

Predictive Value of Cardiac Troponin I and T for Subsequent Death in End-Stage Renal Disease

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Background—This study determined the prevalence of increased cardiac troponin I (cTnI) and T (cTnT) in end-stage renal disease (ESRD) patients and whether an increased troponin was predictive of death.

Methods and Results—Serum was obtained from 733 ESRD patients and measured for cTnI and cTnT. Relative risks were estimated using Cox proportional hazards regressions univariately and adjusted for age, time on dialysis, and coronary artery disease. Kaplan-Meier curves compared time to event data between groups. Greater percentages of patients had an increased cTnT versus cTnI at each cutoff, as follows: 99th percentile, 82% versus 6%; 10% coefficient of variation, 53% versus 1.0%; and receiver operator characteristic, 20% versus 0.4%. Increased versus normal cTnT was predictive of increased mortality using all cutoffs and only above the 99th percentile for cTnI. Two-year cumulative mortality rates increased ($P<0.001$) with changes in cTnT from normal ($<0.01 \mu\text{g/L}$, 8.4%) to small (≥ 0.01 to $<0.04 \mu\text{g/L}$, 26%), moderate (≥ 0.04 to $<0.1 \mu\text{g/L}$, 39%), and large ($\geq 0.1 \mu\text{g/L}$, 47%) increases. Two-year mortalities were 30% for cTnI $<0.1 \mu\text{g/L}$ and 52% if $\geq 0.1 \mu\text{g/L}$. Univariate and adjusted relative risks of death associated with elevated (>99 th percentile) cTnT were 5.0 (CI, 2.5 to 10; $P<0.001$) and 3.9 (CI, 1.9 to 7.9; $P<0.001$) and cTnI were 2.0 (CI, 1.3 to 3.3; $P=0.008$) and 2.1 (CI, 1.3 to 3.3; $P=0.007$). Age, coronary artery disease, and time on dialysis were also independent predictors of mortality.

Conclusions—Increases in cTnT and cTnI in ESRD patients show a 2- to 5-fold increase in mortality, with a greater number of patients having an increased cTnT. (*Circulation*. 2002;106:2941-2945.)

Key Words: mortality ■ cardiovascular diseases ■ myocardial infarction ■ kidney

Cardiac disease is the major cause of death in patients with end-stage renal disease (ESRD), accounting for $\approx 45\%$ of all deaths.¹⁻³ In dialysis patients, $\approx 20\%$ of cardiac deaths are attributed to acute myocardial infarction (AMI).¹⁻³ AMI is a catastrophic clinical event in ESRD patients, with a 2-year mortality of 73%.³ Increased cardiac death rates in ESRD patients occur more frequently on Mondays and Tuesdays (20%) compared with other days of the week (14%).⁴ One challenge confronting the nephrology community is to explore more aggressive treatment modalities for cardiovascular disease in these patients. Recent evidence demonstrates that serum or plasma cardiac troponin T (cTnT) is an important predictor of long-term, all-cause mortality and cardiovascular mortality in patients with ESRD.^{5,6}

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Over the last 10 years, increases in cTnT and cardiac troponin I (cTnI) have been observed in ESRD patients,⁵⁻¹³ and the prevalence of increased troponins is correlated with increased risk of coronary artery disease.⁷ Recent guidelines

endorsed by the European Society of Cardiology (ESC), the American College of Cardiology (ACC), and the American Heart Association (AHA) state that cTnI and cTnT are the preferred biomarkers for the detection of myocardial injury and diagnosis of myocardial infarction (MI).¹⁴⁻¹⁶ In the clinical setting of ischemia, evidence of increased cardiac troponins has been defined as the cornerstone of the redefinition of MI. In addition to the role of cardiac troponin as a diagnostic tool, a strong prognostic value for increased troponins exists, irrespective of the mechanism of injury, in acute coronary syndrome (ACS) patients with or without renal insufficiency.¹⁷⁻¹⁹ Furthermore, early pharmacological intervention trials with low molecular weight heparin as well as with glycoprotein IIb/IIIa inhibitors have demonstrated a significant decrease in risk of death and nonfatal MI in cardiac troponin-positive ACS patients.^{20,21} Whether aggressive interventional management in ESRD patients results in improved clinical outcomes has not been studied. Furthermore, no large studies have investigated the prognostic value of cTnT compared with cTnI in ESRD patients. In the present

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study, we prospectively examined the prognostic value for all-cause mortality of cTnT and cTnI using the ESC/ACC recommended troponin cutoff concentrations in a large cohort of ESRD patients studied up to 3 years.

