High-Sensitivity Troponin Assays: Evidence, Indications, and Reasonable Use
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With advances in technology, a new era in troponin assays is approaching. Previous-generation troponin assays have been used as diagnostic and prognostic markers in acute coronary syndrome patients and for risk stratification to guide triage decisions and aid in treatment selection.\(^1\)\(^,\)\(^2\) New, high-sensitivity troponin assays represent an important advance with added sensitivity for cardiac myocyte necrosis,\(^3\)\(^–\)\(^5\) but there remains a need for judicious interpretation with these tests. These new troponin assays could have several distinct roles in clinical practice: (1) facilitation of earlier diagnosis and rule out of myocardial infarction (MI); (2) risk stratification in acute cardiac conditions and prognostic information in stable disease states; and (3) therapeutic monitoring and drug toxicity evaluation. However, because they are not specific for the etiology of cardiac cell death, the clinician has an increasing responsibility to interpret each test in clinical context.\(^6\) When commercially available in the United States (US), these high-sensitivity analyses are expected to offer both advantages and disadvantages to practicing clinicians and to enhance current roles of the troponin assay as well as to open doors to new uses for troponin testing. However, they will also create new challenges in clinical applications, epidemiology, and research. The aim of this review is to discuss the potential clinical and research roles of high-sensitivity cardiac troponin assays and the challenges they may create.

Assay Development
High-sensitivity troponin assays detect concentrations of the same proteins that conventional sensitivity assays are aimed at detecting, just in much lower concentrations.\(^4\) Before 2009, there was no agreed-on definition of what constituted a high-sensitivity assay or a consensus on nomenclature for these much more sensitive tests, but that seems to have been resolved in 2012. High-sensitivity assays, by expert consensus,\(^4\) should have a coefficient of variance (CV) of <10% at the 99th percentile value in the population of interest. To be classified as high-sensitivity assays, concentrations below the 99th percentile should be detectable above the assay’s limit of detection for >50% of healthy individuals in the population of interest. Using these criteria, there are several contemporary assays that are available on an experimental basis in the US but presumably would soon be available clinically as well. The assays and their characteristics are shown in Table 1. Just as with the conventional-sensitivity assays, there are a growing number of companies that are producing high-sensitivity assays (most are producing troponin I assays; however, there is a single troponin T assay, both conventional and high sensitivity, allowing for standardization across centers). As shown in Table 1 there is wide variability in assay characteristics between manufacturers. This prevents comparison between assays and often between clinical centers and hospital systems for conventional troponin assays\(^4\) and will be no less a challenge with the advent of high-sensitivity troponin testing. This problem is just one of several that face the high-sensitivity assays. Importantly, just as with the earlier troponin assays, interpretation of high-sensitivity troponin values needs to have basis in the 99th percentile value in the general population. Using this value in clinical practice, for each assay, has previously been shown to optimize the sensitivity and specificity of troponin and serves to minimize false-positive testing.\(^3\)\(^,\)\(^7\) However, determination of this value and, more specifically, the population in which to derive this value consistently, is not universally agreed on. Previous research to determine the 99th percentile for high-sensitivity troponin assays has yielded different values for the same assay based on different sample populations.\(^8\) Nonetheless, there should
be collaboration at clinical centers among physicians and laboratory managers to identify the 99th percentile value for the preferred assay, from either the assay manufacturer’s guidelines or laboratory reference literature. This will aid in consistent interpretation of the test.

