THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Troponin Testing for Clinicians

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ABSTRACT

The analytical performance of troponin assays has improved markedly in the last 2 decades. The variety of assays, their evolution over time, and their critical importance in influencing care, mandates the need for skills in their use. There are 3 critical elements necessary for optimal use of troponin testing in clinical care, as follows: 1) the analytical performance of the assay; 2) the clinical sensitivity and specificity of the test result; and 3) the clinical reasoning for ordering and the proper clinical context for interpreting the test result. This paper provides further explanation that will assist clinicians in their clinical decision making and interpretation of troponin test results. Schematic visual explanations are provided to help clinicians develop a more intuitive understanding of troponin testing. (J Am Coll Cardiol 2016;68:2365–75) © 2016 by the American College of Cardiology Foundation.

The 2014 American Heart Association/ American College of Cardiology Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes document states that troponin is the preferred biomarker for diagnosing acute myocardial infarction (1). This recommendation acknowledges the fact that laboratory methods for troponin testing have markedly improved over the past 2 decades, resulting in lower limits of detection and improved assay precision (2). The laboratory advances in troponin testing have been extraordinary, but the optimal use of the test also requires good clinical reasoning by practitioners who use troponin testing in clinical practice.

There are 3 critical elements necessary for optimal use of troponin testing in clinical care, as follows: 1) the analytical performance of the assay; 2) the clinical sensitivity and specificity of the test result; and 3) the clinical reasoning for ordering and the proper clinical context for interpreting the test result. All 3 elements are integral to foster optimal clinical utility. Most clinicians rely on their clinical laboratories to address the analytical performance of the assay and are unfamiliar with the laboratory science of troponin testing. The clinical sensitivity and specificity of troponin testing have been a source of confusion for clinicians because definitions have changed as the test has evolved and because there are many different assays available. Additionally, for clinical reasoning, there is generally little attention as to how to integrate these test results with other clinical information. Excellent review papers have explained the operating characteristics and proper use of troponin testing (3-5), but further explanation may be beneficial.

The paper provides further explanation that will assist clinicians in their clinical decision making and interpretation of troponin test results. Schematic visual explanations are provided to help clinicians develop a more intuitive understanding of troponin testing (6-8). Improving our understanding of troponin testing is particularly important now because high-sensitivity assays are already in use in Europe, and we anticipate they will be approved in the United States in the near future.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ANALYTICAL PERFORMANCE OF TROPONIN ASSAYS

Troponin is a protein complex that regulates the excitation and contraction of striated muscle. The troponin complex consists of 3 molecules: troponin C, troponin I, and troponin T, each of which has different functions and are encoded by separate genes (9,10). Troponin I and troponin T have amino acid sequences specific to cardiac tissue, making these molecules ideal biological markers (11,12). In the late 1980s, investigators developed immunoassays for troponin I and troponin T (13,14). Refinements in the antibodies, reagents, and automation have made the current commercial troponin assays exquisitely sensitive and precise (12). The newest, most sensitive assays are able to detect troponin in the bloodstream of patients without myocardial damage, perhaps due to normal myocardial cell turnover or formation of exosomes that release small amounts of free troponin into the bloodstream (10).

Assay manufacturers measure and report the analytical performance characteristics of each assay. The analytical sensitivity of the troponin assay is defined by the limit of detection (LOD), which is the lowest concentration of an analyte that is consistently detectable. The precision of the assay is defined by the coefficient of variation (CV). Because the CV is a measurement of the assay's variability relative to the concentration of the analyte, the CV increases at lower concentrations. Ideally the CV of an assay is 10% or less at the level that is chosen as a diagnostic cutpoint. Automated assays performed in central laboratories have better precision and lower 10% CV levels than point-of-care troponin assays (11). A point-of-care assay may have a 10% CV level that is an order of magnitude higher than an assay performed in the central laboratory. Point-of-care assays are not used for serial troponin measurements because the imprecision of these assays could give the misleading appearance of a rise or fall in the troponin level (12).

There is only 1 commercially available troponin T assay because of an exclusive patent. The fourth generation of this assay is currently in use in the United States, and a new generation troponin T assay that is more analytically sensitive is now in use in Europe. There are many commercially available troponin I assays, and these assays have also gone through several generations of refinements over the years. Each 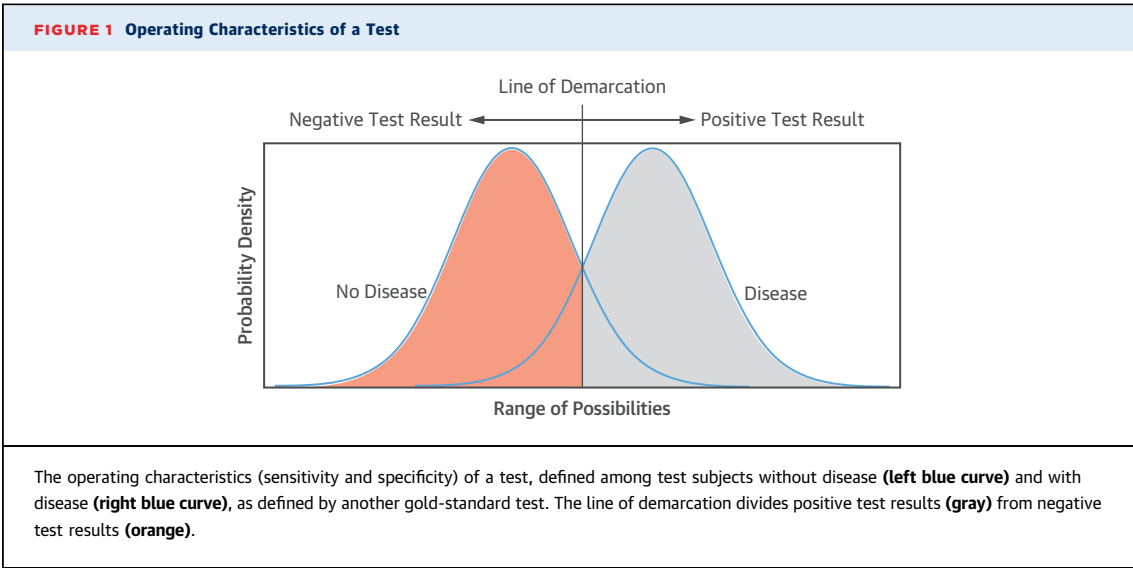of the various commercial troponin I assays recognizes a unique amino acid sequence (epitope) of the troponin I molecule, causing each assay to have different analytical characteristics (12). These differences have created challenges for investigators and regulators who are attempting to develop industry standardization among troponin assays. The differences also create challenges for clinicians who are attempting to understand the published medical reports of troponin testing and apply research findings in practice.

