

Use of Cardiac Biomarkers in End-Stage Renal Disease

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ABSTRACT

Mortality among patients with ESRD remains high because of an excessive cardiovascular risk related to a very high incidence of cardiac hypertrophy, cardiomyopathy, heart failure, and coronary artery disease. Identifying serum biomarkers that are useful in profiling cardiovascular risk and enabling stratification of early mortality and cardiovascular risk is an important goal in the treatment of these patients. This review examines current evidence pertaining to the role and utility of two emerging cardiac biomarkers, B-type natriuretic peptide and cardiac troponin T, in patients with ESRD. Together, these data demonstrate how these two cardiac biomarkers may play an adjunctive role to echocardiography in assessing cardiovascular risk and how they may aid in the clinical treatment of these patients.

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Cardiovascular disease is the leading cause of morbidity and mortality in patients with ESRD, accounting for more than 50% of all deaths¹ Early identification of patients who have ESRD and are at a heightened cardiovascular risk may facilitate more aggressive and focused treatment. Additional tools are often required to aid clinical assessment and to increase the ability to early identify “vulnerable” patients who have ESRD with cardiovascular risk.

The term “biomarker” (biologic marker) was first introduced in 1989 as a Medical Subject Heading (MeSH) term,² and the definition was further standardized by the National Institutes of Health working group in 2001 as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”³ For a biomarker to be considered clinically useful, it should be highly sensitive and specific in detecting disease. It should be reproducible and standardized across different clinical laboratories and should be relatively easy to perform so that

the information is readily available to clinicians. In addition, the inherent error in the technical measurement, that is, the coefficient of variation, should be sufficiently low over the entire spectrum of values for the biomarker such that small changes in the biomarker reflect true changes in the clinical condition of the patient. In this article, we review the emerging role of two serum cardiac biomarkers, namely, the B-type natriuretic peptide (BNP) and cardiac troponin T (cTnT), which hold promise for diagnostic and prognostic use in the ESRD population.

BNP and N-Terminal Pro-BNP (NT-pro-BNP)

BNP belong to a family of vasopeptide hormones that have major role in regulating BP and volume through direct effects on the kidney and systemic vasculature and represent a favorable aspect of neurohumoral activation.^{4,5} Three different natriuretic peptides have been characterized, namely, A-type (atrial) natriuretic peptide,^{6,7} B-type (brain)

natriuretic peptide (BNP),⁸ and C-type natriuretic peptide.⁹ BNP is synthesized as an amino acid precursor protein and undergoes intracellular modification to a prohormone (proBNP) that comprises 108 amino acids and is secreted from the left ventricle (LV) in response to increased myocardial wall stress.¹⁰ On release into the circulation, proBNP is cleaved in equal proportions into the biologically active 32-amino acid BNP, which represents the C-terminal fragment, and the biologically inactive 76-amino acid N-terminal fragment (NT-pro-BNP). In the systemic circulation, BNP mediates different biologic effects through interactions with the natriuretic peptide receptor type A, causing intracellular cGMP production, and is eliminated from plasma by binding to the natriuretic peptide receptor type C or through proteolysis by neutral endopeptidases. Although these enzymes are found in the kidney, glomerular filtration has only a minor role in the elimination of BNP. In contrast, NT-pro-BNP is thought to be principally cleared by renal excretion.^{5,11} Both BNP and NT-pro-BNP can be measured by fully automated and commercially available assays (AxSYM BNP, Abbott, Illinois; ADVIA centaur BNP, Bayer, New York; Elecsys NT-pro-BNP, Roche Diagnostics, Indianapolis, IN), which have proven excellent test precision. Reliable “point of

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care” tests are also available for both markers (Triage BNP, Biosite, San Diego, CA; Cardiac Reader NT-pro-BNP, Roche Diagnostics). The half-life of BNP is 20 min, whereas the half-life of NT-pro-BNP is 120 min.⁵ This explains why the circulating NT-pro-BNP level is approximately six-fold higher than that of BNP despite that they are being produced in an equal proportion. BNP and NT-pro-BNP plasma concentrations are expressed as pmol/L or pg/ml. The conversion factor for BNP is 1 pg/ml = 0.289 pmol/L, whereas that for NT-pro-BNP is 1 pg/ml = 0.118 pmol/L. BNP values obtained with different assays are not comparable, and there is no conversion factor for the comparison of BNP and NT-pro-BNP values.

BNP or NT-pro-BNP as a Marker of Increased LV Wall Stress

The main stimulus for BNP or NT-pro-BNP synthesis and secretion is increased LV wall stress.^{12,13} Thus, circulating BNP or NT-pro-BNP levels reflect the degree of LV overload.¹² Numerous studies have reported elevated plasma BNP and NT-pro-BNP levels in patients with heart failure.^{14–19} Plasma BNP levels showed strong correlation with LV filling pressure and increase in proportion to the severity of LV systolic dysfunction and diastolic dysfunction.^{12,20} Furthermore, both plasma BNP and NT-pro-BNP levels increase with increasing severity of heart failure as assessed by the New York Heart Association class and functional capacity in the general population.^{21,22} Population-based studies suggested that plasma levels of BNP and NT-pro-BNP are useful screening tests for heart failure²³ and asymptomatic LV dysfunction.^{22,24} In the Breathing Not Properly (BNP) trial, BNP testing provided the highest test accuracy than any clinical variable in predicting a final diagnosis of heart failure for patients who presented to the emergency department with acute shortness of breath. A BNP cutoff of 100 pg/ml had a sensitivity of 90% for diagnosing heart failure and a negative predictive value of 90%, making it especially useful for excluding heart failure in the general population.²³ In the NT-pro-

BNP Investigation of Dyspnea in the Emergency Department (PRIDE), similar predictive value was observed with NT-pro-BNP in the diagnosis of heart failure. An NT-pro-BNP cutoff value of 300 pg/ml had a negative predictive value of 99% in ruling out heart failure^{19,25}; however, both studies did not include patients with stage 5 chronic kidney disease (CKD; GFR <15 ml/min per 1.73 m² or dialysis dependence). The BNP trial²³ and a study by Mueller *et al.*²⁶ suggested that kidney disease reduces the usefulness of BNP testing in the diagnosis of heart failure and that a higher BNP cutoff level is likely required for excluding heart failure in patients with estimated GFR <60 ml/min per 1.73 m².

