

Cardiac Troponins and Renal Function in Nondialysis Patients with Chronic Kidney Disease

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Background: Serum cardiac troponin concentrations are commonly increased in end-stage renal disease (ESRD) in the absence of an acute coronary syndrome (ACS). The data on cardiac troponin I (cTnI) are more variable than those for cardiac troponin T (cTnT). There is little information on cardiac troponin concentrations in patients with chronic kidney disease (CKD) who have not commenced dialysis.

Methods: We studied 222 patients: 56 had stage 3 (moderate CKD); 70 stage 4 (severe CKD); and 96 stage 5 (kidney failure). Patients underwent echocardiography and were followed prospectively for a median of 19 months; all-cause mortality was recorded.

Results: Overall, serum cTnT was increased above the 99th percentile reference limit in 43% of all CKD patients studied, compared with 18% for cTnI. Serum cTnT and cTnI concentrations were more commonly increased in the presence of more severe CKD (11 and 6 patients in stage 3, 27 and 8 in stage 4, and 57 and 24 in stage 5 ($P < 0.0001$ and < 0.02 , respectively)). Among 38 patients with detectable cTnI, 32 had detectable cTnT ($r_s = 0.67$; $P < 0.0001$). There was evidence that decreasing estimated glomerular filtration rate increased the odds of having detectable cTnT ($P < 0.001$) but not cTnI ($P = 0.128$). There was no evidence to support an adjusted association of detectable cardiac troponins with increasing left ventricular mass index. Increased cTnT ($P = 0.0097$), but not cTnI, was associated with decreased survival.

Conclusions: Increased cTnT and cTnI concentrations are relatively common in predialysis CKD patients, in

the absence of an ACS, including among those with stage 3 disease. The presence of left ventricular hypertrophy alone does not explain these data. Detectable cTnT was a marker of decreased survival.

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Cardiovascular disease is prevalent and the leading cause of death in patients with end-stage renal disease (ESRD)⁴ (1). Cardiovascular disease begins early in the course of chronic kidney disease (CKD), and the glomerular filtration rate (GFR) is an independent risk factor for it (2): individuals with CKD are more likely to die of cardiovascular disease than to develop kidney failure requiring dialysis (3). The most common manifestation of CKD is left ventricular hypertrophy (LVH), predominantly as a result of hypertension and anemia. LVH is a powerful independent predictor of cardiovascular mortality in uremic patients. Traditional cardiac risk factors (e.g., diabetes mellitus, hypertension, hypercholesterolemia, obesity, and smoking), as well as those specifically or more commonly associated with renal disease (e.g., anemia, LVH, hyperparathyroidism, and the calcium \times phosphate product), can be modified by aggressive therapy, leading to improved survival. This does, however, require early identification and treatment of patients at increased risk (4, 5). Although tests to assess cardiac function and diagnose ischemic heart disease in asymptomatic patients are available (in the form of cardiac echocardiography, myo-view scans, and exercise electrocardiograms), for health economics reasons they are not offered to all CKD patients. The ability to detect significant cardiac disease at an early stage could facilitate more aggressive and focused treatment of those at increased risk.

Cardiac troponin T (cTnT) and troponin I (cTnI) are low-molecular-weight proteins that form part of the tro-

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Received June 8, 2005; accepted August 16, 2005.

Previously published online at DOI: 10.1373/clinchem.2005.055665

⁴ Nonstandard abbreviations: ESRD, end-stage renal disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; cTnT and cTnI, cardiac troponin T and I, respectively; ACS, acute coronary syndrome; PTH, parathyroid hormone; LVMI, left ventricular mass index; OR, odds ratio; BMI, body mass index; and CI, confidence interval.

ponin complex and are integral components of the myofibrillar contractile apparatus of the heart. Loss of integrity of cardiac myocyte membranes causes release of cardiac troponins into the circulation, which can be detected by highly sensitive assays developed for cTnT and cTnI to diagnose acute coronary syndrome (ACS) (6). However, increases in serum cardiac troponin concentration can occur in the absence of an ACS (7), including among patients with ESRD [reviewed in Refs. (8–12)]. Most studies have focused on hemodialysis patients, in whom increased cardiac troponin concentrations are associated with increasing age, presence of cardiovascular risk factors, history of ischemic heart disease, diabetes, and LVH (13–15) and predict increased cardiac and all-cause mortality (15–21).

