Hopes, fears as users switch to new troponin

Karen Titus

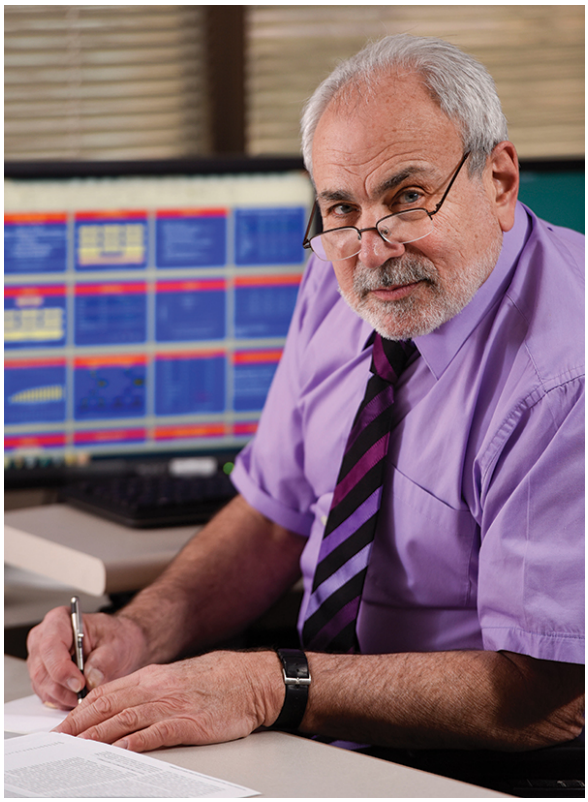
December 2017—The questions that arise over the use of highly sensitive cardiac troponin are as riveting as, if less historically fraught than, the Jefferson-Hamilton debates over the shape of their newborn country. Who should lead—the states or a strong central government? Cardiologists or the emergency department? What cutoffs represent the right balance between admissions, referrals, and sending patients home? And will Lin-Manuel Miranda ever write a smash musical about this cardiac assay?

Theory is now turning to reality, with the FDA's approval early this year of a next-generation troponin assay, Roche's TnT Gen 5 Stat. Like independence, its arrival has been eagerly awaited. And now that it's here?

Second of two parts

Cardiologists and emergency medicine physicians continue to look for that sweet spot, says Allan S. Jaffe, MD, with the former more interested in specificity and the latter more attuned to sensitivity. Because the new assay promises to deliver more sensitivity, "There is a reluctance by cardiologists to move forward," says Dr. Jaffe, who speaks from the pulpits of both pathology and cardiology at Mayo Clinic, Rochester, Minn.

"The reality is that when you use high-sensitivity troponin, you're going to have a lot more elevations," says Dr. Jaffe, chair, Division of Clinical Core Laboratory Services, with a joint appointment in the Department of Cardiovascular Medicine. "Cardiologists are concerned that many of the low-level elevations could be due to structural heart disease or other types of nonischemic etiologies that exist in many critically ill patients.



With the new highly sensitive troponin, says Dr. Allan Jaffe (right), "Rule-outs will be more secure. Rule-ins will be more secure. But only if we educate

people in how to use it properly."

"The ED's philosophy, because the ED tends to be risk averse," he continues, "is that they're concerned about not missing something. So they have a tendency to want to admit a lot of those people if they don't know what to do."

From there, the cardiologists' worries come roaring back. "Whether it's right or wrong, the cardiologists' point of view is, What do we do with these people? Do they all need angiograms?" says Dr. Jaffe, who is also a professor of laboratory medicine and pathology and a professor of medicine, noting that troponin as a marker is not specific for ischemic heart disease. And as testing increases, so do costs, potential morbidities, and fear.

These concerns aren't unique to Mayo. David Morrow, MD, director, Levine Cardiac Intensive Care Unit, Brigham and Women's Hospital, and professor of medicine, Harvard Medical School, says that if he were to ask an audience of cardiologists whether they desire a more sensitive troponin assay, he knows how the vote will go. "Less than half will raise their hands."

Nevertheless, use of the higher-sensitivity assay has many clinicians excited and willing to battle inertia. Those who champion the new test could channel their inner Alexander Hamilton, who—in the eponymous musical at least—repeatedly sings that he's not going to throw away his shot. Or as Dr. Jaffe puts it, "The time to do it is now. Don't miss the chance. This assay will add a tremendous amount of benefit when it's implemented."

