Clinician's Guide to Early Rule-Out Strategies With High-Sensitivity Cardiac Troponin

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Despite uneasiness among clinicians about the increasing sensitivity of assays for cardiac troponin (cTn), it is rare that clinical algorithms for laboratory-based tests have as much data to guide decision making as do high-sensitivity assays for cTn (hsTn) for diagnosis (rule-in) or exclusion (rule-out) of myocardial infarction (MI). Rather, the proliferation of research evaluating variations in such algorithms in the emergency department (ED) has the potential to overwhelm clinicians with options. In this issue of *Circulation*, 2 observational studies[1,2] that directly compare the diagnostic performance of multiple hsTn-based testing strategies are a step forward in helping providers. These 2 studies illustrate several critical principles and tradeoffs driving the ongoing evolution of early rule-out strategies using hsTn. As a mandatory reminder, although the principles are informative, the specific algorithms discussed in this editorial are not applicable to the "contemporary sensitive"[3] assays that predominate in current practice in the United States. In addition, the specific concentration values reported as cut points are for the hsTnI assay used in the 2 studies and will differ from the assay for hsTnT that has recently been approved in the United States.

Of the emerging applications for hsTn, the rapid rule-out of MI in the ED is the application most likely to be embraced by clinicians.[4] This application most directly leverages the superior analytic and clinical sensitivity of hsTn assays as an advantage by translation into a robust negative predictive value (NPV) for MI. Consistent with the focus of the reports by Chapman et al[1] and Boeddinghaus et al,[2] this editorial addresses the negative predictive rather than positive predictive performance of these strategies and illustrates 3 major components of evolving early rule-out strategies with hsTn (Figure).

CONCEPTS BEHIND TROPONIN STRATEGIES IN THE ED

Acute MI is defined by evidence of myocardial injury in a clinical setting consistent with acute myocardial ischemia.[5] The presence of myocardial injury is necessary but not sufficient for the diagnosis of acute MI. To diagnose MI, clinical indicators of an ischemic mechanism must accompany evidence of acute myocardial injury. However, on the flip side, in the absence of myocardial injury, an acute MI cannot be present. Thus, MI is easier to rule out than to rule in. Provided that sufficient time has elapsed for myocardial structural proteins to be released in measureable quantity into the circulation, cTn will be detectable whenever myocardial injury has occurred.[6] Therefore, the absence of cTn >99th percentile upper reference limit (URL) ≥6 hours after the onset of ischemia is considered to exclude a diagnosis of MI.[5] Compared with earlier-generation assays, hsTn can establish biochemical evidence of myocardial injury at lower concentrations and thereby earlier after the onset of

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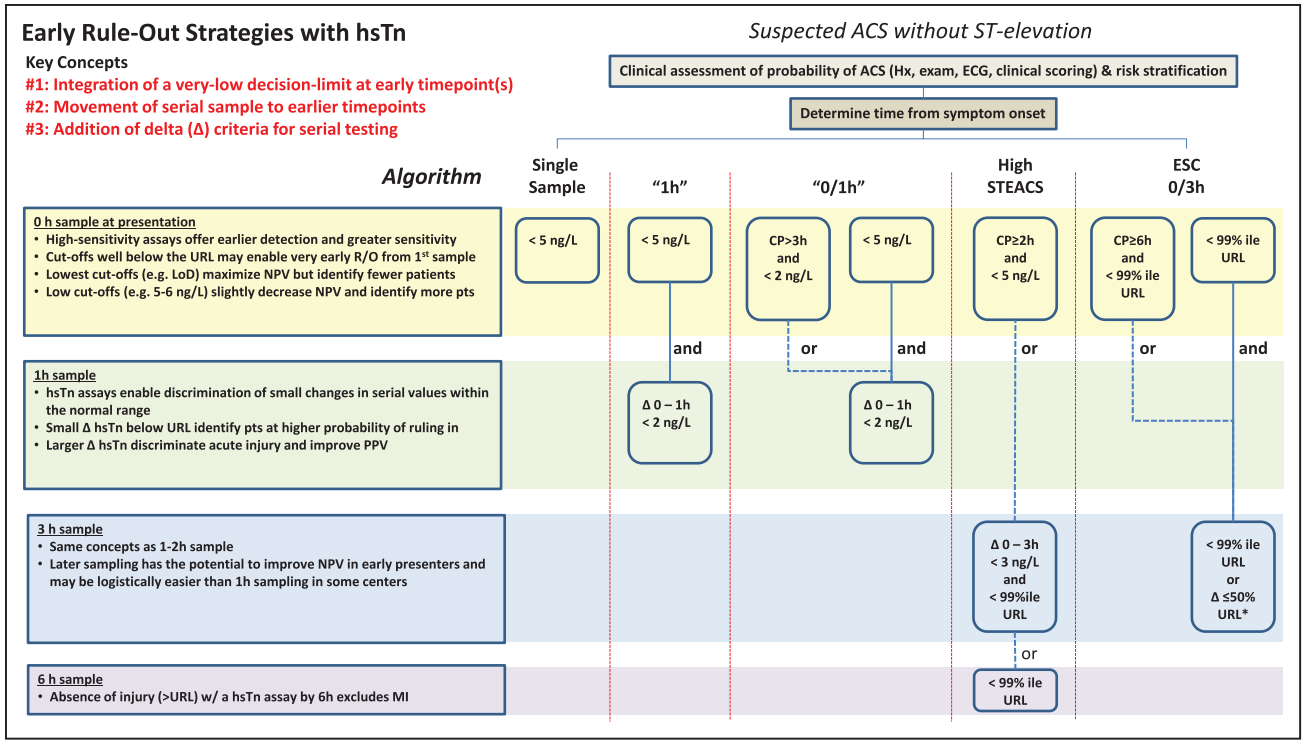