Information about cardiac troponins and their relationship with comorbidity is sparse in patients with CKD who are not receiving dialysis treatment. With increasing emphasis on the prevention and management of cardiovascular disease in CKD patients who have not reached ESRD (22), there is an urgent need for studies addressing the gaps in our understanding in such patients. We studied predialysis patients with moderate and severe kidney disease and kidney failure to address the questions of (a) at which stage in the progression of kidney disease the increase in cardiac troponin concentration occurs and (b) whether there is a relationship between LVH and cardiac troponin concentrations in pre-ESRD patients.

Materials and Methods

PATIENTS

Between June 2003 and June 2004, 227 Caucasian patients with CKD attending nephrology outpatient clinics were recruited to the study. Exclusion criteria included patients <18 years of age or other vulnerable groups; patients with acute renal failure, a functioning renal transplant, or receiving dialysis; and patients having had a recent (<1 month) cardiac event. One patient subsequently withdrew from the study, and in 4 patients insufficient blood was available for further analyses, leaving a total study population of 222. All patients gave informed consent, and the study had ethics approval from the Kent and Medway Strategic Health Authority Research Ethics Committee (REC no. EK050/3/03).

A detailed clinical history was recorded, including age, sex, weight, height, primary renal diagnosis, blood pressure (mean of last 3 measurements), smoking history, other comorbidity (diabetes mellitus, respiratory disease, connective tissue disease, malignancy, and liver disease), and drug history. Cardiovascular disease was considered present if there was a history of myocardial infarction, angina, arrhythmia, valvular disease, or congestive cardiac failure or a requirement for intervention (angioplasty, coronary artery bypass graft, pacemaker). Arteropathy was considered present if there was a history of

any of the above (except arrhythmia and valvular disease) or cerebrovascular or peripheral vascular disease.

GFR was estimated (eGFR) based on the abbreviated Modification of Diet in Renal Disease (23) study formula. Patients were stratified into stage 3 CKD [moderate; eGFR = 30–59 mL·min⁻¹·(1.73 m²)⁻¹], stage 4 CKD [severe; eGFR = 15–29 mL·min⁻¹·(1.73 m²)⁻¹], and stage 5 CKD [failure; eGFR <15 mL·min⁻¹·(1.73 m²)⁻¹] according to guidelines (22). The primary renal diagnoses were diabetic nephropathy (n = 41), obstructive uropathy (n = 26), renovascular disease (n = 22), primary glomerulonephritis (n = 19), hypertensive nephropathy (n = 18), autosomal dominant polycystic kidney disease (n = 16), bilateral small kidneys (n = 14), chronic pyelonephritis (n = 9), anti-neutrophil cytoplasmic antibody-positive vasculitis (n = 9), tubulointerstitial nephritis (n = 9), miscellaneous (n = 14; n = 1 each for amyloidosis, Alport disease, cholesterol embolization, chronic lymphocytic leukemia, cyclosporin toxicity, Fanconi syndrome, lithium toxicity, and sarcoidosis; n = 2 for kidney myeloma; and n = 4 for analgesic nephropathy), and unknown etiology (n = 25).

ANALYTICAL METHODS

Blood and urine samples were collected in the nonfasting state. Routine analyses, including cTnT, were performed within 4 h. Serum for cTnI measurement was stored frozen at –80 °C for up to 1 year before analysis. Serum cTnT was measured with a third-generation electrochemiluminescent immunoassay on an Elecsys 1010 analyzer (Roche Diagnostics Ltd.). The 99th percentile upper reference limit of this assay and the limit of detection are both 0.01 µg/L (24, 25). Between-day imprecision (CV) was 5.7% at a concentration of 0.11 µg/L. Serum cTnI was measured in 215 patients for whom sufficient sample allowed use of the ADVIA Centaur cTnI immunoassay on a Centaur analyzer (Bayer plc). The 99th percentile upper reference limit of this assay and the limit of detection are both 0.07 µg/L (25). Between-day imprecision was 6.4% at a concentration of 0.64 µg/L. Serum creatinine was measured by a compensated rate Jaffe method on an Integra 800 analyzer (Roche Diagnostics Ltd.) with standardization traceable to isotope-dilution mass spectrometry. Between-day imprecision was 3.2% and 2.2% at concentrations of 99 and 332 µmol/L, respectively. Additionally, blood hemoglobin, serum C-reactive protein, albumin, cholesterol, calcium and phosphate, intact plasma parathyroid hormone (PTH; Nichols Institute Diagnostics Ltd.), and the urinary protein:creatinine ratio were measured by standard laboratory methods.

