Clinical Biochemistry 48 (2015) 247–253

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

Use and interpretation of high sensitivity cardiac troponins in patients with chronic kidney disease with and without acute myocardial infarction

Ravi H. Parikh [a,*], Stephen L. Seliger [b], Christopher R. deFilippi [a]

[a] Department of Medicine, Division of Cardiovascular Medicine, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
[b] Department of Medicine, Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD, 21201, USA

ARTICLE INFO

Article history:
Received 5 December 2014
Received in revised form 9 January 2015
Accepted 12 January 2015
Available online 22 January 2015

Keywords:
Chronic kidney disease
High sensitivity
Troponin
Prognosis
Acute myocardial infarction
Cardiovascular mortality
Review

ABSTRACT

It is well known that the population with chronic kidney disease (CKD) is at greater risk for cardiovascular disease and death than the general population. The use and interpretation of high sensitivity cardiac troponin (hs-cTn) assays have been particularly challenging in these patients with the majority having elevated levels at baseline. The diagnostic accuracy of acute myocardial infarction (AMI) may be decreased in patients with CKD when using these newer troponins. In order to improve the sensitivity and specificity for the diagnosis of AMI, one must look at the change in cTn and consider using higher cut-off values. In asymptomatic patients with CKD, research has shown increased prevalence of cardiovascular risk factors and underlying structural heart disease with increasing cTn levels. Prognostically, elevated cTn has been associated with adverse outcomes including incident heart failure and cardiovascular mortality. The purpose of the review is to evaluate hs-cTn in patients with CKD for the diagnosis of AMI and for the prognostic significance of elevated levels in CKD patients without AMI. Although the underlying etiology of persistently elevated cTn in the CKD population remains unclear, the review will also evaluate studies attempting to explain whether the source of cTn is from increased cardiac production versus decreased renal clearance. Further longitudinal studies are required in order to bridge the gap between the prognostic importance of elevated cTn and clinical management to prevent symptomatic cardiac disease.

Contents

Introduction

Since the advent of high-sensitivity (hs) cardiac troponin assays, few studies have evaluated the diagnostic and prognostic significance of elevated hs cardiac troponin T (hs-cTnT) or cardiac troponin I (cTnI) in patients with chronic kidney disease (CKD, typically defined as an estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) and end-stage renal disease (ESRD, typically defined as the requirement for renal replacement therapy). These studies have included asymptomatic subjects from community-dwelling cohorts as well as patients with known or suspected cardiac pathology such as heart failure and acute coronary syndrome (ACS). The goal of this review is to critically evaluate current literature relating to the use and interpretation of the hs troponin assays in patients with CKD across a wide range of conditions. Many prior studies have reported an increased risk of cardiovascular disease

* Corresponding author at: Department of Medicine, Division of Cardiovascular Medicine, University of Maryland School of Medicine. 110 S Paca St, 7th floor. Baltimore, MD, USA 21201, USA.
E-mail address: rparikh@medicine.umaryland.edu (R.H. Parikh).

http://dx.doi.org/10.1016/j.clinbiochem.2015.01.004
0009-9120/

among patients with CKD compared to those with normal renal function, independent of traditional cardiovascular risk factors [1–4]. In asymptomatic patients with either CKD or ESRD, the presence of elevated troponin levels using earlier generation assays, including the contemporary sensitive assays (but not hs), is associated with increased risk for adverse cardiovascular events and all-cause mortality [5–9]. In addition, an elevated troponin level in the setting of ACS in patients with CKD portends a poor short-term and long-term prognosis [10]. What remains uncertain is whether these findings from studies using earlier generations of cTn assays would be applicable to the interpretation of new generation hs troponin assays where one might anticipate detectable levels in nearly all patients and "elevated" levels in a majority of patients with CKD [11]. Given that cardiac troponins are now the standard biomarker and centerpiece for diagnosing acute myocardial infarction ([AMI] note that AMI is a subset of ACS which also incorporates the diagnosis of unstable angina. However in the era of hs-cTn the diagnosis of unstable angina is rare and AMI and ACS are often used interchangeably), an improved understanding of cross-sectional associations with cardiovascular disease, prognosis, and potential importance of reliance on changing values of troponin over time in CKD and ESRD patients may assist both laboratorians and clinicians in understanding the significance of elevated hs troponin values in a variety of clinical scenarios.

Interpretation of hs troponin assays in patients with chronic kidney disease and AMI

Previous studies in unrestricted patient populations with signs and symptoms suggestive of AMI show that hs troponin assays have significantly improved the sensitivity of detection for AMI compared to conventional assays [12–19]. However, the CKD population presents challenges in this biomarker-based diagnosis. Asymptomatic patients with CKD and ESRD have a markedly higher prevalence of CAD [1, 20–25] compared to the general population. Given the frequent finding of chronic elevations of hs-cTn in CKD and ESRD patients, the importance of the change in cTn levels must be emphasized when determining whether or not a symptomatic patient has an AMI. An elevation of cTn in patients with AMI and CKD is associated with poorer prognosis [10,26,27]. Baseline troponin values from asymptomatic patients with CKD without AMI are also often elevated above the 99th percentile of the reference range (middle aged, disease-free general population). Identifying values of troponin above the 99th percentile for the specific assay is a critical first step for the diagnosis of AMI in the absence of ST segment elevation on the ECG [28].

