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Increasing B-type natriuretic peptide levels predict mortality in unselected haemodialysis patients

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Aims Cardiac disease is the major cause of death in patients undergoing chronic haemodialysis. Recent studies have found that B-type natriuretic peptide (BNP) levels accurately reflect the cardiovascular burden of dialysis patients. However, the prognostic potential of BNP measurements in dialysis patients remains unknown.

Methods and results The study included 113 chronic dialysis patients who were prospectively followed up. Levels of BNP were measured at baseline and every 6 months thereafter. The potential of baseline BNP and annual BNP changes to predict all-cause and cardiac mortality were assessed as endpoints. Median follow-up was 735 (354–1459) days; 35 (31%) patients died, 17 (15%) of them from cardiac causes. Baseline BNP levels were similar among survivors and non-survivors, and failed to predict all-cause and cardiac death. Cardiac death was preceded by a marked increase in BNP levels. In survivors BNP levels remained stable [median change: +175% (+20–+384%) vs. −14% (−35–+35%) over the 18 months preceding either death or the end of follow-up, $P < 0.001$]. Hence, annual BNP changes adequately predicted all-cause and cardiac death in the subsequent year {$AUC_{all\text{-}cause} = 0.70$ [SD 0.05, 95% CI (0.60–0.81)]; $AUC_{cardiac} = 0.82$ [SD 0.04, 95%CI (0.73–0.90)]}. A BNP increase of 40% provided the best cut-off level. Cox regression analysis confirmed that annual increases over 40% were associated with a seven-fold increased risk for all-cause and cardiac death.

Conclusions Annual BNP increases above 40% predicted all-cause and cardiac death in the subsequent year. Hence, serially measuring BNP levels may present a novel tool for risk stratification and treatment guidance of end-stage renal disease patients on chronic dialysis.

Keywords Dialysis • Cardiovascular Disease • B-type natriuretic peptide • Cardiac death • Prognosis

Introduction

Patients with end-stage renal disease (ESRD) undergoing chronic haemodialysis are at a substantially increased risk of death. Recent analyses found 1-, 3-, and 5-year mortality rates in chronic haemodialysis patients in Switzerland to be around 15, 35, and 55%, respectively.[1,2] The latest US Renal Data System (USRDS) annual report also showed an annual mortality rate of 221 deaths per 1000 patient years in the USA.[3] Causes of the excess mortality observed in ESRD are only partly understood. Cardiovascular events are a major player in these dire mortality figures, with left-ventricular hypertrophy and coronary artery disease present in 75 and 40% of all ESRD patients, respectively. Thus, over 40% of all ESRD patients die due to cardiac causes.[3] Primary chronic kidney disease leading to decreased cardiac function and an increased risk of adverse cardiovascular events has even been termed as the chronic reno-cardiac syndrome, or cardiorenal syndrome type IV.[4] The predictive potential of classic

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cardiovascular risk factors such as hypertension, obesity, and hyperlipidaemia appear to be less reliable in patients with cardiorenal syndrome type IV,[5] making risk stratification of patients on chronic haemodialysis especially difficult. Hence, a rapid and reliable predictor of overall and cardiovascular death could help physicians to identify patients requiring closer monitoring, intensified dialysis or changes in medical treatment.

B-type natriuretic peptide (BNP), a 32-amino-acid polypeptide, is predominately released by the left and right cardiac ventricles and regulates a wide range of physiological effects including natriuresis, diuresis, and vasodilatation.[6] The main stimulus for the secretion of BNP is cardiac stress reflected by myocardial stretch and pressure, or volume overload.[6] In heart failure and coronary artery disease, BNP levels have been established as powerful predictors of mortality and cardiovascular events.[6,7] Importantly, a recent study enrolling patients from a community-based heart failure programme found natriuretic peptide levels to decrease significantly after the optimization of heart failure therapy.[8] Natriuretic peptide levels obtained after therapy optimization provided stronger prognostic information than either the baseline value or other conventional risk factors. Consequently, long-term natriuretic peptide-guided therapy is often discussed[9] and a recent meta-analysis suggests that long-term BNP-guided therapy may reduce all-cause mortality in patients with chronic heart failure in comparison with current standard clinical care.[10]

Recently, a series of studies found that BNP correlated with the degree of left-ventricular hypertrophy, left-ventricular end-diastolic wall stress and the extent of coronary artery disease in patients on chronic haemodialysis.[11–13] Consequently, rising BNP levels may accurately mirror the cardiovascular burden of ESRD patients on maintenance haemodialysis and signify a progression of the cardiac disease. In this study, we therefore aimed to evaluate the use of serial BNP measurements to mirror the course of the cardiorenal syndrome and predict mortality in unselected patients on chronic haemodialysis.

