. TIMI indicates thrombosis in myocardial infarction; TRS, TIMI risk score.

an adverse cardiac event within 30 days (NPV 98%, 95% CI 90% to 100%). The specificity was poor, with 132 (72%) of the 184 patients without an event being labeled as high risk. The modified ADAPT rule correctly identified all 47 patients who developed ACS as high risk (sensitivity 100%) but identified only 18 patients as low risk, of whom none had an event (NPV 100%). As with the expanded classification strategy, the specificity for ADAPT was poor, with 166 (90%) of 184 event-free patients being labeled as high risk. Our classification strategy concurred on 15 of the 18 patients ADAPT identified as low risk. We identified an additional 38 patients as being low risk, of whom 1 patient experienced a revascularization procedure within 30 days of hospital admission.

Application of Risk Classification Strategies to the Cohort

To examine the clinical relevance of our classification strategy, we determined how many procedures might have been avoided in our cohort had all patients identified as low risk been discharged without further testing. We found that many of the patients identified as low risk by our strategy (24/53, 45%) underwent stress testing or cardiac catheterization during the index hospitalization. Had every patient identified as low risk by our rule been discharged before further testing, 27% (24/89) of stress tests and left heart catheterizations performed in our cohort would not have been performed (9 patients underwent both stress testing and catheterization). One patient identified by our strategy as low risk had a true-positive stress test and subsequently underwent revascularization; no other patient had a true-positive stress test or left heart catheterization demonstrating significant CAD. No patient identified as low risk by our strategy had a positive stress test without further evaluation by cardiac catheterization. Discharging all patients identified as low risk

Table 2. Comparison of a New Classification Strategy With Troponins at 2 Time Points Versus the ADAPT Score

	New Risk Score, 2 cTnI Measures	
	Low Risk	High Risk
Patients with no cardiovascular event in 30 days		
ADAPT		
Low risk	37	3*
High risk	15 [†]	129
Patients with cardiovascular event in 30 days		
ADAPT		
Low risk	0	0 [†]
High risk	1*	46

ADAPT indicate 2-Hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Using Contemporary Troponins as the Only Biomarker.

The ideal score would identify all patients without an event as low risk and all patients with an event as high risk. cTnI indicates cardiac troponin I.

*Identify the number of patients where the comparator score correctly identified patients but the new score did not.

[†]Identify the number of patients where the new risk score appropriately identified patients and the comparator did not.

by ADAPT would have prevented 4 (4.5%) of the cardiac testing procedures, fewer than by using the new strategy ($P<0.0004$ compared with our strategy by Fisher's exact test) (Figure 2).

Sensitivity Analysis of a Strategy Incorporating Only Troponin at Presentation

To determine whether our risk stratification strategy may have applicability as an ADP, we performed a sensitivity analysis, adjusting our risk classification strategy to include only a single cTn level at presentation below the LOD of the assay, along with no known history of CAD prior to presentation and a nonischemic ECG. This adjusted risk stratification strategy identified 25.5% ($n=59$) of patients as low risk (Table 3). Similar to the original risk stratification strategy, of the 47 patients who developed a cardiovascular event within 30 days, the adjusted strategy identified as high risk 46 patients (sensitivity 98%, 95% CI 89% to 100%); of the 59 low-risk patients, 58 did not have an adverse cardiac event within 30 days (NPV 98%, 95% CI 91% to 100%). Adjusting the ADAPT rule to include only troponin at presentation identified 14.3% ($n=33$) of patients as low risk; of these 33 low-risk patients, 32 did not have an adverse cardiac event within 30 days (NPV 97%, 95% CI 84% to 100%).

