Chest pain is the most common reason for presentation to an emergency department (ED) in the United States. However, of the >8 million related ED visits annually, <30% will have a final diagnosis of an acute coronary syndrome (ACS) (1). Despite this low pretest probability, clinicians are obligated to exclude myocardial ischemia with a high degree of certainty and habitually use time-consuming and costly testing strategies (2). Despite >3 decades of research, the clinical approach to patients with suspected ischemic symptoms remains very heterogeneous between institutions and providers, leaving us with the uneasy sense that the evaluation of these patients continues to be as much an art as a science. Fortunately, well-designed, prospective studies such as the one from Hillinger et al. (3) in this issue of Clinical Chemistry move us forward to evidence-based strategies incorporating sensitive cardiac biomarkers for more rapid diagnosis of patients with suspected ACS.

Approach to the Patient with Chest Pain

The initial and most important step in the evaluation of a patient with suspected ACS is to accurately estimate the clinical probability that the patient’s symptoms are due to myocardial ischemia (e.g., definite, high, intermediate, or low) by integrating elements of the history, physical exam, and electrocardiograph (ECG) findings, while at the same time considering other life-threatening acute diseases. The priority is to rapidly exclude both extremes of presentation: at one end, patients with ST-elevation myocardial infarction (MI) that require immediate repertusion, and at the other end, patients with such low probability for ACS (<0.5%–1%) that they can be discharged quickly with minimal additional testing.

Any strategy to rule out a high-risk condition must be able to exclude the diagnosis with reliability, reflected as a high negative predictive value (NPV) of the testing strategy. For the evaluation of a patient with suspected ischemic symptoms, an acceptable NPV for a rule-out strategy is >99%; in other words, the strategy would miss <1% of confirmed ACS in every 100 patients.

Role of Cardiac Biomarkers

In 1988, Goldman et al. constructed a simple computer protocol using the history and ECG to identify patients presenting with acute MI (4). Although the clinical history and ECG have undergone little innovation since 1988, cardiac biomarkers have evolved dramatically. The introduction of cardiac troponin, and more recently high-sensitivity assays for cardiac troponin (widely used only outside of the United States), has substantially altered the approach to the patient with suspected ACS.

Cardiac biomarkers have proven to be attractive tools to aid in identifying patients at the lowest probability of an unstable ischemic syndrome. Whereas cardiac troponin has been the cornerstone of this application of cardiac biomarkers, because of the obligatory delay in the release of cardiomyocyte structural proteins required for cardiac troponin to be detected, other biomarkers have been studied with the aim of improving the NPV of biomarker-based strategies. However, cardiac troponin assays with progressively better analytical performance are able to detect myocardial damage earlier after onset and in quantities well below those of previous assays (5). When used alone, serial high-sensitivity cardiac troponin testing delivers an NPV ranging from 92% to 100% (6). The NPV falls to <90% when a single cardiac troponin is measured soon after the onset of symptoms (e.g., <3 h) (7). A threshold at the limit of detection delivers a higher NPV than does using the 99th percentile, at the cost of fewer patients being identified as low probability of ACS.

Dual-marker strategies that pair cardiac troponin with another rapidly rising biomarker have aspired to rapidly exclude ACS based on low concentrations of 2 cardiac markers on a single measurement without the need for serial laboratory testing. The blood concentration of copeptin, the C-terminal of the prohormone arginine vasopressin, increases within 90 min of MI onset. Compared with prior-generation cardiac troponin testing, copeptin is released earlier after symptom onset and
theoretically allows for earlier detection of myocardial stress (8). Combined with negative conventional cardiac troponin results, a single normal copeptin value at presentation has been shown to improve the NPV compared with cardiac troponin alone (9, 10). For this reason, investigation has progressed to evaluate copeptin in combination with high-sensitivity cardiac troponin assays.

**Current State of the Rapid Rule-Out**

Accelerated diagnostic protocols (ADPs) that incorporate elements of the clinical history, the ECG, and laboratory assessments provide a framework to rapidly evaluate and triage patients in the ED with chest pain suspicious for ischemia. Most established ADPs include serial measurements of cardiac troponin. Using contemporary “sensitive” cardiac troponin assays, a strategy of measurement at presentation and 3–6 h later will provide acceptable NPV in otherwise low-risk patient populations (e.g., no ischemic changes on the ECG). Accumulating data support the proposal that with high-sensitivity cardiac troponin assays, this testing interval can be reduced even more.

