The Relationship of NT-proBNP and Dialysis Parameters with Outcome of Incident Haemodialysis Patients: Results from the Membrane Permeability Outcome Study

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Key Words

NT-proBNP · BNP · Cardiovascular diseases · Haemodialysis · Mortality · High flux membrane · Randomised trials

Abstract

Background/Aims: The association of raised levels of natriuretic peptides with elevated risk of mortality was investigated in the present analysis of the Membrane Permeability Outcome study. **Methods:** N-terminal probrain type natri-

uretic peptide (NT-proBNP) was measured in 618 incident haemodialysis patients, randomised to either high-flux or low-flux. Characteristics of patients with NT-proBNP levels below or above the median were descriptively analysed and survival analysis was performed. **Results:** Median NT-proBNP value was 2,124 pg/ml, with 1,854 pg/ml in the high-flux and 2,919 pg/ml in the low-flux group. Survival probability was lowest in patients with both a history of cardiovascular disease and NT-proBNP values above the median ($p < 0.001$). A multivariate Cox proportional hazard model showed inter-

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action between presence of cardiovascular diseases and NT-proBNP levels above the median. **Conclusions:** NT-proBNP is an independent predictor of mortality also in incident haemodialysis patients. Lower concentrations associated with high-flux dialysis suggest a possible biological link to improved survival in this group.

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Introduction

Brain natriuretic peptide (BNP) belongs to the family of natriuretic peptides, which play a major role in the regulation of blood pressure and extracellular volume through stimulation of natriuresis [2]. BNP is produced by the ventricular myocardium in response to increased myocardial wall stress [3] as a prehormone (proBNP), which, upon release into the circulation, is cleaved into the biologically active C-terminal fragment (BNP) and the biologically inactive N-terminal fragment (NT-proBNP) [4].

In the general population, elevated NT-proBNP levels have been found to be associated with an increased risk of death and of cardiovascular events [5]. In patients with heart failure, both BNP and NT-proBNP are elevated, and the concentrations are related to the stages of heart failure as classified by the New York Heart Association [6]. Patients with chronic kidney disease (CKD) stages 3–4 have NT-proBNP levels that are elevated to some extent [7], and in patients with CKD 5 on dialysis (CKD 5D), these concentrations are several times higher than in the general population. NT-proBNP levels have prognostic value for left ventricular disorders, coronary artery disease, hypervolaemia and mortality [3, 8–10] and have been found to be associated with residual diuresis and dialysis dose [8]. As BNP and NT-proBNP are renally cleared, the concentration cut-off needs to be raised to maintain the predictive prognostic value in patients with both heart failure and CKD [11]. Thus, high levels of NT-proBNP in CKD patients are not only due to the higher prevalence of cardiovascular diseases, which develop for many causes including inadequate volume control, but also increase in parallel with decreasing renal function [8].

NT-proBNP and BNP are composed of 76 and 32 amino acids (8.5 and 3.5 kDa), respectively. The different molecular size of these two peptides could explain their disproportionate increase in concentration observed in CKD 5D [12] due to variable elimination by the kidney and across the dialysis membrane. Thus, the haemodi-

alysis (HD) procedure could influence NT-proBNP concentrations, as suggested by the correlation with Kt/V [8] and as an effect of membrane flux. Increased NT-proBNP levels have been observed after HD sessions with low-flux [13] and decreased levels after sessions with high-flux dialysers [14–16]. As NT-pro BNP has a longer half-life time than the biologically active compound BNP, it is less prone to laboratory artefacts and might better reflect the pathophysiological situation leading to elevated BNP levels [17]. Moreover, as for BNP itself, also NT-proBNP has been identified as a strong predictor of mortality, and even a more reliable predictor of cardiovascular events [18]. For these reasons, NT-proBNP was chosen as a marker in this secondary analysis of the Membrane Permeability Outcome (MPO) study, the aim of which was to generate novel evidence of the effect of dialysis membrane flux and clinical parameters on NT-proBNP levels and their relationship with the risk of mortality in incident HD patients.

