

## Elevated N-terminal pro-brain natriuretic peptide levels predict an enhanced anti-hypertensive and anti-proteinuric benefit of dietary sodium restriction and diuretics, but not angiotensin receptor blockade, in proteinuric renal patients

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### Abstract

**Background.** Renin–angiotensin aldosterone system (RAAS) blockade only partly reduces blood pressure, proteinuria and renal and cardiovascular risk in chronic kidney disease (CKD) but often requires sodium targeting [i.e. low sodium diet (LS) and/or diuretics] for optimal efficacy. However, both under- and overtreatment of sodium targeting can easily occur. We evaluated whether N-terminal pro-brain natriuretic peptide (NT-proBNP), a biomarker of volume expansion, predicts the benefits of sodium targeting in CKD patients.

**Methods.** In a cross-over randomized controlled trial, 33 non-diabetic CKD patients (proteinuria  $3.8 \pm 0.4$  g/24 h, blood pressure  $143/86 \pm 3/2$  mmHg, creatinine clearance  $89 \pm 5$  mL/min) were treated during 6-week periods with placebo, angiotensin receptor blockade (ARB; losartan 100 mg/day) and ARB plus diuretics (losartan 100 mg/day plus hydrochlorothiazide 25 mg/day), combined with LS ( $93 \pm 52$  mmol Na<sup>+</sup>/24 h) and regular sodium diet (RS;  $193 \pm 62$  mmol Na<sup>+</sup>/24 h,  $P < 0.001$  versus LS), in random order. As controls, 27 healthy volunteers were studied.

**Results.** NT-proBNP was elevated in patients during placebo + RS [90 (60–137) versus 35 (27–45) pg/mL in healthy controls,  $P = 0.001$ ]. NT-proBNP was lowered by LS, ARB and diuretics and was normalized by ARB + diuretic + LS [39 (26–59) pg/mL,  $P = 0.65$  versus controls]. NT-proBNP levels above the upper limit of normal ( $>125$  pg/mL) predicted a larger reduction of blood pressure and proteinuria by LS and diuretics but not by ARB, during all steps of the titration regimen.

**Conclusions.** Elevated NT-proBNP levels predict an enhanced anti-hypertensive and anti-proteinuric benefit of sodium targeting, but not RAAS blockade, in proteinuric CKD patients. Importantly, this applies to the untreated condition, as well as to the subsequent treatment steps,

consisting of RAAS blockade and even RAAS blockade combined with diuretics. NT-proBNP can be a useful tool to identify CKD patients in whom sodium targeting can improve blood pressure and proteinuria.

**Keywords:** N-terminal pro-brain natriuretic peptide; dietary sodium restriction; diuretics; hypertension; proteinuria

### Introduction

Blockade of the renin–angiotensin aldosterone system (RAAS) reduces blood pressure and proteinuria, improves long-term renal and cardiovascular outcome and is the first choice therapy in chronic kidney disease (CKD) [1–3]. Despite RAAS blockade, blood pressure and proteinuria exceed the treatment target in many CKD patients and the residual risk remains high [4–6].

Previous research showed that inappropriate sodium retention is a main determinant of poor blood pressure control in CKD patients [7–9]. Furthermore, excessive dietary sodium intake blunts the anti-hypertensive and anti-proteinuric response to RAAS blockade in hypertensive [10] and CKD patients [11–13]. Vice versa, sodium targeting (i.e. dietary sodium restriction and/or diuretics) can reduce blood pressure and proteinuria when instituted as monotherapy and, moreover, can potentiate the therapeutic efficacy of RAAS blockade [14–17].

However, the responses of blood pressure and proteinuria to sodium targeting are different between individuals [18–20] and in the absence of overt signs of volume overload or volume deficit it can be cumbersome to assess whether or not further sodium targeting is required for optimizing the therapy response [7, 21]. Accordingly, both under- and

overtitration of sodium targeting can easily occur [22–24]. A simple test that predicts the anti-hypertensive and anti-proteinuric benefits of dietary sodium restriction and/or diuretics would be useful but is currently not available.

For this reason, we aimed to evaluate N-terminal pro-brain natriuretic peptide (NT-proBNP), a biomarker of the cardiac response to volume expansion, as a candidate marker in this respect [25–27]. To this purpose, we performed a *post hoc* analysis on the responses of blood pressure and proteinuria to sodium targeting, in a previously published study in patients with proteinuric CKD, who underwent a treatment schedule including sodium targeting measures in the untreated condition as well as during RAAS inhibition by angiotensin receptor blockade (ARB) [14], specifically investigating the prognostic impact of elevated NT-proBNP for the responses of blood pressure and proteinuria to sodium intervention with sodium restricted diet, diuretic treatment or their combination, during ARB.