As the analytical capabilities of troponin testing have improved over the years, the term sensitivity has become a source of confusion for clinicians. Laboratory experts usually use the word sensitivity to describe the analytical sensitivity, or the ability of an assay to detect low concentrations of an analyte. Clinicians, in contrast, use the word to describe clinical sensitivity, an operating characteristic of a test that is usually a tradeoff with specificity, as discussed in the next section.

DEFINING THE OPERATING CHARACTERISTICS OF TESTS

For proper interpretation of a test result, clinicians must know the clinical operating characteristics of the test, namely the sensitivity and specificity. The conventional way to characterize a test's operating characteristics is by graphing the range of possible test results for subjects with and without disease, as defined by another gold-standard assessment, as shown in **Figure 1**. Where the line is drawn determines the sensitivity and specificity of the test.

Sensitivity and specificity can be confusing terms. They are rates, but the words themselves do not explicitly define what the numerator and the denominator represent. Having to remember what is in the numerator and denominator of these terms can make it difficult to use the terms for clinical reasoning in everyday practice (15,16). The terms true positive rate (TPR) for sensitivity and true negative rate (TNR) for specificity may be less confusing, because these terms are more relevant to practice and the way that the numbers are used. To demonstrate how specificity is the true negative rate and sensitivity is the true positive rate, these rates are shown separately in **Figure 2**. The figure displays a test with a specificity of 80% and a sensitivity of 95%. The left panel shows, the distribution of test results for subjects with no disease (displayed by blue curve) and the right panel shows the distribution of test results for patients with disease (also displayed by the blue curve). The blue curves show the probability of having a particular test result, shown on the left y-axis, for any point along

FIGURE 1 Operating Characteristics of a Test

The operating characteristics (sensitivity and specificity) of a test, defined among test subjects without disease **(left blue curve)** and with disease **(right blue curve)**, as defined by another gold-standard test. The line of demarcation divides positive test results **(gray)** from negative test results **(orange)**.
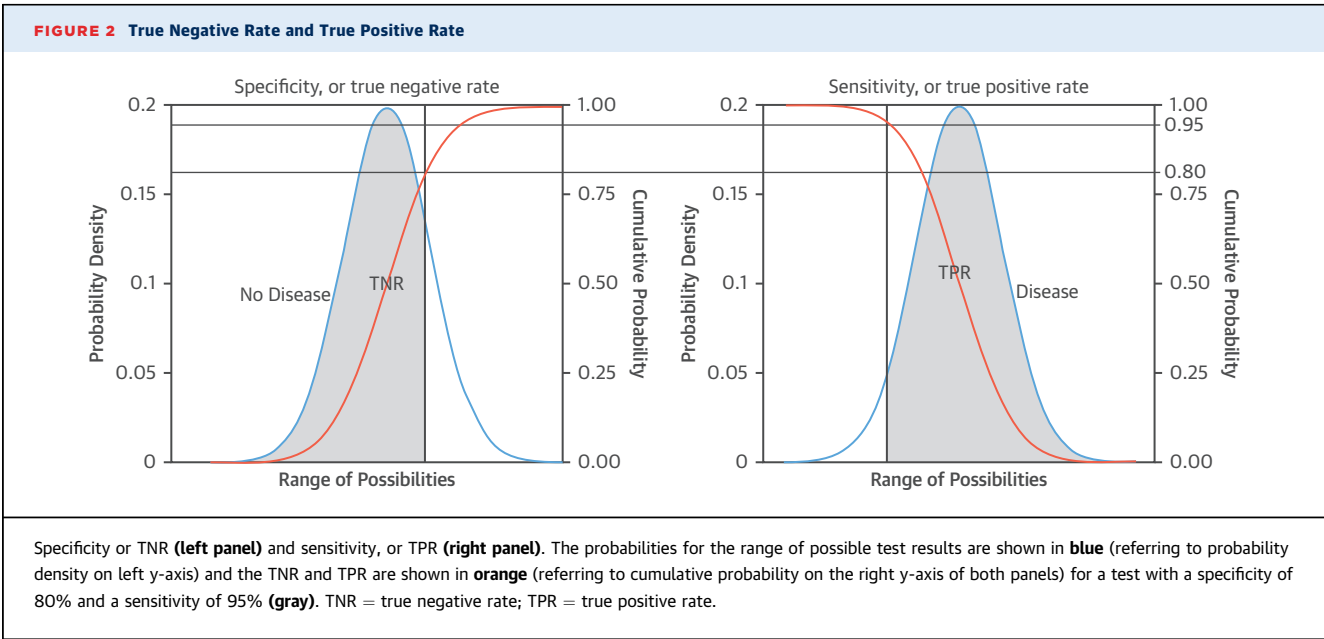
the range of possible test results, shown on the x-axis. The red curves show the cumulative probabilities (shown on the right y-axis), which are the sums of the probabilities within a defined range of possible test results (shown in gray). Specificity, demonstrated by the red curve in the left panel (TNR), is the cumulative probability of having a negative test result. As shown in the left panel, the specificity or TNR increases from left to right depending on the location of the line of demarcation. Sensitivity, demonstrated by the red curve in the right panel (TPR), is the cumulative probability of having a positive test result. As shown in the right panel,

sensitivity or TPR increases from right to left, again depending on the location of the line of demarcation.

Designers of any test draw the line of demarcation at the point that maximizes the usefulness of the test. Investigators usually use receiver operating characteristic (ROC) curves (which plot sensitivity against [1 − specificity]) to determine the optimal cutpoint.