Materials and Methods

Study Design and Objectives

The primary objective of the MPO study was to examine the mortality rates in incident CKD patients being treated with either high-flux or low-flux haemodialysis [1]. The present secondary analysis of the MPO study was carried out to study the effect of membrane flux on NT-proBNP serum concentrations and their effect on patient outcome. This open, prospective, randomised, controlled clinical trial was implemented in 59 HD centres in 9 European countries. A total of 738 incident HD patients who had received less than two months of dialysis were enrolled between December 1998 and June 2003.

The study adhered to the Declaration of Helsinki, and was approved by the national or local ethics committees of all participating centres according to national legislation. All patients gave informed consent before being enrolled into the study. Patients meeting the inclusion and exclusion criteria were enrolled, and demographic data, medical history, concomitant medication, current dialysis treatment parameters and residual renal function at study entry were recorded. Then patients were randomised to be treated with either high-flux or low-flux membranes. After randomisation and start of treatment in the respective study group, the patients underwent a one-month run-in phase on the allocated dialyser to adjust treatment parameters to achieve a dialysis dose (Kt/V) of at least 1.2. At month 0, the first serum samples were taken to determine biochemical parameters. All patients were observed until the latest enrolled patients reached a maintenance period of 3 years. The study design of this trial is described in more detail elsewhere [19].

NT-proBNP in serum samples from month 0 were analysed centrally using the Roche Elecsys[®] kit, an electrochemiluminescence ‘sandwich’ immunoassay based on polyclonal antibodies against NT-proBNP [20].

Table 1. NT-proBNP at month 0 by membrane flux and serum albumin at study entry

	n	NT-proBNP (pg/ml)		
		mean $\pm$ SD	median (min.–max.)	p value
All patients	618	6,224 $\pm$ 8,953	2,124 (5–35,000)	
High-flux	301	5,100 $\pm$ 7,827	1,854 (5–35,000)	<0.001
Low-flux	317	7,291 $\pm$ 9,798	2,919 (88–35,000)	
Serum albumin $\leq$ 4 g/dl	470	6,443 $\pm$ 9,159	2,367 (5–35,000)	0.07
Serum albumin >4 g/dl	148	5,330 $\pm$ 8,253	1,833 (88–35,000)	
Albumin $\leq$ 4 g/dl				
High-flux	235	5,139 $\pm$ 7,962	1,829 (5–35,000)	<0.001
Low-flux	235	7,746 $\pm$ 10,066	3,402 (110–35,000)	
Albumin >4 g/dl				
High-flux	66	4,963 $\pm$ 7,380	1,971 (134–35,000)	0.71
Low-flux	82	5,987 $\pm$ 8,913	1,778 (88–35,000)	

Statistical Analysis

The parameters used in the present analysis were collected at patient inclusion (e.g. medical history), at the start of the run-in phase (treatment parameters and Kt/V) or at month 0 (4 weeks after patient enrolment) for laboratory parameters. Cardiovascular diseases included congestive heart failure, previous myocardial infarction, cardiac arrhythmia, coronary artery disease, and peripheral vascular disease. Descriptive analysis, including means and frequencies depending on the type of parameter, was performed for patient and treatment characteristics. Statistical significance of differences was tested with the ANOVA test for continuous and normally distributed parameters, the Mann Whitney U test for non-normally distributed parameters or Fisher's exact test for categorical parameters.

Separate Kaplan-Meier survival analyses were performed for the composite endpoint death and cardiovascular death (applying censoring for patients dying from non-cardiovascular causes). Patients were censored at the time of premature study termination for the defined reasons.

Statistical significance of the difference between the Kaplan-Meier survival curves was calculated with the log-rank test. In a Cox proportional hazards model, NT-proBNP, membrane permeability, and baseline parameters (age, gender, body mass index, presence of diabetes mellitus, cardiovascular diseases), together with laboratory parameters, blood pressure, and ultrafiltration volume at month 0 were included to assess the relative risk of mortality. These factors were used first in a univariate model. All parameters showing an association with mortality at a p value <0.1 were included in a multivariate model; membrane flux was forced into the model irrespective of the p value.