Methods

Setting and study population

This study specifically investigated the potential of baseline BNP levels to predict death during the observational period and the first year, respectively. We further assessed whether annual plasma BNP changes could predict cardiac and all-cause mortality in the subsequent year in patients undergoing maintenance haemodialysis. We prospectively enrolled all patients already on chronic haemodialysis in April 2002, and all of those starting chronic haemodialysis between April 2002 and December 2006. There were no factors excluding enrollment into this study. No patients objected to their enrollment into the trial. Overall 113 patients were included. All patients underwent a clinical assessment including medical history, physical examination, and routine blood tests including creatinine, urea, parathyroid hormone, and BNP at the beginning of the study. Baseline echocardiography was performed in 59 patients at the time of their enrollment into the study. Systolic dysfunction was defined as an ejection fraction $<45\%$. A longitudinal follow-up was conducted until May 2007. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participating patients. All treating physicians were blinded to BNP levels measured for study purposes. However, clinically indicated BNP measurements (e.g. episodes of acute dyspnoea) were allowed during the study period.

Outcome

All patients were re-evaluated at 6-month intervals during their first routine haemodialysis sessions at the beginning of the month. The follow-up assessment included medical history, physical examination, and BNP sampling. Besides baseline plasma BNP values, three annual BNP dynamics were explored. These included: (i) the change during the first year of follow-up (BNP at 12 months − BNP at study entry), (ii) the change in BNP between 6 months and 18 months, and (iii) the change in BNP during the second year of follow-up (BNP at 24months − BNP at 12 months). The subsequent year was defined as the 12 months following the corresponding second BNP measurement (i.e. deaths between 12 months and 24 months after enrollment were attributed to the first annual BNP change). Hence, a change in BNP during a given time period was interpreted by considering the outcomes during the next year. Patients, who survived until the end of follow-up or the subsequent year, respectively, were defined as survivors. Patients who died within the respective follow-up period were defined as non-survivors. The cause of death was adjudicated by two board-certified nephrologists after reviewing all medical records pertaining to the patient and interviewing the next of kin for patients who died out of hospital. The four cardiac causes of death were: coronary artery disease, heart failure, arrhythmias, and other heart diseases. Sudden deaths were operationally defined as witnessed and unwitnessed unexpected deaths, with a preceding duration of symptoms of less than 24 h for witnessed deaths, and less than the interval since the last dialysis session for unwitnessed deaths.

Measurement of B-type natriuretic peptide

B-type natriuretic peptide was detected in ethylenediaminetetraacetic acid plasma drawn prior to the respective dialysis session, using a fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA). In brief, the coefficient of variation within a given assay has been reported as 9.5, 12.0, and 13.9% for levels of 28.8, 584.0, and 1180.0 pg/mL, respectively, while the coefficient of variation among assays is 10.0, 12.4, and 14.8%, respectively. All draws were performed at the start of dialysis and after a three-day interdialytic interval. The pre-dialytic time point of the biomarker blood draw was chosen to achieve the greatest comparability to previous studies.

Haemodialysis modalities

Each patient underwent at least 3–4-h dialysis sessions per week. All patients were dialysed using standard dialysis techniques with Fresenius 4008 (Fresenius Medical Care, Bad Homburg, Germany) and Gambro AK 200 machines (Gambro AB, Stockholm, Sweden); polysulfone dialyser membranes (FX100; Fresenius Medical Care) and standard bicarbonate-based baths. Ultrafiltration was provided during dialysis by adjusting transmembrane pressure based on pre-established target weights for each patient.

Statistical analysis

Statistical analyses were performed using the SPSS/PC software package (version 16.0, SPSS Inc., Chicago, IL, USA). A statistical significance level of 0.05 was used. Discrete variables are expressed as counts (percentages) and continuous variables as means $\pm$ standard deviation (SD) or median and interquartile range (IR), unless stated otherwise. Comparisons between the two groups were drawn by means of the χ^2 test and Fisher's exact test in relation to categorical

variables and *t*-test in relation to continuous variables if normally distributed or Mann–Whitney test if not normally distributed. B-type natriuretic peptide values in the two groups were compared using the Kruskall–Wallis test, Mann–Whitney test and one-way analysis of variance analysis for repeated measurements.