## Materials and methods

### Patients and protocol

This is a *post hoc* analysis of a randomized, double-blind, placebo-controlled cross-over trial. The protocol was described in detail elsewhere [14]. In short, all patients ( $n = 33$ ) had stable proteinuria ( $>2$  and  $<10$  g/day) due to non-diabetic CKD, were middle aged (18–70 years) and had stable creatinine clearance ( $>30$  mL/min,  $<6$  mL/min/year decline). Only three patients had a history of cardiovascular disease, namely myocardial infarction (all  $>5$  years ago). Patients were randomized to a low sodium diet (LS; average sodium intake  $92 \pm 8$  mmol  $\text{Na}^+$ /24 h) or a regular sodium diet (average sodium intake  $196 \pm 9$  mmol  $\text{Na}^+$ /24 h,  $P < 0.001$ ). They remained on the assigned diet for 18 weeks, consisting of three 6-week treatment periods with consecutively placebo, ARB (losartan 100 mg/day) and ARB plus diuretic (losartan 100 mg/day plus hydrochlorothiazide 25 mg/day), in random order (Figure 1). After 18 weeks, the patients changed their diet and the three 6-week periods (placebo, ARB and ARB + diuretic) were repeated, again in random order. Additional anti-hypertensive drugs were allowed for blood pressure control (except for RAAS blockers or diuretics) and were kept stable during the study.

### Healthy controls

Healthy volunteers ( $n = 27$ ) with an unrestricted sodium intake served as controls. By definition, healthy subjects had no diabetes mellitus, renal function impairment or history of cardiovascular disease.

### Measurements

Proteinuria was measured by the pyrogallol red-molybdate method in 24-h urine samples. Blood pressure was measured at 1-min intervals by an automatic device (Dinamap®; GE Medical Systems, Milwaukee, WI), with the patient in supine position. After 15 min of measurements, the mean of the last four readings was used for further analysis. Dietary sodium intake was assessed from urinary sodium excretion. Peripheral blood was drawn by venipuncture, and aliquots from serum were stored ( $-80^\circ\text{C}$ ) until NT-proBNP analysis. NT-proBNP quantification was performed using electrochemiluminescent sandwich immunoassay (Elecsys ProBNP; Roche Diag-

nostics, Mannheim, Germany). The intra- and inter-assay coefficients of variation were 1.2–1.5% and 4.4–5.0%, respectively, with an analytical range of 5–35 000 pg/mL [28]. According to local laboratory reference values, NT-proBNP levels  $\leq 125$  pg/mL were considered as within the normal range. Peripheral pitting oedema was assessed at the pretibial area of both legs by visual and manual examination and scored as absent or present.

### Data analysis

Data are given as mean  $\pm$  SE when normally distributed or geometric mean (95% confidence interval) if skewed. Before statistical testing, skewed variables were natural-log transformed to obtain normality. Associations between variables in patients were evaluated with Pearson's correlation tests. Drug effects in patients were determined using paired *t*-tests. Variables in patients versus healthy controls were compared using unpaired *t*-tests.

In this *post hoc* exploratory analysis, no Bonferroni correction for multiple comparisons was used.  $P < 0.05$  was considered statistically significant. SPSS 16.0 for Windows (SPSS Inc., Chicago, IL) was used for all analyses.

