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Best Practices for Monitoring Cardiac Troponin in Detecting Myocardial Injury

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Cardiac troponin [cardiac troponin I (cTnI) and cTnT] has become globally recognized as the standard biomarker for the diagnosis of acute myocardial infarction (AMI).[8] With improvements in the analytical characteristics of cardiac troponin assays, particularly imprecision at low measurable concentrations, high-sensitivity cardiac troponin (hs-cTn) assays are now being implemented worldwide; but not in the US since the Food and Drug Administration has not yet cleared them for clinical use. With the implementation of hs-cTn assays, improvements in clinical care are beginning to be observed in the peer-reviewed literature. These improvements include early rule out (early hospital discharge) and rule in (right bed for appropriate patient) for MI and improved risk stratification for patients presenting with symptoms suggestive of ischemia, with improved short- and long-term outcomes. Further hs-cTn assays have been part of solidifying the definition of myocardial injury, based on an increased cardiac troponin concentration above the 99th percentile upper reference limit. The high-sensitivity assays have improved the clinical understanding that not all cardiac troponin increases are MI and that patients with nonischemic disease also have increases in cardiac troponin that must be managed accordingly. This Q&A provides the opportunity for 3 cardiologists, 2 laboratory medicine scientists, and 1 emergency medicine physician to share their experiences with the evolving role of cardiac troponin testing in their practices. Ideally, the messages they share will assist in better harmonizing the appropriate utilization of high-sensitivity assays worldwide as we transition away from contemporary cardiac troponin assays.

Should all medical centers have a uniform serial order set to assist in ruling in/out AMI? Should a single cardiac troponin order be available? What would your ideal serial order set (timing) be?

Allan S. Jaffe: Medical centers would benefit from developing consistent, uniform serial orders to rule in/out AMI. These serial orders should be agreed to by emergency medicine, cardiology, internal medicine, and laboratory medicine. Given that we do not have hs-cTn assays available in the US, the best timing is still 0 (presentation), 3, and 6 h. Because many patients present late, the vast majority of rule in/out and risk stratification action is likely to occur within 3 h of the onset. Single cardiac troponin orders with the current contemporary assays are rarely of use but may have a role if one is interested in estimating infarct size. The value that correlates best with MRI-determined infarct size is the 72–96-h value. What should be discouraged, however, is the idea that one should start to rule in/out AMI and then truncate that procedure. In essence, when you start such a procedure it implies that there is at least some reasonable possibility that acute ischemic heart disease is present.

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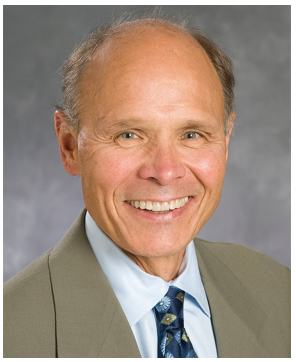
[8] Nonstandard abbreviations: AMI, acute myocardial infarction; cTnI, cardiac troponin I; cTnT, cardiac troponin T; hs-cTn, high-sensitivity cardiac troponin; ACS, acute coronary syndrome; ECG, electrocardiogram; LoD, limit of detection; EHR, electronic health records; URL, upper reference limit; LV, left ventricular; ICD, International classification of diseases.



Scott Sharkey: Cardiac troponin testing should be standardized throughout the US and preferably internationally, and single cardiac troponin testing should be allowed. Admission (0 h), 3, and 6 h serial orders are preferred. Timing should be from admission and not from symptom onset, as it is too hard to make a determination when symptoms began in many patients and would make timing difficult.

Peter Kavsak: Having a standard serial order set would be an ideal situation. However, this is often difficult to achieve. In our hospital network, it was only through collaboration between emergency medicine, internal medicine, laboratory medicine, and cardiology that we were able to go to a standard serial order set in the emergency department and this was only possible when we transitioned to an hs-cTn assay. Presently, the laboratory does not place any restrictions on cardiac troponin testing. We have observed that a number of emergency department patients do not have a second cardiac troponin order, so clinically a single cardiac troponin result is being used. Currently, with an hs-cTn assay we have adopted a 0- and 3-h protocol, with interest from emergency medicine to shorten this time frame further.