In all these models, interaction of NT-proBNP with prevalence of cardiovascular disease was examined. Patients were grouped into 4 classes according to NT-proBNP values below or above the median and the presence/absence of cardiovascular disease. The synergy index was calculated as a measure to describe the amount

of interaction (according to de Mutsert et al. [21]). Unless stated otherwise, all data are given as mean $\pm$ standard deviation. Statistical significance was assumed for a p value <0.05.

Results

Patient Characteristics

Out of 647 patients representing the analysis population of the MPO study, NT-proBNP levels were available from 618 patients. The mean NT-proBNP concentration was 6,224 $\pm$ 8,953 pg/ml with a median of 2,124 pg/ml (table 1), indicating a skewed distribution of this parameter in HD patients.

When serum samples were drawn for the first time (month 0), patients had already been treated for 4 weeks with their study dialyser. Accordingly, the median NT-proBNP level was significantly lower (1,854 pg/ml) in patients in the high-flux than in those in the low-flux group (2,919 pg/ml, p = 0.0002). Following classification of patients into a higher or lower risk group [1], patients with serum albumin levels $\leq$ 4 g/dl had a nonsignificantly higher median concentration of NT-proBNP (2,367 pg/ml) than patients with serum albumin levels >4 g/dl (1,833 pg/ml, p = 0.07). Within the hypoalbuminaemic patients, the median NT-proBNP level was significantly lower in the high-flux than in the low-flux group (table 1). On the other hand, such a difference was not visible in the smaller patient group with albumin levels >4 g/dl.

Table 2. Patient characteristics according to concentration of NT-proBNP at month 0

	NT-proBNP <2,124 pg/ml (n = 309)	NT-proBNP ≥2,124 pg/ml (n = 309)	p value
Age, years	57.1±13.8	62.9±12.3	<0.001
Male gender	215 (69.6)	183 (59.2)	0.009
Diabetes	64 (20.7)	84 (27.2)	0.07
Cardiovascular disease*	56 (18.1)	112 (36.2)	<0.001
Congestive heart failure	4 (1.3)	24 (7.8)	<0.001
Previous myocardial infarction	12 (3.9)	31 (10.0)	0.004
Cardiac arrhythmia	8 (2.6)	38 (12.3)	<0.001
Coronary artery disease	24 (7.8)	59 (19.1)	<0.001
Peripheral vascular disease	33 (10.7)	51 (16.5)	0.046
Blood pressure			
Systolic, mm Hg	139±21	147±21	<0.001
Diastolic, mm Hg	78±12	79±12	0.14
Body mass index	25.3±4.4	25.3±4.2	0.86
Residual diuresis >100 ml/day	251 (81.2)	232 (75.1)	0.08
Glomerular filtration rate, ml/min	4.3±3.8	3.1±2.7	<0.001
CRP, mg/l			
Mean ± SD	6.8±10.3	13.3±22.4	
Median (range)	1.9 (b.d.–93)	5.3 (b.d.–158)	<0.001
Phosphate, mg/dl	5.1±1.5	5.1±1.7	0.97
Low-density lipoprotein, mg/dl	111.8±36.2	112.5±40.4	0.81
Albumin, g/dl	3.9±0.5	3.8±0.5	<0.001
β ₂ -Microglobulin, mg/l	18.4±7.6	21.7±8.3	<0.001
Membrane flux, high-flux	170 (55.0)	131 (42.4)	0.002
Kt/V	1.34±0.28	1.37±0.28	0.17
Ultrafiltration volume, l	1.8±1.0	2.0±1.0	0.05

Data given as mean ± standard deviation or number with percentage in parentheses, unless stated otherwise.

* Since patients may be affected by multiple cardiovascular diseases, the percentages of the individual diseases do not add up to the percentage of patients affected by any cardiovascular disease. b.d. = Below detection limit.

