Background: High-sensitivity cardiac troponin (hs-cTn) assays seem to improve the early diagnosis of acute myocardial infarction (AMI), but it is unknown how to best use them in clinical practice. Our objective was to develop and validate an algorithm for rapid rule-out and rule-in of AMI.

Methods: A prospective multicenter study enrolling 872 unselected patients with acute chest pain presenting to the emergency department. High-sensitivity cardiac troponin T (hs-cTnT) was measured in a blinded fashion at presentation and after 1 hour. The final diagnosis was adjudicated by 2 independent cardiologists. An hs-cTnT algorithm incorporating baseline values as well as absolute changes within the first hour was derived from 436 randomly selected patients and validated in the remaining 436 patients. The primary prognostic end point was death during 30 days of follow-up.

Results: Acute myocardial infarction was the final diagnosis in 17% of patients. After applying the hs-cTnT algorithm developed in the derivation cohort to the validation cohort, 259 patients (60%) could be classified as “rule-out,” 76 patients (17%) as “rule-in,” and 101 patients (23%) as in the “observational zone” within 1 hour. Overall, this resulted in a sensitivity and negative predictive value of 100% for rule-out, a specificity and positive predictive value of 97% and 84%, respectively, for rule-in, and a prevalence of AMI of 8% in the observational zone group. Cumulative 30-day survival was 99.8%, 98.6%, and 95.3% (P < .001) in patients classified as rule-out, observational zone, and rule-in, respectively.

Conclusions: Using a simple algorithm incorporating hs-cTnT baseline values and absolute changes within the first hour allowed a safe rule-out as well as an accurate rule-in of AMI within 1 hour in 77% of unselected patients with acute chest pain. This novel strategy may obviate the need for prolonged monitoring and serial blood sampling in 3 of 4 patients.


Patients with symptoms suggestive of acute myocardial infarction (AMI) account for approximately 10% of all emergency department (ED) consultations.1 Electrocardiography (ECG) and cardiac troponin (cTn) assay form the diagnostic cornerstones and complement clinical assessment.2-4 A limitation of former-generation cTn assays is a delayed increase of circulating levels for 3 to 4 hours, often requiring serial sampling for 6 to 12 hours.2,3,5 Delays in diagnosing disease ("rule-in") holds back prompt use of evidence-based therapies.2,3 Delays in excluding disease ("rule-out") interferes with evaluation of alternative diagnoses and contributes to expensive overcrowding in the ED.6

The recently developed sensitive and high-sensitivity cardiac troponin (hs-cTn) assays have enabled measurement of cTn concentrations not reliably detected with prior generations of tests.7 The new tests have been shown to improve the diagnostic accuracy in the early diagnosis of AMI, and it has been suggested that rule-in and rule-out of AMI might be feasible more rapidly with the new tests.8-10 Improvements in assay sensitivity, on the other hand, have significantly increased the number of positive hs-cTn test results in various acute and chronic conditions with cardiac involvement other than AMI.11-14 As a consequence, the positive predictive value (PPV) of an elevated hs-cTn level has decreased8,9,15,16 and many physicians treating patients with symptoms suggestive of AMI have been confused.17

See Invited Commentary at end of article

Author Affiliations are listed at the end of this article.
It is currently unknown how to best take advantage of the novel hs-cTn tests in clinical practice. Accordingly, there is an ongoing debate whether and to what extent a shortening of the time interval to the second sample is feasible and safe. The aim of our study therefore was to develop and validate an algorithm for rapid rule-in and rule-out of AMI using high-sensitivity cardiac troponin T (hs-cTnT) baseline levels and absolute changes within 1 hour.

STUDY DESIGN AND POPULATION

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international multicenter study designed and coordinated by the University Hospital Basel (clinicaltrials.gov Identifier: NCT00470587). From April 2006 to June 2009, a total of 1247 unselected patients presenting to the ED with acute chest pain symptoms suggestive of AMI such as acute chest pain and angina pectoris with an onset or peak within the last 12 hours were recruited. 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. Written informed consent was obtained from all patients.

