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Review Article

A 0/1-Hour Algorithm Using High-Sensitivity Cardiac Troponin

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The European Society of Cardiology (ESC) guidelines recommend the use of high-sensitivity cardiac troponin (hs-cTn) 0-hour/1-hour algorithms in patients presenting with suspected non ST elevation myocardial infarction (NSTEMI) as Class I, Level B. This algorithm stratified patients into three group including, rule-out, observe, and rule-in. The introduction of a time axis consisting of a relatively short time, 0-hour/1-hour, is worth mentioning in this algorithm. The specificity and negative predictive value to rule-out of myocardial infarction (MI) was more than 95%, respectively. In prospective Asian study consist of around 400 patients with suspected NSTEMI, "elective" catheter intervention was performed on 13 patients in both rule-out and observe group. None of them had MI, or needed an urgent coronary angiography (CAG) within 30 days. Although there was two patients on whom CAG and percutaneous coronary intervention (PCI) were performed less than 7 hours after presenting to the emergency department (ED), they were classified as moderate risk according to the Framingham Risk Score. The diagnostic performance for patients with suspected NSTEMI to combine the novel risk score with the algorithm would be much improved. The development of excellent assays was also key to establish the algorithm. The hs-cTn assay has limits of detection (LoD) approximately 10-fold lower than those of conventional assays, and their 99th percentiles are analytically very precise. After the emergence of the hs-cTn assays, rises in the cases of NSTEMI were accompanied by a reciprocal reduction in the percentage of patients diagnosed with unstable angina (UA). This excellent algorithm has a possibility to reduce ED crowding and unnecessary CAG.

Key words: *high-sensitivity cardiac troponin, hs-cTn, troponin, non ST elevation myocardial infarction, risk stratification*

Introduction of High-Sensitivity Cardiac Troponin

Triage of emergency department (ED) patients with possible non ST elevation myocardial infarction (NSTEMI) remains one of the most challenging dilemmas in medical practice. The initial electrocardiogram (ECG) is non-diagnostic in up to 50% of cases of acute myocardial infarction (AMI).[1] Furthermore, less than 40% of patients admitted to coronary care units (CCUs) are diagnosed as with coronary ischemia.[2] Patients with myocardial infarction (MI) erroneously sent home have approximately a 2-fold higher risk-adjusted 30-day mortality than those hospitalized. However, it is not feasible or cost-efficient to hospitalize all patients to rule out MI. Establishing an accurate diagnosis in patients with chest discomfort is crucial because erroneous discharge can lead to preventable AMI or sudden death.[3,4] Recently, the European Society of Cardiology (ESC) guidelines recommended the use of high-sen-

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sitivity cardiac troponin (hs-cTn) 0-hour/1-hour algorithms in patients presenting with suspected NSTEMI (Class I, Level B).[5] The algorithm has immense potential for improving the detection of acute coronary syndrome (ACS), and may allow the identification of candidates for early discharge and outpatient management. In this review, we will focus on the following issues of such clinically relevant diagnostic research: (1) hs-cTn, (2) unstable angina (UA), and (3) ESC 0-hour/1-hour algorithm using hs-cTn.

High-Sensitivity Troponin

Guidelines for the definition of AMI were updated in 2007 by both clinical (American College of Cardiology/ESC/American Heart Association) and biochemical (National Academy of Clinical Biochemistry) expert groups. These groups recommend the use of cardiac troponin (cTn) (type T or I) for the diagnosis of AMI.[6,7] Evidence of myocardial necrosis has been defined as the detection of an increase in cTn with at least 1 value above the 99th percentile of a normal reference population. The guideline also stated that the assay used should have an optimal coefficient of variation (CV) of 10% at or below the 99th percentile decision limit for troponin.[6,8] The sensitivity of conventional cTn assays is not as high at the time of patient presentation. It depends on the onset time of chest pain, and the assay takes 4–6 hours to change to a positive result for the diagnosis of patients with AMI. Therefore, newer generations of cTn assays now require not only improved analytical sensitivity but improved precision as well. The fourth-generation assays produced by Roche diagnostics use fragment antigen-binding fragments in conjunction with two mouse monoclonal antibodies, which recognize the 125_131 and 135_147 amino acid positions in the central part of the cTnT molecule. The constant C1 region in the monoclonal mouse antigen-binding fragment was replaced with a human immunoglobulin G (IgG) C1 region.[9] This mouse-human chimeric detection antibody can further reduce the susceptibility to interference by heterophillic antibodies. As a result, the sensitivity was improved by increasing the sample volume from 15 to 50 μL, increasing the ruthenium concentration of the detection antibody, and lowering the background signal via buffer optimization. The high-sensitivity assays have limits of detection (LoD) approximately 10-fold lower than those of conventional assays, and their 99th percentiles are analytically very precise. The limit of blank (LoB) and LoD are 3 ng/L and 5 ng/L, respectively. There is no significant cross-reactivity with human skeletal muscle troponin types T, I and C. Reichlin et al. evaluated several hs-cTn assays, including the new Roche hs-cTnT, Abott-Architect TnI, and Simenes Toroponin I Ultra.[10] The uniqueness of high-sensitivity assays lies in their ability to detect much smaller MIs or earlier (less than 3 hours from the onset of the MI), both of which would be otherwise undetectable by conventional assays.

