

# Biomarkers in predicting mortality and treatment in hemodialysis patients

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## Abstract

Circulating natriuretic peptides are useful biomarkers of left ventricular dysfunction and heart failure in the general population. Cardiac troponin T (cTnT) is also considered a sensitive marker of myocardial injury. However, the fact that levels of circulating natriuretic peptides and cTnT are almost invariably increased in end-stage renal disease patients has been considered a major limitation for their use as diagnostic or prognostic tools in this population. We provide an updated review on the role of natriuretic peptides and cTnT as biomarkers in predicting outcome and treatment in the hemodialysis population.

## Introduction and context

Cardiovascular disease is the leading cause of mortality in patients with end-stage renal disease (ESRD) and is partly attributed to the very high prevalence of left ventricular (LV) abnormalities, including LV hypertrophy, systolic dysfunction and congestive heart failure. The Kidney Disease Outcome Quality Initiative (KDOQI) guidelines have, therefore, made the recommendation that echocardiography be performed at initiation of dialysis in all ESRD patients and every 3 years thereafter [1]. However, echocardiography services are very often stretched in hospitals and not routinely performed in most dialysis centers. Therefore, circulating biomarkers that identify patients with subclinical heart disease or diseased myocardium may have a potentially important clinical value in allowing early detection, intervention and possibly ongoing surveillance of high-risk patients. In recent years, the natriuretic peptides have emerged as promising cardiac biomarkers in this aspect.

The B-type, or brain natriuretic peptide (BNP) is a 32 amino acid peptide hormone predominantly released from the ventricles in response to LV volume expansion and pressure overload [2–4] and has a circulating half-life of 23 minutes. N-terminal pro-BNP (NT-pro-BNP) is

a 76 amino acid peptide hormone also cleaved from the prohormone; it is biologically inactive but has a much longer half-life (120 minutes). BNP levels are well known to correlate with LV filling pressures and are elevated in patients with LV dysfunction [2,5]. Both BNP and NT-pro-BNP levels increased in proportion to the severity of heart failure as assessed using the New York Heart Association classification in the general population [6,7]. In patients without chronic kidney disease (CKD), BNP and NT-pro-BNP testing are found to be most useful in ruling out the diagnosis of heart failure in those presenting with dyspnoea [8–11]. The value of BNP or NT-pro-BNP testing in predicting prognosis has also been established in the general population [12].

In stage 5 CKD patients receiving hemodialysis or peritoneal dialysis, BNP and NT-pro-BNP are almost invariably increased compared to normal cutoffs [13–19]. These elevations were partly attributed to decreased renal clearance, chronic volume overload as well as to the very high prevalence of cardiac abnormalities [13–19]. NT-pro-BNP has been shown to be inversely related to residual renal function in both hemodialysis and peritoneal dialysis patients [15,16]. A study in the non-ESRD population also confirmed renal dysfunction as a

potential cause of markedly elevated BNP and NT-pro-BNP in the absence of LV systolic dysfunction [20]. Thus, in dialysis patients, BNP and NT-pro-BNP levels have to be interpreted in light of the presence or absence of residual renal function. BNP and NT-pro-BNP have been shown to be strongly associated with LV hypertrophy and dilation, and systolic dysfunction, in both hemodialysis and peritoneal dialysis patients [14–19]. NT-pro-BNP was also associated with coronary artery disease in non-dialysis CKD patients [21].

On the other hand, cardiac troponin T (cTnT) is a sensitive marker of myocardial injury and is the current gold standard test for diagnosis of acute myocardial necrosis in the general population. However, levels of cTnT are frequently elevated in the absence of acute coronary syndrome among patients with varying degrees of kidney disease [22–28]. Using the 99<sup>th</sup> percentile cutoff of 0.1 µg/L, the prevalence of cTnT elevation was reported to range from 30 to 85% in ESRD patients [22–27]. This led to the initial suggestion that cTnT may have limited diagnostic or prognostic value in patients with CKD. In the GUSTO IV (Global Use of Strategies to Open Occluded Coronary Arteries IV) trial, elevated cTnT was strongly predictive of poor short-term prognosis irrespective of creatinine clearance in patients with suspected acute coronary syndrome [29]. Notably, cTnT elevation had even greater prognostic importance among patients with mild to moderate degrees of kidney disease, clearly confirming the specificity of cTnT as a marker of myocardial injury among patients with kidney disease.

