Cardiac Troponins in Kidney Disease

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Abstract

Cardiovascular disease is a major cause of morbidity and mortality in individuals with kidney disease. In recent years, biomarkers such as cardiac troponins have become indispensable to the diagnosis and prognosis of cardiac disease, such as MI and heart failure. However, these biomarkers behave differently in the general population compared with people with kidney disease, who may have higher baseline levels and reactions to acute disturbance due to a combination of reduced renal clearance of biomarker molecules and increased production due to concurrent cardiovascular disease and cardiorenal syndrome. Three decades of research into cardiac biomarkers have produced a range of literature investigating their applications in different patient groups and healthcare settings. This review explores the evidence surrounding measurement and interpretation of cardiac troponin levels in people who have chronic kidney disease, and have had dialysis and/or kidney transplantation, with reference to baseline levels and changes over time, their relationship to incident cardiovascular morbidity and mortality, and their application in acute settings.

Keywords

Chronic kidney disease, dialysis, kidney transplantation, troponin

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Over the past 30 years, cardiac biomarkers, such as cardiac troponins I (cTnI) and T (cTnT), have become essential to the diagnosis and prognosis of acute and chronic cardiovascular disease (CVD). However, cardiac biomarkers behave differently in baseline levels and reactions to cardiovascular injury in individuals with chronic kidney disease (CKD) compared to the non-CKD population.[1,2] Individuals with CKD are at greater risk of CVD than those with normal kidney function: more than half of those with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 have a concurrent cardiovascular condition, such as heart failure or ischaemic heart disease, and the risk of CVD rises with declining glomerular function and increasing albuminuria.[3–5]

Cardiac troponins are commonly used for the diagnosis of MI in the emergency setting, but this becomes complicated in the CKD population because these patients have raised average baseline levels of cTnI and cTnT compared to the general population.[6] There is a growing body of research examining normal levels of cardiac biomarkers in individuals with stable kidney disease, including those with pre-dialysis CKD, those receiving dialysis and kidney transplant recipients. In addition, recent research has aimed to examine whether high average levels of cardiac biomarkers in individuals with kidney disease are due predominantly to reduced renal clearance of biomarker molecules or due to increased cardiac production of biomarkers, which may be associated with an increased burden of cardiac disease and risk of adverse cardiovascular outcomes.

This review aims to summarise research into average levels of cardiac troponins in individuals with kidney disease and examine the extent to which evidence suggests increased biomarker levels are associated with cardiovascular morbidity and mortality.

Physiology of Cardiac Troponins

To be able to interpret levels of cardiac troponins, it is useful to understand their normal physiology. cTnI (molecular weight 23.9 kDa) and cTnT (molecular weight 35.9 kDa) are cardiac muscle-specific components of the troponin–myosin complex, which exist within that complex and also in intracellular vesicles, and control the interaction of actin and myosin in cardiac myocytes as mediated by intracellular Ca^{2+}. Damage to cardiac myocytes, for example due to ischaemia, results in a release of cTnI and cTnT into the bloodstream, from where they can be measured using specific monoclonal antibodies which do not cross-react with non-cardiac troponins.[7,8] Cardiac troponins and troponin fragments are cleared from the blood by macrophages and the reticuloendothelial system, generic proteinases found throughout the vasculature, and glomerular filtration.[9] The ability to measure levels more accurately has evolved over years and with the implementation of fifth-generation 'high-sensitivity' cTnT assays (often referred to as hs-cTnT) since 2018 has improved the sensitivity of testing for MI.[10]