Michael C. Kontos: The optimal order pathway/order set should include 2–3 samples, with the second sample collected 2–3 h after the first (depending on assay) and the third one 6 h after the first. The third sample should be an optional one that is based on risk (i.e., low-risk patients based on standard scoring scheme would have 2 samples, while intermediate-risk 3 samples). Our current pathway allows this ability to check specific samples and a 0-, 3-, and 6-h set. Although much has been made of using a single sample for patients who present hours after symptom onset, I believe this can be confounded by an inaccurate history, in which the symptoms have been waxing/waning and the patient presents acutely due to substantially worsening symptoms. A single sample should be limited to those who have been symptom free for 2–3 h. Not asked in the question is what the optimal reporting should be. For patients having serial sampling, the absolute change between the 2 values should be reported, highlighting those values that exceed the recommended value defining a significant change for that assay. We implemented this approximately 1–2 years ago, and it has decreased the degree of confusion in trying to determine if the patient has acute coronary syndrome (ACS).

Amy K. Saenger: I think that a standardized chest pain protocol with defined serial draws should be implemented within a medical center/health system. Ultimately this would provide measurable results in terms of optimizing patient care and outcomes. In my experience, streamlining the phlebotomy draws in the order set helps substantially. In the emergency department the clinician only has to order the chest pain protocol and all of the subsequent timed cardiac troponin samples are automatically queued and ordered behind the scenes. This eliminates errors related to missed orders and/or forgetting to draw the cardiac troponin sample at a specific time. A standard timed collection protocol also helps define what a clinically significant "rise and/or fall" of cardiac troponin is in a given AMI population because δ calculations require fairly stringent collection protocols. One challenge is adhering to the American Heart Association, College of American Cardiology Non-ST Elevation-ACS (AHA/ACC NSTE-ACS) guidelines, which state that clinical laboratory reports should indicate whether a clinically significant acute change in cardiac troponin has occurred, specific to the assay used. While a uniform ±20% change or ±3 SDs of the baseline cardiac troponin concentration is recommended to define a clinically significant change, in reality we do not know for certain if these are the most accurate values for each assay, nor is this information defined in the manufacturer's package insert. Ideally, a clinical study would probe and define an appropriate δ (change value) using the same set of patient samples and adjudicated based on the hs-cTn result as the gold standard. Without this information it is unrealistic to expect clinical laboratories to broadly implement reporting deltas. I would not completely limit ordering cardiac troponin as a serial order set, although one could argue that

only serial order sets (not single cardiac troponin orders) should be available in the emergency department. Cardiac troponin is also used for risk stratification in other, non-ACS populations. Therefore, limiting cardiac troponin orders to only a serial order set could lead to inappropriate and/or overutilization of the test. An ideal serial order set would be 0, 3, and 6 h based on contemporary cardiac troponin assays. With hs-cTn assays I would advocate for a 0 and 2 h protocol, with the option to order additional testing at a later time point to account for late presenters. I have reservations about a baseline and 1-h sample providing relevant information regarding an acute serial change in hs-cTn unless the phlebotomy collection timing is very strict and turnaround time for results is rapid. Limits around the timing of collections should also be defined and implemented based on the efficiency and logistics of the clinical practice.

Stephen Smith: Yes, there should be some flexibility in select cases. For instance, there are times when it is beneficial to get a second cardiac troponin measurement very soon after the first. In such a case, strict adherence to an every 3 or 4 h schedule could delay diagnosis. In some patients with acute coronary occlusion, the electrocardiogram (ECG) is not normal but also not diagnostic of ischemia, and the first cardiac troponin is below the limit of detection (LoD) or <99th percentile. These patients frequently have delayed diagnosis, and by the time the second cardiac troponin result returns it may be 4 h after presentation in the emergency department (e.g., the first cardiac troponin is drawn at 30 min after arrival, is resulted at 60 min and is "negative"; the second is drawn at 3.5 h after presentation and resulted at 4 h). By this time, the infarct is complete. In occasional cases in which the first cardiac troponin (0 h) is negative, it is beneficial to check a 1 h to be certain that cardiac troponin is not rising rapidly. There are studies using 0 and 1 h or 0 and 2 h hs-cTn to "rule in" MI, but they have not been promoted for contemporary cardiac troponin assays, which are the only cardiac troponin methods currently available in the US. I would not promote every 1-h contemporary cardiac troponin for rule out MI. There is only anecdotal data on such an approach for rapid rule in of MI, but I believe it may be important in select cases. A single cardiac troponin should be available in patients for whom AMI is a secondary concern. It is important for patients who need to be admitted to the hospital for 1 condition, but also need to be screened for myocardial injury. A single cardiac troponin is also very useful for low risk patients with prolonged chest pain who will be discharged. For them, any subsequent orders in a set will be automatically cancelled when the patient is no longer in the hospital and available for blood sampling. Clinical orders would be as follows. For a usual patient and when using contemporary cardiac troponin assay: 0, 3, 6, 9 h; revised when using hs-cTn to 0, 1, 3, 6 h, or 0, 2, 6 h, depending on the assay. For a high-risk patient and using contemporary cardiac troponin assay: 0, 1, 2, 3, 6, 9 h; revised when using an hs-cTn assay to 0, 1, 2, 3, 6 h.