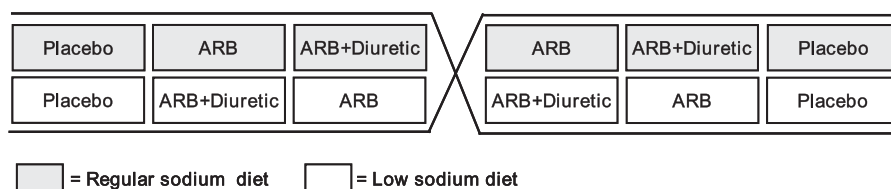
## Results

### Baseline characteristics

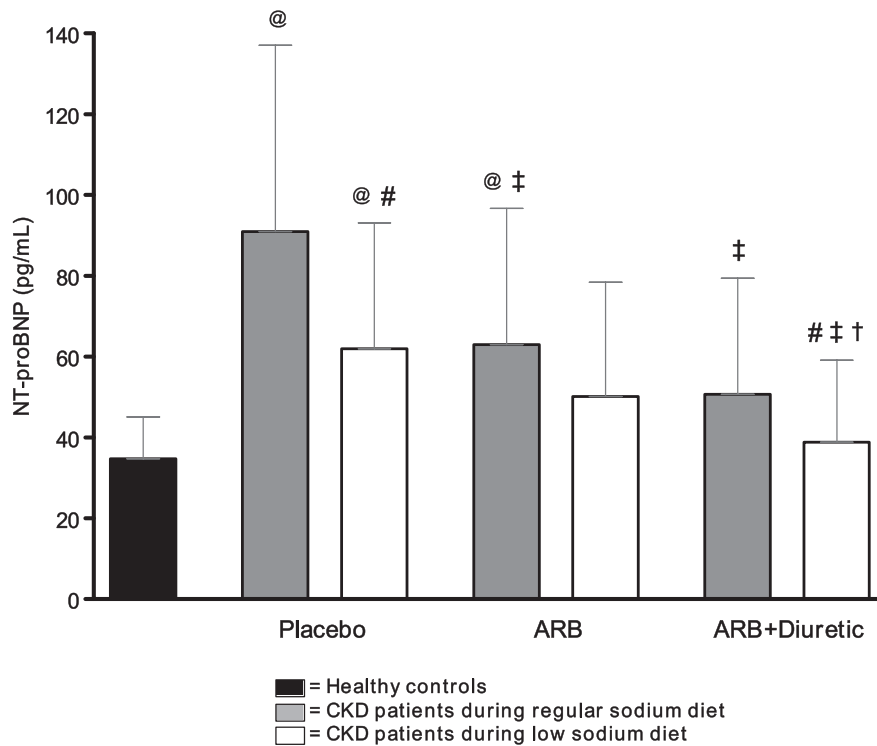
Data obtained during treatment with a placebo combined with a regular sodium diet were taken as baseline values in CKD patients. CKD patients and controls were well matched for age ( $50 \pm 2$  versus  $51 \pm 3$  years,  $P = 0.98$ ), gender (73 versus 59% male,  $P = 0.28$ ) and race (all Caucasian). At baseline, patients had overt proteinuria ( $3.8 \pm 0.4$  g/24 h), on average a blood pressure slightly above the treatment target (systolic and diastolic blood pressure  $143/86 \pm 3/2$  mmHg), and a mildly impaired creatinine clearance (CrCl;  $89 \pm 5$  mL/min). The control subjects appeared indeed healthy: blood pressure ( $123/72 \pm 3/2$  mmHg,  $P < 0.001$  versus CKD) and renal function (CrCl  $114 \pm 6$  mL/min,  $P = 0.001$  versus CKD) were normal and there was no proteinuria ( $0.15 \pm 0.02$  g/24 h,  $P < 0.001$  versus CKD). The dietary sodium intake, as reflected by urinary sodium excretion, was comparable in patients at baseline and controls ( $199 \pm 10$  versus  $177 \pm 14$  mmol  $\text{Na}^+$ /24 h,  $P = 0.17$ ).

### NT-proBNP level in proteinuric CKD and its response to LS, ARB, diuretics and their combination

At baseline, the NT-proBNP levels in the proteinuric CKD patients were  $\sim 2$ -fold higher than in healthy controls [91 (60–137) versus 35 (27–45) pg/mL,  $P < 0.001$ ; Figure 2]. LS reduced NT-proBNP up to 62 (41–93) pg/mL ( $P = 0.001$  versus baseline) in these patients. ARB lowered NT-proBNP up to 63 (41–97) pg/mL ( $P = 0.005$  versus baseline). Addition of LS plus diuretics to ARB further reduced NT-proBNP up to levels comparable to controls [39 (26–59) pg/mL,  $P = 0.002$  versus ARB,  $P = 0.65$  versus controls]. In line with this, body weight ( $91 \pm 3$  kg at baseline) was significantly reduced by the addition of LS ( $89 \pm 3$  kg,  $P = 0.013$ , RS +



**Fig. 1.** Study design. In this cross-over study, non-diabetic proteinuric CKD patients were treated during six 6-week treatment periods with placebo, ARB (losartan 100 mg/day) and ARB plus diuretic (losartan 100 mg/day plus hydrochlorothiazide 25 mg/day). Regular sodium diet and low sodium diet (intake  $196 \pm 9$  versus  $92 \pm 8$  mmol  $\text{Na}^+$ /day,  $P < 0.001$ ) were in random order.



**Fig. 2.** NT-proBNP levels at baseline and during (combinations of) LS, ARB and diuretic. <sup>@</sup>P < 0.05 versus healthy controls, <sup>#</sup>P < 0.05 versus same medication on a regular sodium diet in CKD patients (effect of low sodium diet), <sup>‡</sup>P < 0.05 versus placebo on same diet in CKD patients and <sup>†</sup>P < 0.05 versus ARB on same diet in CKD patients (effect of diuretic).