Patients with ST-segment elevation myocardial infarction (n=50) were excluded from this analysis because cardiac biomarkers are of limited clinical value in these patients. Among the remaining 1197 patients, samples at presentation as well as after 1 hour for measurement of hs-cTnT were available in 872 patients. The most common reasons for missing values after 1 hour (n=327) were early transfer to the catheterization laboratory or coronary care unit and diagnostic procedures around the 1-hour window that precluded blood draw at 1 hour, but not the draw of future follow-up samples. No differences in baseline characteristics were found between patients with and without a sample after 1 hour (eTable; http://www.archintemed.com).

ROUTINE CLINICAL ASSESSMENT

All patients underwent an initial clinical assessment that included clinical history, physical examination, 12-lead ECG, continuous ECG-monitoring, pulse oximetry, standard blood tests, and chest radiography. Timing and treatment of patients were left at discretion of the attending physician.

INVESTIGATIONAL hs-cTnT ANALYSIS

Blood samples for determination of hs-cTnT (Roche Diagnostics) were collected in serum tubes at presentation to the ED. Additional samples were collected after 1, 2, 3, and 6 hours. Serial sampling was discontinued when the diagnosis of AMI was certain and treatment required transferring the patient to the catheterization 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 dedicated core laboratory. For hs-cTnT, 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. Glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula.

ADJUDICATED FINAL DIAGNOSIS

To determine the final diagnosis for each patient, adjudication of final diagnoses was performed centrally in the core laboratory (University Hospital Basel) for all patients according to levels of hs-cTnT. More specifically, 2 independent cardiologists (T.R., M.R., P.H., and M.P.) reviewed all available medical records (including patient history, physical examination, results of laboratory testing including hs-cTnT levels, radiologic testing: ECG, echocardiography, cardiac exercise test, lesion severity, and morphology in coronary angiography) pertaining to the patient from the time of ED presentation to 60-day follow-up. In situations of diagnostic disagreement, cases were reviewed and adjudicated in conjunction with a third cardiologist (C.M.).

Acute myocardial infarction was defined and hs-cTnT levels interpreted as recommended in current guidelines. In brief, AMI was diagnosed when there was evidence of myocardial necrosis with a notable rise and/or fall in a clinical setting consistent with myocardial ischemia. The 99th percentile (14 ng/L) was used as cutoff for myocardial necrosis. Absolute cTn changes were used to determine significant changes based on the diagnostic superiority of absolute over relative changes.

On the basis of the biological variation of cTnT as well as on data from previous chest pain cohort studies, a significant absolute change was defined as a rise or fall of at least 10 ng/L within 6 hours, or, in an assumption of linearity, as an absolute change of 6 ng/L within 3 hours, 4 ng/L within 2 hours, or 2 ng/L within 1 hour. If discordant findings occurred, the longest time interval available was required to fulfill the change criteria.

Unstable angina (UA) was diagnosed in patients with normal hs-cTnT levels or stable elevations of hs-cTnT levels not fulfilling the criteria for AMI and typical angina at rest, in patients with a deterioration of a previously stable angina, in cases of positive cardiac exercise testing or cardiac catheterization with coronary arteries found to have a stenosis of 70% or greater, and in ambiguous cases in which follow-up information revealed AMI or a sudden unexpected cardiac death within 60 days. Further predefined diagnostic categories included cardiac symptoms of origin other than coronary artery disease (CAD) with cardiomyocyte damage (absence of overt CAD and conditions such as myocarditis, apical ballooning syndrome, acute heart failure or tachyarrhythmias), cardiac symptoms of origin other than CAD without cardiomyocyte damage (eg, pericarditis, hypertensive urgency, tachyarrhythmias, acute heart failure), and noncardiac chest pain. If AMI was excluded in the ED according to the hs-cTnT assay, but no sufficient further diagnostic procedures were performed for conclusive diagnosis, symptoms were classified as to be of unknown origin.

FOLLOW-UP AND CLINICAL END POINTS

After hospital discharge, patients were contacted after 3, 12, and 24 months by telephone calls or in written form. Information regarding death was furthermore obtained from the national registry on mortality, the hospital’s diagnosis registry, and the family physician’s records. The primary prognostic end point was 30 days’ all-cause mortality.