Pathophysiology of Cardiorenal Syndrome

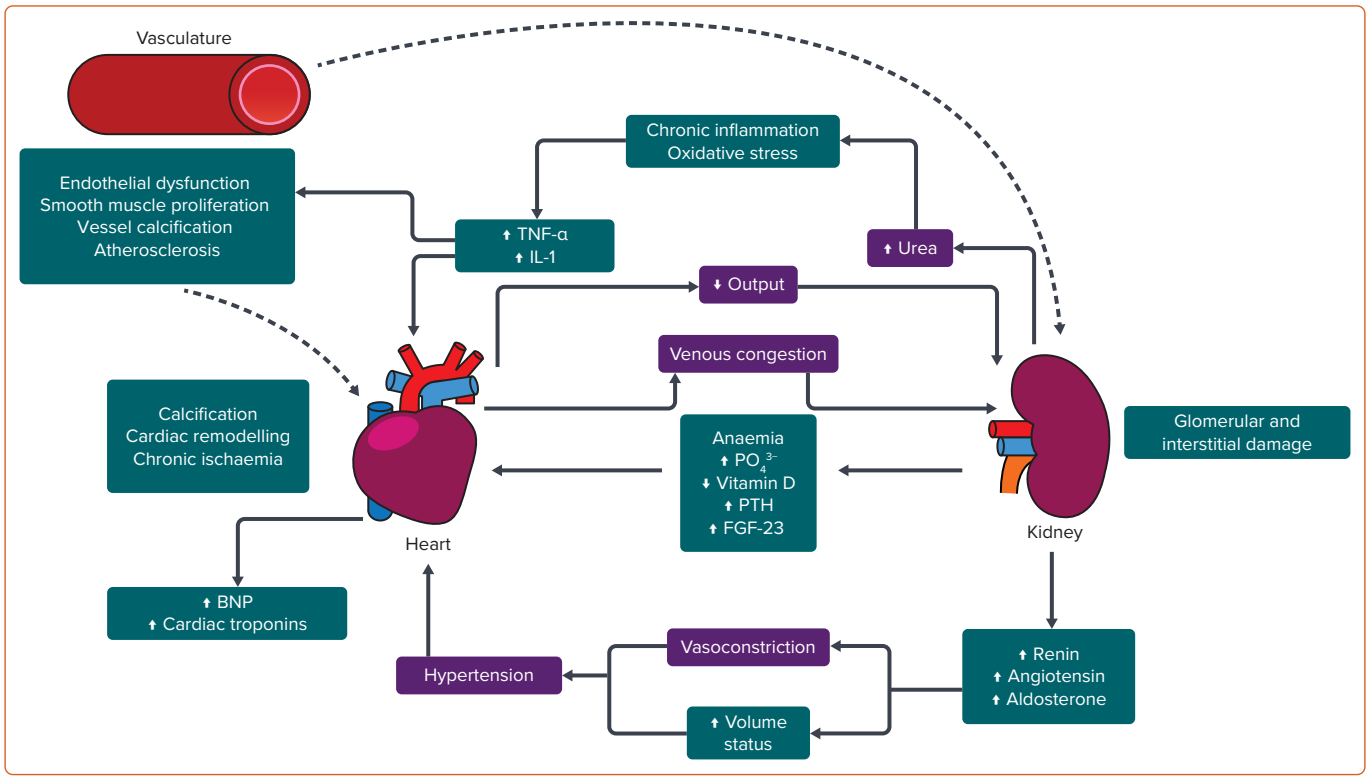
The Acute Dialysis Quality Group (ADQG) defines five subtypes of cardiorenal syndrome (*Table 1*).[11] These may be divided into acute (subtypes 1 and 3) versus chronic (subtypes 2 and 4), cardiorenal (subtypes 1 and 2) versus nephrocardiac (subtypes 3 and 4), and primary (subtypes 1–4) versus secondary (subtype 5).

Table 1: Classification of Cardiorenal Syndrome

Type	Definition	Examples of Causes
Acute cardiorenal	Acute worsening of cardiac function leading to renal dysfunction	Acute decompensated heart failure; MI
Chronic cardiorenal	Chronic abnormalities in cardiac function leading to renal dysfunction	Chronic heart failure
Acute nephrocardiac	Acute worsening of renal function causing cardiac dysfunction	Acute kidney injury leading to fluid overload, electrolyte abnormalities, uraemia
Chronic nephrocardiac	Chronic abnormalities in renal function leading to cardiac disease	Chronic kidney disease leading to uraemic cardiomyopathy, cardiac remodelling
Secondary	Systemic conditions causing simultaneous disease of the heart and kidney	Sepsis; systemic lupus erythematosus; amyloidosis; diabetes

Data source: Ronco et al. 2010.[11]

Figure 1: Overview of Pathophysiology in Cardiorenal Syndrome



An overview of key pathological mechanisms in combined CKD–CVD. BNP = B-type natriuretic peptide; CKD = chronic kidney disease; CVD = cardiovascular disease; PO_4^{3-} = phosphate ion; PTH = parathyroid hormone; TNF-α = tumour necrosis factor α.

