SCIENTIFIC LETTER

Raised plasma N-terminal pro-B-type natriuretic peptide concentrations predict mortality and cardiac disease in end-stage renal disease

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Heart 2006;92:1518–1519. doi: 10.1136/hrt.2005.082313

N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations are raised in a proportion of patients with heart failure and acute coronary syndrome and provide diagnostic and prognostic information. Inclusion cut-off values vary according to age, sex and estimated glomerular filtration rate (eGFR).^{1,2} Raised NT-proBNP concentrations are found in a proportion of patients with end-stage renal disease (ESRD). The significance and reasons for this remain uncertain.

The objective of this study was to investigate whether NT-proBNP predicts mortality in a group of patients with ESRD. The secondary end point was to examine differences in patients with and without raised NT-proBNP, according to the cut-off value that best predicted mortality.

METHODS

One hundred and forty renal transplant candidates were prospectively studied. Long-term survival status was obtained in all patients. The study was approved by the local ethics committee. All participants gave written informed consent.

All patients had baseline transthoracic echocardiography, dobutamine stress echocardiography (DSE) and coronary angiography. The protocol for these was previously described.³ A positive DSE response was described by the occurrence under stress of hypokinesia, akinesia or dyskinesia in one or more resting normal segments or worsening of wall motion in one or more resting hypokinetic segments. Significant coronary artery disease (CAD) was defined as luminal stenosis > 70% in one or more epicardial artery.

Whole blood venous samples were collected at the time of DSE before infusion of dobutamine. Cardiac troponin T (cTnT) was measured with the third-generation Elecsys 2010 STAT immunoassay (Roche Diagnostics, Lewes, UK). NT-proBNP concentrations were determined on the Elecsys 2010 (Roche Diagnostics) assay and high sensitivity C reactive protein (hs-CRP) on the Immulite-1 (Diagnostic Products Corporation, Los Angeles, California, USA) assay.

For comparisons, Student's *t* test or χ^2 analysis was used and for correlation analysis, Pearson or Spearman analysis was used as appropriate. Cut-off values for the optimal NT-proBNP concentration to predict mortality were determined by receiver operating characteristic curve analysis. Cumulative survival according to the NT-proBNP concentration was displayed as Kaplan–Meier curves. Stepwise logistic regression analysis was used to determine those parameters independently associated with raised NT-proBNP. Univariate and multivariate associates of mortality were determined by the Cox proportional hazard model. A value of *p* < 0.05 was regarded as significant.

RESULTS

Mean (SD) age was 52 (13) years, 90 were men, and 50 (36%) received haemodialysis and 29 (20%) peritoneal

Table 1 Univariate and multivariate predictors of mortality by Cox regression analysis in patients with end-stage renal disease

	HR for prediction of mortality (95% CI)	p Value
Univariate predictors		
Age	0.44 (0.12 to 0.88)	0.33
Sex	0.39 (0.18 to 0.95)	0.51
Dialysis	2.89 (2.01 to 5.98)	0.07
Diabetes	7.42 (3.54 to 9.48)	0.006
Cardiac troponin T	6.12 (2.81 to 10.11)	0.01
NT-proBNP	5.57 (3.14 to 8.21)	0.02
LVESD	3.13 (1.62 to 7.81)	0.05
LVEF	3.75 (1.46 to 8.19)	0.02
Left atrium	4.92 (2.14 to 8.11)	0.02
Mitral E:Ea ratio	8.14 (3.45 to 9.53)	0.001
LV mass index	0.29 (0.07 to 1.89)	0.24
Positive DSE result	6.32 (2.17 to 9.13)	0.009
Significant CAD	6.46 (2.33 to 10.11)	0.008
Multivariate predictors		
Diabetes	8.12 (3.96 to 10.88)	0.001
Mitral E:Ea ratio	6.18 (2.17 to 9.94)	0.006
Significant CAD	5.87 (2.96 to 9.14)	0.02

CAD, coronary artery disease; DSE, dobutamine stress echocardiography; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

dialysis. Mean eGFR was 15 (8) ml/min with residual urine production (*n* = 108). Forty (29%) patients had significant CAD and 41 (30%) a positive DSE result. Fifty-four (38%) patients had diabetes. Mean (SD) follow-up time was 2.25 (0.71) years (range 0.19 to 3.27). Over this period 45 patients received a renal transplant, eight were taken off the transplant list, and 21 died (14 cardiac deaths). Mean (SD) time to death was 1.02 (0.48) years. Nine patients had coronary artery bypass surgery and 12 had percutaneous intervention. The decision for revascularisation was driven by the DSE and coronary angiogram results.