Table 1 summarizes the contemporary studies evaluating hs-cTn for the diagnosis of AMI in patients with CKD. A prospective, multi-center study of 367 adults (among those, 75 with CKD) presenting to the emergency room with chest pain evaluated the diagnostic performance of the hs-cTnT assay with sub analysis focusing on elderly patients, many with CKD for AMI. Older patients (age > = 70 years) were more frequently found to have a history of CAD, heart failure, and HTN in addition to higher baseline hs-cTn levels and lower eGFR than their younger counterparts. Using ROC analysis in patients with CKD, a higher cut-off for hs-cTnT at 35.8 ng/L resulted in a sensitivity of 94% and increased specificity of 86% (compared to a sensitivity of 100% and specificity of 54% when using a cut-off 14 ng/L) for the diagnosis of AMI. This compared favorably to the sensitivity of 90% and specificity of 86% in patients without CKD and hs-cTnT > 14 ng/L. Multivariate analysis showed that CKD, age > 70, and history of heart failure were independent predictors of a hs-cTnT > 14 ng/L at time of admission [29]. Another single center study involving serial biomarker measurements (hs-cTnT) of 122 CKD patients with chest pain or equivalent from a total of 1514 patients found that hs-cTnT had higher sensitivity and lower specificity with significantly lower area under the receiver operating curve for diagnosis of AMI among CKD patients versus those with symptoms and eGFR > 60 mL/min/1.73 m^2 [30]. Another prospective study involving 836 patients was conducted in which absolute and relative (percent) changes in hs-cTnT collected at baseline, 1 h, and 2 h after presentation were evaluated in the diagnosis of AMI. In the 125 patients with CKD, absolute changes were found to be more accurate than

Table 1
CKD and AMI.

Study	n	Diagnosis (single or multiple measurements)	cTn assay	Patient characteristics	AUC	Sensitivity	Specificity	Outcomes	Comments
Chenevier-Gobeaux [29]	367 (75 with CKD)	Serial	hs-cTnT (Roche Elecsys)	CKD + AMI, hs-cTnT > 14	0.96	1.00	0.54	N/A	Diagnosis based on Global Consensus on MI
			hs-cTnT (Roche Elecsys)	CKD + AMI, hs-cTnT > 35.8		0.94	0.86		
			hs-cTnT (Roche Elecsys)	CKD + NSTEMI, hs-cTnT > 14	N/A	1.00	0.54		
			hs-cTnT (Roche Elecsys)	CKD + NSTEMI, hs-cTnT > 43.2		0.92	0.88		
Pfortmueller [30]	122	Serial	hs-cTnT (Roche Modular E170)	CKD with chest pain or dyspnea	0.535	0.74	0.31	N/A	Cross-sectional analysis. Diagnosis of AMI based on clinical picture
Reichlin [31]	836 (125 with CKD)	Serial	hs-cTnT (Roche Elecsys)	CKD + AMI @ 1 h	Abs 0.88, Rel 0.62	N/A	N/A	N/A	Diagnosis based on Universal definition of MI and ACC guidelines
				CKD + AMI @ 2 h	Abs 0.94, Rel 0.70				
Haaf [32]	1117 (160 with CKD)	Serial	hs-cTnI (Siemens)	CKD	0.58	0.35	0.89	Death in first 730 days specifically to CKD	AUC and sensitivity/specificity shown for outcome of death in first 730 days in patients with CKD and AMI
			hs-cTnI (Beckman Coulter)	CKD	0.63	0.68	0.57		
			cTnT (Roche Elecsys)	CKD	0.66	0.41	0.89		
			hs-cTnT (Roche Elecsys)	CKD	0.69	0.74	0.63		

Note: In Haaf study, diagnostic performance of high-sensitivity cTn in different assays was reported in all-comers. Only certain prognostic information was provided specifically in relation to CKD.

Table 2
ESRD Prognosis.

Study	n	cTn assay	Type of study (C-S, longitudinal, both)	Key cross-sectional findings	Key longitudinal findings	Comments
Jacobs [41]	32	hs-cTnT	Both	Significant association with history of cardiac disease	All patients had elevated cTn at least once during follow-up	
McGill [42]	143	hs-cTnT	Longitudinal	N/A	Variables that are independently predictive of all-cause mortality included age, log hs-cTnT, log CRP, and albumin. After 46.7 months, hs-cTnT replaced NT-proBNP as the most powerful predictor of mortality (risk increased 1.4 fold for every 2.72 ng/L increase in hs-cTnT)	Median 46.7 months. Analyzed cTn on continuous scale.
Wolley [43]	239	hs-cTnT	Cross-sectional	Increase in baseline troponin levels by 100 units increased odds of CV death (OR 1.5, CI 1.2–1.9). Multivariate analysis after adjustment for CRP and LVEF resulted in OR 1.3 (CI 1.1–1.7).	N/A	hs-cTnT presented as continuous variable. 6 month follow-up.
Hassan [44]	393	hs-cTnT	Both	HD patients had significantly more DM, viral hepatitis, PVD when compared to PD patients	Increasing MI and mortality across hs-cTnT quartiles for HD patients but only increasing MI across hs-cTnT quartiles for PD patients	12 months follow-up.
Gaiki [45]	51	hs-cTnI	Longitudinal	N/A	Positive hs-cTnI and history of CAD were predictive of future cardiac events (ACS, coronary revascularization, sudden cardiac death, cardiac arrest) but not all-cause mortality	2 years follow-up.
Assa [46]	90	hs-cTnI	Longitudinal	N/A	Adjusted HR for every 10 ng/L increase in cTn after dialysis was 1.21 (CI 1.06–1.38) for MACE but was not significant for all-cause mortality	Study evaluated prognostic significance of intradialysis rise of hs-cTnI. 52 month follow-up

relative troponin changes for the diagnosis of AMI based on AUC analysis at both time intervals ($p < 0.001$) [31]. Another study compared long-term prognosis of three hs-cTn assays in patients presenting to the ER with acute chest pain. In a subgroup analysis of 160 patients with CKD, the hs-cTnT (AUC 0.69, Roche) and hs-cTnI (AUC 0.63, Beckman-Coulter) assays were similar to the 4th generation conventional cTnT assay (AUC 0.66) and more accurate than the hs-cTnI (AUC 0.58, Siemens) assay when predicting death in the first 730 days [32].