Methods

Seven hundred thirty-three ESRD patients, treated by chronic intermittent hemodialysis for at least 30 days (Monday, Wednesday, and Friday or Tuesday, Thursday, and Saturday) throughout Minneapolis and St Paul, Minnesota, metro outpatient dialysis units of DaVita (formerly Total Renal Care) were enrolled from April 1998 to March 1999, after institutional review board approval. Patient demographic data, past medical histories, and follow-up data were obtained at chart review by personnel unaware of cardiac troponin results.

A predialysis blood (serum) sample was obtained. cTnT was measured on the third generation Roche Elecsys 2010 analyzer.²² The manufacturer's stated detection limit is $<0.01 \mu\text{g/L}$, with an imprecision of 10% CV (coefficient of variation) at $0.03 \mu\text{g/L}$ as determined in our laboratory. The receiver operator characteristic (ROC) curve medical decision cutoff for MI is $0.1 \mu\text{g/L}$.²³ The 99th percentile of a reference population is $0.01 \mu\text{g/L}$. Total imprecision was 7.0% at $0.07 \mu\text{g/L}$. cTnI was measured on the second generation Dade-Behring Dimension RxL analyzer.²⁴ The manufacturer's stated detection limit is $0.04 \mu\text{g/L}$, with an imprecision of 10% CV at $0.4 \mu\text{g/L}$ as determined in our laboratory. The ROC curve medical decision cutoff value for MI is $0.6 \mu\text{g/L}$.^{24,25} The 99th percentile of a reference population is $0.07 \mu\text{g/L}$. However, because all results $<0.1 \mu\text{g/L}$ were reported as $<0.1 \mu\text{g/L}$, we have used $<0.1 \mu\text{g/L}$ as the 99th percentile cutoff. Total imprecision was 8.5% at $0.6 \mu\text{g/L}$. Laboratory personnel performing the assays were unaware of patient data or outcomes.

Three different cutoff criteria were used to define elevated cTnT and cTnI, as follows: the 99th percentile of a reference population, the lowest concentration to give a 10% imprecision (10% CV), and the ROC curve determined value optimized for diagnostic sensitivity and specificity for detection of MI. These concentrations were $0.01 \mu\text{g/L}$, $0.03 \mu\text{g/L}$, and $0.1 \mu\text{g/L}$ for cTnT and $0.1 \mu\text{g/L}$, $0.4 \mu\text{g/L}$, and $0.6 \mu\text{g/L}$ for cTnI, respectively. Differences in cumulative 1-, 2-, and 3-year survival rates were compared between patients with elevated and normal troponin concentrations. Exposure was computed from date of blood draw until date of death with censoring for first of the following: length of time interval of interest (1, 2, or 3 years), renal transplant, transfer of patient to another dialysis facility, or regaining renal function. Unadjusted and adjusted relative risks (RRs) of death and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models. All adjusted models were fit with variables for independent risk factors. Additional models were fit including these variables and others. Survival curves were computed using the Kaplan-Meier method and compared between risk stratification groups using the log-rank statistic. ROC curves were constructed and compared. All tests were two-sided, and statistical significance was accepted at the 0.05 level. Analyses were done using SPSS PC software.

