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ORIGINAL ARTICLE

The effect of natriuretic C-type peptide and its change over time on mortality in patients on haemodialysis or haemodiafiltration

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ABSTRACT

Background. C-type natriuretic peptide (CNP) and its co-product N-terminal proCNP (NTproCNP) have been associated with beneficial effects on the cardiovascular system. In prevalent dialysis patients, however, a relation between NTproCNP and mortality has not yet been investigated. Furthermore, as a middle molecular weight substance, its concentration might be influenced by dialysis modality.

Methods. In a cohort of patients treated with haemodialysis (HD) or haemodiafiltration (HDF), levels of NTproCNP were measured at baseline and 6, 12, 24 and 36 months. The relation between serum NTproCNP and mortality and the relation between the 6-month rate of change of NTproCNP and mortality were analysed using Cox regression models. For the longitudinal analyses, linear mixed models were used.

Results. In total, 406 subjects were studied. The median baseline serum NTproCNP was 93 pmol/L and the median follow-up was 2.97 years. No relation between baseline NTproCNP or its rate of change over 6 months and mortality was found. NTproCNP levels remained stable in HD patients, whereas NTproCNP decreased significantly in HDF patients. The relative decline depended on the magnitude of the convection volume.

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Conclusions. In our study, levels of NTproCNP appear strongly elevated in prevalent dialysis patients. Second, while NTproCNP remains unaltered in HD patients, its levels decline in individuals treated with HDF, with the decline dependent on the magnitude of the convection volume. Third, NTproCNP is not related to mortality in this population. Thus NTproCNP does not seem to be a useful marker for mortality risk in dialysis patients.

Keywords: C-type natriuretic peptide, convection volume, end-stage kidney disease, haemodiafiltration, haemodialysis, mortality, NTproCNP

INTRODUCTION

Mortality in haemodialysis (HD) patients remains unacceptably high despite various treatment improvements and continuous research. A large proportion of mortality can be attributed to cardiovascular causes [1]. As such, it is of utmost importance to investigate new potential therapeutic targets.

C-type natriuretic peptide (CNP) is a relatively unknown member of the natriuretic peptide family, with its main expression in the brain, chondrocytes and vascular endothelial cells [2]. Although much remains to be elucidated, several stimuli have been reported to trigger its secretion: pro-inflammatory cytokines, bacterial polysaccharides, transforming growth factor beta and shear stress [3–5]. CNP is a middle molecular weight substance (2.2 kDa) produced by cleavage of proCNP into the N-terminal fragment (NTproCNP; 5 kDa) and biologically active CNP. Plasma concentration of CNP is very low and has a very short half-life, whereas its bio-inactive co-product NTproCNP circulates at higher concentrations. Therefore NTproCNP is often used as a reflection of CNP biosynthesis. In a healthy population, the mean NTproCNP level is ~7.4 ± 0.3 pmol/L (range 5.7–10.7) [6].

In animal studies, arteries dilate as a result of an increase in CNP [7]. Furthermore, CNP suppresses adrenocorticotropic hormone and vasopressin secretion [8, 9]. It stimulates endothelial growth, prevents the development of intimal thickening and impedes atherogenesis by regulating smooth muscle cell migration, cellular adhesion and expression of P-selectin [10, 11]. It exerts direct inotropic and chronotropic cardiac effects and plays an important role in the regulation of bone growth [12–14]. In short, these studies suggest important cardiovascular protective effects of CNP. In a non-renal human study, CNP was positively associated with cardiovascular disease and mortality [15] that was supposed to comprise a compensatory mechanism or a reflection of underlying disease. Previous studies found a strong and positive relation between creatinine and NTproCNP in both patients with normal kidney function [16, 17] and patients with chronic renal failure [18, 19], which indeed could indicate widespread (cardio)vascular damage. Moreover, in end-stage renal disease (ESRD), levels might further increase due to diminished renal clearance of CNP, upregulation of renal CNP as reported with renal interstitial fibrosis [20] and increased renal CNP synthesis, associated with renal tubular injury [21]. However, literature on this subject is scarce and no previous study has investigated the relation between NTproCNP and mortality in prevalent dialysis patients, which was the primary aim of this study. Second, we investigated whether the concentration of NTproCNP can be influenced by treatment with haemodiafiltration (HDF), given the middle molecular weight of NTproCNP, and, if so, whether the magnitude of the convection volume determined the rate of change. Finally, the relation between the rate of change in NTproCNP and mortality was investigated.