Patients (n = 201) underwent 2-dimensional targeted M-mode echocardiography using a Hewlett Packard Sonos 5500 (Phillips Medical). Left ventricular mass (LVM) was calculated from the formula of Devereux and Reichek (26) and indexed to body surface area (27) to obtain the LVM index (LVMI). LVH was considered present when LVMI exceeded 125 g/m² (28).

Table 1. Patient characteristics by CKD stage.^a

	CKD				P for difference
	Overall	Stage 3	Stage 4	Stage 5	
n	222	56	70	96	
M/F, n	145/77	43/13	49/21	53/43	0.0161
Age, years	67.0 (58.0–75.0)	68.0 (58.0–76.0)	71.0 (64.3–75.0)	64.5 (53.8–71.0)	0.0049
Body surface area, m ²	1.94 (0.24)	2.00 (0.21)	1.93 (0.25)	1.90 (0.25)	0.0639
n	216		68	92	
Body mass index, kg/m ²	28.9 (24.0–32.5)	29.1 (25.6–32.8)	29.2 (24.8–33.2)	26.5 (23.0–31.8)	0.1487
n	216		68	92	
Mean arterial blood pressure, mmHg	97.3 (92.3–103.4)	96 (90–102)	95 (91–104)	99 (94–104)	0.0757
Receiving antihypertensive medication, n	200	47	67	86	0.0868
Hemoglobin, g/L	122 (17)	133 (13)	124 (15)	115 (16)	<0.0001
n	221			95	
Receiving erythropoietin, n	74	3	13	58	<0.0001
LVMI, g/m ²	142.4 (116.1–177.8)	126.8 (113.1–158.9)	142.1 (114.2–173.9)	154.5 (122.8–199.3)	0.0029
n	201	55	63	83	
Presence of LVH, ^b n	130/201	29/55	41/63	60/83	0.0624
Diabetes, n	59	11	25	23	0.0948
History of cardiovascular disease, ^b n	73	22	31	20	0.0032
History of arteriopathic disease, ^b n	89	27	34	28	0.0150
Current smokers, n	20	4	6	10	0.7841
Serum cholesterol, mmol/L	4.4 (3.8–5.2)	4.9 (4.0–5.8)	4.7 (3.8–5.1)	4.2 (3.6–5.1)	0.0091
Receiving HMG-CoA ^c reductase inhibitors, n	135	33	52	50	0.0144
Plasma PTH, ng/L	105 (57–198)	69 (47–106)	118 (56–153)	142 (79–287)	<0.0001
n	208				
Serum calcium × phosphate product, mmol/L	3.13 (2.74–3.70)	2.76 (2.46–3.14)	2.89 (2.63–3.18)	3.72 (3.12–4.36)	<0.0001
Serum albumin, g/L	42 (39–44)	43 (41–45)	41 (39–44)	42 (39–44)	0.0419
Serum CRP, mg/L	4.8 (2.4–9.2)	4.7 (2.4–9.2)	6.0 (2.5–9.8)	4.6 (1.8–9.5)	0.6152
Urinary protein:creatinine ratio, mg/mmol	108 (37–243)	30 (16–67)	64 (30–146)	208 (111–308)	<0.0001
n	181	44	57	80	
cTnT ≥0.01 μg/L, n (%)	95 (43)	11 (20)	27 (39)	57 (59)	<0.0001
cTnI ≥0.07 μg/L, n (%)	38/215 (18)	6/56 (11)	8/67 (12)	24/92 (26)	0.0197

^a Data are given as the mean (SD) when gaussian distributed or as the median (interquartile range) when not gaussian distributed. Data were available for all patients unless otherwise indicated.

^b See text for definition.

