Cardiac Natriuretic Peptides Are Related to Left Ventricular Mass and Function and Predict Mortality in Dialysis Patients

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Abstract. This study was designed to investigate the relationship among brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) and left ventricular mass (LVM), ejection fraction, and LV geometry in a large cohort of dialysis patients without heart failure ($n = 246$) and to test the prediction power of these peptides for total and cardiovascular mortality. In separate multivariate models of LVM, BNP and ANP were the strongest independent correlates of the LVM index. In these models, the predictive power of BNP was slightly stronger than that of ANP. Both natriuretic peptides also were the strongest independent predictors of ejection fraction, and again BNP was a slightly better predictor of ejection fraction than ANP. In separate multivariate Cox models, the relative risk of death was significantly higher in patients of the third tertile of the distribution of BNP and ANP than in those of the first tertile (BNP, 7.14 [95% confidence interval (CI), 2.83 to 18.01, $P = 0.00001$]; ANP, 4.22 [95% CI, 1.79 to 9.92, $P = 0.001$]), and a similar difference was found for cardiovascular death (BNP, 6.72 [95% CI, 2.44 to 18.54, $P = 0.0002$]; ANP, 3.80 [95% CI, 1.44 to 10.03, $P = 0.007$]). BNP but not ANP remained as an independent predictor of death in a Cox's model including LVM and ejection fraction. Cardiac natriuretic peptides are linked independently to LVM and function in dialysis patients and predict overall and cardiovascular mortality. The measurement of the plasma concentration of BNP and ANP may be useful for risk stratification in these patients.

End-stage renal disease is the classical clinical situation in which the cardiac natriuretic peptides are almost universally raised. Extracellular volume expansion, concomitant heart disease (1), and severely reduced or abolished renal clearance (2,3) are the main factors responsible for the high plasma concentration of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in uremic patients who are on chronic dialysis. ANP in these patients is related closely to cardiac filling pressure or to atrial volume (4–7), and the plasma concentration of both cardiac peptides declines after ultrafiltration-dialysis treatment (8–10). It has been suggested that the measurement of the plasma concentration of ANP may help to define better the ideal body fluid volume status (the "dry weight") (5,10), which is a problem in patients who are on chronic dialysis (11). However, it is widely recognized that cardiac function is a major confounder for the interpretation of prevailing ANP and BNP plasma concentration in chronic renal failure (12).

Although the hemodynamic determinants of circulating natriuretic peptides have been investigated thoroughly, the relationship between ANP and BNP and cardiac mass and function in dialysis patients has received only very scant attention (13). The issue is of importance because there is consistent evidence that cardiac natriuretic peptides are raised substantially in essential hypertensive patients with LV hypertrophy (LVH) and/or LV dysfunction (14–18) and that these hormones predict mortality (19–21). Because LVH is exceedingly frequent in the dialysis population and is the strongest predictor of death (22), we investigated the relationship among cardiac natriuretic peptides, cardiac mass, and geometry in a large cohort of dialysis patients without heart failure and tested the predictive power of these peptides for total and cardiovascular mortality.

Materials and Methods

Protocol

The protocol conformed to the ethical guidelines of our institutions, and informed consent was obtained from each participant. All studies were performed during a nondialysis day, between 8:00 a.m. and 1:00 p.m.

Study Cohort

A total of 246 patients with end-stage renal disease (137 men and 109 women) who had been on regular dialysis treatment (212 on

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hemodialysis [HD] and 34 on chronic ambulatory peritoneal dialysis) for at least 6 mo, with LV ejection fraction (LVEF) >35% and without history of clinical evidence of circulatory congestion (defined as dyspnea in addition to two of the following conditions: raised jugular pressure, bibasilar crackles, pulmonary venous hypertension or interstitial edema on chest x-ray, requiring hospitalization or extra ultrafiltration (23)), were eligible for the study. The main demographic and clinical characteristics of the patients included in the study are detailed in Table 1. All participants were in sinus rhythm at the time of the study. These patients represented approximately 70% of the whole dialysis population of four dialysis units. The remaining 30% of patients were excluded because of the presence of circulatory congestion or major infections (20%) or because they were hospitalized for intercurrent illnesses or for logistic reasons or unwillingness to participate in the study (10%). The prevalence of diabetes mellitus in this cohort was 15% (37 of 246 patients).