Adds Judd Hollander, MD, an emergency medicine physician and senior VP for health care delivery innovation, Thomas Jefferson University: "Everyone is going to be using this within two years. There's really no reason to wait."

Playing the role of eager early adopter is Cleveland Clinic Health System emergency physician Rakesh Engineer, MD, whose institution rolled out the new assay on its main campus and one of its community hospitals in June.

A downside of early adoption was he and his colleagues could not turn to data from other U.S. institutions to guide them. On the other hand, creating something fresh allowed them to be responsive to the needs of their colleagues—a bottom-up approach.

The FDA's approval came at an opportune time, says Dr. Engineer, noting that Cleveland Clinic had been in the midst of a major cost-cutting initiative. The ED alone was tasked with trimming several million dollars from its budget. Given that 95 percent of the budget was allotted to staff salaries, "There wasn't a lot of fat to cut within the department, contrary to popular belief," says Dr. Engineer, director of best practices and innovations in the Emergency Services Institute. So he and his colleagues looked to reduce nonproductive observation stays, among other things. "We realized there's a lot of variability in the admitting process, or at least in who you decide to observe in the hospital to rule out for myocardial infarction."

Last month: Next-gen troponin: out of the gate, into labs

Originally the plan was to rely on the HEART score, a clinical decision rule that scores five components (patient history, ECG, age, risk factors, and earlier generation troponin measurement) from zero to two points. "My institute was pleased with this idea and thought it would work well," says Dr. Engineer. By some estimates, observations would drop by about 20 percent.

The plan jumped the track when it was presented to the cardiologists. As Dr. Engineer recalls, the negative predictive value of the tests was 98.3 percent—"which they felt was too low to be using systematically." Furthermore, he notes, American College of Cardiology guidelines state that despite widespread use of the HEART score, a two-troponin strategy is preferable.

With cardiologists uneasy, a two-troponin path seemed like the only possibility. But that didn't sit well with emergency physicians. "The problem is, if you get two troponins, then you've turned a short visit into one that's

maybe five or six hours, which would end up slowing down the emergency department and making the waiting room explode at the seams," Dr. Engineer says.

"So we had to find another strategy. And right about this time is when the FDA approved the assay," he says.

Given the lack of prospective U.S. studies, Dr. Engineer says he and his colleagues wanted to proceed cautiously. "We have to protect patients whenever starting something new and make sure everything was safe. And then we also needed to fine-tune the algorithm a little bit."

He and his colleagues relied on several European studies to develop their own algorithm, with one in particular doing the heavy lifting (Mokhtari A. *J Am Coll Cardiol.* 2016;67:1531–1540). This trial looked at a one-hour combination algorithm for fast rule out and rule in of patients with chest pain for predicting 30-day major adverse cardiac events. The approach combined a non-high-risk history, a nonischemic ECG, an initial high-sensitivity troponin less than 12, and a one-hour repeat delta <3, according to Dr. Engineer.

The negative predictive value was 99.5 percent, "and they missed zero MIs and 0.5 percent unstable angina in the subsequent 30 days," says Dr. Engineer.

For comparison's sake, Dr. Engineer offers a study, from 2000, of miss rates in U.S. EDs, which demonstrated a composite miss rate of 4.4 percent. Given the study is approaching legal voting age, Dr. Engineer says he suspects rates have since dropped. "But it's currently the best evidence that I'm aware of."

The Cleveland cardiologists agreed to the proposed algorithm. The initial plan was to start at a community hospital, he says, "for the reason that if you can succeed at one community hospital, most of the others will buy in. But if you succeed at the academic hospital, the community hospitals won't buy into that—the resources are completely different, the work force is different, the culture is really different." But the cardiologists asked for a main campus rollout as well, "because we had cardiology fellows available to consult on some of the sicker patients," including those with chronic kidney disease, end-stage renal disease, cardiomyopathy, congestive heart failure, and other conditions that can lead to a higher troponin level.

They also asked that during the pilot phase, the first blood draw be generally two hours after onset of pain. "That was just to be a little more cautious, so that we really were certain that we were hitting the upslope of a troponin if there was a myocardial infarction," says Dr. Engineer.

In addition to following the Mokhtari trial, Cleveland Clinic physicians used a modification of the HEART score. "We wanted to have a modified score of less than three," he says, adding, "It's completely reasonable to start with a low-prevalence population. This way we had a very, very low likelihood of missing anybody."

