**NEPHROLOGY** 2004; **9**, 83–88

Review Article

# Cardiac troponins and renal disease

JANAK R DE ZOYSA

*The John Walls Renal Unit, Leicester, United Kingdom*

***SUMMARY:*** Cardiovascular disease is the most common cause of death in patients with renal failure. Patients with renal failure are at greater risk of atypical presentations of myocardial ischaemia. Traditional markers of myocardial damage are often increased in renal failure in the absence of clinically suspect myocardial ischaemia. The cardiac troponins are specific markers of myocardial injury. Large-scale trials, excluding patients with renal disease, have shown the importance of the cardiac troponins in predicting adverse outcome and in guiding both therapy and intervention in acute coronary syndromes. Cardiac Troponin T and cardiac Troponin I are increased in patients with renal failure and this is likely to represent multifactorial pathology including cardiac dysfunction, left ventricular hypertrophy and cardiac microinfarctions. Increases in serum troponin from baseline, in patients with renal disease with acute coronary syndromes, may represent a poor prognosis. Small studies of patients with renal failure have suggested that elevation of the cardiac troponins is associated with an increased risk of cardiac death.

***KEY WORDS:*** **chronic renal failure, myocardial ischaemia, troponin.**

## INTRODUCTION

Cardiovascular disease remains the leading cause of death in patients with chronic renal failure.[1] Patients with acute coronary syndrome (ACS) and renal disease are more likely to present with silent ischaemia[2] or atypical chest pain[3] than the general population. Serum markers of myocardial injury such as creatine kinase, the MB-fraction of creatine kinase and myoglobin, are often elevated in patients with renal failure even in the absence of clinically suspected myocardial ischaemia,[4,5] thus making their interpretation difficult. The troponins are proteins found in striated muscle. The serum concentration of their cardiac isoform may be ascertained accurately and rapidly by assay using monoclonal antibodies. Large-scale trials, which have excluded patients with renal disease, have shown that cardiac troponins are sensitive markers of myocardial damage, prognostic indicators of future cardiovascular events and that they can guide therapeutic intervention. This paper will review the biochemisty of the troponins and their significance in cardiac disease for patients with renal disease.

Correspondence: Dr Janak R de Zoysa, The John Walls Renal Unit, Leicester General Hospital, University Hospitals of Leicester, NHS Trust, Gwendolen Road, Leicester LE5 4PW, UK. Email: jdz1@le.ac.uk

Accepted for publication 28 November 2003.

## BIOCHEMISTRY

The troponins form complexes with actin and tropomyosin on the thin filament of the contractile apparatus in striated muscle (Fig. 1). The troponin complex consists of three subunits: Troponin C, Troponin T and Troponin I. Troponin C binds calcium and regulates activation of the thin filaments during contraction. Troponin T binds the troponin complex to tropomyosin. Troponin I is inhibitory and prevents contraction in the absence of calcium and Troponin C. When muscle is depolarized, there is an intracellular release of calcium, which binds Troponin C resulting in a conformational change in the troponin–tropomyosin complex. Actin and myosin can then interact resulting in the muscle contracting.

Troponin I has three specific isoforms: fast skeletal, slow skeletal and cardiac muscle.[6] Cardiac Troponin I (TnI) is mostly bound to the myocardial contractile apparatus[7] and has a molecular weight of 22.5 kDa. Tn I becomes the sole Troponin I expressed in myocardial cells after postnatal development, prior to which slow skeletal Troponin I predominates.[8] Tn I is not expressed in normal skeletal muscle.[9]

Troponin T also has three specific isoforms: fast skeletal, slow skeletal and cardiac muscle. In skeletal muscle, there are many slightly different subforms.[10,11] Cardiac Troponin T (TnT) is also mostly bound to the myocar-

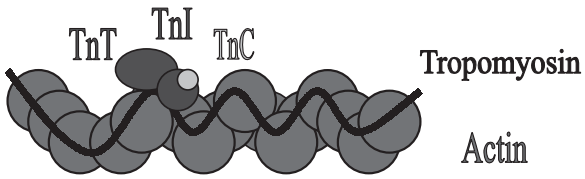


**Fig. 1** Actin_Tropomyosin_Troponin Complex. The thin filament of striated muscle consists of actin, tropomyosin and the troponin complex of Troponin T (TnT), Troponin I (TnI) and Troponin C (TnC). Contraction of muscle is mediated by calcium interacting with the troponin complex.