Should the ordering of cardiac troponin be limited to the diagnostic use for AMI? For what other clinical situation would you order cardiac troponin?

Allan S. Jaffe: Using contemporary assays, cardiac troponin is predominantly used to diagnose AMI. However, even with contemporary assays there are data to suggest that there is useful risk stratification information in patients with congestive heart failure and that chemotherapy toxicity can be detected with approaches that might mitigate or to some extent obviate the severity of such toxicity. In addition, critically ill patients with increased concentrations are at increased risk of adverse events, predominantly mortality. It is not clear how one should use the data in this latter group; it does suggest, however, that once these patients survive the acute episode, and assuming they do not need emergent cardiovascular care, they should be evaluated to determine the reasons for the underlying increases in cardiac troponin, which likely reflect either chronic or acute cardiovascular issues.

Scott Sharkey: Other reasons for ordering cardiac troponin include suspected pulmonary embolism, aortic dissection, Takotsubo cardiomyopathy, acute myopericarditis, and possibly other conditions (chemotherapy, sepsis, acute stroke, and even post-noncardiac surgery).

Peter Kavsak: Cardiac troponin ordering should be limited to the investigation of myocardial injury, of which AMI is a subset. This is aptly illustrated in the Third Universal Definition of Myocardial Infarction. This is an exciting area and the possibilities are not endless, but there are many potential roles for cardiac troponin, especially for high-sensitivity assays, to improve patient care.

Michael C. Kontos: Cardiac troponin can be ordered for myocarditis, pericarditis, pulmonary embolism, and chest pain.

Amy K. Saenger: Although there is presently a large focus on defining the clinical performance of hs-cTn assays for the diagnosis of AMI and strategies for rapid rule out, the greatest potential for hs-cTn likely resides out-

side the emergency department. Cardiac troponin is equally important in the area of risk stratification, where increases clearly hold prognostic significance with contemporary cardiac troponin assays. This is magnified to an even greater extent with hs-cTn assays; applications include chronic kidney disease, amyloidosis, and heart failure patients. It would be challenging, even from an operational standpoint, to completely limit use of cardiac troponin for only the diagnosis of AMI.

Stephen Smith: Cardiac troponin helps to risk stratify many acute and chronic pathological conditions involving myocardial injury. It is useful to identify and/or risk stratify myocarditis, Takotsubo cardiomyopathy, pulmonary embolism, and other acute conditions that are not listed as type 1 or 2 AMI. Cardiac troponin is useful even to risk stratify patients independent of coronary artery disease, including chronic conditions such as heart failure and renal failure.

Would you support an electronic health record limitation to 1 cardiac troponin order set, with the requirement that an electronic justification must be entered for an additional set?

Allan S. Jaffe: Electronic health records (EHR) are very valuable, but one must be careful not to clutter them with so many alerts that the user ends up experiencing what has been termed "alert fatigue." It is probably worthwhile to build into the EHR what is agreed to by all parties, including those circumstances in which a solitary cardiac troponin could be ordered. If the frequency of the alerts is rare and only occur when there is something that is substantially different from what has been agreed to by all of the interested parties, this would be reasonable. If not done in that way, the fear would be that it would end up simply becoming another hassle for what is already a huge hassle with the EHR.

