With high-sensitivity troponins, watching and waiting continue

Karen Lusky

May 2016—Laboratories and hospitals in the U.S. continue to look forward to high-sensitivity troponin assays. Judd E. Hollander, MD, says all he's heard for the past five years is that an assay will be out at the end of the year. "And once you get halfway through the year, it will be out next year," says Dr. Hollander, chair of the Department of Emergency Medicine and associate dean of strategic health initiatives at Sidney Kimmel Medical College of Thomas Jefferson University.

Robert Christenson, PhD, DABCC, professor of pathology at the University of Maryland School of Medicine, sees the odds as good that the FDA will clear one such assay this year. He predicts it will be a Roche or an Abbott assay.

Agim Beshiri, MD, Abbott's senior medical director of global medical and scientific affairs for diagnostics, says, "The requirements for U.S. regulatory approval for any troponin test are very high, and the complexity is enhanced with high-sensitivity troponin methods. It is not possible to predict when these tests will become available."

Dr. deFilippi

The FDA appears to have two concerns, says cardiologist Christopher deFilippi, MD. "First, there is the whole 'false-positive' issue for diagnosis of acute myocardial infarction." The FDA fears too many patients will receive unneeded testing, which could potentially include cardiac catheterization. Second, by excluding patients with recent MIs, end-stage renal disease, or cardiac procedures, prior studies may not have reflected the all-comers population that presents to the ED, which implicitly decreased the number of subjects who had elevated cardiac troponin values without an acute MI, says Dr. deFilippi, vice chair of academic affairs, Inova Heart and Vascular Institute, Fairfax, Va.

Fred S. Apple, PhD, medical director of clinical laboratories at Hennepin County Medical Center in Minneapolis, says he's concerned about the FDA's slowness to clear high-sensitivity cardiac troponin I and T assays. "The evidence-based literature on these assays is overwhelmingly positive for improving patient management and outcomes," he says. "Internationally, hospitals are replacing contemporary assays. Only the U.S. hasn't been allowed to bring these high-sensitivity assays into the mix."

Dr. Apple doesn't know whether the problem lies with the FDA or the companies or both. He proposes that the FDA have a white paper to hand to every company that details the basics of analytical and clinical studies that need to be performed for the FDA to look at a high-sensitivity troponin submission for 510(k) clearance. "Imagine the positive impression this would have on diagnostics and clinical research allowing for uniform submission and better comparisons between assays," he says.

Experts agree that getting the tests to market soon is important.

"Getting to use high-sensitivity troponin in the U.S. is terribly important and will revolutionize the ability to detect patients who have chronic comorbidities and improve the ability to ferret out those who have acute myocardial infarction from those who do not," says Allan S. Jaffe, MD, professor of medicine and cardiology and professor of

laboratory medicine and pathology, Mayo Clinic, Rochester, Minn.

Speaking last year in an AACC session on troponin, Dr. Hollander said the high-sensitivity troponins from the emergency department perspective "can be a game-changer, but we need to be smart."

"The way that I think we need to think about this, particularly in the emergency department, is troponin is myocardial injury if it's elevated—always," he said. "We need to determine acute from chronic." Acute myocardial injury has a changing troponin value. "It's going up or it's going down. But not all acute myocardial injury is acute myocardial infarction.

"Probably most acute myocardial infarction needs a cardiologist. Not all acute myocardial injury may need a cardiologist," he added. There may be, for example, a pneumonia or sepsis to treat. "So we need to determine acute MI from other causes of acute injury, and I think that's our challenge as we look at this."

Dr. deFilippi said in a talk at CAP '15 that looking at the change in high-sensitivity cardiac troponin and the absolute value of change may be "what saves the day" and differentiates patients who have underlying cardiovascular disease that's not acute coronary syndrome from those who have ACS.

Aside from acute MI, most elevations of cardiac troponin are due to chronic etiologies, but suspicion should be maintained for other causes of an acute elevation, Dr. deFilippi says, such as a pulmonary embolism.