The pathophysiology of each subtype of cardiorenal syndrome differs from the others. Here, we will focus on cardiorenal syndrome as it presents in individuals with CKD. This may take the form of CVD which occurs after the onset of CKD, i.e. type four in the ADQG system, or it may be that cardiac and renal dysfunction occur and develop simultaneously or in an unknown order. Regardless of the exact sequence of organ dysfunction in these cases, common pathological mechanisms will result in damage to both heart and kidney function, with the decline of each furthering the decline of the other.

An overview of some of the key pathological mechanisms in cardiorenal syndrome is presented in *Figure 1*. Broadly, declining kidney function causes an accumulation of uraemic toxins, precipitating a chronic inflammatory state that induces endothelial dysfunction, smooth and cardiac muscle proliferation and remodelling, atherosclerosis and bone remodelling, all of which contribute to cardiac and renal dysfunction.[12] Reduced glomerular filtration leads to chronic over-activation of the renin–angiotensin system, thereby leading to volume overload, hypertension and accelerated cardiac disease. Corollaries of CKD, such as vitamin D deficiency, hyperparathyroidism, hyperphosphataemia, pro-inflammatory lipoproteins and high circulating levels of growth factors, such as FGF23, potentiate the remodelling of bone and soft tissues, while impaired cardiac function may lead to hypoperfusion and venous congestion.[13,14]

Together, these mechanisms of inflammation, oxidative stress and remodelling lead to an environment where not only are cardiac troponins subject to reduced renal clearance, but are increasingly released from a myocardium under stress. High cardiac troponin levels in individuals with CKD must therefore be understood as a product of cardiovascular and renal pathology in combination, rather than solely reduced renal clearance.

Levels of Cardiac Troponins in Kidney Disease

Individuals with pre-dialysis CKD have increased average cardiac troponin levels compared to the general population. Studies measuring cardiac

Table 2: Studies Reporting Cardiac Troponin Levels in Chronic Kideney Disease According to eGFR Classification

Study	Age (Years), Mean ± SD	Biomarker	cTn (ng/l), Median (IQR)		
			eGFR ≥90 ml/min/1.73 m^2	eGFR 60–90 ml/min/1.73 m^2	eGFR <60 ml/min/1.73 m^2
Martens et al. 2017[19]	59.8 ± 8.2	cTnI	1.7 (1.1–2.6)	2.1 (1.4–3.4)	3.7 (2.5–5.5)
		cTnT	4.6 (3.2–6.5)	6.0 (4.4–8.8)	11.3 (7.3–17.2)
Vinnakota et al. 2019[20]	By eGFR group >90 ml/min/1.73 m^2: 57.9 ± 8.5 60–90 ml/min/1.73 m^2: 65.2 ± 10.2 <60 ml/min/1.73 m^2: 74.8 ± 9.3	cTnT	2.4 (1.4–4.2)	3.3 (2.0–5.7)	6.3 (3.9–10.3)
Pang et al. 2020[21]	60.6 ± 16.5	cTnI	2 (1–5)	4 (1–9)	10 (5–34)
Rehm et al. 2022[22]	51.4 ± 12.1	cTnI	2.1 (1.3–3.8)	NA	4.7 (3.0–7.3)

CKD = chronic kidney disease; cTnI = cardiac troponin I; cTnT = cardiac troponin T; eGFR = estimated glomerular filtration rate.

troponins in a mixed cohort of CKD patients report 43–68% of individuals having cTnI and cTnT levels over the 99th percentile of the general population.[15–18] Average troponin levels increase as kidney function deteriorates. One 2017 study reported median cTnI levels of 1.7 ng/l (interquartile range [IQR] 1.1–2.6 ng/l), 2.1 ng/l (IQR 1.4–3.4 ng/l), and 3.7 ng/l (IQR 2.5–5.5 ng/l) in individuals with eGFR ≥90 ml/min/1.73 m^2, 60–90 ml/min/1.73 m^2 and <60 ml/min/1.73 m^2, respectively.[19] Similarly, the same study reported median cTnT levels of 4.6 ng/l (IQR 3.2–6.5 ng/l), 6.0 ng/l (IQR 4.4–8.8 ng/l) and 11.3 ng/l (IQR 7.3–17.2 ng/l) in individuals with eGFR ≥90 ml/min/1.73 m^2, 60–90 ml/min/1.73 m^2 and <60 ml/min/1.73 m^2, respectively.[19]