Peter Kavsak: This is an interesting question. In the past, we did have restrictions on ordering cardiac troponin that required a biochemist's approval. What we encountered were complaints from cardiologists. Collaboration and education may be another route to achieve more optimal utilization.

Michael C. Kontos: I would support a single order set, and I think most hospitals currently do this. However, I would not require an EHR justification for going outside the pathway. I think there are too many situations in which cardiac troponin sampling would be necessary outside the standard pathway to mandate justification of an alternative sampling that would be done off protocol (following a patient with myocarditis or peri-myocarditis, or stress cardiomyopathy) in which serial sampling at varying time points over 1–3 days may be important. It would be better to put the appropriate energy into optimally designing and implementing a care set to provide the easiest way to order cardiac troponin, such that it becomes the default for the physician.

Amy K. Saenger: I would support limiting 1 cardiac troponin order set per patient if there was a documented issue with overutilization of cardiac troponin order sets within my institution and/or cases where multiple cardiac troponin order sets created confusion and led to poor patient care. If this were not a high volume occurrence, then I would not prioritize or put a substantial amount of effort towards limiting orders or requiring justification. In my experience, requiring justification for an acute, potentially critical test puts potential barriers in place that may actually result in poor patient care, although you could just as easily argue multiple order sets cause unanticipated and unnecessary consequences. Optimizing and working within the constraints of the electronic ordering system is critically important, regardless of the specific test(s) involved.

Stephen Smith: There is no need for more cardiac troponin orders once MI is ruled in or ruled out. The only reason for an additional order set is a change in clinical condition such as a new episode of chest pain.

Can you comment of the implementation of sex-specific 99th percentile upper reference limits for males and females with hs-cTn assays?

Allan S. Jaffe: For hs-cTn assays, sex-specific 99th percentiles are essential. Not only are there differences in reference intervals but the majority of data, when there are large numbers of patients evaluated, suggest that sex-specific 99th percentiles improve discrimination of risk in both men and women. Specifically, in individuals with heart failure with chronic ischemic heart disease, and in the community population, the use of sex-specific cutoffs optimizes identification of patients at risk. The situation with acute ischemic heart disease is more controversial and I would argue that it is predominantly because the studies do not contain enough individuals with small MIs. It is known that women tend to have over twice the incidence of nonobstructive coronary artery disease as males and therefore have an increased frequency of having a subset of their MIs that are difficult to detect. If one has only a modest number of MIs it would be very easy to miss this effect. Therefore, it is likely that those studies that have had a large number of patients with MI showed improved detection of MI in women.

Scott Sharkey: I believe sex- and age-specific values should be used, and possibly even geographically specific

values, to reflect the population served by the healthcare institution. A US databank could be established and used for harmonization.

Peter Kavsak: This is an evolving area with much interest. When we implemented hs-cTn testing in 2014 through discussions with emergency medicine, internal medicine, and cardiology, we opted to use the overall 99th percentile as the upper reference limit (URL). This URL cutoff was determined in a Canadian population and was also evaluated in a large clinical study with health outcomes.

Michael C. Kontos: This is reasonable if adequately defined using appropriate numbers of patients in the subgroups. Age-specific reference limits are likely to be necessary as well. There would clearly need to be education involved since there would no longer be a single value to remember. Although many of our laboratory tests also use different reference intervals, there are very few in which a small change in the result can dramatically alter care decisions. Having the appropriate alerts are clearly necessary to make it easier for the physician to interpret the results.

Amy K. Saenger: I am a strong advocate for use of and reporting sex-specific 99th percentiles for hs-cTnI and -cTnT assays. From an analytical perspective several studies demonstrate clear, statistically significant sex-specific 99th percentiles. For any other analyte in the clinical laboratory where there is differentiation between sex-specific reference intervals, such as creatinine, there are no major debates about reporting sex-specific reference intervals; we just report them. For some reason cardiac troponin is different. Some individuals argue that clinical evidence is required showing that sex-specific 99th percentiles are superior before those URLs can be adopted. There is, and continues to be, a growing body of evidence supporting use of sex-specific 99th percentiles, but not all questions have been answered. If the healthy reference population used to derive the reference intervals is defined appropriately and the study is powered accordingly, and if a statistically significant difference in the analyte concentration between males and females exists (which it does), then we should adopt and report those URLs. Unlike age, which is known to inappropriately influence the 99th percentile due to subclinical or underlying disease, one's sex alone is not an indicator of disease.