ALGORITHM DEVELOPMENT AND VALIDATION

The algorithm for use of hs-cTnT was developed in a randomly selected derivation sample of 436 patients. The algorithm incorporates both baseline hs-cTnT levels and absolute hs-cTnT changes within the first hour. Selection of these 2 parameters was based on the previously published, very high diag-
nostic accuracy of their combination.18,25 Optimal thresholds for rule-out were selected to allow for a 100% sensitivity and negative predictive value (NPV). Optimal thresholds for rule-in were obtained based on a classification and regression tree (CART) analysis.26,27 The CART algorithm provides a sequence of partitions of a given data set aimed at optimizing the prediction of a binary outcome variable. Each subsequent partition is obtained by splitting one of the preceding partition sets (nodes) into 2 parts. If quantitative predictor variables are used, a pair of new nodes is obtained by splitting an existing node at a given threshold value of one of these variables. The algorithm stops if no further improvement is possible or if any further split would violate a predefined criterion (eg, on the minimal node size).26,27 Nodes in the CART tree were constrained to have a minimal number of cases of 20 in parent and child nodes. In addition to baseline hs-cTnT levels and absolute hs-cTnT changes within the first hour, age (as a continuous variable), sex, ECG features (signs of ischemia or not) and time since onset of symptoms (as a continuous variable) were included in the CART model as well. The algorithm developed in the derivation sample was then tested for its diagnostic accuracy in a validation sample consisting of the remaining 436 subjects.

STANDARD ANALYSIS

Continuous variables are presented as mean (standard deviation) or median (interquartile range [IQR]); categorical variables, as numbers and percentages. Differences in baseline characteristics between patients with and without AMI and between patients in the derivation and validation cohort were assessed using the Mann-Whitney test for continuous variables and the Pearson \( \chi^2 \) test for categorical variables.

Survival during 30 days of follow-up according to the classification provided by the hs-cTnT algorithm was plotted in Kaplan-Meier curves, and the log-rank test was used to assess differences in survival between groups. Hazard ratios (HRs) and 95% confidence intervals were obtained from Cox proportional hazard models to quantify the magnitudes of group differences.

All hypothesis testing was 2-tailed, and \( P < .05 \) was considered statistically significant. All statistical analyses were performed using SPSS for Windows 19.0 (SPSS Inc).

RESULTS

CHARACTERISTICS OF PATIENTS

Among the 872 patients presenting to the ED with acute chest pain, the adjudicated final diagnosis was AMI in 147 patients (17%), UA in 104 (12%), cardiac symptoms of origin other than CAD in 128 (15%), noncardiac symptoms in 416 (48%), and symptoms of unknown origin in 77 (9%). Baseline characteristics are given in Table 1.

QUANTITATIVE INTERPRETATION OF hs-cTnT LEVELS

Baseline levels of hs-cTnT were significantly higher in patients with AMI compared with the other final diagnoses (Figure 1). Of all patients, 35% had hs-cTnT baseline levels above the 99th percentile of healthy individuals (14 ng/L). Using this value as a qualitative cutoff for baseline levels to diagnose AMI resulted in a sensitivity of 88%, an NPV of 97%, a specificity of 76%, and a PPV of 43%.

The prevalence of AMI in patients presenting with acute chest pain differed significantly according to quantitative levels of hs-cTnT (Figure 2). In patients with hs-cTnT
levels lower than 14 ng/L (99th percentile of healthy individuals) at presentation, the incidence of AMI was 3.2%, and there was a rise to 21% in patients with levels between 14 and 49 ng/L, 65% in patients with levels between 50 and 99 ng/L, 88% in patients with levels between 100 and 199 ng/L, and 93% in patients with levels of 200 ng/L or higher (P = .49 for comparison of 100-199 ng/L vs ≥200 ng/L; P < .001 for all other comparisons).

