3. Chamney PW, Wabel P, Moissl UM *et al.* A whole-body model to distinguish excess fluid from the hydration of major body tissues. *Am J Clin Nutr* 2007; 85: 80–89
4. Wabel P, Chamney P, Moissl U *et al*. Importance of whole-body bioimpedance spectroscopy for the management of fluid balance. *Blood Purif* 2009; 27: 75–80
5. Moissl UM, Wabel P, Chamney PW *et al*. Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Meas* 2006; 27: 921–933
6. Wabel P, Rode C, Moissl U *et al*. Accuracy of bioimpedance spectroscopy (BIS) to detect fluid status changes in hemodialysis patients (abstract). *Nephrol Dial Transplant* 2007; 22 (Suppl 6): VI 129
7. Wieskotten S, Heinke S, Wabel P *et al*. Bioimpedance-based identification of malnutrition using fuzzy logic. *Physiol Meas* 2008; 29: 639–654
8. Wizemann V, Rode C, Wabel P. Whole-body spectroscopy (BCM) in the assessment of normovolemia in hemodialysis patients. *Contrib Nephrol* 2008; 161: 115–118
9. Kraemer M, Rode C, Wizemann V. Detection limit of methods to assess fluid status changes in dialysis patients. *Kidney Int* 2006; 69: 1609–1620
10. Agarwal R, Peixoto AJ, Santos SF *et al*. Pre- and postdialysis blood pressures are imprecise estimates of interdialytic ambulatory blood pressure. *Clin J Am Soc Nephrol* 2006; 1: 389–398
11. Alborzi P, Patel N, Agarwal R. Home blood pressures are of greater prognostic value than hemodialysis unit recordings. *Clin J Am Soc Nephrol* 2007; 2: 1228–1234
12. Wabel P, Moissl U, Chamney P *et al*. Towards improved cardiovascular management: the necessity of combining blood pressure and fluid overload. *Nephrol Dial Transplant* 2008; 23: 2965–2971

Received for publication: 14.8.08; Accepted in revised form: 4.9.09

Nephrol Dial Transplant (2010) 25: 551–557
doi: 10.1093/ndt/gfp395
Advance Access publication 12 August 2009

NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients

Ramón Paniagua[1], María-de-Jesús Ventura[1], Marcela Ávila-Díaz[1], Héctor Hinojosa-Heredia[2], Antonio Méndez-Durán[3], Alfonso Cueto-Manzano[4], Alejandra Cisneros[5], Alfonso Ramos[6], Clara Madonia-Juseino[6], Francisco Belio-Caro[7], Fernando García-Contreras[8], Pedro Trinidad-Ramos[9], Rosario Vázquez[10], Begoña Ilabaca[11], Guadalupe Alcántara[1] and Dante Amato[12]

[1]Unidad de Investigación Médica en Enfermedades Nefrológicas, Hospital de Especialidades, CMN Siglo XXI, [2]Hospital General de Zona 47, [3]Hospital General Regional 25, Mexico City, [4]Hospital de Especialidades CMN Occidente, Guadalajara, Jal, [5]Hospital General de Zona 27, Mexico City, [6]Hospital General Regional 2, Hermosillo, Sonora, [7]Hospital General Regional 1, Morelia, Michoacan, [8]Hospital General de Zona 2A, Mexico City, [9]Hospital de Especialidades CMN Siglo XXI, Mexico City, [10]Hospital General de Zona 194, Naucalpan, Estado de México, [11]Hospital General de Zona 1A, Mexico City, Instituto Mexicano del Seguro Social, México and [12]Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Tlalnepantla, Estado de México, México

Correspondence and offprint requests to: Ramón Paniagua; E-mail: jpaniaguas@cis.gob.mx, ramon.paniagua@imss.gob.mx

Abstract

Background. N-terminal fragment of B-type natriuretic peptide (NT-proBNP) is a marker of both fluid volume overload and myocardial damage, and it has been useful as a predictor of mortality in patients with end-stage renal disease (ESRD). It has been suggested that continuous ambulatory peritoneal dialysis (CAPD), automated peritoneal dialysis (APD) and haemodialysis (HD) may have different effects on fluid volume and blood pressure control; however, whether the independent predictive value of NT-proBNP for mortality is preserved when analysed in conjunction with fluid overload and dialysis modality is not clear.

Methods. A prospective multicentre cohort of 753 prevalent adult patients on CAPD, APD and HD was followed up for 16 months. Plasmatic levels of NT-proBNP, extracellular fluid volume/total body water ratio (ECFv/TBW) and traditional clinical and biochemical markers for cardiovascular damage risk were measured, and their role as predictors of all-cause and cardiovascular mortality was analysed.

Results. NT-proBNP level, ECFv/TBW and other cardiovascular damage risk factors were not evenly distributed among the different dialysis modalities. NT-proBNP levels and ECFv/TBW were correlated with several inflammation, malnutrition and myocardial damage markers. Multivariate analysis showed that NT-proBNP levels and ECFv/TBW were predictors of both all-cause and cardiovascular mortality, independently of dialysis modality and the presence of other known clinical and biochemical risk factors.

Conclusions. NT-proBNP is a reliable predictor of death risk independently of the effect of dialysis modality on fluid volume control, and the presence of other clinical and biochemical markers recognized as risk factors for all-cause and cardiovascular mortality. NT-pro-BNP is a good

predictor of mortality independently of fluid volume overload and dialysis modality.

