Is the 99th Percentile the Optimal Reference Limit to Diagnose Myocardial Infarction With High-Sensitivity Cardiac Troponin Assays in Patients With Chronic Kidney Disease?

Bernard R. Chaitman, MD

The estimated annual incidence of myocardial infarction (MI) in the United States is ≈525,000 new attacks per year and ≈210,000 recurrent attacks. The large number of events results in many emergency room visits for diagnostic evaluation to determine the presence or absence of acute coronary syndrome (ACS) and the need for hospital admission. The third universal definition of MI requires abnormal cardiac biomarkers in the context of acute myocardial ischemia supported by clinical, ECG, or cardiac imaging findings. Cardiac troponin (cTn) is recommended as the preferred biomarker to document myocardial necrosis. A rise or fall of cTn with at least 1 value >99th percentile of a reference control population using an assay with total imprecision of cTn with at least 1 value >99th percentile is recommended to meet biomarker criteria for types 1, 2, and 4b/c MI. For procedure-related type 4a and 5 MI events, multiples >99th percentile are recommended.

In the last few years, more sensitive cTn assays and high-sensitivity cTn (hs-cTn) assays have been introduced that allow more rapid diagnosis of myocardial necrosis and detection of smaller MI events than previously possible with the standard cTn assay. Many patients previously classified as having unstable angina are now able to be reclassified as having an MI with more sensitive cTn assays. Early detection of acute myocardial necrosis may allow the introduction of earlier treatment, which would reduce morbidity and mortality. However, detection of lower levels of cTn than was previously possible with older assays allows the detection of cTn in patients with stable coronary artery disease and in patients with nonischemic conditions associated with low-level cTn elevations in the absence of coronary disease, thus increasing the false-positive rate for MI diagnosis. This decreased specificity in more complex triage in the emergency room and cardiac consultations owing to elevated troponin levels.

Chronic Kidney Disease

Patients with chronic kidney disease (CKD) represent a large group of patients in whom the diagnosis of ACS can be challenging, particularly the diagnosis of a non–ST-segment–elevation MI. It is estimated that >20 million US adults have CKD. ACS evaluation in a patient with CKD is complex. Initial cTn levels using a standard cTn assay often exceed the 99th percentile; elevated troponin levels may be the result of chronic structural heart disease (eg, heart failure) rather than acute myocardial ischemia; and ECG repolarization abnormalities are common. Sensitive cTn assays and hs-cTn assays (hs-cTn is available in Europe and some parts of the world) further increase the number of patients with initial abnormal troponin values and raise the question of whether the 99th percentile is the appropriate clinical decision value (CDV) to use for CKD patients presenting with ACS.

To address this question, Twerenbold et al tested 3 sensitive cTn assays and 4 hs-cTn assays in the Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) multicenter, prospective, observational registry, examining the frequency of MI in patients with CKD (estimated glomerular filtration rate <60 mL·min⁻¹·1.73m⁻²) and without CKD. Strengths of APACE are that all cTn assays were measured in a core laboratory; patients were enrolled within 12 hours of symptom onset; the protocol specified that blood samples be taken at presentation and 1, 2, 3, and 6 hours until the diagnosis of MI was ruled in or out; and the end point of MI was adjudicated by a clinical event committee. The committee used the universal definition of MI; serial levels of hs-cTnT using the Roche assay; all available medical records, including whether cTn levels were elevated on prior admissions; and ECG and angiographic findings when available to classify events. MI was considered if at least 1 hs-cTnT value exceeded the 99th percentile. A significant absolute change in hs-cTnT was defined as a rise or fall of at least 10 ng/L within 6 hours or a change of 6 ng/L within 3 hours.

Of the 2813 APACE patients, 447 (16%) had CKD. Adjudicated MI was the final diagnosis in 36% versus 18% of the CKD versus non-CKD patients. Receiver-operating characteristics curve analysis revealed that the diagnostic accuracy for MI diagnosis was less in patients with versus those without CKD. Optimal receiver-operating characteristics curve–derived cTn cutoff levels in patients with renal dysfunction were significantly higher compared with those in patients with normal renal function (factor of 1.9–3.4). For sensitive cTn assays, the optimal cut point determined by receiver-operating...
characteristics curve analysis in the CKD cohort approximated the manufacturer’s 99th percentile, whereas the optimal cut point was significantly higher than the 99th percentile for the 4 hs-cTn assays. Long-term survival was worse in patients with elevated cTn levels with the more sensitive cTn assays, similar to data published with less sensitive assays. CKD patients ruled out for adjudicated MI had higher baseline levels of cTn than non-CKD patients with all 7 cTn assays; the frequency of elevated baseline values above the 99th percentile ranged from 12% to 71%, depending on the assay type used. Levels of cTn values were inversely correlated to CKD severity.