dial contractile apparatus[7] and has a molecular weight of 37 kDa. TnT is expressed in developing skeletal muscle, and is gradually downregulated after birth until no TnT is expressed in normal adult skeletal muscle.[10]

Troponin C has two isoforms. The fast isoform is found in skeletal muscle while the slow isoform is found in both skeletal and cardiac muscle.[12] The lack of cardiac specificity has meant that no assay has been developed to test for this protein.

## MYOCARDIAL DAMAGE AND THE TROPONINS

Damage to the myocardium results in release of the cardiac troponins. They are initially detectable 4–6 h after necrosis, peak at 14–18 h and remain elevated for at least 7 days.[13–18] TnI is released in complexes of Troponin T-I-C and Troponin I-C while TnT is released in as free Troponin T or a Troponin T-I-C complexes.[19,20]

Early coronary reperfusion is associated with a more rapid peak and generally an improved outcome.[17,21,22] The half-life of the troponins is 2 h.[14] The initial detection of troponin is thought to be because of the release of the free cytoplasmic component, while the prolonged presence of troponins in serum is caused by the continued breakdown of the structurally bound component.[14,15]

Between 15 and 48% of patients with chest pain, not fulfilling the traditional criteria for myocardial infarction, may have an elevated serum cardiac troponin.[17,23,24] This has prognostic importance as patients with an elevated cardiac troponin are often found to have unstable plaques at angiography, while patients without elevated cardiac troponins are often found to have stable plaques.[25] Elevation of serum TnT or TnI thus identifies patients with ACS at risk of a worse outcome. A consensus document jointly published by the European Society of Cardiology and the American College of Cardiology has recognized the importance of this observation and has proposed that an elevated cardiac troponin is diagnostic of a myocardial infarction.[26]

Cardiac Troponin I (TnI) has been shown to be elevated in acute myocarditis.[27] Although the troponins are known not to exist in the pericardium, TnI has been found to be elevated in pericaditis.[28] This is likely to represent associated inflammation of the underlying epicardium rather than pericardial damage, per se. The cardiac troponins appear specific at excluding myocardial contusion in cases of blunt chest trauma.[29–31] Direct current (DC) cardioversion does not appear to elevate TnT.[32,33]

## NON-CARDIAC CAUSES OF ELEVATED CARDIAC TROPONINS

An elevated cardiac troponin, unrelated to myocardial damage, has been found in a number of conditions including cerebrovascular accidents, subarachnoid haemorrhage, endocrine disease, polymyositis, dermatomyositis, and haematological malignancies.[34–36]

Studies in intensive care units have shown an increased TnT and TnI in septic, intubated patients. The concentration of the cardiac troponins appears to correlate with left ventricular dysfunction and the presence of multi-organ failure, but it is unclear whether elevation affected either hospital length of stay or survival.[37–42]

## TROPONINS IN RENAL DISEASE

Both TnT and TnI are found to be elevated in patients with end-stage renal disease (ESRD) in the absence of active cardiac disease. Between 17 and 75% of dialysis patients have elevated TnT,[43–48] while between 4 and 21% of patients have elevated TnI.[47–51] Even when using more specific second generation TnT assays, up to 53% of asymptomatic patients with ESRD have an elevated serum concentration.[43,52–60] The concentration of the cardiac troponins can vary over time, with up to a 50% variation being noted over a year.[46] An elevated concentration identifies patients at greater risk of all-cause mortality.[44,59]

Given the lower frequency of abnormal TnI in asymptomatic patients with ESRD, it has been suggested that this may be a more specific marker of cardiac ischaemia than TnT for this group of patients.[44,61,62] Several factors are likely to explain this disparity:

(a) Free cytosolic proteins are released earlier when cells are damaged and it is estimated 7% of TnT and 3.5% of TnI is free in the myocardial cytoplasm.[63]
(b) There is roughly twice as much TnT as TnI per gram of myocardium.[64]
(c) The assays for TnI use different monoclonal antibodies and have different thresholds for an abnormal value unlike TnT for which there is a single standardized assay (Table 1).[20]