^c HMG-CoA, hydroxymethylglutaryl-CoA; CRP, C-reactive protein.

DATA ANALYSIS

Data were analyzed with Analyze-It™ (Analyze-it Software Ltd.), InStat™ (GraphPad.com), StatsDirect, and SAS, Ver. 8.01 (SAS Institute Inc.). A *P* value <0.05 was considered significant.

Comparisons between the CKD groups were based on either 1-way ANOVA or Kruskal–Wallis ANOVA for continuous variables, as appropriate, with further testing between CKD groups being undertaken with either the unpaired *t*-test or Dunn multiple-comparisons test when indicated. For categorical variables, the χ^2 test was used. Spearman rank analysis was used to explore relationships between continuous variables.

The number of patients exceeding the 99th percentile upper reference limit for cardiac troponins were compared between stages 3, 4, and 5 CKD by the χ^2 test.

Unadjusted odds ratios (ORs) for serum cardiac troponin concentrations above the 99th percentile upper reference limit were obtained by logistic regression on the following single clinical variables: sex, age, eGFR, body mass index (BMI), mean arterial pressure, hemoglobin, LVH, diabetes, known preexisting cardiovascular or arteriopathic disease, cholesterol, PTH, and calcium × phosphate product. For sex, the OR is expressed as the odds for males/odds for females. For associated clinical diagnoses (e.g., LVH and diabetes), the ORs are expressed as odds if condition present/odds if condition absent. For continuous variables (e.g., age), the ORs are expressed as the odds with an increase in value of 1 unit/odds at current value. Because of the interdependence of many of the clinical correlates (e.g., the positive relationship observed between cTnT and LVMI with increasing age), a logistic

regression approach was used to investigate the independent effect of clinical variables on cardiac troponin concentration, including LVMI and eGFR.

Patients were prospectively followed for a median (range) period of 19 (13–25) months. All-cause mortality was recorded. Exposure was computed from date of blood draw until date of death with censoring for renal transplantation ($n = 5$ patients) or loss from the study (1 patient). Differences in survival between patients with cardiac troponin concentrations above and below the 99th percentile upper reference limit were illustrated by Kaplan–Meier curves: the log-rank test was used to compare survival among the 2 patient groups.

Results

Patient characteristics for the whole study population and by CKD stage are given in Table 1. Overall, serum cTnT concentrations were increased ($\geq 0.01 \mu\text{g/L}$) in 95 of 222 (43%) CKD patients. Serum cTnT differed significantly ($P < 0.0001$) between CKD stages, being more commonly increased in the presence of more advanced CKD [increased in 11 of 56 (20%), 27 of 70 (39%), and 57 of 96 (59%) patients with stage 3, 4, and 5 CKD, respectively; Tables 1 and 2]. Increased cTnT was associated with reduced eGFR [OR = 0.939; 95% confidence interval (CI), 0.916–0.963; $P < 0.001$; Fig. 1].

Echocardiographic data were available for 201 patients: the prevalence of LVH was $>50\%$ in all 3 CKD stages. LVMI increased with decreasing eGFR ($r_s = -0.26$; $P = 0.0002$) and increased with age ($r_s = 0.21$; $P = 0.0030$). Increased cTnT was associated with LVH (67 of 130 patients) compared with those with no evidence of LVH on echocardiogram (19 of 71 patients; OR = 2.911; 95% CI, 1.553–5.454; $P < 0.001$) and with increased LVMI (OR = 1.012; 95% CI, 1.006–1.018; $P < 0.001$). There were significant associations between increased cTnT and increased

age and calcium \times phosphate product and between increased cTnT and decreased hemoglobin and cholesterol (Table 3). cTnT was more likely to be increased in patients with diabetes (39 of 59) than in those without diabetes (56 of 163; OR = 3.726; 95% CI, 1.987–6.985; $P < 0.001$). There was no univariate association between an increased cTnT concentration and known preexisting cardiovascular or arteriopathic disease, BMI, mean arterial pressure, PTH, or sex (Table 3).

eGFR was initially excluded from a model to identify the significant variables affecting cTnT. After backward elimination with a 5% significance level, the following variables remained: age, diabetes, hemoglobin concentration, and LVMI. eGFR was then tested for significance against this initial model. From this comparison there was evidence ($P < 0.001$) of a relationship between eGFR and increased cTnT independent of other variables (OR = 0.927; 95% CI, 0.894–0.960; Table 4). This approach was repeated, but including eGFR and excluding LVMI from the initial model. After backward elimination, the model included sex, age, diabetes, and eGFR. When LVMI was tested against this model, there was no evidence to support a significant relationship between LVMI and cTnT independent of other variables ($P = 0.305$).