There is robust evidence that cTnT is a powerful prognostic marker in ESRD patients. One of the earliest and largest studies, by Apple *et al.* [26], showed that an elevated cTnT > 99<sup>th</sup> percentile cutoff was predictive of both short-term and long-term mortality in hemodialysis patients. Numerous other studies have demonstrated similar prognostic importance of cTnT in hemodialysis patients [22–25,27].

### Recent advances

#### **Diagnostic value of BNP or NT-pro-BNP for LV systolic dysfunction in hemodialysis patients**

In a recent small study, a serum NT-pro-BNP cutoff  $\geq 7200$  ng/L was suggested to be useful in diagnosing LV systolic dysfunction in hemodialysis patients, regardless of the patients' fluid status, with a specificity of 90% and a sensitivity of 79%. Further reducing the cutoff to approximately 5000 ng/L increased the sensitivity in diagnosing LV systolic dysfunction to >90% but reduced the specificity to 80% [30]. This observation was very similar to the earlier Cardiovascular Risk Evaluation Extension (CREED) study, suggesting the potential value

of BNP testing in ruling out systolic dysfunction in the dialysis population [14]. However, the best cutoff of BNP or NT-pro-BNP in diagnosing or ruling out systolic dysfunction will need stratification according to residual renal function and will require further confirmation in a larger cohort of the dialysis population. Notably, in patients with LV systolic dysfunction, persistent post-dialytic volume overload was significantly related to serum levels of NT-pro-BNP [30]. A number of other studies reported similar correlations between markers of hypervolemia and high plasma BNP or NT-pro-BNP [31,32]. However, so far there are no convincing data to suggest that BNP or NT-pro-BNP represent useful markers of volume status in hemodialysis patients [16,33].

#### **Prognostic value of baseline BNP and NT-pro-BNP in dialysis patients**

BNP and NT-pro-BNP are increasingly recognized to be powerful predictors of mortality and cardiovascular death in the dialysis population. In one of the earliest prospective cohort studies, performed in 399 hemodialysis patients, NT-pro-BNP was associated with 2-year all-cause mortality and, in a smaller study, with 3-year cardiac morbidity and mortality [13]. The CREED study showed that plasma BNP taken on a non-dialysis day was predictive of overall and cardiovascular death in hemodialysis patients [34]. A more recent study by Madsen *et al.* [16] also showed that both pre- and post-hemodialysis NT-pro-BNP were predictive of 2-year mortality. These data clearly suggested that levels of BNP and NT-pro-BNP had powerful prognostic implications irrespective of whether the measurement was taken before, shortly after or in-between dialysis. One study showed that both pre- and post-dialysis BNP and NT-pro-BNP were strongly correlated [35]. However, given that levels of BNP and NT-pro-BNP were altered by hemodialysis [16,35], it is important to standardize the timing of measurement of BNP or NT-pro-BNP in relation to the dialysis session in hemodialysis patients.

In peritoneal dialysis patients, NT-pro-BNP was predictive of long-term (3 years) all-cause mortality, cardiovascular death and events as well as cardiovascular congestion independent of echocardiographic measures of LV mass and ejection fraction [15]. *Post hoc* analysis from the Adequacy of Dialysis in Mexico (ADEMEX) study also showed a similar finding that the baseline NT-pro-BNP level was independently predictive of overall survival and cardiovascular death in peritoneal dialysis patients, irrespective of treatment arm [36].