**Table 1** Charactersitics of selected troponin assays

| Manufacturer | System | Assay type | Lowest detection limit (μg/L) | 99th percentile of normal (μg/L) | Intermediate range (μg/L) | Acute MI cut-off (μg/L) |
|---|---|---|---|---|---|---|
| Abbott Laboratories | AxSYM | Troponin I | 0.14 | 0.50 | 0.51–1.99 | >2.00 |
| Bayer Diagnostics | Centaur | Troponin I | 0.02 | 0.10 | 0.11–1.49 | >1.50 |
| Beckman Coulter | Access | Troponin I | 0.01 | 0.04 | 0.04–0.06 | >0.06 |
| Ortho-Clinical Diagnostics | Vitros ECi | Troponin I | 0.02 | 0.08 | 0.09–0.39 | >0.40 |
| Roche | Elecsys | Troponin T | 0.01 | 0.01 | 0.02–0.03 | >0.03 |
| Tosoh Corporation | AIA-600II | Troponin I | 0.06 | <0.06 | 0.07–0.59 | >0.60 |

MI, myocardial infarction.

Two meta-analyses of published trials suggest that, at least in patients without renal impairment, both TnT and TnI are of similar prognostic value.[65,66]

Haemodialysis appears to affect the serum concentration of TnT and TnI differently. TnI concentration tended to decrease while TnT concentration tended to increase after haemodialysis, irrespective of whether a high- or low-flux membrane was used.[53] The study suggested that this was either because TnI may bind to proteins which are membrane bound or that dialysis may modify the epitope recognized by the monoclonal antibody used in the assay.

Uraemia increases the free serum concentration and clearance of protein-bound drugs. TnI is released from the myocardium only as a complex, while TnT is released as both a complex and as free TnT. It is unclear what effect uraemia may have on the detection, release or clearance of different troponin subunits. Once released, TnI may be modified by phosphorylation, oxidation or proteolysis.[20,67,68] Cardiac Troponin T may undergoes proteolysis.[67] It is unclear what effect uraemia may have on biochemical modifications of the cardiac troponins.

## AETIOLOGY OF AN ELEVATED CARDIAC TROPONIN IN RENAL FAILURE

Several subtypes of TnT have been described in myocardial tissues. TnT has been found in human foetal skeletal muscle, however, these subtypes decrease and eventually disappear in non-diseased adult human skeletal muscle. Several groups have hypothesized that uraemic-induced skeletal myopathy may promote re-expression of TnT. By using polymerase chain reaction and Western blot techniques, cardiac-like isoforms of troponins T and messenger ribonucleic acid have been identified in skeletal muscle of patients with ESRD.[43,69,70] Use of the second-generation assays, however, has not detected the cardiac TnT isoform in these samples.[69,70] There appears to be no relationship between an elevated TnT and clinical or electrophysiological markers of uraemic myopathy.[71] Thus, there is inadequate information to support this hypothesis.

Free and bound TnT are large molecules (37 and 77 kDa), making it unlikely the kidney is responsible for clearance. Most studies have not shown a relationship between serum creatinine and frequency or the degree of troponin elevation.[43,72–74] The half-life and clearance of TnI after an acute myocardial infarction appears similar between patients with normal renal function and ESRD.[75]

Death of cardiac cells occurs in heart failure. Patients with heart failure, without ACS, have been shown to have increased TnT and TnI.[76,77] Changes in the cardiac troponin is associated with both the prognosis and the severity of heart failure.[76,78] Patients with ESRD have a greater incidence and prevalence of heart failure.

Increased TnT and TnI have been associated with left ventricular hypertrophy in an animal model.[79] Left ventricular hypertrophy is common and has been correlated with increased TnT in patients with ESRD without acute myocardial ischaemia.[80]

Serum elevation of cardiac troponins may be the result of subclinical myocardial infarction. Post-mortem evidence suggests the presence of micro-infarction in patients with elevated serum troponins.[81] It is possible that patients with ESRD may sustain repeated subclinical microinfarctions.