Keywords: end-stage renal disease; dialysis modality; NT-proBNP; fluid overload; mortality

Introduction

Cardiovascular diseases (CVD) are the most frequent cause of comorbidity and mortality in patients with end-stage renal disease (ESRD) [1–3]. An important number of traditional risk factors for CVD, such as diabetes mellitus, advanced age, fluid volume overload, hypertension and hyperlipidemia, frequently coexist in patients with ESRD [4,5]. The frequency of CVD participation on the clinical outcomes of ESRD patients has prompted the search of biochemical markers with a high predictive value for all-cause mortality and cardiovascular mortality. Such tests should be easy to perform and widely available. Serum albumin and C-reactive protein have been useful as predictors of death, but they are more related to inflammation and malnutrition than to CVD, and therefore, their specificity is low [6]. The plasmatic concentration of the N-terminal fragment of B-type natriuretic peptide (NT-proBNP) has been useful to predict all-cause and cardiovascular mortality in ESRD patients. The elevation of NT-proBNP levels has a dual meaning as a marker of both myocardial damage and fluid volume overload [7–9].

The different dialysis modalities, such as continuous ambulatory peritoneal dialysis (CAPD), automated peritoneal dialysis (APD) and haemodialysis (HD) have different effects on fluid volume control. Therefore, dialysis modality may indirectly affect the NT-proBNP concentration. The patients on HD have cycles of extracellular fluid volume (ECFv) expansion and contraction 3 days a week, associated with the ultrafiltration obtained in each HD session. CAPD has a more uniform effect, but its effect on ECFv control depends on the characteristics and concentration of the osmotic agent used in the dialysis solution, and the peritoneal membrane permeability characteristics to achieve an optimal ultrafiltration volume [10–12]. APD shares some characteristics with CAPD, but with the shorter dwell times used in APD, higher ultrafiltration volumes may be obtained. Sodium removal is partially related to ultrafiltration, so it is less effective in APD [13,14].

The value of NT-proBNP as a predictive marker of clinical outcomes has been independently proven in patients on HD, CAPD and APD, but the interaction among NT-proBNP, fluid volume control and dialysis modality has not been tested. The aim of this study is to analyse the value of NT-proBNP plasma concentration as an independent predictor of all-cause and cardiovascular mortality, and its interaction with fluid volume control and dialysis modality.

Patients and methods

Design

A prospective cohort of patients with ESRD, from 14 dialysis centres of the Instituto Mexicano del Seguro Social (IMSS) in four Mexican cities, was followed up for 16 months. The protocol was approved by the Institutional Review Board at each participating centre. The patients signed a written informed consent form to participate in the study.

Patients

Prevalent patients in any of the three dialysis modalities studied (CAPD, APD and HD) were invited to participate. A random sample was selected from the list of patients on chronic dialysis programmes from each centre. All patients were adults ($\geq$18 years). No restrictions were applied regarding gender, ESRD cause or time on the therapy. All patients were clinically in a steady state, free from infections or acute complications within 1 month before enrolment. The patients with HIV seropositivity, cancer or immunosuppressive therapy were excluded. The patients on HD received a conventional schedule of three sessions per week, 4 h per session; all of them were dialyzed using high-flux polysulfone filters. The CAPD patients were on four exchanges of a 2 L dextrose solution per day. The APD patients received the conventional schemes with the dextrose solutions.

Procedures

Clinical charts of all selected patients were reviewed to get the relevant clinical and demographic data. Upon enrolment, body composition was measured by multifrequency electric bioimpedance (Biodynamics, Seattle, WA, USA) [15,16]. After an overnight fast, a venous blood sample was drawn; plasma was separated and kept frozen in aliquots at -70°C until assayed. For the HD patients, blood samples were drawn at the non-dialysis day between the first and second session of the week (mid week). Urine output was registered as the average of 3 consecutive days. Ultrafiltration was also registered as the average of 3 consecutive days in the PD patients and the average of three consecutive sessions in the HD patients and then corrected as mL/day for comparison with the PD group. Scheduled visits were programmed every month. The patients were allowed to consult personally or by phone call as required. The mean follow-up period was 16 months. Each surviving individual patient was followed up for at least 12 months.

Laboratory assays

Glucose, BUN, creatinine, albumin, total cholesterol and triglycerides were measured in the frozen plasma samples with conventional methods (Hitachi 902 Automatic Analyzer, Roche Diagnostics, GMBH Mannheim, Germany). C-reactive protein was measured by high-sensitivity immunoturbidimetry (Tina-quant CRP-HS, Roche Diagnostics, GMBH Mannheim, Germany). NT-pro-BNP was measured by immunoassay (ECLIA Roche Diagnostics, GMBH Mannheim, Germany), and Troponin I (TPN-1) by RIA (Diagnostic Automation Inc. Calabasas, CA, USA). C-reactive protein levels $>$3.0 mg/L were considered as a marker of active inflammation [17].

Statistical analysis

Values are shown as absolute frequencies and percentages or as mean $\pm$ standard deviation as appropriate. For differences among groups, one-way ANOVA with *post hoc* Bonferroni's test, Student's *t*-test or chi-squared test was applied according the number of groups to compare and the type of variable. Pearson's correlation coefficients with Bonferroni's adjustment among serum albumin, CRP, NT-proBNP, TPN-1 and ECFv/TBW (total body water), controlling for gender, diabetic status and dialysis modality were calculated. Utility of NT-proBNP in predicting mortality was analysed with the Receiver Operating Characteristic (ROC) curve. Mortality was analysed by the Cox proportional risks model. All statistical calculations were done with SPSSw, version 10.0 (Chicago, IL, USA).