Results

Clinical characteristics and demographic information available for the 733 ESRD patients are summarized in Table 1. Just over half of patients were male, just under two thirds were white, and the average patient age was 62 years. Diabetes and a history of CAD were found in 46% and 29%, respectively. Forty percent of patients had been on dialysis <1 year, 44% for 1 to 5 years, and 16% for >5 years. Median patient follow-up was 1.6 patient-years (range, 30 days to 3 years), with a total of 192 deaths occurring during 1052 patient-years of follow-up. Patient exposure was censored for renal transplant ($n=34$), discontinuation of hemodialysis

TABLE 1. Clinical Characteristics and Demographics of 733 ESRD Patients

Age, y, mean (range)	62 (18 to 93)
Males, %	56
Ethnicity, %*	
White	60
Black	23
Hispanic	3
Asian	7
Native American/other	6
Diabetes mellitus, %	46
History of CAD, %	29
History of MI, %	13
Years of dialysis, median (range)	1.6 (0.1 to 22)

CAD indicates coronary artery disease.

*Ethnicity data unavailable in 175 patients.

because of regaining renal function ($n=5$), and transfer of patient to other renal dialysis unit ($n=41$).

Substantially greater proportions of patients had increased cTnT relative to cTnI regardless of cutoff criteria used, specifically, 99th percentile, 82% ($0.01 \mu\text{g/L}$) versus 6% ($0.1 \mu\text{g/L}$); 10% CV, 53% ($0.03 \mu\text{g/L}$) versus 1.0% ($0.4 \mu\text{g/L}$); and ROC, 20% ($0.1 \mu\text{g/L}$) versus 0.4% ($0.6 \mu\text{g/L}$), respectively. One-, two-, and three-year cumulative mortality rates were increased for patients with elevated versus normal cTnT (all $P<0.001$, Table 2) using any of the 3 cutoffs. The 1-year ($P=0.07$), 2-year ($P=0.003$), and 3-year ($P=0.003$) cumulative mortality rates were also increased with elevated cTnI above the 99th percentile cutoff. Three of seven patients with increased cTnI above the 10% CV cutoff and 1 of 3 patients with increased cTnI above the ROC cutoff died during follow-up. No additional analyses were done because of small numbers in these groups.

Unadjusted for other risk factors for mortality, the risk of death was increased 2- to 5-fold with elevated cTnT and 2-fold for elevated cTnI regardless of duration of follow-up (Table 2). Independent risk factors identified in the data were age (RR per 10-year increase, 1.4; 95% CI, 1.3 to 1.6), history of CAD (RR, 1.4; 95% CI, 1.0 to 1.9), and time since initial dialysis (1 to 5 years: RR, 1.5; 95% CI, 1.0 to 2.0; >5 years: RR, 1.4; 95% CI, 0.9 to 2.2). Sex, diabetes, and history of MI were not independently predictive. After adjustment for the independent risk factors, the risk of death remained increased 2- to 4-fold with elevated cTnT and 2-fold with elevated cTnI (Table 2). Fitting additional models showed that the RRs of death associated with an elevated cTnI (any cutoff) or cTnT (cutoff 0.1) were not higher among those with a history of CAD or diabetes (each test for interaction, $P>0.4$).

Kaplan-Meier survival curves for cTnT (Figure, a) and cTnI (Figure, b) based on increased and normal concentrations are shown in the Figure. Significant increases in 2-year mortality rates were observed with minor, moderate, and larger increases in cTnT as defined by the 99th percentile, 10% CV, and ROC cutoffs ($P<0.001$ overall, $P\leq 0.02$ for each pairwise comparison). The 2-year mortality rate for those with cTnT <0.01 ($n=132$) was 8.4% versus 26% for

TABLE 2. Univariate and Adjusted RRs for Death by cTnT and cTnI Concentrations at Baseline