## CLINICAL SIGNIFICANCE OF CARDIAC TROPONINS IN CHRONIC RENAL FAILURE

A number of studies have investigated the prognostic role of serum troponins in patients with renal failure using the newer cardiac troponin assays.[58,82–88] The largest of these was of 733 patients with ESRD.[82] TnT was more commonly elevated than TnI, and both an increased TnT and an increased TnI were predictive of increased mortality. A number of other studies have confirmed the prognostic value of TnT.[58,83–86] Smaller studies examining the prognostic efficacy of TnI have given variable results.[85,87]

The significance of an elevated cardiac troponin in the setting of ACS is less clear. Two prospective studies have suggested TnI is more sensitive and specific than the MB-fraction of creatine kinase in predicting myocar-

dial ischaemia.[61,62] A further study suggested TnT and TnI are less predictive of adverse outcomes in patients with ACS and renal failure.[74] A recent analysis of over 7000 patients from the Global Use of Strategies To Open occluded coronary arteries (GUSTO) -IV trial found that TnT was of prognostic benefit in predicting adverse outcome in both patients with and without renal failure.[89]

## CONCLUSIONS

Serum cardiac troponin concentration is frequently increased in asymptomatic patients with renal failure. This is likely to represent multifactorial pathology potentially including cardiac dysfunction, left ventricular hypertrophy and subclinical myocardial infarction. An elevated TnT or TnI is a poor prognostic factor and is associated with an increased risk of morbidity and mortality in patients with renal failure. There are no specific guidelines for intervention in patients with an elevated serum troponin, however, risk factor modification with smoking cessation, antihypertensive therapy, lipid lowering therapy, and aspirin is reasonable. The role of further diagnostic testing for coronary artery disease is unclear, but should be considered. Left ventricular function should be assessed with echocardiography and appropriate therapy initiated. A negative troponin is a good prognostic factor in both the acute and chronic setting.