Results

Table 1 summarizes some clinical and biochemical characteristics of the 753 studied patients, grouped by treatment modality. The mean follow-up time was 16.7 $\pm$ 1.7 months for the patients that survived all planned follow-up period.

Table 1. Clinical and biochemical characteristics of the 753 patients studied

	CAPD	APD	HD	Total
N	230	135	388	753
Gender (male/female)	128/102	79/56	208/180	415/338
Diabetes, n (%)	142 (62%)	54 (40%)	134 (35%)	330 (44%)
Baseline cardiovascular comorbidity, n (%)	41 (17.8%)	17 (12.6%)	62 (16.0%)	120 (15.9%)
Age (years)	55.55 ± 13.66**,‡	41.90 ± 19.88‡	46.90 ± 17.44	48.64 ± 17.55
Height (cm)	157.74 ± 10.06	156.51 ± 11.77	157.03 ± 10.93	157.15 ± 10.82
Weight (kg)	64.87 ± 12.53**	59.18 ± 19.86	62.88 ± 15.78	62.82 ± 15.81
BMI (kg/m^2)	26.13 ± 5.14**,†	24.01 ± 5.33	25.10 ± 5.00	25.22 ± 5.15
W/H	0.95 ± 0.06	0.95 ± 0.06	0.94 ± 0.07	0.94 ± 0.07
SBP (mmHg)	140.37 ± 23.85**	131.34 ± 22.68‡	142.05 ± 26.58	139.62 ± 25.38
DBP (mmHg)	84.41 ± 14.82	81.83 ± 14.80	83.58 ± 16.99	83.52 ± 15.98
Urine output (mL/day)	189 ± 276	178 ± 284	140 ± 241	162 ± 261
Urine output <100 mL/day (%)	72.2	78.5	81.5	78.2
Ultrafiltration (mL/day)	910 ± 167	885 ± 164	921 ± 198	911 ± 183
Fat (% Body weight)	29.82 ± 10.56	27.94 ± 9.86	27.85 ± 10.95	28.47 ± 10.67
TBW (% Body weight)	57.21 ± 8.40	56.26 ± 7.73	57.56 ± 9.61	57.22 ± 8.94
ECFv (% Body weight)	26.03 ± 3.42	26.17 ± 4.29	26.63 ± 4.28	26.37 ± 4.04
ECFv/TBW	0.455 ± 0.032*	0.467 ± 0.046	0.460 ± 0.043	0.460 ± 0.040
Serum glucose (mg/dL)	112.51 ± 63.09	118.85 ± 80.69†	102.59 ± 53.14	108.54 ± 62.20
BUN (mg/dL)	113.20 ± 37.39**	115.88 ± 41.23	126.04 ± 53.60	120.29 ± 47.35
Serum creatinine (mg/dL)	9.80 ± 3.68**	11.66 ± 3.81‡	9.37 ± 3.63	9.91 ± 3.77
Cholesterol (mg/dL)	185.75 ± 42.72*,‡	196.95 ± 51.40‡	156.32 ± 38.70	172.61 ± 45.76
Triglycerides (mg/dL)	225.89 ± 154.22‡	236.37 ± 142.75‡	154.76 ± 101.22	191.16 ± 132.56
Serum albumin (g/dL)	3.39 ± 0.58**,‡	3.78 ± 0.55‡	4.17 ± 0.53	3.86 ± 0.65
Troponin T (ng/mL)	429.19 ± 521.51	558.95 ± 416.75	732.24 ± 725.50	615.14 ± 640.43
NT-proBNP (pg/mL)	17 181 ± 27 914	12 455 ± 17 092†	19 973 ± 25 671	17 893 ± 25 252
CRP (mg/L)	0.93 ± 1.25‡	1.10 ± 1.42†	1.44 ± 1.57	1.22 ± 1.47
Transferrin (mg/dL)	193.01 ± 51.77	200.73 ± 52.80	193.11 ± 56.64	194.45 ± 54.52

Values are expressed as mean ± standard deviation.
BMI = body mass index; W/H = waist to hip ratio; TBW = total body water; ECFv = extra cellular fluid volume; NT-proBNP = N-terminal fragment of B-type natriuretic peptide; CRP = C-reactive protein; SBP = systolic blood pressure; DBP = diastolic blood pressure.
*$P < 0.05$ versus APD; **$P < 0.01$ versus APD; †$P < 0.05$ versus HD; ‡$P < 0.01$ versus HD.

The patients on CAPD were older and had higher weight and body mass index (BMI). The patients on APD were younger and showed better blood pressure control and the highest values of ECFv/TBW ratio, fasting glucose, total cholesterol and triglycerides levels. The HD patients had the highest values of systolic blood pressure and serum albumin levels. There were no differences among the groups in urine output, number of functionally anuric (urine output <100 mL/day) patients and daily ultrafiltration, neither previous CV comorbidities at baseline. When previous cardiovascular comorbidities were disaggregated by specific causes, patterns were similar in all groups (for CAPD: heart failure 7, myocardial infarct 8, angor 9, pericarditis 2, stroke 11, peripheral vascular disease 15; for APD: heart failure 3, myocardial infarct 2, angor 2, pericarditis 1, stroke 3, peripheral vascular disease 6; for HD: heart failure 8, myocardial infarct 9, angor 11, pericarditis 1, stroke 14, peripheral vascular disease 21). More than one cardiovascular comorbidity coexists in some patients.