Use of High-Sensitivity Assays and Potential Challenges

Based on their analytic capabilities, the high-sensitivity assays offer several advantages over their conventional assay counterparts. As previously mentioned, they are extremely sensitive, perhaps allowing for earlier and faster recognition of MI patients9 and giving clinicians an avenue to more quickly diagnose and treat patients appropriately. The new assays are also precise, having small CV levels even at the 99% in reference populations.4,5 They are specific for myocardial necrosis, although this topic is controversial. There are conflicting opinions on the specificity of troponin for myocardial infarction versus ischemia. In brief, there are limited data in the setting of stress tests, during which standard-sensitivity troponin assays are static, while high-sensitivity assays detect a small rise in troponin.10 In addition, experimental models of ischemia, achieved by pacing patients from the coronary sinus, have shown a low-level elevation in troponin appreciated only with high-sensitivity troponin assays.11 Some authors have interpreted similar findings as consistent with ischemia12,13; however, it has also been argued that the high-sensitivity assays are detecting minute levels of myocyte necrosis (thus, miniscule Mls).14 In addition, there are several proposed mechanisms of troponin release that are not related to necrosis, namely apoptosis, cellular release of proteolytic products, increased cell wall permeability with stress or stretch, and the production of membranous blebs that contain troponin.15 Despite the controversy, conventional-sensitivity assays are specific for myocyte necrosis, and we believe high-sensitivity troponin assays will also have high specificity once appropriate threshold values have been determined. Finally, there is a considerable amount of data that indicate that increasing values (and perhaps changes in values over time) correlate with risk of adverse cardiac events16,17 However, most of these advantages also bring disadvantages. With higher sensitivity comes the responsibility of understanding and interpreting very low levels of high-sensitivity troponin elevation. Despite the high specificity of these assays, no troponin assay alone allows a clinician to determine the etiology of myocyte necrosis. While high precision is quite valuable in these tests, especially at low levels, biological variability again makes interpretation of high-sensitivity troponin elevations difficult, and new thresholds will have to be defined for clinical use. Finally, as with current troponin I assays, there is no industry standard to the high-sensitivity troponin assays, and they have varying assay characteristics that will make comparisons between hospitals and medical systems difficult at present (Table 2).

With the increased sensitivity of these new assays and the evaluation of their precision and sensitivity in healthy populations (although not completely agreed on), investigators have discovered biological variability in the low detectable levels of healthy individuals. Biological variability is a type of preanalytic variation due to changes over time in normal individuals. These changes may be secondary to circadian rhythm, monthly changes, or seasonal changes inherent to a species. In addition there is random biological fluctuation around an inherent set point that may be specific to an individual. This certainly affects the utility of these new assays

**Table 1. Analytic Comparisons of Contemporary High-Sensitivity Cardiac Troponin Assays***

|             | Limit of Detection (ng/L) | 99% (CV) (ng/L) | 10% CV (ng/L) |
|-------------|---------------------------|-----------------|--------------|
| Hs-cTn-T    |                           |                 |              |
| Roche Elecsys | 5.0                      | 14 (13%)        | 13           |
| Hs-cTn-I    |                           |                 |              |
| Abbot ARCHITECT | 1.2                      | 16 (5.6%)       | 3            |
| Beckman ACCESS | 2 to 3                   | 8.6 (10%)       | 8.6          |
| Mitsubishi Pathfast | 8.0                      | 29 (5%)         | 14           |
| Nanosphere | 0.2                       | 2.8 (9.5%)      | 0.5          |
| Radiometer AQT90 | 9.5                      | 23 (17.7%)      | 39           |
| Singulex Erenna | 0.09                     | 10.1 (9.0%)     | 0.88         |
| Siemens Vista | 0.5                      | 9 (5.0%)        | 3            |
| Siemens Centaur | 6.0                      | 40 (10%)        | 30           |

CV indicates coefficient of variance; Hs-cTn-T, high-sensitivity cardiac troponin T; Hs-cTn-I, high-sensitivity cardiac troponin I.

*Typical units for troponin and hs Tn assays are μg/L.

Created with data from Jaffe et al3 and Apple et al.4

**Table 2. Potential Utility and Challenges of the High-Sensitivity Troponin Assay****

| Potential Utility                  | Potential Challenges          |
|-----------------------------------|------------------------------|
| More rapid diagnosis in ACS       | Nonspecific to etiology       |
| Population screening              | False-positive interpretation|
| Prognostic information in stable patients | Biological variability |
| Drug development and cardiotoxicity | Lack of assay standardization |