## REFERENCES


1. Wolfe RA, Port FK, Webb RL *et al*. Annual data report of the United States renal data system. VI. Causes of death. *Am. J. Kidney Dis. Suppl*. 1998; **32**: S81–8.
2. Aronow WS, Ahn C, Mercando AD, Epstein S. Prevalence of coronary artery disease, complex ventricular arrhythmias, and silent myocardial ischemia and incidence of new coronary artery events in older persons with chronic renal insufficiency and with normal renal function. *Am. J. Cardiol*. 2000; **86**: 1142–3.
3. Nakamura S, Uzu T, Inenaga T, Kimura G. Prediction of coronary artery disease and cardiac events using electrocardiographic changes during hemodialysis. *Am. J. Kidney Dis*. 2000; **36**: 592–9.
4. Robbins MJ, Epstein EM, Shah S. Creatine kinase subform analysis in hemodialysis patients without acute coronary syndromes. *Nephron* 1997; **76**: 296–9.
5. Jaffe AS, Ritter C, Meltzer V, Harter H, Roberts R. Unmasking artifactual increases in creatine kinase isoenzymes in patients with renal failure. *J. Lab. Clin. Med*. 1984; **104**: 193–202.
6. Cummins P, Perry SV. Troponin I from human skeletal and cardiac muscles. *Biochem. J*. 1978; **171**: 251–9.
7. Bleier J, Vorderwinkler KP, Falkensammer J *et al*. Different intracellular compartmentations of cardiac troponins and myosin heavy chains: A causal connection to their different early release after myocardial damage. *Clin. Chem*. 1998; **44**: 1912–18.
8. Hunkeler NM, Kullman JAM, Murphy AM. Troponin I isoform expression in human heart. *Circulation Res*. 1991; **69**: 1409–14.
9. Bodor GS, Porterfield D, Voss EM, Smith S, Apple FS. Cardiac troponin-I is not expressed in fetal and healthy or diseased adult human skeletal muscle tissue. *Clin. Chem*. 1995; **41 Part 1**: 1710–15.
10. Anderson PA, Malouf NN, Oakley AE, Pagani ED, Allen PD. Troponin T isoform expression in humans: A comparison among normal and failing adult, fetal heart, and adult and fetal skeletal muscle. *Circulation Res*. 1991; **69**: 1226–33.
11. Pearlstone JR, Carpenter MR, Smillie LB. Amino acid sequence of rabbit cardiac troponin T. *J. Biol. Chem*. 1986; **261**: 16 795–810.
12. Parmacek MS, Leiden JM. Structure and expression of the murine slow/cardiac troponin C gene. *J. Biol. Chem*. 1989; **264**: 13217–25.
13. Cummins B, Auckland ML, Cummins P. Cardiac-specific troponin-I radioimmunoassay in the diagnosis of acute myocardial infarction. *Am. Heart J*. 1987; **113**: 1333–44.
14. Katus HA, Remppis A, Looser S, Hallermeier K, Scheffold T, Kuebler W. Enzyme linked immuno assay of cardiac troponin I for the detection of acute myocardial infarction in patients. *J. Mol. Cell. Cardiol*. 1989; **21**: 1349–53.
15. Mair J, Thome-Kromer B, Wagner I *et al*. Concentration time courses of troponin and myosin subunits after acute myocardial infarction. *Coron. Artery Dis*. 1994; **5**: 865–72.
16. Wu AH, Feng YJ, Contois JH, Pervaiz S. Comparison of myoglobin, creatine kinase-MB, and cardiac troponin I for diagnosis of acute myocardial infarction. *Ann. Clin. Lab. Sci*. 1996; **26**: 291–300.
17. Burlina A, Zaninotto M, Secchiero S, Rubin D, Accorsi F. Troponin T as a marker of ischemic myocardial injury. *Clin. Biochem*. 1994; **27**: 113–21.
18. Murthy VV, Karmen A. Troponin-T as a serum marker for myocardial infarction. *J. Clin. Lab. Anal*. 1997; **11**: 125–8.
19. Katrukha AG, Bereznikova AV, Esakova TV *et al*. Troponin I is released in bloodstream of patients with acute myocardial infarction not in free form but as complex. *Clin. Chem*. 1997; **43 Part 1**: 1379–85.
20. Wu AH, Feng YJ, Moore R *et al*. Characterization of cardiac troponin subunit release into serum after acute myocardial infarction and comparison of assays for troponin T and I. *Clin. Chem*. 1998; **44 Part 1**: 1198–208.
21. Katus HA, Remppis A, Scheffold T, Diederich KW, Kuebler W. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. *Am. J. Cardiol*. 1991; **67**: 1360–7.
22. Mair J, Artner-Dworzak E, Lechleitner P *et al*. Cardiac troponin T in diagnosis of acute myocardial infarction. *Clin. Chem*. 1991; **37**: 845–52.
23. Ravkilde J, Horder M, Gerhardt W *et al*. Diagnostic performance and prognostic value of serum troponin T in suspected acute myocardial infarction. *Scand. J. Clin. Lab. Invest*. 1993; **53**: 677–85.
24. Collinson PO, Moseley D, Stubbs PJ, Carter GD. Troponin T for the differential diagnosis of ischaemic myocardial damage. *Ann. Clin. Biochem*. 1993; **30**: 11–16.
25. Hamm CW, Ravkilde J, Gerhardt W *et al*. The prognostic value of serum troponin T in unstable angina. *N. Engl. J. Med*. 1992; **327**: 146–50.
26. Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined: A consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J. Am. Coll. Cardiol*. 2000; **36**: 959–69.