Overall, serum cTnI was increased in 38 of 215 (18%) CKD patients. Serum cTnI differed significantly ($P = 0.0197$) among CKD stages, being more commonly increased ($\geq 0.07 \mu\text{g/L}$) in the presence of more advanced CKD [increased in 6 of 56 (11%), 8 of 67 (12%), and 24 of 92 (26%) patients with stage 3, 4, and 5 CKD, respectively; Tables 1 and 2], although the difference between stages 3 and 4 was not significant. Increased cTnI was associated with a diminished eGFR (OR = 0.961; 95% CI, 0.931–0.992; $P = 0.015$; Fig. 1).

Echocardiographic data were available for 194 patients with cTnI results. Increased cTnI was significantly asso-

Table 2. Differences in patient characteristics by CKD stage.

	<i>P</i>		
	CKD 3 vs CKD 4	CKD 3 vs CKD 5	CKD 4 vs CKD 5
M/F	NS ^a	<0.05	NS
Age	NS	NS	<0.01
Hemoglobin	<0.01	<0.001	<0.001
Receiving erythropoietin	NS	<0.0001	<0.0001
LVMI	NS	<0.01	NS
History of cardiovascular disease	NS	<0.05	<0.01
History of arteriopathic disease	NS	<0.05	<0.05
Serum cholesterol	NS	<0.01	NS
Receiving HMG-CoA reductase inhibitors	NS	NS	<0.01
Plasma PTH	<0.05	<0.001	NS
Serum calcium \times phosphate product	NS	<0.001	<0.001
Serum albumin	NS	NS	NS
Urinary protein:creatinine ratio	<0.05	<0.001	<0.001
cTnT $\geq 0.01 \mu\text{g/L}$	<0.05	<0.0001	<0.005
cTnI $\geq 0.07 \mu\text{g/L}$	NS	<0.05	<0.05

^a NS, not significant; HMG-CoA, hydroxymethylglutaryl-CoA.

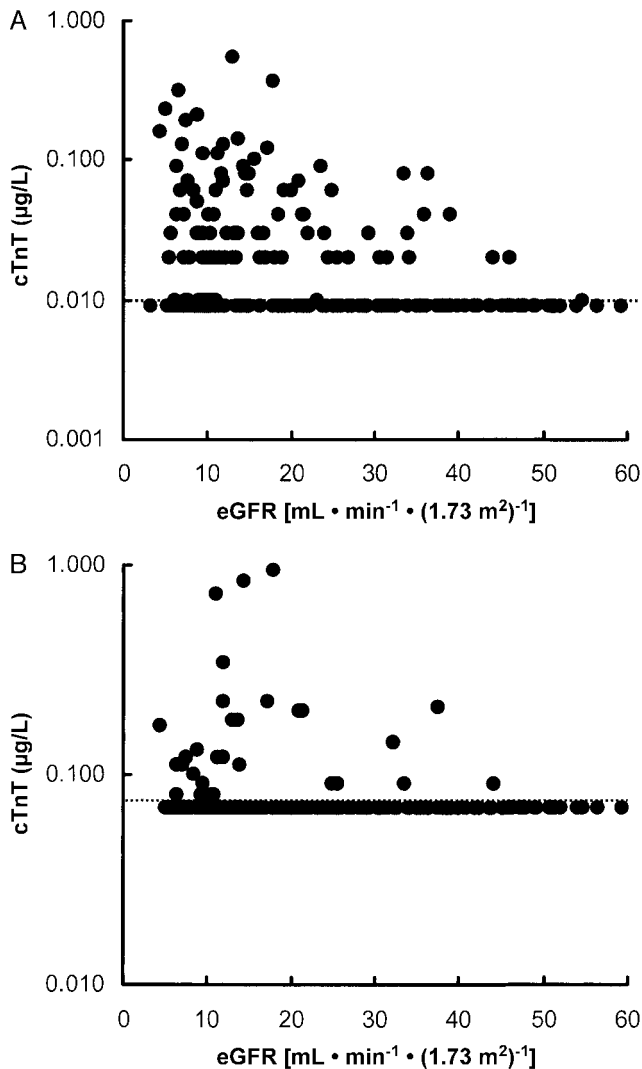


Fig. 1. Relationship of serum cTnT (top) and cTnI (bottom) concentrations with eGFR in patients with CKD.