There were significant negative correlations of serum albumin with CRP (-0.24, $P < 0.001$), albumin with NT-proBNP (-0.21, $P < 0.001$), and positive correlations of NT-proBNP with TPN-1 (0.1 $P = 0.05$) and TPN-1 with ECFv/TBW (0.12, $P < 0.01$) in Pearson's correlation analysis. The correlation analysis adjusted by gender, diabetic status and dialysis modality is shown in Table 2.

There were 182 deaths. Death causes are listed in Table 3. The distribution of death causes was different among the dialysis modalities groups. Acute myocardial infarction and arrhythmias were more frequent in the HD group. Peritonitis episodes were present only in the CAPD group. Univariate analysis showed that the group of patients who died had significantly greater age, higher BMI, diabetes frequency, TBW, ECFv, serum glucose and NT-proBNP levels, and lower serum albumin and creatinine levels than the surviving patients (Table 4). Urine output, number of functionally anuric (urine output <100 mL/day) patients, daily ultrafiltration or CV comorbidities were not different between survivors and non-survivors.

The prognostic value of NT-proBNP (normal values 188 ± 100 pg/mL), for all-cause mortality analysed with the ROC curve, showed an area under the curve of 0.66 (95% CI 0.61–0.70) that refuted ($P < 0.001$) statistical indifference (0.50). The cut-off point of 5700 pg/mL gave values of 0.80 for sensitivity and 0.40 for specificity. For cardiovascular mortality, the area under the curve was 0.72 (95% CI 0.66–0.78) ($P < 0.001$), and the cut-off point of 8900 pg/mL gave values of 0.80 for sensitivity and 0.54 for specificity. Figure 1 shows a survival analysis by NT-proBNP quartiles. NT-proBNP levels had a significant effect on survival. Higher NT-proBNP levels were associated with lower survival.

Survival (Cox proportional risks model) analysis showed that diabetes, dialysis modality, serum albumin, CRP and NT-proBNP levels were significantly and independently associated with all-cause mortality (Table 5).

Table 2. Pearson's correlation coefficients of serum albumin, CRP, NT-proBNP, TPN-1 and ECFv/TBW, controlling for gender, diabetes and dialysis modality

	Serum albumin (g/dL)	CRP (mg/L)	NT-proBNP (pg/mL)	TPN 1 (ng/mL)	ECFv/TBW
Serum albumin (g/dL)	1				
CRP (mg/L)	−0.42 $P = 0.01$	1			
NT-proBNP (pg/mL)	−0.25 $P = 0.01$	0.19 $P = 0.01$	1		
TPN 1 (ng/mL)	−0.03 $P =$ NS	0.03 $P =$ NS	0.08 $P =$ NS	1	
ECFv/TBW	−0.05 $P =$ NS	0.04 $P =$ NS	0.01 $P =$ NS	0.14 $P = 0.01$	1

Correlations are considered significant if $P < 0.01$ (according with Bonferroni's correction). NS = non-significant.

Table 3. Causes of death by treatment modality

Cause of death	CAPD	APD	HD	Total
Uraemia/hyperkalaemia/ acidosis	8	3	11	22
Acute myocardial infarction	3	3	10	16
Congestive chronic heart failure/pulmonary oedema	4	1	5	10
Arrhythmia	5	5	10	20
Stroke	5	1	11	17
Other cardiovascular causes	2	0	2	4
Infections (except peritonitis)	8	1	12	21
Peritonitis	9	0	0	9
Sudden death	6	2	10	18
Unknown	11	1	13	25
Hypovolaemic shock	1	1	1	3
Malnutrition	0	1	0	1
Intestinal occlusion	0	1	0	1
Respiratory insufficiency, bronchial aspiration	0	0	1	1
Other non-infectious non-CV	1	3	10	14
Total	63	23	96	182

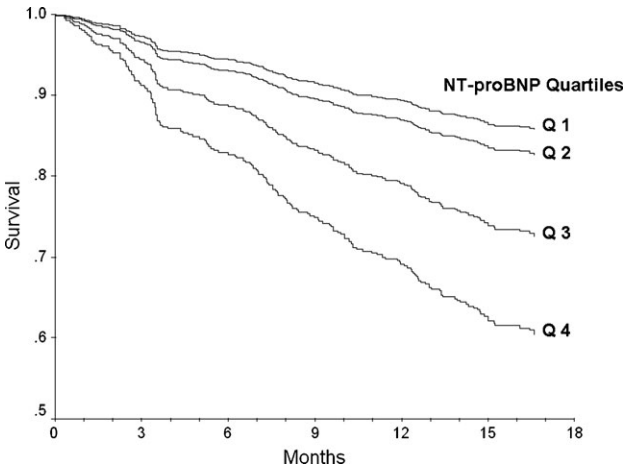

Fig. 1. Survival analysis by NT-proBNP quartiles. Cox proportional risks model, $P < 0.001$.

Eighty-five deaths were attributed to cardiovascular events (acute myocardial infarction, cardiac failure, arrhythmia, stroke, peripheral arterial insufficiency and sudden death). Univariate analysis showed that patients with cardiovascular death had higher age (57.8 ± 13.5 versus 47.5 ± 17.7 years, $P < 0.001$), SBP (148 ± 25 versus 139 ± 28 mmHg, $P < 0.001$), ECFv (27.2 ± 4.9 versus 26.3 ± 3.9% BW, $P < 0.04$), NT-proBNP levels (31 827 ± 33 110 versus 16 042 ± 23 463 pg/mL, $P < 0.001$), CRP levels (1.96 ± 1.85 versus 1.13 ± 1.39 mg/dL, $P < 0.001$), and lower serum albumin levels (3.55 ± 0.71 versus 3.90 ± 0.63 g/dL, $P < 0.001$) than patients with non-cardiovascular death. Multivariate analysis showed that age, dialysis modality, serum albumin, CRP, NT-proBNP levels and ECFv/TBW ratio were significantly and independently associated with cardiovascular death (Table 6).

