The interpretation of elevated troponin in the presence of kidney disease.

Everyday in emergency departments across the county troponins are routinely being utilized as part of the workup for patients with chest pain. The reason for this is that troponins indicate damage to myocardium and elevated levels suggest myocardial cell injury. Elevated troponins in a patient presenting with acute coronary syndrome may be an indication for early interventional therapies, however it has long been noted that troponins may be elevated in certain non-cardiac conditions as well. The most common of these conditions is pulmonary embolism, sepsis and renal insufficiency. (4) In patients with end stage renal disease (ESRD), elevated troponins are present without any signs or symptoms of acute coronary syndrome (ACS). The clinical value of elevated troponins in such patients poses a dilemma for physicians in terms of treatment and management.

Cardiovascular disease is prevalent in patients with renal disease and accounts for 50% of deaths in this population. It is well noted that patients with chronic renal failure often have silent ischemic events and atypical symptoms for acute coronary syndrome. Additionally, complicating matters further, in this patient population EKGs may be unreliable secondary to electrolyte disturbance, conduction abnormalities and left ventricular hypertrophy. (2)

Cardiac troponins have long been regarded as the gold standard biomarker for cardiac injury. Creatinine phosphokinase (CK) MB are also found in large quantities in cardiac muscle, though they can be seen in skeletal muscle as well. Elevation of CK-MB may not indicate solely a cardiac event and can be due to a number of conditions that result in muscle breakdown. (4) There are three troponin proteins present in cardiac and skeletal muscles: troponin C, T, and I. Troponin C is primarily found in skeletal muscle while troponin T and I (TnT, TnI) are present in cardiac muscle. (2) The troponins inherent in cardiac muscle are genetically distinct from those in skeletal muscle and are highly specific for cardiac muscle injury. TnT and TnI are similar in utility.
for indicating cardiac damage and have similar time periods for which they can be detected after myocardial injury. Troponins can be noticed as early as 3 hours after myocardial damage and can be detected for up to 7 days. This is in contrast to CK-MB that can be seen for only 2-3 days after cardiac injury. (4)

Patients with end-stage renal disease (ESRD) have long been noted to have elevated troponins in the absence of acute myocardial ischemia (MI). Some studies quote as high as 70% of patients with kidney disease have elevated troponins without an acute MI. (1) The source of this elevation in patients with ESRD remains unclear though several studies have proposed various causes for this increase. Second generation antibody assays evaluate TnI rather than TnT as it was found that the first generation assays had cross-reactivity with skeletal muscle TnT. (2) Studies using the first generation assays found that in ESRD patients who were not having an acute MI, 71% of patients had elevation in TnT while only 7% of these patients had elevation in TnI. (2) There have been many hypotheses to the cause of this elevation, some state that uremia causes expression of TnT from injured skeletal muscle fibers. It has been found that there are several isoforms of TnT some of which are found in skeletal muscles and the first generations assays did not have the ability to distinguish between these isoforms. (2) Though Song et al. refuted this theory and the results obtained from their study showed that the newer TnI assays had troponin elevations in patients with kidney disease that was comparable to those of TnT in the first generation assays. (5)
Further possibilities for troponin elevations in kidney disease might be that patients with kidney disease have atypical presentations of acute MI and these elevations may be the result of clinically silent myocardial infarcts. Though these theories do not explain why elevated troponins are seen in patients without CAD. Many patients with ESRD are found to have left ventricular hypertrophy (LVH), usually a product of significant history of hypertension and anemia. Patients with LVH have increased myocyte damage, which releases troponin and may indicate why troponins are elevated in asymptomatic ESRD patients. It has been hypothesized that these hypertrophied hearts utilize a different mechanism of release of troponin though the mechanism by which this occurs has not been well documented (2) Abaci et al. illustrated in their study that LVH was identified as an independent predictor of elevated TnT and the only significant independent predictor of elevated TnI. In their study it was concluded that the cause of elevated troponin in ESRD patient was cardiac damage as a result of LVH. (1) There is also indication that higher serum phosphate levels are associated with increased troponin. Patients with ESRD have been found to have elevated phosphate levels which has been associated with elevated troponin levels likely the result of increased vascular calcification (3)

A popular explanation for the cause of elevated troponins in ESRD is that there is decrease clearance of troponin by the kidneys. Benjamin et al. refuted this common misconception by indicating that troponins are large molecules comparable to the size of albumin making it unlikely that the kidney is responsible for its clearance. It was also noted that improvement in kidney function by renal transplantation in such patients did not alter the frequency of elevated troponin. Additionally, there has not been any direct relationship between creatinine concentration and the frequency of the degree of troponin elevation . (2)

The main issue that arises in ESRD patients with elevated troponin is how should this be interpreted in terms of management of these patients and diagnosis of ACS. One suggestion is that a patient’s “baseline” troponin level should be identified and if troponin levels exceed a patient’s “baseline” level in
the appropriate clinical setting that patient should be treated for ACS. The problem with this is that there has really been no strong evidence to support if patients actually have a stable “baseline” troponin. Kumar et al. indicated that TnI levels were stable in 75% of ESRD over a 3 month time period and they proposed frequently checking troponins on ESRD patients to monitor their baseline levels. It was also found that these levels remained the same pre- and post- hemodialysis refuting previous theories that troponin levels decrease after hemodialysis. (3)

Though the exact cause of elevated troponins in ESRD patients is still to be determined it has been shown that elevations in troponin in this patient population is consistent with myocardial injury. Thus, indicating an increased risk of morbidity and mortality in these patients regardless of the presence of symptoms consistent for an acute MI (2). There are no specific guidelines as of yet to the treatment of ESRD patients with suspected ACS and increased troponins and most of the decisions are made clinically on a case-by-case scenario. Factors that should be analyzed in these patients are their clinical stability and results of EKG. It is suggested that aspirin, beta-blockers, nitroglycerin, and oxygen should all be administered to such patients. Echocardiogram and angiography are also suggested in these patients to establish diagnosis of heart disease. It is important to note that the timing of blood sampling in relation to hemodialysis should not be a concern as there is no changes in serum troponin levels seen pre- and post- hemodialysis.

In conclusion, the diagnosis of ACS and acute MI in ESRD patients proves to be complicated as the gold standard use of serum troponin levels are not as helpful in these patients compared to patients without kidney disease. Based on multiple studies evaluated it seems as though there are several theories as to why serum troponin levels are elevated in ESRD patients though no concrete evidence has been established. How does this direct physicians in their management of ESRD patients is the subject of multiple papers and discussions. It appears as though one useful measure is to trend troponins and any acute changes from the patient’s baseline troponin value may indicate new myocardial
injury. It can also be said that all patients with ESRD have significant risk factors for cardiac events and should be treated appropriately for ACS regardless of symptoms. The use of antithrombin inhibitors and glycoprotein IIb/IIIa antagonist has not been well studied in patients with renal disease. Furthermore, any patient with ESRD and hemodynamic instability or clinically concerning features for cardiac injury should be treated appropriately regardless of troponin levels.

References: