One-Hour Rule-out and Rule-in of Acute Myocardial Infarction Using High-Sensitivity Cardiac Troponin T

Tobias Reichlin, MD; Christian Schindler, PhD; Beatrice Drexler, MD; Raphael Twerenbold, MD; Miriam Reiter, MD; Christa Zellweger, MD; Berit Moehring, MD; Ronny Ziller, MD; Rebeca Hoeller, MD; Maria Rubini Gimenez, MD; Philip Haaf, MD; Mihael Potocki, MD; Karin Wildi, MD; Cathrin Balmelli, MD; Michael Freese, RN; Claudia Stelzig, MSc; Heike Freidank, MD; Stefan Osswald, MD; Christian Mueller, MD, FESC

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.
value (PPV) of an elevated hs-cTn level has decreased,\(^8,9,15,16\) and many physicians treating patients with symptoms suggestive of AMI have been confused.\(^17\)

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.

**METHODS**

**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).\(^6,16\) 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 the remaining 1197 patients, samples at presentation as well as on data from previous chest pain cohort studies,\(^9,24\) 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),\(^2\) 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.

Glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula.\(^19\)

**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.\(^2,4,20,21\) 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.\(^16\) On the basis of studies of the biological variation of cTn,\(^12,23\) as well as on data from previous chest pain cohort studies,\(^9,24\) 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),\(^2\) 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.

**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 3 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.\(^7\) Glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula.\(^19\)
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 diagnostic accuracy of their combination. Optimal thresholds for rule-out were selected to allow for a 100% sensitivity and negative predictive value (NPV). Optimal thresholds for rule-in were based on a classification and regression tree (CART) analysis. 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). 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.

STATISTICAL 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 χ² 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 100 and 199 ng/L, and 93% in patients with levels between 50 and 99 ng/L, 88% in patients with levels between 14 and 49 ng/L, 65% for cardiac but not coronary artery disease (CAD), 13% for noncardiac chest pain, and 31% for patients with unknown causes.

**Figure 1.** Levels of high-sensitivity cardiac troponin T (hs-cTnT) at presentation. Baseline hs-cTnT levels at presentation to the emergency department in all patients according to the adjudicated final diagnoses. Boxes represent interquartile ranges, while whiskers display ranges (without outliers further than 1.5 interquartile ranges from the respective end of the box). The proportion of patients above the 99th percentile were 88% for acute myocardial infarction (AMI), 36% for unstable angina (UA), 45% for cardiac but not coronary artery disease (CAD), 13% for noncardiac chest pain, and 31% for patients with unknown causes.

**Figure 2.** Prevalence of acute myocardial infarction (AMI) according to absolute levels of high-sensitivity cardiac troponin T (hs-cTnT) at presentation.

**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 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.

PROGNOSTIC PERFORMANCE OF THE hs-cTnT ALGORITHM TO PREDICT DEATH DURING FOLLOW-UP

There were 12 deaths in the whole cohort within 30 days and 55 within 24 months. Survival up to 30 days of follow-up was significantly associated with the categories "rule-out," "observational zone," and "rule-in," as classified by the hs-cTnT algorithm (Figure 4). Cumulative 30-day survival rates in Kaplan-Meier curves were 99.8%, 98.6% and 95.3% (P < .001 by log rank test) in 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 group 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-month 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 group 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.

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.

Abbreviations: AMI, acute myocardial infarction; hs-cTnT high-sensitivity cardiac troponin T.

Table 3. Performance of the hs-cTnT Algorithm for Rule-in and Rule-out of AMI

<table>
<thead>
<tr>
<th>Overall Cohort</th>
<th>Derivation Cohort</th>
<th>Validation Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients diagnosed after 1 h, No. (%)</td>
<td>660 (76)</td>
<td>325 (75)</td>
</tr>
<tr>
<td>Rule-out</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Negative predictive value, %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Rule-in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity, %</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>Positive predictive value, %</td>
<td>76</td>
<td>69</td>
</tr>
</tbody>
</table>

Figure 3. Algorithm for diagnosis of acute myocardial infarction (AMI) using high-sensitivity cardiac troponin T (hs-cTnT) in patients presenting with chest pain. Results are displayed for the validation cohort (n = 436). High-sensitivity cardiac troponin T (hs-cTnT) values are presented in nanograms per liter. Oh indicates hs-cTnT at presentation to the emergency department; Delta 1h, absolute change of hs-cTnT within the first hour; NPV, negative predictive value; and PPV, positive predictive value.