Discussion

These data suggest that NT-proBNP plasma levels and ECFv/TBW ratio are significant predictors of both all-cause and cardiovascular mortality in ESRD patients, independently of the dialysis modality and the influence of other known risk factors such as diabetes, age, blood pressure, CRP and serum albumin.

Previously reported NT-proBNP high levels in ESRD patients [7,8,18–20] were corroborated. Also, the association of NT-proBNP levels with inflammation and malnutrition markers such as serum albumin and CRP was confirmed [18,21]. Cardiac functional tests were not done in the present study, but there was a significant correlation between NT-proBNP and TPN-1, a myocardial damage marker [22,23].

There are previous reports that the plasmatic levels of natriuretic peptides are increased in non-dialyzed ESRD patients, and in patients on any dialysis modality; plasmatic levels of natriuretic peptides were directly correlated with left ventricular mass, fluid volume overload and inflammation, and inversely correlated with residual renal function [7–10,18–20]. Other factors such as diabetes and obesity were not clearly correlated with natriuretic peptides levels [18,24].

Plasmatic levels of natriuretic peptides are tightly correlated with all-cause mortality, and especially with cardiovascular mortality. However, not all members of the natriuretic peptides family have the same value as predictors of clinical outcomes [18]. Two studies have directly compared BNP and NT-proBNP [25,26]. Both found that the N-terminal pro-hormone was slightly superior to BNP for predicting death or re-hospitalization for heart failure. The longer half-life of NT-proBNP may make it a more accurate index of ventricular stress and hence a better predictor of prognosis. Therefore, we chose NT-proBNP over BNP for our study. NT-proBNP is a precursor of BNP synthesized in the left ventricle in response to stimuli that demand

Table 4. Univariate analysis of clinical and biochemical characteristics between survivor and non-survivor groups

	Survivors	Non-survivors	Total	*P*-value
N	567	182	749	
Gender (F/M)	249/318	88/94	337/412	NS
Diabetes (Y/N)	85.7/62.9	14.3/37.1	56.1/43.9	0.001
Baseline cardiovascular comorbidity, n (%)	84 (14.8%)	36 (19.8%)	120 (15.9%)	NS
Age (years)	45.81 ± 17.69	57.70 ± 13.70	48.70 ± 17.56	0.001
Height (cm)	157.18 ± 11.10	157.03 ± 10.02	157.14 ± 10.84	NS
Weight (kg)	62.38 ± 16.54	64.27 ± 13.40	62.84 ± 15.85	NS
BMI (kg/m^2)	25.01 ± 5.16	25.92 ± 5.12	25.23 ± 5.16	0.040
W/H	0.94 ± 0.07	0.95 ±± 0.07	0.94 ± 0.07	NS
SBP (mmHg)	137.60 ± 24.83	145.83 ± 26.31	139.60 ± 25.43	0.001
DBP (mmHg)	83.77 ± 16.27	82.67 ± 15.16	83.50 ± 16.01	NS
Urine output (mL/day)	154.6 ± 254.6	182.1 ± 278.8	162 ± 261	NS
Urine output <100 mL/day (%)	80.6	75.3	78.2	NS
Ultrafiltration (mL/day)	899.7 ± 175.9	957.4 ± 270.3	911 ± 183	NS
Fat (% Body weight)	28.17 ± 10.34	29.61 ± 11.57	28.51 ± 10.66	NS
TBW (% Body weight)	56.77 ± 8.51	58.54 ± 10.05	57.19 ± 8.93	0.020
ECFv (% Body weight)	26.10 ± 3.63	27.17 ± 5.05	26.36 ± 4.05	0.002
ECFv/TBW	0.46 ± 0.04	0.46 ± 0.04	0.46 ± 0.04	NS
Serum glucose (mg/dL)	100.79 ± 49.79	133.27 ± 86.61	108.66 ± 62.30	0.001
BUN (mg/dL)	120.63 ± 46.69	119.38 ± 49.81	120.33 ± 47.44	NS
Serum creatinine (mg/dL)	10.31 ± 3.79	8.65 ± 3.44	9.91 ± 3.77	0.001
Cholesterol (mg/dL)	173.59 ± 45.28	169.61 ± 47.32	172.62 ± 45.78	NS
Triglycerides (mg/dL)	192.45 ± 128.66	188.34 ± 145.08	191.45 ± 132.74	NS
Serum albumin (g/dL)	3.97 ± 0.59	3.53 ± 0.71	3.86 ± 0.65	0.001
Transferrin (mg/dL)	196.86 ± 52.76	186.97 ± 59.42	194.46 ± 54.57	NS
Troponin T (ng/dL)	632.92 ± 702.86	554.02 ± 386.15	613.81 ± 641.30	NS
NT-proBNP (pg/dL)	15 390.92 ± 23 297.86	25 781.09 ± 29 408.64	17 907.89 ± 25 288.22	0.001
CRP (mg/L)	1.02 ± 1.30	1.85 ± 1.76	1.22 ± 1.47	NS