The findings from the APACE registry using the hs-cTn assays indicate that patients with CKD presenting with an ACS are more likely to have elevated cTn levels on initial presentation than was previously published with older cTn assays. An increased number of patients with elevated cTn will predictably lead to more cardiac consultations from the emergency room and perhaps more hospital admissions, raising the question of whether the hs-cTn assays offer an advantage over the older cTn assays in these patients. Many institutions in Europe have already switched over to hs-cTn assays. Therefore, clinicians need to take into consideration the assay type used at their particular institution, the degree of renal impairment, and the initial and subsequent cTn levels when determining whether a patient with CKD and ACS has had an MI. For patients with CKD using hs-cTn assays (which are not commercially available in the United States at the time of this writing), a cut point > 99th percentile should improve diagnostic accuracy. Other approaches such as using the delta (changing pattern of values) rather than absolute change in hs-cTn as used by Twerenbold et al requires further study in a CKD population.

The 99th Percentile Upper Reference Limit

The finding that different cTn assays are not biologically equivalent is well known because of biochemical differences between assays and the fact that various manufacturers use different reference populations to determine the 99th percentile upper reference limit (URL). Several studies have shown that the 99th percentile URL as reported by the manufacturer may not replicate values seen in large community-based cohort studies and can result in major differences in determining the 99th percentile URL. To further examine the issue of establishing an appropriate CDV for hs-cTn assays in a general population of patients presenting with an ACS, Wildi et al studied 2300 patients in the APACE registry, 473 of whom (21%) had an adjudicated MI diagnosis. The primary outcome measure was the percentage of patients with an adjudicated MI or no MI diagnosis at presentation using the approved manufacturer CDV for the hs-cTnI Abbot and hs-cTnI Roche assays; the frequency of discordant MI results with the 2 assays were compared. For hs-cTn levels measured at presentation and at all time points, hs-cTnI and hs-cTnT levels were closely correlated (r=0.813 and r=0.790) and had comparable accuracy for early diagnosis of MI. However, among the 473 patients with adjudicated MI, 86 (18%) had discordant MI diagnoses using the approved CDV; 14.1% for women and 22.7% for men. Approximately 20% of the time, MI was diagnosed by 1 assay but not the other. The authors tested other sensitive cTn assays and hs-cTn assays and obtained similar results, not confirming the superiority of 1 assay over the other but rather illustrating that all assays are not biologically equivalent. Inconsistencies between the hs-cTnI and hs-cTnT assays were able to be reduced to ≈10% after adjustment of the cTnI CDV to approximate the biological equivalence to the cTnT assay.

The findings from both APACE article in Circulation this week expand and enhance multiple prior observations from this group of investigators and point out additional data that should be considered when the 99th percentile is used to diagnose MI.

APACE Registry

An important consideration when evaluating data from the APACE registry is the cardiologists’ use of the Roche hs-cTnI assay to diagnose MI. The cardiologists used the 99th percentile URL of 14 ng/L as reported by the manufacturer. In population-based studies, the 99th percentile URLs for the Dallas Heart Study (DHS), the Atherosclerosis Risk in Communities (ARIC) study, and the Cardiovascular Health Study (CHS) were 14, 21, and 28 ng/L, respectively. Within each cohort, the 99th percentile URL value increased with age and was higher in men. Thus, the manufacturer’s URL value does not always replicate values seen in other “healthy” patient cohorts. In APACE, the cardiologists used an absolute change defined as a rise or fall of cTnT at least 10 ng/L within 6 hours or a change of 6 ng/L within 3 hours. It is not clear whether these absolute numeric values optimize performance of the other assays tested, if sex considerations would improve performance, and if delta rather than absolute change would improve diagnostic accuracy. These differences might explain some of the interassay differences observed in both articles, as well as the relatively high rate (36%) of confirmed MI (mainly non–ST-segment–elevation MI) in the CKD cohort.

The implications of the data from the APACE registry for clinical patient management and clinical trials that use MI as an end point are substantial. Clearly, some patients presenting with non–ST-segment–elevation ACS may be misclassified simply because adoption of the manufacturer’s reference population chosen to establish the 99th percentile URL is not representative of the population being studied. Furthermore, with hs-cTn assays, certain patient phenotypes (eg, CKD) may require higher thresholds than the 99th percentile or other algorithms such as the delta change to optimize MI diagnostic accuracy. The use of a standardized approach for approval of hs-cTn assays that would allow clinicians or investigators to determine biological equivalence across all of the multiple manufactured cTn assays would be invaluable. For the time being, clinicians involved in the daily management of ACS patients in a hospital using more sensitive assays should be aware of non-ACS conditions associated with elevations in cTn and determine the pretest likelihood of MI from all available data to estimate the posttest MI likelihood. A standardized blood sampling protocol should be used to facilitate an earlier diagnosis of MI, with samples drawn at initial assessment (time 0) and repeated at least 3 and 6 hours later as required.
to establish the diagnosis for patients with (or without) initial cTn values above the CDV.

Disclosures
None.

References


KEY WORDS: Editorials • coronary artery disease • diagnosis • myocardial infarction
Is the 99th Percentile the Optimal Reference Limit to Diagnose Myocardial Infarction With High-Sensitivity Cardiac Troponin Assays in Patients With Chronic Kidney Disease?

Bernard R. Chaitman

_Circulation_. 2015;131:2029-2031; originally published online May 6, 2015;
doi: 10.1161/CIRCULATIONAHA.115.016848

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/131/23/2029

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/