In addition to the ROC method for determining a cutpoint, another method uses a distribution of test results from a group of subjects who are clearly normal. Typically (and arbitrarily), the inner 95th percentile is used (which is 2 SDs from the mean in a normal distribution), and patients below the 2.5th

FIGURE 2 True Negative Rate and True Positive Rate

Specificity or TNR **(left panel)** and sensitivity, or TPR **(right panel)**. The probabilities for the range of possible test results are shown in **blue** (referring to probability density on left y-axis) and the TNR and TPR are shown in **orange** (referring to cumulative probability on the right y-axis of both panels) for a test with a specificity of 80% and a sensitivity of 95% **(gray)**. TNR = true negative rate; TPR = true positive rate.

percentile and above the 97.5th percentile are considered abnormal. For cardiac biomarkers, only the upper cutpoint (the 97.5th percentile) would be relevant.

We can also express the capability of a test using likelihood ratios. Likelihood ratios are derived from sensitivity and specificity and give us an idea of the strength of a positive or negative test result. The advantage of likelihood ratios is that they are dimensionless numbers, which eliminates the need to keep track of what is represented by the numerator and denominator. Therefore, likelihood ratios are even more intuitive than TPR and TNR values once one becomes familiar with their use. A likelihood ratio is defined as the percentage of diseased patients with a given test result divided by the percentage of well people with the same test result. Thus, a positive likelihood ratio is the TPR/false positive rate or [sensitivity/(1 – specificity)]. A negative likelihood ratio is the [false negative rate/TNR] or [(1 – sensitivity)/specificity]. Calculating a likelihood ratio is easy, and once calculated, it gives an intuitive sense of the strength of the test result. For example, the positive likelihood ratio for a test with 95% sensitivity and 80% specificity is 4.75 (0.95/0.20), a dimensionless number indicating that the test result, if positive, is a fairly robust signal.

CLINICAL SENSITIVITY AND SPECIFICITY OF TROPONIN ASSAYS

When the early troponin assays were developed, it became apparent that the test was superior to other available tests, such as creatine phosphokinase (CK) and CK-MB. The early troponin assay had virtually no false positives from skeletal muscle injury, and when used in a narrowly defined population, it had high sensitivity and specificity for diagnosing acute myocardial infarction (as defined using clinical criteria including CK-MB measurement as the gold standard) (14). Several subsequent studies, however, showed that detectable troponin levels below the ROC-determined cutpoint for acute myocardial infarction had prognostic significance (17-19). Clinical trials showed that unstable angina patients with detectable troponin levels below the ROC-determined cutpoint for acute myocardial infarction had better outcomes when treated with antithrombotic medications and interventional procedures (20-23). Therefore, a lower cutpoint for acute myocardial infarction was considered. The alternate method of setting a cutpoint uses the 97.5th percentile from a normal reference group; however, this would have set the cutpoint so low that it would have potentially generated too many false positive tests. In addition, most of the available assays at that time were too imprecise at the 97.5th percentile level (24).

On the basis of these considerations, a 1999 international panel of experts decided to draw the cutpoint for troponin testing at a point that coincided with the 99th percentile of a normal reference group, as shown in the **Central Illustration** (25,26). Manufacturers of troponin assays have reported the various 99th percentiles, which are slightly different for each assay (12). At the time that this definition was determined, troponin assays were not as analytically sensitive as current tests, and the 99th percentile for a normal population was near the limits of detection for most assays, as shown in the **Central Illustration**. Almost all patients in a normal population had undetectable troponin levels (the presumed troponin distribution beyond the limit of detection is shown by the dotted curves). The cutpoint, which was defined by an analytical specificity of 99% in a normal population, was so low that it happened also to define a higher clinical sensitivity (further to the left on the x-axis) than the ROC-derived cutpoint.

With each new generation of troponin assay, there have been improvements in the assay's analytical sensitivity and precision. Also, with each new generation, the 99th percentile has been defined in different cohorts of normal test subjects. As a result, the shape of the distribution curves that define the 99th percentile has narrowed, which has moved the 99th percentile cutpoint to the left (**Figure 3**). The figure shows the distribution, limits of detection, and 99th percentile for second-generation and fourth-generation troponin T assays. Lowering the 99th percentile cutpoint has adversely affected the clinical specificity of the assays, which led one commentator to remark, "when troponin was a lousy assay it was a great test, but now that it's becoming a great assay, it's getting to be a lousy test" (27).

Because of the high limits of detection of the early assays, most clinicians have been conditioned to think that any detectable troponin is due to myocardial necrosis or injury. Now, with increasing analytical sensitivity of troponin assays, troponin is detectable in many more normal subjects and in many patients with myocardial necrosis for reasons other than acute myocardial ischemia due to plaque rupture.

Investigators have also examined how the definition of a "normal" population can affect the measurement of troponin and the 99th percentile cutoff. They have shown that by narrowly defining the population, using questionnaires or preliminary testing by using electrocardiograms, the distribution of normal troponin levels becomes narrower, again

