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How should clinicians interpret cardiac troponin values in patients with ESRD?

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Cardiovascular (CV) mortality is the predominant cause of death in patients with end-stage renal disease (ESRD). The cause-specific hospitalization rates for CV events and coronary revascularization remain high in chronic dialysis patients (1). Chest pain or anginal equivalents are frequently encountered symptoms in the dialysis unit, and early risk stratification for acute coronary syndrome (ACS) is required, as early intervention such as immediate reperfusion therapy improves outcomes. The American College of Cardiology and the American Heart Association guidelines incorporated cardiac-specific troponin T (cTnT) and troponin I (cTnI) in the definition of acute myocardial infarction (AMI) and deemed troponins as the preferred marker for myocardial injury and early risk stratification of patients who present with suspected ACS (2). The European Society of Cardiology defines AMI as “detection of rise and or fall of cardiac biomarkers (preferably troponins) with at least one value above the 99th percentile of the upper reference limits (URL), together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, EKG changes indicative of new ischemia, development of pathological Q waves on EKG, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (3).” The diagnostic utility of troponins in patients with ESRD, however, is challenging because the URL were initially derived in subjects without kidney disease.

It is important to understand the unique biochemical and analytical differences in cTnT and cTnI assays to better interpret these diagnostic tests in patients with ESRD. Sufficient dissimilarity between the amino acid sequences of the skeletal and cardiac isoforms of both TnT and TnI has allowed development of monoclonal antibody-based immunoassays for their detection. cTnT and cTnI have different release kinetics after myocardial injury (biphasic vs. monophasic) because of differential compartmentation in the cardiac myocyte, and it was proposed that the kinetics may be altered in dialysis patients (4). Free cTnT is the predominant form of released TnT as compared to binary/ternary complexes released with cTnI. Some cTnI is also released in oxidized, phosphorylated, or reduced forms. This may alter the epitope conformation recognized by the monoclonal antibodies in the assays and account for low TnI levels in the serum (4). cTnI assays have been developed using different monoclonal/ polyclonal antibodies directed to various epitopes or isoforms. Another challenge for developing cTnI assays arises from its instability and high susceptibility to proteolysis. Therefore, standardization is lacking in cTnI assays as compared to cTnT (5).

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Overall, troponins have evolved from a marker of “no significance” in ESRD, (6) given reports of troponin elevations in patients with asymptomatic ESRD, to a “diagnostic and prognostic marker” (7). Predialysis cTnT levels were more commonly elevated in patients with asymptomatic ESRD as compared to cTnI. In a study of 733 patients with asymptomatic ESRD treated with chronic intermittent dialysis, 82% had cTnT levels above the 99th percentile of referent ($>0.01 \mu\text{g/l}$) vs. 6% for cTnI ($>0.1 \mu\text{g/l}$). When the ROC curve-determined value optimized for detection of AMI was used, the values were 20% for cTnT ($>0.1 \mu\text{g/l}$) vs. 0.4% for cTnI ($>0.6 \mu\text{g/l}$) (8). Plausible mechanisms for these differential elevations include adsorption of cTnI on the dialyzer membrane imparting increased clearance, degradation of the labile cTnI molecule, advanced glycosylation of cTnT imparting decreased clearance, or the differential release of these molecules from the ternary Troponin TIC complex because of uremic toxins (9–11). Uremia may cause conformational changes in the epitope region of these molecules (5), which alters the interaction with the capture/signal antibodies in the assays.

Despite the differences in standardization and immunoreactivities, cTnT and cTnI have unequivocally been confirmed to be highly sensitive and specific diagnostic markers of myocardial damage, as well as prognostic markers for death or recurrent AMI in symptomatic patients without kidney disease (3). What about troponin elevations in symptomatic patients with kidney disease? A secondary analysis of the Global Use of Strategies to Open Occluded Coronary Arteries IV trial reported that in 7033 patients with ACS, elevation of cTnT was independently associated with 30-day composite of death or AMI across all quartiles of creatinine clearance, with an adjusted odds ratio of 2.5, 95% CI (1.8–3.3) for the lowest quartile (11). Limitations included the small percentage of participants with severe or end-stage kidney disease.