Values are expressed as mean ± standard deviation, and as numbers.
BMI = body mass index; W/H = waist to hip ratio; TBW = total body water; ECFv = extra cellular fluid volume; NT-proBNP = N-terminal fragment of B-type natriuretic peptide; CRP = C-reactive protein; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 5. Multivariate analysis of all-cause mortality

Variable	*P*-value	Exp (B)	Lower 95% CI	Upper 95% CI
Age (years)	0.002	1.024	1.009	1.040
Gender (male)	0.724	0.915	0.560	1.496
Diabetes (non-DM)	0.009	0.611	0.442	0.884
Dialysis modality	0.013			
CAPD	0.034	0.491	0.306	0.790
APD	0.159	0.068	0.398	1.163
Waist/hip ratio	0.718	0.625	0.049	8.038
Body fat (% BW)	0.725	1.004	0.983	1.025
Systolic BP (mmHg)	0.059	1.008	0.999	1.016
Diastolic BP (mmHg)	0.563	0.996	0.983	0.009
Serum albumin (g/dL)	0.000	0.469	0.336	0.654
C-reactive protein (mg/L)	0.007	1.152	1.039	1.227
ECFv/TBW	0.087	84.639	0.520	13 778.551
NT-proBNP (1000 pg/mL)	0.025	1.006	1.001	1.011
Troponin T (ng/mL)	0.469	0.999	0.999	1.001

Table 6. Multivariate analysis of cardiovascular mortality

Variable	*P*-value	Exp (B)	Lower 95% CI	Upper 95% CI
Age (years)	0.017	1.026	1.004	1.047
Gender (male)	0.599	0.835	0.426	1.637
Diabetes (non-DM)	0.173	0.703	0.423	1.167
Dialysis modality	0.030			
CAPD	0.009	0.401	0.203	0.794
APD	0.166	0.574	0.262	1.258
Waist/hip ratio	0.724	1.912	0.052	69.878
Body fat (% BW)	0.576	1.008	0.979	1.038
Systolic BP (mmHg)	0.108	1.009	0.998	1.021
Diastolic BP (mmHg)	0.522	0.994	0.976	1.012
Albumin (g/dL)	0.003	0.493	0.308	0.792
C-reactive protein (mg/L)	0.023	1.177	1.023	1.354
ECFv/TBW	0.018	1171.330	3.347	409 899.370
NT-proBNP (1000 pg/mL)	0.001	1.010	1.004	1.016
Troponin T (ng/mL)	0.297	0.999	0.999	1.001

more ventricular work and lead to re-modelation. The immature molecule NT-proBNP is larger and has a longer half-life than the active form, facilitating its measurement, and making it less dependent on acute changes that affect the concentration of other natriuretic peptides [21]. NT-proBNP or BNP levels may also be influenced by some HD-related factors; this has been recently updated [27]. Natriuretic peptides fall with acute and chronic reductions in blood volume or ECFv [28,29], low flux dialyzer membranes were found to increase NT-proBNP plasma levels and membranes with high ultrafiltration coefficients had the opposite effect [30,31]. Increments in NT-proBNP levels were seen in the days following arteriovenous fistula creation [32]. Patients herein reported were free of recent surgical procedures or acute complications, all of them were sampled in the morning of the non-dialysis day between the first and second sessions (mid week) and were dialyzed with the same kind of dialyzers to avoid those confounding effects. For the clinical care of the patients, it is important to keep in mind that our cut-off points (5700 pg/mL

for all-cause mortality and 8900 pg/mL for cardiovascular mortality) have an acceptable sensitivity (0.80), but a low specificity (0.40 and 0.54, respectively).

Our data confirm the role of NT-proBNP as a predictor of all-cause and especially cardiovascular mortality in ESRD patients, independently of the dialysis modality, and confirm the tight correlation of mortality with markers of inflammation such as serum albumin and CRP levels [6,18,33].

The effect of the dialysis modality on patients' survival is still controversial. Studies comparing HD and PD show that survival in both modalities is similar. PD has a slight advantage in the first years after the initiation of the therapy and a slight disadvantage in diabetic older women [34,35]. Analysis of the effects of dialysis modalities on mortality is beyond the scope of the present study. However, our data show that some important risk factors for mortality such as age, diabetes, BMI, ECFv/TBW, NT-proBNP, serum albumin and lipids are not evenly distributed among the different dialysis modalities. These differences are not necessarily owed to the modality *per se*, since the criteria for selecting each modality have an important role.

It is important to point out that the population under study consisted of prevalent rather than incident patients and as such, the modality had already been selected. Furthermore, some patients, particularly those currently in HD modality, were formerly initiated in PD, but had been shifted to HD due to loss of peritoneal capacity as a dialysis membrane. It is also important to note that patients on APD have been allocated in that modality due to the greater opportunity to re-integrate into daily activities, as the majority is students or productive workers. This factor partially explains the differences in some variables, such as age and diabetes, and consequent variations in comorbidities among groups.