Figure. Schematic representation of five variations of rule-out strategies using high-sensitivity assays for troponin (hsTn) and the key concepts that underlie each element.

The concentrations reported in these examples are specific to the assay used in the studies by Chapman et al[1] and Boeddinghaus et al[2] and cannot be generalized to other high-sensitivity assays. The 1-hour algorithm requires sampling at both baseline (0 hours) and 1 hour. In contrast, the 0/1-hour algorithm includes a criterion that permits rule-out at the 0-hour sample without further testing. ACS indicates acute coronary syndrome; CP, chest pain; ESC, European Society of Cardiology; Hx, history; LoD, limit of detection; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value; R/O, rule-out; High- STEACS, High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome; and URL, upper reference limit.

ischemia.[6] In addition, hsTn assays enable discrimination of small changes in concentration starting within the normal reference range, above the limit of detection of the assay but below the URL. Small dynamic increases (delta values) are associated with a higher probability of subsequent rises above the URL and future major cardiovascular events. Moreover, stable concentrations of hsTn in the detectable range below the URL are associated with structural heart disease, atherosclerosis risk factors, and a higher risk of future cardiovascular events.[7,8] Consequently, nondetectable or very low hsTn concentrations, well below the URL, identify patients with lower cardiovascular risk.

EVOLUTION OF HSTN-BASED EARLY RULE-OUT STRATEGIES

These concepts have framed the evolution of hsTn-based rule-out strategies in the ED aimed at reliably excluding myocardial injury as early as possible through staged measurement of hsTn in conjunction with other clinical assessments for the probability of MI. Within this context, 3 major components have emerged: movement of serial samples for hsTn to earlier time points, addition of criteria for a delta hsTn between measurements, and integration of very low decision limits well below the 99th percentile URL at the early time points.

Both US and European professional guidelines recommend serial measurement of cTn at presentation (0 hours) and 3 to 6 hours later with additional testing beyond 6 hours in patients who have electrocardiographic changes or intermediate- or high-risk clinical features.[5,9,10] However, the 2015 European Society of Cardiology (ESC) practice guidelines also included an alternative (Class I) strategy, reducing the sampling interval to 1 hour when an hsTn assay with a validated 0/1-hour algorithm is used.[10] Such algorithms incorporate all 3 of the components highlighted above, including a very low cutoff applied at the initial hsTn value aimed at excluding MI after the first sample in patients who arrive >3 hours after symptom onset and delta criteria that direct patients with dynamic hsTn concentrations to additional testing (Figure). As an example, Shah et al[11] reported that a single 0-hour hsTnI <5ng/L (Abbott

ARCHITECT) could exclude ≈50% of the population with an NPV of 99.6%. Others have advocated that an even lower threshold at the limit of detection is necessary to support acceptable sensitivity with a single sample (18.8% of patients; NPV, 99.5%; sensitivity, 99.0%).[12]

The 2 reports in this issue[1,2] tie together this expanding evidence with direct comparisons of several of these strategies using the same assay (Abbott). Chapman et al[1] compared the standard ESC 0/3-hour strategy based on the 99th percentile URL at both time points with the High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome) 0/3/6-hour algorithm that incorporates a 0-hour criterion at a very low cutoff (5 ng/L) and a 3-hour criterion that directs patients with either a rising hsTn concentration (meaningful delta) or an absolute concentration above the URL to additional testing (Figure). Among 1218 patients with suspected MI (MI rate, 21%; 26.8% at <2 hours of symptom onset), the High-STEACS algorithm delivered both a higher proportion ruled out for MI at 0 hours (40.7% versus 28.1%) and a higher NPV (99.5% versus 97.9%). Both algorithms ruled out ≈75% of patients by the 3-hour sample. Framed around sensitivity, the High-STEACS algorithm identified 97.7% of MIs, whereas 89.3% were detected by the ESC 0/3-hour algorithm. Performance of the ESC 0/3-hour algorithm improved when coupled with the ECG and GRACE (Global Registry of *Acute Coronary* Event) risk score, as is recommended in clinical practice; however, the High-STEACS algorithm remained superior (NPV, 99.7% versus 98.3%). For the purposes of ruling out MI, their findings demonstrate the value of adding a very low 0-hour cutoff to facilitate earlier rule-out and a delta criterion to exclude increasing values among patients who progress to 3-hour sampling with absolute concentrations that remain less than the URL.