All HD patients were virtually anuric (24-h urine volume <200 ml/d), whereas a minority ($n = 6$) of chronic ambulatory peritoneal dialysis patients had a 24-h diuresis >500 ml/d. HD patients were being treated three times per week with standard bicarbonate dialysis (138 mmol/L Na, 35 mmol/L HCO_3, 1.5 mmol/L K, 1.25 mmol/L Ca, 0.75 mmol/L Mg) and cuprophan or semisynthetic membranes (dialysis filter surface area, 1.1 to 1.7 m^2). Dry weight was established for each patient on a trial-and-error basis and was defined as the weight below which the patient experienced frequent hypotensive episodes during the latter part of the dialysis session and experienced malaise, cramps, and dizziness postdialysis. Ninety-nine patients were habitual smokers (21 ± 16 cigarettes/d). A total of 130 patients were on treatment with erythropoietin. A total of 109 patients were on antihypertensive treatment (76 on monotherapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor type I antagonists, calcium channel blockers, and α- and β-blockers and 33 on double or triple therapy with various combinations of these drugs). After the initial assessment, patients were followed up for 26 ± 10 mo (range, 10 to 37). During the follow-up, cardiovascular events (ECG-documented anginal episodes and myocardial infarction, heart failure, ECG-documented arrhythmia, transient ischemic attacks, and stroke) and death were recorded accurately. Each death was reviewed and assigned an underlying cause by a panel of five physicians. As a part of the review process, all available medical information about each death was collected. This information always included study and hospitalization records. In the case of an out-of-hospital death, family members were interviewed by telephone to ascertain better the circumstances surrounding the death.

Table 1. Demographic, anthropometric, biochemical, and hemodynamic characteristics of the study population[a]

Characteristic	Quantity
Age (yr)	60.2 ± 15.3
Men/women	138/108
BMI (kg/m^2)	24.9 ± 4.4
Duration of dialysis treatment (mo)	43 (18–99)
Hemoglobin (g/L)	106.4 ± 19.0
Serum albumin (g/L)	40 ± 6
Serum C-reactive protein (mg/L)	7.4 (3.4–16.4)
Serum cholesterol (mmol/L)	5.33 ± 1.41
Serum phosphate (mmol/L)	1.90 ± 0.44
Serum calcium (mmol/L)	1.13 ± 0.13
Serum iPTH (pg/ml)	147 (60–331)
Kt/V[b]	
hemodialysis patients	1.22 ± 0.27
CAPD patients	1.66 ± 0.32
Systolic pressure (mmHg)	133.9 ± 22.4
Diastolic pressure (mmHg)	75.3 ± 12.3
Heart rate (beats/min)	80.9 ± 10.8

[a] Data are expressed as mean ± SD or as median (interquartile range), as appropriate. BMI, body mass index; iPTH, parathormone; Kt/V, fractional urea clearance; CAPD, chronic ambulatory peritoneal dialysis.

[b] Kt/V was calculated according to Sargent and Gotch (27) for hemodialysis patients and by a standard formula (28) for CAPD patients.

Laboratory Measurements

Blood sampling was performed between 8:00 a.m. and 10:00 a.m. during a nondialysis day. After 20 to 30 min of quiet resting in semirecumbent position, samples were taken into chilled ethylenediaminetetraacetic acid Vacutainers, placed immediately on ice, and centrifuged within 30 min at −4°C, and the plasma was stored at −80°C before assay. The plasma concentrations of α-human ANP and BNP were measured by commercially available RIA kits (Peninsula Laboratory Europe Ltd, St. Helens, Merseyside, UK) after preextraction by reverse chromatography (Seppak C-18 cartridges; Waters, Milford, MA). Recovery was >80% for both ANP and BNP. There was no cross reactivity between the two assays. The between-assay and within-assay coefficients of variability were 8 and 10%, respectively, for ANP and 9 and 11%, respectively, for BNP. The reference group was formed by 39 healthy, normotensive volunteers (22 men and 17 women; age, 40.5 ± 12.1 yr).

Echocardiography

Echocardiography studies were performed within 2 h after blood sampling. All echocardiographic measurements were carried out according to the recommendations of the American Society of Echocardiography by an observer who was unaware of biochemical results. LV mass (LVM) was calculated according to the Devereux formula and indexed to height$^{2.7}$ (LVMI) (24). LVH was defined by an LVMI of more than 47 g/$m^{2.7}$ in women or more than 50 g/$m^{2.7}$ in men. The height-based indexing of LVM was chosen specifically to minimize any potential distortion attributable to extracellular volume expansion (surface area indexing being weight sensitive). The relative wall thickness (2*posterior wall thickness/LV end diastolic diameter) also was calculated, as an index of the LV geometric pattern. Values indicative of concentric and eccentric LV geometry were established on the basis of age-specific reference standards (25). Systolic dysfunction was defined as an LVEF <45%.