**Table 1.** Characteristics of patients with NT-proBNP ≤125 and >125 pg/mL<sup>a</sup>

	Baseline		ARB		ARB + diuretic	
	NT-proBNP ≤ 125 pg/mL	NT-proBNP > 125 pg/mL	NT-proBNP ≤ 125 pg/mL	NT-proBNP > 125 pg/mL	NT-proBNP ≤ 125 pg/mL	NT-proBNP > 125 pg/mL
Number of patients (n)	20	13	24	9	25	8
NT-proBNP (pg/mL)	42 (31–57)	285 (200–406)*	37 (25–55)	260 (196–346)*	30 (20–45)	254 (171–376)*
Oedema prevalence (%)	42	31	35	33	14	19
Serum albumin (g/L)	39 ± 1	38 ± 1	39 ± 1	39 ± 1	41 ± 1	39 ± 1
Urinary Na <sup>+</sup> excretion (mmol/24 h)	205 ± 13	194 ± 17	200 ± 14	188 ± 14	175 ± 14	198 ± 13
Proteinuria (g/24 h)	3.3 ± 0.5	4.6 ± 0.6	2.3 ± 0.3	3.5 ± 0.7	1.4 ± 0.2	2.4 ± 0.9
Systolic blood pressure (mmHg)	133 ± 4	158 ± 7*	131 ± 4	146 ± 6*	124 ± 3	128 ± 5
Diastolic blood pressure (mmHg)	83 ± 2	91 ± 4*	77 ± 1	87 ± 4*	75 ± 1	77 ± 3
Creatinine clearance (mL/min)	102 ± 5	69 ± 6*	108 ± 6	59 ± 4*	93 ± 7	64 ± 5*

<sup>a</sup>Baseline: placebo combined with a regular sodium diet; ARB: angiotensin receptor blockade combined with a regular sodium diet; ARB + diuretic: angiotensin receptor blockade plus diuretics combined with a regular sodium diet.

\*P < 0.05 versus patients with an NT-proBNP ≤125 pg/mL.

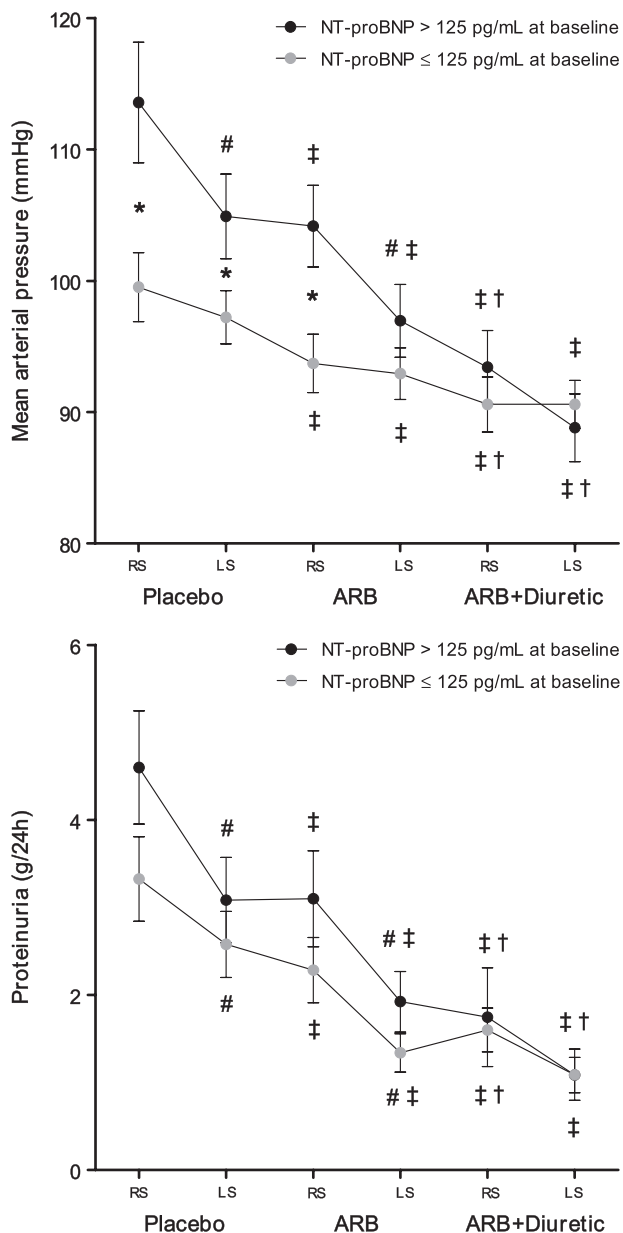
placebo versus LS + placebo), diuretic (89 ± 3, P = 0.003, RS + ARB versus RS + ARB + diuretic) and LS + diuretic (88 ± 3 kg, P < 0.001, RS + ARB versus LS + ARB + diuretic) but not by ARB as such (90 ± 3 kg, P = 0.46, RS + placebo versus RS + ARB), consistent with a negative fluid balance during LS and/or diuretic.

*Baseline NT-proBNP and its association with the subsequent effect of LS, ARB, diuretics and their combination on blood pressure and proteinuria*

The baseline NT-proBNP level exceeded the laboratory reference value of 125 pg/mL in 39% (13/33) of patients.

These patients could not be identified by the clinical assessment of volume or sodium status (peripheral pitting oedema, serum albumin, urinary sodium excretion; Table 1), but systolic and diastolic blood pressure were higher (P = 0.002 and P = 0.047), creatinine clearance was lower (P < 0.001) and proteinuria tended to be higher (4.6 ± 0.6 versus 3.3 ± 0.5 g/24 h, P = 0.13) in patients with baseline NT-proBNP >125 pg/mL than in those with baseline NT-proBNP ≤125 pg/mL.