	Cumulative Mortality, %		Univariate RR	P	Adjusted RR*	P
	Normal	Elevated				
1-Year follow-up						
T 0.01	3.4	19	6.2 (2.3 to 17)	<0.001	4.7 (1.7 to 13)	<0.001
T 0.04	11	22	2.2 (1.5 to 3.3)	<0.001	1.8 (1.2 to 2.8)	0.003
T 0.10	14	28	2.3 (1.6 to 3.5)	<0.001	2.4 (1.6 to 3.5)	<0.001
I 0.10	16	25	1.8 (0.9 to 3.3)	0.10	1.8 (1.0 to 3.4)	0.08
2-Year follow-up						
T 0.01	8.4	36	5.0 (2.5 to 10)	<0.001	3.9 (1.9 to 7.9)	<0.001
T 0.04	19	42	2.5 (1.8 to 3.4)	<0.001	2.1 (1.5 to 3.0)	<0.001
T 0.10	28	47	2.2 (1.6 to 3.0)	<0.001	2.3 (1.6 to 3.1)	<0.001
I 0.10	30	52	2.0 (1.3 to 3.3)	0.008	2.1 (1.3 to 3.3)	0.007
3-Year follow-up						
T 0.01	8.4	51	5.5 (2.7 to 11)	<0.001	4.3 (2.1 to 8.7)	<0.001
T 0.04	28	57	2.5 (1.8 to 3.4)	<0.001	2.1 (1.6 to 3.0)	<0.001
T 0.10	42	56	2.1 (1.6 to 2.9)	<0.001	2.2 (1.6 to 3.0)	<0.001
I 0.10	44	60	2.0 (1.3 to 3.2)	0.007	2.1 (1.3 to 3.3)	0.005

*Adjusted for age, pre-draw history of coronary artery disease, and time since initial hemodialysis (<1 year, 1 to 5 years, >5 years); the number of the 733 patients with an increased troponin by cutoff (mg): cTnT ≥0.01, n=601; cTnT ≥0.04, n=387; cTnT ≥0.10, n=148; cTnI ≥0.10, n=45.

those with minor increases (cTnT ≥0.01 but <0.04 μg/L; n=214), 39% with moderate increases (cTnT ≥0.04 but <0.1 μg/L; n=239), and 47% with larger increases (cTnT ≥0.1 μg/L; n=148). Two-year mortality rates were 30% for cTnI <0.1 μg/L versus 52% for cTnI ≥0.1 μg/L (P=0.003). ROC curve analysis for death at 2 years revealed a significantly greater (P<0.001) area under the curve for cTnT (0.67) compared with cTnI (0.53). There were no differences between ROC curves areas at years 1, 2, and 3 within assays (change in area <0.02).

Discussion

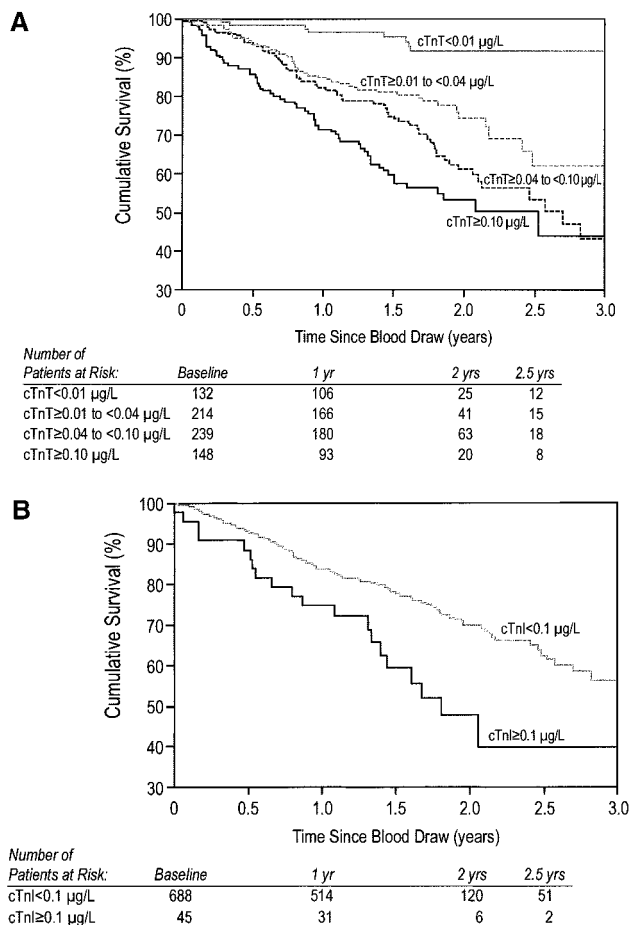
This is the first study to evaluate short- and long-term survival in a large (n=733) ESRD patient cohort based on predialysis cTnT and cTnI concentrations. Importantly, we assessed mortality risk for those with troponin above and below both the 99th percentile concentration, which is used for detection of myocardial injury according to the European Society of Cardiology/American College of Cardiology re-definition of MI consensus document,^{14,15} and the 10% CV cutoff,^{31,32} which is suggested by cardiology and laboratory medicine to optimize assay precision. Cutoff concentrations used for cTnT were as follows: 99th percentile cTnT 0.01 μg/L, cTnI 0.1 μg/L; 10% CV cTnT 0.03 μg/L, cTnI 0.4 μg/L; and ROC cTnT 0.1 μg/L, cTnI 0.6 μg/L. The findings of the present study are both unique and confirmatory of smaller studies in several aspects.