Other studies examining cardiac troponin levels across a range of eGFR values report similar findings (*Table 2*).[20–22] However, what is unclear from these observational studies is whether higher average troponin levels are due solely to reduced kidney function or whether the inflammatory milieu precipitated by CKD and known cardiovascular pathology which accompanies cardiorenal syndrome contribute to chronic cardiac damage and troponin release. In pre-dialysis CKD, factors including older age, male sex, Black ethnicity and higher BMI, and higher levels of HDL cholesterol, LDL cholesterol, triglycerides and haemoglobin have been associated with higher average troponin levels.[23]

A 2019 study examined how troponin levels change over time in pre-dialysis CKD. Chesnaye et al. followed 176 individuals for 24 months and found that cTnT levels in the cohort increased by an average of 16% per year.[24] The authors also reported that for each 5 ml/min/1.73 m^2 reduction in average eGFR, average cTnT levels increased by 8% and the rate of increase rose by 3%.[24]

Most research examining cTn levels in the dialysis population has focussed on individuals receiving haemodialysis. Average cTn levels in the dialysis population are higher than those in individuals with pre-dialysis CKD. One 2021 study investigating 198 stable outpatient haemodialysis patients demonstrated a median cTnI level of 25 ng/l (IQR 14–43 ng/l) and a median cTnT level of 70 ng/l (IQR 44–129 ng/l).[25] Other recent studies of cTnI and cTnT levels in the haemodialysis population have shown similar values.[26–31] Three studies examining cTn levels over time in the dialysis population showed no significant increase in average cTn levels over time.[29,32,33]

Research on the impact of a haemodialysis session on cTn levels has yielded conflicting results. One study from 2000, before the use of high-sensitivity assays, reported a significant decrease in cTnI and levels from pre- to post-dialysis blood samples on average, but a significant increase in cTnT levels.[34] One 2019 study similarly found that cTnI levels decreased from median 54.3 ng/l before dialysis to median 27.1 ng/l after dialysis.[31] Other studies have reported no significant overall change in cTnI and cTnT levels pre- and post-dialysis.[35,36]

Although these studies' findings differ regarding average changes, all studies reported that some individuals demonstrate an increase in cTn levels post-dialysis. Tarapan et al. reported that higher dialysate flow rate and higher haemoglobin concentration were associated with an intra-dialysis increase in cTnI levels on multivariate analysis, suggesting that some individuals may experience silent myocardial injury during haemodialysis.[31] Similarly, Assa et al. reported that increased age and dialysis vintage were associated with a positive intra-dialysis change in cTnI, also reporting that a +10 ng/l change was associated with an adjusted HR of 1.21 for major adverse cardiac events (MACE).[37]

Evidence demonstrates that some individuals on haemodialysis experience myocardial stunning, with onset of echocardiographic wall motion abnormalities following a dialysis session, which is associated with declining left ventricular ejection fraction (LVEF) over time and worse mortality.[38,39] No studies have been identified that have linked this to intradialytic troponin elevations, which should be a target for future research.

Individuals on dialysis may also demonstrate significant variability in cTn levels across serial measurements. The above-mentioned 2021 study by Snaedal and colleagues measured cTnI and cTnT at monthly intervals, reporting reference change values (RCVs) – interpreted as the percentage change above which a change in troponin value may be interpreted as not being due to random variability – of +67/–40% for cTnI and +30/–23% for cTnT, suggesting that cTnI has a greater normal variability.[25] They also reported that older age, male sex and heart failure were associated with greater cTn variability.[25]

In a similar study, Fahim et al. reported reference change values of +33%/–25% for weekly cTnT measurements over 5 weeks and +58%/–37% for monthly cTnT measurements over 5 months.[27] They also reported no significant difference in intra-person variability between haemodialysis and peritoneal dialysis patients, between individuals with and without ischaemic heart disease and across cTnT quartiles.[27] One 2013 study quantified the variability in cTnT in 78 haemodialysis patients, reporting that 95% of their cohort had a variability of <62 ng/l over 1 month.[40] Changes in troponin values outside of these published ranges should

therefore raise suspicions about underlying cardiovascular pathology as a causative factor.