Figure 3 shows the responses of blood pressure and proteinuria to LS, ARB and diuretics compared between patients with an NT-proBNP >125 pg/mL and patients with an NT-proBNP ≤125 pg/mL. The differences in blood



**Fig. 3.** Predictive value of baseline NT-proBNP on the benefit of (combinations of) LS, ARB and diuretic. Blood pressure and proteinuria at baseline and during (combinations of) LS, ARB and diuretic compared between patients with an NT-proBNP >125 pg/mL and patients with an NT-proBNP ≤125 pg/mL. RS, regular sodium diet; LS, low sodium diet. #P < 0.05 versus same medication on a regular sodium diet (effect of low sodium diet), †P < 0.05 versus placebo on same diet, ‡P < 0.05 versus ARB on same diet (effect of diuretics) and \*P < 0.05 versus patients with an NT-proBNP ≤125 on same treatment.

pressure and proteinuria between both patient groups get progressively less during the subsequent treatment steps and are eventually annihilated, both groups achieving a similar maximum response for blood pressure and proteinuria during ARB + diuretic + LS.

Interestingly, the institution of LS, the addition of LS on top of ARB, and the addition of diuretics on top of ARB + LS induced an additional reduction of blood pressure in patients with an NT-proBNP >125 pg/mL (LS versus RS,  $P = 0.001$ ;

ARB + LS versus ARB,  $P = 0.002$  and ARB + LS + diuretic versus ARB + LS,  $P = 0.002$ ) but not in patients with an NT-proBNP ≤125 pg/mL (LS versus RS,  $P = 0.10$ ; ARB + LS versus ARB,  $P = 0.60$  and ARB + LS + diuretic versus ARB + LS,  $P = 0.12$ ). This is consistent with the sodium sensitivity of blood pressure in patients with an NT-proBNP >125 pg/mL, whereas blood pressure in patients with an NT-proBNP ≤125 pg/mL seems rather sodium resistant. In contrast, ARB reduced blood pressure both in patients with an NT-proBNP >125 pg/mL ( $P = 0.001$  versus baseline) and in patients with an NT-proBNP ≤125 pg/mL ( $P = 0.007$  versus baseline).

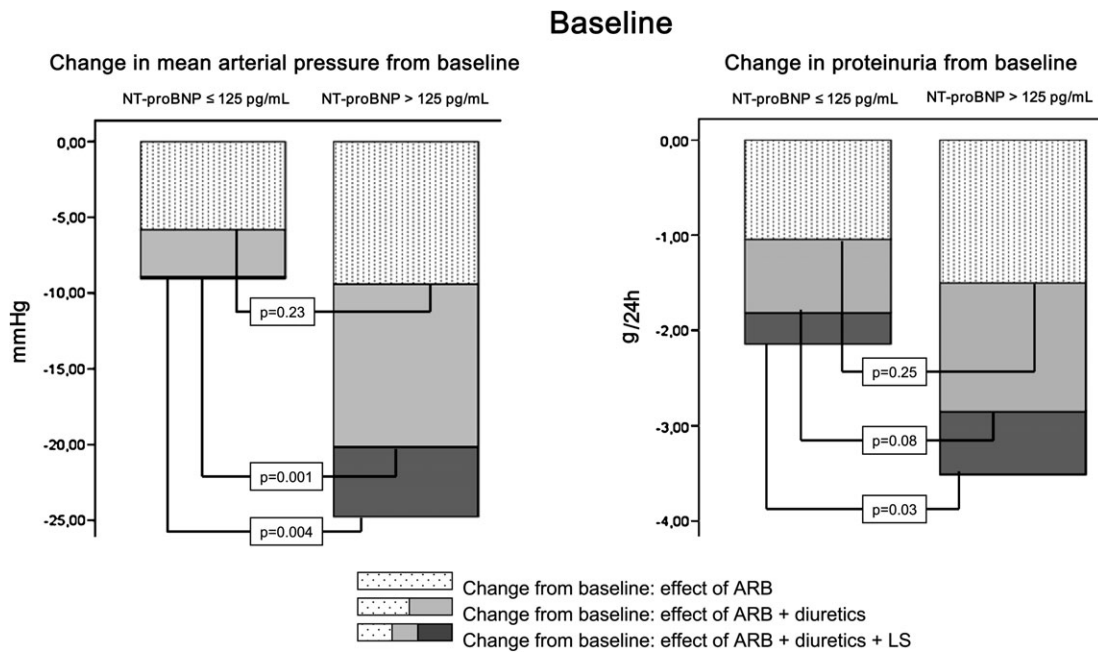
The proteinuria was reduced by all interventions in both patient groups, except for the addition of diuretics on top of ARB + LS which did not induce an additional reduction of proteinuria in patients with an NT-proBNP ≤125 pg/mL (ARB + LS + diuretic versus ARB + LS,  $P = 0.15$ ), consistent with the larger sodium sensitivity of proteinuria in patients with an NT-proBNP >125 pg/mL than in those with an NT-proBNP ≤125 pg/mL.