A recent study compared the prognostic value of NT-pro-BNP and cTnT in hemodialysis patients and showed that

NT-pro-BNP was strongly correlated with LV systolic dysfunction and was indeed more strongly associated with mortality than cTnT [17]. However, the combination of cTnT and NT-pro-BNP did not improve the association with all-cause and cardiovascular mortality compared to NT-pro-BNP alone. NT-pro-BNP was a marker of mortality even after adjusting for LV mass index and midwall fractional shortening. These data suggest that NT-pro-BNP may be a more powerful prognostic marker compared to cTnT.

#### **Role of serial monitoring of NT-pro-BNP for outcome prediction in dialysis patients**

More recently, a prospective cohort study performed in 2,990 incident hemodialysis patients reported similar findings; increased NT-pro-BNP level was independently associated with increased risk of mortality at 90 days and 1 year [37]. Furthermore, in a smaller subset of 585 incident hemodialysis patients, repeat measurement of NT-pro-BNP was performed at 3 months. Patients with the greatest increase in NT-pro-BNP after 3 months of dialysis showed a 2.4-fold higher risk of mortality than those with the greatest decrease in NT-pro-BNP. These data for the first time suggested that serial changes in NT-pro-BNP levels also carried important prognostic information, independent of baseline NT-pro-BNP level, and were predictive of subsequent mortality [37].

Notably, in the recent *post hoc* analysis of the German Diabetes Dialysis Study (4D Study), which evaluated atorvastatin in 1,255 type 2 diabetic ESRD patients on maintenance hemodialysis, it was found that increased NT-pro-BNP over at least a 6-month period was strongly predictive of an increased risk of sudden death, cardiovascular event and mortality. Doubling of NT-pro-BNP was associated with a 46% increase in the risk of death. Furthermore, the increased risk of mortality with rising NT-pro-BNP was independent of baseline NT-pro-BNP and baseline co-morbidity [38].

#### **Prognostic value of cardiac troponin T in dialysis patients**

In a recent meta-analysis based on 28 studies published between 1999 and 2004 and including 3,931 patients, cTnT was shown to be a useful risk stratification tool in the ESRD population. The pooled analysis indicated that an elevated cTnT ( $>0.1 \mu\text{g/L}$ ) is useful in identifying a subgroup of asymptomatic ESRD patients with poor survival and a higher risk of cardiac death [39]. Recently, the Food and Drug Administration has approved the use of cTnT as a biomarker for mortality risk stratification in ESRD patients. Similarly, the use of cTnT for predicting prognosis has also been recommended by the KDOQI [1]. Of note, the NECOSAD (Netherlands Cooperative Study on the Adequacy of Dialysis) showed only limited

added predictive power of cTnT over other clinical risk factors in a combined cohort of hemodialysis and peritoneal dialysis patients [40]. This observation was somewhat contrary to our recent finding that cTnT had a significant additional value for prognostication beyond the standard clinical, biochemical, dialysis and echocardiographic measures, including LV mass and ejection fraction in chronic peritoneal dialysis patients [41]. More importantly, our study showed that the prognostic value of cTnT was independent of inflammation, residual renal function, LV hypertrophy and dysfunction, clearly supporting the additional value of measuring cTnT for early identification of high-risk ESRD patients. A recent study also showed that cTnT is a useful biomarker in predicting the development of circulatory congestion in chronic peritoneal dialysis patients [42]. These data suggest that cTnT serves as an important adjunct to echocardiography in identifying peritoneal dialysis patients at risk of circulatory congestion. Whether the findings are also applicable to hemodialysis patients requires further evaluation.