MATERIALS AND METHODS

Patients and study design

For the present analysis, a subset of patients from the Dutch CONvective TRAnsport STudy (CONTRAST) was used. The design and methods of the CONTRAST (NCT00205556) have been described extensively elsewhere [22, 23]. Briefly, the CONTRAST was a randomized controlled trial comparing the effect of online post-dilution HDF versus low-flux HD on all-cause mortality and cardiovascular events. In total, 714 patients were enrolled in the primary study between June 2004 and December 2009 in 29 dialysis centres located in the Netherlands ($n = 26$), Canada ($n = 2$) and Norway ($n = 1$).

Patients were eligible if >18 years of age and treated with HD two or three times per week for at least 2 months. Patients were excluded if they had been treated with HDF or high-flux HD in the preceding 6 months, in case of severe incompliance to dialysis prescription, had a life expectancy <3 months due to non-renal disease or participated in another clinical intervention trial evaluating cardiovascular outcome. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by central and local Medical Ethics Committees [Central Medical Ethics Review Board of VU University Medical Centre, Amsterdam, the Netherlands (METC VUmc 2003/97)].

Data

At baseline, relevant data on demographics, cardiovascular risk factors, time on dialysis, aetiology of renal insufficiency and use of medication were collected. Follow-up visits were planned every 3 months to monitor laboratory measurements, blood pressure, body weight and accomplished ultrafiltration and substitution per treatment. Serum samples for routine laboratory assessments were drawn before dialysis and analysed using standard techniques in local laboratories.

Serum samples

Besides routine blood collection, additional serum samples were collected and stored at −80°C at baseline and 6, 12, 24 and 36 months thereafter in centres in which this was logistically feasible ($n = 17/29$ centres).

Outcome and follow-up

No patients were lost to follow-up, as follow-up continued even after the randomized treatment was discontinued (e.g. in case of changing to another, non-participating dialysis centre, discontinuation of dialysis, switch to peritoneal dialysis or renal transplantation). The occurrence of cardiovascular events,

hospitalization and death was documented. An independent event committee evaluated all endpoints, including causes of death.

Statistical analysis

Descriptive statistics were calculated as mean [standard deviation (SD)], median [interquartile range (IQR)] or number (percentage), when appropriate. Potential determinants of NTproCNP were investigated by calculating the correlation coefficient between NTproCNP and various variables, including demographic characteristics, medical history, laboratory values, medication and dialysis characteristics, using Spearman's rank correlation coefficient. Thereafter the variables with a significant univariate relation with NTproCNP ($P < 0.05$) were entered in a multivariable linear regression model to identify the variables with an independent relation with NTproCNP. These variables were used as confounders in the survival analyses.

The relation between quartiles of baseline serum NTproCNP and mortality was investigated using Cox proportional hazards models. A model with an interaction term between baseline NTproCNP and dialysis modality was fitted to investigate whether the relation between baseline NTproCNP quartiles and mortality differed for the two dialysis modalities. As there was no interaction, hazard ratios (HRs) were calculated for the pooled cohort. Furthermore, the relation between the relative change in 6-month NTproCNP and mortality was also investigated with Cox proportional hazards models. Here, a model with an interaction term between the relative rate of change of NTproCNP and dialysis modality was also fitted to investigate whether the effect of change in NTproCNP on mortality differed for the two dialysis modalities. Given the absence of a significant interaction, we continued analyses with the pooled cohort. For both, the relation between baseline NTproCNP and mortality as well as the relation between the rate of change of NTproCNP and mortality in crude and adjusted models were fitted. Follow-up time was defined as intention-to-treat (i.e. complete follow-up). Adjusted models were corrected for age, sex, diabetes, residual kidney function, interdialytic weight gain and serum albumin.