Some studies have demonstrated subgroups of haemodialysis patients who retain very high cTn levels over time. Katerinis et al. reported four out of 50 asymptomatic haemodialysis patients in their study had cTnI levels ≥90 ng/l for four consecutive months.[41] All four were men with a history of coronary artery disease and heart failure.[41] Similarly, Kumar et al. reported several individuals in their study who, despite being asymptomatic, had significant rises in cTnI to either >34 ng/l or >120 ng/l on monthly testing.[42] In a 2018 study, Mavrakanas et al. measured cTnI every month for 3 months in 128 haemodialysis patients, reporting that 81 had all three values ≤60 ng/l, 29 had one or two values >60 ng/l, and 18 had all three values >60 ng/l.[43] Hence, we can see that there can be significant changes in cTn values over time in asymptomatic dialysis patients and that some can have above-average values sustained over time.

As we will see in the next section, higher average cTn levels are associated with risk of MACE. Further research is required to ascertain how individual variability in cTn levels translates into risk of adverse events.

There is a relative dearth of research into cTn levels in kidney transplant recipients. One study of 177 stable transplant recipients with mean ± SD eGFR 48.9 ± 26.5 ml/min/1.73 m^2 reported a median cTnT level of 11 ng/l (IQR 11–26 ng/l).[44] The authors reported older age, male sex and lower eGFR to be associated with higher cTnT levels.[44] In addition, a 2021 study of 177 stable renal transplant recipients with mean ± SD eGFR 46 ± 17 ml/min/1.73 m^2 reported median cTnT 17 ng/l (IQR 11–31 ng/l).[45] A 2017 study reported median cTnI 5.6 ng/l (IQR 3.3–10.5 ng/l) in a stable transplanted cohort with mean ±SD eGFR 45.9 ± 18.2 ml/min/1.73 m^2, with 6% of individuals having cTnI levels greater than the assay's 99th percentile.[46] Another study of 372 stable transplant recipients with mean ± SD eGFR 52.5 ± 20.2 ml/min/1.73 m^2 reported 21 individuals with cTnT ≥30 ng/l and reported that cTnT above this threshold was associated with increased mortality over follow-up.[47]

Comparison of these studies' findings with those examining individuals with pre-dialysis CKD suggests that kidney transplant recipients may have higher baseline troponin levels compared to individuals with non-transplant CKD at a similar eGFR, possibly due to the lasting effects of CKD and cardiorenal syndrome prior to transplantation, but further research directly comparing these two groups over time is needed.

Cardiac Troponin Levels and Mortality

In the pre-dialysis CKD population, multiple studies have demonstrated that higher average cardiac troponin levels confer an increased risk of cardiovascular mortality (CVM) and all-cause mortality (ACM).[48–51] However, a minority of studies have reported that risk of mortality does not increase with average troponin levels when models account for declining eGFR or urine albumin–creatinine ratio.[15,52] The vast majority of studies measure troponin levels at a single time point, limiting our ability to interpret the association of troponin levels and their changes over time with adverse outcomes. There is conflicting evidence on whether increasing troponin levels over time confers any additional mortality risk. Wang and colleagues measured cTnT twice, 2 years apart, in a cohort of 842 CKD patients and found that neither an increase nor a decrease in cTnT over time was significantly associated with mortality risk.[53] However, Chesnaye and colleagues measured cTnT six times in 176 CKD patients over a median period of 2.4 years, demonstrating not only that higher average levels at any time were associated with an increased risk of mortality, but also that the rate of change of cTnT and the area under the cTnT curve were also associated with increased risk.[54] Longitudinal studies such as this demonstrate that we should not ignore raised or rising cardiac troponin levels in individuals with CKD. Instead, they demonstrate evidence that an individual is at risk of adverse cardiovascular outcomes and mortality, which should prompt clinicians to carry out further investigations.

In the dialysis population, again, most studies demonstrate that higher average troponin levels over time are associated with greater risk of CVM and ACM.[28,30,55,56] Again, a minority of studies measured troponin levels over time in this population. Mavrakanas and colleagues reported that three consecutive cTnI measurements >60 ng/l conferred a HR of 6.45 for MACE or ACM compared with individuals with three values ≤60 ng/l.[43] Snaedal and colleagues performed a longitudinal study, which reported that individuals with cTnT values persistently in the middle or highest tertiles were at increased risk of ACM compared to those with values in the lowest tertile (HR 2.11 and 2.38, respectively).[25] Hence, higher-than-average troponin levels over time in CKD and dialysis populations are not just incidental findings. They are associated with highly adverse outcomes and should prompt clinicians to consider further investigations such as coronary or cardiac imaging and appropriate risk-reduction strategies.