27. Lauer B, Niederau C, Kuhl U *et al*. Cardiac troponin T in patients with clinically suspected myocarditis. *J. Am. Coll. Cardiol*. 1997; **30**: 1354–9.
28. Godon P, Guerard S, Bonnefoy E *et al*. Increase of troponin I during acute pericarditis. 69 cases at an emergency service. *Presse Med*. 2000; **29**: 1271–4.
29. Ferjani M, Droc G, Dreux S *et al*. Circulating cardiac troponin T in myocardial contusion. *Chest* 1997; **111**: 427–33.
30. Adams JE, Davila-Roman VG, Bessey PQ, Blake DP, Ladenson JH, Jaffe AS. Improved detection of cardiac contusion with cardiac troponin I. *Am. Heart J*. 1996; **131**: 308–12.
31. Bertinchant JP, Polge A, Mohty D *et al*. Evaluation of incidence, clinical significance, and prognostic value of circulating cardiac troponin I and T elevation in hemodynamically stable patients with suspected myocardial contusion after blunt chest trauma. *J. Trauma* 2000; **48**: 924–31.
32. Grubb NR, Cuthbert D, Cawood P, Flapan AD, Fox KA. Effect of DC shock on serum levels of total creatine kinase, MB-creatine kinase mass and troponin T. *Resuscitation* 1998; **36**: 193–9.
33. Neumayr G, Hagn C, Ganzer H *et al*. Plasma levels of troponin T after electrical cardioversion of atrial fibrillation and flutter. *Am. J. Cardiol*. 1997; **80**: 1367–9.
34. Kobayashi S, Tanaka M, Tamura N, Hahimoto H, Hirose SI. Serum cardiac troponin T I polymyositis/dermatomyositis (letter). *Lancet* 1992; **340**: 726.
35. Missov E, Calzolari C, Davy JM, Leclerq F, Rossi M, Pau B. Cardiac troponin I in patients with hematologic malignancies. *Coron. Artery Dis*. 1997; **8**: 537–41.
36. Khan IA, Tun A, Wattanassauwan N *et al*. Elevation of serum cardiac troponin I in noncardiac and cardiac diseases other than acute coronary syndromes. *Am. J. Emerg. Med*. 1999; **17**: 225–9.
37. Fernandes CJ, Akamine N, Knobel E. Cardiac troponin: a new serum marker of myocardial injury in sepsis. *Intens. Care Med*. 1999; **25**: 1165–8.
38. Turner A, Tsamitros M, Bellomo R. Myocardial cell injury in septic shock. *Crit. Care Med*. 1999; **27**: 1775–80.
39. Edouard AR, Benoist JF, Cossan C, Mimoz O, Legrand A, Samii K. Circulating troponin I in trauma patients without cardiac contusion. *Intens. Care Med*. 1998; **24**: 569–73.
40. Guest TM, Ramanthan AV, Tuteur PG, Schechtman KB, Ladenson JH, Jaffee AS. Myocardial injury in critically ill patients. A frequently unrecognized complication. *J. Am. Med. Assoc*. 1995; **273**: 1945–9.
41. Spies C, Haude V, Fitzner R *et al*. Serum cardiac troponin T as a prognostic marker in early sepsis. *Chest* 1998; **113**: 1055–63.
42. Kollef MH, Laderson JH, Eisenberg PR. Clinically recognized cardiac dysfunction: An independent determinant of mortality among critically ill patients. Is there a role for serial measurement of cardiac troponin I? *Chest* 1997; **111**: 1340–7.
43. McLaurin MD, Apple FS, Voss EM, Herzog CA, Sharkey SA. Cardiac troponin I, cardiac troponin T, and creatine kinase MB in dialysis patients without ischemic heart disease: Evidence of cardiac troponin T expression in skeletal muscle. *Clin. Chem*. 1997; **43**: 976–82.
44. Apple FS, Sharkey SW, Hoeft P *et al*. Prognostic value of serum cardiac troponin I and T in chronic dialysis patients: A 1-year outcomes analysis. *Am. J. Kidney Dis* .1997; **29**: 399–403.
45. Collinson PO, Hadcocks L, Foo Y *et al*. Cardiac troponins in patients with renal dysfunction. *Ann. Clin. Biochem*. 1998; **35**: 380–6.