A recent review/meta-analysis by the Agency for Healthcare Research and Quality reported the accuracy of cardiac troponin testing for the diagnosis of AMI in patients with CKD, including those with ESRD [33]. Although the review focused on studies using standard rather than hs troponin assays, the results still have relevance for newer hs assays. Table 2 in the paper details the diagnostic findings of each study. In summary, the review reported that sensitivity and specificity for the cTnT assay in patients not on dialysis ranged from 41–100% and 31–86%, where as in dialysis patients, the sensitivity and specificity of the cTnT assay ranged from 91–100% and 42–85%. The sensitivity and specificity for the cTnI assay in patients not on dialysis ranged from 43–83% and 48–94%, while the values for those on dialysis ranged from 45–94% and 81–100%. The analysis had several limitations. Studies that used CK and CK–MB levels as well as those that used only a single troponin value to confirm a diagnose of AMI were included. In addition, studies varied in design, type of troponin assay, cut-off values used for diagnosis, and patient populations. These limitations aside, it does highlight that the accuracy of cTn testing for AMI diagnosis can be lower than in non-CKD subjects and that attention to methodological detail is important when assessing the results from diagnostic studies in the CKD population.

In summary, elevated hs-cTn among CKD patients with chest pain is highly sensitive for the diagnosis of AMI, although specificity may be limited. The importance of serial changes, especially absolute changes and possible use of higher hs-cTn cut-off values, will assist in the diagnosis of AMI. Similar to patients without CKD, higher levels of hs-cTn among the CKD population in the setting of AMI are predictive of a worse prognosis compared to lower levels.

hs-cTn in patients with CKD without AMI

There have been many studies evaluating the prognostic significance of detectable cardiac troponin levels in CKD patients without ACS using non-hs assays, particularly patients with ESRD on dialysis. A few of these studies have used the hs-cTn assays. Detectable levels and elevations (above the 99th percentile of the general population) of hs-cTn levels are very common in renal patients without ACS. In a study of 148 asymptomatic outpatients with CKD not requiring renal replacement therapy (RRT), the study group had significantly higher hs-cTnT and hs-cTnI values in comparison to historical control groups without CKD. On cross-sectional analysis there were increasing structural cardiac abnormalities (coronary artery calcium by CT scan, left ventricular mass by echocardiography), urine albumin to creatinine ratio, history of coronary disease, and decreasing eGFR associated with the higher levels of troponin. Consistent with results from an earlier study using a sensitive, but not hs-cTnI assay (detectable cTnI in 33% of CKD subjects) [34], an association was found between long-term all-cause mortality and higher levels of either hs-cTn level. This association lost significance once adjusted for severity of CKD, leaving uncertainty regarding the role of renal filtration function in modulating cardiac troponin levels in CKD [11]. Other studies have also shown cross-sectional relationships between the serum concentration of hs-cTn and LV structure and function in patients with CKD. One study of 93 non-diabetic patients with CKD showed that hs-cTnT level was a significant correlate of diastolic dysfunction in multivariate analysis [35].

The large National Institute of Health (NIH)-sponsored multicenter chronic renal insufficiency cohort (CRIC) study with 3243 well-characterized subjects has provided the most definitive results with respect to baseline hs-cTnT levels, cross-sectional associations with cardiovascular risk factors, echocardiographic evidence of cardiac pathology [36,37], and longitudinal outcomes [38]. In the cohort, hs-cTnT was detectable in 84%, with higher levels strongly associated with left ventricular hypertrophy (LVH), more modest associations with LV systolic function which did not persist in adjusted

analysis, and no association with diastolic dysfunction based on echocardiography. The area under the receiver operating curve was 0.64 for LVH, 0.59 for systolic dysfunction, and 0.56 for diastolic dysfunction [36]. Further cross-sectional analysis showed that elevations in hs-cTnT was associated with higher risk demographics and other risk factors such as older age, black and Hispanic race, male gender, increased LV mass, diabetes, higher blood pressure, and decreased eGFR. Increased CRP, LDL/total cholesterol, phosphate, and FGF-23 levels and decreased HDL, albumin, and hemoglobin were also seen with higher baseline hs-cTnT levels. On multivariate analysis, decreased eGFR and increased urine albumin/creatinine remained correlated with hs-cTnT [37]. Longitudinal outcomes recently published for CRIC showed increased incident heart failure (adjusted HR 4.77, 95% CI 2.49 to 9.14) when comparing the groups with undetectable hs-cTnT (<3 ng/L) and the highest quartile (>26.5 ng/L) of hs-cTnT after a median follow-up of 6 years [38]. These findings confirmed the prior large PREVEND observational study involving 1505 patients with mostly mild CKD, which had similar findings although no structural data besides LVH by ECG criteria was presented. In the PREVEND study, hs-cTnT was a significant prognostic marker of CVD events after adjustments were made for demographics, eGFR, urinary albumin excretion, cardiovascular risk factors, and ECG abnormalities [39].

A systematic review published by Michos et al. this year by the Agency for Healthcare Research and Quality looked specifically at the prognostic value of cTn elevations in patients without ACS. The pooled adjusted hazard ratios for all-cause mortality were 3.0 (CI 2.4–4.3) for cTnT and 2.7 (CI 1.9–4.6) for cTnI and for cardiovascular mortality were 3.3 (CI 1.8–5.4) for cTnT and 4.2 (CI 2.0–9.2) for cTnI. The analysis encompassed all generations of cTn assays with few publications using hs-cTn assays. Furthermore, the recently published CRIC longitudinal data was not included in the review [40].