**DERIVATION OF THE hs-cTnT ALGORITHM FOR THE DIAGNOSIS OF AMI**

For use in clinical practice, an algorithm incorporating baseline hs-cTnT values as well as absolute hs-cTnT changes within the first hour was developed in a derivation sample of 436 patients. Baseline characteristics of the patients in the derivation and the validation sample were similar and are given in **Table 2**.

**VALIDATION OF THE hs-cTnT ALGORITHM FOR THE DIAGNOSIS OF AMI**

The algorithm was then tested in a validation sample of the remaining 436 subjects. The performance indices of the final algorithm in the derivation cohort, the validation cohort, and the overall cohort are given in **Table 3**, and the final algorithm and its performance in the validation cohort is depicted in **Figure 3**.

After applying the hs-cTnT algorithm to the validation cohort, 259 patients (60%) could be classified as “rule-out.” No patient with AMI was missed, and sensitivity and NPV accordingly were 100%. Seventy-six patients (17%) were classified as “rule-in,” which resulted in a specificity and PPV of 97% and 84%, respectively. Doing so, 64 of 72 patients (89%) with AMI were ruled in after 1 hour. The final adjudicated diagnoses in patients falsely ruled in for AMI (n = 12) based on the algorithm

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**Table 2. Baseline Characteristics of the Patients in the Derivation and Validation Cohort**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Derivation Cohort (n = 436)</th>
<th>Validation Cohort (n = 436)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>65 (52-75)</td>
<td>63 (50-75)</td>
<td>.01</td>
</tr>
<tr>
<td>Male sex</td>
<td>281 (64)</td>
<td>307 (70)</td>
<td></td>
</tr>
<tr>
<td>Risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>295 (68)</td>
<td>263 (60)</td>
<td>.02</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>205 (47)</td>
<td>205 (47)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Diabetes</td>
<td>87 (20)</td>
<td>90 (21)</td>
<td>.80</td>
</tr>
<tr>
<td>Current smoking</td>
<td>107 (25)</td>
<td>94 (22)</td>
<td>.30</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>164 (38)</td>
<td>156 (38)</td>
<td>.57</td>
</tr>
<tr>
<td>History of smoking</td>
<td>150 (34)</td>
<td>170 (39)</td>
<td>.16</td>
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<tr>
<td>History of smoking</td>
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<td></td>
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<tr>
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<tr>
<td>History of smoking</td>
<td>150 (34)</td>
<td>170 (39)</td>
<td>.16</td>
</tr>
</tbody>
</table>

Abbreviations: ECG, electrocardiogram; IQR, interquartile range.

*Data are presented as number (percentage) unless otherwise specified.*

For “rule-out” of AMI, the optimal thresholds were selected to allow for a 100% sensitivity and NPV. The rule-out criteria were defined as a baseline hs-cTnT level lower than 12 ng/L and an absolute change within the first hour of lower than 3 ng/L.

For “rule-in” of AMI, the optimal thresholds as obtained by CART analysis were either a baseline hs-cTnT value at presentation of 52 ng/L or higher or an absolute change in hs-cTnT within the first hour of 5 ng/L or higher. The additional variables in the CART analysis (age, sex, ischemic ECG changes, and time since onset of symptoms) did not improve the accuracy and did not emerge as contributors to the final decision tree.

Patients fulfilling neither of the aforementioned criteria for rule-in or for rule-out were classified in a third group called “observational zone.”
were cardiac arrhythmias (n = 4), myocarditis (n = 1), pulmonary embolism (n = 2), hypertensive crisis (n = 1), heart failure decompensation (n = 1), and chest pain of unknown origin (n = 3). Taken together, the algorithm allowed for a definite diagnosis after 1 hour in 77% of patients (either rule-in or rule-out). The remaining 101 patients (23%) were classified as in the “observational zone,” and 8 of these patients were finally classified as having AMI, reflecting a prevalence of AMI of 8% in the observational zone group.