ACS indicates acute coronary syndrome.
High-Sensitivity Troponin Assays  Sherwood and Kristin Newby

and should inform the use of threshold values and change values that might be used for diagnostic and prognostic clinical evaluation. Wu et al demonstrated a mean biological variability in healthy individuals using the Singulex cTnl assay in the range of ≈10% over 4 hours and ≈15% over 8 weeks. With this level of variability, the authors calculated a reference change value of 81% for increasing serial assays and −45% for decreasing serial assays to define abnormality. Vasile et al, using the Roche hs-Troponin T assay, showed that mean delta values within 24-hour studies were ±58%, while values over multiple days could vary by ±90%. Given this biological variability, the authors determined that a short-term (eg, 4 hours) change of 85% or long-term (eg, 8 weeks) change of 315% would be necessary to be reasonably certain that abnormality was present. Sharnhorst et al and Frankenstein et al also evaluated healthy individuals and found similar values for variability and reference change values.

This variation raises numerous questions about the clinical use of these tests. Biological variability would alter how high-sensitivity troponin assays are interpreted in nearly all clinical applications in which >1 value is measured. Due to variability with time in an individual and detectable levels at healthy state, further study and statistical testing are needed to determine what levels of change are necessary and sufficient to signal an abnormality, rather than either biological variability or imprecision. Also, European guidelines for the diagnosis of MI indicate that appropriate thresholds, reference values, and change values should be determined for each high-sensitivity assay.

Diagnosis of Acute Coronary Syndrome

The primary role for the troponin assay since its inception has been to diagnose patients with acute MI (AMI). While the improved sensitivity and specificity of troponin (over creatine kinase–MB) may have improved diagnostic accuracy for AMI in the emergency department and hospital, its shortcomings may be that, depending on the time between symptom onset and presentations, there is a delay of several hours in elevation of the biomarker. This delay causes a delay in diagnosis and, thus, longer emergency department and observation stays both for patients with and those without AMI. New high-sensitivity assays have overcome this weakness with their improved sensitivity, making the first low-level elevations of troponin detectable within 90 to 180 minutes of the event. Two large prospective studies performed in the emergency department setting showed that the high-sensitivity troponin assays are more accurate than previous assays in the successful diagnosis of AMI within 3 hours of the onset of symptoms. The increase in accuracy and speed could be beneficial in multiple ways. Patients are diagnosed more quickly and, as a result, may be treated more rapidly, including earlier invasive therapy. For the majority of patients, the improved assays will lead to a quicker rule-out of MI. This may allow for more prompt subsequent evaluation and perhaps to earlier discharge of appropriate patients, decreasing further costs. However, there has not been adequate prospective evaluation of the use of these new assays in a diagnostic algorithm, and these assays may perform in a less-specific manner in the general chest pain population outside of the strict criteria required to enter a randomized clinical trial. Also, the cost-effectiveness of these new algorithms and strategies has not yet been established.

Despite increases in accuracy and earlier detection with new troponin assays, there are new problems for the diagnosis of MI with these assays. Previously, the use of troponin for the diagnosis of AMI was more straightforward in that an elevated value was deemed an AMI, whereas a value below a set threshold was not. Research with high-sensitivity assays shows both a nominal level of high-sensitivity troponin at baseline in apparently healthy individuals and the presence of biological variability over time. These features affect how clinicians use the high-sensitivity assays (currently commercially available in Europe but not yet in the US). Some have proposed that an absolute change value over time should be used to diagnose AMI. The threshold is based on testing of reference populations, which vary widely among industry producers. There is also variation in how reference populations are defined, thus adding more questions to what threshold values might be for these new assays. Others have suggested using a percent change in troponin, a delta troponin. Keller and colleagues compared the use of a relative change in troponin at 3 hours significantly increased the positive and negative predictive values for these high-sensitivity assays. Reichlin et al, in a prospective observational study, evaluated the utility of an absolute change versus a relative change in high-sensitivity troponin from baseline to 2 hours after presentation. In their analysis, an absolute change of high-sensitivity troponin was more accurate than relative change for diagnosis of MI. Mueller et al also found that absolute change (within 3 to 6 hours) in high-sensitivity troponin had superior diagnostic value (c-statistic 0.898 versus 0.752, P<0.0001) compared with relative changes in the same period. However, for either strategy, establishment of thresholds will be difficult, as will be standardization across assays.