Dr. Christenson

"All the information," Dr. Christenson tells CAP TODAY, "is that an elevated troponin is bad whatever the cause," whether it's heart failure, MI, myocarditis, or trauma. "They all portend a worse diagnosis." Thus, clinicians would look for some reason for the elevated troponin even if it's a suspected interference, which would mean a false-positive. Will interferences be a problem with high-sensitivity troponin? Yes, he says, "at least to some extent, and possibly the diagnostic specificity may be lower. We must remember that even high-sensitivity cardiac troponin is an organ-specific marker and not a disease-specific biomarker." Manufacturers will do everything they can to mitigate interferences, he says, but eliminating 100 percent of interferences is going to be complicated.

Dr. Hollander believes a pathway and guidelines need to be developed that say it's acceptable to discharge patients from the ED with elevated troponins or to put them in observation. "We're not going to go overnight from admitting everybody with a whiff of troponin to sending home a bunch of people with elevated troponin," he says. "So we need to bridge the gap." Using a contemporary sensitive assay with an upper reference limit of .01 ng/mL, Jefferson is putting patients in observation as long as troponin levels are below 0.1 ng/mL and not rising. "People get used to that really fast," he says. "But that's a bridge to ultimately being able to send some of those people home."

The Royal Wolverhampton NHS Trust (RWT) in the United Kingdom has been using the Abbott Architect Stat High Sensitive Troponin-I assay with a chest pain pathway since April 2013, say Kate Willmer, MBBS, FRCP, consultant acute physician, and Clare Ford, PhD, consultant clinical scientist, in the Department of Clinical Chemistry at RWT. "The way the pathway has been developed means that we have a reliable method of assessing those patients with elevated troponin levels for any cause which has meant the number of negative workups has not increased significantly," they told CAP TODAY in an email.

Before bringing the high-sensitivity troponin I assay on board, RWT used a high-sensitivity cardiac troponin T assay with a 12-hour pathway that had been for contemporary sensitive assays, they explained.

According to an updated abstract on the new chest pain pathway, which Dr. Willmer made available to CAP TODAY, RWT has an admission high-sensitivity troponin I of ≤1.9 ng/L cutoff for discharging patients with suspected ACS. They do not discharge patients whose first troponin value was obtained within one hour after their chest pain began, Dr. Willmer noted. "The troponin may not yet have had time to go up, as evidenced by the patient who had her troponin taken 15 minutes after collapsing with a cardiac arrest outside the ED and had a troponin less than 2 ng/L," she said.

The abstract says that low-risk patients who have a high-sensitivity troponin I above the cutoff go to a clinical decision unit to wait for a troponin result from another specimen, which initially was drawn six hours after admission. Now the interval between samples is three hours based on the October 2014 NICE (National Institute for Health and Care Excellence) guidance for early rule out of MI. Patients determined to be high risk go to the acute medical unit.

Using the pathway with the Abbott assay reined in hospital admissions for chest pain from 60.9 percent to 38.4 percent. The authors write in the abstract: "The negative predictive value of hs-cTnI ≤1.9 ng/l on admission for MACE [major adverse cardiac events] at 30 days and 9 months was 99.6 percent (95 percent CI 98.9–99.9) and 98.4 percent (95 percent CI 97.2–99.1) respectively."

In addition to the rapid triage approaches that can be adopted when using high-sensitivity troponin assays, there are already "hints," Dr. deFilippi says, that the lower troponin values they detect can be used to guide treatment. For example, the PLATO study showed that the antiplatelet drug ticagrelor was superior overall to the generally lower-cost generic clopidogrel in treating patients with acute MI, he says. An abstract of a study published in Circulation, however, says: "Ticagrelor versus clopidogrel reduced the rate of cardiovascular death, myocardial infarction, and stroke in patients with NSTE-ACS [non-ST-elevation acute coronary syndrome] and hs-TnT ≥14.0 ng/L in both invasively and noninvasively managed patients; in patients with hs-TnT Circulation. 2014;129:293–303). Although the research is a post-hoc retrospective analysis, Dr. deFilippi says, "it raises the possibility that care can be directed by [troponin] levels only measurable with high-sensitive assays. More studies will be forthcoming."