BP Measurements

In HD patients, pre- and postdialysis BP were calculated as the average value of all recordings (12 measurements [3/wk]) taken during the month before the study. The mean value of pre- and postdialysis BP then was obtained for each patient and considered for global statistical assessment. In chronic ambulatory peritoneal dialysis patients, the BP values were obtained by averaging home BP measurements (10 to 20 measurements/mo).

Statistical Analyses

Data are reported as mean ± SD or as median and interquartile range. Comparisons between groups were made by the *t* test or the

Mann-Whitney U test or χ^2 test, as appropriate. Variables that showed a positively skewed distribution were log transformed (ln). Relationships between paired parameters were analyzed by the least square method (continuous variables).

For the performance multiple regression analyses of LVMI and LVEF (outcome variables), a set of independent variables were identified including gender, age, diabetes mellitus, treatment modality and time on regular dialysis treatment, fractional urea clearance (Kt/V) (26,27), smoking, antihypertensive therapy, systolic arterial pressure, hemoglobin, plasma ANP and BNP, albumin and C-reactive protein, cholesterol, calcium, phosphate, and parathormone. These variables then were used for a backward elimination strategy. Finally, the significant independent variables were ordered according to their standardized effect, defined as regression coefficient/standard error of the regression (β). By this strategy, we constructed models of adequate statistical power (at least 50 subjects for each variable in the final model).

Probability of survival was analyzed with the use of the multivariate Cox's proportional hazards model. Variables that had an independent influence on survival were identified by a backward elimination strategy starting with the same set of variables considered for the models of LVMI and LVEF. The relationship between natriuretic peptides and survival then was tested in Cox's models stratifying patients into three tertiles according to the plasma concentration of ANP and BNP and adjusting for all variables that had an independent effect on survival. Hazard ratios and their 95% confidence intervals (CI) were calculated with the use of the estimated regression coefficients and their standard errors in the Cox regression analysis. All calculations were made with the use of a standard statistical package (SPSS for Windows Version 9.0.1; SPSS, Inc., Chicago, IL).

Results

Heart Geometry in Dialysis Patients

A total of 194 (79%) patients displayed LVH on echocardiography. Eccentric LVH was the most frequent pattern (n = 98; 40%), followed by concentric LVH (n = 96; 39%) and concentric remodeling (n = 16; 6%). Only a minority of patients (n = 36; 15%) showed normal LVMI and geometry. Systolic dysfunction was present in 31 patients (13%).

Correlates of ANP and BNP

The plasma concentration of the two peptides was very close (ANP: median, 23.7 pmol/L [interquartile range, 15.8 to 44.9 pmol/L]; BNP: 24.4 pmol/L [10.4 to 48.2 pmol/L]), and there was a strong correlation between them (r = 0.81, $P < 0.0001$). On univariate analysis, both natriuretic peptides were related to age, time on regular dialysis treatment, smoking, systolic and pulse pressure, serum albumin and triglycerides, and all echocardiographic parameters of heart geometry analyzed (all $P <$ 0.02). Both peptides were inversely related to ejection fraction. Data analysis according to LV geometry showed that plasma ANP and BNP in patients with normal heart geometry were slightly but significantly increased in comparison with healthy volunteers. The natriuretic peptide concentrations were moderately elevated in patients with concentric remodeling and substantially raised in those with LVH (Figure 1).

The elevation in plasma BNP in patients with concentric remodeling or hypertrophy was relatively more pronounced than that of ANP so that the BNP/ANP ratio was higher (P = 0.001) in patients that showed these geometric patterns (median, 0.97; interquartile range, 0.72 to 1.32) in comparison with those that had normal geometry or eccentric hypertrophy (median, 0.74; interquartile range, 0.46 to 1.30).