While the new assays can provide more accurate, rapid detection of myocardial necrosis, they do not indicate the cause of cell death. Improved assay performance will have to be accompanied by improved clinical evaluation of patients to effectively interpret the results and apply them in clinical practice. The universal definition of MI (Table 3) was a broad
consensus developed by representatives from the American College of Cardiology Foundation, European Society of Cardiology, American Heart Association, and World Heart Federation that provided increased structure and clarity around the diagnosis of MI in the era of a troponin gold standard. Importantly, it firmly established the importance of clinical symptoms in conjunction with elevated troponin levels occurring with a characteristic rise and/or fall to establish type 1 MI. It also allowed for diagnosis in the setting of sudden cardiac death, as well as enhanced categorization for periprocedural MIs. As sensitivity and precision of troponin assays have improved, false-positive results due to assay imprecision are becoming less of a problem. However, the pressure on clinical perspective in interpretation of positive troponin results has increased, given that there is a large differential diagnosis generated by a positive troponin assay (Figure).

### Risk Stratification

#### Acute Coronary Syndrome Population

In AMI, troponin not only serves a diagnostic purpose but also can be useful for prognosis. The earlier-generation assays showed troponin is a strong prognostic marker for cardiovascular death and recurrent ischemic events in both non–ST-segment elevation myocardial infarction (STEMI) and STEMI. The new high-sensitivity assays share this prognostic ability. In a single-center study of nearly 1000 patients presenting to the emergency department with chest pain, troponin measured with a high-sensitivity assay was a more robust predictor of cardiovascular death at 1-year follow-up than the conventional troponin assay. The same authors also evaluated whether a delta high-sensitivity troponin level between presentation and 2 hours later would provide prognostic information but found that the absolute value was superior to the delta value at 2 hours for prognostication of cardiovascular death at 1 year.33

The prognostic information gained from troponin not only can give clinicians information on risk but also may help to guide therapy, although these management strategies have only been studied with standard-sensitivity troponin assays. Troponin can be a useful measure for assigning patients to higher-level monitoring, such as the cardiac care unit or telemetry. Previous research used standard sensitivity troponin as one of several factors that might direct triage to an invasive strategy for NSTEMI. Indeed, its use has also been suggested as part of clinical risk scores to influence timing of cardiac catheterization for NSTEMI patients. Troponin levels also have been associated with a benefit of more aggressive medical antiplatelet therapy, specifically for glycoprotein IIb/IIIa inhibitors. Further investigation is needed to provide thresholds by which high-sensitivity assays might also be used to guide therapeutic strategies.

#### Acute Pulmonary Embolism

Troponin has also been recognized as a strong predictive biomarker in other acute clinical situations, such as acute pulmonary embolism (PE). While echocardiographic and chest computed tomography parameters have been used as signals of worsening cardiac function, troponin is a routine laboratory biomarker that is drawn in the vast majority of patients with suspected PE. A recent meta-analysis of 20 studies with 1985 patients showed that troponin was independently associated with greater risk for short-term death and morbidity after PE. Troponin measured with high-sensitivity assays has also been studied. Lankeit et al performed a prospective study of 526 normotensive patients admitted with acute PE. They found that high-sensitivity troponin results, alone and as part of a clinical risk score, were independently associated with cardiovascular death and in-hospital complications. In the specific population of patients studied, the authors suggested that high-sensitivity troponin might aid in selection of a low-risk subgroup that could be treated as outpatients. This finding has led to further research on the combination of

### Table 3. Universal Definition of Myocardial Infarction

| 1 | Spontaneous | MI related to ischemia from primary coronary event such as plaque rupture, erosion, fissuring, or dissection |
| 2 | Demand/supply imbalance | MI related to secondary ischemia due to myocardial oxygen supply/demand imbalance such as spasm, anemia, hypotension, arrhythmia |
| 3 | Sudden death | Unexpected cardiac death, perhaps suggestive of MI, but occurring before blood samples can be obtained |
| 4a | PCI | MI associated with PCI procedure |
| 4b | Stent thrombosis | MI associated with stent thrombosis as seen on angiography or autopsy |
| 5 | CABG | MI associated with CABG |

CABG indicates coronary artery bypass graft surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention. Adapted with permission from Thygesen et al.7
laboratory and echocardiographic biomarkers to risk stratify patients with PE. Acute coronary syndrome and acute PE represent the advances in clinical risk stratification that could be accomplished with high-sensitivity troponin assays.

