Letters

Invited Commentary

High-Sensitivity Cardiac Troponin Assay in Patients With Kidney Impairment: A Challenge to Clinical Implementation

High-sensitivity cardiac troponin (hs-cTn) assay was approved by the US Food and Drug Administration in 2017,[1] and its appropriate use is currently being investigated. In this issue of *JAMA Internal Medicine*, Gallacher et al[2] examine the use of hs-cTn assays in patients with kidney impairment in a prespecified secondary analysis of a randomized clinical trial of patients with suspected acute coronary syndrome (ACS). Their major finding is that while the frequency of elevated levels of hs-cTn increases as kidney function deteriorates, two-thirds of patients with kidney impairment and elevated hs-cTn concentrations do not have a type 1 myocardial infarction (MI related to coronary thrombosis). Despite the discovery of more patients with elevated troponin levels by hs-cTn assays, 1-year rates of a type 1 MI or type 4b MI (occurring ≤48 hours after percutaneous coronary intervention) or cardiovascular death were unchanged before and after implementation of hs-cTn testing in patients with and without kidney impairment.

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The scale of the challenge of hs-cTn testing implementation, combined with the challenge of interpreting elevated hs-cTn values in patients with conditions that may produce an elevated hs-cTn value not directly related to acute myocardial injury (such as kidney impairment), is difficult to overstate. Acute coronary syndrome is the leading cause of worldwide mortality and morbidity, and chest pain—a symptom that often triggers an ACS workup—is the second most frequent reason for all US emergency department (ED) visits.[3] Although a minority of chest pain ED visits are related to ACS, the rate of missed ACS after an ED evaluation is 2% to 4% and is associated with doubled mortality.[4] Perhaps unsurprisingly, missed ACS remains the top reason for malpractice claims against ED physicians. Thus, there are enormously high stakes, both clinically and medicolegally, for appropriate evaluation of patients with chest pain and use of hs-cTn testing to improve efficiency of diagnosis and treatment without increasing unnecessary testing and admissions.

This analysis by Gallacher et al[2] highlights the need for thoughtful use of hs-cTn testing, particularly in patients with kidney impairment. While hs-cTn testing has acceptable sensitivity as part of a workup to rule out MI,[5] kidney impairment poses a particular challenge. Decreased kidney clearance of troponin often results in elevated serum levels that do not reflect true myocardial injury. However, patients with kidney disease are at elevated risk for cardiovascular disease, and kidney disease is often comorbid with conditions that are cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes. Thus, there is a need to accurately detect myocardial injury in this high-risk population, but the lower specificity of hs-cTn testing compared with conventional troponin assays[6] for all populations has the potential to trigger unnecessary stress tests, angiograms, coronary revascularization procedures, and admissions for all patients, and this potential is particularly high in the population with kidney impairment. Despite these challenges, it is not operationally feasible to use different troponin assays (conventional vs high sensitivity) for different patient populations; therefore, this topic is pressing.

The hope for hs-cTn assays was both to enable earlier diagnosis of acute MI (type 1) than by conventional troponin assays[7] and to reduce costs and improve efficiency by allowing more rapid discharge of low-risk patients,[8] thereby helping to relieve strained ED and hospital capacity by safely reducing the number of patients with suspected ACS who are admitted or observed for serial troponin measurements and provocative cardiac testing. Many EDs have adopted protocols to expedite diagnostics, such as laboratory or radiographic testing. These protocol-driven evaluations, such as standing nurse-driven chest pain triage protocols or physician-in-triage models, have led to overuse of troponin assays in patients with low pretest probability of ACS. Adoption of hs-cTn testing means that more patients—most who do not have ACS—will have a falsely positive troponin result and undergo protocol-driven but unnecessary additional testing or observation, particularly patients with kidney impairment, as shown by Gallacher et al.[2] Thus, adoption of hs-cTn assays may increase resource utilization, including admission or observation, stress testing, and cardiology consultation, without benefit to patient outcomes.

While much of the analysis on this topic centers on an outcome of type 1 MI, the problem of elevated hs-cTn values in patients with kidney impairment poses another challenge for the ED physician: the diagnosis of type 2 MI (associated with mismatches in myocardial oxygen supply and demand, rather than coronary thrombosis) in patients with kidney impairment and, in particular, when to treat patients with myocardial oxygen supply-and-demand mismatch with heparin. While this same problem existed prior to use of hs-cTn assays, the relative increase in the proportion of patients with kidney impairment who have elevated cardiac troponin values increases with hs-cTn testing compared with conventional troponin testing, meaning that the scale of this question is greater. Does the clinician obtain serial values to determine the delta, in which case the patient is at risk for further myocardial damage during this interval? Or does the clinician initiate anticoagulation, and all the risks entailed therein, in a patient whose diagnosis is not yet clear? There is little established guidance on these questions. While serial measurements will be crucial in patients with kidney impairment to determine the delta (or lack thereof) between the first and second troponin measurements and therefore help to rule in or rule out MI, the question of whether to make a diagnosis of type 2 MI after a single

hs-cTn measurement in a patient with kidney impairment presenting with chest pain currently has no clear answer. Clinicians will have to rely on the pretest probability of myocardial injury, incorporating risk factors, medical history, and clinical gestalt, in making these early diagnostic and treatment decisions.

The pressing question seems not to be how to interpret a single hs-cTn value in a patient with kidney disease suspected to have ACS, but rather to selectively order troponin testing in patients with higher pretest likelihood of ACS and how to integrate hs-cTn testing into the broader workup of such patients. These questions include whether and at what interval to obtain serial hs-cTn values, how to interpret the change in value when obtaining serial hs-cTn measurements, and how to weigh clinical factors, such as the patient's age, comorbidities, prior history of cardiovascular or cerebrovascular disease, history and physical examination findings, and electrocardiogram changes.

While the optimal strategy for management of myocardial injury without ACS is unknown, it is clear that elevated troponin levels are strongly related to increased long-term mortality. Without a clearer understanding of elevated hs-cTn values in patients with kidney impairment and alternative risk stratification tools that are easily implemented in the ED environment, such as a modified HEART score[9] adapted to this population, the clinical and medicolegal risks associated with missed myocardial injury still favor a conservative approach of increased testing and closer monitoring for those with elevated hs-cTn results.

Gallacher et al[2] highlight the challenges that accompany determining the appropriate use of hs-cTn assays. Further research focused on the performance characteristics of comprehensive strategies to rule in and rule out suspected MI in patients with kidney impairment, with an emphasis on composite cardiac outcomes, is necessary to guide clinical implementation.

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