Cardiac troponins in patients with kidney disease

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INTRODUCTION

Cardiac-specific troponin biomarkers are used in conjunction with symptoms, electrocardiographic changes, and cardiac imaging to diagnosis acute myocardial infarction (AMI) in patients with chronic kidney disease (CKD) [1]. Cardiac troponins are also used to predict short- and long-term adverse outcomes. The principal cardiac-specific troponins are cardiac troponin T (cTnT) and cardiac troponin I (cTnI).

This topic reviews the clinical use of cardiac troponins in patients with CKD. The use of cardiac troponins in patients with normal kidney function is discussed separately. (See "Troponin testing: Clinical use".)

The use of liver and pancreatic enzymes in patients with CKD is discussed separately. (See "Serum enzymes in patients with kidney failure".)

The risk of coronary artery disease among patients with CKD, including those on dialysis, is presented elsewhere. (See "Chronic kidney disease and coronary heart disease" and "Clinical manifestations and diagnosis of coronary artery disease in end-stage kidney disease (dialysis)".)

INTERPRETING TROPONIN LEVELS IN PATIENTS WITH CKD

Effect of CKD on troponin levels — Cardiac troponin levels are challenging to interpret among patients with chronic kidney disease (CKD). This is due to the high prevalence of stably elevated troponin levels in the absence of clinical evidence of acute myocardial infarction (AMI) among patients with CKD [2-5]. The Fourth Universal Definition of Myocardial Infarction directly addresses this concept and designates elevations of cardiac troponins above the 99th percentile value established in healthy adults in the absence of other clinical evidence substantiating a diagnosis of AMI as "myocardial injury."

The cause of low-level cardiac troponin elevations in patients with CKD is likely chronic myocardial injury that is not a result of epicardial coronary disease. It is not clear, however, whether chronic elevation of troponin levels in patients with CKD is related to decreased kidney clearance or increased cardiac release. Several lines of evidence support that increased cardiac release of troponins, rather than decreased clearance, is the primary cause of elevated basal levels in patients with CKD [6]. (See 'Use of troponins in prognosis' below.)

With the transition to highly sensitive (hs) troponin assays throughout the world, the vast majority of patients with CKD will have measurable troponin levels. In the National Institutes of Health Chronic Renal Insufficiency Cohort study of 2464 subjects with measured hs cardiac troponin T (hs-cTnT) levels, 81 percent had a detectable level (>3 ng/L) with a median level of 9.4 ng/L and a 75th percentile of 18.3 ng/L [2]. By comparison, the 99th percentile sex neutral value for this assay in the United States is 19 ng/L. In another study of patients presenting for the evaluation of possible AMI at two Scottish hospitals, the proportion of patients with CKD who had a hs cardiac troponin I (hs-cTnI) value above the 99th percentile increased with progressively impaired kidney function, with over 60 percent exceeding this threshold when the estimated glomerular filtration rate was <30 mL/min per 1.73 m^2 [3]. Thus, many patients with CKD will have baseline hs-cTn values that exceed the 99th percentile for healthy adults, a cutoff above which a patient is considered to have "myocardial injury" by the Fourth Universal Definition of Myocardial Infarction.

Effect of dialysis on troponin levels — Hemodialysis may change the concentration of cardiac troponins. Levels of these biomarkers could potentially increase due to hemoconcentration or decrease due to clearance or binding to dialysis membrane of cardiac troponin fragments. Thus, differences may in part be related to the diffusion rates, dialysis gradient, and pore size of the dialysis membranes in use. Studies have yielded conflicting results:

- In one study, hemodialysis was shown to minimally change MB isoenzyme of creatine kinase (CK-MB) levels and not change cardiac troponin I (cTnI) levels [7].

- Another study showed a decrease in both cTnI and cardiac troponin T (cTnT) levels (27 to 37 percent decrease, respectively) following hemodialysis with a high-flux membrane but not with a low-flux membrane [8].

- A third study found that cTnT concentrations were more likely to rise after dialysis in patients with known cardiovascular disease compared with those without known disease, suggesting that the rise in cTnT may be a result of cardiac injury [9].

Data on the effect of peritoneal dialysis on cardiac troponin levels are more limited. One study found lower cTnI levels among patients on peritoneal dialysis compared with those on hemodialysis [10].

Cardiac troponin levels may also be altered by continuous kidney replacement therapy (CKRT) when used as a therapy. As an example, a study of 10 critically ill patients with acute kidney injury requiring CKRT found a 52 percent decline in hs-cTnT in the first 5 to 10 hours, followed by a plateau for the duration of time on CKRT; serum albumin remained stable and creatinine declined over the entire course of treatment [11].

The timing of hemodialysis and CKRT should be considered when interpreting serial levels for AMI diagnosis among patients receiving such modalities. However, we believe that the criteria for a diagnosis of AMI should be the same for patients on dialysis as for patients with CKD who are not on dialysis. (See 'Diagnosis of acute myocardial infarction' below.)

DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

Based upon the Fourth Universal Definition of Myocardial Infarction, cardiac troponins T and I (cTnT and cTnI) are the blood-based biomarkers that are used for the diagnosis of myocardial injury or infarction among patients who present with clinical, electrocardiogram, or imaging findings suspicious for acute myocardial infarction (AMI) [1]. Detection of an elevated cardiac troponin level above the 99th percentile upper reference limit is defined as "myocardial injury." Cardiac troponins are preferred to the MB isoenzyme of creatinine kinase (CK-MB) because of their superior specificity and sensitivity for myocardial injury. (See "Troponin testing: Clinical use".)

Given the challenges of interpreting cardiac troponin levels in the setting of chronic kidney disease (CKD), we take the following approach to using troponins in the diagnosis of AMI among patients with CKD:

- **Use of serial troponin levels** – Among patients with CKD who present with signs and symptoms suspicious for AMI, a change in troponin concentration (ie, rise or fall over three to six hours after presentation) should be used to define AMI, rather than a single value obtained on presentation or even a rapid change over a period of one hour [3,4,12]. The use of a dynamic change in troponin rather than a single value is consistent with the criteria for AMI for all patients (not just those with CKD) established by the Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and the World Heart Federation [1]. (See "Diagnosis of acute myocardial infarction", section on 'Definitions'.)

- **Choice of troponin** – We believe that either cTnT or cTnI may be used, provided that serial concentrations are followed rather than single values and that the appropriate clinical context is present. Some clinicians prefer to use cTnI for the diagnosis of AMI among patients with CKD. This is because of the belief that, compared with cTnT, cTnI is more specific for myocardial injury in patients with CKD. This belief arose from the observation that, compared with cTnT, stably increased cTnI was less prevalent in patients with CKD [13-20].

  However, the detection of cTnI in asymptomatic patients with CKD has become more common with the use of more sensitive generations of the cTnI assay [21,22]. Consensus guidelines do not specify a preference for cTnI over cTnT for patients with CKD [1,12]. Observational data in an emergency department population suggest that results are similar with a highly sensitive cTnI (hs-cTnI) and highly sensitive cTnT (hs-cTnT) with respect to both diagnosis and prognosis [4].

- **Threshold for diagnosis** – The degree of elevation of either cTnT or cTnI that is required for the diagnosis of AMI among patients with CKD is not known. The Fourth Universal Definition of Myocardial Infarction specifies that, to meet the biomarker criteria for AMI, at least one troponin value should be above the 99th percentile upper reference limit provided by the manufacturer [1] (see "Diagnosis of acute myocardial infarction", section on 'Definitions'). However, as noted above, cardiac troponin values are commonly above the upper reference limit in patients with CKD in the absence of AMI.

  For patients with CKD in whom all troponin levels are at or above the 99th percentile, a greater than 20 percent rise or fall in serially measured troponins is probably an acceptable threshold change for a positive AMI diagnosis, although there are no data available to support this approach. In addition, requiring such a serial change in this setting may lead to erroneously failing to diagnosis AMI in some patients [23]. Contemporary guidelines do not provide specific guidance for patients with CKD but

suggest considering a greater than 20 percent change at or above the 99th percentile for all patients [1]. Using smaller absolute changes that are capable of being accurately measured with highly sensitive cardiac troponin assays has not been shown to improve diagnostic accuracy in patients with CKD compared with those without CKD [4].

Some studies have attempted to define the optimal upper-limit threshold specifically for patients with CKD. We recommend using the 99th percentile value provided by the cardiac troponin assay manufacturer or local institution as the upper-limit threshold, rather than an alternative higher cutoff, to rule out or rule in an AMI.

The diagnostic accuracy of hs-cTnI and hs-cTnT among patients with CKD presenting to emergency departments with suspected AMI has been evaluated in three prospective, observational studies [3-5]:

- In one study, an initially low hs-cTnI value of <5 ng/L at presentation had a similar negative predictive value (NPV) for the diagnosis of AMI among patients with and without CKD (98.4 versus 99.7 percent, respectively) [3]. The positive predictive value (PPV) of a hs-cTnI at the 99th percentile was lower for patients with CKD compared with those without CKD (50 versus 62 percent, respectively).

- Similar findings were reported in a second study that evaluated the diagnostic accuracy of baseline and serial hs-cTnI measurements for AMI among 1555 adults presenting to the emergency department with symptoms suggesting ischemia [5]. Kidney function impairment did not affect the NPV of serial hs-cTnI for diagnosing AMI; however, PPV decreased with worsening kidney function (51 to 57 percent with normal kidney function versus 27 to 42 percent with severely impaired kidney function [estimated glomerular filtration rate <30 mL/min per 1.73 m^2] versus 15 to 32 percent on dialysis).

- An alternative approach to the evaluation of patients with CKD presenting for the evaluation of AMI is the accelerated diagnostic protocol (ADP), which can measure a troponin using a high-sensitivity assay at baseline and again at one hour [24]. The ADP triages patients in this time frame to "rule-out," "observation," and "rule-in" status. The efficacy of the "protocol is determined by the percentage of patients who can be triaged to "rule-out" or "rule-in" and not "observation" status. In a multicenter European study of 3254 patients (15 percent with CKD), the efficacy of the ADP using hs-cTnT was 51 percent in patients with CKD, compared with 81 percent in those without CKD; similar findings were seen with a simultaneously measured hs-cTnI assay [4]. Optimization of hs-cTn "rule-in" and "rule-out" thresholds for patients with CKD did not improve efficacy of the ADP.