The report by Hillinger et al. (3) effectively illustrates the diagnostic performance of a contemporary ADP using high-sensitivity cardiac troponin. In that analysis, the authors evaluated the value of serial copeptin and high-sensitivity cardiac troponin measurements in the Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) study, a multicenter European study that enrolled consecutive patients presenting to the ED within 12 h of onset (or peak) of symptoms suggestive of ACS, excluding patients with ST-segment elevation. Both copeptin and high-sensitivity cardiac troponin T (hs-cTnT) were measured in a core laboratory, and the final diagnosis was adjudicated using serial hs-cTnT values. Of the 1439 patients with complete laboratory data, 267 (18.6%) had an adjudicated diagnosis of acute MI. Almost two-thirds (n = 941) of all patients had baseline hs-cTnT concentrations <14 ng/L (99th percentile), of whom only 27 (7.4%) had a final diagnosis of MI. Baseline hs-cTnT alone achieved an NPV of 97.1%. The addition of a second serial hs-cTnT at 1 h improved the NPV to 99.6%. Framed alternatively, a strategy of serial baseline and 1-h hs-cTnT measurements missed only 3 patients with acute MI of the entire cohort of 1439 patients (0.2%). Moreover, in the 25% of patients with undetectable concentrations of hs-cTnT (<5 ng/L) at presentation, the NPV for MI was 99.7%, suggesting that further testing, including serial biomarkers, may be unnecessary in this circumstance.

These data are consistent with previous studies, including those that overlap with this population, demonstrating that measurement of high-sensitivity cardiac troponin at presentation and 1–2 h later can deliver a NPV near or above 99% (11, 12). In light of these and similar data, the 2015 European Society of Cardiology (ESC) practice guidelines for management of non-ST-elevation ACS recommend that, for hospitals using a high-sensitivity cardiac troponin assay, when pain starts >6 h before presentation, a single high-sensitivity cardiac troponin below the upper reference limit, together with low-risk clinical features, is sufficient to exclude ACS. If the most recent pain was <6 h from presentation, a second high-sensitivity cardiac troponin measurement at 3 h is recommended. The ESC guidelines also propose, as an alternative (class I) when high-sensitivity cardiac troponin assays with a validated algorithm are available, a 1-h strategy based on the baseline and Δ (i.e., “change”) at 1 h (13). Current US practice guidelines continue to recommend testing at presentation and 3–6 h later.

In our view, a 1-h rule-out strategy with high-sensitivity cardiac troponin is feasible in appropriately selected patients. An approach that uses low absolute values plus the absence of a Δ is likely to yield the highest NPV. There are reasons to believe that the available data may overstate the diagnostic performance of a 1-h rule-out strategy (14). We will look to additional studies conducted in more diverse health care settings than APACE, including in the United States, to provide additional robustness to the estimated NPV. Nonetheless, in patients with low-risk clinical features, the best available evidence supports the notion that a 1-h strategy using high-sensitivity cardiac troponin can significantly expedite the ED evaluation without need for further testing. We continue to favor a 3- to 6-h sample in very early presenters (or with ambiguous timing) and in those who have clinical high-risk features. Institutions implementing a 1- to 2-h ADP should consider a quality assurance program to monitor outcomes. A 1-h rule-out strategy cannot be applied in the United States until high-sensitivity cardiac troponin assays become clinically available.

**Dual-Marker Strategy**

In addition to providing insight into the performance of an ADP, the report by Hillinger et al. addresses whether there is value to testing copeptin together with high-sensitivity cardiac troponin (3). A total of 705 patients had normal baseline concentrations of both high-sensitivity cardiac troponin and copeptin, with an NPV for this combination of 98.6%, slightly better than troponin alone (97.1%). In contrast to high-sensitivity cardiac troponin, a second copeptin at 1 h did not improve the NPV above that achieved with the baseline measurement. This observation adds to the trail of other putative biomarkers of ischemia that have similarly proven not to meaningfully improve diagnostic accuracy or NPV with analytically well-performing assays for cardiac troponin (15).
Summary

Old habits die hard. The study by Hillinger et al. (3) provides a framework for several observations regarding the current state of ADPs for rapid rule-out of ACS. ADPs that incorporate serial assessments of high-sensitivity cardiac troponin appear to provide a viable approach to rule out ACS with sampling over ≤3 h with a high NPV. The actual interval (1, 2, or 3 h) and optimal Δ thresholds are issues still to be refined for each assay. A dual-marker strategy using copeptin does not provide incremental clinical information beyond high-sensitivity cardiac troponin, and it seems unlikely that other biomarkers will substantially improve the NPV achieved with serial high-sensitivity cardiac troponin testing alone.

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References