Elevated versus normal cTnT defined by any of the cutoff concentrations was associated with increased risk of death. However, only the 99th percentile cutoff (the reference limit for normal subjects) for cTnI revealed an increased risk, because only a handful of patients had elevated cTnI above

the 10% CV cutoff (the lowest troponin concentration that demonstrates a 10% total precision) and ROC cutoff (optimized for sensitivity and specificity for MI detection). The relative risk of death remained increased after adjustment for other risk factors. No differences in relative risk of mortality associated with an elevated cTnT were found between patients with or without a known history of CAD or diabetes; the RR of mortality was increased 2- to 4-fold in the presence or absence of these coexisting conditions. These findings were quite striking, suggesting a more prominent role for risk assessment in ESRD patients for cTnT versus cTnI.

We observed no difference in risk assessment between diabetic and nondiabetic patients based on troponin findings. These findings contrast with a smaller (n=49) study that reported patients with diabetes were more likely to have increased troponins.⁶ We do recognize limitations of our patient data set, including incomplete information pertaining to a history of congestive heart failure, left ventricular hypertrophy, and angiographic data. Furthermore, we did not examine whether there is an interaction between medication and cardiac troponin risk nor did we determine the influence of a Monday/Tuesday sampling time versus outcomes.⁴ Both need to be determined in future research.

Our study should help clarify the persistently vexing clinical problem of the interpretation of modest elevations in cardiac troponin in hospitalized dialysis patients. In the past this finding has been ascribed to false-positive elevations in cardiac troponins, because the literature is replete with condemnations of the specificity of these biomarkers for the assessment of ACS in dialysis patients.¹² We would argue that cardiac troponin increases are not a spurious finding, because the biomarker is indeed elevated. In our study, the



Kaplan-Meier survival curves by baseline troponin cutoffs. A, cTnT using the 99th percentile 0.01 µg/L, 10% CV 0.03 µg/L, and the ROC 0.1 µg/L. B, cTnI using the 99th percentile 0.1 µg/L. The number of patients at risk at baseline, 1 year, 2 years, and 2.5 years for each cutoff is shown at the bottom of the graphs. The 99th percentile refers to the normal reference limit. The 10% CV refers to the lowest concentration that demonstrates a 10% total precision. The ROC cutoff refers to concentrations optimized for the sensitive and specific detection of MI.

troponin elevation detected in outpatient dialysis patients was a powerful predictor of all-cause mortality. It is quite plausible that other mechanisms beside ACS are responsible for the troponin elevation and adverse outcome. Several studies have now demonstrated that significant angiographic findings are linked to cTnT and cTnI elevations, identifying patients with ACS who will benefit from antithrombotic therapy.^{33,34} However, no similar data are presently available in the ESRD population relating cardiac troponin status and angiography findings. Paradoxically, the same patient's tests in a hospital setting could be dismissed as false-positives, particularly given the proportion of patients in our study above the cTnT 0.1 cutoff. The clinical duality of cardiac troponin testing in dialysis patients must be acknowledged to avoid incorrect clinical judgments, ie, defining acute coronary syndromes and prediction of mortality (complementary but discrete tasks).