Receiver operating characteristic (ROC) curve analyses and calculations of the area under the curve were used to evaluate the ability of baseline plasma BNP values and the three annual BNP changes to correctly predict cardiac and all-cause mortality. Cut-off points were calculated by maximizing clinical sensitivity and specificity using Youden's J index for the overall ROC curve. Cox regression analysis was applied to identify predictors of death in univariate and multivariate analysis. The variables were entered into the model in a stepwise selection process (entry into the multivariate analysis: univariate P value <0.1 or significant baseline difference). Age, time on dialysis, history of coronary artery disease, history of heart failure, beta-blocker therapy, and annual BNP changes exceeding 40% were identified as candidate variables and were included into the multivariate analysis. All hypothesis testing was two tailed.

Results

Baseline characteristics

The demographic characteristics and biological parameters of the study cohort are displayed in *Table 1*. *Table 2* shows baseline characteristics for three patient subgroups based on their survival status at the end of the follow-up [median days of follow-up: 735 (354–1459)]: survivors, patients dying from all-causes, and patients dying from cardiac causes. Survivors ($n = 78$, 69%) were younger, on chronic haemodialysis for shorter periods and were less likely to have coronary artery disease or chronic heart failure. There were no further baseline differences between survivors and patients dying from all-causes ($n = 35$, 31%) (*Table 2*). Differences between survivors and patients dying of cardiac causes ($n = 17$, 15%) further included a higher incidence of beta-blocker use in the cardiac mortality subgroup (*Table 2*). Importantly, cardiac and non-cardiac decedents only differed in the frequency of coronary artery disease (*Table 3*). Cardiac death was primarily caused by sudden death (eight cases; five of eight at home) and therapy-resistant heart failure (seven cases). Two patients died of arrhythmias (one bradycardia, one tachycardia). Non-cardiac decedents died primarily of cancers (seven cases), acute infections (six cases), and dialysis withdrawal (five cases). Volume status, as assessed by body mass index, interdialytic weight gain, and serum albumin levels were similar among all groups at the beginning of the observational period.

B-type natriuretic peptide levels and survival status

Baseline BNP levels were similar among all subgroups. Baseline BNP values correlated positively with age ($r = 0.30$, $P < 0.01$), interdialytic weight gain ($r = 0.24$, $P = 0.02$) and were negatively associated with left ventricular ejection fraction ($r = -0.33$, $P = 0.02$). There were no correlations between baseline BNP values and other known confounders (haemoglobin, C-reactive protein, systolic blood pressure, urine output, or body mass index). In a batch analysis of all BNP levels measured throughout the observational period, BNP levels were greater in patients dying either of all-causes or of cardiac causes in comparison with survivors (both $P < 0.001$). Batch analysis did not reveal significant BNP changes over time in survivors and all-cause or cardiac non-survivors (both $P > 0.5$). *Figure 1* shows that cardiac death was

Table 1 Baseline characteristics of the 113 dialysis patients

Age—years (Mean ± standard deviation)	67.9 ± 13.5
Male sex—*n*. (%)	68 (60)
Months on dialysis before enrollment [Median (IR)]	2 (0–32)
Interdialytic weight gain (kg) [Median (IR)]	1.0 (0.5–2.1)
Smoking status	
Current smoker—*n* (%)	17 (15)
Former smokers—*n* (%)	28 (25)
Coexisting illnesses	
Chronic obstructive pulmonary disease	13 (12)
Coronary artery disease—*n* (%)	49 (43)
Congestive heart failure—*n* (%)	27 (24)
Diabetes mellitus—*n* (%)	41 (36)
Atrial fibrillation—*n* (%)	9 (8)
Cause of CKD	
Vascular — *n* (%)	14 (12)
Diabetic— *n* (%)	33 (29)
Glomerular— *n* (%)	21 (19)
Interstitial— *n* (%)	7 (6)
Hereditary— *n* (%)	5 (4)
Malignant— *n* (%)	4 (4)
Others— *n* (%)	26 (23)
Vital signs	
BP systolic (mmHg)	151 ± 26
BP diastolic (mmHg)	76 ± 14
Heart rate (bpm)	74 ± 13
Laboratory parameters	
Haemoglobin (g/L)	109 ± 17
Urea (mmol/L)	25.0 ± 10.3
Creatinine (mmol/L)	660.1 ± 278.8
Parathyroid hormone (pg/mL)	250 (46–274)
B-type natriuretic peptide (pg/mL)	459 (166–918)
Ejection fraction (%)[a]	60 (44–67)
Systolic dysfunction— *n* (%)	13 (22)
Enrollment therapy	
ACE inhibitors— *n* (%)	13 (11)
Beta-blockers— *n* (%)	49 (43)
Statins— *n* (%)	19 (17)
Outcome	
Renal transplant— *n* (%)	14 (12)
Overall deaths— *n* (%)	35 (31)
Cardiac Death— *n* (%)	17 (49)
Withdrawal of dialysis—*n* (%)	8 (23)
Infection— *n* (%)	3 (9)
Others— *n* (%)	7 (6)