The most important finding in the present study is that NT-proBNP levels and fluid volume overload keep their predictive value as markers of mortality independently of the dialysis modality. This issue seems relevant since control of fluid volume and blood pressure are related to the dialysis modality, and affect NT-proBNP levels. Therefore, the dialysis modality may exert some influence on the value of NT-proBNP levels as a mortality risk marker [7–12]. Some studies have suggested that fluid volume overload and hypertension are more frequently seen in patients on PD than in patients on HD, and that these differences may have important consequences on the clinical outcomes [10,12]. Nevertheless, dialysis modality is not the only factor influencing fluid volume control. Residual renal function, dietary prescription and patients' compliance with the prescription are also important factors [36–40]. Balance between intake and removal rather than isolated measurements of one of the balance components is the best way to analyse the effect of sodium and water on clinical outcomes. The dialysis component of sodium and water removal is a relatively easy measurement. The renal component is cumbersome in patients with very low or variable daily urine output. Evaluation of sodium intake through questionnaires is indirect and has a low reproducibility. In the present study, urine output and ultrafiltration were similar among groups, as well as between survivors and non-survivors, so they were not considered in the analysis. Instead, we analysed TBW, ECFv and ECFv/TBW ratio steady state measurements that summarize the balance between sodium and water intake and removal, and are recognized predictors of mortality in PD patients [40]. A small but significant difference was found in body fluid compartments, ECFv/TBW was lower in CAPD and TBW and ECFv were higher in non-survivors. Taken together, ultrafiltration, urine output and body fluids suggest that diet intake has similar significance as fluid or sodium removal in determining body composition, and influencing clinical outcomes. Additional measurements of fluid overload were not available to this study; however, a combination of bioimpedance and blood pressure may be used to discern if the corporal overhydration is related to positive fluid balance or related to cardiac dysfunction. In the multivariate analysis, both ECFv/TBW and systolic BP were independent predictors of mortality.

The number of patients included in the present study was high. Patients on three different modalities, with a wide age interval, and a follow-up period enough to evaluate important clinical outcomes, were recruited from 14 different dialysis centres. However, as in all studies without intervention, there are limitations. It is possible that the patients on HD are overrepresented, taking into account that PD is the most frequent dialysis modality in Mexico. On the other hand, only prevalent patients were included, which may introduce a bias because of the different comorbidity among the groups prior to inclusion, and the possible interaction between the dialysis modality and comorbidity. The association of NT-proBNP and ECFv/TBW to mortality does not necessarily reflect a causal relationship, and there is a possibility that other unsuspected factors act as an additional link between the analysed variables. Additionally, the fact that interventions reducing NT-proBNP and fluid volume overload, independently or together, also have a positive effect, reducing the mortality of ESRD patients, lends support to the suspected role of these markers as mortality predictors.

Our data support that plasmatic NT-proBNP levels and fluid volume overload are significant and independent predictors of both all-cause and cardiovascular mortality, even in the presence of other traditional and non-traditional risk factors. In conclusion, NT-proBNP is a good predictor of mortality independently of fluid volume overload and dialysis modality.

Acknowledgements. This paper was sponsored by the Instituto Mexicano del Seguro Social (Grant FP/2003/102). The authors want to thank Roche Diagnóstico, SA de CV México, for invaluable and unrestricted biochemical analysis and technical support, to Ms Susan Drier Jonas for her help in the preparation of this manuscript and to Mr Alejandro Hinojosa for database management.

Conflict of interest statement. None declared.

(See related article by F. Locatelli and S. Viganò. Are natriuretic peptides a reliable marker for mortality in ESRD patients? *Nephrol Dial Transplant* 2010; 25: 347–349.)

References

1. Greaves SC, Sharpe DN. Cardiovascular disease in patients with end-stage renal failure. *Aust N Z J Med* 1992; 22: 153–159