To determine the change over time, longitudinal slopes were visualized. Hereafter, generalized linear mixed models were used to quantify the change over time, using a random slope, intercept or both, depending on the lowest Aikake's information criterion. As the intercept between the measurements differed (i.e. either 6 or 12 months), a continuous autoregressive covariance matrix was used. An interaction term between time and dialysis modality was used to investigate whether the rate of change in NTproCNP differed between HD and HDF patients. Finally, relative changes in 6-month NTproCNP were calculated between tertiles of mean achieved convection volume in patients treated with HDF to determine if the change in NTproCNP depended on the achieved convection volume.

Sensitivity analyses

Two sensitivity analyses were performed. First, the HRs for quartiles of baseline serum NTproCNP were calculated using an on-treatment protocol, that is, censoring patients at the time of randomized treatment discontinuation during the study, for example, due to moving to a non-participating centre, switching to peritoneal dialysis or renal transplantation. Second, the relation between NTproCNP and mortality was also analysed using NTproCNP as a time-varying covariate. When an event took place, the last known serum NTproCNP was entered into the model. This enhances the accuracy of risk estimates for NTproCNP. As the relation between NTproCNP and mortality, if any, appeared to be nonlinear (as shown in Table 2), NTproCNP was divided into four groups at each time point as determined by baseline serum NTproCNP quartiles. Both crude and adjusted models were fitted.

RESULTS

Baseline characteristics and determinants of NTproCNP

NTproCNP was measured in 406 patients at baseline. The median serum NTproCNP was 93 pmol/L (IQR 45–101). The mean age in the NTproCNP cohort was 63.6 years, 61.6% were male and the median dialysis vintage was 1.83 years. All baseline characteristics of the participants in the CONTRAST and NTproCNP cohort are shown in Table 1. No marked differences were observed between these two groups. The third column of Table 1 shows the univariate relation between a specific variable and NTproCNP and the fourth column shows the relation between a variable and NTproCNP in the multivariable model. As can be seen from this table, an independent positive relation between NTproCNP and gender, albumin and ultrafiltration volume was found, and a negative relation was seen with age, diabetes and residual kidney function.

Baseline NTproCNP and mortality

A total of 143 patients died during follow-up. As can be seen from the results in Table 2, patients in the lowest quartile of the NTproCNP cohort had a significantly higher all-cause mortality risk compared with the highest quartile in a crude analysis {HR 1.97 [95% confidence interval (CI) 1.24–3.12]}. After adjustment for relevant confounders, however, no statistically significant relation between NTproCNP and mortality was observed.

NTproCNP levels over time

Figure 1 shows the longitudinal data as stratified by dialysis modality. The rate of change in NTproCNP differed significantly between the two treatment groups (P for interaction <0.0005). Stratified models showed that in HD patients, NTproCNP remained stable while a significant decrease in NTproCNP was observed in patients treated with HDF [Δ −6.6 pmol/L/year (95% CI −8.7 to −4.5 pmol/L/year)].

Convection volume and NTproCNP

The relative change in 6 months in NTproCNP for HDF patients by tertiles of convection volume is shown in Figure 2. NTproCNP levels decreased over 6 months with an upward trend in higher magnitudes of convection volume: −14.1% (IQR −24.9–4.33), −21.4% (IQR −42.5 to −4.01) and −25.0% (IQR −36.4 to −8.6) in low-, medium- and high-volume HDF, respectively (P for trend <0.0005).