[a]Echocardiographic parameters were assessed in 59 patients

Table 2 Patient characteristics at enrollment according to survival status

	Survivors *n* = 78	Non-survivors (all-cause) *n* = 35	*P* value	Non-survivors (cardiac) *n* = 17	*P* value
Age (years)	65 ± 14	73 ± 12	<0.01	73 ± 13	<0.01
Male sex	55 (73)	23 (66)	0.42	13 (76)	0.13
Months on dialysis	1 (0–9)	28 (6–47)	<0.01	20 (3–45)	<0.05
Interdialytic weight gain (kg)	0.9 (0.2–2.0)	1.2 (0.3–2.3)	0.20	1.9 (0.3–2.5)	0.17
Medical history					
Heart failure	14 (18)	22 (63)	0.02	13 (76)	<0.01
CAD	27 (36)	13 (37)	<0.01	10 (59)	<0.01
COPD	7(9)	6 (17)	0.21	3 (17)	0.40
Diabetes mellitus	28 (29)	13 (37)	0.89	6 (35)	0.93
Baseline treatment					
Beta-blockers	30 (38)	19 (54)	0.12	12 (71)	0.01
ACE/ARB	10 (13)	3 (8)	0.52	0 (0)	0.11
Statins	16 (20)	3 (8)	0.12	2 (12)	0.55
Cardiac parameters					
Atrial fibrillation	4 (5)	5 (14)	0.09	3 (18)	0.11
Systolic dysfunction[a]	7 (9)	6 (17)	0.62	4 (24)	0.57
Ejection fraction[a]	54 (44–67)	60 (45–67)	0.48	60 (35–66)	0.70
Baseline BNP	414 (164–867)	591 (179–1210)	0.44	591 (128–1300)	0.38

Data are presented as median (interquartile range), number of patients (%), or years ± standard deviation, all *P* values are calculated versus survivors
CAD, coronary artery disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker
[a]Echocardiographic parameters were assessed in 59 patients.

Table 3 Patient characteristics of cardiac versus non-cardiac decedents at enrollment

	Non-survivors (non-cardiac) *n* = 18	Non-survivors (cardiac) *n* = 17	*P*-value
Age (years)	73 ± 13	73 ± 13	0.37
Male sex	10 (55)	13 (76)	0.19
Months on dialysis	32 [8–50]	20 [3–45]	0.55
Interdialytic weight gain (kg)	0.7 [0.3–2.1]	1.9 [0.3–2.5]	0.56
Medical History			
Heart failure	9 (50)	13 (76)	0.11
CAD	3 (17)	10 (59)	0.01
COPD	3 (17)	3 (17)	0.94
Diabetes mellitus	7 (39)	6 (35)	0.83
Baseline Treatment			
Beta-blockers	7 (39)	12 (71)	0.06
ACE/ARB	3 (17)	0 (0)	0.08
Statins	1 (6)	2 (12)	0.51
Cardiac Parameters			
Atrial fibrillation	2 (11)	3 (18)	0.58
Systolic dysfunction[a]	2 (11)	4 (24)	0.48
Ejection fraction[a]	66 (51–79)	60 (35–66)	0.30
Baseline BNP	559 (184–799)	591 (128–1300)	0.55

Data are presented as median (interquartile range), number of patients (%), or years ± standard deviation.
[a]Echocardiographic parameters were assessed in 59 patients.