Elevations of troponins in patients with ESRD in the setting of ACS and EKG changes are much less challenging to interpret than the conundrum of modest elevations in those who may be asymptomatic or present with nonspecific symptoms such as dyspnea, fatigue, or nausea, interpreted by some to represent an “anginal equivalent” but by others as merely another dialysis-related symptom. As clinicians, we walk a thin line of dismissing these elevations as false-positives vs. obligating patients to unneeded invasive cardiac procedures.

Data regarding the prognostic implications of troponins in patients with asymptomatic ESRD are less conclusive (7,8,11). Several mechanisms have been implicated for troponin elevations in these high-risk asymptomatic patients. “Troponinemia” could reflect chronic microinfarctions (2) or correlate with left ventricular hypertrophy (12). In sixty-seven asymptomatic chronic hemodialysis patients, multivessel coronary artery disease (CAD) on coronary angiography was more prevalent across progressively higher quartiles of cTnT, and cTnT level above the median was an independent predictor of multivessel disease after adjusting for a history of CAD (13). Regardless of mechanism, several observational studies revealed that cTnT was consistently associated with all-cause mortality and CV events in patients with ESRD (Table 1), with increases in mortality of 2- to 5-fold. The data are not as robust for cTnI, and although elevated cTnI was also associated with increased risk in some studies, the exact effect size is difficult to assess because of a lack of standardization of assays (14).

The ultimate prognostic role of cardiac troponins in chronic dialysis patients is attractive. A paradigm shift may occur where chronic troponin elevation is used for risk stratification in this high-risk population. cTnT clearly stands out with greater promise for its diagnostics and prognostic capabilities. cTnI has its own inherent heterogeneity in analytical standards limiting its standardization and prognostic utility in patients with ESRD. However, cTnI still remains more specific than cTnT in the diagnosis of AMI. If troponin levels are to be

measured, they should be obtained just before dialysis, as the dialysis procedure can affect levels (14). What remains to be established is whether ESRD patients with acute elevations in troponins are accurately identified as those who would benefit from early coronary interventions, such as administration of IIb/IIIa anti-platelet inhibitors or coronary revascularization, as was confirmed in the general population. Further studies are needed to investigate whether more specific diagnostic tests, such as coronary angiography, would lead to interventions that improve the dire outcomes of patients with ESRD who have chronic elevations of troponins.

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TABLE 1

Studies measuring troponins as predictors of all-cause mortality and CV events

Study*	Sample (N)	Study design	Primary outcome	Follow-up	Results
Khan et al. (7)	ESRD (3931)	Meta-analysis (28 studies)	All-cause mortality	23 months	cTnT strong predictor of all-cause mortality cTnI not predictor of all-cause mortality
Needham et al. (15)	CKD + ESRD (3899)	Meta-analysis (39 studies)	All-cause mortality	12–24 months	cTnT strong predictor of all-cause mortality cTnI not predictor of all-cause mortality
Iliou et al. (16)	Hemodialysis (258)	Cohort	All-cause mortality	24 months	cTnT strong predictor of all-cause mortality cTnI not predictor of all-cause mortality
Han et al. (17)	Peritoneal dialysis (107)	Cohort	CV events	36 months	cTnT predicts future CV events. cTnI not measured
Apple et al. (8)	ESRD (733)	Cohort	Death	1.6 patient-years	cTnT stronger predictor of mortality as compared to cTnI, independent of diabetes or history of CAD
Wayand et al. (10)	ESRD (59)	Observational	CV events	24 months	cTnT predicted CV events. cTnI not studied

ESRD, End-Stage Renal Disease; CKD, Chronic Kidney Disease; cTnT, cardiac-specific troponin T; cTnI, cardiac-specific troponin I; CV, cardiovascular; CAD, coronary artery disease; RR, relative risk.

* All the studies used third-generation cTnT test and second generation of cTnI test, except Iliou where Trop T stat was used for cTnT measurement.