CENTRAL ILLUSTRATION Troponin Testing for Clinicians
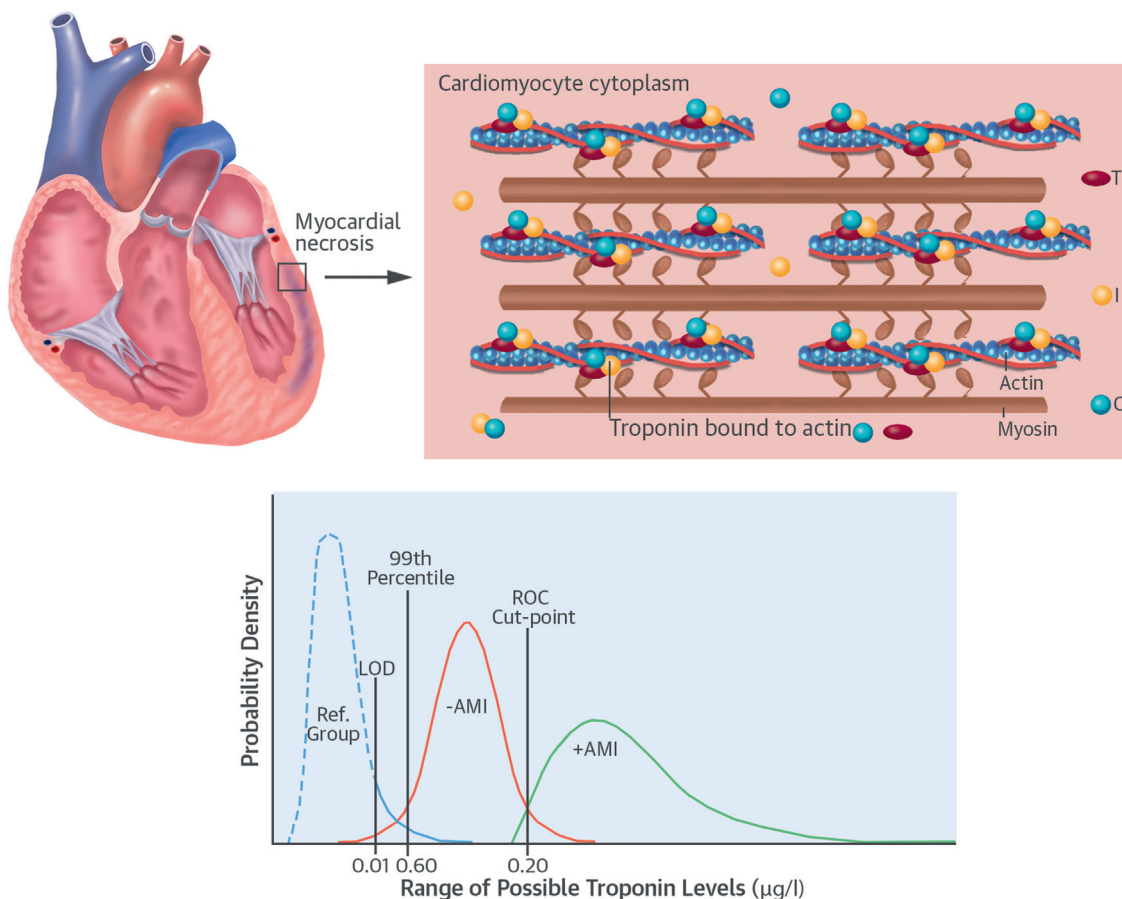
Brush, Jr., J.E. et al. J Am Coll Cardiol. 2016;68(21):2365–75.

Troponin is a protein complex released into the blood stream when heart tissue is damaged by AMI or other causes **(upper left)**. The troponin complex consists of 3 molecules, troponin C, troponin I, and troponin T, which are bound to actin or free in the cytoplasm of the cardiomyocyte **(upper right)**. Troponin I and troponin T have amino acid sequences that are cardio-specific, making them ideal biomarkers for cardiac injury. The graph shows how troponin levels may be distributed in patients with suspected acute myocardial infarction and subjects in a normal reference group (Ref. Group). Initially, the cutpoint for distinguishing patients with AMI (+AMI) **(green curve)** from patients without AMI (−AMI) **(orange curve)** was determined using the ROC method, using CK-MB and other clinical criteria as the gold standard. However, clinical trials showed that detectable troponin levels below the ROC-determined cutpoint for AMI had prognostic significance, and unstable angina patients with detectable troponin levels below that point had better outcomes when treated with antithrombotic medications and interventional procedures. Thus, a 1999 consensus panel decided to draw the cutpoint for defining an AMI lower, at the 99th percentile of a normal reference group **(blue curve)**. Most patients in this reference group had troponin levels below the LOD of the early assays **(dashed segment of blue curve)**. The 99th percentile definition and the progressively lower 99th percentile levels of various newer generation troponin assays have created confusion for clinicians who are frequently asked to interpret troponin levels. AMI = acute myocardial infarction; CK-MB = creatine phosphokinase-MB; LOD = limit of detection; ROC = receiver operating characteristic.

causing the 99th percentile cutoff to shift to the left, as shown in the purple curve in **Figure 4**. Further narrowing of the definition of a normal population creates a narrower definition of normal, moving the 99th percentile cutpoint to the left, as shown in the grey curve in **Figure 4** (28).

The left panel of **Figure 5** shows that the current fourth-generation troponin T assay commonly used in the United States is pushing the limit of a test's analytical capabilities, with the 99th percentile reported at 0.01 μg/l, the limit of detection around the same value, and the level for the 10% CV at 0.03 μg/l. The newer high-sensitivity troponin assays that are currently available in Europe have greater analytical sensitivity and precision, resulting in a much lower limit of detection and a lower point for the 10% CV
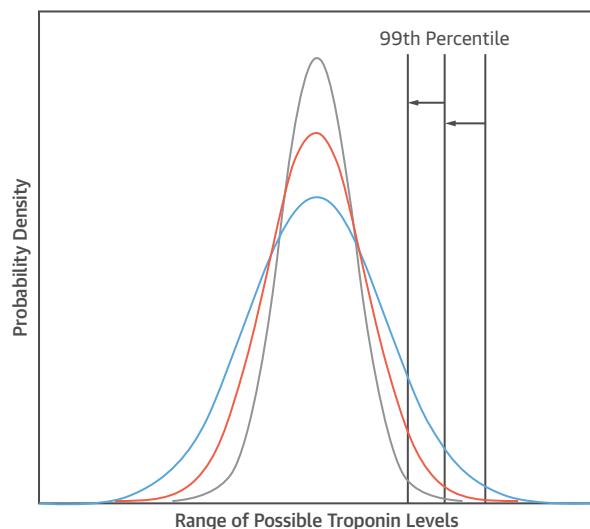
FIGURE 3   Distributions of Troponin Levels in Second- and Fourth-Generation Assays
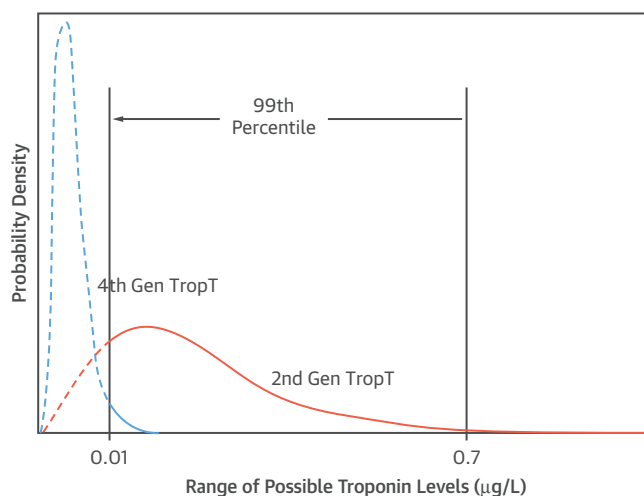
Distributions of troponin levels for a normal reference group using the second-generation troponin T assay (2nd Gen Trop T) and the fourth-generation troponin T assay (4th Gen Trop T). **Dotted** portion of the curves shows the presumed distributions below the level of detection of the assay.