The median of 2,124 pg/ml was taken to form two groups with NT-proBNP higher or lower than this value at month 0. The demographic, clinical and biochemical parameters of these two groups are given in table 2. The group of patients with high NT-proBNP was older, contained a higher percentage of females, a higher percentage of patients with diagnosed diabetes and/or cardiovascular diseases, and had a higher mean systolic blood pressure. Further, this group included a nonsignificantly higher percentage of anuric patients and consequently had a lower mean glomerular filtration rate. Of the relevant laboratory parameters, C-reactive protein (CRP) and β₂-microglobulin were significantly elevated in the group with higher NT-proBNP and serum albumin was slightly lower, whereas no differences were seen for phosphate and low-density lipoprotein cholesterol. There was a statistically nonsignificantly higher mean ultrafiltration volume in the patient group with high NT-proBNP ($p = 0.05$; table 2).

Survival Analysis

During the observation period, 270 patients prematurely terminated the study due to kidney transplantation ($n = 170$), change of dialysis centre ($n = 58$), withdrawal of their consent to participate in the study ($n = 15$), change to peritoneal dialysis for more than 60 days ($n = 7$), recovery of renal function ($n = 1$), or to other not predefined reasons ($n = 19$). In the Kaplan-Meier survival analysis, these patients were censored at the time when premature termination occurred.

In this population of 618 patients, 157 deaths from all causes including 73 deaths from cardiovascular causes were recorded. A Kaplan-Meier survival analysis was performed to study the relationship of NT-proBNP and presence of cardiovascular disease with survival probability. Patients with NT-proBNP levels >2,124 pg/ml and cardiovascular disease at baseline ($n = 112$) showed particularly low survival probability, even less than expected

Fig. 1. Kaplan-Meier survival curves (all-cause mortality) for patients with/without cardiovascular diseases (CVD/no CVD) and NT-proBNP levels below and above median (low BNP/high BNP). Log-rank test $p < 0.001$.

when looking at both factors in a univariate analysis (fig. 1, $p < 0.001$). This is also reflected by a synergy index of 2.40, clearly deviating from 1, which indicates an additive interaction of both risk factors.

Univariate and Multivariate Analysis

A univariate analysis of the relationship of defined parameters with all-cause (table 3) and cardiovascular risk of mortality (table 4) was performed. The combination of increased NT-proBNP and presence of cardiovascular disease, age, diabetes, ultrafiltration volume and serum albumin concentration significantly affected the hazard ratio for all-cause and cardiovascular mortality. Low-density lipoprotein cholesterol, CRP (median split) and diastolic blood pressure were only associated with all-cause mortality. The multivariate model, including and adjusting for those parameters with a p value < 0.1 in the univariate model, demonstrated significant effects of NT-proBNP/cardiovascular predisposition, age, diabetes, and serum albumin on all-cause mortality as well as on cardiovascular mortality.

In particular, the multivariate model confirmed the more-than-additive risk increase for patients with high NT-proBNP and presence of cardiovascular disease (for all-cause mortality: HR 2.61, $p < 0.001$), whereas patients showing high NT-proBNP but no cardiovascular disease

(HR 1.095, $p = 0.70$) and patients with low NT-proBNP and cardiovascular disease (HR 1.29, $p = 0.39$) showed no significantly increased risk compared to patients without both risk factors. Also in a multivariate model with adjustment, the synergy index of 5.85 indicates an additive interaction.

Discussion

The results of this Pan-European study of more than 600 patients provide novel evidence of the role of NT-proBNP as an independent predictor of mortality in incident HD patients. This corroborates recently published data indicating that BNP is a predictor of mortality in incident HD patients [22, 23] and supports earlier findings that the serum concentration of NT-proBNP is an independent predictor of all-cause mortality in the general population and in all CKD stages.

Moreover, our data confirm that NT-proBNP levels in CKD 5D patients are higher by far than in patients with congestive heart failure and normal kidney function. In such clinical settings, the cut-off point for diagnosis of heart failure has been proposed to be at 300 pg/ml [11], whereas in other studies, concentrations measured in CKD patients show median values and interquartile ranges which are even higher than in our population [8, 24]. The longer dialysis vintage time in these two studies and the likely consequent lower residual renal function could explain the higher concentrations observed. On the other hand, the dependency of NT-proBNP concentrations on dialysis vintage and treatment parameters such as Kt/V [8] may weaken the prognostic value of BNP for heart failure in the dialysed population. However, the standardised minimum dialysis dose with a Kt/V of 1.2 in our study and the same dialysis vintage throughout our incident HD population might have minimised the effect of such potential confounders. Despite the possible influence of such factors, we, as others previously [8, 24, 25], could demonstrate a higher frequency of congestive heart failure in the group of patients with levels of NT-proBNP higher than the median and an increased hazard ratio of death associated with higher NT-proBNP concentrations.

