

EDITORIAL COMMENT

How Good Does It Need to Be?*



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High-sensitivity cardiac troponin (hs-cTn) assays reportedly allow early definitive triage of patients with possible acute myocardial infarction (AMI). To be confident that one can implement such strategies safely, fastidious data are required. In their paper in this issue of the *Journal*, Mokhtari et al. (1) build on the protocol included in the European Society of Cardiology guidelines to rule AMI in and out (2).

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The authors (1) presume the algorithm works and ask whether a risk assessment and the finding of a “nonischemic” electrocardiogram (ECG) helps the approach. It is not surprising these additions enhance the number of patients in the rule-out arm and improve the negative predictive value from 97.8% to 99.5% (3). They also improve sensitivity in the rule-in arm. Although the concept was confirmed, neither a defined risk score nor standardized ECG criteria were used, making extrapolation of these additions problematic.

Although the paper (1) is titled as if it is focused on ruling out adverse events, the focus is actually on ruling-in and ruling-out AMI as the primary goal. From that perspective, the data have difficulties similar to other investigations that use this approach (3). Given the importance of AMI, sufficient numbers of patients of all types must be assessed to ensure that there are no gaps. Some residual problems include:

1. Rapid strategies must work in early as well as late presenters. Patients who overlap with the rule-out

strategy are those who present early when some still have very low levels of hs-cTn (4). Because biomarker release is blood flow dependent (5), it can take time in some situations for biomarkers to reach the circulation. There were 78 patients with AMI in this study, and only one-half presented <3 h after onset of symptoms. How many of these 39 patients presented in ≤ 2 h and how long it took to obtain baseline samples is unclear. In TRAPID-AMI (High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction), which is the earliest validation trial of this approach, it took 1.5 h (3). This issue of timing was highlighted by Vorlat et al. (6) in a study of hs-cTn release in angioplasty patients, in which significant delays before definitive biomarker signals were often seen. Shah et al. (4), utilizing very low values of hs-cTn I, reported that the negative predictive value of low values decreased from 99% to 95% in 125 patients evaluated within 2 h of symptom onset. Thus, there are early patients who have not only normal values but very low values. As indicated earlier, certain situations can cause later increases in hs-cTn levels. The lack of adequate numbers of these patients is a common problem with validation studies of this approach (3).

2. Sex matters. The paucity of patients with AMI makes it unlikely there will be differences in sex-associated parameters. However, sex differences are apparent in studies with hs-cTn that included larger numbers of patients with AMI (7). The frequency of AMI in the study by Mokhtari et al. (1) was not high, and roughly 60% occurred in male subjects. Because nonobstructive coronary artery disease is more common in women, the likelihood of finding smaller MIs when one enrolls only modest numbers is remote (8).
3. Specificity is not ideal. The specificity of the rule-in arm in the study by Mokhtari et al. (1) was 50% (Table 1); in TRAPID-AMI, it was 77% (3). This issue

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is important for cardiologists. The diagnosis of AMI requires a rising and/or falling pattern of cardiac troponin with at least 1 value >99th percentile of the upper reference limit and an appropriate clinical scenario (9). Many situations can cause rising and/or falling patterns of hs-cTn without AMI, and some of them do not require primary cardiologic care (10). In addition, the rule-in metrics, if applied to a broader population, would further degrade specificity. Focusing on a primary chest pain cohort includes fewer patients who present atypically, reducing the numbers of elderly patients and those with renal failure and diabetes. The specificity of a value such as 52 ng/l may look reasonable; however, in a population enriched with these groups who have higher baseline high-sensitivity cardiac troponin T (hs-cTnT) levels, the specificity will likely be lower. Furthermore, the precision of the hs-cTnT assay does not permit a distinction to be made between 3 and 5 ng/l, especially at low levels (11). For these reasons and the fact that it is unlikely that emergency departments will use different criteria for different subsets of patients, we risk admitting many patients to cardiology because they fit the rule-in arm when they have other primary medical problems, such as structural heart disease or chronic hs-cTn elevations, or because of assay imprecision.

4. Timing is always critical. The report (1) was sensitive to the issue of late presenters but provided few data about them. Patients who present late after AMI often do not manifest significant changes in hs-cTnT. In some studies, this group comprises 26% of the AMI population (3).

One of the aspects reinforcing the potential clinical applicability of the study by Mokhtari et al. (1) is that the 30-day major adverse cardiac event rate was modest: only 0.5% in the rule-out group compared with 2.2% when the risk assessment and ECG components were not applied. Thus, these additions help. However, how were these good outcomes achieved? More than 50% of the population received additional cardiovascular evaluations and perhaps even more noncardiac evaluations. The distribution of that

testing is unclear but likely contributed to their excellent outcomes. Is it possible that some patients at risk, such as those with unstable angina, were missed and salvaged by follow-up? It is unclear if—or how often—this occurred, and if it was in patients in whom only 1 sample was obtained before discharge. Indeed, the results of the present trial suggest that perhaps the good results seen in prior studies were helped by follow-up because their short-term incidence of mortality was trivial (0.1%) (12) as opposed to 2.2%.

The way forward is complex but clear. This trial (1) added a critical conceptual point about risk stratification and low-risk ECGs. However, before we implement these strategies, we need prospective clinical trials more than observational ones. Such trials should:

- Employ defined risk stratification and ECG criteria.
- Be of sufficient size to include large numbers of patients with AMI, including those who present early.
- Enroll diverse populations, including more women.
- Enroll “all comers” evaluated for AMI to refine the cutoff values necessary to optimize specificity. It is unlikely that any biomarker approach will ever allow these algorithms to have close-to-perfect specificity, but we should be able to get much closer.
- Compare this approach versus a strategy using very low values to rule out AMI (4).
- Evaluate the extent to which these approaches rely on follow-up investigations for their good results.

It should be clear that approaches should be capable of excluding AMI but not unstable angina. In addition, fulfilling criteria for “ruling-in” is not synonymous with AMI. We have started an important process, but at this point, the approaches suggested are not yet “good enough.”

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