Prevalence and Causes of Increased BNP or NT-pro-BNP Levels in ESRD

BNP and NT-pro-BNP are frequently elevated in patients with CKD.^{27–30} In a survey of asymptomatic patients who had CKD and did not yet require dialysis, more than half of the patients were noted to have elevated NT-pro-BNP levels.²⁷ In patients who had ESRD and received hemodialysis (HD) or peritoneal dialysis (PD), BNP and NT-pro-BNP levels were almost invariably increased compared with the normal cutoff values.^{31–36} One of the major contributing factors for the markedly elevated BNP and NT-pro-BNP levels in this population is the very high prevalence of LV structural and functional abnormalities. BNP and NT-pro-BNP levels are strongly associated with LV hypertrophy and systolic dysfunction in patients who have ESRD and are on maintenance HD or PD.^{32–35,37–40} Similar findings were reported in nondialysis CKD populations.^{27,28,30} In the study by Takami *et al.*,²⁹ plasma BNP was a reliable marker of LV overload and had powerful predictive potential for heart failure in nondialysis patients with CKD. BNP or NT-pro-BNP elevation also reflected the presence of myocardial ischemia in asymptomatic patients with CKD.^{27,28} Likewise, higher BNP and NT-pro-BNP levels were observed in both HD and PD patients with underlying coronary artery disease.^{35,41}

A major factor that confounds the in-

terpretation of elevated BNP and NT-pro-BNP and limits the current utility of BNP and NT-pro-BNP in the ESRD population is renal dysfunction. Both BNP and NT-pro-BNP increased with deteriorating renal function.^{27,28,30,42,43} In our previous study,³⁵ NT-pro-BNP strongly correlated with residual renal function, followed by ejection fraction and LV mass in PD patients. In HD patients, a strong inverse association exists between NT-pro-BNP and 24-h urine production.³² Vickery *et al.*³⁰ observed similar findings, namely that GFR has an independent confounding effect on BNP and NT-pro-BNP and that NT-pro-BNP is even more affected by declining kidney function than BNP. Another survey in asymptomatic patients with CKD suggested that GFR is a more important determinant of serum BNP than LV function.⁴² Conversely, Takami *et al.*²⁹ showed that even though BNP correlates with renal function, markers of LV overload, including LV end-diastolic volume and pressure, remain important determinants of plasma BNP level independent of renal function. Taken together, this suggests that although BNP and NT-pro-BNP are useful markers of LV hypertrophy and dysfunction, their levels have to be interpreted in light of the degree of renal dysfunction, and optimal cutoff levels should be defined according to the degree of renal dysfunction.

Given that BNP and NT-pro-BNP are secreted in response to increases in myocardial wall stretch, it is tempting to hypothesize that circulating BNP and NT-pro-BNP levels are useful markers of volume status. Indeed, an earlier but very small study of HD patients suggested an association between plasma BNP and extracellular water estimated by bioimpedance⁴⁴; however, subsequent studies of HD and PD patients that compared the use of BNP and NT-pro-BNP with measurements of extracellular water by bioimpedance or inferior vena cava diameter to assess volume status have so far yielded disappointing results^{40,45} and failed to confirm a consistent link between BNP and NT-pro-BNP with extracellular water. A more recent study demonstrated that NT-pro-BNP levels

showed small decrements with HD and ultrafiltration; however, the decrements had no correlation with volume removal or interdialytic weight gain.³² Another study showed a significant relationship between serum NT-pro-BNP and extracellular water/body weight ratio only in HD patients with LV systolic dysfunction but not in those without systolic dysfunction.⁴⁶ Summarizing the current available evidence, it seems that even though BNP and NT-pro-BNP may increase with volume overload, they have a limited role in assessing actual changes in fluid status or extracellular volume in the dialysis population, given their strong correlations with LV hypertrophy, systolic dysfunction, and residual renal function.

The dialysis procedure itself also influenced BNP and NT-pro-BNP levels. HD may partially clear and reduce BNP and NT-pro-BNP levels as shown in several studies.^{32,47} Whereas BNP is reduced by dialysis with both high- and low-flux dialysis membranes, NT-pro-BNP seems to be significantly reduced only by high-flux membranes.⁴⁸ A rise in plasma BNP levels has also been reported after fistula creation.⁴⁹ Thus, these different confounding factors have to be considered when evaluating the diagnostic and prognostic potentials of BNP and NT-pro-BNP in HD patients.

Diagnostic Utility of BNP and NT-pro-BNP in ESRD

Numerous studies demonstrated a close

association between BNP or NT-pro-BNP level and LV mass and systolic function in the ESRD population^{32–35,37–40}; however, only very few studies examined the diagnostic potential of BNP or NT-pro-BNP for LV hypertrophy and systolic dysfunction. These data are summarized in Table 1.^{32,42,46} The Cardiovascular Risk Extended Evaluation (CREED) study, which includes a combined cohort of HD and PD patients without overt heart failure, represents the most comprehensive study to date that examined this important question.³³ In that study, 79% of the patients displayed LV hypertrophy on echocardiography and 13% had systolic dysfunction. BNP had a sensitivity of 88% and a positive predictive value of 87% in diagnosing LV hypertrophy; however, the specificity was only 50% and the negative predictive value was only 53%. In the same study, BNP had a sensitivity of 94% in detecting LV systolic dysfunction, but the specificity was only 15%. The negative predictive value for LV systolic dysfunction was 96%, but the positive predictive value was only 15%. These data suggest that levels of BNP could be reliably applied in the ESRD population to rule out systolic dysfunction and to detect the presence of LV hypertrophy but have very limited value in excluding LV hypertrophy; however, it is important to caution that this study may have limited applicability in that dialysis patients with a history of heart failure and severe car-

diac dysfunction were specifically excluded from the analysis.

Very few studies have investigated the diagnostic potentials of BNP or NT-pro-BNP for coronary artery disease, hypervolemia, and death in patients with CKD (Table 2). One small study showed that BNP had a specificity of 93% in predicting previous cardiac events in HD patients.⁵⁰ Sommerer *et al.*⁵¹ showed that NT-pro-BNP had a high predictive value for hypervolemia in HD patients as defined by a composite score based on clinical assessment of edema, weight change, respiratory collapse of inferior vena cava, and echocardiographic assessment of pulmonary arterial pressure or septal and posterior wall thickness. Two other studies showed moderate predictability of NT-pro-BNP for death in dialysis patients.⁵² Of note is that the best cutoff values of BNP or NT-pro-BNP derived from these studies were much higher than the cutoff used in the general population.

Prognostic Value of BNP and NT-pro-BNP in ESRD

The ability of BNP and NT-pro-BNP to predict mortality and adverse cardiovascular outcomes in the ESRD population has been examined in numerous studies.^{31,32,34,35,37–39,50–53} A summary of these studies appears in Table 3. All except three studies were performed on HD patients. Irrespective of whether patients with LV systolic dysfunction and previous heart failure were included,

Table 1. Summary of studies that evaluated the diagnostic potentials of BNP or NT-pro-BNP for LV disorders in CKD^a

Author	No. of Patients	AUC for LVH, LVSD	Best Cutoff for LVH and LVSD
Mallamaci <i>et al.</i> , ³³ 2000	212 HD and 34 PD	0.81, 0.78	LVH (BNP): 23.4 pmol/L (sens 62%, spec 88%, PPV 95%, NPV 61%) LVSD (BNP): 38.9 pmol/L (sens 74%, spec 76%, PPV 31%, NPV 95%)
Mark <i>et al.</i> , ⁴² 2006	55 HD	0.664, 0.532	LVH (BNP): ND (sens 68%, spec 67%, PPV 79%, NPV 53%)
David <i>et al.</i> , ⁴⁶ 2007	62 HD	ND, 0.95	LVSD (BNP): ND (sens 94%, spec 21%, PPV 46%, NPV 83%)
deFilippi <i>et al.</i> , ²⁷ 2005	207 with stages 1 through 5 CKD	0.73, ND (based on 99 patients)	LVSD (NT-pro-BNP): 7168 pg/ml (sens 98%, spec 79%)
Khan <i>et al.</i> , ²⁸ 2006	54 with CKD	0.72, ND (NT-pro-BNP) 0.72, ND (BNP)	LVH (NT-pro-BNP): 271 pg/ml (sens 76%, spec 60%) LVH (NT-pro-BNP): 762 pg/ml (sens 63%, spec 67%, PPV 70%, NPV 57%) LVH (BNP): 200 pg/ml (sens 60%, spec 71%, PPV 72%, NPV 59%)

^aAUC, area under the curve; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; ND, not documented; NPV, negative predictive value; PPV, positive predictive value; sens, sensitivity; spec, specificity.