(**Figure 5**, right panel) (12). Interestingly, the shape of the distribution of troponin levels using the newer high-sensitivity troponin T assay is apparently similar to the presumed shape of the fourth-generation assay

FIGURE 4   Distributions of Troponin Levels in Narrowly Defined Normal Populations

Distributions of troponin levels for a normal reference group that is defined with increasingly narrower inclusion criteria, causing the 99th percentile of the distribution of a normal reference group to shift to the left on the x-axis.

because the 99th percentile is essentially the same (0.014 µg/l compared with 0.01 µg/l for the fourth-generation assay). For the newer assays, "high sensitivity" has been defined as an assay that has imprecision of <10% at the level of the 99th percentile and that is able to detect troponin at concentrations that are lower than 50% of the level of the 99th percentile (2,12).

TROPONIN USE IN CURRENT PRACTICE

In practice, the ordering criteria for troponin in emergency departments are often less stringent than in the controlled conditions of a clinical research study. In a busy emergency department (ED), the need for rapid ED turnover times drives the practice of initial bundling of laboratory tests to eliminate time-consuming sequential processes (clinical evaluation followed by testing). Thus, troponin tests often are drawn before the ordering physician sees the patient and takes a detailed history. This practice is reinforced by the need to rapidly establish a diagnosis for patients with acute coronary syndromes (ACS) and is also motivated by defensive medicine to minimize medico-legal liability. Similar ordering practices also often occur in other areas of hospitals, such as intensive care units. As a result, troponin testing is used as a screening test in a broad spectrum of non-ACS patients including patients with end-stage renal disease, sepsis, and congestive heart failure, all of which are known to have elevated troponin levels (2,3).

SPECTRUM BIAS

Using a test in a broad, unselected group of patients can result in a phenomenon known as spectrum bias (29,30). Spectrum bias can markedly change the operating characteristics (sensitivity and specificity) of a test from those that were carefully defined in a controlled research setting. As discussed earlier and shown in **Figure 4**, the probability curves of a test result become narrower when the definition of a normal population is more narrowly defined. With spectrum bias, the opposite occurs and the probability curve widens. Because the line of demarcation remains fixed, the specificity of the test falls as the curve widens (**Figure 6**).

To demonstrate the effect of spectrum bias, we can compare the operating characteristics of troponin testing in a research study to the operating characteristics that we may see in practice in a busy ED. In a published study describing the operating characteristics of troponin T (31), the test was used in a strictly defined population of patients presenting with chest

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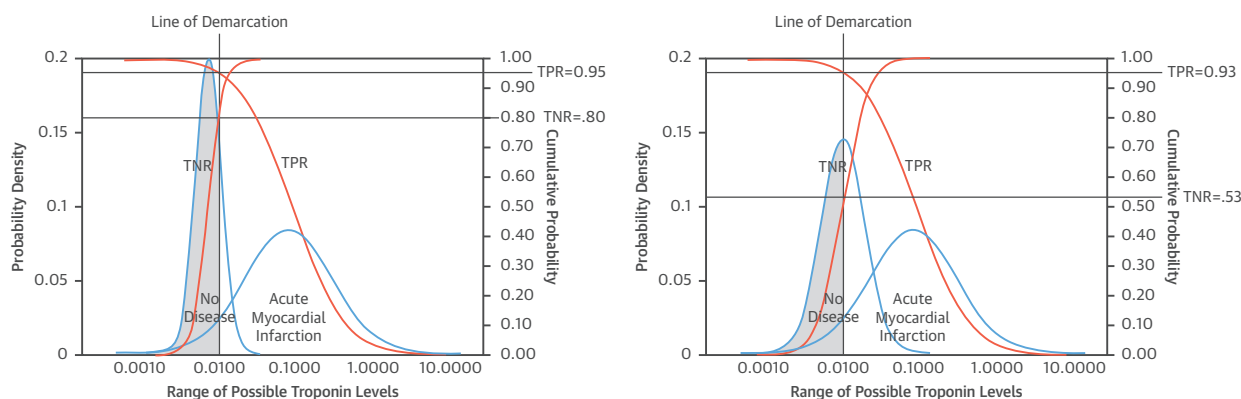**FIGURE 5   Distributions of Troponin Levels in Fourth-Generation and High-Sensitivity Assays**
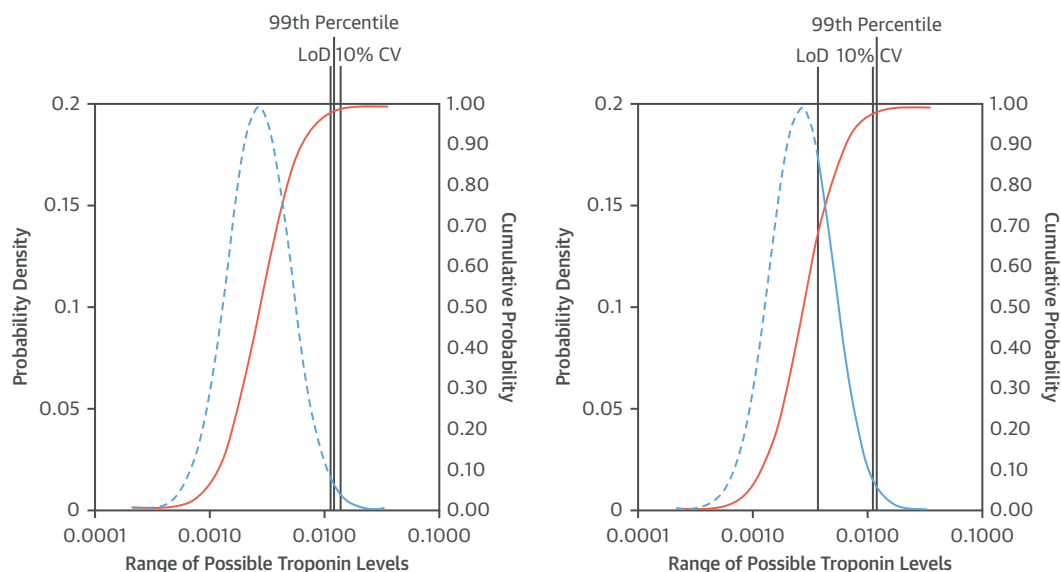
Distribution of troponin levels are shown for a normal reference group using the fourth-generation troponin T assay **(left panel)** and the high-sensitivity troponin T assay **(right panel)**. The LOD and 10% CV have shifted to the left for the high-sensitivity assay, whereas the 99th percentile has remained essentially unchanged. CV = coefficient of variation; LOD = limit of detection.