**Asymptomatic Population**

**Stable Coronary Artery Disease and Congestive Heart Failure**

High-sensitivity troponin has also expanded the possibilities for risk assessment in asymptomatic patients. In a large observational cohort of patients with known coronary artery disease (CAD), but without congestive heart failure (CHF) or acute coronary syndrome (PEACE [Prevention of Events with Angiotensin Converting Enzyme Inhibition] trial population), and follow-up for a median of 5.2 years, high-sensitivity troponin was independently associated with cardiovascular mortality and the development of CHF, although it was not associated with MI. In a similar study of patients at high risk for CAD events (HOPE [Heart Outcomes Prevention Evaluation] study population), high-sensitivity troponin levels were independently associated with the composite outcome of cardiovascular death and future MI over a mean follow-up of 4.5 years. Troponin is also a prognostic marker in stable CHF. Previous investigation showed that troponin was often present in the blood of both acute and chronic heart failure patients and has been hypothesized to be due to an imbalance in myocardial oxygen demand or extreme cardiac stress in these states. The use of high-sensitivity assays to measure serial levels of troponin in stable CHF patients has been examined in several analyses. In a large retrospective study of 2 clinical trial populations (Val-HeFT [Valsartan Heart Failure Trial] and GISSI-HF [Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico–Heart Failure]), even low levels of troponin using high-sensitivity assays,
detected at baseline and at an initial visit 4 months later, were independently associated with CHF-related mortality and all-cause mortality at 2 and 4 years of follow-up. In smaller populations of stable CHF patients, high-sensitivity troponin was consistently associated with cardiovascular deaths and CHF admissions during long-term follow-up, regardless of ischemic versus nonischemic etiology. Given that in each of these studies patients were known to have CAD or CHF and were at risk for future adverse cardiac events, the additional risk stratification imparted by high-sensitivity troponin may not result in expansion or intensification of treatment and, thus, may have limited utility. However, high-sensitivity troponin may provide a sensitive, noninvasive window into cardiac structure and function.

Stable Chronic Kidney Disease/End-Stage Renal Disease

Chronic kidney disease is an important clinical condition that is associated with worse outcomes in coronary artery disease, and end-stage renal disease patients are at high risk for adverse cardiovascular events. Troponin elevation in these patients has been shown to be a prognostic factor, though the mechanism of this relationship is unclear. Khan et al performed a meta-analysis of 28 studies with nearly 4000 patients with stable end-stage renal disease, and without acute coronary syndrome. They evaluated troponin elevation at baseline and determined that there was a significant, independent, association of troponin with cardiovascular death and all-cause mortality. With new-generation high-sensitivity assays, mild troponin elevations are present in a large proportion of asymptomatic end-stage renal disease patients. Additional study has found that troponin measured with these high-sensitivity assays is more elevated in patients with a history of CAD, but no prognostic studies have yet shown a relationship with future events. Further research is necessary to determine how high-sensitivity troponin assays might be used in patients with end-stage renal disease on dialysis given that the majority of patients have elevated values at baseline.

### Screening

While elevated troponin might signal worse prognosis among patients with known CAD or CHF or who are otherwise at significant risk, high-sensitivity assays may provide a means of screening a general population of patients for cardiac dysfunction. In a prospective observational cohort of general patients randomly enrolled from a large metropolitan area (Dallas Heart Study), elevated levels of high-sensitivity troponin were associated with greater rates of structural heart disease, including left ventricular hypertrophy and systolic dysfunction, as well as all-cause mortality within a median follow-up of 6.4 years. In a nationwide prospective cohort study of ambulatory older adults (≥65 years) without heart failure, high-sensitivity troponin values (both baseline and absolute change over 2 years) were associated with incident heart failure and cardiovascular death over a median follow-up of 11.8 years (Table 4). Thus, in a general population, high-sensitivity troponin might play a role in screening for structural and coronary heart disease, potentially prompting further evaluation and more aggressive primary prevention measures. However, there are several obstacles to overcome before such a clinical strategy could be used. Biological variability will have to be further explored and quantified to establish reasonable threshold change values. Standardization of high-sensitivity troponin assays would be extremely important to allow for appropriate interpretation of troponin values with time and across different medical systems.