In the kidney transplant population, again evidence demonstrates that higher cardiac troponin levels are associated with adverse outcomes including ACM as well as CVM, MI and transplant failure requiring dialysis.[45–47] In one 2022 study, cTnT levels >31 ng/l at baseline were associated with a 50% risk of MACE or death over 5 years compared to <10% risk for those with cTnT <11 ng/l.[45] While evidence demonstrates that other cardiac biomarkers such as B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide (NT pro-BNP) decline rapidly post-transplantation, we have not found any data examining comparable trends in cardiac troponins.[57] Hence, transplant recipients should be considered for active troponin monitoring in conjunction with regular clinical review and cardiac imaging to enable appropriate further investigation and risk reduction strategies.

Cardiac Troponin Levels, MACE and Other Cardiovascular Outcomes

Aside from mortality, some research has examined other cardiovascular associations of troponin levels in the pre-dialysis CKD population. Several studies have demonstrated that individuals with higher average troponin levels are more likely to experience MACE, usually defined as MI, stroke or cardiovascular hospital admission, with or without cardiovascular death.[18,20,51,58,59] Research has also demonstrated an association between higher average troponin levels and severity of coronary artery disease on angiography in the pre-dialysis CKD population.[60,61] This is perhaps another indication that high troponin levels in the kidney disease population are not simply due to reduced filtration, but due to cardiovascular pathology which may be modifiable.

The relationship between troponin levels and incident heart failure in the CKD population is unclear. Some studies have reported an association between higher average troponin levels and risk of incident diagnosis of HF, including one which suggests higher average troponin levels in CKD confer greater risk of HF compared to the non-CKD population.[61–63] However, a large, harmonised population data study of individuals with and without CKD demonstrated no predictive value of cTnI for incident HF, unlike NT-proBNP.[22] Several studies have shown consistently that higher average troponin levels are associated with left ventricular hypertrophy and incident AF in the pre-dialysis population.[16,64–67]

There is less research examining the relationship between troponin levels and cardiovascular outcomes in the dialysis population. However, four studies have identified positive associations between higher average cTnI or cTnT levels and coronary artery disease, whether assessed by cardiac stress testing, carotid artery intima–media thickness scores, or stenosis on angiography, in the dialysis population.[41,68,69,70] Further study, including longitudinal work, is required to ascertain the predictive value of troponin levels in this context.

Cardiac Troponin Levels and Emergency Presentations

One of the most common clinical challenges related to troponin levels in the individual with kidney disease is suspected acute coronary syndrome (ACS). In the general population, a cardiac troponin level above the 99th percentile of the reference population is called myocardial injury.[71] When this injury is accompanied by signs or symptoms of myocardial ischaemia, it is termed MI. In the CKD population, higher-than-average baseline troponin levels – combined with a higher likelihood of atypical presentation of ACS – can complicate the diagnostic process. This is not an academic concern; individuals with kidney disease are exposed to a high burden of cardiovascular risk factors and have high rates of ACS with often atypical presenting features compared to the general population.[72,73] In addition, a large registry study of 330,367 patients presenting with MI in the UK has demonstrated that average peak troponin levels are higher in individuals with CKD.[74]

Most studies analysing this issue receiver operator characteristic (ROC) analysis, which generates values for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Any alteration of a threshold for a 'positive' diagnosis will impact both sensitivity and specificity. A lower threshold will include more true positive diagnoses, improving the sensitivity of the test, while also including more false positive diagnoses, worsening its specificity and vice versa. ROC analysis also produces an area under the curve value, which can be interpreted as the average sensitivity value for all possible specificity values or the average specificity value for all possible sensitivity values and is useful for comparing the overall performance of different testing thresholds.

An overview of the nine studies related to this topic is provided in *Supplementary Table 1*. All studies examined focused on diagnosis of non-ST elevation MI (NSTEMI), excluding individuals presenting with ECG changes consistent with ST elevation MI (STEMI). One challenge in the synthesis of existing evidence on the use of troponin testing for ACS in kidney disease lies in the variable testing and reporting strategies used by researchers in this field. While the majority use ROC analysis, there is wide variability in the thresholds used for a 'positive' test. Additionally, some studies perform testing at multiple timepoints and aim to test whether a certain level of change provides a useful testing threshold.