Table 2. Summary of studies that evaluated the predictive value of BNP or NT-pro-BNP for coronary artery disease, hypervolemia, and mortality in CKD

Author	Patients	End Point	AUC	Best Cutoff
Goto <i>et al.</i> , ⁵⁰ 2002	53 HD	Previous cardiac events	0.788	BNP: 390 pg/ml (sens 62%, spec 93%)
deFilippi <i>et al.</i> , ²⁷ 2005	207 with stages 1 through 5 CKD	Previous coronary artery disease	0.69	NT-pro-BNP: 318 pg/ml (sens 78%, spec 56%)
Khan <i>et al.</i> , ²⁸ 2006	54 with CKD	Coronary artery disease	0.80 (NT-pro-BNP) 0.82 (BNP)	NT-pro-BNP: 979 pg/ml (sens 79%, spec 70%, PPV 48%, NPV 90%) BNP: 228 pg/ml (sens 86%, spec 73%, PPV 52%, NPV 94%)
Takami <i>et al.</i> , ²⁹ 2004	103 with CKD	LV overload	0.73	BNP: 150 pg/ml (sens 52%, spec 93%)
Sommerer <i>et al.</i> , ⁵² 2007	134 HD	Hypervolemia	0.815	NT-pro-BNP: 5300 pg/ml (sens 77%, spec 77%)
Madsen <i>et al.</i> , ³² 2007	109 HD	Death	0.718 (pre-HD) 0.729 (post-HD)	NT-pro-BNP: 4079 pg/ml (sens 82%, spec 61%)
Sharma <i>et al.</i> , ⁵³ 2007	50 HD and 29 PD	Death	0.74	NT-pro-BNP: 350 pg/ml (sens 72%, spec 76%)

BNP and NT-pro-BNP levels consistently have powerful prognostic value for mortality and cardiovascular death. The largest study, by Apple *et al.*,³¹ examined the predialysis NT-pro-BNP levels in 399 HD patients and showed that after a median follow-up of 24 mo, tertile analysis of NT-pro-BNP was significantly predictive of mortality, and the area under the receiver operating characteristic curve in relation to mortality was higher with NT-pro-BNP than with cTnT or high sensitivity C-reactive protein (hs-CRP). The results were similar to the CREED study which demonstrated that plasma BNP measured on a nondialysis day for HD patients was predictive of overall and cardiovascular death.³⁸ In our study of 240 chronic PD patients, which represents the largest study in the PD population, patients in the highest quartile of NT-pro-BNP had significantly greater risk of mortality, cardiovascular death and events after a median follow-up of 36 mo.³⁵ A more recent study, by Madsen *et al.*,³² demonstrated both pre- and post-HD NT-pro-BNP levels were predictive of 2-yr mortality. All of these data suggest the prognostic importance of BNP or NT-pro-BNP level at a single time point, irrespective of whether the measurement was taken before dialysis, after dialysis, or midweek between dialysis. In addition, numerous studies showed the prognostic value of BNP and NT-pro-BNP to be independent of

and well beyond that contributed by LV mass and systolic function,^{34,35,38,39} clearly confirming a role of BNP and NT-pro-BNP for additional prognostication of mortality and cardiovascular risk in the ESRD population. Contrary to echocardiographic measurement of LV mass and ejection fraction, which have a large coefficient of variation of >10%, the coefficient of variation for BNP or NT-pro-BNP was much lower; thus, BNP and NT-pro-BNP may be useful in reflecting residual variance not captured by LV mass and function. Furthermore, even though BNP and NT-pro-BNP are not pure markers of volume status, their elevation may partly reflect extracellular volume expansion and may thus explain their additional value for prognostication. Indeed, quartile stratification of NT-pro-BNP levels was useful in identifying long-term PD patients who were at risk for developing circulatory congestion during a 3-yr longitudinal follow-up. Irrespective of whether there was baseline systolic dysfunction or severe LV hypertrophy, the baseline median NT-pro-BNP level was noted to be at least three-fold higher among patients who developed subsequent circulatory congestion compared with those with no subsequent circulatory congestion.³⁵ This finding gives important evidence that serum NT-pro-BNP plays an important, adjunctive role to echocardiography in early identification of PD

patients who are at risk for circulatory congestion.

Prognostic Value of BNP or NT-pro-BNP in Comparison with Other Cardiac Biomarkers

A recent study³⁴ compared the prognostic value of NT-pro-BNP with cTnT in asymptomatic HD patients and demonstrated a stronger association between NT-pro-BNP than cTnT with LV systolic dysfunction. That study also indicated superiority of NT-pro-BNP over cTnT in predicting all-cause mortality and cardiovascular death. In PD patients, NT-pro-BNP also emerges as a more powerful predictor for mortality, cardiovascular death and events, and circulatory congestion compared with hs-CRP.³⁵ Zoccali *et al.*³⁸ found that BNP but not A-type natriuretic peptide was an independent predictor of mortality in the Cox model including LV mass and ejection fraction. All of these data suggest superiority of NT-pro-BNP over other cardiac biomarkers for prognostication and risk stratification in the ESRD population. No studies have compared the prognostic value of BNP and NT-pro-BNP in the ESRD population despite that NT-pro-BNP levels have the theoretical advantage of being more stable with a longer half-life than BNP. A head-to-head comparison⁴³ in nondialysis patients with CKD had a very similar correlation between BNP and NT-pro-BNP with renal dysfunction, and both have

Table 3. Summary of studies that evaluated the prognostic value of BNP and NT-pro-BNP in ESRD^a