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pain and suspected acute myocardial infarction. The study explicitly excluded patients with renal failure. Seventeen percent of patients had the final diagnosis of acute myocardial infarction. In this defined population, the high sensitivity troponin T assay had a sensitivity of 95% and a specificity of 80% (**Figure 6**, left panel) Thus, the positive likelihood ratio for

high-sensitivity troponin testing in this setting was 4.75, [(0.95/1) − 0.80]), and the negative likelihood ratio was 0.063, [(1 − 0.95/0.80)]. Both of these positive and negative likelihood ratios are quite compelling, indicating that a positive or a negative troponin T test result, when the test is used in this way, should yield persuasive clinical information.

FIGURE 6   Distributions of Troponin Levels in a Tightly Controlled Setting and in a Typical Clinical Setting

Distribution of troponin levels for patients with no disease and with AMI. **(Left)** Distributions in a carefully controlled research setting and **(right)** distributions in a clinical setting that is less carefully controlled (see discussion in Spectrum Bias section). TNR = true negative rate; TPR = true positive rate.

TABLE 1 Test Results in Patients With Suspected Acute Myocardial Infarction

Test Result	Disease	No Disease	Total
Positive Test	162	166	328
Negative Test	8	664	672
Total	170	830	1,000

The table shows the results of a test with 95% sensitivity (true positive rate) and 80% specificity (true negative rate) in 1,000 patients with a disease prevalence of 17%.

Table 1 shows how these operating characteristics would determine the test results for 1,000 consecutive patients. Of 1,000 patients, 17% (n = 170) have disease and 83% (n = 830) have no disease. A test with 95% sensitivity (TPR) is positive in 162 patients of 170 patients with disease. A test with 80% specificity (TNR) is negative in 664 patients of 830 people with no disease, as shown in Table 1.

Now imagine using this same test in a busy ED without the strict exclusion criteria of a controlled research trial. Given that approximately 15% of ED patients will have renal insufficiency and additional patients will have other diagnoses, such as congestive heart failure, sepsis, and trauma (all of which can elevate troponin levels without ischemic myocardial injury), it is reasonable to assume that 25% of the patients screened with troponin testing in this setting could have an alternate cause of an elevated troponin level other than acute myocardial infarction. Given these assumptions, we can imagine a different patient population (Table 2). The 250 patients with confounding diagnoses that cause elevated troponin levels are added to the patients with the other false positive test results (250 + 166 = 416), decreasing both the number of true positive and the true negative test results (Table 2). This reduces the specificity (TNR) of the test from 80% (664 of 830) shown in Table 1 to 53% (468 of 884) in Table 2, whereas the sensitivity (TPR) is slightly reduced from the 95% (162 of 170) shown in Table 1 to 93% (108 of 116) in Table 2.

TABLE 2 Test Results in Unselected ED Patients

Test Result	Disease	No Disease	Total
Positive test	108	416	524
Negative test	8	468	476
Total	116	884	1,000

The table shows the test results in 1,000 patients after adding 250 patients with elevated troponin due to diagnoses other than AMI to the 166 patients with false positive test results, yielding a new total of 416 patients with false positive test results. This has reduced prevalence of disease to 12% and specificity of the test to 53% (468 of 884) but only slightly reducing the sensitivity of the test to 93% (108 of 116).

AMI = acute myocardial infarction; ED = emergency department.