Change in NTproCNP and mortality

No difference was found between the two dialysis modalities in the effect of relative 6-month change of NTproCNP on mortality (P for interaction = 0.73). In the pooled cohort, as shown in Supplementary data, Table S1, the relative change in 6 months in NTproCNP was not associated with mortality in crude or adjusted models. The association between an absolute change in 6-month NTproCNP and mortality as well as the association between the relative (and absolute) 12-month change in

Table 1. Baseline patient characteristics and associations with NTproCNP

Determinant	Entire cohort ($n = 714$)	Investigated patients ($n = 406$)	Univariate association with NTproCNP	Multivariable association with NTproCNP
Demographic characteristics				
Age (years)	64.1 (13.7)	63.6 (13.9)	−0.29*	−0.27*
Sex (male), *n* (%)	445 (62.3)	250 (61.6)	0.29*	0.33*
BMI (kg/m^2), mean (SD)	25.4 (4.8)	25.0 (4.8)	NS	–
Medical history, *n* (%)				
Diabetes (yes)	170 (23.8)	85 (20.9)	−0.14*	−0.12*
History of cardiovascular event (yes)	313 (43.8)	176 (43.3)	−0.15*	−0.05
MAP (mmHg)	100 (14)	101 (13)	0.14*	0.03
Residual kidney function[a] (yes)	376 (52.7)	229 (56.4)	−0.38*	−0.26*
Laboratory values, mean (SD)				
Haemoglobin (g/dL)	11.8 (1.3)	11.8 (1.3)	NS	–
Phosphorus (mg/dL)	5.08 (1.53)	5.20 (1.60)	0.17*	0.03
Albumin (g/dL)	4.04 (0.38)	4.01 (0.41)	0.17*	0.12*
Cholesterol (mg/dL)	142.0 (37.0)	142.0 (38.0)	NS	–
IL-6 (pg/mL)	NA	2.07 (1.21–3.82)	NS	–
CRP (mg/L)	NA	4.02 (1.38–10.70)	NS	–
Medication, *n* (%)				
β-blocker (yes)	381 (53.4)	229 (56.4)	−0.11*	−0.06
Calcium antagonist (yes)	230 (32.2)	135 (33.3)	NS	–
RAS inhibitor (yes)	351 (49.2)	217 (53.4)	NS	–
Statin (yes)	369 (51.7)	208 (51.2)	−0.12*	0.03
Platelet aggregation inhibitor (yes)	240 (33.6)	119 (29.3)	NS	
Dialysis characteristics				
Dialysis vintage (years), median (IQR)	2.00 (1.00–4.00)	1.83 (0.92–3.33)	0.20*	−0.03
spKt/V_{urea}, mean (SD)	1.40 (0.22)	1.38 (0.21)	ns	–
Ultrafiltration volume (L), median (IQR)	1.9 (1.3–2.6)	1.9 (1.3–2.5)	0.33*	0.10*
HDF treatment, *n* (%)	358 (50.1)	202 (49.8)	NS	–

[a]Defined as a diuresis >100 mL/24 h.
*Significant at the level of $P < 0.05$.
BMI, body mass index; IL-6, interleukin 6; CRP, C-reactive protein; RAS, renin–angiotensin system; NS, not significant; MAP, mean arterial pressure; NA, not available.

Table 2. Mortality risk for quartiles of baseline NTproCNP

Quartiles	Crude analysis[a]	Adjusted[a,b]
All-cause mortality (143 events)		
Q1 versus Q4	1.97 (1.24–3.12)*	1.60 (0.90–2.84)
Q2 versus Q4	1.75 (1.10–2.78)*	1.04 (0.61–1.77)
Q3 versus Q4	1.40 (0.88–2.22)	1.05 (0.63–1.76)

[a]Results are shown as HRs with 95% CIs. Follow-up until death or end of the study (intention-to-treat).
[b]Adjusted for age, sex, diabetes, residual kidney function, mean ultrafiltration rate and serum albumin.
*Indicates a significant difference in hazard at the level of $P < 0.05$.

NTproCNP and mortality yielded similar results (data not shown).