**Comment**

By using a well-characterized prospective multicenter cohort of 872 unselected patients presenting with symptoms suggestive of AMI, this study aimed to develop strategies for the clinical application of hs-cTnT in the early diagnosis of AMI. We report 4 major novel findings:

First, the proportion of patients with AMI continuously increases with increasing hs-cTnT values. Levels of hs-cTnT should be interpreted as quantitative rather than qualitative, and the terms positive and negative should be avoided. The respective categories. The HR for the risk of death within 30 days was 6.9 (95% CI, 0.7-66.8) (P = .09) for patients in the observational zone and 23.7 (95% CI, 3.0-189.2) (P = .003) for patients in the rule-in group compared with patients in the rule-out group. This pattern continued up to a follow-up of 24 months with cumulative survival rates of 98.1%, 89.1%, and 85.4% (P < .001 by log rank test). The HR for the risk of death within 24 months was 5.8 (95% CI, 2.7-12.5) (P < .001) for patients in the observational zone and 8.3 (95% CI, 3.9-17.9) (P < .001) for patients in the rule-in group compared with patients in the rule-out group.
The trade-off for the enhanced assay sensitivity is an increased number of positive hs-cTn test results in various acute and chronic conditions with cardiac involvement other than AMI. Accordingly, the PPV for AMI of a positive hs-cTn test result (elevated above the 99th percentile of healthy individuals) is reduced. Our study provides evidence that the reduced PPV found for the 99th percentile cutoff can be overcome by quantitative rather than qualitative interpretation of hs-cTnT levels.

Using quantitative categories of baseline hs-cTnT levels as well as absolute hs-cTnT changes within the first hour, we developed and validated an algorithm for rule-in and rule-out of AMI. A recent study investigated the incorporation of a point-of-care biomarker panel including standard cTn, creatine kinase-MB, and myoglobin into an algorithm for the assessment of patients with chest pain. Using a 2-hour algorithm, the authors identified a subset of low-risk patients (10% of all patients with chest pain) suitable for early discharge. However, in clinical practice, hs-cTnT levels are interpreted in conjunction with all other available information including 12-lead ECG, patient history and physical examination, and other diagnostic investigations. The accuracy of the algorithm in clinical practice, when used in conjunction with the aforementioned information and supported ideally by an automated electronic laboratory reporting system, will likely be even higher than reported in this hs-cTnT–only analysis. And the prognostic data with a 30-day mortality rate of only 0.2% in the rule-out group underscores the suitability of these patients for early discharge.

Potential limitations of the present study merit consideration. First, our study was conducted in ED patients with symptoms suggestive of AMI. This is the pretest probability setting where the algorithm should be used. Second, the proportion of patients with M1 (17%) was in line with different cohorts, but rather high compared with other chest pain studies. The algorithm therefore requires confirmation and external validation in a second multicenter study in a lower-risk cohort. Third, the data presented were obtained in an observational study, and studies applying these data prospectively for clinical decision making are warranted. Fourth, we cannot comment on the performance of the hs-cTnT algorithm in patients with terminal kidney failure requiring dialysis, since such patients were excluded from our study.

In conclusion, using a simple algorithm incorporating hs-cTnT baseline values and absolute changes within the first hour, a safe rule-out as well as an accurate rule-in of AMI could be performed within 1 hour in 77% of all patients with chest pain. The use of this algorithm seems to be safe, significantly shortens the time needed for rule-out and rule-in of AMI, and may obviate the need for prolonged monitoring and serial blood sampling in 3 of 4 patients with chest pain.

Accepted for Publication: June 10, 2012.

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Financial Disclosure: Dr Reichlin has received research grants from the Swiss National Science Foundation (grant PASMP3-136995), the Swiss Heart Foundation, the Professor Max Cloetta Foundation, the University of Basel, and the Department of Internal Medicine, University Hospital Basel, as well as speaker honoraria from Brahms and Roche. Dr Mueller has received research support from the Swiss National Science Foundation (grant PP00B-102853), the Swiss Heart Foundation, the Novartis Foundation, the Krokus Foundation, Abbott, Astra Zeneca, Biosite, Brahms, Nanosphere, Roche, Siemens, and the Department of Internal Medicine, University Hospital Basel, as well as speaker honoraria from Abbott, Biosite, Brahms, Roche, and Siemens.