We observed lower NT-proBNP concentrations in the group treated with high-flux membranes compared with the group treated with low-flux membranes. As the first blood sampling for laboratory analyses was performed at month 0, i.e. after randomisation and one month of dialysis treatment with the respective study dialyser, we interpret this difference as an effect of membrane flux, sim-

Table 3. Univariate and multivariate Cox proportional hazards model on all-cause mortality

	Univariate model			Multivariate model		
	HR	95% CI	p value	HR	95% CI	p value
Age (years)	1.059	1.040–1.078	<0.001	1.040	1.020–1.060	<0.001
Gender (ref.: male)	0.760	0.542–1.067	0.11	–	–	–
Diabetes (ref.: absent)	2.232	1.621–3.074	<0.001	1.780	1.274–2.486	<0.001
Residual diuresis (ref.: <100 ml/day)	1.040	0.698–1.549	0.85	–	–	–
Membrane flux (ref.: low-flux)	0.808	0.590–1.107	0.19	0.877	0.633–1.216	0.43
CRP (ref.: ≤1.9 mg/l)	1.557	1.123–2.153	0.008	–	–	–
Phosphate (mg/dl)	0.990	0.900–1.089	0.84	–	–	–
Low-density lipoprotein (mg/dl)	0.996	0.991–1.000	0.04	–	–	–
Albumin (g/dl)	0.919	0.891–0.948	<0.001	0.947	0.915–0.980	0.002
Systolic blood pressure (mm Hg)	0.998	0.990–1.006	0.55	–	–	–
Diastolic blood pressure (mm Hg)	0.984	0.970–0.997	0.02	–	–	–
BMI	1.017	0.983–1.052	0.34	–	–	–
Ultrafiltration volume (ml)	0.799	0.675–0.944	0.009	–	–	–
BNP/cardiovascular disease (ref.: –/–)						
BNP +/cardiovascular disease –	1.210	0.767–1.908	0.41	1.095	0.686–1.746	0.70
BNP –/cardiovascular disease +	1.979	1.128–3.474	0.02	1.290	0.720–2.313	0.39
BNP +/cardiovascular disease +	4.323	2.848–6.563	<0.001	2.614	1.662–4.110	<0.001

Table 4. Univariate and multivariate Cox proportional hazards model on cardiovascular mortality

	Univariate model			Multivariate model		
	HR	95% CI	p value	HR	95% CI	p value
Age (years)	1.049	1.024–1.075	<0.001	1.034	1.007–1.062	0.02
Gender (ref.: male)	0.788	0.481–1.291	0.34	–	–	–
Diabetes (ref.: absent)	2.976	1.879–4.714	<0.001	2.453	1.535–3.920	<0.001
Residual diuresis (ref.: <100 ml/day)	0.972	0.550–1.715	0.92	–	–	–
Membrane flux (ref.: low-flux)	0.818	0.516–1.298	0.39	0.882	0.552–1.409	0.60
CRP (ref.: ≤1.9 mg/l)	1.315	0.823–2.101	0.25	–	–	–
Phosphate (mg/dl)	1.078	0.944–1.230	0.27	–	–	–
Low-density lipoprotein (mg/dl)	0.999	0.994–1.005	0.84	–	–	–
Albumin (g/dl)	0.920	0.880–0.962	<0.001	0.947	0.901–0.995	0.03
Systolic blood pressure (mm Hg)	0.999	0.988–1.011	0.90	–	–	–
Diastolic blood pressure (mm Hg)	0.994	0.975–1.014	0.58	–	–	–
BMI	1.008	0.958–1.060	0.77	–	–	–
Ultrafiltration volume (l)	0.758	0.592–0.971	0.03	–	–	–
BNP/cardiovascular disease (ref.: –/–)						
BNP +/cardiovascular disease –	1.134	0.589–2.185	0.71	1.018	0.525–1.972	0.96
BNP –/cardiovascular disease +	2.043	0.934–4.467	0.07	1.245	0.558–2.781	0.59
BNP +/cardiovascular disease +	3.667	1.998–6.729	<0.001	2.154	1.135–4.088	0.02