Author	Patients	Follow-up	No. of Events	Outcome and HR (95% CI)
Studies using BNP				
Zoccali <i>et al.</i> , ³⁸ 2000	212 HD and 34 PD	26 ± 10 mo	63 deaths, 74 CV events	Death: HR 1.62 (1.20 to 2.17), <i>P</i> = 0.001 for 1-unit increase in log-BNP CV death, T3 versus T1: HR 6.72 (2.44 to 18.54), <i>P</i> = 0.0002
Cataliotti <i>et al.</i> , ³⁷ 2001	112 HD	26 ± 10 mo	16 CV deaths	CV death: HR 2.18 (1.26–3.76), <i>P</i> = 0.005 for 1-unit increase in log-BNP
Naganuma <i>et al.</i> , ³⁹ 2002	164 HD	36 mo	13 cardiac deaths	Cardiac death, Q4 versus Q1: HR 51.9 (6.5 to 416.3)
Goto <i>et al.</i> , ⁵⁰ 2002	53 HD	11.3 ± 0.3 mo	13 CV events	CV events: HR not given (<i>P</i> < 0.0001)
Rutten <i>et al.</i> , ⁵¹ 2006	68 PD	At least 18 mo	10 deaths	Death, BNP > median: HR 8.5 (1.0 to 73.8), <i>P</i> = 0.05
Studies using NT-pro-BNP				
Apple <i>et al.</i> , ³¹ 2004	399 HD	24 mo	101 deaths	Death, upper tertile: NT-pro-BNP >18,692 pg/ml increased mortality
Wang <i>et al.</i> , ³⁵ 2007	240 PD	36 mo	66 deaths, 87 circulatory congestion, 43 CV deaths, 78 CV events	Death, Q4 versus Q1: HR 4.97 (1.35 to 18.28), <i>P</i> = 0.016 Circulatory congestion, Q4 versus Q1: HR 4.25 (1.56 to 11.62), <i>P</i> = 0.005 CV death – Q4 versus Q1: HR, 7.50 (1.36 to 41.39), <i>P</i> = 0.021 CV events, Q4 versus Q1: HR 9.10 (2.46 to 33.67), <i>P</i> = 0.001
Madsen <i>et al.</i> , ³² 2007	190 HD	24 mo	34 deaths	Death, pre-HD log-NT-pro-BNP: HR 1.42 (1.10 to 1.82), <i>P</i> = 0.007 Death, post-HD log-NT-pro-BNP: HR 1.52 (1.18 to 1.96), <i>P</i> = 0.001
Sommerer <i>et al.</i> , ⁵² 2007	134 HD	36 mo	74 deaths and CV events	Death and CV events: HR 3.2 (1.70 to 6.02), <i>P</i> < 0.001
Satyan <i>et al.</i> , ³⁴ 2007	150 HD	24 mo	46 deaths, 26 CV deaths	Death, Q4 versus Q1: HR 4.03 (1.31 to 12.40), <i>P</i> = 0.02 CV death: HR 8.54 (1.04 to 69.98), <i>P</i> = 0.05
Sharma <i>et al.</i> , ⁵³ 2007	50 HD and 29 PD	2.25 ± 0.71 yr	21 deaths	Death: HR 5.57 (3.14 to 8.21), <i>P</i> = 0.02 (univariate analysis)

^aCI, confidence interval; CV, cardiovascular; HR, hazard ratio; Q, quartile; T, tertile.

similar diagnostic accuracy for LV hypertrophy and coronary artery disease (Table 2).²⁸

BNP and NT-pro-BNP in the ESRD Population: A Guide to Therapy?

The powerful prognostic value of BNP and NT-pro-BNP and the relative ease and reproducibility of measuring them raise some important questions: (1) Whether plasma levels of BNP or NT-pro-BNP may serve as a simple and objective clinical guide in treating ESRD patients, (2) whether BNP or NT-pro-BNP targeted therapy may improve the cardiovascular outcomes of patients with ESRD, and (3) whether serial monitoring of BNP and NT-pro-BNP

levels may be useful in identifying patients who have ESRD and are at increased cardiovascular and mortality risk. Troughton *et al.*⁵⁴ found that treatment guided by lowering plasma

NT-pro-BNP levels reduced cardiovascular events and delayed time to first cardiovascular event compared with usual clinically guided treatment of patients with chronic heart failure. A recent study⁵⁵ also observed similar findings that a BNP-guided strategy reduced the risk for heart failure-related death or hospital stay for heart failure compared with standard clinical care. These observations form an important basis for similar investigations of patients with ESRD; however, the complexities in interpreting BNP and NT-pro-

BNP levels in this population have to be fully appreciated. Indeed, a small study showed that metoprolol reduced BNP levels and markedly attenuated LV remodeling in HD patients with dilated left ventricle.⁵⁶

CARDIAC TROPONINS

Troponins T, I, and C are components of the contractile apparatus of muscle. Specific forms of troponin T and I are present in the heart muscle, namely cTnT and troponin I (cTnI), and are released into the circulation with myocardial injury. Thus, measuring circulating cTnT and cTnI level using high-sensitivity assays has become

the gold standard approach in diagnosing acute myocardial necrosis.^{57,58}

Frequency of cTnT and cTnI Elevations in ESRD

Levels of cardiac troponin are frequently elevated in the absence of acute coronary syndrome among patients with varying degrees of kidney disease,^{59–65} and cTnT is more frequently increased compared with cTnI in asymptomatic patients with ESRD.⁶⁴ Using the 99th percentile cutoff of 0.1 $\mu\text{g/L}$, the prevalence of cTnT elevation is reported to range from 30 to 85% in patients with ESRD compared with <5 to 18% in similar patients for cTnI.⁶⁴ A recent survey⁵⁹ in nondialysis patients with ESRD reported that serum cTnT was increased above the 99th percentile in 43% of all patients with ESRD, compared with 18% for cTnI. In addition, the prevalence of increased serum cTnT and cTnI increased with increasing severity of CKD.

The lower incidence of cTnI elevations and lack of expression of cTnI in noncardiac tissue^{66,67} have led to the initial suggestion that cTnI may be a more specific diagnostic and prognostic marker than cTnT in reflecting myocardial injury in patients with renal failure^{68,69}; however, the Global Use of Strategies to Open Occluded Coronary Arteries IV (GUSTO IV) trial, which included 7033 patients with suspected acute coronary syndrome, indicated that an elevated cTnT was strongly predictive of poor short prognosis regardless of creatinine clearance.⁷⁰ In fact, cTnT elevation had even greater prognostic importance among patients with mild to moderate degrees of kidney disease,⁷⁰ clearly confirming the specificity of cTnT as a marker of myocardial injury among patients with kidney disease; however, the pathophysiologic mechanisms causing random increases in troponin T concentrations in patients with kidney disease are not clear.

Prognostic Importance of Elevated Troponin T and Troponin I

There is robust evidence that cTnT is a powerful prognostic marker in the ESRD population.^{61–65,71–75} Apple *et al.*⁶⁴

showed in the largest study of 773 patients with ESRD that an elevated cTnT >99th percentile cutoff was associated with an increased risk for death after 1, 2, and 3 yr of follow-up. The all-cause mortality was at least two to five times higher among patients with cTnT >99th percentile cutoff compared with those with undetectable level. The meta-analysis by Khan *et al.*,⁷⁵ which pooled data from 28 studies (3931 patients) published between 1999 and 2004, concluded that cTnT is a promising risk stratification tool in the ESRD population and may help frame therapeutic decisions. The pooled analysis indicated that an elevated cTnT (>0.1 $\mu\text{g/L}$) is useful in identifying a subgroup of asymptomatic patients with ESRD and poor survival and a higher risk for cardiac death; however, the clinical interpretation of elevated cTnI levels remains inconclusive, largely because of the lack of standardization of assays. Whereas some studies suggested predictive value of cTnI for mortality in patients with ESRD irrespective of the assay method,^{31,64} other studies showed only limited value of cTnI for prognostication in this group of patients.⁷⁶ The Food and Drug Administration recently approved the use of cTnT as a biomarker for mortality risk stratification in ESRD, and the use of cTnT for prognostication is also recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI)⁷⁷; however, it is important to note that this measurement should be obtained just before dialysis, because there is evidence that dialysis may affect cardiac troponin levels. cTnI level may decrease by up to 86% after dialysis; however, cTnT increased after dialysis.⁷⁸

More recently, our study⁷² found that cTnT had significant additional value for prognostication beyond the standard clinical, biochemical, dialysis, and echocardiographic measures, including LV mass and ejection fraction, in chronic PD patients. Furthermore, the predictive value of cTnT for mortality, cardiovascular outcomes, and noncardiovascular death was independent of inflammation, residual renal function, LV hypertrophy and dysfunction, and clearing, confirming the additional value of measuring

cTnT in early identified high-risk patients with ESRD. Our study also demonstrated superiority of cTnT over hs-CRP in predicting long-term mortality and cardiovascular risk in chronic PD patients; however, our results differed from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study, which found limited additional predictive power of cTnT over other clinical risk factors in a combined cohort of HD and PD patients.⁷⁹ The reason for these differences is not clear.