The diagnostic accuracy of the high-sensitivity assay may be further decreased among patients on dialysis since almost all patients have a baseline value above the 99th percentile. In one series of 670 consecutive patients on dialysis who presented with chest pain or dyspnea, the area under the curve for receiver operating characteristic based on the initial hs-cTnT was only 0.68 but improved to 0.9 with the addition of evaluation of relative change of ≥24 percent at three hours [25].

Clinical judgment with a high index of suspicion remains a critical component for the diagnosis of AMI among patients with CKD. While using a dynamic change in troponin values improves the specificity for a diagnosis of AMI in this population, exclusive reliance on such a change in addition to an elevated value could be associated with missing as many as 12 percent of non-ST elevation AMIs in all patients irrespective of kidney function [26].

USE OF TROPONINS IN PROGNOSIS

Increased troponins are associated with increased risk of short-term adverse cardiac outcomes among patients with chronic kidney disease (CKD) who are diagnosed with acute myocardial infarction (AMI) [4,27-41]. As an example, a meta-analysis of three studies of patients with CKD and suspected acute coronary syndrome found that the risk of cardiac mortality, AMI, ischemia, revascularization, dysrhythmia, heart failure, and a composite of these outcomes increased with elevated cardiac troponin T (cTnT) [27]. Data from subsequent multicenter studies have also shown that levels of both high-sensitivity cardiac troponin I (cTnI) and high-sensitivity cTnT can effectively prognosticate patients with and without CKD [3,4].

Stably increased serum troponin levels also predict worse long-term cardiovascular outcomes and poor survival in asymptomatic patients with CKD in the absence of AMI, whether or not they receive dialysis [36,41,42]. Higher values are associated with a worse prognosis.

The prognostic utility of the high-sensitivity assay has been evaluated among patients with CKD who are not on dialysis. Among 2464 individuals identified from the Chronic Renal Insufficiency Cohort, increased cardiac troponin, measured using a high-sensitivity assay, was detected in 81 percent of subjects; higher cardiac troponin was associated with worse kidney function, traditional cardiovascular risk factors, increased left ventricular mass, and increased incidence of heart failure [2,42].

Cardiac troponins, particularly cTnT, have been used in some transplant centers to determine candidacy for kidney transplantation [39,43]. This issue is discussed elsewhere. (See "Kidney

transplantation in adults: Evaluation of the potential kidney transplant recipient", section on 'Cardiovascular disease'.)

SUMMARY AND RECOMMENDATIONS

- **Effect of chronic kidney disease on troponin levels** – Cardiac troponin levels are challenging to interpret among patients with chronic kidney disease (CKD). This is due to the high prevalence of stably elevated troponin levels in the absence of clinical evidence of acute myocardial infarction (AMI) among patients with CKD. The cause of low-level cardiac troponin elevations in patients with CKD is likely chronic myocardial injury that is not a result of epicardial coronary disease. (See 'Effect of CKD on troponin levels' above.)

- **Diagnosis of acute myocardial infarction** – Given the challenges of interpreting cardiac troponin levels in the setting of CKD, we take the following approach to using troponins in the diagnosis of AMI among patients with CKD (see 'Diagnosis of acute myocardial infarction' above):

  - **Use of serial troponin levels** – Among patients with CKD who present with signs and symptoms suspicious for AMI, a change in troponin concentration (ie, rise or fall over three to six hours after presentation) should be used to define AMI, rather than a single value obtained on presentation or even a rapid change over a period of one hour.

  - **Choice of troponin** – Either cardiac troponin T or I (cTnT or cTnI) may be used, provided that serial concentrations are followed rather than single values and that the appropriate clinical context is present. Some clinicians prefer to use cTnI for the diagnosis of AMI among patients with CKD based on the belief that, compared with cTnT, cTnI is more specific for myocardial injury in patients with CKD.

  - **Threshold for diagnosis** – The degree of elevation of either cTnT or cTnI that is required for the diagnosis of AMI among patients with CKD is not known. We use the 99^{th} percentile value provided by the cardiac troponin assay manufacturer or local institution as the upper-limit threshold, rather than an alternative higher cutoff, to rule out or rule in an AMI. For patients with CKD in whom all troponin levels are at or above the 99^{th} percentile, a greater than 20 percent rise or fall in serially measured troponins is probably an acceptable threshold change for a positive AMI diagnosis, although there are no data available to support this approach.

- **Use of troponins in prognosis** – Increased troponins are associated with increased risk of short-term adverse cardiac outcomes among patients with CKD who are diagnosed with

AMI. Stably increased serum troponin levels also predict worse long-term cardiovascular outcomes and poor survival in asymptomatic patients with CKD in the absence of AMI, whether or not they receive dialysis. Higher values are associated with a worse prognosis. (See 'Use of troponins in prognosis' above.)

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