ilar to our findings for β_2 -microglobulin, as all other parameters were well balanced [1]. We have indications that the difference of NT-proBNP concentrations in the high-flux and the low-flux group persisted also over time (12 months, data not shown). This is further supported by findings in earlier studies, reporting reductions of NT-proBNP levels by high-flux dialysers and lower NT-proB-

NP levels in prevalent patients treated with high-flux membranes [8, 15, 16]. The hypothesised effect of reduced levels of NT-proBNP in the high-flux group might be related either to the molecule acting itself as a uraemic toxin, or to the increased removal of other uraemic toxins with a positive effect on congestive heart failure and thus indirectly on BNP and patient outcome.

The MPO study primarily addressed a patient population at higher risk, defined by serum albumin levels ≤ 4 g/dl. In this group, we found higher NT-proBNP levels than in patients with serum albumin levels >4 g/dl. Based on the observed differences in median NT-proBNP levels in the hypoalbuminaemic patients, it is tempting to speculate that the lower levels achieved with high-flux membranes may contribute to the higher survival probability in this group [1]. Moreover, we also found a higher median CRP concentration in the group with NT-proBNP levels above the median in our population. In the multivariate model, the effect of increased CRP on overall mortality risk disappeared. This confirms that the prognostic value of NT-proBNP in CKD patients has to be interpreted with caution, as outlined above. An inverse correlation of NT-proBNP with serum albumin has been observed earlier [12, 26]. This could be an indication of fluid overload, which leads to an increased production of BNP as well as the expression of an inflammatory state. The reported positive correlation between NT-proBNP levels and CRP [12, 25] is thus in line with our findings. The link between fluid overload and elevated BNP production in our study population is also supported by the (nonsignificantly) higher mean ultrafiltration volumes applied in the high NT-proBNP group.

Patients with NT-proBNP levels in the upper range of our study population were around twice as likely to be affected by cardiovascular disease, confirming that these high levels are likely associated with an inflammatory process and the result of both the cardiac diseases associated with volume overload and impaired renal function. The contribution of impaired elimination by dialysis or via the kidney to elevated NT-proBNP levels is supported by a higher percentage of patients treated with low-flux dialysers and, although not statistically significant, a higher proportion of anuric patients in the group with NT-proBNP levels above the median. This underlines the complexity of elevated NT-proBNP levels as a result not only of the pathophysiological state but also of renal impairment and strategies of renal replacement therapy, and of patient-related factors, such as age and gender [27].

In our multivariate analysis, NT-proBNP concentration above the median, together with the presence of cardiovascular disease, was an independent predictor of all-cause mortality in addition to age, presence of diabetes and lower serum albumin. This prognostic value was found to be independent of the presence of residual renal function. In a similar model applied for cardiovascular mortality in our study, NT-proBNP concentration above the median together with the presence of cardiovascular diseases was

a significant prognostic factor. The synergy index, showing a more than additive effect, demonstrates an interaction between these two factors in their effect on outcome.

Although such models in other studies did not use exactly the same covariates for the adjustment, and mostly included prevalent patients [8, 25, 28], our data show that NT-proBNP is also a prognostic risk factor of mortality in incident HD patients, thus supporting aggressive care of these high-risk patients, in particular when cardiovascular diseases are also present.