Dialysis patients are at an increased risk for developing circulatory congestion. The presence of preexisting systolic dysfunction predisposed dialysis patients to a greater risk for circulatory congestion.⁸⁰ In a prospective study⁸¹ of 222 chronic PD patients, we demonstrated the usefulness of cTnT measured at a single time point in early identification of chronic PD patients who were at risk for developing circulatory congestion during 3 yr of follow-up. Of importance was the incremental value of cTnT when used in combination with LV mass and ejection fraction in predicting circulatory congestion. Compared with patients with cTnT ≤ 0.06 $\mu\text{g/L}$ (median) and preserved LV systolic function, those with cTnT > 0.06 $\mu\text{g/L}$ but preserved LV systolic function showed a nearly two-fold increase risk for circulatory congestion, whereas those with systolic dysfunction but cTnT ≤ 0.06 $\mu\text{g/L}$ were at no greater risk for circulatory congestion. This gives important evidence of superiority of cTnT over echocardiographic measures in predicting circulatory congestion. Furthermore, the combination of cTnT with LV mass index and ejection fraction enhanced the ability to identify PD patients with highest risk for developing circulatory congestion.

Mechanisms of Elevated Cardiac Troponins in Patients with ESRD

Even though there are data to suggest an association between renal function and cardiac troponins,^{59,72} elevated cTnT in patients with ESRD is unlikely the result of decreased clearance by the failing kidney, given that free and bound cTnT

both are relatively large molecules of 37 and 77 kD, respectively. Improvement in renal function after renal transplantation did not alter the occurrence of elevated serum troponin.⁸² During myocardial necrosis, the elimination half-life and apparent half-life of serum cTnI was not significantly different between patients with normal renal function or ESRD.⁸³

There is emerging evidence that increases in cTnT in asymptomatic patients with ESRD indicates subclinical myocardial necrosis or injury. In the study by Ooi *et al.*,⁸⁴ elevation of cTnT levels was invariably associated with pathologic evidence of old, recent, or healing myocardial necrosis or microinfarction. deFilippi *et al.*⁷⁴ found that the degree of cTnT elevation closely correlated with the extent and severity of angiographic coronary artery disease in long-term HD patients. Our recent analysis observed similar findings of an increased prevalence of symptomatic coronary artery disease with increasing cTnT levels in chronic PD patients.⁸¹ cTnT was also shown to correlate with the degree of coronary artery calcification in asymptomatic HD patients.⁸⁵ In addition, Fahie-Wilson *et al.*⁸⁶ found that circulating cTnT detected in patients with kidney failure was predominantly the free-intact form, as in patients with acute coronary syndrome, lending further evidence that circulating cTnT in patients with ESRD is indeed a marker of cardiac pathology.

Circulating cTnT is also linked to LV hypertrophy in both HD and PD patients.^{72,73,87} In the study by Mallamaci *et al.*,⁷³ cTnT seemed more strongly associated with LV mass than cardiac ischemia or diabetes. cTnT elevation was also associated with systolic dysfunction in PD patients.⁷² In uremic cardiac hypertrophy, myocardial capillary growth did not keep pace with cardiomyocyte hypertrophy.⁸⁸ This resulted in cardiomyocyte/capillary mismatch, increased oxygen diffusion distance, and reduced ischemic tolerance of the heart,⁸⁹ which further increased subclinical ischemia of the myocardium and amplified the leakage of cardiac troponins across the plasma membrane of myocardial cells into the

circulation. Furthermore, increased mechanical stress altered the permeability of cardiomyocyte plasma membranes,⁹⁰ predisposing to leakage of troponins. Thus, the link between elevated cTnT and LV hypertrophy may partly reflect leakage of this protein from hypertrophic cardiomyocytes and may signify the presence of microvascular heart disease that occurs in uremia. Using late gadolinium enhancement of cardiac magnetic resonance imaging to detect occult myocardial infarction, a recent small study found that although myocardial infarction was absent in the setting of very low cTnT, high cTnT cannot be explained solely by previous subclinical myocardial necrosis or LV hypertrophy.⁹¹ This leads to speculation that additional myocardial pathologies such as myocardial fibrosis may contribute to increased cTnT in patients with ESRD.

As shown in the general population, even minimally increased cTnT represents subclinical myocardial injury.⁹² This is in keeping with our study showing an increased prevalence of diabetes and coronary artery disease and a greater risk for mortality and adverse cardiovascular events even among patients with minimally increased cTnT between 0.01 and 0.1 $\mu\text{g/L}$ compared with patients with undetectable cTnT.⁷² Thus, instead of using an absolute cutoff of cTnT to define risk, these data suggest that any degree of elevation in cTnT signifies the presence of subclinical myocardial injury and indicates an increased cardiovascular risk profile. The greater the elevation of cTnT, the more severe is myocardial injury and higher is the risk for mortality and cardiovascular events.

Utility of Cardiac Troponins in Patients with ESRD

An important clinical question is how to distinguish between elevations of cardiac troponins as a result of acute coronary syndrome and those as a result of chronic myocardial injury. One approach is to obtain baseline values. This allows not only for prognostication but also for an evaluation of changes over time. An increase in cardiac troponins above baseline levels may suggest an acute problem

or chronic changes. Absence of an acute process that is known to cause elevations in cardiac troponins would be more indicative of chronic changes. In the recently released National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines, measurement of cardiac troponins is recommended for the evaluation of acute coronary syndrome in patients with ESRD (level of evidence A). For patients who have ESRD and present with possible acute coronary syndrome, a dynamic change in cardiac troponins of $\geq 20\%$ after presentation should be used to define acute coronary syndrome (level of evidence B). Baseline cardiac troponins can aid in defining mortality and cardiovascular risk for patients with ESRD and also provide baseline levels for subsequent comparison (level of evidence B). Furthermore, cTnT is more useful on a routine basis than cTnI in patients with ESRD because the frequency of elevated cTnI associated with increased risk for adverse events is markedly lower than that for cTnT.⁹³ The mechanism for this difference is not clear but may relate to the differential release, degradation, and clearance of cardiac troponins in the circulation.