Sensitivity analysis

Both the on-treatment mortality analysis (i.e. censoring patients in case of discontinuation of randomized treatment) and the sensitivity analysis using NTproCNP as a time-varying covariate assessing its relation with mortality yielded similar results to the analysis of quartiles of baseline NTproCNP with mortality using an intention-to-treat approach, as is shown in Supplementary data, Tables S2 and S3.

DISCUSSION

From this study, two important conclusions can be drawn. First, after correction for relevant confounders, no relation could be found between NTproCNP and mortality, neither calculated with a single value at baseline nor with its changes over time. Second, NTproCNP decreases in HDF patients depending on the magnitude of the convection volume, that is, the larger the convection volume, the greater the decrease in NTproCNP.

Only a limited number of studies have investigated the relation between NTproCNP and mortality. An American study with a median follow-up of 12.1 years in a randomly selected general population ($n = 1841$) found a positive relation between NTproCNP and mortality [15], as did another study ($n = 2129$) investigating patients after an acute coronary syndrome [16]. At last, a Dutch study in patients with heart failure ($n = 567$) found similar results, especially in patients with a preserved ejection fraction [24]. Obviously the results of these observational studies are no proof of causality. This study, to the best of our knowledge, is the first to investigate the relation between NTproCNP and mortality in a population with ESRD. Actually, the absence of a positive relation in this cohort raises several questions and hypotheses. First, it is possible that NTproCNP is excreted because of a compensatory mechanism but cannot exert its protective function due to persistent high levels in ESRD, thus reflecting a ceiling of the protective effect. This hypothesis would also explain the positive relation in other, non-renal cohorts. Second, the protective effects of NTproCNP could be

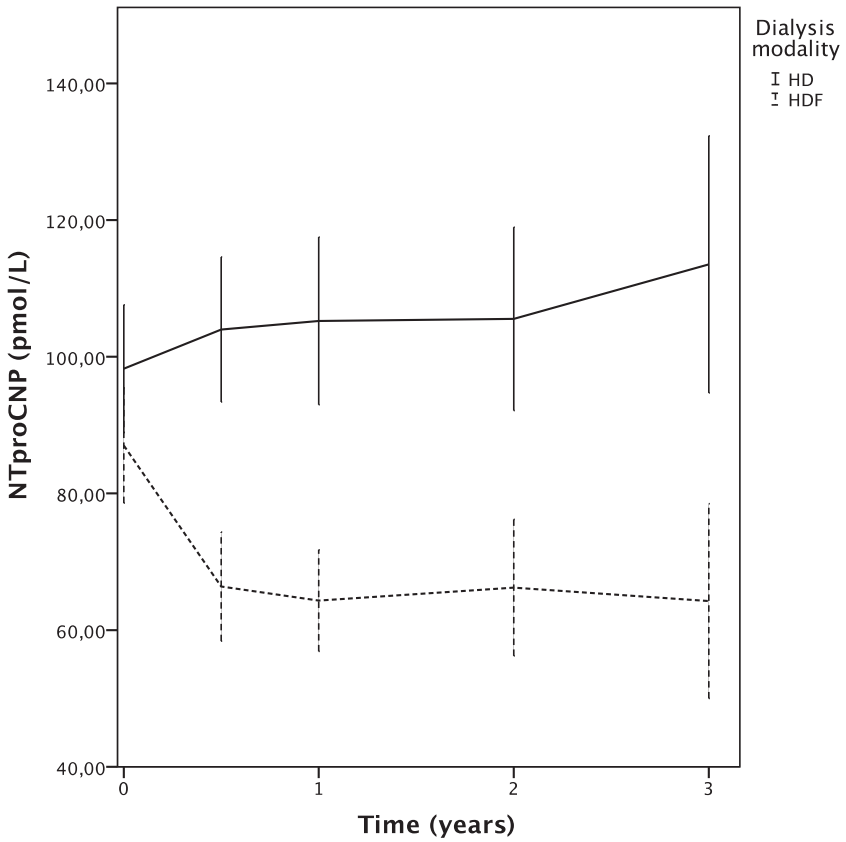

FIGURE 1: Change in serum NTproCNP over time as stratified by treatment modality.