Discussion

In this retrospective cohort study performed in an older population (mean age >65) with multiple cardiac risk factors

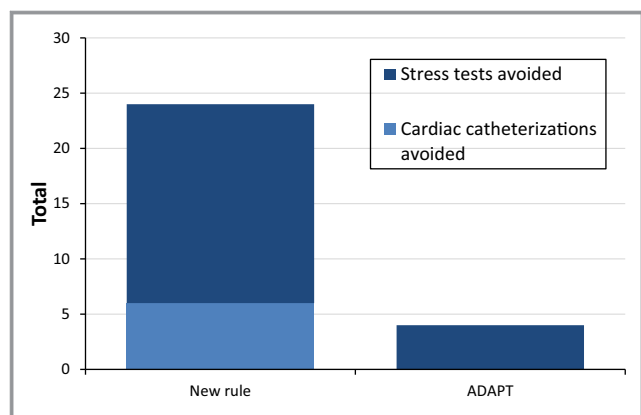


Figure 2. Universal application of the new risk assessment rule would have prevented 24 cardiac procedures had all patients identified as low risk been discharged prior to further testing, significantly more than would have been avoided by universal application of the ADAPT rule. ADAPT indicate 2-Hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Using Contemporary Troponins as the Only Biomarker.

presenting to the ED with concern for ACS, we found that a simple risk classification strategy that incorporated a cTn value below the LOD at baseline and after 4 to 14 hours, ECG without ischemic changes, and no history of CAD identified a substantial percentage (22.9%) of patients at low risk for 30-day cardiac events with high sensitivity and NPV. Applying this strategy to a patient population with a lower preexisting rate of CAD would likely enable even more patients to be categorized as low risk with similar sensitivity.

Those patients identified as low risk by our study are potentially appropriate for discharge from the ED without

Table 3. Comparison of the New Classification Strategy With Troponins at 2 Time Points Versus the New Classification Strategy With Troponins at Baseline Only

	New Risk Score, 2 cTn Measures	
	Low Risk	High Risk
New risk score using baseline cTn only		
Patients with no cardiovascular event in 30 days		
Low risk	52	6*
High risk	0†	126
Patients with cardiovascular event in 30 days		
Low risk	1	0†
High risk	0*	46

The ideal score would identify all patients without an event as low risk and all patients with an event as high risk. cTnI indicates cardiac troponin I.

*Identify the number of patients where the new score using baseline cTnI only correctly identified patients but the new score using 2 cTnI measurements did not.

†Identify the number of patients where the new risk score using 2 cTnI measurements correctly identified patients but the new risk score using baseline cTnI only did not.

admission for additional testing; in our population, more than one-fourth of all cardiac procedures performed potentially could have been avoided. Application of this strategy could have a substantial impact on health services utilization by decreasing the need for inpatient procedures.

Whether any risk stratification tool is sufficiently sensitive to be used in clinical practice is highly dependent on the preferences of the provider. ED physicians display significant variability in their tolerance for missed diagnoses of ACS, although a majority prefer a miss rate $\leq 1\%$.¹¹ However, a miss rate this low may not be feasible in clinical practice: In a large, multicenter cohort of patients with acute chest pain receiving standard ED care, the miss rate for ACS was 2.1%.¹² There was no significant difference in unadjusted or adjusted mortality between patients with a missed diagnosis of MI or unstable angina and those correctly diagnosed (adjusted risk ratio 1.9, 95% CI 0.7 to 5.2 for MI; adjusted risk ratio 1.7, 95% CI 0.2 to 52 for unstable angina), although the point estimates suggested a signal toward higher mortality in those with a missed diagnosis and the 95% CIs were wide.¹² Though there is potential harm associated with a missed diagnosis of ACS and failure to institute prompt treatment, individual providers must balance this risk with the risks of overdiagnosis and further testing.

Compared with a modified version of ADAPT, a high-sensitivity rule validated in a population with fewer traditional cardiac risk factors and higher percentage of patients with low TIMI risk scores,⁷ our new rule identified a larger percentage of patients in our cohort as low risk with similar sensitivity and NPV. Our rule differs from ADAPT and similar risk prediction rules in its elimination of cardiac risk factors and chest pain history from consideration in favor of an increased focus on cTn and ECG. The sensitivity our strategy sacrifices in comparison to other risk classification schemes by enabling patients with cardiovascular risk factors and concerning chest pain histories to be categorized as low risk is offset by the increased sensitivity conferred by its more stringent limit on cTn values. Using a lower cut-off for a positive test may also allow early-presenting patients with evolving MIs to be appropriately characterized as high risk, even before cTn values rise above the 99th percentile. Further, among stable patients without CAD, hs-cTn values increase in conjunction with an increasing burden of several cardiovascular risk factors,¹³ raising the possibility that setting a lower troponin threshold helps eliminate patients with these risk factors. As hs-cTn assays become widely available in clinical practice, the cut-offs chosen for a “positive” test will have important implications on test performance.