Prior generation cTnT assays are predictive of mortality in the ESRD population who are often asymptomatic at baseline [5]. Table 2 summarizes the studies looking at hs-cTn (both cTnT and cTnI) in this ESRD population. A prospective study by Jacobs et al. of 32 ESRD patients on hemodialysis (HD) with cTn measured every two months found that 100% of the patients had elevated hs-cTnT, a greater proportion than with standard cTn assays. Median hs-cTnT concentration was 17 ng/L (IQR 11–29 ng/L) [41]. Another prospective study of 143 dialysis patients showed that over a median 46.7-month follow-up, hs-cTnT was more predictive than NT-proBNP for all-cause mortality [42]. These findings were confirmed in another cross-sectional study evaluating baseline hs-cTnT levels of 239 dialysis patients followed up for 6 months; however, multivariate analysis did not take NT-proBNP into account [43]. A recent study evaluating hs-cTnT in stable HD and peritoneal dialysis (PD) patients over a year-long period found stable troponin values over the course of the year regardless of cardiovascular events. It also found incremental increases in AMI and mortality observed with increasing cTn quartiles in HD patients and increases in only AMI with increasing cTn quartiles in PD patients. As a predictor of mortality using hs-cTnT alone, the area under the receiver operator curve was 0.65 but was lower in the subgroup of PD patients. As a predictor of AMI, area under the receiver operator curve was modest at 0.7 ($p < 0.001$) with 0.65 for the HD group and 0.81 for the PD group [44].

Table 2 also summarizes studies evaluating hs-cTnI as a prognostic marker in patients with ESRD. The first study, a small prospective cohort study following 51 asymptomatic dialysis patients for 2 years, found that hs-cTnI > 35 ng/L was associated with cardiac events [45]. The second study evaluated changes in hs-cTnI level from pre- to post-dialysis in 90 patients over a follow-up of 52 months. The median increase of hs-cTnI post-dialysis was 3 ng/L and an increase was seen in 66% of the patients. Longitudinally, there was an increased risk of major adverse cardiovascular events (MACE) but not all-cause mortality in patients who had an increase in troponin [46].

Etiology of persistent cTn

The etiology of chronically elevated hs-cTn in patients with CKD remains incompletely explained and under active investigation. The underlying process is probably multifactorial, with explanations including ongoing myocyte damage as a result of uremic toxicity, macrovascular or microvascular ischemia, and decreased renal clearance [47]. Several of these mechanisms have been studied with conflicting and limited data [48,49].

Decreased renal clearance resulting in an elevated level of cTn has often been hypothesized as the underlying mechanism not only in the setting of patients on dialysis, but also those with CKD. However, the data supporting this contention as a primary mechanism to explain elevated levels are modest. Studies have explored the presence of troponin fragments in the blood, urinary troponin excretion, and influence of dialysis and renal transplantation on troponin levels. One study of 63 patients on HD found that immunoreactive troponin fragments ranging from 8–25 kDa in size could be detected in blood, suggesting that these fragments may be filtered renally due to their small size. There was a statistically significant association between the duration of dialysis and the cTnT concentration [50]. However, this study did not use the same antibodies for detection of cTn that are used in the clinical cTnT assays, and it remains unclear if antibodies targeting different epitopes used for clinical measurements would have detected these same fragments. As a follow-up using a different assay, two studies found that troponin only existed in the free intact form not in the fragmented version in CKD patients [51,52]. Given the nature of cardiac troponin and its fragments, studies like these are methodologically challenging and data confirming these findings would be reassuring. Another study of 24 patients with varying renal function showed that cTnT in the urine was not detectable in patients with normal renal function after myocardial injury but was detected in patients with ESRD and residual kidney function suggesting a renal tubular component to excretion [53]. Further evidence supporting a role for renal clearance was the decline of serum cTn concentration following renal transplantation [54–56] although other studies have not had such results [57,58]. There is also evidence further discounting the renal clearance theory. A retrospective study analyzing rates of decline in plasma cTnI following AMI in patients with ESRD on HD found that these rates were not statistically different from patients with normal renal function [59]. It is worthy to note that none of the studies described above were conducted with the hs-cTn assays.

Other studies evaluating possible renal elimination of cTn by looking at the effect of a dialysis treatment on levels of circulating cTn have had discrepant results [60–73]. Only a few such studies used the hs-cTn assays. A prospective observational study with hs-cTnT showed the median level decreasing from 76 ng/L pre-dialysis to 66 ng/L post-dialysis [43]. In contrast to this study, another found a significant intra-dialysis rise in hs-cTnI (median 3 ng/L, IQR 0–8 ng/L) in 66% of 90 total patients [46]. To further point out the inconsistent results in peridialysis troponin measurements, another similar study with cTnI did not show any significant changes between levels pre- and post-HD [74]. The methodology of dialysis may ultimately influence levels by either resulting in more cardiac injury related to myocardial perfusion deficits [75–77] or actually clearing the troponin molecules or fragmenting them so they are no longer recognizable fragments that contain both the epitopes for detection and indicator antibodies used in the assay.

Additional mechanisms have been considered other than the factors related to HD mentioned above. These include oxidative injury [78,79], supply/demand mismatch with resulting ischemia [80], increased inflammation [81,82], and dialysis related physiologic changes such as hemodynamic shifts and anemia [83]. In a postmortem analysis of 6 ESRD patients who had premortum elevated cTnT levels, all had underlying cardiac pathology regardless of the cause of death including old or recent MI, atherosclerosis, congestive heart failure, and myocardial fibrosis suggesting that there is ongoing myocardial injury in this patient

population [84]. Another anatomic study analyzing left ventricular endomyocardial biopsies in 40 dialysis patients with dilated cardiomyopathy found severe myocyte hypertrophy (40%) and occasional disarray (30%) as well as interstitial fibrosis (22.3 ± 18.4%, not statistically significant when compared to control) [49], processes which may plausibly lead to greater cTn release into the circulation. Finally studies, looking at the cardiac structure in patients who have elevated troponin showed diffuse left ventricular dysfunction in stress echocardiogram [85] and cMRI [86].