The dashed horizontal lines represent the 99th percentile upper reference limits. For graphical purposes, patients with cTnT concentrations $<0.01 \mu\text{g/L}$ and cTnI concentrations $<0.07 \mu\text{g/L}$ have been assigned concentrations of 0.009 and 0.069 $\mu\text{g/L}$, respectively. Some of the data points in Fig. 1 represent several patients.

ciated with LVH (27 of 124 patients) compared with those with no evidence of LVH on echocardiogram (4 of 70 patients; OR = 4.593; 95% CI, 1.535–13.738; $P = 0.006$) and with increased LVMI (OR = 1.011; 95% CI, 1.004–1.017; $P < 0.001$). There were significant associations between increased cTnI and increased age and PTH and between increased cTnI and decreased hemoglobin. cTnI was more likely to be increased in patients with diabetes or cardiovascular disease. There was no unadjusted association between increased cTnI concentrations and known preexisting arteriopathic disease, BMI, cholesterol, calcium \times phosphate product, mean arterial pressure, or sex (Table 2).

The addition of eGFR to the underlying model, which incorporated age, LVMI, and PTH, did not provide evidence to support a relationship between eGFR and cTnI independent of other variables ($P = 0.128$). This approach was repeated, but including eGFR and excluding LVMI initially. The underlying model indicated dependence on age, eGFR, and presence of diabetes, cardiovascular, and arteriopathic disease. Including LVMI did not provide evidence to support a relationship between LVMI and cTnI independent of other variables ($P = 0.105$).

There was reasonable concordance between cTnT and cTnI, albeit that cTnT was increased above the 99th percentile upper limit of normal in more than twice as many patients as cTnI. Among the 38 patients with detectable cTnI, 32 had detectable cTnT: the association (r_s) among these patients was 0.67 ($P < 0.0001$).

In the follow-up period, there were 23 deaths. Sixteen of these patients had detectable cTnT concentrations, and 7 had detectable cTnI concentrations. In 1 patient who died, there was insufficient serum for cTnI measurement. Overall survival was decreased among patients with baseline cTnT concentrations above the 99th percentile upper reference limits ($P = 0.0097$). The difference in survival among patients with baseline cTnI concentrations above and below the 99th percentile upper reference limits was not quite significant at the 5% level ($P = 0.0821$; Fig. 2). The OR for death with a detectable cTnT concentration was 3.471 (95% CI, 1.274–10.394; $P = 0.0075$), whereas that for cTnI failed to achieve significance (OR = 2.439; 95% CI, 0.771–6.977; $P = 0.0786$).

Discussion

Increases in serum cTnT concentrations in patients with ESRD have been observed in 20%–90% of hemodialysis patients (8). The prevalence of increased serum cTnI in such patients is generally lower: between 0% and 19% (13, 14, 16, 20, 21, 29). For CKD patients who are not receiving dialysis, however, data are limited and conflicting (30–32). Goicoechea et al. (33) noted cTnT concentrations $\geq 0.01 \mu\text{g/L}$ in a lower proportion (16%) of CKD patients than in the present study, and none exceeded 0.1 $\mu\text{g/L}$ (cTnI was not measured). In our cohort, 43% and 18% of patients had cTnT and cTnI concentrations exceeding the 99th percentile upper reference limits, respectively. Increased concentrations were more common in patients with more advanced CKD, although for cTnI the association with eGFR was not independent of other variables. The increased prevalence of increased cTnT concentrations in our study compared with the study of Goicoechea et al. (33) probably reflects the relatively inferior renal function in our cohort (median eGFR of our patients was 18 mL/min compared with 27 mL/min in their study, and very few of their patients had kidney failure).