NT-proBNP was significantly correlated with cTnT (*r* = 0.61, *p* ≤ 0.001), Hs-CRP (*r* = 0.34, *p* = 0.05), left ventricular end systolic diameter (LVESD; *r* = 0.38, *p* = 0.001), left ventricular ejection fraction (*r* = −0.41, *p* = 0.05) and mitral E:Ea ratio (*r* = 0.31, *p* = 0.01).

Table 1 shows univariate and multivariate predictors of mortality. Both NT-proBNP and cTnT were univariate predictors of mortality. However, with multivariate analysis, diabetes, mitral E:Ea ratio and significant CAD were the only

Abbreviations: CAD, coronary artery disease; cTnT, cardiac troponin T; DSE, dobutamine stress echocardiography; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; hs-CRP, high sensitivity C reactive protein; LVESD, left ventricular end systolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Figure 1 Kaplan-Meier survival curves according to N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration.

independent predictors of mortality. From receiver operating characteristic curve analysis, NT-proBNP concentrations ≥ 350 pg/ml predicted mortality with sensitivity 72% and specificity 76% (area under the curve 0.74, 95% confidence interval (CI) 0.53 to 0.95, $p = 0.04$). Figure 1 shows Kaplan-Meier survival curves for NT-proBNP according to these cut-off values. Patients with raised concentrations had significantly higher mortality than those without ($n = 66$, 47%, $p = 0.03$). These patients had significantly impaired left ventricular ejection fraction ($p = 0.02$), higher LVESD ($p = 0.001$) and higher estimated LV filling pressure by mitral E:Ea ($p = 0.03$) ratio than those without. Age ($p = 0.07$) and the proportion on dialysis ($p = 0.004$), with diabetes ($p = 0.09$) and with significant CAD ($p = 0.001$) were significantly higher and eGFR ($p = 0.04$) lower in the NT-proBNP-positive group. Stepwise logistic regression analysis identified LVESD (odds ratio 9.6, 95% CI 2.6 to 21.3, $p = 0.001$) and LV long axis velocity (odds ratio 5.9, 95% CI -9.8 to -2.1 , $p = 0.004$) to be independently associated with raised NT-proBNP.

DISCUSSION

This study shows that NT-proBNP does predict mortality in a group of renal transplant candidates at a cut-off value of 350 pg/ml, comparable with that suggested for the diagnosis of acute heart failure in the emergency department.² Our findings are similar to those of Apple *et al.*,⁴ who concluded that NT-proBNP predicted mortality in a group of haemodialysis patients only at the highest tertile cut-off value. However, cTnT and NT-proBNP were not independent markers of mortality. Patients with raised NT-proBNP had a larger LV cavity, reduced systolic function and higher LV filling pressure than those without. CAD, inducible ischaemia, lower eGFR and dialysis were associated with raised NT-proBNP but none were independent associates. The results suggest that, while raised NT-proBNP concentrations in ESRD are in part due to reduced renal excretion, they also reflect cardiac damage.

NT-proBNP and cTnT were significantly correlated. Both these biomarkers probably reflect cardiac damage in ESRD due to several processes such as CAD, diabetes, dialysis and as yet unidentified mechanisms such as microinfarction, myocarditis and non-excreted uraemic toxins. The association of hs-CRP and NT-proBNP suggests a possible role for inflammation. Alternatively, both may reflect generalised arterial disease. The higher proportion of patients on dialysis and with diabetes, CAD and inducible ischaemia would in part explain the echocardiography findings and observed higher mortality with raised NT-proBNP. Our findings are consistent with those of deFilippi *et al.*,⁵ who concluded that NT-proBNP correlated with cTnT, left ventricular hypertrophy and CAD in a group of patients with chronic kidney disease not on dialysis.

A potential role for biochemical markers as a cheap and rapid method for the risk stratification of renal transplant candidates is attractive. Waiting times for echocardiography and coronary angiography often mean a delay in receiving a new kidney. This study suggests that NT-proBNP, like cTnT, is a marker of mortality, CAD and LV dysfunction in ESRD. However, multivariate analysis for mortality suggests these biomarkers act mainly as confounding factors. Moreover, no studies thus far have reported an improved outcome with medical or surgical intervention in patients with ESRD with raised cTnT or NT-proBNP. We therefore believe that biochemical markers cannot be recommended for the cardiac screening of renal transplant candidates at this time. Evaluation should be based on clinical risk, with stress testing and coronary angiography reserved for high-risk patients.

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Accepted 3 April 2006

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