**Editorial**

**Sometimes Earlier May not be Better**

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Conflicts of interest

Dr. Jaffe has or presently consults for most of the major diagnostic companies including all of those whose assays have been involved in the analyses discussed.

Dr. Collinson has no conflicts

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The recent ESC guidelines f*or the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation* *(NSTE-ACS)* added an avant-garde rapid one hour rule-in and rule-out algorithms using high sensitivity cardiac troponins (hscTn) as a clinical option.1 In our opinion, the guidelines overlook some gaps in the information that defined these approaches that could inadvertently disadvantage patients. Others report less optimistic results with hscTn assays with early approaches in “early presenters” with ischemia-induced myocardial injury.2 The following identifies our concerns about that guidelines so that clinicians can take them into account.

**Gaps in the population providing the knowledge base**

Guideline mandated diagnostic assessments should be applicable to all possible patients within a given disease state. To accomplish this goal, the one hour algorithm would have required a more extensive database than the one used.1 The studies relied on included large numbers of low risk patients presenting early after onset of symptoms but lacked substantial numbers of early patients with acute myocardial infarction (AMI).. This group is critical to study to be sure that these patients manifest elevations even early after AMI so they can be distinguished from those without AMI. The largest number of AMIs in the studies evaluating the approach was 443 with only 106 patients presenting in < 3 hours after onset.3 How many presented in <2 hours is unclear. Thus, we have insufficient knowledge about how the algorithm works in patients early after AMI. This would have been missed by the CART analysis developing the protocol since that study had even fewer AMIs. too lacked adequate numbers of early patients.4 That is why the data indicating that rapid biomarker protocols underestimate AMI is important albeit generated with a different model.2 The recent report from Shah et al. using a single measurement at admission supports this concern in a study with 782 AMI patients of whom 125 (personal communication per NLM) were evaluated within 2 hours of onset of symptoms.5

The one hour approach does not define the nature of the patients who ruled out. A low hs-cTn value in patients with normal ECGs and low GRACE scores is different than similar values in patients with high GRACE scores.6 An elevated hscTn value in a low risk patient should prompt a search for alternative explanations whereas a similar value in high risk patients may prompt clinicians to intensify treatment and consider intervention. However, these data are not available because risk stratification was not part of the approach. A recent analysis suggests the benefit of adding risk stratification.7

 In selecting patients the studies used to develop this approach focused on patients whose primary problem was chest pain. 3,4 Even those with chest pain alone may not always have high specificity for AMI.7  Patients with other presentations and possible AMI who are likely to be evaluated with this approach who have critical illnesses were likely under enrolled as were those with severe renal dysfunction and the elderly who often present atypically8 These patients often have values > 52 ng/L.6  These exclusions means that this approach will likely lack specificity when applied to all patients with possible AMI.

In patients who present at least six hours after the onset of symptoms, conventional cTn assays do an excellent job at ruling out AMI and identifying those with a good prognosis.9 Therefore, although appropriate to enroll consecutive patients, the critical patients in studies looking at earlier approaches should have large numbers who present early after the onset of symptoms to make sure that the approach works in this group. As indicated above, this did not occur. The mean time to presentation in the studies used for these guidelines was usually 3-3.5 hours.3 In TRAPID, it was 1.9 hours but it took 1.5 hours to obtain the initial samples.10 By the time of the one hour follow up sample, many patients were close to the six hour mark. This is important to appreciate.

**Considerations regarding the assays**

The one hour approach depends on the use of hs-cTn assays).1 It does not work with non hscTn assays11

Most hs-cTn assays use sex specific cut off values. Recent data suggest they make the diagnostic evaluation of women better.12 To recognize sex differences, large study numbers of women with AMI are needed which are not the case in the studies that led to the one hour algorithm.3,4 The cut off value of 12 ng/L hs-cTnT reached by CART analysis4 may help deal with this issue since it is mid-way between the cut offs proposed for men and women.

An important caveat is whether the assays are capable analytically of making the distinctions proposed. From the published data, it does not appear to have the ability to distinguish between a change of 3 and 5 ng/L.13 The assay is even less precise when used on older instruments. 14

When hs-cTn values are elevated, the use of change valuesimprove specificity but reduce sensitivity.15 A change of 50-80% is needed to be sure that one has exceeded conjoint biological and analytical variation..15 But the use of large change values decreases sensitivity for detection of AMI. However, the use of very low change values as advocated by the 1 hour algorithm diminishes specificity. 15 This issue needs to be understood by clinicians.

Finally, extrapolation of the data partially validated predominately with the hs-cTnT assay to other assays was less than ideal. Choosing one assay (hscTnT) as the gold standard to determine assay values for another assay as done in the ESC guidelines biases the analysis against the non gold standard assay whenever there are discrepancies. This is particularly important given suggestions that the hs-cTnT assay may not be a high sensitivity assay.16 As such, the fact that there are more elevations of hs-cTnTin some studies4, 17despite the detection of many fewer normal subjects is of concern. The proper explanation for this is not clear. These concerns are furthered by the fact that analyses for hscTnI were done on samples stored for long periods of time (years) after measurement of hscTnT which could well change the relationship between the values. 17 The proper way to do such an analysis is with “fresh” samples.

**Precautions for clinicians**

1. For now, only apply the rapid 1-hour algorithm utilizing small changes to low risk patients. This will mitigate some of the concern about the paucity of data concerning patients with AMI who present early after the onset of symptoms2,5 until additional studies clarify this issue.
2. The use of a single cutoff value to diagnose AMI should be avoided. If used on an “all comers” population, these values will include large numbers of patients with comorbidities and not AMI. The best way to diagnose AMI according to the guidelines, is by observing a rising and/or falling pattern of cTn. This standard should be adhered to.
3. The low change values of 3 and 5 ng/L for hscTnT suggested are below the ability of most hs-cTn assays to provide accurate information if baseline values are low. Clinicians should be cautious about patients at high risk and those who came in early.2,5 If there are questions, one should obtain additional samples to make sure one is not missing a rising pattern of values.
4. It will take a longer time to rule in some patients with AMI; perhaps as long as 6 hours.18
5. Cutoff values for assays other than hs-cTnT are insufficiently validated and should be used with caution if at all.
6. Sex specific cutoff values are recommended by the guidelines at present.6 Data evaluating women with AMI who present early after the onset of symptoms are needed.

It is likely that some components of the 1 hour algorithm will work well. It may be that low hs-cTn values at presentation is a good way to exclude AMI, not because they are sensitive at detecting myocardial injury but because the risk factors associated with ischemic heart disease cause increases in hscTn within the normal range so baseline values are not apt to be low. Thus, low values define a low risk group.3 However, we are less confident about some of the other recommendations such as utilizing a solitary fixed cutoff for diagnosis of AMI and the application of this approach too all patients with possible AMI including those with renal failure, acute illness, the elderly and those who present early. Until these issues are clarified clinicians should take an extra caution in the interest of safe patient care.

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