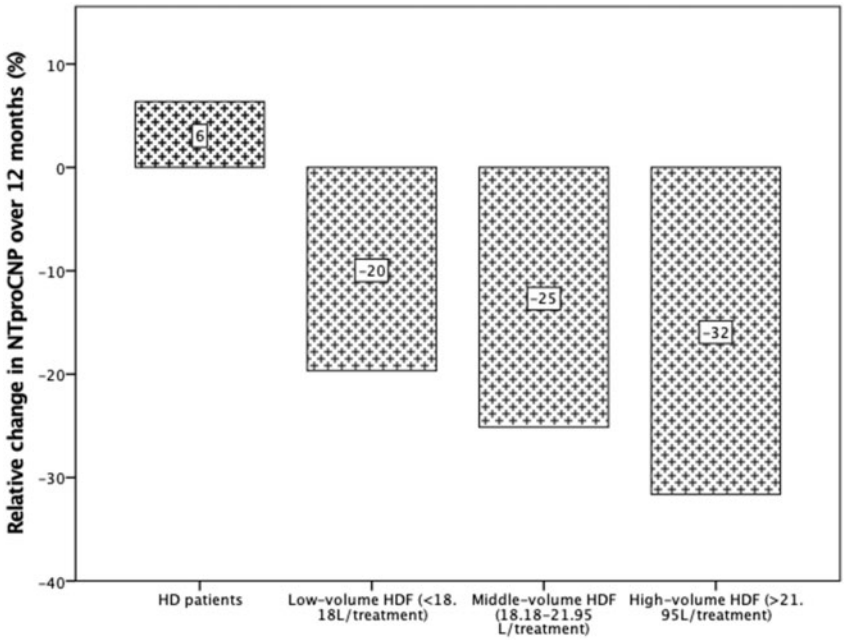

FIGURE 2: Relative change in 6-month serum NTproCNP over time as stratified by categories of convection volume.

limited to sclerosis of the intima (atherosclerosis) [25], whereas chronic kidney failure induces calcification of the media (arteriosclerosis). Third, if NTproCNP accumulates to extremely high levels due to renal failure as such, measurement of NTproCNP levels might no longer correlate with the production of NTproCNP and mask more subtle positive effects that were previously found in non-renal populations. At last, NTproCNP could be elevated in this population with ESRD without any damaging or protective effects and hence be considered an 'innocent bystander'.

While NTproCNP remained stable in individuals who were treated with HD, its levels decreased in HDF patients, depending on the magnitude of the convection volume. Since HDF may have a beneficial effect on survival [26], the absence of a relation between the change in NTproCNP and mortality suggests that the beneficial effect(s) of HDF are not the result of increased clearance of NTproCNP. Given limited power, however, this hypothesis remains to be confirmed in other studies.

This study has several limitations and strengths. The most important strengths of this study are the prospective, meticulous collection of data and the long and complete follow-up, even after discontinuation of the randomized treatment. Third, serial measurements from a central laboratory were used, which eliminates potential intercentre measurement differences. Due to the randomization of HD or HDF, it was possible to investigate causality in the different clearances of NTproCNP in these modalities. Finally, two sensitivity analyses were performed to increase the robustness of our findings.

Obviously our conclusions should be interpreted with caution as the survival analyses should be considered as observational. Furthermore, the collection and storing of samples presented a logistical challenge that appeared only possible in just over half (57%) of the participating centres. As a result, selection bias cannot be fully excluded. Finally, the limited number of events prevents us from evaluating cause-specific death.

In conclusion, neither baseline NTproCNP levels nor the change over time were associated with mortality in this cohort of dialysis patients. While NTproCNP levels remained unaltered in individuals who were treated with HD, its levels decreased in HDF patients depending on the magnitude of the convection volume. NTproCNP appears not to be a useful marker for mortality risk in ESRD patients. Future research is necessary to confirm and further elucidate our findings and to gain more insights into the pathophysiology of increasing NTproCNP levels in this population.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

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