In conclusion, the underlying cause of circulating cTn is not completely known in patients with CKD, particularly those on HD, whether it is from increased cardiac production or reduced renal clearance. Most literature to this point indicates the former as the most likely cause.

hs-cTn in Renal Transplant Patients

Studies using the conventional troponin assay have shown an increased mortality in pre-renal transplant patients who have elevated circulating levels. In a study of 1206 patients, greater cTnT pre-transplant was associated with increased post-transplant death and cardiac events independent of other cardiovascular risk factors. Lack of normalization of troponins after transplant (25% within 3 weeks, 11.4% within 1 year) was associated with adverse outcomes [54]. The recommendation per 2012 American Heart Association/American College of Cardiology Foundation statement regarding cardiac evaluation and management among kidney and liver transplant candidates is that cTnT can be measured peri-transplant for prognostic purposes (class IIb with data and efficacy of testing yet to be clearly established) although all of the studies reviewed in the guidelines used the conventional cTn assay [87]. Not surprisingly, renal transplant recipients who have persistently elevated circulating levels of troponin have an increased mortality [88]. The only study examining hs-cTnT levels in kidney transplant recipients was cross-sectional and showed that male gender, age, CKMB, and lower eGFR had an independent association with hs-cTnT in asymptomatic patients [89].

Conclusions and future directions

The presence of elevated hs-cTn levels (both cTnI and cTnT) in any patient with CKD is associated with an increased presence of underlying structural heart disease and cardiovascular risk factors and increased probability to progress to symptomatic heart disease, particularly heart failure and death. With regard to AMI, the diagnostic accuracy using cTn is reduced in patients with CKD, at least at cut-points employed in the general population. The use of hs-cTn assays in the CKD population, although associated with more persistently elevated values, appears to be able to accelerate the time to diagnosis, as it does with patients with normal renal function. To improve sensitivity and specificity for the diagnosis of AMI, it is crucial to evaluate a change in cTn even more so than in the healthy population without renal disease. The majority of the research thus far has been limited and focused on the prognostic significance of cTn in patients with CKD. Further longitudinal studies are needed to determine the role of cTn in clinical management and therapies in asymptomatic CKD patients to prevent or slow progression to cardiovascular disease, and to identify mechanisms which account for asymptomatic elevation of hs-cTn.

References

[1] Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003;108(17):2154–69.

[2] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351(13):1296–305.

[3] Hostetter TH. Chronic kidney disease predicts cardiovascular disease. N Engl J Med 2004;351(13):1344–6.

[4] McCullough PA, Li S, Jurkovitz CT, Stevens L, Collins AJ, Chen SC, et al. Chronic kidney disease, prevalence of premature cardiovascular disease, and relationship to short-term mortality. Am Heart J 2008;156(2):277–83.

[5] Khan NA, Hemmelgarn BR, Tonelli M, Thompson CR, Levin A. Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: a meta-analysis. Circulation 2005;112(20):3088–96.

[6] Wang AY, Lam CW, Chan IH, Wang M, Lui SF, Sanderson JE. Sudden cardiac death in end-stage renal disease patients: a 5-year prospective analysis. Hypertension 2010; 56(2):210–6.

[7] Lowbeer C, Ottosson-Seeberger A, Gustafsson SA, Norrman R, Hulting J, Gutierrez A. Increased cardiac troponin T and endothelin-1 concentrations in dialysis patients may indicate heart disease. Nephrol Dial Transplant 1999;14(8):1948–55.

[8] Goicoechea M, Garca de Vinuesa S, Gomez-Campdera F, Gutierrez MJ, Blanco P, Amann R, et al. Clinical significance of cardiac troponin T levels in chronic kidney disease patients: predictive value for cardiovascular risk. Am J Kidney Dis 2004; 43(5):846–53.

[9] Abbas NA, John RI, Webb MC, Kempson ME, Potter AN, Price CP, et al. Cardiac troponins and renal function in nondialysis patients with chronic kidney disease. Clin Chem 2005;51(11):2059–66.

[10] Aviles RJ, Askari AT, Lindahl B, Wallentin L, Jia G, Ohman EM, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. N Engl J Med 2002;346(26):2047–52.

[11] deFilippi C, Seliger SL, Kelley W, Duh SH, Hise M, Christenson RH, et al. Interpreting cardiac troponin results from high-sensitivity assays in chronic kidney disease without acute coronary syndrome. Clin Chem 2012;58(9):1342–51.

[12] Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med 2009;361(9):868–77.

[13] Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361(9):858–67.

[14] Januzzi Jr JL, Bamberg F, Lee H, Truong QA, Nichols JH, Karakas M, et al. High-sensitivity troponin T concentrations in acute chest pain patients evaluated with cardiac computed tomography. Circulation 2010;121(10):1227–34.

[15] Kavsak PA, Wang X, Ko DT, MacRae AR, Jaffe AS. Short- and long-term risk stratification using a next-generation, high-sensitivity research cardiac troponin I (hs-cTnI) assay in an emergency department chest pain population. Clin Chem 2009;55(10): 1809–15.

[16] Freund Y, Chenevier-Gobeaux C, Bonnet P, Claessens YE, Allo JC, Doumenc B, et al. High-sensitivity versus conventional troponin in the emergency department for the diagnosis of acute myocardial infarction. Crit Care 2011;15(3):R147.

[17] Zuily S, Chenevier-Gobeaux C, Claessens YE, Wahbi K, Weber S, Meune C. High diagnostic performance of a high-sensitivity cardiac troponin T assay in patients with suspected acute coronary syndrome. Int J Cardiol 2011;146(1):115–6.