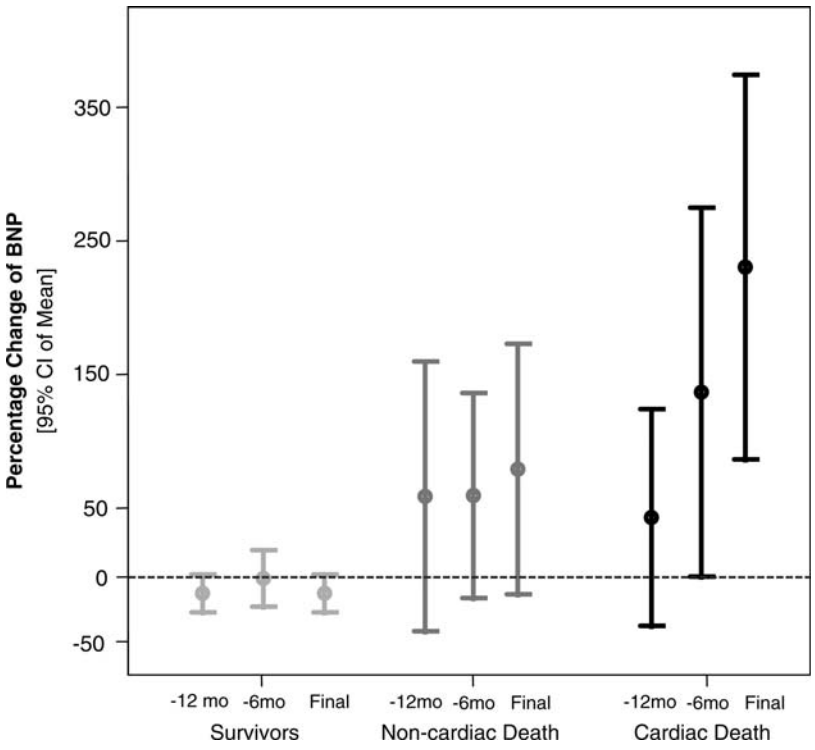

Figure 1 Error bars showing percentage change of B-type natriuretic peptide over the value measured at 18 months before either the end of follow-up (survivors) or non-cardiac and cardiac death. The dotted line denotes no change over baseline value.

preceded by a marked increase in BNP levels while in survivors BNP levels remained stable [median change: +175% (+20−+384%) vs. −14% (−35−+35%) over the 18 months preceding either death or the end of follow-up, $P < 0.001$]. Interestingly, patients dying of non-cardiac causes displayed an intermediate BNP response during the 18 months preceding death [median change: 52% (−18−+102%)]. In addition, a BNP increase above 100% occurred, at least once in 10 out of 17 (59%) patients dying of cardiac causes compared with 5 out of 18 (28%) patients dying of non-cardiac causes and 3 out of 49 (6%) survivors over the 18 months preceding either death or the end of follow-up.

It should be noted that there was no correlation between the BNP increase preceding cardiac death and changes in markers of hypervolaemia (body weight: $r = 0.26$, $P = 0.43$; interdialytic weight gain: $r = 0.20$, $P = 0.51$; systolic blood pressure: $r = -0.01$, $P = 0.97$) and known predictors of negative patient outcome (urine output: $r = 0.30$, $P = 0.32$; C-reactive protein: $r = -0-34$, $P = 0.28$; serum albumin: $r = 0.20$, $P = 0.56$; haemoglobin: $r = -0.33$, $P = 0.08$). In fact, in patients dying of cardiac causes body weight [median change: +2.8% (−1.2−+5.8)], intradialytic weight gain [median change: 0 kg (−1.0−+0.6)], systolic blood pressure [median change: 2 mmHg (−30−+20)], C-reactive protein [median change: 5 mg/L (−12−+18)] haemoglobin levels [median change: 0 g/dL (−0.8−+1.4)], and serum albumin [median change: −3 g/L (−6−+4)] remained largely unchanged over the 18 months preceding death. Urine excretion volumes of patients dying of cardiac causes changed by a median of 50 mL (range: −800 to +420 mL); three cardiac non-survivors were anuric throughout the observational period.

We further assessed whether baseline BNP levels, measured at the beginning of the study, could predict all-cause or cardiac death. Baseline BNP levels failed to predict all-cause [hazard ratio (HR) 1.0; $P = 0.89$] or cardiac (HR 1.0; $P = 0.77$) mortality in the first year. Similarly, baseline BNP levels failed to predict long-term all-cause (HR 1.0; $P = 0.20$) or cardiac death (HR 1.0; $P = 0.23$) during the entire observational period.