Figure 4 shows the change in blood pressure and proteinuria from baseline, induced by the different steps of the titration regimen as performed in clinical practice compared between patients with an NT-proBNP >125 pg/mL and patients with an NT-proBNP ≤125 pg/mL. The change in blood pressure ( $P = 0.23$ ) and proteinuria ( $P = 0.25$ ) by ARB was similar in both patient groups. However, the change in blood pressure ( $P = 0.001$  and  $P = 0.004$ ) and proteinuria ( $P = 0.08$  and  $P = 0.03$ ) from baseline by ARB + diuretic and by ARB + diuretic + LS tended to be larger in patients with an NT-proBNP >125 pg/mL than in those with an NT-proBNP ≤125 pg/mL, consistent with increased sodium sensitivity of blood pressure and proteinuria in patients with an NT-proBNP >125 pg/mL.

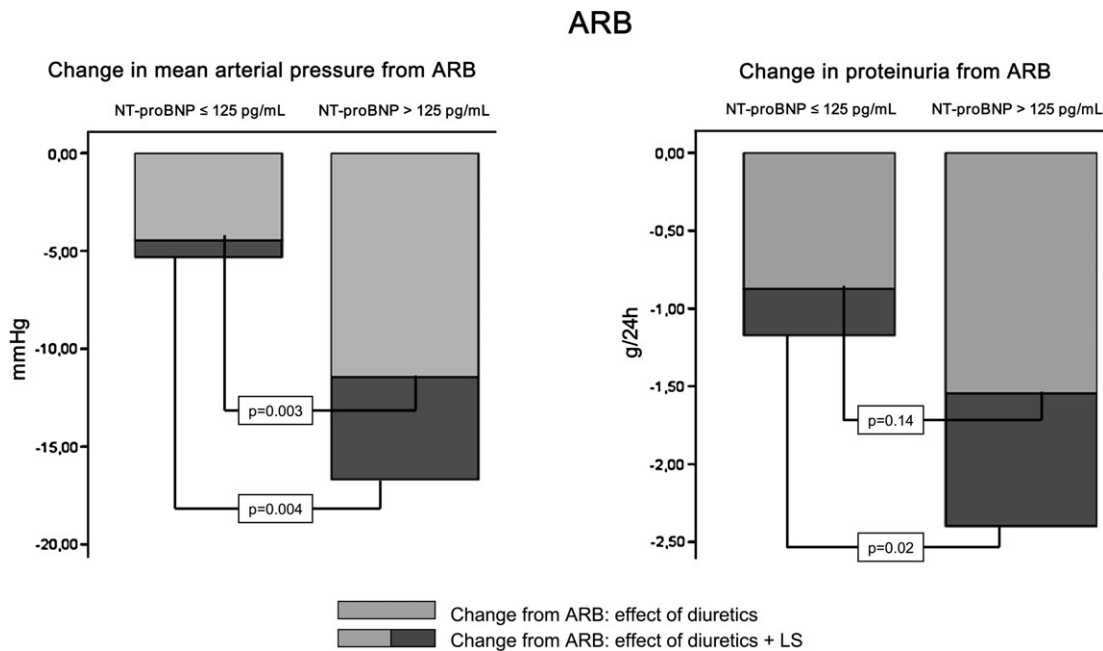
#### *NT-proBNP during ARB and its association with the subsequent effect of LS, diuretics and their combination on blood pressure and proteinuria*

During ARB, 27% (9/33) of patients had an NT-proBNP >125 pg/mL. These patients could not be identified by the clinical assessment of volume or sodium status (Table 1), although the systolic and diastolic blood pressure were higher ( $P = 0.029$  and  $P = 0.003$ , respectively), the creatinine clearance was lower ( $P < 0.001$ ) and the proteinuria tended to be higher ( $3.5 \pm 0.7$  versus  $2.3 \pm 0.3$  g/24 h,  $P = 0.10$ ) in patients with a baseline NT-proBNP >125 pg/mL than in those with a baseline NT-proBNP ≤125 pg/mL.

Figure 5 shows the change in blood pressure and proteinuria from ARB, induced by the different steps of the titration regimen as usually performed in clinical practice, compared between patients with an NT-proBNP >125 pg/mL during ARB and patients with an NT-proBNP ≤125 pg/mL during ARB. The change in blood pressure by diuretics ( $P = 0.003$ ) and by diuretic + LS ( $P = 0.004$ ) was larger in patients with an NT-proBNP >125 pg/mL than in those with an NT-proBNP ≤125 pg/mL, consistent with the increased sodium sensitivity of blood pressure in patients with an NT-proBNP >125 pg/mL. The change in proteinuria by



**Fig. 4.** Predictive value of baseline NT-proBNP on the benefit of ARB, diuretics and LS as titrated in clinical practice. Change in blood pressure and proteinuria from baseline, induced by the different steps of the titration regimen as usually performed in clinical practice, compared between patients with a baseline NT-proBNP >125 pg/mL and patients with a baseline NT-proBNP ≤125 pg/mL. LS, low sodium diet.