#### **Mechanisms of elevated cTnT in dialysis patients**

Elevated cTnT has been linked to LV hypertrophy, LV dilation, diabetes, and impaired systolic and diastolic dysfunction in hemodialysis patients [43–45]. There is evidence that elevated cTnT in asymptomatic ESRD patients reflects subclinical myocardial injury. Ooi *et al.* [46] showed that elevated cTnT was invariably associated with pathological evidence of old, recent or healing myocardial necrosis or micro-infarction. In another study, cTnT elevation was closely correlated with the severity of angiographic coronary artery disease in chronic hemodialysis patients [47]. cTnT elevation has also been linked to the degree of coronary artery calcification in asymptomatic hemodialysis patients [48]. Even though cTnT was significantly confounded by residual kidney function [41], circulating cTnT in patients with kidney failure was noted to be predominantly the free-intact form, as in patients with acute coronary syndrome [49]. This was important evidence to support that circulating cTnT in ESRD patients is indeed a marker of cardiac pathology. Given that free and bound cTnT are both relatively large molecules of 37 and 77kDa, respectively, elevated cTnT in ESRD patients is unlikely to be the result of decreased renal clearance. Using contrast magnetic resonance imaging, a recent study showed that elevated cTnT cannot be solely attributed to previous subclinical myocardial necrosis or LV hypertrophy [50]. It was speculated that additional myocardial pathologies, such as myocardial fibrosis, may contribute to increased cTnT in ESRD patients and require further evaluation.

## Implications for clinical practice

### **Clinical utility of BNP/NT-pro-BNP in hemodialysis patients**

Together, these data suggest that serial monitoring of NT-pro-BNP levels may represent a novel and useful clinical tool in guiding treatment efficacy in the dialysis population and warrant further investigation. Treatment guided by lowering plasma NT-pro-BNP levels has been shown to reduce cardiovascular events and delay time to first cardiovascular event, compared with usual clinically guided treatment in patients with chronic heart failure [51]. A BNP-guided strategy has also been shown to reduce the risk of heart-failure related death or length of hospital stay for heart failure, compared to standard clinical care in the general population [52]. In a recent small prospective study of 21 stable hemodialysis patients with preserved systolic function, changes in LV mass index over 6-month and 12-month periods were closely correlated with changes in NT-pro-BNP levels [53]. All these observations prompt further investigation into the application of serial BNP and NT-pro-BNP monitoring as biomarkers for assessing changes in LV mass index or systolic function in hemodialysis patients. Whether BNP or NT-pro-BNP guided therapy may be useful in monitoring treatment efficacy and improving clinical outcomes of hemodialysis patients needs further prospective evaluation.

### **Clinical utility of cTnT in hemodialysis patients**

How can cTnT testing be applied in daily clinical practice? Given that cTnT is confounded by residual kidney function, we believe a baseline level should first be obtained in all hemodialysis patients in order to distinguish subsequent cTnT elevation due to acute coronary syndrome and/or chronic myocardial injury. The measurement should best be obtained before dialysis because cTnT levels may increase post-dialysis [54]. A baseline level not only allows outcome prediction and identifies high-risk patients, but also forms an important basis to evaluate changes over time. Our recent data suggested that even minimally increased cTnT is associated with an increased risk of mortality and cardiovascular death in peritoneal dialysis patients [41]. This is well in accord with observations in the general population suggesting that a minimally increased cTnT concentration reflects increased cardiovascular risk [55]. According to the recent National Academy of Clinical Biochemistry (NACB) laboratory medicine practice guidelines, measurement of cardiac troponins should also be used to evaluate acute coronary syndrome in ESRD patients [56]. In ESRD patients who 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. In addition,

testing for cardiac troponins may be used as an aid in defining the risk of mortality in ESRD patients. Whether cTnT testing may be a useful screening test for cardiovascular disease in the hemodialysis population warrants further evaluation.

## Abbreviations

BNP, brain natriuretic peptide; CKD, chronic kidney disease; CREED, Cardiovascular Risk Evaluation Extension; cTnT, cardiac troponin T; ESRD, end-stage renal disease; KDOQI, Kidney Disease Outcome Quality Initiative; LV, left ventricular; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide.

## Competing interests

The author declares that she has no competing interests.

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