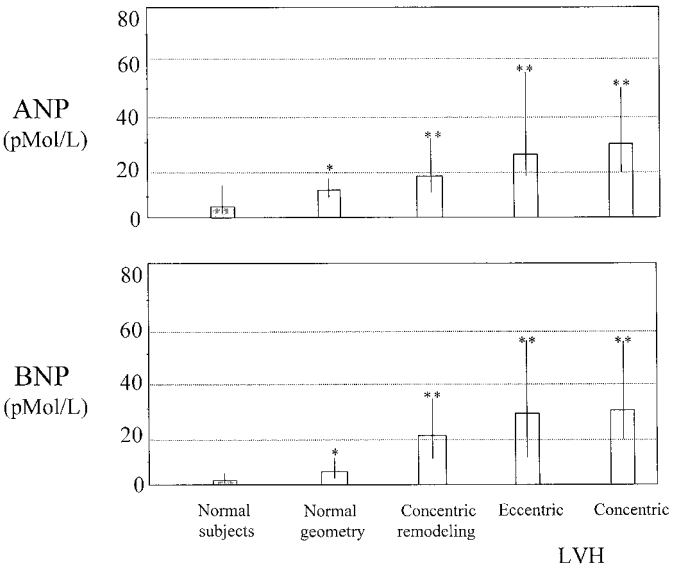

Figure 1. Plasma atrial natriuretic peptide (ANP) brain natriuretic peptide (BNP) in healthy volunteers and in patients with normal left ventricular (LV) geometry, concentric remodeling, and LV hypertrophy (LVH; see also Results section). Data are expressed as median and interquartile range. *, $P < 0.01$; **, $P < 0.0001$ *versus* healthy volunteers.

Multivariate Analysis: ANP and BNP, LVMI, and LVEF

In separate multivariate models of LVMI, ANP and BNP were the strongest independent correlates of LVMI (Table 2). In these models, the predictive power of BNP was slightly stronger than that of ANP, and only BNP remained as an independent correlate of LVM when both cardiac peptides were introduced into the same model. The natriuretic peptides also were the strongest independent predictors of LVEF (Table 2), and again BNP was a slightly better predictor than ANP. Accordingly, the plasma ANP and BNP concentrations were significantly higher ($P < 0.0001$) in patients with systolic dysfunction (LVEF <45%) than in those with normal systolic function (LVEF ≥45%; Figure 2), and the difference in BNP (adjusted, +145%; unadjusted, +150%) was more marked than that in ANP (adjusted, +83%; unadjusted, +100%).

Cardiac Natriuretic Peptides and Mortality

Seventy-four patients had one or more cardiovascular events during the follow-up period (Table 3). Plasma natriuretic peptides were higher ($P < 0.0001$) in those who had cardiovascular events (ANP: 33.5 pmol/L, 23.1 to 54.9 pmol/L; BNP: 36.4 pmol/L, 21.7 to 55.2 pmol/L) than in event-free patients (ANP: 19.2 pmol/L, 13.0 to 36.7 pmol/L; BNP: 16.5 pmol/L, 7.2 to 36.1 pmol/L). Overall, 63 patients died, 35 (56%) of cardiovascular causes (Table 3). Plasma

Table 2. Multivariate analyses of LVMI and LVEF[a]

Independent Variables	β	P
LVMI		
ANP-based model[b]		
ln ANP	0.33	0.0001
ln albumin	−0.21	0.0001
systolic pressure	0.16	0.006
age	0.15	0.009
antihypertensive therapy	0.12	0.03
diabetes mellitus	0.11	0.04
ln iPTH	0.10	0.05
BNP-based model[c]		
ln BNP	0.37	0.0001
ln albumin	−0.19	0.001
systolic pressure	0.16	0.002
age	0.16	0.003
diabetes mellitus	0.11	0.04
LVEF		
ANP-based model[d]		
ln ANP	−0.32	0.0001
gender	0.18	0.002
ln iPTH	−0.18	0.002
diabetes mellitus	−0.16	0.005
antihypertensive therapy	−0.13	0.02
BNP-based model[e]		
ln BNP	−0.40	0.0001
gender	0.20	0.0001
diabetes mellitus	−0.18	0.001
ln iPTH	−0.18	0.001

[a] LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; ANP, atrial natriuretic peptide; ln, logarithm (natural); BNP, brain natriuretic peptide. Because of the strong ANP–BNP collinearity (see Results) the predictive power of the two peptides for LVMI and LVEF was tested in separate multiple regression models. Data are standardized regression coefficient (β) and P values. Factors that did not contribute significantly to the models may be deducted from the description of the multivariable strategy adopted in this study (see Statistical Analyses section).
[b] Multiple R = 0.64; $P = 0.0001$.
[c] Multiple R = 0.63; $P = 0.0001$.
[d] Multiple R = 0.49; $P = 0.0001$.
[e] Multiple R = 0.52; $P = 0.0001$.