The more sensitive testing could be a plus for women. Dr. Apple, who is also a professor of laboratory medicine and pathology at the University of Minnesota, says laboratorians and clinicians who know the cardiac biomarker area sufficiently well should understand that men usually have larger hearts than women, and with the natural turnover of cells, different distributions of cardiac troponin can be expected to be seen. "We haven't been able to see that male-female difference because the contemporary assays currently used only measure less than 20 percent of the normal population and even a smaller percentage of women," he says.

Dr. Jaffe

Dr. Jaffe of Mayo Clinic says he's an advocate of using sex-specific cutoffs for high-sensitivity troponin. It's known that women who have heart disease or have had an MI do worse than men despite the effective therapies seeming to help women just as much as they help men, he says. One reason women don't fare as well, Dr. Jaffe adds, is they aren't as rapidly detected and treated or in some cases they're not treated at all.

“In almost all of the studies with high-sensitivity troponin, there are substantial differences in the normal ranges between men and women, with men having higher values than women.”

In addition, women have a higher percentage of nonobstructive coronary artery disease and therefore are less likely to have higher troponin values, Dr. Jaffe says. “So women with ischemic heart disease are enriched with that subset that can be hard to detect. In order to bring that out, you need to have large numbers of women who are having heart attacks, and most studies do not have adequate numbers to document the need for sex-specific cutoff values.” The large studies show, he adds, that the use of sex-specific cutoffs markedly improves the diagnosis of acute MI and, with treatment, lives are saved.

Dr. Apple reports that Hennepin County Medical Center recently closed the database on a clinical trial called UTROPIA (Use of Abbott High Sensitivity Troponin I Assay in Acute Coronary Syndromes), funded partially by Abbott. In the study of 1,700 patients, they found that the assay’s cutoff of 16 ng/L for females and 34 ng/L for males resulted in more women being diagnosed with MIs. “The male MI rate didn’t really change compared to the contemporary [Abbott] assay,” he says.

Dr. Apple

In the AACC session last year, however, Dr. Apple presented the case of a 56-year-old woman who was thought to have acute MI based on the contemporary troponin assay. Using the overall cutoff for the high-sensitivity troponin I assay, the patient’s troponin values seemed to be normal. But in applying the sex-specific cutoff for a female, they saw a trend in which all the values were abnormal without a rising or falling pattern. The patient had a chronic troponin elevation that would be diagnosed as a non-ACS myocardial injury.

Dr. Apple explains that the “analytical noise of imprecision” of the contemporary assays may show false troponin elevations that might be, and in the aforementioned case were, interpreted differently compared with the more precise analytics of the high-sensitivity troponin assay, which would not have shown imprecision-related changes. He says that in their study, they probably saw five to 10 cases like that out of the approximately 200 MIs identified by the contemporary assay that wouldn’t have been MIs if adjudicated based on the high-sensitivity troponin I assay.

Dr. Jaffe presented the case of a 78-year-old male with a history of coronary bypass who had an aortic aneurysm repair. The man “had claudication, so was living with angina but in point of fact really wasn’t exerting himself very much,” he says. His chest X-ray and creatinine were okay and a high-sensitivity troponin was at the upper limit of normal. A baseline NT-proBNP was in line with someone with heart disease. The patient was taking numerous cardiac medications and had a lengthy surgery.

“On day two something went wrong, and when we got some additional values, his troponin was elevated, his NT-proBNP was elevated, his ECG was unchanged. So what’s the diagnosis? Well, you could argue this is heart failure, acute heart failure,” he said. “But you could also argue that this guy had had some ischemic injury.”