We acknowledge limitations of this study. This is a secondary analysis, although of a randomised trial, where many variables, but certainly not all, were controlled. The attempt to first stabilise the delivered dialysis dose during a 4-week run-in period, before starting the maintenance phase of the study, meant that no baseline values were available before the patients were randomised to the respective membrane flux groups. Also only one value of NT-proBNP was used to address outcomes. Serial measurements are now recommended in the follow-up of chronic heart failure and a single determination may not have been able to capture less dramatic changes in the prognosis of intermediate risk patients (e.g. with cardiovascular history and low NT-proBNP levels or no cardiovascular history and high NT-proBNP levels).

The results of this study provide evidence from a large population that the serum concentration of NT-proBNP is a predictor, in part associated with history of cardiovascular disease, of all-cause and, marginally, also of cardiovascular mortality in incident HD patients.

NT-proBNP levels in CKD 5D patients are much higher than in patients with congestive heart failure and normal kidney function. These high levels are likely the result of cardiac diseases combined with volume overload, systemic inflammation, impaired renal function and dialyser membrane flux. This confirms that NT-proBNP can act as an integrative prognostic marker in CKD 5D, and provides predictive value for total mortality, particularly in incident patients with less confounding variables. Finally, lower NT-proBNP concentrations in patients treated with high-flux membranes suggest a possible biological link to improved survival in this group.

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Board of Baxter Health Care and Mitsubishi. S.S. has participated in advisory boards for Bristol Myers & Squibb and for Pfizer. J.M.L.G. has received consultancy fees from Fresenius Medical Care. A.G. is full time employee of Fresenius Medical Care. No other conflicts of interest were disclosed.