Figure 4. Kaplan-Meier curves for the cumulative survival according to classification provided by the high-sensitivity cardiac troponin T (hs-cTnT) algorithm. Kaplan-Meier curves display the cumulative survival during 30 days of follow-up (A) and 2 years of follow-up (B) in all patients with chest pain (n = 872) according to the classification into “rule-out” (n = 491), “observational zone” (n = 212), and “rule-in” (n = 169) provided by the hs-cTnT 1-hour algorithm. Differences in survival were assessed using the log-rank test.
of hs-cTnT should be interpreted as quantitative rather than qualitative, and the terms positive and negative troponin should be avoided. Second, we developed and validated a simple algorithm incorporating hs-cTnT baseline values and absolute changes within the first hour. With the use of this algorithm, a safe rule-out as well as an accurate rule-in of AMI can be performed within 1 hour in 77% of patients with chest pain, with a sensitivity and NPV of 100%, a specificity of 97%, and a PPV of 84%. Third, using this algorithm 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 consecutive patients with acute chest pain. And fourth, 30-day mortality was 0.2% in patients ruled out for AMI, which underscores the suitability of these patients for early discharge.

Our findings extend and corroborate recent results regarding hs-cTn assays and are of great clinical importance. Although the newly developed hs-cTn assays have been shown to improve the early diagnosis of AMI, their introduction into daily clinical practice turned out to be difficult, and many physicians treating patients with chest pain have been confused. Simple "how-to-use" instructions for clinical decision making are critically needed to take clinical advantage of the new assays and to shorten the time to rule-in and rule-out AMI.

With older cTn assays, the term troponin positive was often appropriate. A large amount of myocardial necrosis was needed to get a cTn signal, and the PPV for AMI of such largely elevated cTn levels was high. The new hs-cTn assays are more sensitive and detect smaller amounts of cardiomyocyte damage within a shorter time after the onset of symptoms. 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. Using our algorithm, we were able to rule out AMI in 60% and to rule in AMI in 17% of all patients with chest pain within 1 hour with very high diagnostic accuracy. Of the patients, 23% fulfilled neither criteria, were classified “observational zone” and would require more than 1 hour for triage, and many of them probably will need additional diagnostic testing such as coronary angiography, exercise stress test, or echocardiography. Compared with the 6- to 9-hour window for a follow-up cTn test sample recommended in current guidelines, the shortening to a 1-hour follow-up period would be substantial. In clinical practice, hs-cTn 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 pre-test probability setting where the algorithm should be used. Second, the proportion of patients with MI (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. Fifth, we used one specific hs-cTn assay for derivation and validation of the algorithm (hs-cTnT). We hypothesize that similar algorithms can be developed for other hs-cTn assays, but this requires validation in chest pain patient cohorts first.

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.

Author Affiliations: Department of Cardiology (Drs Reichlin, Drexlerr, Twerenbold, Reiter, Zellweger, Moehring, Ziller, Hoeller, Gimenez, Haaf, Potocki, Wildi, Oswald, and Mueller; Mr Freese; and Ms Stelzig), Department of Internal Medicine (Drs Reichlin, Drexlerr, Twerenbold, Reiter, Zellweger, Moehring, Ziller, Hoeller, Rubini Gimenez, Haaf, Potocki, Wildi, Balmelli, and Mueller; Mr Freese; and Ms Stelzig), and Laboratory Medicine (Dr Freidank), University Hospital Basel, Basel, Switzerland; Cardiovascular Division, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts (Dr Reichlin); and Swiss Tropical and Public Health Institute, University of Basel, Basel (Dr Schindler).

Correspondence: Christian Mueller, MD, FESC, Department of Cardiology, University Hospital Basel, Basel, Switzerland; Tropical and Public Health Institute, University of Basel, Basel (Dr Schindler).
Petersgraben 4, CH-4031 Basel, Switzerland (chmueller @uhbs.ch).


Financial Disclosure: Dr Reichlin has received research grants from the Swiss National Science Foundation (grant P30MP-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 P30MP-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.

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 Chavierio, 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 Geo, MD (Hospital del Mar, IMIM, Barcelona, Spain), Stefano Bassetti, MD (Kantonsspital Olten, Switzerland), and Stefan Steuer, MD (Limmattalspital 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 conventional assays at all serial time points, but high-sensitivity troponin 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-