The performance of cardiac risk factors and chest pain history in diagnosing ACS is limited in comparison to cTn and ECG,¹⁴ and these findings further reinforce their limitation. In addition to enabling more patients to be classified as low risk,

elimination of these variables from our rule allows a simplified stratification scheme that is easy to apply.

This study has some limitations. First, performance of the study at a single center with a single cTn assay may limit the broader applicability of our risk classification scheme. However, despite coming from a single institution, our cohort was treated by a broad and varied group of physicians with different approaches to the management of patients presenting with concern for ACS. The ED is staffed by a combination of trained ED physicians, internists, and moonlighting subspecialty fellows. The internal medicine service to which patients with chest pain are admitted is staffed by nearly 100 residents and interns supervised either by 1 of 10 hospitalists or by one of a number of internists with subspecialty training in fields such as infectious diseases or rheumatology. Second, our study population was 95% male and composed entirely of veterans, many of whom have a high burden of cardiac risk factors. This population was chosen deliberately, as it is one that is not well-represented in studies of existing risk prediction tools that identify a large number of patients at low risk for coronary events in populations with a “standard” burden of cardiac risk factors. Still, before this risk classification scheme could be applied to women, a generally lower-risk population, or a population at another center that uses a different cTn assay, it would need to be tested more broadly.

Third, the study does not test an ADP, as the second cTn test was drawn between 4 and 14 hours after patient presentation. However, given the ability of modern cTn assays to detect low-level elevations in cTn, it is likely that collecting a second cTn sample 2 hours after presentation would not change the results, though this would need to be confirmed prospectively. Indeed, in a sensitivity analysis, changing our classification strategy to require only a single cTn value at presentation below the LOD of the assay (an approach that would theoretically allow for ACS to be ruled out immediately on ED arrival) had no effect on sensitivity or negative predictive value and enabled 25% of patients to be characterized as low risk. This suggests that an ADP based on our risk classification scheme, with patients defined as low risk if they have no prior CAD, a nonischemic ECG, and 2 cTn values below the LOD of the assay at baseline and 2 hours after presentation, may have adequate sensitivity to rule out ACS in a considerable cohort of patients with a high burden of cardiac risk factors.

Last, the retrospective design could be problematic in a diagnostic study, as the information our risk assessment protocol used to determine risk was also available to the clinicians making care decisions. Though the simplicity and availability of the elements of our rule allow for easy application in clinical practice, this simplicity and availability also may have allowed physicians treating the patients included in the study to intuitively assess the patients’ risk

and avoid testing in low-risk patients. Patients identified as low risk based on our rule may have been less likely to undergo stress testing or cardiac catheterization than were patients not identified as low risk; thus, the ability to detect ACS in these patients may have been reduced. This is an unavoidable consequence of the design of our study, in which physicians treated patients according to their best clinical judgment and had access to the same clinical variables as were included in our risk prediction scheme. Moreover, without standardized troponin collection times, the ADAPT rule could not be applied to our cohort exactly as it was applied in its derivation study.

For all of these reasons, our results should be considered hypothesis generating and will need confirmation in prospective studies in which patients are treated according to a specific protocol, rather than according to their physician’s best clinical judgment.

Conclusions

This retrospective cohort study demonstrated that a predictive rule categorizing as low risk patients with no prior CAD, a nonischemic ECG, and 2 cTn values below the LOD of the assay identifies 23% of patients as low risk for 30-day cardiac events and potentially appropriate for early ED discharge with >98% NPV. If confirmed by prospective studies, this new risk assessment strategy could substantially reduce the number of stress tests performed, and an ADP based on this strategy could potentially identify patients for early ED discharge, reducing ED lengths of stay and costs related to caring for patients with acute chest pain.

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Disclosures

None of the authors have conflicts of interest to report relative to this manuscript.

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