2. Huting J, Schutterle G. Cardiovascular factors influencing survival in end-stage renal disease treated by continuous ambulatory peritoneal dialysis. *Am J Cardiol* 1992; 69: 123–127
3. London GM, Marchais SJ, Metivier F *et al*. Cardiovascular risk in end-stage renal disease: vascular aspects. *Nephrol Dial Transplant* 2000; 15(Suppl 5): 97–104
4. Gilbert RE, Connelly K, Kelly DJ *et al*. Heart failure and nephropathy: catastrophic and interrelated complications of diabetes. *Clin J Am Soc Nephrol* 2006; 1: 193–208
5. Collins AJ, Hao W, Xia H *et al*. Mortality risks of peritoneal dialysis and hemodialysis. *Am J Kidney Dis* 1999; 34: 1065–1074
6. Zethelius B, Berglund L, Sundstrom J *et al*. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med* 2008; 358: 2107–2116
7. Vickery S, Price CP, John RI *et al*. B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis* 2005; 46: 610–620
8. Haug C, Metzele A, Steffgen J *et al*. Changes in brain natriuretic peptide and atrial natriuretic peptide plasma concentrations during hemodialysis in patients with chronic renal failure. *Horm Metab Res* 1994; 26: 246–249
9. Gangji AS, Helal BA, Churchill DN *et al*. Association between N-terminal propeptide B-type natriuretic peptide and markers of hypervolemia. *Perit Dial Int* 2008; 28: 308–311
10. Enia G, Mallamaci F, Benedetto FA *et al*. Long-term CAPD patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. *Nephrol Dial Transplant* 2001; 16: 1459–1464
11. Plum J, Ziyaie M, Kemmer FW *et al*. Intraindividual comparison of ANP, cGMP and plasma catecholamines between HD and CAPD. *Adv Perit Dial* 1990; 6: 211–219
12. Günal AI, Ilkay E, Kirciman E *et al*. Blood pressure control and left ventricular hypertrophy in long-term CAPD and hemodialysis patients: a cross-sectional study. *Perit Dial Int* 2003; 23: 563–567
13. Struijk DG. Volume status in CAPD and APD: does treatment modality matter and is more always better? *Perit Dial Int* 2007; 27: 641–644
14. Rodriguez-Carmona A, Pérez-Fontán M, Garca-Naveiro R *et al*. Compared time profiles of ultrafiltration, sodium removal, and renal function in incident CAPD and automated peritoneal dialysis patients. *Am J Kidney Dis* 2004; 44: 132–145
15. Hannan WJ, Cowen SJ, Plester CE *et al*. Comparison of bio-impedance spectroscopy and multi-frequency bio-impedance analysis for the assessment of extracellular and total body water in surgical patients. *Clin Sci (Lond)* 1995; 89: 651–658
16. Sun G, French CR, Martin GR *et al*. Comparison of multifrequency bioelectrical impedance analysis with dual-energy X-ray absorptiometry for assessment of percentage body fat in a large, healthy population. *Am J Clin Nutr* 2005; 81: 74–78
17. Pearson TA, Mensah GA, Alexander RW *et al*. Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; 107: 499–511
18. Paniagua R, Amato D, Vonesh E *et al*. for the Mexican Nephrology Collaborative Study Group. Predictive value of natriuretic peptides in patients on peritoneal dialysis: results from the ADEMEX trial. *Clin J Am Soc Nephrol* 2008; 3: 407–415
19. Horl WH. Natriuretic peptides in acute and chronic kidney disease and during renal replacement therapy. *J Investig Med* 2005; 53: 366–370
20. Suresh M, Farrington K. Natriuretic peptides and the dialysis patient. *Semin Dial* 2005; 18: 409–419
21. Clerico A, Recchia FA, Passino C *et al*. Cardiac endocrine function is an essential component of the homeostatic regulation network: physiological and clinical implications. *Am J Physiol Heart Circ Physiol* 2006; 290: H17–H29
22. Apple FS, Murakami MM, Pearce LA *et al*. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation* 2002; 106: 2941–5294
23. Khan NA, Hemmelgarn BR, Tonelli M *et al*. Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: a meta-analysis. *Circulation* 2005; 112: 3088–3096
24. Schleiffer T, Nagel D, Franz H *et al*. Endothelin and atrial natriuretic peptide in non-insulin-dependent diabetic versus nondiabetic patients on chronic hemodialysis. *Ren Fail* 1994; 16: 747–758
25. Masson S, Latini R, Anand IS *et al*. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clin Chem* 2006; 52: 1528–1538
26. Omland T, Sabatine MS, Jablonski KA *et al*. Prognostic value of B-type natriuretic peptides in patients with stable coronary artery disease: the PEACE trial. *J Am Coll Cardiol* 2007; 50: 205–214
27. Khalifeh N, Haider D, Hörl WH. Natriuretic peptides in chronic kidney disease and during renal replacement therapy: an update. *J Investig Med* 2009; 57: 33–39
28. Biasioli S, Zamperetti M, Borin D *et al*. Significance of plasma B-type natriuretic peptide in hemodialysis patients: blood sample timing and comorbidity burden. *ASAIO J* 2007; 53: 587–591
29. Paniagua R, Orihuela O, Ventura MJ *et al*. Echocardiographic, electrocardiographic and blood pressure changes induced by Icodextrin solution in diabetic patients on peritoneal dialysis. *Kidney Int* 2008; 73(Suppl 108): S125–S130
30. Sommerer C, Heckele S, Schwenger V *et al*. Cardiac biomarkers are influenced by dialysis characteristics. *Clin Nephrol* 2007; 68: 392–400
31. Dautin G, Boudjeltia S, Soltani Z *et al*. The changes in NT-proBNP plasma concentrations during dialysis are highly dependent of the dialysis membrane ultrafiltration coefficient. *Clin Chim Acta* 2007; 376: 237–239
32. Iwashima Y, Horio T, Takami Y *et al*. Effects of the creation of arteriovenous fistula for hemodialysis on cardiac function and natriuretic peptide levels in CRF. *Am J Kidney Dis* 2002; 40: 974–982
33. Ortega O, Gallar P, Muñoz M *et al*. Association between C-reactive protein levels and N-terminal pro-B-type natriuretic peptide in predialysis patients. *Nephron Clin Pract* 2004; 97: c125–c130
34. Vonesh EF, Snyder JJ, Foley RN *et al*. The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis. *Kidney Int* 2004; 66: 2389–2401
35. Jaar BG, Coresh J, Plantinga LC *et al*. Comparing the risk for death with peritoneal dialysis and hemodialysis in a national cohort of patients with chronic kidney disease. *Ann Intern Med* 2005; 1430: 174–183
36. Ozkahya M, Ok E, Cirit M *et al*. Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. *Nephrol Dial Transplant* 1998; 13: 1489–1493
37. Van Biesen W, Vanholder R, Verbeke F *et al*. Is peritoneal dialysis associated with increased cardiovascular morbidity and mortality? *Perit Dial Inter* 2006; 26: 429–434
38. Van Biesen W, Verbeke F, Devolder I *et al*. The relation between salt, volume, and hypertension: clinical evidence for forgotten but still valid basic physiology. *Perit Dial Inter* 2008; 28: 596–600
39. He FJ, MacGregor GA. Salt intake and cardiovascular disease. *Nephrol Dial Transplant* 2008; 23: 3382–3385
40. Fein P, Chattopadhyay J, Paluch MM *et al*. Enrollment fluid status is independently associated with long-term survival of peritoneal dialysis patients. *Adv Perit Dial* 2008; 24: 79–83

Received for publication: 8.12.08; Accepted in revised form: 13.7.09