Stephen Smith: It is clear that cardiac troponin values considered normal for females are on average lower than those seen in males, and it has been shown that more clinically significant MIs are detected when the URL is appropriately lowered for females.

How do you envision the role of a single cardiac troponin result at a very low concentration with a negative predictive value of >99th percentile as a tool for rapid discharge of patients from the emergency department?

Allan S. Jaffe: One must be quite careful about this. The likelihood that this will work is high, particularly in low-risk patients. A very low cardiac troponin at baseline, using an hs-cTn assay, would suggest that the patient lacks most of the comorbidities that lead to coronary heart disease. This is because almost all of those comorbidities result in increases in cardiac troponin, albeit usually within the normal range. Thus, a very low value is highly reassuring. On the other hand, the attention here has to do with the possibility that some patients who present very early after the onset of AMI may not have increases at all. It has been shown that patients who presented within 2 h of onset often had a far less negative predictive value, 99% vs 95%, suggesting that some patients with AMI can have very low values at presentation. This patient group is understudied in most of the large series that look at these very early rule outs. I would advocate the use of this strategy in the low-risk group, and perhaps in the intermediate-risk group, but would counsel against such use in high-risk patients and/or those who present early after the onset of symptoms.

Peter Kavsak: We anticipated this utility of a very low and measurable cardiac troponin concentration with a high-sensitivity assay in that when we implemented the hs-cTn assay we concurrently began measuring a QC sample in the low normal range. A low cardiac troponin concentration with other clinical parameters and/or tests might be superior to just a low cardiac troponin concentration alone for the rapid discharge of emergency department patients.

Michael C. Kontos: If used appropriately, it could reduce length of stay for emergency department patients. However, I would not be surprised if the benefit has been overstated. There is the likelihood that a significant number of patients who have other causes for chest pain or possible myocardial ischemia that would require a work up, thus delaying the time to discharge. Also, intensive education around the meaning of a "positive" cardiac troponin will need to be implemented. In addition, the negative predictive value would likely have to exceed 99.5% with small confidence intervals for emergency physicians to feel comfortable. I think that we have substantially increased our knowledge base around how to reduce the MI exclusion period. What has not been defined to my satisfaction is, for which patients the application of this strategy is appropriate? Another consideration is that the vast majority of studies have been based

around use of hs-cTnT, which appears to be inferior to hs-cTnI assays.

Amy K. Saenger: This strategy appears to work well in those hs-cTn assays with greater specificity and lower sensitivity. More patients qualify for a single rapid rule out at <LoD or <limit of blank strategy using the hs-cTnT assay (Roche) compared to a hs-cTnI assay (Abbott) with higher sensitivity. The hs-cTnI assay is analytically more sensitive; by definition, all hs-cTn assays are required to quantify values in >50% of normal individuals. Therefore, it becomes a rare occurrence to encounter patients presenting with chest pain and an undetectable hs-cTnI since the assay is sensitive enough to quantify a majority of nondiseased healthy individuals. Conversely, the hs-cTnT assay only quantifies values in approximately 25%–50% of normal subjects, making the assay less analytically sensitive but more specific, which allows more rule out AMI with this assay. Manufacturers were challenged to develop cardiac troponin assays with improved sensitivity but not improved specificity. At the time of patient presentation, clinical sensitivity is key, with serial changes (δ criteria) early after presentation having the ability to also improve clinical specificity. I do not foresee these things changing in the near future to move towards a single low hs-cTn concentration to rule out AMI. I think there is a great potential for adoption of accelerated diagnostic protocols, i.e., simultaneous use of low hs-cTn values with clinical risk scores. A single biomarker result does not substitute for clinical judgment, particularly given the high-risk involved if a seemingly undetectable result was due simply to mild sample hemolysis, which is known to affect the hs-cTnT assay.

Stephen Smith: I think the use of hs-cTn at a very low concentration will be a valuable tool for select patients, especially those with chest pain of at least 2–3 h duration. Presently, cardiac troponin concentrations <LoD have a very high negative predictive value to rule out AMI. However, low cardiac troponin concentrations do not necessarily rule out unstable angina, which requires additional risk score testing independent of cardiac troponin testing to optimize risk assessment of patients. For contemporary cTnI assays, I now use concentrations <LoD to rule out MI in patients with 3–6 h of constant chest pain.