A Requiem for UA Pectoris

The term UA was introduced by Fowler in 1971,[11] and proposed by Braunwald et al. in a guideline published in 1994.[12] There are three principal clinical presentations of UA including (1) resting angina usually lasting more than 20 min, (2) worsening angina, and (3) new onset angina. In the absence of AMI, any one of these presentations was required for the diagnosis of UA. After the emerging of the use of troponins assays, ACS was divided into three groups: (1) STEMI, (2) NSTEMI, and (3) UA. In 2008, the World Health Organization (WHO) declared that new or worsening symptoms of ischemia (or changing symptom pattern) and ischemic ECG changes with normal biomarkers were required for the diagnosis of UA. After the emergence of the hs-cTn assays, troponin measurements became more sensitive and the population of patients diagnosed with NSTEMI began increase. As a result, the rises in the cases of NSTEMI were accompanied by a reciprocal reduction in the percentage of patients diagnosed with UA (Fig. 1).[13] Braunwald and Morrow stated that "patients with ischemic heart disease will again be divided into the original 2 rather than 3 major groups.[14] One group will be patients with angina pectoris, whose angina may be of widely varying severity and classified by the Canadian Cardiovascular Society system. The second group will comprise patients with AMI as defined by the third universal definition, which includes the type of MI (type I, type II, etc.), the ECG changes (i.e., STEMI and NSTEMI), and the extent of myocardial damage that is related to the magnitude of cTn release." In fact, the prognosis of UA is good, and the ESC advises that patients with UA do not require admission to CCU for monitoring, or their discharge may be allowed without the performance of urgent coronary angiography (CAG).[5] Given the faces, it

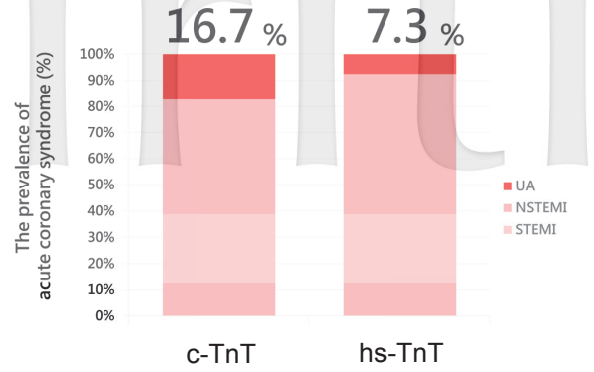

Fig. 1. Effect of the use of high-sensitivity troponin T (hs-TnT) instead of conventional troponin T (c-TnT) on the prevalence of unstable angina (UA) in the Protective effect of Rosuvastatin and Antiplatelet Therapy On (PRATO) trial. In the PRATO trial, there were 16.7% of patients with UA who were identified using conventional troponin T. However using a high-sensitivity assay reduced the population to 7.3%.

NSTEMI: non ST elevation of myocardial infarction; STEMI: ST elevation of myocardial infarction.

may be deemed appropriate for the term of UA to be changed to "non-unstable" angina.