The addition of patients with elevated troponin from conditions other than acute myocardial infarction and the resulting spectrum bias markedly changes the likelihood ratios for the test, with the positive likelihood ratio decreasing from 4.75 to 1.98 and the negative likelihood ratio changing from 0.063 to 0.132.
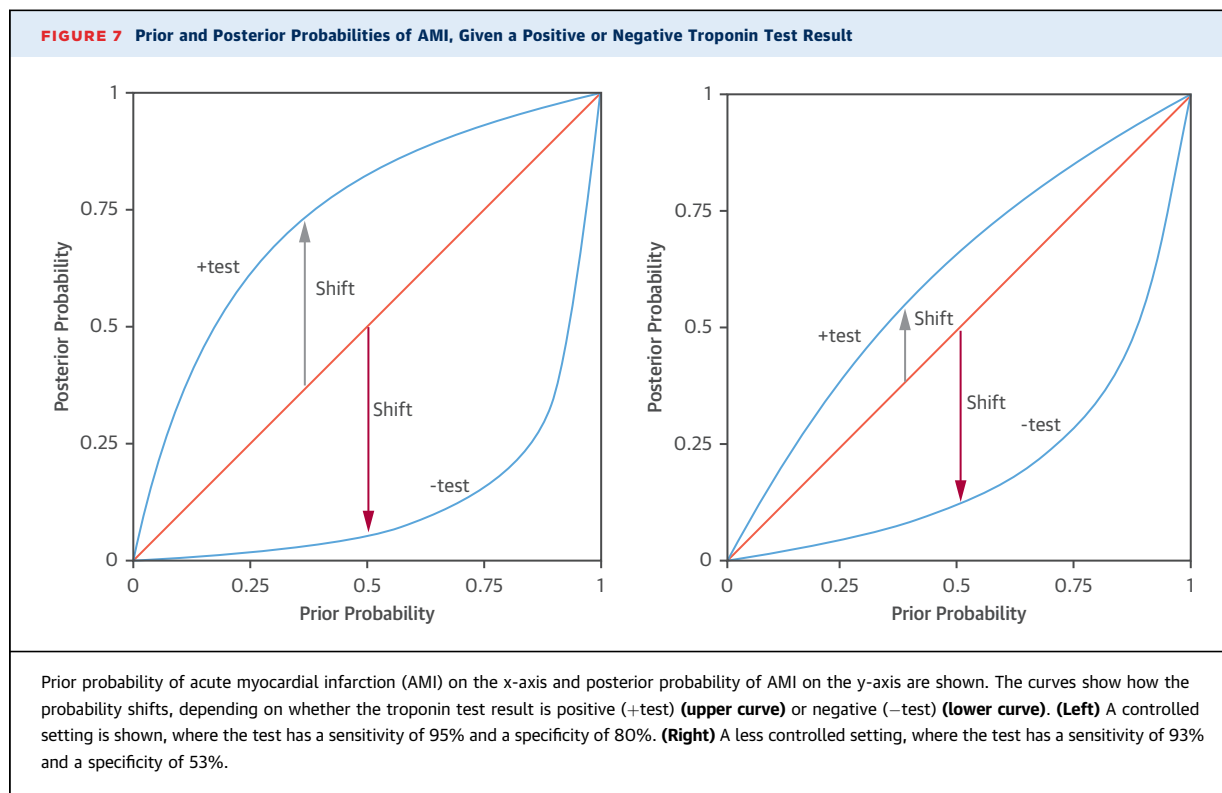
The right panel of Figure 6 shows how this will affect the separation of our patients with no disease from patients with acute myocardial infarction. The shape of the probability density curve (Figure 7, shown in blue) for the patients with no disease has become wider and shorter, with more overlap with the curve for the patients with acute myocardial infarction, and the specificity (Figure 7, TNR, shown in red) has dropped from 80% to 53%. Broadening the inclusion criteria for troponin testing broadened the shape of the probability density curve for the normal population, the opposite of what we saw in Figure 4, and because the line of demarcation remained fixed, widening the curve markedly decreased the specificity (TNR).

BAYESIAN REASONING

How should a test's clinical sensitivity and specificity affect our thinking about an individual patient? In clinical practice, we generate hypotheses (provisional diagnoses) that might explain a patient's presentation and use iterative hypothesis testing to determine the plausibility of the initial provisional diagnoses. Bayesian reasoning is a method that enables us to incorporate our original thinking about a patient with a test result to determine the post-test probability of a diagnosis. In clinical medicine we usually estimate the probabilities subjectively and intuitively, using a heuristic (mental process) called anchoring and adjusting [8]. We estimate an initial or prior probability of a diagnosis on the basis of clinical presentation, history of cardiovascular disease or risk factors, and electrocardiographic changes, which becomes the anchor; and then we adjust our initial probability estimate on the basis of the strength of a test result to determine the posterior probability of a diagnosis. If we become too anchored to our prior probability estimate, we commit a fallacy known as anchoring. If we use the test result without considering the prior probability, we commit another fallacy known as base-rate neglect. Experienced clinicians often have an intuitive ability to estimate prior probabilities and appropriately adjust on the basis of an intuitive sense of the strength of a test result.

Likelihood ratios are very useful in this regard because they are a measurement of the strength of

FIGURE 7 Prior and Posterior Probabilities of AMI, Given a Positive or Negative Troponin Test Result

Prior probability of acute myocardial infarction (AMI) on the x-axis and posterior probability of AMI on the y-axis are shown. The curves show how the probability shifts, depending on whether the troponin test result is positive (+test) **(upper curve)** or negative (−test) **(lower curve)**. **(Left)** A controlled setting is shown, where the test has a sensitivity of 95% and a specificity of 80%. **(Right)** A less controlled setting, where the test has a sensitivity of 93% and a specificity of 53%.

the test result (32). They can help us know how much we should adjust our initial probability estimate as we attempt to determine the final probability estimate. We can multiply a likelihood ratio with the pretest odds to yield the post-test odds of a diagnosis. Or, if we are using the anchoring-and-adjusting heuristic, we can use likelihood ratios to calibrate our intuition, giving us a sense of how much we should adjust our initial probability estimate.