One long discussion centered on whether to have separate cutoffs for men and women. In the end, they decided against sex-specific cutoffs. Dr. Engineer says there was concern about providers who were trying to learn and incorporate a new test having to remember both a low rule-out cutpoint and a high rule-in cutpoint. Additional gender-specific cutpoints, they feared, would only add to the confusion and possibly introduce errors. There are no plans to revisit this, he says, since the current cutpoint is already more conservative.

Dr. Engineer notes that the algorithm was created with the input of laboratory medicine, cardiology, internal medicine, and the Emergency Services Institute. "We all signed off to say that this is going to be the new standard of care in the Cleveland Clinic—I think it's important to give providers some backing that the Cleveland Clinic believes in this process." It's not that physicians can't use the older methods, he says; rather, those who want to update their practices know they are doing so with the support of the health system. This is not trivial, he says. "Chest pain and myocardial infarction is the highest liability area for emergency medicine. So to ask people to change their practice, without some backing, will make people anxious."

He also says that those who plan to switch should expect ED physicians to feel a cognitive burden during the transition. "They're used to dealing with an algorithm that has a dichotomous cutpoint—the fourth-generation

troponin was either positive or negative. Now we have to separate cutpoints and make essentially three decisions: you're very low risk and go home; you're in the intermediate zone and need an extended rule out; or you're a high-risk patient and need to be admitted."

They also have to deal with new units—the new assay uses ng/L, rather than ng/mL. "Units are scary to people," Dr. Engineer says. "The intimidation factor is something we have to take into account."

He continues: "Yes, this is science. But there's also the emotional aspect of change." He keeps that in mind as he and his colleagues contemplate removing the older troponin test from the menu. "I can't force change upon people. I can help them gradually change so that they're comfortable, and only when everyone is ready will we get rid of the old test." It may take awhile. "We're trying to get CK-MB off the menu. At one hospital we're still trying to remove myoglobins." He pauses. "Certain people say it helps them."

As with any group, some physicians will adapt to the new routine more quickly than others. "Some people like change," he says matter-of-factly. "Some people don't."

Dr. Morrow is familiar with the concept. As Brigham and Women's has moved to set up the assay, "The fear by some cardiologists is much greater than the reality of what we will encounter," he observes.

The hospital has no shortage of physicians with research experience using high-sensitivity assays and who recognize their value, he says. Even so, they have expressed trepidation about the increased sensitivity, "in particular the increased number of patients who will have measurable values and what that may mean for clinical practice."

Dr. Morrow

Dr. Morrow predicts that high-sensitivity assays will eventually nudge users to take a different approach to evaluating troponin, as they grapple with whether an increased concentration reflects acute myocardial insult or chronic structural heart disease. "As many leaders in the field and the guidelines have said for a while, being attentive to the delta will be absolutely critical," he says.

He supports the idea of laboratories calculating their own deltas, saying it would be helpful to clinicians. "But I do recognize that each institution may have different potential barriers, depending on how their information systems are set up." At Brigham and Women's, he and his colleagues are still working out the details. Calculating deltas is relatively easy for ED troponins, he says, given the structured reevaluation over one to three hours. "But for the multitude of values that are measured in the hospital, you may have one-hour differences, you may have 12-hour differences, you may have troponins measured over three days," Dr. Morrow says. "And how to handle that is not something that has been tackled in the literature."

He and his colleagues are also grappling with whether to use the package insert. But the biggest day-to-day issue, apart from seeing a spike in patients with measurable values, may be the change in units, Dr. Morrow says. "Everyone is going to have to get used to seeing 100 rather than 0.1." Referrals may add to the stress. "We may get patients coming in from outside hospitals who are using a current-generation assay. So I think we will have to recalibrate clinicians, too, and their clinical instincts, when they undergo unit changes between assays and hospitals."

Ultimately, says Dr. Morrow, for clinicians who use a higher sensitivity assay with good understanding, "you will only improve medical care. I think it will be critical for laboratorians to help cardiologists understand that."

Dr. Jaffe speaks bluntly about the challenges posed by some of his colleagues. "Cardiologists have been opposed to even think about it," he says. Their negativity has been matched by an unwillingness by many to follow developments in the troponin literature, he says, which in turn means more effort will have to be pumped into educational efforts before Mayo can adopt the assay.