| Study Authors       | Populations Study Size | Change Units (Assay) | Outcomes                  | Adjusted Hazard Ratios |
|---------------------|------------------------|----------------------|---------------------------|------------------------|
| de Filippi et al    | Cardiovascular Health Study (mixed stable) (n=4221) | ≥12.94 pg/mL (hsTnT) | CV mortality              | 2.91 (2.37 to 3.58)    |
| de Lemos et al      | Dallas Heart Study (mixed stable) (n=3546)         | ≥0.0014 ng/mL (hsTnT) | Mortality                 | 6.0 (4.7 to 11.3)      |
| Omland et al        | PEACE (stable CAD) (n=3679)                          | ≥0.0096 µg/L (men)   | CV mortality              | 2.39 (1.85 to 3.09)    |
|                     |                                                      | ≥0.0074 µg/L (women) | (for hsTnT as a cont. variable) |
| Masson et al        | Val-HEFT GISSI-HF (stable CHF for both) (n=5284)     | ≥13.5 ng/L for both (hsTnT) | Mortality for both        | 1.60 (1.41 to 1.82)    |
|                     |                                                      |                      |                           | 1.97 (1.58 to 2.46)    |
| Kavsak et al        | HOPE (stable at risk for CAD/CHF) (n=2572)           | ≥10 ng/L (hs-cTnI Beckman Coulter) | CV mortality              | 2.2 (1.3 to 3.5)       |

CAD indicates coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; HsTnT, high-sensitivity troponin T; Hs-cTnI, high-sensitivity cardiac troponin I.
Future Directions

The new high-sensitivity troponin assays may allow clinicians to better stratify risk in other potentially high-risk populations. However, the utility of troponin testing in these settings is unclear and awaits further investigation. A recent example is atrial fibrillation, which represents an important population of patients with few, if any, useful biomarkers currently available to aid clinical risk stratification. Traditionally, clinical risk scores are used to estimate risk for thromboembolic events in atrial fibrillation; then, anticoagulant medication is considered depending on embolic risk and bleeding risk, medication adherence, etc. Roldan et al\(^5\) found that in a large cohort of chronic atrial fibrillation patients on oral anticoagulation for atrial fibrillation, high-sensitivity troponin levels were independently associated with an increased risk for thrombotic and vascular events as well as cardiovascular death. This relationship was maintained even after CHADS\(_2\) (which estimates risk based on the presence of congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack) risk factors and HAS-BLED (defined as hemorrhage involving a critical anatomic site, for example, intracranial, or a bleed requiring hospitalization, transfusion of ≥2 units of packed cells, or associated with a decrease in hemoglobin level of ≥2 g/L) risk factors were added to the model.

In addition, there are few clinical tools to identify which patients will have recurrent atrial fibrillation. A prospective cohort substudy of GISSI AF (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico–Atrial Fibrillation), a trial to determine the effects of valsartan on recurrence of atrial fibrillation, studied the utility of several biomarkers to predict recurrent of AF.\(^5^7\) Over 2-year follow-up, high-sensitivity troponin was independently associated with the recurrence of AF, as were 2 other biomarkers. While high-sensitivity troponin may add to prognostic information and elevated troponin levels may warrant increased surveillance of high-risk patients, it remains uncertain whether any therapies might be triggered by this type of risk stratification (eg, prolonged antiarrhythmic medications, atrial fibrillation ablation, or atrial occluder devices).

