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ARTICLE

L. Tarnow · P. Hildebrandt · B. V. Hansen ·
K. Borch-Johnsen · H.-H. Parving

Plasma N-terminal pro-brain natriuretic peptide as an independent predictor of mortality in diabetic nephropathy

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Abstract *Aims/hypothesis:* Raised N-terminal pro-brain natriuretic peptide (NT-proBNP) is independently associated with an increased risk of death in chronic heart failure and acute coronary syndromes in nondiabetic populations. Diabetic nephropathy is characterised by an increased risk of cardiovascular morbidity and mortality. This study investigated the prognostic value of NT-proBNP in a large cohort of type 1 diabetic patients with and without diabetic nephropathy. *Methods:* In a prospective observational follow-up study, 198 type 1 diabetic patients with overt diabetic nephropathy (122 men, age [mean±SD] 41±10 years, duration of diabetes 28±8 years, GFR 74±33 ml min^{-1}) and a matched control group of 188 patients with longstanding type 1 diabetes and persistent normoalbuminuria (114 men, age 43±10 years, duration of diabetes 27±9 years) were followed for 9.3 (0.0–9.5) years. Plasma NT-proBNP concentration was determined by immunoassay at baseline. *Results:* In patients with diabetic nephropathy, plasma NT-proBNP concentration was elevated to (median [range]) 110 (5–79640) ng l^{-1} vs. 27 (5–455) ng l^{-1} in normoalbuminuric patients ($p<0.0001$). Among patients with nephropathy, 39 (39%) patients with plasma NT-proBNP concentrations above the median and 12 (12%) with values below the median died from any cause (unadjusted hazard ratio 3.86 [95% CI 2.02–7.37], $p<0.0001$; covariate-adjusted hazard ratio 2.28 [1.04–4.99], $p=0.04$). This lower mortality rate was attributable to fewer cardiovascular deaths: 31 (31%) and 7 (7%) above and below the median NT-proBNP level respectively (unadjusted hazard ratio 5.25 [2.31–11.92], $p<0.0001$; covariate-adjusted hazard ratio 3.81 [1.46–9.94], $p=0.006$). *Conclusions/interpretation:* Elevated circulating NT-proBNP is a new independent predictor of the excess overall and cardiovascular mortality in diabetic nephropathy patients without symptoms of heart failure.

Keywords Cardiovascular mortality · Diabetic nephropathy · Mortality · NT-proBNP · Type 1 diabetes

Abbreviations BNP: brain natriuretic peptide · JNC-V: The Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure · NT-proBNP: N-terminal pro-brain natriuretic peptide

Introduction

The increased mortality seen in type 1 diabetes is predominantly caused by the extremely poor prognosis in patients with nephropathy [1, 2]. Diabetic nephropathy is a clinical syndrome characterised by persistent albuminuria, a relentless decline in glomerular filtration rate, raised arterial blood pressure, and a 37-times-higher relative mortality from cardiovascular disease, which cannot be explained by abnormalities in well-known cardiovascular risk factors alone [1–3].

Natriuretic peptides possess natriuretic, diuretic and vasodilatory properties. Furthermore, brain natriuretic peptide (BNP) blocks cardiac sympathetic nervous system activity, inhibits the renin–angiotensin–aldosterone axis, and has relaxing effects on the myocardium [4]. BNP is synthesised as a precursor protein and constitutively released predominantly in response to increased myocyte stretch in the

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L. Tarnow (✉) · B. V. Hansen · K. Borch-Johnsen · H.-H. Parving
Steno Diabetes Center,
Niels Steensens Vej 2,
2820 Gentofte, Denmark
e-mail: Ltar@steno.dk
Tel.: +45-44439952
Fax: +45-44438160

P. Hildebrandt
Department of Cardiology and Endocrinology, Copenhagen University Hospital,
Frederiksberg, Denmark

K. Borch-Johnsen · H.-H. Parving
Faculty of Health Science, Aarhus University,
Aarhus, Denmark

ventricular wall as the active hormone BNP and the N-terminal fragment (NT-proBNP) [4].