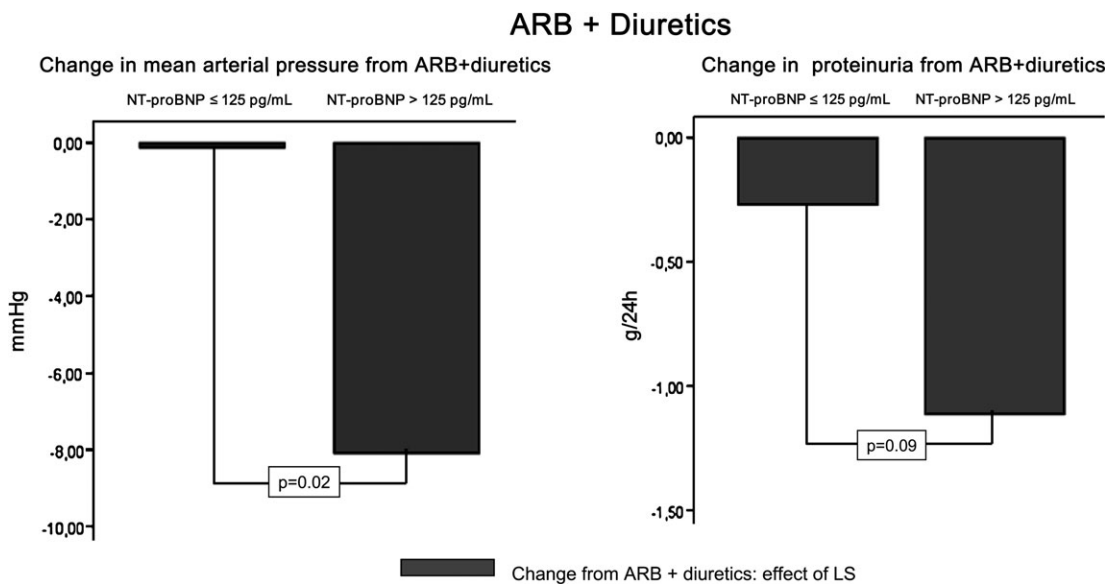
**Fig. 5.** Predictive value of NT-proBNP during ARB on the benefit of diuretics and LS as titrated in clinical practice. Change in blood pressure and proteinuria from ARB, induced by the different steps of the titration regimen as usually performed in clinical practice, compared between patients with an NT-proBNP >125 pg/mL during ARB and patients with an NT-proBNP ≤125 pg/mL during ARB. LS, low sodium diet.

diuretics was not significantly different ( $P = 0.14$ ) between both patient groups, whereas the change in proteinuria by diuretic + LS was larger in patients with an NT-proBNP >125 pg/mL than in those with an NT-proBNP ≤125 pg/mL ( $P = 0.02$ ), consistent with increased sodium sensitivity of proteinuria in patients with an NT-proBNP >125 pg/mL.

*NT-proBNP during ARB + diuretics and its association with the subsequent effect of LS on blood pressure and proteinuria*

During treatment with ARB + diuretics, 24% (8/33) of patients had an NT-proBNP >125 pg/mL. It was not possible to identify these patients by a clinical assessment of





**Fig. 6.** Predictive value of NT-proBNP during ARB + diuretics on the benefit of LS. Change in blood pressure and proteinuria from ARB + diuretics, induced by LS, compared between patients with NT-proBNP >125 pg/mL during ARB + diuretics and patients with NT-proBNP ≤125 pg/mL during ARB + diuretics. LS, low sodium diet.

volume and sodium status, and the small numerical differences in systolic and diastolic blood pressure ( $P = 0.48$  and  $P = 0.56$ ) and proteinuria ( $P = 0.34$ ) between patients with an NT-proBNP >125 pg/mL and patients with an NT-proBNP ≤125 pg/mL were not statistically significant (Table 1). However, renal function was significantly lower in patients with an NT-proBNP >125 pg/mL than in those with an NT-proBNP ≤125 pg/mL ( $P = 0.024$ ).

Figure 6 shows the change in blood pressure and proteinuria from ARB + diuretic, induced by LS, compared between patients with an NT-proBNP >125 pg/mL during ARB + diuretic and patients with an NT-proBNP ≤125 pg/mL during ARB + diuretic. In patients with an NT-proBNP >125 pg/mL LS induced a further fall in the mean arterial pressure of ~8 mmHg, whereas it was without effect in patients with an NT-proBNP ≤125 pg/mL ( $P = 0.02$ ), consistent with an increased sodium sensitivity of blood pressure in patients with an NT-proBNP >125 pg/mL and sodium sensitivity of blood pressure in patients with an NT-proBNP ≤125 pg/mL. This tended to be associated with a further reduction in proteinuria of ~1 g/24 h in patients with an NT-proBNP >125 pg/mL as compared to ~0.3 g/24 h patients with an NT-proBNP ≤125 pg/mL ( $P = 0.09$ ), consistent with an increased sodium sensitivity of proteinuria in patients with an NT-proBNP >125 pg/mL.