46. 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**: 647–52.
47. Willging S, Keller F, Steinbach A. Specificity of cardiac troponins I and T in renal disease. *Clin. Chem. Lab. Med*. 1998; **36**: 87–92.
48. Hafner G, Thome-Kromer B, Schaube J *et al*. Cardiac troponins in serum in chronic renal failure. *Clin. Chem*. 1994; **40**: 1790–1.
49. Adams JE, Bodor GS, Davile-Roman VG, Delmez JA, Apple FS, Ladenson JH. Cardiac troponin I. A marker with high specificity for cardiac injury. *Circulation* 1993; **88**: 101–6.
50. Apple FS, Christenson RH, Valdes R *et al*. Simultaneous rapid measurement of whole blood myoglobin, creatine kinase MB, and cardiac troponin I by the Triage Cardiac Panel for detection of myocardial infarction. *Clin. Chem*. 1999; **45**: 199–205.
51. Bhayana V, Gougoulias T, Cohoe S, Henderson AR. Discordance between results for serum troponin T and Troponin I in renal disease. *Clin. Chem*. 1995; **41**: 312–17.
52. Wu AH, Feng YJ, Roper L, Herbert K, Schweizer R. Cardiac troponins T and I before and after renal transplantation. *Clin. Chem*. 1997; **43**: 411–12.
53. Wayand D, Baum H, Schatzle G, Scharf J, Neumeier D. Cardiac troponin T and I in end-stage renal failure. *Clin. Chem*. 2000; **46**: 1345–50.
54. McNeil AR, Marshall M, Ellis CJ, Hawkins RC. Why is troponin T increased in the serum of patients with end-stage renal disease? *Clin. Chem*. 1998; **44**: 2377–8.
55. Porter GA, Norton T, Bennett WB, Troponin T. A predictor of death in chronic haemodialysis patients. *Eur. Heart J*. 1998; **19** (Suppl. N): N34–7.
56. Musso P, Cox I, Vidano E, Zambon D, Panteghini M. Cardiac troponin elevations in chronic renal failure: Prevalence and clinical significance. *Clin. Biochem*. 1999; **32**: 125–30.
57. Stolear JC, Georges B, Shita A, Verbeelen D. The predictive value of cardiac troponin T measurements in subjects on regular haemodialysis. *Nephrol. Dial. Transplant*. 1999; **14**: 1961–7.
58. Dierkes J, Domrose U, Westphal S *et al*. Cardiac troponin T predicts mortality in patients with end-stage renal disease. *Circulation* 2000; **102**: 1964–9.
59. Ooi DS, Zimmerman D, Graham J, Wells GA. Cardiac troponin T predicts long-term outcomes in hemodialysis patients. *Clin. Chem*. 2001; **47**: 412–17.
60. Roppolo LP, Fitzgerald R, Dillow J, Ziegler T, Rice M, Maisel A. A comparison of troponin T and troponin I as predictors of cardiac events in patients undergoing chronic dialysis at a veteran's hospital: A pilot study. *J. Am. Coll. Cardiol*. 1999; **34**: 448–54.
61. Martin GS, Becker BN, Schulman G. Cardiac troponin-I accurately predicts myocardial injury in renal failure. *Nephrol. Dial. Transplant* 1998; **13**: 1709–12.
62. McLaurin MD, Apple FS, Falahati A, Murakami MM, Miller EA, Sharkey SW. Cardiac troponin I and creatine kinase-MB mass to rule out myocardial injury in hospitalized patients with renal insufficiency. *Am. J. Cardiol*. 1998; **82**: 973–5.
63. Wu AH, Feng YJ. Biochemical differences between cTnT and cTnI and their significance for diagnosis of acute coronary syndromes. *Eur. Heart J*. 1998; **19** (Suppl. N): 25–9.
64. Dean KJ. Biochemistry of troponin. In: AHB Wu, ed. *Cardiac Markers*. Totowa: Humana Press, 1998; 193–204.
65. Fleming SM, Daly KM. Cardiac troponins in suspected acute coronary syndrome: A meta-analysis of published trials. *Cardiology* 2001; **95**: 66–73.
66. Olatidoye AG, Wu AH, Feng YJ, Waters D. Prognostic role of troponin T versus troponin I in unstable angina pectoris for