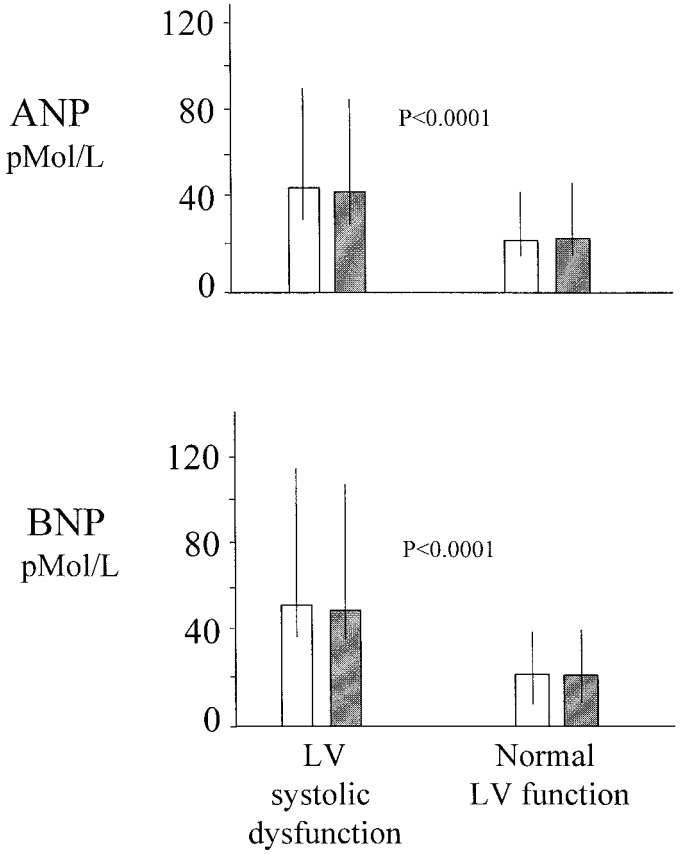

Figure 2. Unadjusted (□) and adjusted (▨) plasma ANP and BNP in patients with normal LV function and in those with systolic dysfunction. Adjustments were done for covariates that had an independent effect on LVEF (see Table 2).

ANP and BNP were significantly higher (both $P < 0.0001$) in patients who died during the follow-up period (ANP: 39.0 pmol/L, 24.4 to 65.0 pmol/L; BNP: 45.1 pmol/L, 26.6 to 71.4 pmol/L) than in those who survived (ANP: 21.1 pmol/L, 14.3 to 37.4 pmol/L; BNP: 20.5 pmol/L, 9.2 to 37.6 pmol/L). Similarly, natriuretic peptides were higher ($P < 0.0001$) in patients who died of cardiovascular causes (ANP: 36.4 pmol/L, 22.1 to 57.5 pmol/L; BNP: 45.1 pmol/L, 26.6 to 58.4 pmol/L) than in patients who did not have cardiovascular events (ANP: 19.2 pmol/L, 13.0 to 36.7 pmol/L; BNP: 16.5 pmol/L, 7.2 to 36.1 pmol/L). In separate multivariate Cox models, both natriuretic peptides were highly significant and independent predictors of overall and cardiovascular death (Table 4). In a stratified analysis (Figure 3), the overall risk of death (adjusted for the other independent predictors; see Table 4) was progressively higher from the first tertile onward. The relative risk of death of patients in the third tertile of the distribution of ANP was 4.22 times higher (95% CI, 1.79 to 9.92; $P = 0.001$) than that of those in the first tertile. BNP was an even stronger predictor of death; the relative risk of patients in the third tertile was 7.14 times higher (95% CI, 2.83 to 18.01; $P = 0.00001$) than that in those of the first tertile. Similar differences were found also for cardiovascular death (ANP: 3.80 [95% CI, 1.44 to 10.03], $P = 0.007$; BNP: 6.72 [95% CI, 2.44 to 18.54], $P = 0.0002$).

Combined Prediction Power of Cardiac Natriuretic Peptides in a Cox's Model Including LVM and LV Function

In a model of overall mortality including plasma ANP and BNP as well as LVM, ejection fraction, and all covariates tested in previous models (see Table 4), BNP was the second independent predictor of death (hazard ratio, 1.62 [95% CI, 1.20 to 2.17]; $P = 0.001$) after LVMI, which was the strongest

Table 3. Cardiovascular events (fatal and nonfatal) and causes of death in the study cohort

Cardiovascular Events	*n*	Causes of Death	*n*
Arrhythmia	15	Cardiovascular arrhythmia	4
Stroke	15	stroke	9
Heart failure	12	heart failure	8
Myocardial infarction	10	myocardial infarction	8
Angina pectoris	9	sudden death	3
Sudden death	3	pulmonary embolism	2
Pulmonary embolism	2	mesenteric infarction	1
Peripheral artery disease	2	Other causes	
Mesenteric infarction	11	cachexia	10
Transient ischemic attack	2	sepsis/infection	9
Major venous thrombosis	2	neoplasia	3
Retinal artery thrombosis	1	hyperkalemia	3
		gastrointestinal hemorrhage	1
		diabetes mellitus, hyperosmolar coma	1
		treatment withdrawal	1
Total	74	Total	63

one (hazard ratio, 1.03 [95% CI, 1.01 to 1.04]; $P = 0.0003$; Table 5).

Discussion

In a large cohort of dialysis patients, the ANP and BNP were linked independently to LVM and function and predicted total and cardiovascular mortality.

Uremic patients are at very high cardiovascular risk, and LVH is a main component of this risk (22). Volume and pressure load are fundamental determinants of LVH in the general population as well as in patients with chronic renal failure (28). Because raised ventricular mass and pressure load independently enhance the synthesis of ANP and BNP, the plasma concentration of these peptides is linked strongly to cardiac mass and function (14–18). Whether these relationships hold true in dialysis patients and whether they predict cardiovascular events and death in end-stage renal disease is unknown.

Natriuretic Peptides, LVMI, and LV Function in Renal Failure

The potential value of BNP as an indicator of LVH and LV dysfunction in dialysis patients was considered previously only in one small study (13), which reported a direct correlation between BNP and LVMI and an inverse correlation with LVEF. In a sizeable cohort of dialysis patients without heart failure, we found that the two main cardiac hormones ANP and BNP were strongly interrelated and associated to LVMI and LVEF. Both peptides were raised slightly in patients with normal LVMI and geometry, moderately in those with concentric remodeling, and most significantly in those with LVH (either eccentric or concentric). Our observation that ANP and BNP were increased only moderately in the absence of alterations in cardiac mass and in cardiac geometry indicates that LVH and LV remodeling are major determinants of raised cardiac natriuretic peptides in dialysis patients. Conversely, the finding that the plasma ANP and BNP concentration was highest in dialysis patients with concentric hypertrophy is of particular interest because this geometric pattern, together with systolic dysfunction, identifies patients who have the worst prognosis (29). BNP was relatively higher than ANP in patients with concentric remodeling or hypertrophy (as indicated by their highly significant increased BNP/ANP ratio) than in those with eccentric hypertrophy or normal geometry, suggesting that, because of the ventricular origin, BNP is a better indicator of these geometric alterations of heart mass than ANP. Overall, our data extend to the uremic population observations made in patients with essential hypertension by Yamamoto *et al.* (15) and by Nishikimi *et al.* (16) and for the first time show that in uremic patients, the plasma natriuretic peptide concentration is determined mainly by LVMI and LVEF. Importantly, our detailed multivariate analysis showed

Table 4. Cox proportional hazard models for overall and cardiovascular mortality based on ANP and BNP[a]

Model	Hazard Ratio	95% CI	*P*
Cox proportional hazard model for overall mortality			
ANP-based model			
ln ANP	2.39	1.59–3.59	0.00001
Kt/V	0.22	0.09–0.56	0.001
age	1.03	1.01–1.05	0.006
ln albumin	0.04	0.004–0.44	0.008
ln cholesterol	4.50	1.43–14.13	0.01
diabetes mellitus	2.10	1.13–3.87	0.02
BNP-based model			
ln BNP	1.93	1.45–2.57	0.00001
Kt/V	0.24	0.10–0.59	0.002
ln cholesterol	5.33	1.75–16.25	0.003
age	1.03	1.01–1.05	0.006
ln albumin	0.04	0.004–0.41	0.006
diabetes mellitus	2.34	1.22–4.50	0.01
systolic pressure	0.99	0.97–1.00	0.02
Cox proportional hazard model for cardiovascular mortality			
ANP-based model			
calcium	2.41	1.39–4.16	0.002
Kt/V	0.11	0.03–0.45	0.002
ln ANP	2.13	1.29–3.52	0.003
age	1.04	1.01–1.07	0.009
BNP-based model			
ln BNP	1.71	1.23–2.38	0.001
calcium	2.33	1.36–3.99	0.002
Kt/V	0.12	0.03–0.47	0.002
age	1.04	1.01–1.07	0.009

[a] Factors that did not contribute significantly to the models may be deducted from the description of the multivariable strategy adopted in this study (see Statistical Analyses section).