A 2013 study by Chenevier-Gobeaux et al. reported that a peak cTnT threshold of 14 ng/l had a dramatically reduced specificity for NSTEMI diagnosis in individuals with eGFR ≤60 compared with >60 ml/min/1.73 m^2 (54% versus 86%).[75] Similarly, Vasudevan et al. have reported higher area under the curve values for troponin testing for NSTEMI diagnosis in individuals with eGFR ≥60 versus <60 ml/min/1.73 m^2.[76] Ballocca et al. demonstrated in 2017 that using peak cTnI or cTnT levels for the diagnosis of NSTEMI confers greater sensitivity and specificity compared with testing levels at 3.5 hours after presentation, and also that sensitivity and specificity for peak cTnI or cTnT for NSTEMI was greater in individuals with eGFR 30–60 compared to <30 ml/min/1.73 m^2.[77] However, while identifying peak levels may be relatively easy *post-hoc* when multiple samples have been taken, using this strategy in real time carries a risk of delayed diagnosis.

In a large study involving 1,555 adults presenting to the emergency department with symptoms suggestive of ACS, serial troponin levels were measured using sex-specific cTnI thresholds of 16 ng/l for women and 34 ng/l for men, and differences in sensitivity and specificity for a range of eGFR values and individuals on dialysis treatment were analysed.[78] The authors demonstrated that cTnI values above sex-specific thresholds had decreasing specificity and PPV with lower eGFR values and dialysis treatment.[78] In addition, they demonstrated that cTnI testing at 6–9 hours after presentation increased PPV for NSTEMI diagnosis compared to testing at presentation in individuals with kidney impairment.[78]

Considering these studies, we see that troponin testing for MI is more specific in individuals with higher eGFR.[75–80] In individuals with lower eGFR, delayed testing or calculation of peak or change in troponin levels may increase sensitivity.[81,82]

Therefore, we can see that cardiac troponin testing in the context of an emergency presentation of possible ACS is less specific in the CKD population. Evidence suggests that higher average troponin levels at presentation are predictive of death over 1 year following MI in individuals with and without kidney dysfunction.[83,84] As such, it is imperative that high troponin levels in individuals with kidney disease presenting with symptoms compatible with MI – which may not be typical in this population – are considered seriously. Clinicians may therefore have to alter their diagnostic strategy, placing differing weights on history and examination and altering thresholds for serial troponin testing or additional investigations such as echocardiography to exclude regional wall motion abnormalities to ascertain a diagnosis and initiate optimal management.

One challenge in synthesising the literature in this area is the differing use of troponin assays and thresholds for positive diagnosis, which vary according to local protocols. Given the evidence discussed, we would advocate for a low threshold for serial troponin testing and additional investigations, such as echocardiography and the possibility of cardiac MRI, if available, in individuals with kidney disease with a possible diagnosis of ACS.

Cardiac Imaging in Kidney Disease

2D echocardiography can be used to measure a variety of cardiac metrics, including left ventricular mass (LVM), LVEF and left ventricular diastolic dysfunction (LVDD). There is robust evidence to suggest that higher cardiac troponin levels are predictive of greater LVM and left ventricular hypertrophy (LVH) in CKD as well as LVDD.[15,16,64,65,85] These are important findings to note as active management of fluid status and renal bone disease may be able to reverse cardiac remodelling with associated mortality benefits.[86,87] LVH may also be a consequence of an underlying cardiorenal disease process, such as amyloidosis, and thus echocardiography forms an important part of diagnostic work-up.

Evidence does not suggest a predictive relationship between cardiac troponin levels and 2D-echocardiographic LVEF in the CKD population.[15,64,65] However, it should be noted that 2D echocardiography has been found to significantly overestimate LVEF in individuals with CKD when compared to gold standard cardiac MRI and 3D echocardiography due to left ventricular geometry.[88,89] Due to the importance of correct LVEF classification for prognostically beneficial treatment of heart failure, individuals with kidney

disease should undergo cardiac MRI or 3D echocardiography for LVEF quantification, where possible.