Diagnostic Strategy of Using 0-Hour/1-Hour Algorithm

Notably, another challenge presented itself. The development of assays with excellent sensitivity caused an increase in the rate of false positives (lack of specificity) or detected biological variability depending on the age and gender.[15,16] The population prevalence of elevated hs-cTn is 1% among individuals aged 40 years old vs. 5.2% for those if 65 years old. This problem attributes to the definition of a "normal reference population" as most assays cannot truly define the value for a "normal reference population." For the selection to be definitive, which medical device should be used to demonstrate "normal reference"? Should it be an imaging study, such as cardiac magnetic resonance, computed tomography, or an echocardiogram? Do a normal physical exam, absence of cardiac history and normal natriuretic peptide lab values not qualify as falling within the "normal reference." As previously mentioned, the level of troponin changes depending on gender, age, and ethnically therefore, each group should be evaluated using some types of device. Such an approach would be very costly. If decile age range and gender dependence are defined, the biomarkers may not be useful because of their impracticality. Reichlin et al. conducted the Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) study. At an ESC meeting in 2017, he reported that this cohort is growing, and presently around 4,000 patients are followed up in 12 EDs in 5 countries. Using this cohort, the first paper explaining the 0-hour/1-hour algorithm was reported.[17] They investigated 1,247 consecutive Caucasian patients who presented to the ED with suspected of NSTEMI from 2006 to 2009. Their symptoms began last within 12 hours of presentation. Patients with chronic kidney disease on hemodialysis and those with STEMI were excluded. The authors obtained blood samples and recorded an ECG at the time of the patients' presentation to the ED, and at 1, 2, 3, and 6 hours after presentation. After centrifugation, samples were frozen at -80°C until they were assayed in a blended fashion. Using 436 patients randomly selected from 872 with suspected NSTEMI from whom baseline and 1-hour hs-cTn samples were obtained, they created algorithms incorporating baseline thresholds and thresholds for the rise of hs-cTn from baseline to 1 hour for both MI rule-in and rule-out. The final rule-out algorithms demonstrated sensitivity and negative predictive value (NPV) at 100%: baseline threshold of less than 12 ng/L and an absolute change of less than 3 ng/L. Applied in another 436-patient validation cohort, a definite diagnosis was made in 72% of patients. The rule-out algorithm demonstrated 100% sensitivity and NPV, and the rule-in algorithm demonstrated 99% specificity and 91% positive predictive value (PPV), misclassifying 5 patients as having had MIs and classifying 23 MIs into an "observation zone," 123 patients met neither rule-in nor rule-out criteria. It is important to note that cut-off value and absolute value were not sensitive to gender, age, or time from symptom onset. This algorithm was followed by multicenter validations in Europe and across 3 continents.[18] As an external variation study, Pickering et al. performed an analysis using 5 cohort studies from 3 counties (Australia, New Zealand, and Canada), and they found similar results; rule-out sensitivity of hs-cTnT was 97.1% (95% confidence interval [CI]: 94.0%–99.8%), and rule-in specificity was 94.6% (95% CI: 93.4%–95.5%).[19] From the APACE study, Nestelberger et al. followed the 2-year prognosis of 523 patients admitted in an observational zone.[20] Although non-cardiac disease was most common (46%) in this group, there were still 15% and 24%

of patients with AMI and UA, respectively. Additional, they were 59 deaths and 36 futures AMI that occurred in 2 years. In this group, there were older, more often male, have atherosclerotic lesions including peripheral artery disease, stroke, and history of MI. Therefore, continuous and careful observation must be applied to patients assigned to these "observe groups." Treatment may be more effective if physicians request should patients to visit the outpatient clinic for a while, and from there they can make a final diagnosis using coronary computed tomography angiography or perform a myocardial perfusion scan for further examination.