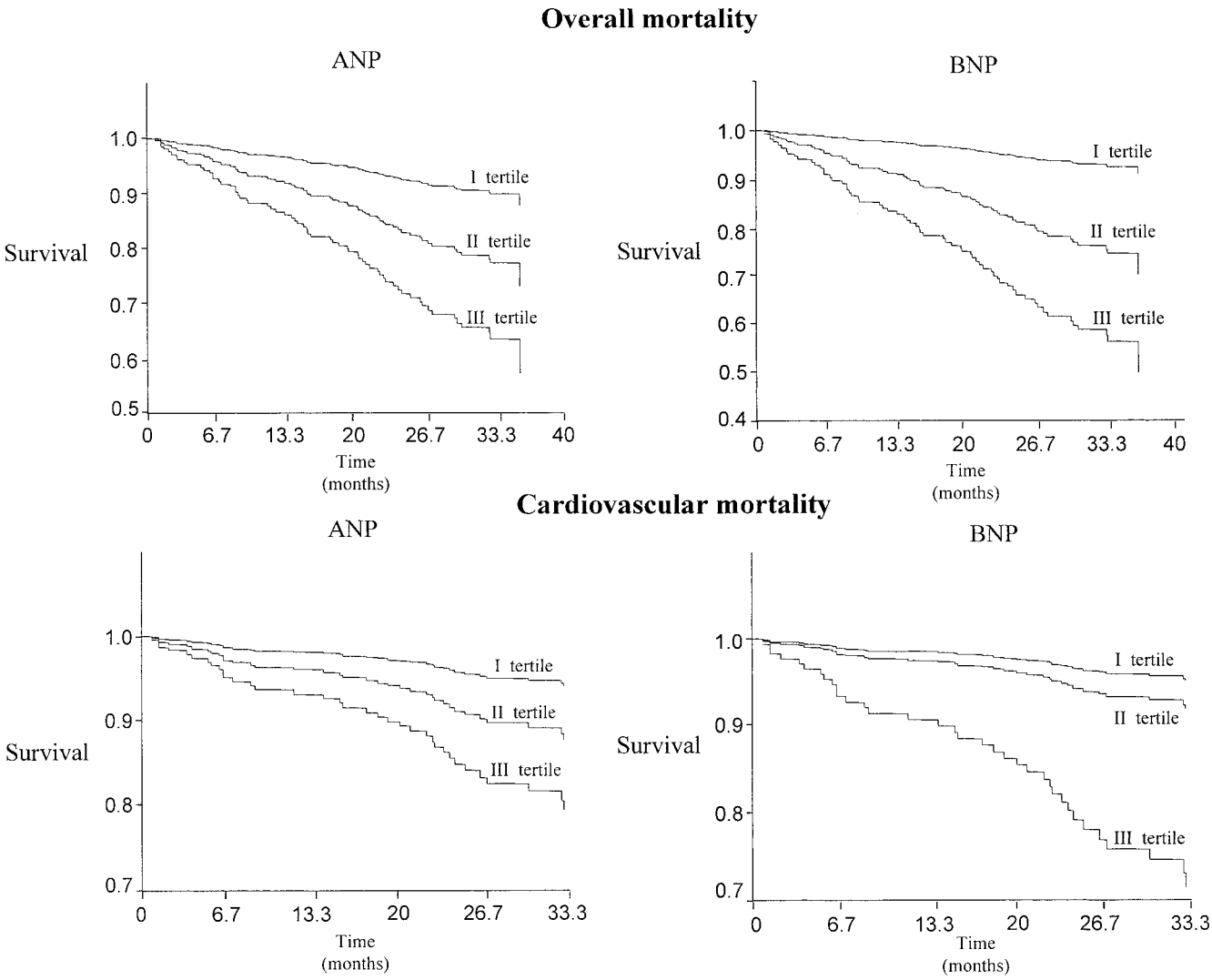

Figure 3. Cox proportional hazard survival curves for overall mortality and for cardiovascular mortality in the study cohort. Patients were stratified into three tertiles according to ANP and BNP plasma concentrations. I tertile, ANP <17.9 pmol/L; BNP <14.3 pmol/L. II tertile, ANP >17.9 and <34.8 pmol/L; BNP >14.3 and <36.1 pmol/L. III tertile, ANP >34.8 pmol/L; BNP >36.1 pmol/L. Data were adjusted for the other independent predictors of death (see Table 4).