## Discussion

In this study in non-diabetic proteinuric CKD patients, NT-proBNP levels were elevated compared to age-matched healthy controls. The NT-proBNP levels were reduced by sodium targeting (i.e. dietary sodium restriction and/or diuretics) and RAAS blockade (i.e. ARB) and were normalized by combining these interventions. The main

finding is that NT-proBNP levels exceeding the upper limit of normal (i.e. >125 pg/mL), but not RAAS blockade, predict an enhanced anti-hypertensive and anti-proteinuric benefit of sodium targeting, in proteinuric patients. This predictive effect was observed during the untreated condition (placebo), as well as during the subsequent treatment steps consisting of RAAS blockade and even RAAS blockade combined with diuretics. Hence, an elevated NT-proBNP appears to reflect the sensitivity of blood pressure and proteinuria to sodium intervention and can be a useful adjunct tool to identify patients that will effectively respond to sodium targeting with lowering of blood pressure and proteinuria.

The observation of elevated NT-proBNP levels in non-diabetic CKD patients with a relatively preserved renal function, but overt proteinuria, is a novel finding. In advanced renal disease, elevated NT-proBNP levels are associated with a faster progression to end-stage renal disease, a larger burden of cardiovascular disease and increased mortality [29–32]. In our proteinuric patients with a relatively preserved renal function, NT-proBNP levels were only mildly elevated and substantially lower than in patients with advanced renal disease. Yet, similar mild increases of NT-proBNP have been found to independently predict cardiovascular outcome and mortality in the general population, suggesting that such mild elevations can be associated with clinical consequences [33, 34].

The reduction of NT-proBNP levels by diuretics and RAAS blockade in our proteinuric CKD patients is in line with previous findings in cardiac patients and is probably explained by a reduction of cardiac volume and pressure overload by diuretics and RAAS blockade through natriuresis and vasodilation [25–27].

The main finding of the current study is that elevated NT-proBNP levels predict a stronger reduction of blood

pressure and proteinuria by sodium targeting, both in the untreated condition and during subsequent treatment steps. As RAAS blockade as a single intervention often insufficiently reduces blood pressure, proteinuria and renal and cardiovascular risk in CKD, optimization of its efficacy is warranted [4–6]. Sodium targeting (dietary sodium restriction and/or diuretics) can potentiate the effects of RAAS blockade but can easily be under- or overtitrated. A simple test that predicts the anti-hypertensive and anti-proteinuric benefits of dietary sodium restriction and/or diuretics would be useful but is currently not available.

Interestingly, the predictive value of NT-proBNP on the anti-hypertensive and anti-proteinuric benefits of sodium targeting applies to the untreated condition (placebo), as well as to the subsequent treatment steps consisting of RAAS blockade and even RAAS blockade combined with diuretics. Hence, NT-proBNP appears to reflect the sodium sensitivity of blood pressure and proteinuria in this patient population, which is in agreement with a previous study in healthy volunteers, showing that the degree of salt sensitivity is related to baseline concentrations of N-terminal atrial natriuretic peptide levels [35].

A limitation of our study is the lack of information on the isolated effect of diuretics (i.e. without ARB). Also, the *post hoc* nature of the study dictates that the predictive properties of NT-proBNP need to be prospectively tested as a next step. One question to be resolved is whether a level of NT-proBNP can be defined below which (additional) sodium intervention is unwarranted. NT-proBNP might then be useful to prevent the adverse events associated with too intensive sodium intervention, such as symptomatic hypotension, renal ischaemia and gout. Finally, the interpretation of our study in terms of mechanisms would have benefited from direct measurements of volume status, but no such data were available for this *post hoc* study.

With respect to the diet, the ‘regular sodium diet’ very well reflected the average sodium intake in CKD and general populations, ranging from 150 to 200 mmol/day [36–38]. The ‘low sodium diet’ was well in excess of physiological needs (i.e. >10 to 20 mmol Na<sup>+</sup>/24 h [38]) and corresponded with the recommendations in current guidelines [3].

To summarize, NT-proBNP levels are mildly elevated in non-diabetic CKD patients with overt proteinuria and a relatively preserved renal function and are reduced by sodium targeting and RAAS blockade. NT-proBNP levels exceeding the upper limit of normal predict the anti-hypertensive and anti-proteinuric benefit of dietary sodium restriction and/or diuretics, but not RAAS blockade, during the different steps of the titration regimen. Hence, NT-proBNP can be a useful adjunct tool to identify proteinuric patients in whom (additional) sodium targeting can improve blood pressure and proteinuria.

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**Conflict of interest statement.** None declared.

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