Dr. Jaffe recently coauthored a paper addressing the issues and controversies related to use of the higher sensitivity assay (Sandoval Y, et al. *Am J Med.* 2017;130:1358–1365). Among other items, the authors suggest using 1) sex-specific 99th percentile upper reference limit values of 10 ng/L for women and 15 ng/L for men, and 2) a two-hour rule-out strategy, including a value less than the 99th percentile upper reference limit and the lack of a change in values of 100 ng/L, a change ≥10 ng/L at two hours, or both.

Dr. Jaffe disagrees with arguments that sex-specific cutoffs don't make a difference. "I think one of the reasons they don't seem to make a difference is because it hasn't been looked at adequately," he says. "There would likely be differences if people looked specifically at female groups in a more comprehensive manner," especially given that women have a higher number of subtle, atypical disease presentations and thus may be screened out in many studies that focus on chest pain patients. Sex-specific cutoffs will be important for many of the other uses of high-sensitivity troponin assays, such as in primary and secondary prevention, Dr. Jaffe says. "So I think that it's worth doing and getting clinicians used to different cutoffs."

He also takes issue with an aspect of the one-hour rule-out algorithm in European Society of Cardiology guidelines—a small change criteria of 5 ng/L to rule in. "This assay does not have adequate precision to make that distinction," Dr. Jaffe argues. Moreover, many European studies on which the guideline is based screen many patients out. "They don't take the critically ill patients. They eliminate renal failure patients. They don't include many of the elderly and women because they present atypically. Thus, you're going to end up needing a whole other set of metrics for another large set of patients, and it's going to get cumbersome and complicated."

From the lab's perspective, he says, "We're perfectly capable of developing whatever metrics we need to. But we've got to get everyone on the same page. We can report anything we want in the lab, but if it doesn't meet the metrics that the clinicians require, we've got real troubles."

Cardiologists suffer a bit from a not-in-my-backyard syndrome, he says, when they contemplate a bump in the number of elevated values. If they have to care for a substantial number of patients with elevated troponins but noncardiovascular primary disease, "the cardiologists will have an impossible job. There's just too many of those patients," Dr. Jaffe says. "Some people have even said it overtly: 'Why do you want to add an assay that adds more noise to the equation?'"

Going forward, Dr. Jaffe has a clear vision in mind. "We're going to start out conservatively. There are gaps in the data, in my opinion, that has shaped the way this is used in Europe. So I want to be careful, in the interest of protecting patients."

Yet he's clearly excited about the test's potential. "This assay will allow people to move out of the ED much more quickly. Rule-outs will be more secure. Rule-ins will be more secure. But only if we educate people in how to use it properly." Not only does the lab have to provide appropriate materials, "but our colleagues have to be open-minded and willing to listen and deal with the information we're trying to provide. We do that, and it will be a win-win, and everybody will be happy."

If not, he warns, "This could turn out to be really dysfunctional."

For all the cardiologists' concerns, ED physicians have concerns of their own. "A lot of them, actually," says

Dr. Engineer, recalling the rollout at Cleveland Clinic.

Dr. Rakesh Engineer at the Cleveland Clinic. Early adoption of the next-generation troponin had a downside: He and colleagues could not turn to data from other U.S. institutions to guide them. But creating something fresh allowed them to be responsive to the needs of their colleagues—a bottom-up approach.

The first was what to do with an intermediate value (12 to 52 ng/L). Generally, says Dr. Engineer, patients who fall into this category will be observed. But there's a wrinkle: What if a nurse orders a troponin at triage (without the benefit of taking a more detailed history), or a physician's assistant orders the test on a patient who normally would not need to be ruled out? If those results fall into the intermediate range, went the worry, would those patients be kept unnecessarily, and would it lead to increased testing?

Cleveland Clinic decided to implement physician-only ordering at Hillcrest Hospital while allowing nurses and PAs to order it at the main campus. With this approach, the overall discharge rate was much higher at the main campus. The Hillcrest physicians mainly ordered the test on patients they thought could be sent home; at the main campus, the test was ordered on the majority of patients. "Sometimes we were surprised—we had patients we would have thought needed observation who, lo and behold, could actually go home" based on a non-high-risk history, nonischemic ECG, and the serial high-sensitivity troponin, Dr. Engineer says.

He also had to clear up early confusion regarding decision support. His colleagues found the criteria from the Mokhtari trial somewhat befuddling, so Dr. Engineer developed a decision tree. "Almost like a flow chart," he says. "That helped a lot." Then there was the matter of revising a "clumsy" computer clinical decision support tool, as well as removing an awkward decision note within the algorithm that called for using 14 as a rule-in for patients

with either a high-risk history or an ischemic ECG, since those patients would be admitted anyway.