Cardiac MRI studies have demonstrated that native myocardial T2 times, as a marker of myocardial oedema, correlate with increasing cardiac troponin levels, a relationship which is more pronounced at lower eGFR values.[90,91] There is conflicting evidence as to whether myocardial T1 times, a marker of fibrosis, correlate with troponin levels in kidney disease.[90,91] As such, cardiac MRI could be considered in individuals with kidney disease and chronically elevated troponin levels to examine for fibrosis, regional wall motion abnormalities, ventricular geometry and evidence of other pathology such as amyloidosis. Further studies which pair longitudinal measurement of cardiac biomarkers with serial imaging studies to examine the incident relationship between these abnormalities are required to develop further guidance.

There is some evidence that elevated cardiac troponins may predict incident coronary artery disease in CKD and particularly individuals receiving haemodialysis.[61,70] This may be of particular importance when identifying individuals who may require coronary artery screening before kidney transplantation.

Practical Guidance on Troponin Levels in Kidney Disease

As we have seen, there is now robust evidence across different stages of kidney disease that elevated cardiac troponin levels are associated with adverse outcomes, from ACM, CVM to MACE, LVH and coronary disease. While longitudinal studies examining troponin levels over time and their relation to incident pathology are currently lacking and will further inform our appreciation of risk, we would recommend the following practical measures when considering troponin levels in individuals with kidney disease:

- Patients with kidney disease undergo regular blood tests and troponin screening (yearly in early-stage CKD, and more frequently in dialysis patients with multiple cardiovascular risk factors or a newly transplanted individual) may give an early indicator of emergent cardiac pathology which warrants further investigation or imaging to inform risk reduction strategies;
- Individuals with chronically elevated troponin levels, especially when compared to individuals of similar age and kidney function, should be actively screened for a cause, for instance by 2D, 3D, or stress echocardiography and/or by cardiac MRI;
- In the acute setting, normal or baseline troponin levels at presentation in an individual who is suspected of having ACS may be falsely reassuring and a serial testing strategy (perhaps including testing up to 12–24 hours from presentation) in addition to cardiac imaging in the form of echocardiography and MRI if available, should be employed, as individuals with kidney disease are likely to present with ACS in an atypical manner;
- In the dialysis population, a certain degree of fluctuation in troponin levels over time is observed naturally (+67/–40% for cTnI and +30/–23% for cTnT over 1 month, according to one study). However, a significant change outside these published ranges should prompt serious consideration of underlying pathology.[25] We must also acknowledge that new cardiac pathology may emerge without a rise in troponin outside these ranges, which are currently defined by only a few studies, and as such, vigilance and further research are required.

Conclusion

We have seen that cardiac troponin levels are often higher on average in the kidney disease population when compared to those without kidney disease, increasing as eGFR declines and increasing further once people progress to end-stage disease. In the CKD and dialysis populations, there is good evidence to suggest that higher average troponin levels are associated with mortality and a range of adverse cardiovascular outcomes over time, suggesting that higher average levels are not simply a byproduct of reduced troponin elimination, but are a sequela of the myriad pathophysiological aspects of cardiorenal syndrome and represent true cardiac pathology. Whether individuals with higher average troponin levels should be more thoroughly investigated for cardiac disease – and at what threshold this should occur – is a matter which would benefit from further research. There is a growing number of studies reporting longitudinal data on cardiac troponin profiles in kidney disease. These studies are essential and will help to develop guidance on thresholds at which further testing or intervention should be considered.

Individuals who have had kidney transplants may have higher average troponin levels than non-transplanted individuals with comparable eGFR. However, there is a relative dearth of research into troponin levels in the transplant population and further studies to more fully understand this relationship are necessary. Whether higher average levels translate to an increased risk of adverse cardiovascular outcomes over time is a subject requiring further research.

We have also seen that the common clinical scenario of troponin testing in possible ACS is more complicated in the kidney disease population compared to the general population. However, there is good evidence that troponin testing remains sensitive and reasonably specific, although the testing and investigation strategy may need to differ in those with kidney disease – either end-stage or earlier – to those without. As above, we would advocate for a serial troponin testing strategy in conjunction with a thorough history and examination and additional investigations, such as echocardiography, as correct diagnosis in individuals with kidney disease is imperative for the prevention of both short- and long-term adverse outcomes. ❑

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