[18] Giannitsis E, Becker M, Kurz K, Hess G, Zdunek D, Katus H. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. Clin Chem 2010;56(4):642–50.

[19] Chenevier-Gobeaux C, Meune C, Blanc MC, Cynober L, Jaffray P, Lefevre G. Analytical evaluation of a high-sensitivity troponin T assay and its clinical assessment in acute coronary syndrome. Ann Clin Biochem 2011;48(Pt 5):452–8.

[20] deFilippi C, Wasserman S, Rosanio S, Tiblier E, Sperger H, Tocchi M, et al. Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. JAMA 2003; 290(3):353–9.

[21] Hayashi T, Obi Y, Kimura T, Iio K, Sumitsuji S, Takeda Y, et al. Cardiac troponin T predicts occult coronary artery stenosis in patients with chronic kidney disease at the start of renal replacement therapy. Nephrol Dial Transplant 2008;23(9): 2936–42.

[22] Charytan D, Kuntz RE, Mauri L, DeFilippi C. Distribution of coronary artery disease and relation to mortality in asymptomatic hemodialysis patients. Am J Kidney Dis 2007;49(3):409–16.

[23] Chonchol M, Whittle J, Desbien A, Orner MB, Petersen LA, Kressin NR. Chronic kidney disease is associated with angiographic coronary artery disease. Am J Nephrol 2008; 28(2):354–60.

[24] Ohtake T, Kobayashi S, Moriya H, Negishi K, Okamoto K, Maesato K, et al. High prevalence of occult coronary artery stenosis in patients with chronic kidney disease at the initiation of renal replacement therapy: an angiographic examination. J Am Soc Nephrol 2005;16(4):1141–8.

[25] Kawai H, Sarai M, Motoyama S, Harigaya H, Ito H, Sanda Y, et al. Coronary plaque characteristics in patients with mild chronic kidney disease. Analysis by 320-row area detector computed tomography. Circ J 2012;76(6):1436–41.

[26] Melloni C, Alexander KP, Milford-Beland S, Newby LK, Szczech LA, Pollack CV, et al. Prognostic value of troponins in patients with non-ST-segment elevation acute coronary syndromes and chronic kidney disease. Clin Cardiol 2008;31(3):125–9.

[27] Acharji S, Baber U, Mehran R, Fahy M, Kirtane AJ, Lansky AJ, et al. Prognostic significance of elevated baseline troponin in patients with acute coronary syndromes and chronic kidney disease treated with different antithrombotic regimens: a substudy from the ACUITY trial. Circ Cardiovasc Interv 2012;5(2):157–65.

[28] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60(16): 1581–98.