Non-MI patients—those with renal disease, cardiomyopathy, CHF—are treated according to the same algorithm. “If your numbers are really, really low, and you meet the low-risk criteria, you’re going home,” says Dr. Engineer. “But that doesn’t happen very often. Most will be observed and undergo the extended rule-out, like they had previously.”

Dr. Engineer saw two main objectives for adopting the assay. No. 1, he says, was to give emergency physicians a tool to discharge patients when they weren’t 100 percent certain. “Say you’re 95 percent sure—but five percent is too much to miss,” Dr. Engineer says. The new approach gets those patients home. “That’s how most people see this test.”

A second objective—though this one is less talked about—addresses the variability in clinicians’ practices. Dr. Engineer concedes that he might discharge a patient whom another ED colleague would just as easily admit. “If we can reduce that variability, both between providers as well as between facilities, then you’re going to have more happy patients as well as lower costs in delivering that care. So that’s the long-term goal, but it’s going to take a little while to get there.”

Dr. Engineer’s focus, understandably, has been on the needs of his clinical colleagues, both within and outside the ED. But he goes out of his way to praise the role of the laboratory in making the troponin transition. “Our interactions have been fantastic,” he says. If he sounds a bit surprised, well, he is. “The lab has a lot to offer, but as clinicians, we just don’t run into each other very much, the way we do with cardiologists who come down to our department.”

In Philadelphia, Dr. Hollander has long been interested in a higher sensitivity troponin and plans to launch it at Jefferson University Hospitals in the next few months. “Unless somebody stamps up and down and screams too much,” he says.
Does he anticipate a stop-the-wedding moment? “We do,” he says. “But we expect to educate enough that they jump on board.”


Dr. Hollander

Dr. Hollander takes a deep breath and a step back to try to settle physicians’ concerns. “What everyone should get grounded in is the fact that it really is just better for patients. When you play the math, with these higher-sensitivity assays, you should be able to discharge about twice as many patients from the emergency department” versus the older assays, “and you should be able to do it considerably faster, with a lower miss rate and a high negative predictive value.”

There’s no doubt in his mind of the value to patients. “Being able to tell twice as many patients they don’t have a condition that could kill them—because that’s what they’re worried about—and in fact they have nothing wrong, and to send them back home to their families in a couple of hours, is a huge benefit.”

The resistance to higher-sensitivity assays, he says, stems from providers who don’t understand how to use them and haven’t for years. In the early days of troponin use, he notes, education rested on a swift maxim: If a patient’s troponin is elevated, they’re having a heart attack. “That never was true, and it’s not true now. But if you’re a doctor who still believes troponin equals MI, you’ve missed the boat for a long time.” He marvels at the mental fog that continues to envelop the test. “Every time I give the same lecture to the same group of people, it’s like they

never heard it before. I can't dumb it down any more."

Historically, he notes, troponin was the answer to specificity, which has turned out to be one of medicine's Lost Cause myths. And 20 years ago, he continues, 24-hour rule-outs were the norm. Eventually providers became comfortable with six to 12 hours. Given that context, the Twitter-like shift to one to three hours should not be highly discomfiting.

To counter ongoing myths, he and his colleagues plan to ratchet up their educational efforts before the rollout. He anticipates using two non-sex-specific cutpoints (rule in and rule out), with a two-hour second measurement when needed to look for a rising delta.

The new approach will likely boost from 10 percent to 30 percent the number of patients requiring additional care. "If you give them all to the cardiologists, they're going to hate the ER docs," Dr. Hollander says, since the majority won't have coronary disease requiring intervention. "The ER docs are going to have to be smarter, or the cardiologists are going to be miserable"—unless they're fee-for-service, he jokes.

To prepare his colleagues and to nip confusion in the bud, "We're going to have more stuff written on the lab slips than we normally do, and we're going to do town halls, which we never do when we roll out a new assay, and offer to go in-service people on their grand rounds and departmental meetings," he says. "Even though doctors are reasonably smart people, they're not really good at thinking about any one lab test that's not their area of expertise." The goal, at heart, is to educate those who call the cardiologists. The laboratory has been quite involved, he says. "I give them an enormous amount of credit."

The added effort will pay off, Dr. Hollander predicts. "Higher sensitivity troponins are great for patients."
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