We also examined whether annual BNP changes predicted all-cause and cardiac death in the subsequent year. Receiver operating characteristic curve analyses (*Figure 2*) showed that annual BNP changes adequately predicted all-cause mortality within the subsequent year. Cardiac mortality occurring within the subsequent year was even more accurately predictable using these ROC analyses (*Figure 2*). The areas under the overall ROC curves (area under the curve)were 0.70 [SD 0.05, 95% CI (0.60−0.81)] for all-cause death and 0.82 [SD 0.04, 95% CI (0.73−0.90)] for cardiac death, respectively. In both cases, a BNP increase of 40% provided the best cut-off to separate survivors from non-survivors in the subsequent year of follow-up. This threshold provided a specificity of 82% and a sensitivity of 61% for the prediction of all-cause mortality. For the prediction of cardiac mortality in the subsequent year the specificity reached 93% with a sensitivity of 61%.

Kaplan−Meier analysis (*Figure 3*) confirmed that an annual BNP increase over 40% strongly predicted both all-cause ($P = 0.004$)

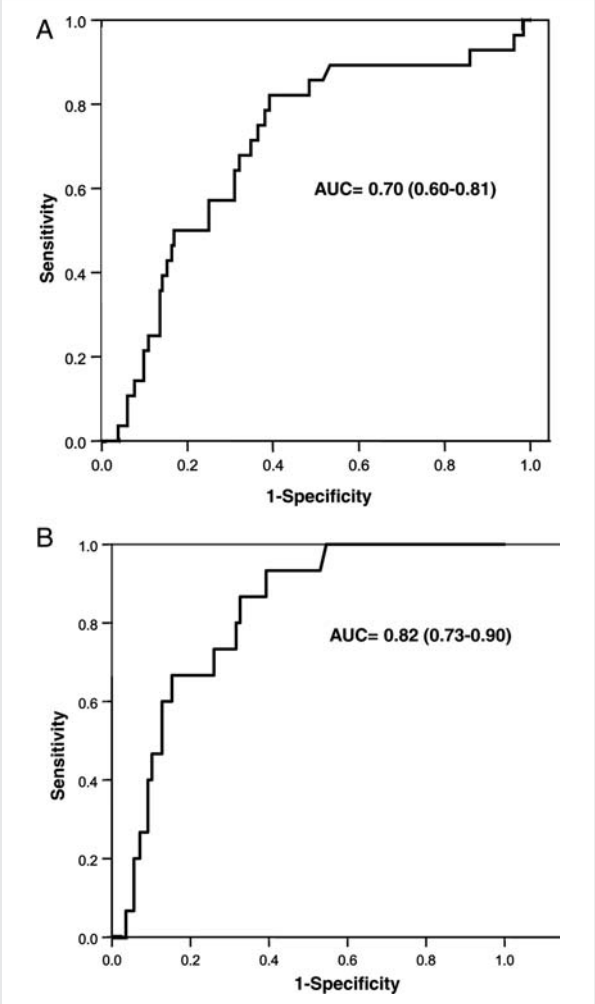

Figure 2 (*A*) Receiver-operating characteristic curves displaying the ability of 1year B-type natriuretic peptide changes to predict all-cause mortality in the subsequent year. (*B*) Receiver-operating characteristic curves displaying the ability of 1year B-type natriuretic peptide changes to predict cardiac death in the subsequent year.

and cardiovascular ($P = 0.002$) death in the subsequent year. Cox-regression analysis also confirmed that an annual increase over 40% predicted all-cause [HR 4.46 (95% CI 1.437–13.827), $P = 0.010$] and cardiac [HR 6.84 (95% CI 1.48–31.7), $P = 0.014$] mortality within the subsequent year. These predictions remained significant in multivariate analysis [HR 6.77 (95% CI 1.44–31.83) $P = 0.015$; and HR 6.84 (1.48–31.72), $P = 0.014$, respectively].

Discussion

This study investigated the potential benefit of serial BNP measurements in the risk stratification of patients undergoing maintenance haemodialysis. Most importantly, we found BNP levels to increase by 175% over the 18 months preceding cardiac death, while remaining stable in survivors. In addition, we established that annual BNP increases over 40% powerfully and independently predicted all-cause and cardiac mortality within the subsequent year. Importantly, BNP increases did not reflect changes in markers of hypervolaemia, urine excretion, or inflammation. Spot BNP measured at baseline failed to predict short- and long-term mortality.