[29] Chenevier-Gobeaux C, Meune C, Freund Y, Wahbi K, Claessens YE, Doumenc B, et al. Influence of age and renal function on high-sensitivity cardiac troponin T diagnostic accuracy for the diagnosis of acute myocardial infarction. Am J Cardiol 2013; 111(12):1701–7.
[30] Pfortmueller CA, Funk GC, Marti G, Leichtle AB, Fiedler GM, Schwarz C, et al. Diagnostic performance of high-sensitive troponin T in patients with renal insufficiency. Am J Cardiol 2013;112(12):1968–72.
[31] Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124(2): 136–45.
[32] Haaf P, Reichlin T, Twerenbold R, Hoeller R, Rubini Gimenez M, Zellweger C, et al. Risk stratification in patients with acute chest pain using three high-sensitivity cardiac troponin assays. Eur Heart J 2014;35(6):365–75.
[33] Stacy SR, Suarez-Cuervo C, Berger Z, Wilson LM, Yeh HC, Bass EB, et al. Role of troponin in patients with chronic kidney disease and suspected acute coronary syndrome: a systematic review. Ann Intern Med 2014;161(7):502–12.
[34] Lamb EJ, Kenny C, Abbas NA, John RI, Webb MC, Price CP, et al. Cardiac troponin I concentration is commonly increased in nondialysis patients with CKD: experience with a sensitive assay. Am J Kidney Dis 2007;49(4):507–16.
[35] Kitagawa M, Sugiyama H, Morinaga H, Inoue T, Takiue K, Kikumoto Y, et al. Serum high-sensitivity cardiac troponin T is a significant biomarker of left-ventricular diastolic dysfunction in subjects with non-diabetic chronic kidney disease. Nephron Extra 2011;1(1):166–77.
[36] Mishra RK, Li Y, DeFilippi C, Fischer MJ, Yang W, Keane M, et al. Association of cardiac troponin T with left ventricular structure and function in CKD. Am J Kidney Dis 2013; 61(5):701–9.
[37] Dubin RF, Li Y, He J, Jaar BG, Kallem R, Lash JP, et al. Predictors of high sensitivity cardiac troponin T in chronic kidney disease patients: a cross-sectional study in the chronic renal insufficiency cohort (CRIC). BMC Nephrol 2013;14:229.
[38] Bansal N, Hyre Anderson A, Yang W, Christenson RH, deFilippi CR, Deo R, et al. High-sensitivity troponin T and N-terminal Pro-B-type natriuretic peptide (NT-proBNP) and risk of incident heart failure in patients with CKD: the chronic renal insufficiency cohort (CRIC) study. J Am Soc Nephrol 2014. pii: ASN.2014010108. [Epub ahead of print].
[39] Scheven L, de Jong PE, Hillege HL, Lambers Heerspink HJ, van Pelt LJ, Kootstra JE, et al. High-sensitive troponin T and N-terminal pro-B type natriuretic peptide are associated with cardiovascular events despite the cross-sectional association with albuminuria and glomerular filtration rate. Eur Heart J 2012;33(18):2272–81.
[40] Michos ED, Wilson LM, Yeh HC, Berger Z, Suarez-Cuervo C, Stacy SR, et al. Prognostic value of cardiac troponin in patients with chronic kidney disease without suspected acute coronary syndrome: a systematic review. Ann Intern Med 2014;161(7): 491–501.
[41] Jacobs LH, van de Kerkhof J, Mingels AM, Kleijnen VW, van der Sande FM, Wodzig WK, et al. Haemodialysis patients longitudinally assessed by highly sensitive cardiac troponin T and commercial cardiac troponin T and cardiac troponin I assays. Ann Clin Biochem 2009;46(Pt 4):283–90.
[42] McGill D, Talaulikar G, Potter JM, Koerbin G, Hickman PE. Over time, high-sensitivity TnT replaces NT-proBNP as the most powerful predictor of death in patients with dialysis-dependent chronic renal failure. Clin Chim Acta 2010; 411(13–14):936–9.
[43] Wolley M, Stewart R, Curry E, Davidson J, White H, Pilmore H. Variation in and prognostic importance of troponin T measured using a high-sensitivity assay in clinically stable haemodialysis patients. Clin Kidney J 2012;6(4):402–9.
[44] Hassan HC, Howlin K, Jefferys A, Spicer ST, Aravindan AN, Suryanarayanan G, et al. High-sensitivity troponin as a predictor of cardiac events and mortality in the stable dialysis population. Clin Chem 2014;60(2):389–98.
[45] Gaiki MR, DeVita MV, Michelis MF, Panagopoulos G, Rosenstock JL. Troponin I as a prognostic marker of cardiac events in asymptomatic hemodialysis patients using a sensitive troponin I assay. Int Urol Nephrol 2012;44(6):1841–5.
[46] Assa S, Gansevoort RT, Westerhuis R, Kobold AC, Voors AA, de Jong PE, et al. Determinants and prognostic significance of an intra-dialysis rise of cardiac troponin I measured by sensitive assay in hemodialysis patients. Clin Res Cardiol 2013; 102(6):439–45.
[47] Dikow R, Hardt SE. The uremic myocardium and ischemic tolerance: a world of difference. Circulation 2012;125(10):1215–6.
[48] Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clin J Am Soc Nephrol 2009;4(5): 914–20.
[49] Aoki J, Ikari Y, Nakajima H, Mori M, Sugimoto T, Hatori M, et al. Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients. Kidney Int 2005;67(1):333–40.
[50] Diris JH, Hackeng CM, Kooman JP, Pinto YM, Hermens WT, van Dieijen-Visser MP. Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients. Circulation 2004;109(1):23–5.
[51] Bates KJ, Hall EM, Fahie-Wilson MN, Kindler H, Bailey C, Lythall D, et al. Circulating immunoreactive cardiac troponin forms determined by gel filtration chromatography after acute myocardial infarction. Clin Chem 2010;56(6):952–8.
[52] Fahie-Wilson MN, Carmichael DJ, Delaney MP, Stevens PE, Hall EM, Lamb EJ. Cardiac troponin T circulates in the free, intact form in patients with kidney failure. Clin Chem 2006;52(3):414–20.
[53] Ziebig R, Lun A, Hocher B, Priem F, Altermann C, Asmus G, et al. Renal elimination of troponin T and troponin I. Clin Chem 2003;49(7):1191–3.
[54] Keddis MT, El-Zoghby ZM, El Ters M, Rodrigo E, Pellikka PA, Jaffe AS, et al. Cardiac troponin T before and after kidney transplantation: determinants and implications for posttransplant survival. Am J Transplant 2013;13(2):406–14.
[55] Wu AH, Feng YJ, Roper L, Herbert K, Schweizer R. Cardiac troponins T and I before and after renal transplantation. Clin Chem 1997;43(2):411–2.
[56] McNeil AR. Implications of a rapid decrease in serum Troponin T levels after renal transplantation. Aust N Z J Med 2000;30(5):638–9.
[57] Bozbas H, Korkmaz ME, Atar I, Eroglu S, Ozin B, Yildirir A, et al. Serum levels of cardiac enzymes before and after renal transplantation. Clin Cardiol 2004;27(10): 559–62.