Both BNP and NT-proBNP have been shown to aid the diagnosis of heart failure and to correlate with functional status in patients with congestive heart failure [5, 6]. Levels of BNP and NT-proBNP also correlate with left ventricular dilatation, remodelling and dysfunction [7]. In addition, several studies have demonstrated a robust association between BNP and NT-proBNP and both short- and long-term risk of death in chronic heart failure [8] and acute coronary syndromes in nondiabetic populations [9].

NT-proBNP also has a putative role in risk stratification in diabetic patients, and therefore our prospective study investigated the prognostic value of NT-proBNP to assess risk of death and cardiovascular death in a large cohort of type 1 diabetic patients with and without diabetic nephropathy. Furthermore, the relation between NT-proBNP and diabetic microvascular and macrovascular complications was evaluated.

Subjects and methods

During 1993, all type 1 diabetic patients with diabetic nephropathy (n=242) attending the outpatient clinic at Steno Diabetes Center, in whom glomerular filtration rate had been measured during the same year, were invited to participate in a case-control study [10, 11]. A total of 199 patients fulfilling the clinical criteria for diabetic nephropathy (persistent macroalbuminuria [>300 mg 24 h^{-1}] in at least two out of three consecutive 24-h urine collections, in the presence of diabetic retinopathy and the absence of other kidney or urinary tract disease [12]) were recruited. A group of 192 patients with long-lasting type 1 diabetes and persistent normoalbuminuria served as controls. Plasma NT-proBNP was measured in 198 patients with nephropathy and in 188 patients with normoalbuminuria. None of the included patients were diagnosed with heart failure at baseline, although dyspnoea was not a specific exclusion criteria.

In a prospective observational study design the patients were followed up until 1 February 2003 or until death (n=62) or emigration (n=3). The study was approved by the local ethics committee, in accordance with the Helsinki Declaration, and all patients gave their informed written consent.

Baseline clinical and laboratory investigations Investigations were performed in the morning after an overnight fast. No antihypertensive medication was ever prescribed in 24% of patients with nephropathy and 88% of the normoalbuminuric patients. All of the remaining patients were asked to stop their antihypertensive and diuretic treatment 8 days before the examination. Not all patients, however, wanted to do so and thus 34% and 4% of patients in the nephropathy and normoalbuminuria groups respectively had taken antihypertensive medication on the day of examination.

Arterial blood pressure was measured twice with an appropriate cuff size following at least 10 min rest in the supine position. Urinary albumin concentration was measured by an enzyme immunoassay [13] from 24-h urine collections. Serum creatinine concentration was assessed by a kinetic Jaffé method. Glomerular filtration rate was measured in patients with diabetic nephropathy after a single injection of 3.7 MBq ^{51}Cr-EDTA by determination of radioactivity in venous blood samples taken 180, 200, 220 and 240 min after the injection [14]. In normoalbuminuric patients glomerular filtration rate was estimated by the Modification of Diet in Renal Disease equation [15]. Diabetic retinopathy was assessed in all patients by fundus photography after papillary dilatation and graded as nil, simplex or proliferative retinopathy. Patients were interviewed using the WHO cardiovascular questionnaire. Major cardiovascular events were diagnosed as a history of stroke and/or myocardial infarction. A 12-lead resting ECG was recorded, and left ventricular hypertrophy diagnosed, by Sokolow–Lyon voltage criteria. Smoking was defined as persons smoking one or more cigarettes/cigars/pipes a day; all others were classified as non-smokers.

Measurement of NT-proBNP After the patients had been at rest for at least 20 min in the supine position, blood samples for determination of NT-proBNP were collected, centrifuged and plasma stored at −80°C until analysis. Plasma concentrations of NT-proBNP were measured by a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Basel, Switzerland). The intra-assay variation is below 3.0% and the total coefficient of variation ranges from 2.2% to 5.8% in low and high ranges of NT-proBNP.

Follow-up All patients were traced through the national register during summer 2003. If a patient had died before 1 February 2003 the date of death was recorded and information on the cause of death was obtained from the death certificate. All death certificates were reviewed independently by two observers and the primary cause of death was recorded. Additional available information from necropsy reports was included. All deaths were classified as cardiovascular deaths unless an unequivocal noncardiovascular cause was established [16].

