Clinical Biochemistry xxx (2015) xxx–xxx

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 Parikh

ARTICLE INFO

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

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 verses 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.

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 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

E-mail address: rparikh@medicine.umaryland.edu.

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

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 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

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
			hs-cTnT (Roche Elecsys)	CKD + AMI, hs-cTnT > 35.8		0.94	0.86		Consensus on MI
			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.

Please cite this article as: Parikh R, Use and interpretation of high sensitivity cardiac troponins in patients with chronic kidney disease with and without acute myocar..., Clin Biochem (2015), http://dx.doi.org/10.1016/j.clinbiochem.2015.01.004