The failure of spot BNP measurements to predict mortality is inconsistent with the results of previous studies, which investigated the potential of BNP monitoring in dialysis patients. In the largest previous analysis, the CREED investigators found baseline BNP levels to independently predict all-cause and cardiac mortality in 246 dialysis patients.[14] Another study, investigating 138 dialysis patients found spot N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels above 5300 pg/mL to predict all-cause mortality. However, both studies largely excluded patients with previous cardiac diseases.[15] In the CREED study, all patients with a history of heart failure or a reduced ejection fraction were excluded, while the second study excluded patients with cardiomyopathies and myocardial infarctions. The enrollment of unselected patients into our study evidently led to a higher cardiac burden and significantly higher baseline BNP values across the entire cohort making spot BNP measurements an inappropriate tool for the risk stratification of unselected dialysis patients. Importantly, the lack of correlation between BNP levels and residual renal function (measured by urine excretion) as well as BNP changes and changes in residual renal function observed in this study, suggest that changes in natriuretic peptide levels in dialysis patients are not primarily mediated through reduced renal clearance.[16,17] Similarly, the extent of anaemia does not appear to significantly impact on BNP levels in dialysis patients.[18]

The high mortality rates described in the present paper are in accordance with the mortality rates of ESDR patients established by large national registry studies. The latest USRDS annual report describes an annual mortality rate of 221 deaths per 1000 patient years in the USA.[3] Similarly, the 3-year mortality rates of Swiss dialysis patients has, in line with the findings of this study, consistently been reported to be about 35%.[1,2] The present paper further confirms cardiac death to be the most important cause of death in haemodialysis patients. In accordance with our results, cardiac death accounted for 41% of the overall mortality in the USRDS database,[3] while in the previous large scale dialysis studies cardiac death contributed to up to 50% of the observed mortality of dialysis patients.[19,20] These observations are characteristic for chronic reno-cardiac interactions, also known as the cardiorenal syndrome type IV, in which primary kidney disease has been postulated to cause decreased cardiac function and an increased risk of adverse cardiovascular events.[4]

Recent studies have shown chronic haemodialysis to be able to induce repeated, transient episodes of myocardial ischaemia that can result in myocardial hibernation, myocardial remodelling, scarring, and an irreversible loss of contractile function.[21] Importantly, this occurrence of dialysis-induced myocardial stunning carries strong prognostic importance. In a study of 70 prevalent dialysis patients, Burton *et al.*[21] found patients with signs of haemodialysis-induced myocardial stunning at baseline to have significantly worse parameters of cardiac structure, cardiac function, and survival after 1 year of follow-up. Unfortunately, a parallel assessment of echocardiographic function and BNP levels is not

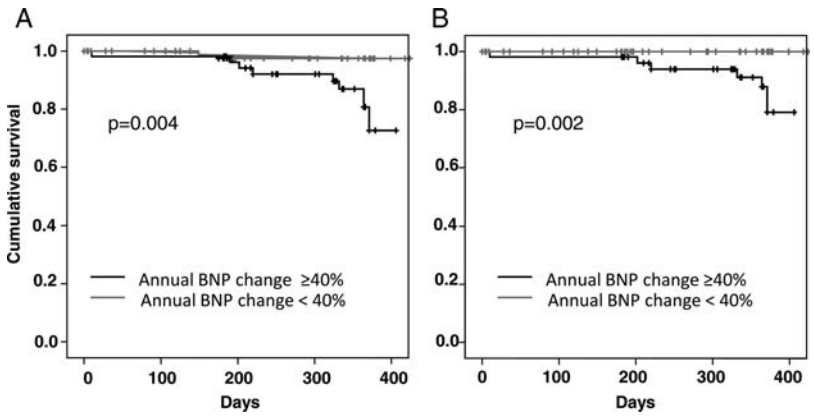

Figure 3 Cumulative overall (*A*) and cardiac (*B*) 1 year survival stratified by calculated optimal B-type natriuretic peptide change cut-off values.

yet available. Nevertheless, it seems reasonable to suggest that the decline in cardiac function described by Burton can be detected by sharply increasing BNP levels and that both are significantly associated with death. In our study, an annual BNP increase exceeding 40% was associated with an almost seven-fold increase in all-cause and cardiac mortality. In contrast, BNP levels remained stable in survivors; only five deaths occurred in patients with stable BNP levels. Importantly, annual BNP changes over 40% induced a delayed rather than an immediate rise in mortality. This was shown by the patients' survival curve, which only started to decline after about 4 months in the subsequent year. Interestingly, this delayed increase in mortality closely resembles the results described by Burton *et al.*,[21] who found dialysis-induced stunning to be associated with an increased mortality after about 4 months.