Goicoechea et al. (33) previously noted that CKD patients with increased cTnT concentrations are at increased risk of cardiovascular events. We were unable to analyze our data for cardiovascular events; however,

Table 3. Univariate OR analysis of the factors associated with an increased cardiac troponin concentration.

	cTnT			cTnI		
	OR	95% CI	P	OR	95% CI	P
Sex	1.383	0.786–2.433	0.261	1.390	0.647–2.988	0.399
Age	1.037	1.014–1.060	0.001	1.053	1.017–1.090	0.003
eGFR	0.939	0.916–0.963	<0.001	0.961	0.931–0.992	0.015
Body mass index	0.994	0.954–1.037	0.790	0.962	0.906–1.021	0.205
Mean arterial blood pressure	1.016	0.990–1.042	0.238	1.025	0.992–1.058	0.144
Hemoglobin	0.723	0.607–0.861	<0.001	0.733	0.586–0.917	0.007
LVH	2.911	1.553–5.454	<0.001	4.593	1.535–13.738	0.006
LVMi	1.012	1.006–1.018	<0.001	1.011	1.004–1.017	0.001
Diabetes	3.726	1.987–6.985	<0.001	2.096	1.003–4.380	0.049
Cardiovascular disease	1.366	0.777–2.401	0.278	2.050	1.005–4.181	0.048
Arteriopathic disease	1.698	0.986–2.925	0.057	1.237	0.610–2.509	0.555
Cholesterol	0.749	0.589–0.951	0.018	1.021	0.771–1.353	0.883
Calcium × phosphate product	1.495	1.080–2.070	0.015	1.300	0.868–1.948	0.204
PTH	1.002	1.000–1.004	0.098	1.003	1.001–1.006	0.012

increases in cTnT, but not cTnI, were associated with poorer survival. The lack of demonstrable association with cTnI in our study may simply reflect the lower prevalence of detectable cTnI concentrations, the relatively short follow-up period, and the low event rate in our cohort. Longer term follow-up of the cohort may clarify the relationship between cardiac troponin concentrations and outcome.

The cause and the significance of increased cardiac troponin concentrations in patients with renal dysfunction in the absence of acute coronary disease are controversial. As a consequence of the powerful prognostic data emerging from the dialysis population, it is increasingly accepted that increased concentrations of cardiac troponins reflect either subclinical myocardial damage caused by silent ischemia or myocardial remodeling in the development of LVH (14, 15). This latter view is given credence by studies demonstrating increased cTnI concentrations in the settings of LVH (34, 35) and cardiac failure in the absence of acute myocardial infarction, unstable angina, or renal failure (36). Ricchiuti et al. (37) demonstrated that left ventricular remodeling is associated with a decrease in intracellular cardiac troponin concentrations and postulated that this might be as a result of chronic loss into the circulation.

Alternatively, increased concentrations of serum cardiac troponins could reflect ongoing subclinical ischemic

events induced by microvascular coronary artery disease although, in a retrospective analysis, normal coronary angiograms were seen in one third of CKD patients admitted with presumed ACS (chest pain and cTnT >0.1 µg/L) (38). Furthermore, Sharma et al. (39) recently demonstrated, using angiography, that an increased cTnT does not predict coronary artery disease in ESRD patients. deFilippi et al. (40) reported greater likelihood of multivessel coronary artery disease in hemodialysis patients even with small increases of cTnT concentrations, but no correlation between LVM and increased cTnT. Although Goicoechea et al. (33) found higher cTnT concentrations in patients with LVH, the latter was not predictive of an increased cTnT concentration. They used electrocardiography to diagnose LVH, whereas we chose to use echocardiography in view of its better sensitivity in detecting LVH (41), and have confirmed that the influence of LVMi on cardiac troponin concentrations was not independent.