CONCLUSIONS

There is accumulating evidence that BNP and NT-pro-BNP are useful serum cardiac biomarkers for prognostication and cardiovascular risk stratification in the ESRD population. Although they do not replace echocardiography, they may evolve to play an important, complementary role to echocardiography in evaluating the cardiovascular risk profile of ESRD patients; however, it remains a very challenging task to define the best cutoff level at each stage of CKD including those on HD and PD, for whom further assessment of LV function and cardiovascular risk is warranted. In addition, elevated cTnT reflects myocardial injury and is also a powerful cardiac biomarker for mortality and cardiovascular risk stratification in the ESRD population. A dynamic change in cTnT is

useful in diagnosing acute coronary syndrome in patients with ESRD.

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DISCLOSURES

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REFERENCES

- US Renal Data System: USRDS 1999 Annual Data Report, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, 1999, pp 1–37
- Vasan RS: Biomarkers of cardiovascular disease: Molecular basis and practical considerations. *Circulation* 113: 2335–2362, 2006
- Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther* 69: 89–95, 2001
- Baughman KL: B-type natriuretic peptide: A window to the heart. *N Engl J Med* 347: 158–159, 2002
- de Lemos JA, McGuire DK, Drazner MH: B-type natriuretic peptide in cardiovascular disease. *Lancet* 362: 316–322, 2003
- Kangawa K, Matsuo H: Purification and complete amino acid sequence of alpha-human atrial natriuretic polypeptide (alpha-hANP). *Biochem Biophys Res Commun* 118: 131–139, 1984
- de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H: A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* 28: 89–94, 1981
- Sudoh T, Kangawa K, Minamino N, Matsuo H: A new natriuretic peptide in porcine brain. *Nature* 332: 78–81, 1988
- Sudoh T, Minamino N, Kangawa K, Matsuo H: C-type natriuretic peptide (CNP): A new member of natriuretic peptide family identified in porcine brain. *Biochem Biophys Res Commun* 168: 863–870, 1990
- Kinnunen P, Vuolteenaho O, Ruskoaho H: Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: Effect of stretching. *Endocrinology* 132: 1961–1970, 1993
- Weber M, Hamm C: Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* 92: 843–849, 2006
- Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, Ogawa H, Okumura K, Mukoyama M, Nakao K: Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 90: 195–203, 1994
- Hosoda K, Nakao K, Mukoyama M, Saito Y, Jougasaki M, Shirakami G, Suga SI, Ogawa Y, Yasue H, Imura H: Expression of brain natriuretic peptide gene in human heart: Production in the ventricle. *Hypertension* 17: 1152–1155, 1991
- Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amimov R, Lenert L, Clopton P, Alberto J, Hlavin P, Maisel AS: Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol* 37: 379–385, 2001
- Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC: Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 350: 1349–1353, 1997
- Davis M, Espiner EA, Yandle T, Richards G, Town I, Neill A, Drennan C, Richards A, Turner J, Billings J: Plasma brain natriuretic peptide in assessment of acute dyspnoea. *Lancet* 343: 440–444, 1994
- Masson S, Vago T, Baldi G, Salio M, De AN, Nicolis E, Maggioni AP, Latini R, Norbiato G, Bevilacqua M: Comparative measurement of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in ambulatory patients with heart failure. *Clin Chem Lab Med* 40: 761–763, 2002
- Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE: Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: Cohort study in representative and high risk community populations. *BMJ* 324: 1498, 2002
- Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, Tung R, Cameron R, Nagurny JT, Chae CU, Lloyd-Jones DM, Brown DF, Foran-Melanson S, Sluss PM, Lee-Lewandrowski E, Lewandrowski KB: The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 95: 948–954, 2005
- Yamamoto K, Burnett J, Jougasaki M, Nishimura RA, Bailey KR, Saito Y, Nakao K, Redfield MM: Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. *Hypertension* 28: 988–994, 1996
- Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA: Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 347: 161–167, 2002
- Hunt PJ, Richards AM, Nicholls MG, Yandle TG, Doughty RN, Espiner EA: Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-PROBNP): A new marker of cardiac impairment. *Clin Endocrinol (Oxf)* 47: 287–296, 1997
- McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, Duc P, Westheim A, Omland T, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS: B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: Analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* 106: 416–422, 2002
- McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, Tunstall-Pedoe H, McMurray JJ, Dargie HJ: Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 351: 9–13, 1998
- Anwaruddin S, Lloyd-Jones DM, Baggish A, Chen A, Krauser D, Tung R, Chae C, Januzzi JL Jr: Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: Results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. *J Am Coll Cardiol* 47: 91–97, 2006
- Mueller C, Laule-Kilian K, Scholer A, Nusbaumer C, Zeller T, Staub D, Perruchoud AP: B-type natriuretic peptide for acute dyspnea in patients with kidney disease: Insights from a randomized comparison. *Kidney Int* 67: 278–284, 2005
- deFilippi CR, Fink JC, Nass CM, Chen H, Christenson R: N-terminal pro-B-type natriuretic peptide for predicting coronary disease and left ventricular hypertrophy in asymptomatic CKD not requiring dialysis. *Am J Kidney Dis* 46: 35–44, 2005
- Khan IA, Fink J, Nass C, Chen H, Christenson R, deFilippi CR: N-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide for identifying coronary artery disease and left ventricular hypertrophy in ambulatory chronic kidney disease patients. *Am J Cardiol* 97: 1530–1534, 2006
- Takami Y, Horio T, Iwashima Y, Takiuchi S, Kamide K, Yoshihara F, Nakamura S, Nakahama H, Inenaga T, Kangawa K, Kawano Y: Diagnostic and prognostic value of plasma brain natriuretic peptide in non-dialysis-dependent CRF. *Am J Kidney Dis* 44: 420–428, 2004
- Vickery S, Price CP, John RI, Abbas NA, Webb MC, Kempson ME, Lamb EJ: B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: Relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis* 46: 610–620, 2005
- Apple FS, Murakami MM, Pearce LA, Herzog