Although not yet proven, “one of the interesting and likely good strategies that will evolve,” Dr. Jaffe predicts, is getting a baseline high-sensitivity troponin result in patients going to surgery who are thought to be at possibly high risk so that it’s known whether they have a rising and/or falling pattern postoperatively. “This is critical because there can be chronic elevations of cardiac troponin associated with chronic structural heart disease. And one always should try to distinguish elevations that are new and acute from those that are due to structural heart disease,” he adds.

This is especially important for older individuals, who tend to have higher troponin values, he says.

Though he favors sex-specific cut-offs, Dr. Jaffe is not an advocate of developing age-specific cutoffs. “Sex isn’t a comorbidity. We could argue about that—but let’s not.” He does believe, based on research he and colleagues have done, that the troponin changes that occur with age reflect comorbidities. “If you start trying to correct for every comorbidity and use different cutoff values, it would confound the field because there are so many things that increase troponin,” Dr. Jaffe says. The better way, he adds, is to rely on a changing pattern of values.

Dr. Apple says it’s important to keep in mind that an elderly person may have increases above the current 99th percentile upper reference limits. “However if you are going to rule in MI, you still have to look for a rising and/or falling pattern. That’s the key to ruling in.”

Dr. Apple predicts that as high-sensitivity assays become better studied, age-related cutoffs will be considered if appropriate reference individuals can be identified. “We already know something happens when you hit 60. You start observing increases above the published 99th percentile that was likely defined in subjects under the age of 60. The problem is, how do you define normality in 60, 70, 80 year olds? Not an easy clinical task.”

Margot LeClair, product manager at Beckman Coulter, which has in development a high-sensitivity troponin assay, says the 99th percentile is specific to each troponin assay. “Unfortunately, troponin assays aren’t standardized across the board, and another issue you get into is that the 99th percentile upper reference limit can vary based on how you set up your reference population study.” Based on two schools of thought, a patient population more representative of an ED population can be selected, or a healthier population can be selected, LeClair says. The 99th percentile upper reference limit will be higher in the former instance, lower in the latter. LeClair notes that a high-sensitivity troponin assay has to be capable of detecting troponin values in more than 50 percent of the healthy population.

It’s likely to be up to each hospital’s ED, cardiology department, and laboratory to work together to determine what reference intervals they want to establish, she says. The manufacturers establish a 99th percentile for their assays based on the reference populations they studied, which laboratories can use.

Is it possible to have an MI with a troponin value that doesn’t exceed the upper reference limit? According to the Third Universal Definition of Myocardial Infarction, a rising and/or falling cardiac troponin pattern must include a cardiac troponin concentration with at least one value above the 99th percentile, Dr. Apple points out. “However, with the new high-sensitivity assays, a rising and/or falling cardiac troponin pattern that remains within the 99th percentile range [with all measurements providing interpretable numbers] should be carefully considered as a potential etiology for a small myocardial injury that may include an MI,” he cautions. In evaluating these patients, clinicians need to consider imaging, ECG, and clinical presentation.

Dr. Hollander

When using the high-sensitivity assays, Dr. Hollander says, “we will be detecting myocardial injury much, much earlier and at smaller values. So in effect what we used to call ischemia, we might now call myocardial injury, but it’s a small degree of myocardial injury.”

Most MI patients have atypical rather than classic chest pain, he adds. “So once you take everybody who rolls through the door with some type of chest pain and you say, ‘Well, the [troponin] markers are negative, it might still

be ischemia,' it's impossible to get out of that loop," Dr. Hollander says. "But if everybody with ischemia actually had a small degree of injury and the [troponin] markers were either positive, meaning you have the disease, or negative, meaning you don't, everything gets much easier." With the high-sensivity assays, "I think we are going to get really, really close to that."
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Karen Lusky is a writer in Brentwood, Tenn.