***What role do you see for hs-cTn in primary prevention*?**

Allan S. Jaffe: Eventually this will be an important role for hs-cTn assays. The preliminary data are very interesting in examining the development of hypertrophy, left ventricular (LV) enlargement, and all kinds of structural heart disease in individuals, and that when these changes are seen they likely reflect some comorbidity that is responsible. Since I believe that treating the comorbidities that lead to cardiovascular disease, such as, hypertension, diabetes, hyperlipidemia, and the like reduce the frequency of disease, using this approach is likely to be of importance. There already are 2 heart failure studies, one called Stop HF, and the other Pontiac, looking at this sort of strategy. Albeit using BNP (brain natriuretic peptide) as a risk tool, the additional knowledge of a low cardiac troponin value found to be within the cardiac troponin reference interval for individuals at high-risk was shown to identify patients who had better outcomes with more aggressive care. What needs to occur is the development of metrics that will be assay specific and guide therapy, so that this is not just a way of increasing the frequency of hs-cTn measurements but actually has a real role in the management of these patients. Most of these algorithms have not yet been developed and thus those who advocate this approach do so without the substrate that eventually will be necessary to make this a viable strategy.

Scott Sharkey: The test has no value unless it can be used to change prognosis through specific treatment.

Peter Kavsak: I would focus first on secondary prevention before primary prevention. However, in both situations more data and specifically the optimal therapy directed to hs-cTn in these settings needs to be determined.

Michael C. Kontos: I think the most exciting area for use of the hs-cTn assays is for identification, risk stratification, and potentially targeted treatment for patients with non-ACS conditions such as heart failure and LV hypertrophy. Obviously, a substantial amount of work remains to be done, but if such studies are positive, they could result in having an objective marker of identifying higher-risk phenotypes at greater risk for adverse events. They may also allow assessment of specific treatment response greater than the natriuretic peptides currently do, thus having the ability to better personalize treatment and the potential to substantially advance care.

Amy K. Saenger: Eventually, I envision hs-cTn could be used for primary, or even primordial, prevention similar to how glucose and lipids are used as screening modalities. However, there is 1 major barrier to this situation and that is the lack of standardization of hs-cTn (particularly hs-cTnI) assays. Results may likely never be standardized or even harmonized between or within manufacturers or instrument platforms. Without this in place the utility for monitoring hs-cTn results over a long period of time does not exist.

Stephen Smith: This is not my area of expertise, but there are many studies correlating chronically increased

hs-cTn with higher mortality for several patient groups, including diabetic patients, and that mortality is related to the degree of baseline cardiac troponin increases. It has also been shown that hs-cTn can be used successfully to guide preventive therapies.

What role do you see for monitoring hs-cTn for risk stratification in patients presenting with ischemic symptoms suggestive of acute coronary syndrome or non-ACS?

Allan S. Jaffe: There is no question that the higher the cardiac troponin concentration, even in some patients within the reference interval, the higher the cardiovascular risk long term. Patients who have increased values for whatever the reason require evaluation. In an ACS setting, the higher the cardiac troponin value, the more adverse the prognosis is, and for most cardiologists that means we would be inclined to treat more aggressively. Whether or not this will prove to be the ideal approach is unclear. The one study that has looked at this approach was BARI 2D, which did not find, in a retrospective analysis, that an invasive strategy was helpful. Thus, we need more information. Similarly, issues have been observed in patients who have non-ACS in that they have some cardiovascular comorbidity, and the increased cardiac troponin was strongly suggestive of adverse prognosis. These patients need to be investigated to see what those comorbidities are in a sensible way with clinical history, physical examination, and a minimal amount of testing. They do not require sophisticated testing but simply due diligence. In the long run, studies should look to see whether or not such an approach has benefit before advocating it on a routine basis.