- CA: Multi-biomarker risk stratification of N-terminal pro-B-type natriuretic peptide, high-sensitivity C-reactive protein, and cardiac troponin T and I in end-stage renal disease for all-cause death. *Clin Chem* 50: 2279–2285, 2004
32. Madsen LH, Ladefoged S, Corell P, Schou M, Hildebrandt PR, Atar D: N-terminal pro brain natriuretic peptide predicts mortality in patients with end-stage renal disease in hemodialysis. *Kidney Int* 71: 548–554, 2007
 33. Mallamaci F, Zoccali C, Tripepi G, Benedetto FA, Parlongo S, Cataliotti A, Cutrupi S, Giaccone G, Bellanuova I, Stancanelli B, Malatino LS: Diagnostic potential of cardiac natriuretic peptides in dialysis patients. *Kidney Int* 59: 1559–1566, 2001
 34. Satyan S, Light RP, Agarwal R: Relationships of N-terminal pro-B-natriuretic peptide and cardiac troponin T to left ventricular mass and function and mortality in asymptomatic hemodialysis patients. *Am J Kidney Dis* 50: 1009–1019, 2007
 35. Wang AY, Lam CW, Yu CM, Wang M, Chan IH, Zhang Y, Lui SF, Sanderson JE: N-terminal pro-brain natriuretic peptide: an independent risk predictor of cardiovascular congestion, mortality, and adverse cardiovascular outcomes in chronic peritoneal dialysis patients. *J Am Soc Nephrol* 18: 321–330, 2007
 36. Sommerer C, Giannitsis E, Schwenger V, Zeier M: Cardiac biomarkers in haemodialysis patients: The prognostic value of amino-terminal pro-B-type natriuretic peptide and cardiac troponin T. *Nephron Clin Pract* 107: c77–c81, 2007
 37. Cataliotti A, Malatino LS, Jougasaki M, Zoccali C, Castellino P, Giaccone G, Bellanuova I, Tripepi R, Seminara G, Parlongo S, Stancanelli B, Bonanno G, Fatuzzo P, Rapisarda F, Belluardo P, Signorelli SS, Heublein DM, Lainchbury JG, Leskinen HK, Bailey KR, Redfield MM, Burnett JC Jr: Circulating natriuretic peptide concentrations in patients with end-stage renal disease: Role of brain natriuretic peptide as a biomarker for ventricular remodeling. *Mayo Clin Proc* 76:1111–1119, 2001
 38. Zoccali C, Mallamaci F, Benedetto FA, Tripepi G, Parlongo S, Cataliotti A, Cutrupi S, Giaccone G, Bellanuova I, Cottini E, Malatino LS: Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. *J Am Soc Nephrol* 12: 1508–1515, 2001
 39. Naganuma T, Sugimura K, Wada S, Yasumoto R, Sugimura T, Masuda C, Uchida J, Nakatani T: The prognostic role of brain natriuretic peptides in hemodialysis patients. *Am J Nephrol* 22: 437–444, 2002
 40. Lee JA, Kim DH, Yoo SJ, Oh DJ, Yu SH, Kang ET: Association between serum n-terminal pro-brain natriuretic peptide concentration and left ventricular dysfunction and extracellular water in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 26: 360–365, 2006
 41. Nishikimi T, Futoo Y, Tamano K, Takahashi M, Suzuki T, Minami J, Honda T, Uetake S, Asakawa H, Kobayashi N, Horinaka S, Ishimitsu T, Matsuoka H: Plasma brain natriuretic peptide levels in chronic hemodialysis patients: Influence of coronary artery disease. *Am J Kidney Dis* 37: 1201–1208, 2001
 42. Mark PB, Stewart GA, Gansevoort RT, Petrie CJ, McDonagh TA, Dargie HJ, Rodger RS, Jardine AG: Diagnostic potential of circulating natriuretic peptides in chronic kidney disease. *Nephrol Dial Transplant* 21: 402–410, 2006
 43. Luchner A, Hengstenberg C, Lowel H, Riegger GA, Schunkert H, Holmer S: Effect of compensated renal dysfunction on approved heart failure markers: Direct comparison of brain natriuretic peptide (BNP) and N-terminal pro-BNP. *Hypertension* 46: 118–123, 2005
 44. Fagugli RM, Palumbo B, Ricciardi D, Pasini P, Santirosi P, Vecchi L, Pastucci F, Palumbo R: Association between brain natriuretic peptide and extracellular water in hemodialysis patients. *Nephron Clin Pract* 95: c60–c66, 2003
 45. Lee SW, Song JH, Kim GA, Lim HJ, Kim MJ: Plasma brain natriuretic peptide concentration on assessment of hydration status in hemodialysis patient. *Am J Kidney Dis* 41: 1257–1266, 2003
 46. David S, Kumpers P, Seidler V, Biertz F, Haller H, Fliser D: Diagnostic value of N-terminal pro-B-type natriuretic peptide (NT-ProBNP) for left ventricular dysfunction in patients with chronic kidney disease stage 5 on haemodialysis. *Nephrol Dial Transplant* December 18, 2007 [epub ahead of print]
 47. Racek J, Kralova H, Trefil L, Rajdl D, Eiselt J: Brain natriuretic peptide and N-terminal proBNP in chronic haemodialysis patients. *Nephron Clin Pract* 103: c162–c172, 2006
 48. Wahl HG, Graf S, Renz H, Fassbinder W: Elimination of the cardiac natriuretic peptides B-type natriuretic peptide (BNP) and N-terminal proBNP by hemodialysis. *Clin Chem* 50: 1071–1074, 2004
 49. Iwashima Y, Horio T, Takami Y, Inenaga T, Nishikimi T, Takishita S, Kawano Y: Effects of the creation of arteriovenous fistula for hemodialysis on cardiac function and natriuretic peptide levels in CRF. *Am J Kidney Dis* 40: 974–982, 2002
 50. Goto T, Takase H, Toriyama T, Sugiura T, Kurita Y, Tsuru N, Masuda H, Hayashi K, Ueda R, Dohi Y: Increased circulating levels of natriuretic peptides predict future cardiac event in patients with chronic hemodialysis. *Nephron* 92: 610–615, 2002
 51. Sommerer C, Beimler J, Schwenger V, Heckele N, Katus HA, Giannitsis E, Zeier M: Cardiac biomarkers and survival in haemodialysis patients. *Eur J Clin Invest* 37: 350–356, 2007
 52. Sharma R, Gaze DC, Pellerin D, Mehta RL, Gregson H, Streater CP, Collinson PO, Brecker SJ: Raised plasma N-terminal pro-B-type natriuretic peptide concentrations predict mortality and cardiac disease in end-stage renal disease. *Heart* 92: 1518–1519, 2006
 53. Rutten JH, Korevaar JC, Boeschoten EW, Dekker FW, Krediet RT, Boomsma F, van den Meiracker AH: B-type natriuretic peptide and amino-terminal atrial natriuretic peptide predict survival in peritoneal dialysis. *Perit Dial Int* 26: 598–602, 2006
 54. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM: Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 355: 1126–1130, 2000
 55. Jourdain P, Jondeau G, Funck F, Gueffet P, Le HA, Donal E, Aupetit JF, Aumont MC, Galinier M, Eicher JC, Cohen-Solal A, Juilliere Y: Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: The STARS-BNP Multicenter Study. *J Am Coll Cardiol* 49: 1733–1739, 2007
 56. Hara Y, Hamada M, Shigematsu Y, Murakami B, Hiwada K: Beneficial effect of beta-adrenergic blockade on left ventricular function in haemodialysis patients. *Clin Sci (Lond)* 101: 219–225, 2001
 57. Alpert JS, Thygesen K, Antman E, Bassand JP: 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* 36: 959–969, 2000
 58. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE III, Steward DE, Theroux P, Alpert JS, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO, Smith SC Jr: ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol* 36: 970–1062, 2000
 59. Abbas NA, John RI, Webb MC, Kempson ME, Potter AN, Price CP, Vickery S, Lamb EJ: Cardiac troponins and renal function in non-dialysis patients with chronic kidney disease. *Clin Chem* 51: 2059–2066, 2005
 60. Ooi DS, House AA: Cardiac troponin T in hemodialyzed patients. *Clin Chem* 44: 1410–1416, 1998
 61. Dierkes J, Domrose U, Westphal S, Ambrosch A, Bosselmann HP, Neumann KH, Luley C: Cardiac troponin T predicts mortality in patients with end-stage renal disease. *Circulation* 102: 1964–1969, 2000