Bayesian reasoning is graphically displayed in **Figure 7**. **Figure 7** left panel shows how a troponin test with a sensitivity of 95% and a specificity of 80% should shift our thinking. We can choose a prior probability of acute myocardial infarction along the range of possible prior probabilities from 0 to 1 (or 0% to 100%) on the x-axis. We can then draw a vertical line from that point to 1 of the 2 curves (the upper curve for a positive test result and the lower curve for a negative test result), and then draw a horizontal line from the point on the curve to the y-axis to determine the posterior probability of acute myocardial infarction.
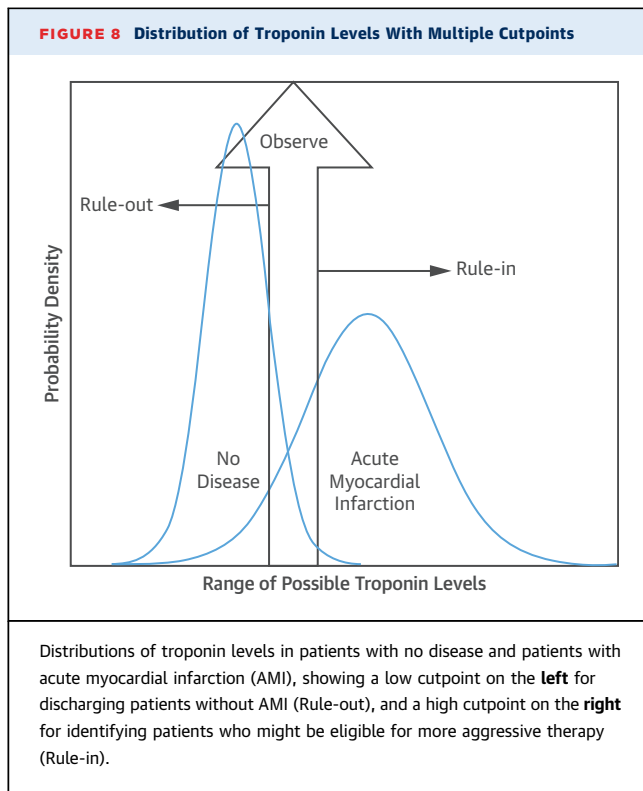
Figure 7 left panel shows how our thinking should shift for either a positive or negative test result, given a sensitivity of 0.95, and a specificity of 0.80. **Figure 7** right panel shows how our thinking about troponin testing is changed by spectrum bias. The way that troponin testing is commonly ordered in practice

lowers the specificity and the positive likelihood ratio, making it much less capable for ruling in a diagnosis. When the test is ordered in this way, a positive troponin test result becomes weaker evidence that is less compelling. If the clinician is unaware of how the spectrum bias can affect the specificity of the test, and if there is the additional problem of base-rate neglect, the 2 errors can compound, resulting in a substantial misinterpretation of a positive test result.

One possible solution would be to change the line of demarcation for troponin testing to make the test more specific. Generally, cardiologists would like to maximize the test specificity to avoid false positive results so that aggressive treatments can be reliably delivered to the patients who stand to benefit most. However, ED physicians would like to keep the cut-point where it is, to maximize sensitivity. ED physicians are much more worried about false negative results and missed diagnoses. The result, however, is needless hospitalizations and downstream testing.

TROPONIN TESTING AND CLINICAL REASONING

Practicing clinicians use medical knowledge to form assumptions and develop rules of thumb called

FIGURE 8 Distribution of Troponin Levels With Multiple Cutpoints

Distributions of troponin levels in patients with no disease and patients with acute myocardial infarction (AMI), showing a low cutpoint on the **left** for discharging patients without AMI (Rule-out), and a high cutpoint on the **right** for identifying patients who might be eligible for more aggressive therapy (Rule-in).

heuristics that enable rapid decisions, often under conditions of uncertainty (8). The underlying assumptions regarding troponin testing have changed as the analytical capabilities of the test have improved. Many of the prior assumptions no longer hold today, and this can potentially lead to suboptimal clinical reasoning.

First, practicing clinicians should remember that the term high-sensitivity troponin refers to the analytical sensitivity not the clinical sensitivity. Early troponin tests were less analytically sensitive, which has conditioned clinicians to think that any detectable troponin level is abnormal. Because the newer high-sensitivity troponin assays can measure detectable troponin levels in most normal test subjects, the rule of thumb that any detectable troponin level is abnormal is no longer valid. Troponin results using newer assays will require comparison to the upper reference limit, just like most other common laboratory tests.

Second, troponin testing was initially thought to be very specific because the test was not affected by skeletal muscle injury, like CK-MB. But troponin levels are affected by a long list of conditions other than myocardial ischemia, markedly decreasing its specificity (TNR) when the test is ordered indiscriminately. It is incumbent on practitioners to re-examine their troponin ordering policies to narrow the spectrum of patients by focusing on patients in

whom the a priori diagnosis of ischemic heart disease is plausible. Current practice that promotes indiscriminate ordering is an inappropriate use of the test and needs to be corrected.

Third, ACS patients with elevated troponin levels may benefit from antithrombotic medications and interventional procedures, but patients with troponin elevations due to other conditions, such as congestive heart failure, sepsis, or demand ischemia (type II myocardial infarction), would not benefit from such interventions. Indiscriminate troponin testing can cause clinicians to jump to conclusions and aggressively treat patients who would not stand to benefit, and may be harmed.

With the newer high-sensitivity troponin assays, new thinking will be required for proper interpretation of the tests. As noted earlier, newer high-sensitivity troponin T and I assays are under review by the U.S. Food and Drug Administration for approval in the United States (33). Once approved, clinicians will need to use these tests thoughtfully.

One solution that has been promoted is to use algorithms that incorporate 2 cutpoints (**Figure 8**) (34). This strategy uses a more sensitive cutpoint (**Figure 8, left**) to enable early rule-out and rapid triage. A more specific cutpoint (**Figure 8**, right) enables early rule-in and rapid treatment of patients with ACS. Patients who fall in the middle will require further observation and serial testing. Other protocols have used the high-sensitivity assays at both time 0 and 1 h to determine the cutpoint, and the difference between the baseline and the 1-h results that optimizes both sensitivity and specificity. Still others have used protocols and cutpoints that maximize sensitivity for early rule-out, while tolerating low specificity (35). As these protocols are defined and implemented, it will be critical for clinicians to have a firm understanding of the definitions of sensitivity and specificity of troponin testing.

This paper provides visual explanations in schematic forms that are meant to give practitioners an intuitive understanding of the statistical issues related to troponin testing. Understanding the statistics that define the cutpoint, sensitivity, and specificity of troponin testing is critical. Misunderstanding these statistics can lead to flawed clinical reasoning and mistakes at the bedside. Mistakes can lead to missed diagnosis, delayed diagnosis, and overdiagnosis, resulting in overtreatment, where the potential harm may exceed the benefit in low-risk patients. Now is a particularly important time to review this important topic. The new high-sensitivity troponin assays will bring with them opportunities for improving the care of patients presenting with

ACS. However, even the best test will fall short of its potential if the clinical reasoning that drives its use is not carefully thought out. It is incumbent on physicians to understand the operating characteristics of these tests so they can use these tests prudently and optimize their utility in clinical care.

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