The findings of our present study substantiate the cTnT, cTnI difference observed in smaller studies.⁴⁻¹² Using the

99th percentile cutoff, 82% (n=601) of cTnT versus only 6% (n=45) of cTnI concentrations were increased. For comparison, using the ROC curve cutoff, 20% (n=148) of cTnT versus only 0.4% (n=3) of cTnI concentrations were increased. We speculate as to the possible causes for the difference in increases in cTnT compared with cTnI. First, increased cTnT but not cTnI reflects increased left ventricular mass in the ESRD population,^{26,27} with a different release pattern of cTnT compared with cTnI. Second, cTnT release from injured myocardium may have a longer circulating half-life compared with cTnI because of advanced glycation end products known to accumulate in diabetic patients with renal disease.²⁸ However, future studies need to evaluate this concept. Third, two small studies have suggested that cTnI decreases after dialysis, either directly attributable to removal by dialysis or indirectly by degradation of the labile cTnI molecule.^{29,30} In contrast, cTnT concentrations trend toward increasing after dialysis. This would result in lower circulating cTnI levels compared with cTnT. Future studies need to evaluate this observation using a large patient database. In theory, the release of the troponin ternary CIT complex from injured myocardium should show equal molar increases of cTnI and cTnT. Additional studies are needed to elucidate the mechanism responsible for the cTnI/cTnT differences found in ESRD patients.

Regardless of the mechanisms of myocardial injury in ESRD patients, our present findings continue to substantiate and add to the growing literature demonstrating the prognostic power of cardiac troponin testing for predicting mortality in ESRD patients. In one study involving 102 ESRD patients, an increased cTnT (0.1 µg/L) resulted in a 3.6-fold greater hazard ratio.⁵ Furthermore, in a study involving 244 ESRD patients, an increasing cTnT over a 6-month period showed an increasing death rate with a risk ratio of 2.0.⁶ Furthermore, increasing cTnT has now been shown to predict an increase in death and MI in ACS patients regardless of their level of creatinine clearance.¹⁹ Future research will need to address whether frequent blood sampling (days, weeks, months) for troponin monitoring will identify or exclude patients with clinically inapparent ACS with or without renal insufficiency. In our present study, we reveal prognostic value for elevated cTnT and cTnI using several cutoff values. It should be noted, however, that a normal cardiac troponin does not preclude risk. Patients below the 99th percentile cutoff had a 2-year mortality rate of 8.4% (cTnT) and 30% (cTnI).

The ultimate role of cardiac troponin testing for risk stratification in chronic hemodialysis patients is speculative but attractive. There are a host of conceivable strategies for the identification of the highest-risk dialysis patients after initiation of renal replacement therapy. Our evidence-based findings suggest that one plausible, cost-effective scenario is the developing role of outpatient cardiac troponin testing. Incorporation of quarterly or semiannual cardiac troponin monitoring in ESRD patients may assist in initiating more aggressive treatment of underlying CAD and detection of subclinical myocardial injury and assist in treatment therapies before renal transplantation. As revealed in our study, not all cardiac troponin assays are equivalent regarding risk assessment in ESRD, and appropriate analytical cutoff values need

to be validated.^{31,32} We are presently considering clinical use of the cTnT assay for risk-assessment purposes. Increased cTnT might trigger a more aggressive approach to diagnosis and therapy of CAD in the ESRD population. Larger prospective clinical trials would be useful to determine, after education of clinicians of the power of troponin for risk stratification, whether the knowledge and response to an increased cardiac troponin concentration would have a favorable socioeconomic impact on patient management or outcomes.

Acknowledgments

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