[58] Fredericks S, Chang R, Gregson H, Bewick M, Collinson PO, Gaze D, et al. Circulating cardiac troponin-T in patients before and after renal transplantation. Clin Chim Acta 2001;310(2):199–203.
[59] Ellis K, Dreisbach AW, Lertora JL. Plasma elimination of cardiac troponin I in end-stage renal disease. South Med J 2001;94(10):993–6.
[60] Mockel M, Schindler R, Knorr L, Muller C, Heller Jr G, Stork TV, et al. Prognostic value of cardiac troponin T and I elevations in renal disease patients without acute coronary syndromes: a 9-month outcome analysis. Nephrol Dial Transplant 1999; 14(6):1489–95.
[61] Peetz D, Schutt S, Sucke B, Faldum A, Wandel E, Hafner G, et al. Prognostic value of troponin T, troponin I, and CK–MB mass in patients with chronic renal failure. Med Klin (Munich) 2003;98(4):188–92.
[62] Farkouh ME, Robbins MJ, Zafar MU, Shimbo D, Davidson KW, Puttappa R, et al. Association between troponin I levels and mortality in stable hemodialysis patients. Am J Med 2003;114(3):224–6.
[63] Wayand D, Baum H, Schatzle G, Scharf J, Neumeier D. Cardiac troponin T and I in end-stage renal failure. Clin Chem 2000;46(9):1345–50.
[64] Lippi G, Tessitore N, Montagnana M, Salvagno GL, Lupo A, Guidi GC. Influence of sampling time and ultrafiltration coefficient of the dialysis membrane on cardiac troponin I and T. Arch Pathol Lab Med 2008;132(1):72–6.
[65] Conway B, McLaughlin M, Sharpe P, Harty J. Use of cardiac troponin T in diagnosis and prognosis of cardiac events in patients on chronic haemodialysis. Nephrol Dial Transplant 2005;20(12):2759–64.
[66] Sommerer C, Beimler J, Schwenger V, Heckele N, Katus HA, Giannitsis E, et al. Cardiac biomarkers and survival in haemodialysis patients. Eur J Clin Invest 2007;37(5): 350–6.
[67] Frankel WL, Herold DA, Ziegler TW, Fitzgerald RL. Cardiac troponin T is elevated in asymptomatic patients with chronic renal failure. Am J Clin Pathol 1996;106(1): 118–23.
[68] Collinson PO, Hadcocks L, Foo Y, Rosalki SB, Stubbs PJ, Morgan SH, et al. Cardiac troponins in patients with renal dysfunction. Ann Clin Biochem 1998;35(Pt 3):380–6.
[69] Ooi DS, House AA. Cardiac troponin T in hemodialyzed patients. Clin Chem 1998; 44(7):1410–6.
[70] Tun A, Khan IA, Win MT, Hussain A, Hla TA, Wattanasuwan N, et al. Specificity of cardiac troponin I and creatine kinase-MB isoenzyme in asymptomatic long-term hemodialysis patients and effect of hemodialysis on these cardiac markers. Cardiology 1998;90(4):280–5.
[71] Deleaval P, Descombes E, Magnin JL, Martin PY, Fellay G. Differences in cardiac troponin I and T levels measured in asymptomatic hemodialysis patients with last generation immunoassays. Nephrol Ther 2006;2(2):75–81.
[72] Mongeon F-P, Dorais M, Lorier JL, Froment D, Letendre É, Rinfret S. Effect of hemodialysis, coronary artery disease and diabetes on cardiac troponin T: a prospective survey over one year. Open Cardiovasc Med J 2009;3:69–77.
[73] Tarakcioglu M, Erbagci A, Cekmen M, Usalan C, Cicek H, Ozaslan J, et al. Acute effect of haemodialysis on serum markers of myocardial damage. Int J Clin Pract 2002; 56(5):328–32.
[74] Kumar N, Michelis MF, DeVita MV, Panagopoulos G, Rosenstock JL. Troponin I levels in asymptomatic patients on haemodialysis using a high-sensitivity assay. Nephrol Dial Transplant 2011;26(2):665–70.
[75] Dasselaar JJ, Slart RHJA, Knip M, Pruim J, Tio RA, McIntyre CW, et al. Haemodialysis is associated with a pronounced fall in myocardial perfusion. Nephrol Dial Transplant 2009;24(2):604–10.
[76] McIntyre CW, Burton JO, Selby NM, Leccisotti L, Korsheed S, Baker CSR, et al. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. Clin J Am Soc Nephrol 2008;3(1): 19–26.
[77] Assa S, Hummel YM, Voors AA, Kuipers J, Westerhuis R, de Jong PE, et al. Hemodialysis-induced regional left ventricular systolic dysfunction: prevalence, patient and dialysis treatment-related factors, and prognostic significance. Clin J Am Soc Nephrol 2012;7(10):1615–23.
[78] Kajimoto H, Kai H, Aoki H, Yasuoka S, Anegawa T, Aoki Y, et al. Inhibition of eNOS phosphorylation mediates endothelial dysfunction in renal failure: new effect of asymmetric dimethylarginine. Kidney Int 2012;81(8):762–8.
[79] Del Vecchio L, Locatelli F, Carini M. What we know about oxidative stress in patients with chronic kidney disease on dialysis—clinical effects, potential treatment, and prevention. Semin Dial 2011;24(1):56–64.
[80] Amann K, Breitbach M, Ritz E, Mall G. Myocyte/capillary mismatch in the heart of uremic patients. J Am Soc Nephrol 1998;9(6):1018–22.
[81] Lowbeer C, Stenvinkel P, Pecoits-Filho R, Heimburger O, Lindholm B, Gustafsson SA, et al. Elevated cardiac troponin T in predialysis patients is associated with inflammation and predicts mortality. J Intern Med 2003;253(2):153–60.
[82] Sezer S, Karakan S, Ozdemir N. Increased cardiac troponin T levels are related to inflammatory markers and various indices of renal function in chronic renal disease patients. Ren Fail 2012;34(4):454–9.
[83] London GM. Left ventricular alterations and end-stage renal disease. Nephrol Dial Transplant 2002;17(Suppl. 1):29–36.
[84] Ooi DS, Veinot JP, Wells GA, House AA. Increased mortality in hemodialyzed patients with elevated serum troponin T: a one-year outcome study. Clin Biochem 1999; 32(8):647–52.

[85] Sharma R, Gaze DC, Pellerin D, Mehta RL, Gregson H, Streather CP, et al. Cardiac structural and functional abnormalities in end stage renal disease patients with elevated cardiac troponin T. Heart 2006;92(6):804–9.
[86] deFilippi CR, Thorn EM, Aggarwal M, Joy A, Christenson RH, Duh SH, et al. Frequency and cause of cardiac troponin T elevation in chronic hemodialysis patients from study of cardiovascular magnetic resonance. Am J Cardiol 2007;100(5):885–9.
[87] Lentine KL, Costa SP, Weir MR, Robb JF, Fleisher LA, Kasiske BL, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the american heart association and the american college of cardiology foundation. Circulation 2012;126(5):617–63.
[88] Connolly GM, Cunningham R, McNamee PT, Young IS, Maxwell AP. Troponin T is an independent predictor of mortality in renal transplant recipients. Nephrol Dial Transplant 2008;23(3):1019–25.
[89] Arroyo D, Quiroga B, Panizo N, Rodriguez-Ferrero M, Macias N, Reque J, et al. High-sensitivity troponin T levels in kidney transplant recipients. Transplant Proc 2012; 44(9):2545–7.