Funding/Support: The study was supported by research grants from the Swiss National Science Foundation (grant PP00B-102853), the Swiss Heart Foundation, Abbott, Roche, Siemens, and the Department of Internal Medicine, University Hospital Basel. The high-sensitivity cardiac troponin T assay was donated by Roche.

Role of the Sponsor: Roche had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

Online-Only Material: The eTable is available at http://www.archinternmed.com.

Additional Contributions: We are indebted to the patients who participated in the study and to the emergency department staff as well as the laboratory technicians of all participating sites for their most valuable efforts. In addition, Kirsten Hochholzer, MS, Fausta Chiaverio, RN, Sabine Hartwiger, MD, Julia Meissner, MD, Willibald Hochholzer, MD, and Roland Bingisser, MD (University Hospital Basel, Switzerland); Esther Garrido, MD, Federico Peter, MD, Isabel Campodarve, MD, and Joachim Gea, MD (Hospital del Mar, IMIM, Barcelona, Spain); Stefano Bassetti, MD (Kantonsspital Olten, Switzerland), and Stefan Steuer, MD (Limmattalpsital Zuerich, Switzerland), helped with data acquisition.

REFERENCES

Myocardial Infarction Rule-out in the Emergency Department

Are High-Sensitivity Troponins the Answer?

Triage of emergency department (ED) patients with possible acute myocardial infarction (MI) without ST-segment elevation remains one of the most challenging dilemmas in medical practice. The stakes are high: patients with MI inappropriately sent home have approximately 2-fold higher risk-adjusted 30-day mortality than those hospitalized. Conversely, it is not feasible or cost-efficient to admit all patients for MI “rule-out.” The advent of chest pain units diminished the strain on in-patient resources, but even these units often use serial electrocardiograms (ECGs) and cardiac marker testing over 6 to 9 hours to confidently confirm or exclude MI. With increasing ED overcrowding, more effective tools are needed to enable rapid triage of patients with possible MI. In addition, although time dependency of treatment for non–ST-segment elevation MI (non-STEMI) is uncertain, earlier diagnosis could lead to more effective use of acute therapies and more efficient, shorter hospital stays.

Cardiac troponins (cTn) are highly specific biomarkers of myocardial necrosis, are much more sensitive than creatine kinase (CK)-MB, and levels strongly correlate with subsequent mortality. These features prompted a cTn gold standard for MI diagnosis. However, despite nearly absolute tissue specificity and superior sensitivity, cTn is not specific for the etiology of myocardial necrosis (eg, elevated cTn levels occur in such disparate conditions as coronary ischemia, pulmonary embolism, heart failure, sepsis, and renal failure). Thus, clinical syndromes consistent with ischemia and a characteristic rise and/or fall in cTn levels during serial testing are critical for MI diagnosis.

More recently, a new generation of high-sensitivity troponin (hsTn) assays has been developed. They have limits of detection approximately 10-fold lower than conventional assays, 99th percentiles in the low nanogram per liter range, and are analytically very precise (coefficients of variation of 10% at or below the 99th percentile). The ability to detect such small amounts of cTn suggests promise for diagnosing smaller MIs otherwise undetected or identifying MI earlier. When abnormal hsTn levels are below detection by conventional assays. Indeed, initial studies demonstrated that hsTn assays could detect smaller amounts of myonecrosis with greater sensitivity for MI than conventional assays at all serial time points, but highlighted challenges created by greater sensitivity and lack of disease specificity. That is, positive predictive value (PPV) was as low as 50%. Other studies suggested possible susceptibility of hsTn results to biological variability across age and sex (population prevalences of elevated hsTn of 1% among individuals <40 years old vs 5.2% if >65 years old, and 2.8% among men vs 1.3% among women) and demonstrated frequent elevation in asymptomatic patients with stable coronary disease (11.1%) and prior heart failure (18.9%). Combined, these factors challenge application of hsTn assays in the ED and suggest they may be better suited for population screening for subclinical disease or as markers of disease activity.

In this issue of Archives, Reichlin et al present evidence supporting an algorithmic approach to interpre-