62. Deegan PB, Lafferty ME, Blumsohn A, Henderson IS, McGregor E: Prognostic value of troponin T in hemodialysis patients is independent of comorbidity. *Kidney Int* 60: 2399–2405, 2001
63. Conway B, McLaughlin M, Sharpe P, Harty J: Use of cardiac troponin T in diagnosis and prognosis of cardiac events in patients on chronic haemodialysis. *Nephrol Dial Transplant* 20: 2759–2764, 2005
64. 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* 106: 2941–2945, 2002
65. Ishii J, Nomura M, Okuma T, Minagawa T, Naruse H, Mori Y, Ishikawa T, Kurokawa H, Hirano T, Kondo T, Nagamura Y, Ezaki K, Hishida H: Risk stratification using serum concentrations of cardiac troponin T in patients with end-stage renal disease on chronic maintenance dialysis. *Clin Chim Acta* 312: 69–79, 2001
66. McLaurin MD, Apple FS, Voss EM, Herzog CA, Sharkey SW: 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* 43: 976–982, 1997
67. 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* 41: 1710–1715, 1995
68. Apple FS, Sharkey SW, Hoefl P, Skeate R, Voss E, Dahlmeier BA, Preese LM: Prognostic value of serum cardiac troponin I and T in chronic dialysis patients: A 1-year outcomes analysis. *Am J Kidney Dis* 29: 399–403, 1997
69. Martin GS, Becker BN, Schulman G: Cardiac troponin-I accurately predicts myocardial injury in renal failure. *Nephrol Dial Transplant* 13: 1709–1712, 1998
70. Aviles RJ, Askari AT, Lindahl B, Wallentin L, Jia G, Ohman EM, Mahaffey KW, Newby LK, Califf RM, Simoons ML, Topol EJ, Berger P, Lauer MS: Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med* 346: 2047–2052, 2002
71. Ooi DS, Veinot JP, Wells GA, House AA: Increased mortality in hemodialysis patients with elevated serum troponin T: A one-year outcome study. *Clin Biochem* 32: 647–652, 1999
72. Wang AY, Lam CW, Wang M, Chan IH, Goggins WB, Yu CM, Lui SF, Sanderson JE: Prognostic value of cardiac troponin T is independent of inflammation, residual renal function, and cardiac hypertrophy and dysfunction in peritoneal dialysis patients. *Clin Chem* 53: 882–889, 2007
73. Mallamaci F, Zoccali C, Parlongo S, Tripepi G, Benedetto FA, Cutrupi S, Bonanno G, Fatuzzo P, Rapisarda F, Seminara G, Stancanelli B, Bellanuova I, Cataliotti A, Malatino LS: Troponin is related to left ventricular mass and predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 40: 68–75, 2002
74. deFilippi C, Wasserman S, Rosanio S, Tiblier E, Sperger H, Tocchi M, Christenson R, Uretsky B, Smiley M, Gold J, Muniz H, Badalamenti J, Herzog C, Henrich W: Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA* 290: 353–359, 2003
75. Khan NA, Hemmelgarn BR, Tonelli M, Thompson CR, Levin A: Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: A meta-analysis. *Circulation* 112: 3088–3096, 2005
76. Khan IA, Wattanasuwan N, Mehta NJ, Tun A, Singh N, Singh HK, Vasavada BC, Sacchi TJ: 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* 38: 991–998, 2001
77. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 45: S1–S153, 2005
78. Wayand D, Baum H, Schatzle G, Scharf J, Neumeier D: Cardiac troponin T and I in end-stage renal failure. *Clin Chem* 46: 1345–1350, 2000
79. Havekes B, van Manen JG, Krediet RT, Boeschoten EW, Vandenbroucke JP, Dekker FW: Serum troponin T concentration as a predictor of mortality in hemodialysis and peritoneal dialysis patients. *Am J Kidney Dis* 47: 823–829, 2006
80. Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS: Congestive heart failure in dialysis patients: Prevalence, incidence, prognosis and risk factors. *Kidney Int* 47: 884–890, 1995
81. Wang AY, Lam CW, Yu CM, Wang M, Chan IH, Lui SF, Sanderson JE: Troponin T, left ventricular mass, and function are excellent predictors of cardiovascular congestion in peritoneal dialysis. *Kidney Int* 70: 444–452, 2006
82. Fredericks S, Chang R, Gregson H, Bewick M, Collinson PO, Gaze D, Carter ND, Holt DW: Circulating cardiac troponin-T in patients before and after renal transplantation. *Clin Chim Acta* 310: 199–203, 2001
83. Ellis K, Dreisbach AW, Lertora JL: Plasma elimination of cardiac troponin I in end-stage renal disease. *South Med J* 94: 993–996, 2001
84. 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* 46: 338–344, 2000
85. Jung HH, Ma KR, Han H: Elevated concentrations of cardiac troponins are associated with severe coronary artery calcification in asymptomatic haemodialysis patients. *Nephrol Dial Transplant* 19: 3117–3123, 2004
86. Fahie-Wilson MN, Carmichael DJ, Delaney MP, Stevens PE, Hall EM, Lamb EJ: Cardiac troponin T circulates in the free, intact form in patients with kidney failure. *Clin Chem* 52: 414–420, 2006
87. Iliou MC, Fumeron C, Benoit MO, Tuppin P, Courvoisier CL, Calonge VM, Moatti N, Buisson C, Jacquot C: Factors associated with increased serum levels of cardiac troponins T and I in chronic haemodialysis patients: Chronic Haemodialysis And New Cardiac Markers Evaluation (CHANCE) study. *Nephrol Dial Transplant* 16: 1452–1458, 2001
88. Amann K, Breitbach M, Ritz E, Mall G: Myocyte/capillary mismatch in the heart of uremic patients. *J Am Soc Nephrol* 9: 1018–1022, 1998
89. Amann K, Ritz E: Cardiac disease in chronic uremia: Pathophysiology. *Adv Ren Replace Ther* 4: 212–224, 1997
90. Kaye D, Pimental D, Prasad S, Maki T, Berger HJ, McNeil PL, Smith TW, Kelly RA: Role of transiently altered sarcolemmal membrane permeability and basic fibroblast growth factor release in the hypertrophic response of adult rat ventricular myocytes to increased mechanical activity in vitro. *J Clin Invest* 97: 281–291, 1996
91. deFilippi CR, Thorn EM, Aggarwal M, Joy A, Christenson RH, Duh SH, Jeudy J, Beache G: Frequency and cause of cardiac troponin T elevation in chronic hemodialysis patients from study of cardiovascular magnetic resonance. *Am J Cardiol* 100: 885–889, 2007
92. Wallace TW, Abdullah SM, Drazner MH, Das SR, Khara A, McGuire DK, Wians F, Sabatine MS, Morrow DA, de Lemos JA: Prevalence and determinants of troponin T elevation in the general population. *Circulation* 113: 1958–1965, 2006
93. Wu AH, Jaffe AS, Apple FS, Jesse RL, Francis GL, Morrow DA, Newby LK, Ravkilde J, Tang WH, Christenson RH, Cannon CP: National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Use of cardiac troponin and B-type natriuretic peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute coronary syndromes and heart failure. *Clin Chem* October 22, 2007 [epub ahead of print]