Boeddinghaus et al[2] advanced a step beyond the 0/3-hour algorithm, shifting the serial sample to 1 hour and comparing the ESC alternative 0/1-hour strategy with 3 other approaches using either a single cutoff at 0 hours or the 1-hour strategy (Figure). Among 2828 patients with symptoms suspicious for MI and no ST-segment elevation (MI rate, 16%; 26% at ≤2 hours of onset), each of these 4 approaches delivered an NPV >99%, comparing favorably with the ESC 0/3-hour algorithm (NPV, 98.4%). Their findings show a predictably enhanced NPV (100%) setting the 0-hour cutoff at the limit of detection, a criterion met by 16% of patients, compared with an NPV ranging from 99.1% to 99.5% with either a higher single cutoff (<5 ng/L, 54% of patients) or staged criteria incorporating a delta from 0 to 1 hour (rule-out in 52%). Although each of the strategies performed similarly among patients presenting >2 hours after symptom onset, among early presenters, the NPV (98.5%) and sensitivity (94.2%) were diminished with the use of the single 0-hour cutoff (5 ng/L).

MOVING TOWARD BEST PRACTICE

The assessment of patients with suspected MI is intrinsically a probabilistic assessment that relies on bayesian principles to formulate an assessment of the probability of acute coronary syndrome.[13] The NPV of a negative test result is dependent on both the clinical sensitivity of the test and the prevalence of MI in the population. I concur with others who have advocated for sensitivity being an important metric in the assessment of diagnostic performance across studies with differing prevalences of MI.[12] However, from the perspective of a clinician evaluating an individual patient considered for discharge, the NPV and likelihood of a false-negative result (100% - NPV) are most relevant to decision making. To generalize a desirable NPV (eg, >99%) from a clinical study, the clinician should have confidence that the study population was representative of his/her practice. This aspect can be gauged by considering the prevalence of MI and the other criteria by which the probability of MI was assessed (eg, ECG or probability instruments such as the Heart Score) and high-risk patients excluded (eg, TIMI [Thrombolysis in Myocardial Infarction] or GRACE score). Studies in populations with a particularly low prevalence of MI will overstate the NPV compared with application in higher-prevalence populations. Notably, most studies of rule-out protocols in the United States have an MI prevalence <10% compared with 16% to 21% in the reports by Chapman et al and Boeddinghaus et al.

I recently summarized 9 lessons for application of hsTn in the ED.[4] The reports from Chapman et al[1] and Boeddinghaus et al[2] provide further validation of several of these lessons and provide a platform for continued refinement of best practice for hsTn-based early rule-out of MI that should integrate the following:

1. Clinical assessment of the probability of MI and timing of onset of symptoms.
2. Serial testing at presentation and at 1 to 3 hours later; 0/1-hour testing appears reasonable in otherwise low-risk patients who have presented >2 hours after symptom onset.
3. Decision limits lower than the 99th percentile URL at early time points.
4. A delta criterion to exclude dynamic values suggesting acute injury.

Using a stringent criterion of very low hsTn on the first sample can reasonably exclude MI in as many as 40% to 50% of patients, provided that they are otherwise low risk and have presented >2 hours after symptom onset. Institutional thresholds for this decision limit may be considered on the basis of balancing the risk of false-negatives and the proportion of patients ruled out. Use of lower cutoffs will rule out fewer patients but with a higher NPV. Accurate calibration of assays in the very low range of concentration is important for this application. Very early presenters should have serial testing to

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support an acceptable NPV, as should patients with other high-risk indicators.[5] Following these rules, Chapman et al and Boeddinghaus et al demonstrate robust NPVs that may expedite discharge, improving patient flow and resource use.

Despite the advance achieved with directly comparative studies, gaps in our knowledge remain. First, neither study provided a comparison of an accelerated 0/1-hour protocol versus the High-STEACS protocol (Figure), which anchors at 3- rather than 1-hour serial sampling. Second, more data are needed among very early presenters to provide confidence around or lead to revision of currently proposed algorithms. Third, it would be advantageous to have algorithms that integrate the actual timing of sampling rather than mandating specific time points. Fourth, there are opportunities to refine how hsTn should be coupled with clinical probability tools (heart, TIMI, GRACE) or imaging to improve diagnostic performance. Fifth, each of these studies is observational with the reported outcomes based on patients who were managed according to local standards of care, often with in-hospital evaluation, rather than reflecting outcomes if patients had been managed according to the early rule-out protocol and actually discharged. Prospective studies, preferably randomized, of the implementation of these testing strategies are warranted. Close attention to the nature of additional outpatient follow-up and testing in such studies is needed to define best practice. Sixth, analytical issues such as the ability to quantify small delta values and the use of sex-specific decision limits are important. Lastly, low cutoffs and small delta criteria designed to optimize the NPV will lower the positive predictive value (eg, PPV of 33.4% with a single cutoff[2]), requiring application of higher delta criteria to rule in MI in conjunction with clinical evidence of ischemia.[10]

DISCLOSURES

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FOOTNOTES

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