Statistical analysis Normally distributed variables are given as means±SD, whereas non-normally distributed variables were log transformed and given as medians (range). Comparisons between groups were performed by an unpaired Student's t test or ANOVA. A chi-square was used to compare noncontinuous variables. Analyses of the relation at baseline between NT-proBNP and presence/absence of nephropathy or major cardiovascular disease were adjusted for sex, age, systolic blood pressure and glomerular filtration rate. A two-tailed p value of 0.05 or less was considered statistically significant.

All time-to-death variables were analysed using a log rank test and displayed on Kaplan–Meier plots according to presence of nephropathy or NT-proBNP levels being above

or below the median value. A Cox proportional hazards regression model with backwards selection was used to evaluate the relative contributions of covariates to mortality, correcting for duration of follow-up. In patients with nephropathy, covariate-adjusted Cox regression models were fitted with the following pre-specified baseline covariates: sex, age, glomerular filtration rate, smoking, history of major cardiovascular disease, ongoing antihypertensive medication at time of blood sampling, and $\log_{10}$ NT-proBNP or NT-proBNP above respective below-the-median value (110 ng l^{-1}). Further adjustments were not performed to avoid overfitting of the model. Results are given as hazard ratios with 95% confidence intervals without or with adjustment for other factors that might affect prognosis.

All calculations were performed using a commercially available program (SPSS for Windows, version 10.0).

Results

Type 1 diabetic patients with and without diabetic nephropathy were closely matched with respect to sex, age and duration of diabetes. As compared with patients with normoalbuminuria, patients with diabetic nephropathy had elevated blood pressure, raised HbA_1c, increased serum cholesterol, and a lower glomerular filtration rate ($p<0.0001$). On average, glomerular filtration rate was well preserved in patients with diabetic nephropathy (Table 1).

In patients with diabetic nephropathy, plasma NT-proBNP concentration was elevated to 110 (5–79,640) ng l^{-1} (median [range]) vs. 27 (5–455) ng l^{-1} in normoalbuminuric patients ($p<0.0001$). This difference persisted after adjustment for differences in glomerular filtration rate and other covariates ($p<0.0001$). NT-proBNP concentration was elevated early in diabetic nephropathy (40 [5–3,111] ng l^{-1}) when glomerular filtration rate was still within the normal range (>100 ml min^{-1}).

In the nephropathy group, plasma concentration of NT-proBNP did not differ significantly between type 1 diabetic men and women ($p=0.28$), but increased with age ($r=0.42$, $p<0.0001$) and systolic blood pressure ($r=0.53$, $p<0.0001$), and decreased with glomerular filtration rate ($r=-0.60$, $p<0.0001$) and haemoglobin ($r=-0.52$, $p<0.0001$). No correlations between NT-proBNP and blood glucose, HbA_1c or serum cholesterol were observed, and no association between diabetic retinopathy and NT-proBNP was found. Among patients with diabetic nephropathy, circulating NT-proBNP concentrations were higher in patients taking antihypertensive medication at the time of sampling. This difference, however, disappeared after adjustment for glomerular filtration rate.

A weak inverse correlation between estimated glomerular filtration rate (median 94 ml min^{-1} [range 45–170]) and plasma NT-proBNP ($r=-0.22$, $p=0.002$) was demonstrated in patients with normoalbuminuria.

The prevalence of major cardiovascular events differed between patients with and without diabetic nephropathy (11% [95% CI 8–14] and 2% [0–4], respectively, $p<0.0001$). In patients with nephropathy, plasma NT-proBNP at baseline was significantly elevated in patients with a history of nonfatal myocardial infarction and/or stroke (671 [34–12,418] ng l^{-1}, $p<0.0001$) as compared with patients without a history of major cardiovascular disease (97 [5–79,640] ng l^{-1}). After adjusting for possible confounders, a ten-fold increase in NT-proBNP conferred an increase in odds ratio of a major cardiovascular event of 3.1 (95% CI 1.2–7.8, $p=0.02$).