References

- Locatelli F, Martin-Malo A, Hannedouche T, Loureiro A, Papadimitriou M, Wizemann V, Jacobson SH, Czekalski S, Ronco C, Vanholder R: Effect of membrane permeability on survival of hemodialysis patients. *J Am Soc Nephrol* 2009;20:645–654.
- Levin ER, Gardner DG, Samson WK: Natriuretic peptides. *N Engl J Med* 1998;339:321–328.
- Wang AY, Lai KN: Use of cardiac biomarkers in end-stage renal disease. *J Am Soc Nephrol* 2008;19:1643–1652.
- Weber M, Hamm C: Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* 2006;92:843–849.
- Linssen GC, Bakker SJ, Voors AA, Gansevoort RT, Hillege HL, de Jong PE, van Veldhuisen DJ, Gans RO, de Zeeuw D: N-terminal pro-B-type natriuretic peptide is an independent predictor of cardiovascular morbidity and mortality in the general population. *Eur Heart J* 2010;31:120–127.
- de Lemos JA, McGuire DK, Drazner MH: B-type natriuretic peptide in cardiovascular disease. *Lancet* 2003;362:316–322.
- Locatelli F, Eckardt KU, Macdougall IC, Tsakiris D, Clyne N, Burger HU, Scherhag A, Druke TB: Value of N-terminal brain natriuretic peptide as a prognostic marker in patients with CKD: results from the CREATE study. *Curr Med Res Opin* 2010;26:2543–2552.
- Madsen LH, Ladefoged S, Corell P, Schou M, Hildebrandt PR, Atar D: N-terminal pro brain natriuretic peptide predicts mortality in patients with end-stage renal disease in hemodialysis. *Kidney Int* 2007;71:548–554.
- Zoccali C, Mallamaci F, Benedetto FA, Tripepi G, Parlongo S, Cataliotti A, Cutrupi S, Giaccone G, Bellanuova I, Cottini E, Malatino LS: Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. *J Am Soc Nephrol* 2001;12:1508–1515.
- Kamano C, Osawa H, Hashimoto K, Nishimura S, Saito SK, Kashiwagi T, Iino Y, Katayama Y: N-Terminal pro-brain natriuretic peptide as a predictor of heart failure with preserved ejection fraction in hemodialysis patients without fluid overload. *Blood Purif* 2012;33:37–43.
- Krupicka J, Janota T, Kasalova Z, Hradec J: Natriuretic peptides – physiology, pathophysiology and clinical use in heart failure. *Physiol Res* 2009;58:171–177.
- Jensen J, Ma LP, Fu ML, Svaninger D, Lundberg PA, Hammarsten O: Inflammation increases NT-proBNP and the NT-proBNP/BNP ratio. *Clin Res Cardiol* 2010;99:445–452.
- Codognotto M, Piccoli A, Zaninotto M, Mion MM, Ruzza L, Barchita A, Naso A, Plebani M: Effect of a dialysis session on the prognostic values of NT-proBNP, troponins, endothelial damage and inflammation biomarkers. *J Nephrol* 2010;23:465–471.
- Racek J, Kralova H, Trefil L, Rajdl D, Eiselt J: Brain natriuretic peptide and N-terminal pro-BNP in chronic haemodialysis patients. *Nephron Clin Pract* 2006;103:c162–c172.
- Sommerer C, Hecke S, Schwenger V, Katus HA, Giannitsis E, Zeier M: Cardiac biomarkers are influenced by dialysis characteristics. *Clin Nephrol* 2007;68:392–400.
- Wahl HG, Graf S, Renz H, Fassbinder W: Elimination of the cardiac natriuretic peptides B-type natriuretic peptide (BNP) and N-terminal proBNP by hemodialysis. *Clin Chem* 2004;50:1071–1074.
- Rosner MH: Measuring risk in end-stage renal disease: is N-terminal pro brain natriuretic peptide a useful marker? *Kidney Int* 2007;71:481–483.
- Sun L, Sun Y, Zhao X, Xu C, Chen D, Li L, Ma Y, Rong S, Mei C: Predictive role of BNP and NT-proBNP in hemodialysis patients. *Nephron Clin Pract* 2008;110:c178–c184.
- Locatelli F, Hannedouche T, Jacobson S, La Greca G, Loureiro A, Martin-Malo A, Papadimitriou M, Vanholder R: The effect of membrane permeability on ESRD: design of a prospective randomised multicentre trial. *J Nephrol* 1999;12:85–88.
- van der Merwe DE, Henley R, Lane G, Field R, Frenneaux M, Dunstan F, McDowell I: Effect of different sample types and stability after blood collection of N-terminal pro-B-type natriuretic peptide as measured with Roche Elecsys system. *Clin Chem* 2004;50:779–780.
- de Mutsert R, Jager KJ, Zoccali C, Dekker FW: The effect of joint exposures: examining the presence of interaction. *Kidney Int* 2009;75:677–681.
- Koch M, Trapp R, Kohnle M, Aker S, Haastert B, Rump LC: B-type natriuretic peptide and severe heart failure at baseline predict overall mortality in incident dialysis patients. *Clin Nephrol* 2010;73:21–29.
- Chazot C, Vo-Van C, Zaoui E, Vanel T, Hurot JM, Lorriaux C, Mayor B, Deleaval P, Jean G: Fluid overload correction and cardiac history influence brain natriuretic peptide evolution in incident haemodialysis patients. *Nephrol Dial Transplant* 2011;26:2630–2634.
- Svensson M, Gorst-Rasmussen A, Schmidt EB, Jorgensen KA, Christensen JH: NT-pro-BNP is an independent predictor of mortality in patients with end-stage renal disease. *Clin Nephrol* 2009;71:380–386.
- Paniagua R, Ventura MD, Avila-Diaz M, Hinojosa-Heredia H, Mendez-Duran A, Cueto-Manzano A, Cisneros A, Ramos A, Madonia-Juseino C, Belio-Caro F, Garcia-Contreras F, Trinidad-Ramos P, Vazquez R, Ilabaca B, Alcantara G, Amato D: NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. *Nephrol Dial Transplant* 2010;25:551–557.
- Alsuwaida A: Influence of erythropoietin dose and albumin level on the plasma brain natriuretic peptide in hemodialysis patients. *Saudi J Kidney Dis Transpl* 2006;17:171–176.
- Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr: Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002;40:976–982.
- Guo Q, Barany P, Qureshi AR, Snaedal S, Heimbürger O, Stenvinkel P, Lindholm B, Axelsson J: N-terminal pro-brain natriuretic peptide independently predicts protein energy wasting and is associated with all-cause mortality in prevalent HD patients. *Am J Nephrol* 2009;29:516–523.