that the link of ANP and BNP with LVMI and LV function is largely independent of other established determinants of these parameters in renal failure, such as serum albumin, systolic pressure, age, diabetes, gender, and parathormone.

Natriuretic Peptides and Mortality

In the general population, the prognostic value of natriuretic peptides for overall and cardiovascular mortality has been tested in patients with myocardial infarction (19–21) and heart failure (30). In both situations, raised plasma ANP and BNP levels were associated with a shorter survival and BNP was a stronger predictor than ANP. Heart failure in dialysis patients almost invariably entails an ominous prognosis; the 2-yr survival in these patients is as low as 33% (31). Perhaps the most important area for cardiovascular intervention in the dialysis population is LVH, which is the proximate forerunner of heart failure (32). In this regard, it is noteworthy that in our cohort of patients without heart failure at baseline, ANP and BNP emerged as powerful predictors of death by multiple forms of analysis. In the simpler analysis, both peptides were higher in patients who had cardiovascular events and/or died during the follow-up. In multivariate models of death and cardiovascular complications (Cox's proportional hazard method), ANP and BNP were the strongest independent predictors of the outcome after age. The prediction power of natriuretic peptides most likely depends on their being closely linked to LV mass and function. However, it is worth noting that BNP remained a significant predictor of survival also in a model incorporating LVM and ejection fraction, which suggests that this peptide is associated with survival also independent of these factors. Furthermore, BNP displayed a greater predictive power for mortality than ANP, thus indicating that the measurement of this substance is more informative than that of ANP.

The problem of reducing cardiovascular risk in dialysis

Table 5. Combined prediction power of cardiac natriuretic peptides for survival in a Cox's model including LV mass and function[a]

Parameter	Hazard Ratio	95% CI	*P*
ln LVMI	1.03	1.01–1.04	0.0003
ln BNP	1.62	1.20–2.17	0.001
KT/V	0.21	0.08–0.53	0.001
ln Cholesterol	5.44	1.71–17.30	0.004
Systolic pressure	0.98	0.97–0.99	0.004
Age	1.03	1.01–1.05	0.007
ln Albumin	0.06	0.01–0.65	0.02
Diabetes mellitus	1.93	1.01–3.69	0.048

[a] Ejection fraction did not contribute significantly to explain the outcome ($P = 0.16$). Other factors that did not contribute significantly to the models may be deducted from the description of the multivariable strategy adopted in this study (see Statistical Analyses section).

patients is now considered an absolute priority (33). Because LVH is a major risk factor for mortality in these patients, it constitutes a potentially important target for intervention. Our findings that natriuretic peptides, particularly BNP, are linked to LVMI and LV function and that they predict mortality indicate that the measurement of the plasma concentration of these cardiac hormones might be useful for risk stratification and for guiding treatment in observational or intervention studies in dialysis patients. This intriguing possibility, whose value has been studied recently in the general population (34), remains to be tested in specifically designed studies in patients with end-stage renal disease.

Appendix: Creed Investigators

Giuseppe Enia, Vincenzo Panuccio, Carmela Marino, and Rocco Tripepi (Centro di Fisiologia Clinica del CNR e Divisione di Nefrologia, Reggio Calabria, Italy); Francesco Rapisarda, Pasquale Fatuzzo, and Grazia Bonanno (Divisione Clinicizzata di Nefrologia Chirurgica, Università di Catania, Italy); Giuseppe Seminara and Benedetta Stancanelli (Istituto di Medicina Interna e Geriatria, Università di Catania, Italy); Vincenzo Candela, Onofrio Marzolla, and Carlo Labate (Servizio Dialisi di Melito Porto Salvo, Reggio Calabria, Italy); and Filippo Tassone (Servizio di Cardiologia Ospedale Morelli, Reggio Calabria, Italy).

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