cardiac events with meta-analysis comparing published studies. *Am. J. Cardiol.* 1998; **81**: 1405–10.
67. Labugger R, Organ L, Collier C, Atar D, Van Eyk JE. Extensive troponin I and T modification detected in serum from patients with acute myocardial infarction. *Circulation* 2000; **102**: 1221–6.
68. Bodor GS, Oakeley AE, Allen PD, Crimmins DL, Ladenson JH, Anderson PA. Troponin I phosphorylation in the normal and failing adult human heart. *Circulation* 1997; **96**: 1495–500.
69. Apple FS, Ricchiuti V, Voss EM, Anderson PA, Ney A, Odland M. Expression of cardiac troponin T isoforms in skeletal muscle of renal disease patients will not cause false-positive serum results by the second generation cardiac troponin T assay. *Eur Heart J.* 1998; **19** (Suppl. N): 30–3.
70. Ricchiutti V, Apple FS. RNA expression of cardiac troponin T isoforms in diseased human skeletal muscle. *Clin. Chem.* 1999; **45**: 2129–35.
71. Zumrutdal ZO, Bakinen O, Ucan H, Atalay HV, Bodur H. Relationship between uremic myopathy and false-positive cardiac troponin T test. *Nephron* 2000; **86**: 522–3.
72. Mockel M, Schindler R, Knorr L *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**: 1489–95.
73. Escalon JC, Wong SS. False-positive cardiac troponin T levels in chronic hemodialysis patients. *Cardiology* 1996; **87**: 268–9.
74. Van Lente F, McErlean ES, DeLuca SA, Peacock F, Rao JS, Nissen SE. Ability of troponin to predict adverse outcomes in patients with renal insufficiency and suspected acute coronary syndromes: A case-matched study. *J. Am. Coll. Cardiol.* 1999; **33**: 471–8.
75. Ellis K, Dreisbach AW, Lertora JJ. Plasma elimination of cardiac troponin I in end-stage renal disease. *South Med. J.* 2001; **94**: 993–6.
76. Del Carlo CH, O'Connor CM. Cardiac troponins in congestive heart failure. *Am. Heart J.* 1999; **138**: 646–53.
77. Sato Y, Yamada T, Taniguchi R *et al.* Persistently increased serum concentrations of cardiac troponin T in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. *Circulation* 2001; **103**: 369–74.
78. La Vecchia L, Mezzena G, Zanolla L *et al.* Cardiac troponin I as diagnostic and prognostic marker in severe heart failure. *J. Heart Lung Transplant.* 2000; **19**: 644–52.
79. Gulati J, Akella AB, Nikolic SD, Starc V, Siri F. Shifts in contractile regulatory protein subunits troponin T and troponin I in cardiac hypertrophy. *Biochem. Biophys. Res. Comm.* 1994; **202**: 384–90.
80. Iliou MC, Fumeron C, Benoit MO *et al.* Factors associated with increased serum levels of cardiac troponins T and I in chronic hemodialysis patients: chronic hemodialysis and new cardiac markers evaluation (CHANCE) study. *Nephrol. Dial. Transplant.* 2001; **16**: 1452–8.
81. Ooi DS, Isotalo PA, Veinot JP. Correlation of antemortem serum creatine kinase, creatine kinase-MB, troponin I, and troponin T with cardiac pathology. *Clin. Chem.* 2000; **46**: 338–44.
82. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation* 2002; **106**: 2941–5.
83. Lowbeer C, Stenvinkel P, Pecoits-Filho R *et al.* Elevated cardiac troponin T in predialysis patients is associated with inflammation and predicts mortality. *J. Intern. Med.* 2003; **253**: 153–60.
84. Mallamaci F, Zoccali C, Parlongo S *et al.* Troponin is related to left ventricular mass and predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am. J. Kidney Dis.* 2002; **40**: 68–75.
85. Chapelle JP, Dubois B, Bovy C, Aldenhoff MC, Gielen J, Rorive G. Comparison of plasma cardiac troponins T and I in chronically hemodialyzed patients in relation to cardiac status and age. *Clin. Chem. Lab. Med.* 2002; **40**: 240–5.
86. Ishii J, Nomura M, Okuma T *et al.* Risk stratification using serum concentrations of cardiac troponin T in patients with end-stage renal disease on chronic maintenance dialysis. *Clin. Chim Acta* 2001; **312**: 69–79.
87. Khan IA, Wattanasuwan N, Mehta NJ *et al.* Prognostic value of serum cardiac troponin I in ambulatory patients with chronic renal failure undergoing long-term hemodialysis: A two-year outcome analysis. *J. Am. Coll. Cardiol.* 2001; **38**: 991–8.
88. Lang K, Schindler S, Forberger C, Stein G, Figulla HR. Cardiac troponins have no prognostic value for acute and chronic cardiac events in asymptomatic patients with end-stage renal failure. *Clin. Nephrol.* 2001; **56**: 44–51.
89. Aviles RJ, Askari AT, Lindahl B *et al.* Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N. Engl. J. Med.* 2002; **346**: 2047–52.