The Earlier, May Not Be the Better

In patients with NSTEMI or UA, the culprit artery is often patent, there is no ongoing transluminal ischemia, and the patients often has a good response to initial treatment.[21] Although meta-analysis revealed that earlier intervention resulted in better outcome,[22,23] these data pose critical problems. Because it contained outdated, percutaneous coronary intervention (PCI) with stent was performed in only around 50–60% of patients, and optimal medical therapy, including statin or beta-blockers was inadequate. After the era of drug eluting stent, several studies revealed that early intervention did not differ greatly from delayed intervention in preventing major advanced cardiovascular events in patients with NSTE-ACS (Fig. 2).[24,25] The technology of used in PCI is improving, and the evidence of medical therapy is also getting more sophisticated. With time, we need to change our perspective. Recently, Shiozaki et al. reported the results of applying the 0-hour/1-hour algorithm using hs-cTnT in Asian cohorts (Japan and Taiwan).[26] This was the first publication involving attending physicians who made tentative diagnoses according to the algorithm, stratified patients, and followed them for 30 days. Around 400 patients with suspected NSTEMI were analyzed, and "elective" catheter intervention was performed on 13 patients. None of them had MI, or needed an urgent CAG within 30 days. Although there was one patient in the rule-out group, and one in the observe group on whom CAG and PCI were performed 4 hours and 7 hours after presenting to the ED, respectively, their symptom (chest pressure with cold sweat) was typical and they were classified as moderate risk according to the Framingham Risk Score. Urgent CAG requires the deployment of not only physicians but also nurses and radiology technicians, resulting in increased medical costs. The 0-hour/1-hour algorithm using hs-cTn may demonstrate the benefit of not rushing management of patients with NSTEMI more clearly.

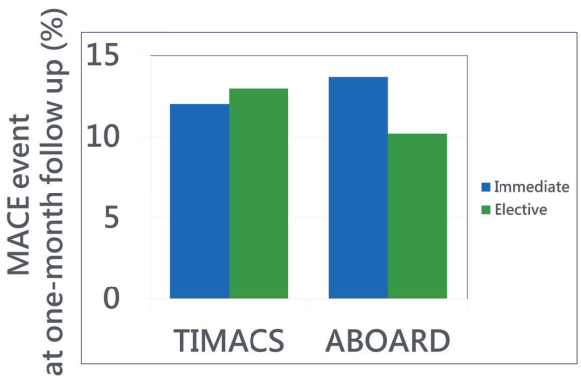

Fig. 2. Major cardiovascular events at one-month follow-up comparing early vs. delayed intervention. The Timing of Intervention in Acute Coronary Syndrome (TIMACS) study[24] compared less than 24 hours (immediate) group and the more than 36 hours (elective) group after randomization. The Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention (ABOARD)[25] study compared an immediate group (average: 70 min; interquartile rage [IQR]: 0.51–123) and an elective group (average: 21 hours; IQR: 18–25). Despite the substantial delay, we were unable to identify any difference in adverse outcomes.

Clinical Usefulness of Using 0-Hour/1-Hour Algorithm

A physician with a low level of confidence in his/her level of diagnostic accuracy is likely to order excessive tests, whereas an overconfident physician may be likely to underestimate a patient's concern. The 0-hour/1-hour algorithm using hs-cTn has been established from practical opinion in clinical situation. The introduction of a time axis consisting of a relatively short time, 0-hour/1-hour, is worth mentioning. The diagnostic performance using hs-cTn has improved. As a result, ED crowding may be reduced, and unnecessary CAGs are less likely to be performed. Medical stuff may not be called in emergencies unnecessary, and medical costs would be reduced (Fig. 3). However, it should be noted that the effectiveness of the diagnostic process depends on diagnostic accuracy and physician confidence in that accuracy. It is of at most importance that every patient

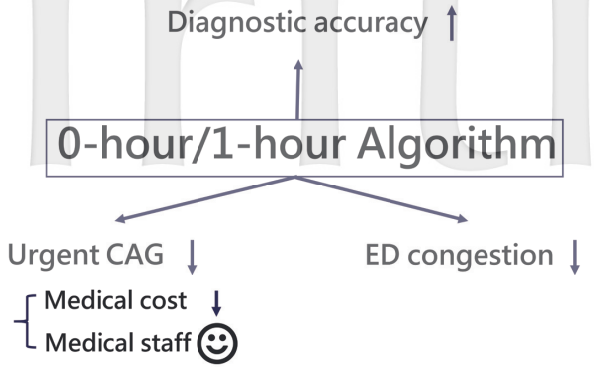

Fig. 3. The benefit of the 0-hour/1-hour algorithm using high-sensitive cardiac troponin assays.
ED: emergency department; CAG: coronary angiography.

is included in the physician's assessment. It is difficult to achieve diagnostic accuracy, especially in women and patients with diabetes who often do not complain of typical chest pain and may present with atypical symptoms.[27] The algorithms should always be integrated with a detailed clinical assessment and repeated ECG in patients with ongoing or recurrent chest pain. If these considerations are taken into account, the algorithm is likely to be an excellent algorithm for patients with suspected NSTEMI.

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