In analogy to the benefits discussed for BNP-guided treatment in chronic heart failure,[10] this delayed response between increases in BNP and death could in the future create a window of opportunity for clinical interventions targeted at decreasing BNP levels. A BNP decreasing effect has, for example, been described with the beta-blocker metoprolol in dialysed patients. In a Japanese study, a 4-week course of metoprolol reduced average BNP levels by 75% in dialysis patients with left ventricular dilation.[22] Comparable results have also been described for carvedilol,[23] suggesting a class effect for beta-blocker therapy. In our study 10/17 patients dying of cardiac causes were on continuous beta-blocker treatment, beta-blockade was stopped in one patient but not initiated in any of the patients in the 18 months preceding cardiac death. The BNP-lowering effect of beta-blocker therapy in dialysed patients probably represents a successful counteraction of the sympathetic hyperactivity present in ESRD. Similarly, it has been documented that the use of renin−angiotensin−aldosterone system (RAAS) blocking agents significantly reduces sympathetic activation, left ventricular mass, and serum BNP levels[24] in dialysed patients. In our study, only two patients continuously received RAAS blocking agents during the 18 months preceding cardiac death, while RAAS blockade was not initiated or stopped in any of the patients during this period.

Furthermore, modifications of the dialysis technique have been shown to significantly decrease BNP levels and the occurrence of myocardial stunning. Odar-Cederlöf *et al.*[25] were able to significantly lower predialysis BNP levels by switching from a conventional thrice-weekly dialysis pattern to a daily dialysis regime while not increasing total weekly dialysis time. The daily dialysis regime completely abolished re-rising BNP levels between dialysis sessions. Similarly, a study directly comparing four patient groups [patients undergoing conventional thrice-weekly haemodialysis, patients undergoing more frequent dialysis (5−6×/week) in-centre, more frequent dialysis (5−6×/week) at home , and patients performing home nocturnal dialysis] found that the number of regional wall motion abnormalities per patient and the extent of myocardial dysfunction decreased with increasing dialysis frequency.[26] Additionally, increasing BNP levels should be used to initiate a search for underlying cardiac diseases aimed at improving cardiac function by decreasing myocardial ischaemia or improving valvular function. It is tempting to speculate that maintaining low BNP levels by frequent dialysis scheduling and medical therapies, may altogether avoid the scenario of a spike in BNP that ultimately leads to higher mortality. This hypothesis is indirectly backed by the significantly improved long-term survival of kidney transplant recipients compared with dialysis patients[27] and the rapidly decreasing BNP levels observed after renal transplantation.[28] We believe that the potential of a BNP-guided therapy should be investigated in further studies.

Our study has several limitations. These include the limited number of patients enrolled at a single dialysis centre. However, we analysed 650 time points of BNP measurements. Additionally, baseline characteristics, dialysis modalities, and mortality rates were similar to those observed in other national and international dialysis studies, as well as the USRDS annual report. Also, two retrospective analyses investigating NT-proBNP[29,30] appear to advocate the use of serial biomarker measurements in dialysis patients to improve their risk stratification. Furthermore, since we did not perform serial echocardiography, we were unable to determine the cardio-morphological changes underlying the

rapidly increasing BNP levels. However, previous studies have found BNP levels in haemodialysis patients to adequately reflect the degree of left-ventricular dysfunction, left-ventricular end-diastolic wall stress, and hypertrophy.[11–13] Nevertheless, the present results seem promising and have led to the initiation of the prospective, multi-centre Risk-Assessment by Cardiovascular BiomarkErs in Chronic DIALysis Patients (RACE-Dial) trial. This study will investigate the clinical potential of serial measurements of cardiac natriuretic peptides to predict cardiac death in chronic dialysis patients.

Conclusion

In patients undergoing chronic dialysis, cardiac death is preceded by a distinct increase in BNP levels, with annual BNP increases above 40% powerfully predicting all-cause and cardiac death in the subsequent year. Hence, serially measuring BNP levels may present a novel tool for the risk stratification and treatment guidance of ESRD patients on chronic dialysis. Whether a BNP-guided therapy has the potential to improve patient outcome should be investigated in further studies.

Conflict of interest: We disclose that C.M. and A.M. have received speaker honoraria from Biosite. All other authors declare that they have no conflict of interest.

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