In the present study, increased serum cTnI concentrations were relatively common, although at a lower frequency than increased cTnT concentrations. cTnI and cTnT are part of the same ternary complex within the myocyte, and one would anticipate equivalence in terms of their release into the circulation, although free cytoplasmic cTnT is more abundant than cTnI [7% vs 4% of total intracellular cardiac troponin, respectively (42)]. Both proteins undergo further modifications after release

Table 4. Unadjusted and adjusted ORs for detectable cardiac troponin concentrations.^a

Factor	cTnT						cTnI					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
eGFR	0.939	0.916–0.963	<0.001	0.927	0.894–0.960	<0.001	0.961	0.931–0.992	0.015	0.969	0.930–1.009	0.128
LVMi	1.012	1.006–1.018	<0.001	1.004	0.997–1.011	0.305	1.011	1.004–1.017	0.001	1.006	0.999–1.014	0.105

^a For cTnT, eGFR was adjusted for age, hemoglobin, diabetes, and LVMi, and LVMi was adjusted for age, sex, eGFR, and diabetes. For cTnI, eGFR was adjusted for age, LVMi, and PTH, and LVMi was adjusted for age, eGFR, diabetes, and cardiovascular and arteriopathic disease.

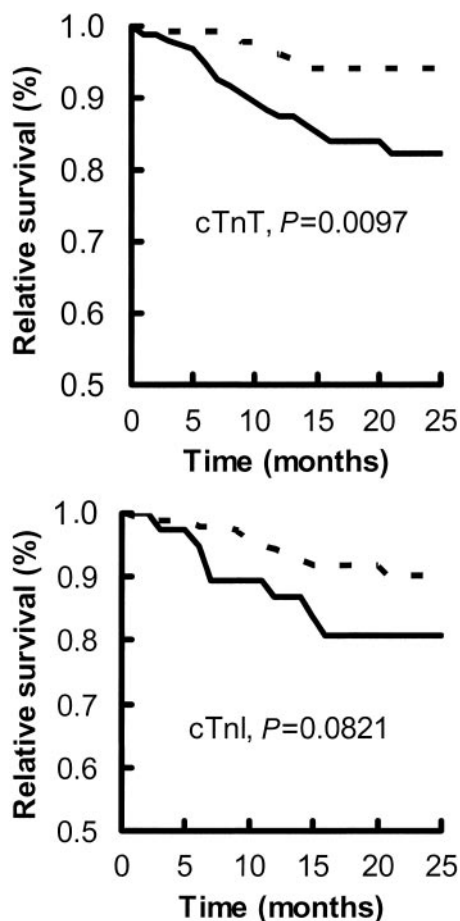


Fig. 2. Kaplan-Meier survival curves showing the association between survival and serum cTnT (*top*) and cTnI (*bottom*) concentrations above (*solid line*) and below (*dashed line*) the 99th percentile upper reference limits.

The numbers of patients at risk with cTnT concentrations above the 99th percentile were 95, 86, and 56 at 1, 10, and 20 months, respectively, compared with 127, 123, and 48 for cTnT concentrations below the 99th percentile. The equivalent numbers of patients at risk with cTnI above the 99th percentile were 38, 34, and 24 compared with 177, 169, and 78 for cTnI concentrations below the 99th percentile.

(42, 43), which may affect their immunogenicity and, potentially, be altered in the uremic state (9). Diris et al. (44) have proposed that the difference is attributable to accumulation of low-molecular-weight (8- to 25-kDa) fragments of cTnT, but not cTnI, in patients with ESRD, although this hypothesis remains unconfirmed and has been criticized (45). Other possible explanations include differences in sensitivity, standardization, and diagnostic thresholds of the respective assays (30, 46).

In summary, we have presented data for increased cardiac troponins in the largest cohort of predialysis CKD patients reported to date. To our knowledge, this is the first study to document the relatively high prevalence of increased cTnI, as well as cTnT, in such patients. Increased cardiac troponin concentrations may occur early in CKD, including among a significant number of patients

with moderate (stage 3) CKD, and is more common as CKD advances.

This work was funded by a grant from the East Kent Hospitals NHS Trust Internal Project Grant Scheme, with the exception of the cTnI measurements, which were funded by Bayer Diagnostics plc. Dr. Colin Cryer, visiting statistician from the Centre for Health Services Studies, University of Kent, provided initial statistical support to this study, and Dr. Alexa Laurence, from the Institute of Mathematics, Statistics and Actuarial Science, University of Kent, provided expert advice at the analysis stage. We thank the staff of the Clinical Biochemistry and Renal Medicine Departments, East Kent Hospitals, for their cooperation and help.

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