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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 deaths[1] 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 failure[23] 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 m^2 or dialysis dependence). The BNP trial[23] 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 m^2.

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 interpretation 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 bioimpedance[44]; 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 cardiac 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 *et al.*,[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 *et al.*,[42] 2006	55 HD	0.664, 0.532	LVH (BNP): ND (sens 68%, spec 67%, PPV 79%, NPV 53%)
David *et al.*,[46] 2007	62 HD	ND, 0.95	LVSD (BNP): ND (sens 94%, spec 21%, PPV 46%, NPV 83%)
deFilippi *et al.*,[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%) LVH (NT-pro-BNP): 271 pg/ml (sens 76%, spec 60%)
Khan *et al.*,[28] 2006	54 with CKD	0.72, ND (NT-pro-BNP)	LVH (NT-pro-BNP): 762 pg/ml (sens 63%, spec 67%, PPV 70%, NPV 57%)
		0.72, ND (BNP)	LVH (BNP): 200 pg/ml (sens 60%, spec 71%, PPV 72%, NPV 59%)

[a]AUC; 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 *et al.*,[50] 2002	53 HD	Previous cardiac events	0.788	BNP: 390 pg/ml (sens 62%, spec 93%)
deFilippi *et al.*,[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 *et al.*,[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 *et al.*,[29] 2004	103 with CKD	LV overload	0.73	BNP: 150 pg/ml (sens 52%, spec 93%)
Sommerer *et al.*,[52] 2007	134 HD	Hypervolemia	0.815	NT-pro-BNP: 5300 pg/ml (sens 77%, spec 77%)
Madsen *et al.*,[32] 2007	109 HD	Death	0.718 (pre-HD) 0.729 (post-HD)	NT-pro-BNP: 4079 pg/ml (sens 82%, spec 61%)
Sharma *et al.*,[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 study[34] 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 comparison[43] 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 *et al.*,[38] 2000	212 HD and 34 PD	26 ± 10 mo	63 deaths, 74 CV events	Death: HR 1.62 (1.20 to 2.17), $P = 0.001$ for 1-unit increase in log-BNP CV death, T3 *versus* T1: HR 6.72 (2.44 to 18.54), $P = 0.0002$
Cataliotti *et al.*,[37] 2001	112 HD	26 ± 10 mo	16 CV deaths	CV death: HR 2.18 (1.26–3.76), $P = 0.005$ for 1-unit increase in log-BNP
Naganuma *et al.*,[39] 2002	164 HD	36 mo	13 cardiac deaths	Cardiac death, Q4 *versus* Q1: HR 51.9 (6.5 to 416.3)
Goto *et al.*,[50] 2002	53 HD	11.3 ± 0.3 mo	13 CV events	CV events: HR not given ($P < 0.0001$)
Rutten *et al.*,[51] 2006	68 PD	At least 18 mo	10 deaths	Death, BNP > median: HR 8.5 (1.0 to 73.8), $P = 0.05$
Studies using NT-pro-BNP				
Apple *et al.*,[31] 2004	399 HD	24 mo	101 deaths	Death, upper tertile: NT-pro-BNP >18,692 pg/ml increased mortality
Wang *et al.*,[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), $P = 0.016$ Circulatory congestion, Q4 *versus* Q1: HR 4.25 (1.56 to 11.62), $P = 0.005$ CV death – Q4 *versus* Q1: HR, 7.50 (1.36 to 41.39), $P = 0.021$ CV events, Q4 *versus* Q1: HR 9.10 (2.46 to 33.67), $P = 0.001$
Madsen *et al.*,[32] 2007	190 HD	24 mo	34 deaths	Death, pre-HD log-NT-pro-BNP: HR 1.42 (1.10 to 1.82), $P = 0.007$ Death, post-HD log-NT-pro-BNP: HR 1.52 (1.18 to 1.96), $P = 0.001$
Sommerer *et al.*,[52] 2007	134 HD	36 mo	74 deaths and CV events	Death and CV events: HR 3.2 (1.70 to 6.02), $P < 0.001$
Satyan *et al.*,[34] 2007	150 HD	24 mo	46 deaths, 26 CV deaths	Death, Q4 *versus* Q1: HR 4.03 (1.31 to 12.40), $P = 0.02$ CV death: HR 8.54 (1.04 to 69.98), $P = 0.05$
Sharma *et al.*,[53] 2007	50 HD and 29 PD	2.25 ± 0.71 yr	21 deaths	Death: HR 5.57 (3.14 to 8.21), $P = 0.02$ (univariate analysis)

[a]CI, 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 study[55] 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 μg/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 survey[59] 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 μg/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 study[72] 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 study[81] 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 $\leq$ 0.06 μg/L (median) and preserved LV systolic function, those with cTnT > 0.06 μg/L but preserved LV systolic function showed a nearly twofold increase risk for circulatory congestion, whereas those with systolic dysfunction but cTnT $\leq$ 0.06 μg/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 μg/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

None.

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