Figure 1 shows Kaplan–Meier curves for overall mortality in patients with and without diabetic nephropathy. During follow-up 51 (26%) patients with and 11 (6%) patients without nephropathy died ($p<0.0001$). Due to the

Table 1 Baseline clinical and laboratory characteristics of 386 type 1 diabetic patients with and without diabetic nephropathy

	Nephropathy $n=198$	Normoalbuminuria $n=188$	p value
Sex (male/female)	122/76	114/74	0.84
Age (years)	41.0 (9.5)	42.5 (9.9)	0.14
Duration of diabetes (years)	27.7 (8.0)	26.8 (8.5)	0.26
Retinopathy (nil/simplex/proliferative)	0/61/137	66/103/19	<0.001
History of myocardial infarction	10 (5.1 %)	2 (1.1 %)	0.036
History of stroke	14 (7.1%)	1 (0.5 %)	0.001
BMI (kg m^{-2})	24.0 (3.3)	23.7 (2.5)	0.20
HbA_1c (%)	9.6 (1.5)	8.5 (1.1)	<0.001
Urinary albumin excretion (mg 24 h^{-1})	794 (16–14 545)	8 (1–30)	–
S-creatinine (μmol l^{-1})	103 (54–684)	76 (40–116)	<0.001
GFR (ml min^{-1})	74 (33)	94 (16)	<0.001
Systolic blood pressure (mm Hg)	151 (23)	132 (18)	<0.001
Diastolic blood pressure (mm Hg)	86 (13)	76 (10)	<0.001
Antihypertensive drugs at sampling (%)	34	4	<0.001
S-cholesterol (mmol l^{-1})	5.6 (1.2)	4.8 (1.0)	<0.001
S-HDL-cholesterol (mmol l^{-1})	1.46 (0.54)	1.56 (0.53)	0.07
S-triglycerides (mmol l^{-1})	1.22 (0.30–9.90)	0.77 (0.30–3.10)	<0.001
Smokers (%)	50	43	0.17

Data are *n*, means (SD), medians (range). Some patients with previously persistent albuminuria receiving antihypertensive medication had a urinary albumin excretion rate below 300 mg 24 h^{-1}

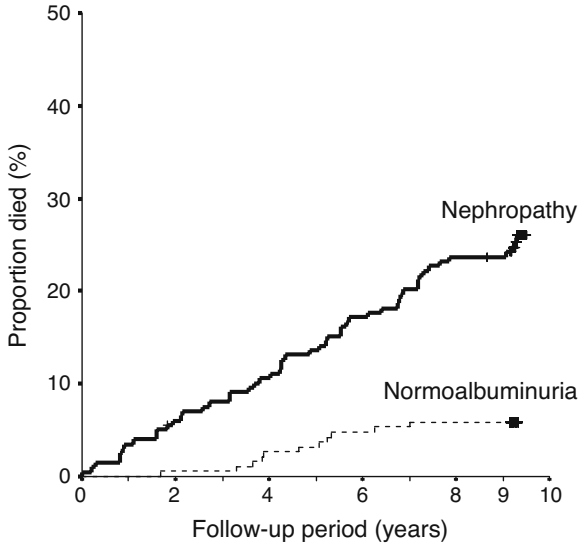

Fig. 1 Kaplan–Meier curves of all-cause mortality in type 1 diabetic patients with and without diabetic nephropathy. Log rank test, $p<0.0001$