Scott Sharkey: Negative values will be helpful. Abnormal values require knowledge of clinical implications. Many physicians equate increased cardiac troponin with ACS. This mindset needs to change. The implication of cardiac troponin increase in the setting of non-ACS is not adequately studied. Presumably, the use of hs-cTn will result in a decrease in the 99th percentile. The implications of these low values should be established for both suspected ACS and non-ACS. It would be useful to examine the implications based on the degree of cardiac troponin increase and the degree of change (i.e., 1–2-fold, 2–3-fold, >3-fold). My sense is that the low values will be quite nonspecific for clinical use.

Peter Kavsak: Multiple studies on health outcomes and hs-cTn concentrations in an emergency department population have made it clear that the higher the cardiac troponin concentration, the higher the risk for an adverse event. What is needed to realize a better patient care is the best treatment directed to the pathophysiological cause of the increased cardiac troponin concentration.

Stephen Smith: hs-cTn will be critical for risk stratification. First, there will be a "rule-out" group that has 1 or more hs-cTn values below a cutoff (e.g., LoD, 99th percentile, or some other low value determined in clinical studies) that will vary depending on the patient's baseline risk, the duration of symptoms, ECG results, and the information available for the assay at hand. Second, there will be a "rule-in" group that will be quickly identified as positive for AMI by either a hs-cTn with a value below the 99th percentile and a subsequent, clinically significant increased δ hs-cardiac troponin, or by an initial hs-cTn far above the 99th percentile or by 2 hs-cTn values with one or more above the 99th percentile and a diagnostic rise and/or fall. Those cutoffs, and the associated deltas, will be specific to the assay used, and there is already sufficient data for several assays to be used this way. The third group will be intermediate: neither ruled in, nor ruled out. These patients may be assessed with still more serial cardiac troponin measurements and/or coronary CT angiogram or a stress imaging test, or standard angiogram.

What is the clinical utility of hs-cTn in patients who are critically ill?

Allan S. Jaffe: This is an important issue. These patients clearly are at increased risk because they have cardiovascular involvement as well as a critical illness. It is not at all clear that anything can be done during the acute phase. What is needed are studies that examine the determinants of this with the idea of looking for therapeutic options. A good example is the recent study showing that, with 3D echo, the best correlation to an hs-cTn increase in patients with sepsis was diastolic abnormalities and right ventricular dilation. This would suggest that the reduced cardiac outputs that are seen in the cardiovascular abnormalities are related more to diastolic abnormalities and that slowing heart rate might be of importance. It is insights like these that could potentially lead to therapeutic opportunities.

Scott Sharkey: This is an enormous problem that may be magnified with the use of hs-cTn. The use of cardiac troponin in critically ill patients requires far more study, including benefit with respect to outcome and presence of underlying acute coronary disease.

Peter Kavsak: Patients who are critically ill represent a heterogeneous group of patients, so using hs-cTn assays in this overall population may be challenging. Higher cardiac troponin concentrations may result from different types of MIs or other conditions that cause myocar-

dial injury. The underlying reason for the increase in cardiac troponin concentration is especially important to determine in this vulnerable population.

Michael C. Kontos: This is one of the greatest areas of clinical confusion: a patient with a critical illness who has a detectable cardiac troponin. To my knowledge, there are limited data on this subset of patients using hs-cTn assays. The use of hs-cTn assays is likely to increase the frequency of encountering values that exceed the 99th percentile. Given the severity of illness in these patients, these findings may result in a large proportion of patients being misdiagnosed with ACS. Additional studies are necessary, and should define the specific subsets of illnesses, and include both short and long term outcomes.

Amy K. Saenger: This is a very interesting area that will continue to evolve. There is clear evidence that hs-cTn in particular provides prognostic information in critically ill patients. There are interesting issues related to measurement of cardiac troponin in critically ill patients and potentially new diagnosis of in-hospital or perioperative MIs. This has implications on financial reimbursement based on International classification of diseases (ICD)-9 or ICD-10 codes as well as potential penalties for patients who readmitted within 30 days.

Stephen Smith: Patients who are critically ill often have increased cardiac troponin values that mostly confirm critical illness, though sometimes they may have prognostic value. I do not anticipate that hs-cTn will have added value for this group. On occasion, critically ill patients may have unexpected type 1 MI that is found by the presence of an extremely increased cardiac troponin, and frequently this is the only way they are identified since the ECG may not reveal the infarction. I do not anticipate that hs-cTn will be substantially different from contemporary cardiac troponin for this purpose.

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