Troponin measured with high-sensitivity assays is also being evaluated for use in cardiac transplant patients. In this population, low levels of troponin are present in the majority of patients shortly after transplantation. Higher levels of troponin, measured with high-sensitivity assays, have been associated with acute allograft rejection\(^5^8\) and cardiovascular death.\(^5^9\) Troponin in conjunction with optical coherence tomography has also been studied in the diagnosis of cardiac allograft vasculopathy. Specifically, high-sensitivity troponin was directly associated with measurements of maximal intimal thickness in posttransplant patients,\(^6^0\) suggesting a potential new use for troponin to rule out vasculopathy in cardiac transplant patients, although this seems premature given how little evidence exists.

Many drugs, both currently used and newly developed, have the potential for cardiac toxicity. These effects are sometimes discovered in preclinical work with animal models and sometimes are not discovered until human studies are undertaken. Given troponin’s high specificity for myocardial necrosis, there would seem to be a biological plausibility for its use in monitoring for cardiotoxicity. However, this does not imply that in practical implementation it would provide similar information in detecting drug-induced cardiotoxic states. First, by definition, high-sensitivity troponin must be detectable below the 99th percentile and above the assay limit of detection in at least 50% of the reference population. Second, the precision of the high-sensitivity assays is limited less by analytical issues than by biological variability at these low levels that may be particularly relevant in serial testing to monitor for early detection of myonecrosis that may reflect cardiotoxicity. Further, it is important to remember that high-sensitivity troponin provides no information on the etiology of cardiac myonecrosis and that there are many nonischemic causes of troponin release (Table 5).

Almost all data available on measuring cardiotoxicity with troponin assays have been produced in laboratory animals.

### Table 5. Selected Nonthrombotic Causes of Troponin Elevation

| Clinical Syndrome                        |
|-----------------------------------------|
| Congestive heart failure                |
| Drug toxicity                           |
| Hypertension                            |
| Hypotension                             |
| Renal failure                           |
| Sepsis                                  |
| Hypothyroidism                          |
| Stress-induced cardiomyopathy           |
| Myocarditis/pericarditis                |
| Post PCI without complication           |
| Post CABG without complication          |
| Pulmonary hypertension (severe)         |
| Stroke or intracerebral hemorrhage      |
| Rhabdomyolysis                          |
| Strenuous exercise                      |
| Transplant vasculopathy                 |
| Traumatic injury                        |

\(^{CABG}\) indicates coronary artery bypass graft surgery; \(^{PCI}\), percutaneous coronary intervention.

Adapted from Newby et al.\(^5^2\)
and mammalian models of disease. There are few data from human subjects, and much of it is in pediatric subjects undergoing treatment for acute leukemia. In the past 5 years, there has been an increase in research on biochemical and echocardiographic biomarkers of myocardial function in adult patients receiving chemotherapy. Two studies of patients treated for breast cancer with anthracyclines and trastuzumab showed that both longitudinal strain and troponin (measured with high-sensitivity assays) were independently associated with cardiac dysfunction as measured by traditional echo parameters. These findings might allow for the development of protocols and standards by which new therapeutics could be measured, including new antidiabetic agents and chemotherapeutic agents. However, additional work is needed to confirm the utility of high-sensitivity troponin testing for cardiotoxicity monitoring, including a better understanding of biological variability and whether patient-specific curves would be needed before treatment. At present, there is no unified approach to monitoring drug safety with troponin, but there has been a call for further investigation and standardization in this area.

Conclusions

Troponin presently has several important diagnostic and prognostic roles in clinical medicine. While high-sensitivity troponin assays are not yet available in the US, it is imperative that clinicians, researchers, and laboratorians begin to understand and consider the strengths, limitations, and unique characteristics of these assays to develop the evidence that will both enable informed implementation into clinical practice and guide future research aimed at harnessing their potential. With the advent of high-sensitivity troponin assays, the roles for troponin testing may expand, potentially allowing for detection of very low levels of troponin in healthy individuals that are meaningful in a variety of clinical scenarios. However, with greater sensitivity comes the responsibility to integrate laboratory biomarker data with clinical data. While troponin is highly specific for myocardial necrosis, it provides no information on the etiology of myocyte death. Thus, more research and cross-disciplinary collaboration are necessary to determine new thresholds and to establish parameters for high-sensitivity troponin testing in practice. This will allow for clinicians to appropriately use these new and more powerful troponin assays.

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