low number of events in the normoalbuminuric group, further analyses are restricted to patients with nephropathy. Significant baseline predictors of all-cause and cardiovascular mortality were plasma NT-proBNP, smoking, antihypertensive medication, systolic blood pressure and serum cholesterol (Table 2). Within the nephropathy group the median value of plasma NT-proBNP was 110 ng l^{-1} (Table 3), and 39 (39%) of patients with values above this value as well as 12 (12%) of patients with values below this value died from any cause. The unadjusted hazard ratio was 3.86 (95% CI 2.02–7.37, $p<0.0001$) and the covariate-adjusted hazard ratio was 2.28 (1.04–4.99, $p=0.04$; Fig. 2). This lower mortality was attributable to fewer cardiovascular deaths: 31 (31%) and 7 (7%) above and below the median NT-proBNP level respectively (unadjusted hazard ratio 5.25 [2.31–11.92], $p<0.0001$; covariate-adjusted hazard ratio 3.81 [1.46–9.94], $p=0.006$; Fig. 3). The effect of plasma NT-proBNP on all-cause and cardiovascular mortality remained significant after adjustment for differences in glomerular filtration rate. Furthermore, the interaction between NT-proBNP and glomerular filtration rate was not significant, thus indicating that the effect of NT-proBNP concentration on mortality and cardiovascular mortality is not dependent on the level of glomerular filtration rate. After exclusion of 24 patients on renal replacement therapy and patients who had a measurement of serum creatinine above 500 μmol l^{-1} before death, NT-proBNP was still a significant predictor of all-cause and cardiovascular mortality (data not shown). Adjustment for serum cholesterol and systolic blood pressure did not alter hazard ratios substantially and results remained significant. Based on resting electrocardiograms, left ventricular hypertrophy was diagnosed in 12 patients with diabetic nephropathy (6%). The effect of NT-proBNP above 110 ng l^{-1} persisted in patients without ECG signs of left ventricular hypertrophy (adjusted hazard ratio 2.18 [1.00–4.78], $p=0.05$ and 3.54 [1.36–9.25], $p=0.01$ for overall and cardiovascular mortality, respectively).

The overall (log rank test, $p=0.06$) and cardiovascular ($p=0.07$) mortality in patients with nephropathy and a plasma NT-proBNP level below 110 ng l^{-1} were not statistically different from the normoalbuminuric group (Figs. 2 and 3).

By applying the cut-off of 125 ng l^{-1} NT-proBNP recommended in the USA, covariate-adjusted hazard ratios for all-cause and cardiovascular mortality were only slightly changed: 2.68 (1.24–5.79, $p=0.01$) and 4.09 (1.61–10.41, $p=0.003$) respectively.

Cox regression analyses including NT-proBNP concentration as a continuous variable revealed an unadjusted hazard ratio for all-cause mortality for each ten-fold increase in NT-proBNP of 3.39 (2.38–4.82, $p<0.0001$); covariate-adjusted hazard ratio 2.67 (1.62–4.42, $p<0.0001$). Accordingly for cardiovascular mortality, the unadjusted hazard ratio for each ten-fold increase in NT-proBNP was 3.58 (2.40–5.36, $p<0.0001$); covariate-adjusted hazard ratio 3.32 (1.90–5.81, $p<0.0001$).

Discussion

Our 9-year prospective observational follow-up study revealed plasma NT-proBNP concentration to be a novel strong and independent risk marker for all-cause and cardiovascular mortality in type 1 diabetic patients with overt diabetic nephropathy without dyspnoea or other

Table 2 Cox proportional hazard model of baseline risk factors for all-cause mortality in 198 type 1 diabetic patients with diabetic nephropathy followed for 9.3 years

	Relative risk (95% CI)	*p* value
NT-proBNP (above vs. below 110 ng l^{-1})	2.49 (1.22–5.08)	0.01
Smoking (yes vs. no)	2.08 (1.12–3.87)	0.02
Ongoing antihypertensive medication (yes vs. no)	2.89 (1.59–5.26)	0.001
Systolic blood pressure (per 10 mm Hg increase)	1.22 (1.08–1.40)	0.002
Serum cholesterol (per 1 mmol l^{-1} increase)	1.31 (1.06–1.61)	0.01

Not included in the final model were sex, age, history of major cardiovascular event, and glomerular filtration rate

Table 3 Baseline characteristics of 198 diabetic nephropathy patients according to baseline plasma value of NT-proBNP above and below the median, 110 ng l^{-1}

	Diabetic nephropathy		*p* value
	NT-proBNP>110 ng l^{-1}	NT-proBNP≤110 ng l^{-1}	
Sex (male/female)	55/44	67/32	0.11
Age (years)	44.2 (9.3)	37.8 (8.8)	<0.001
Duration of diabetes (years)	28.4 (8.6)	27.0 (7.2)	0.23
History of myocardial infarction (%)	9	1	0.02
History of stroke (%)	11	3	0.05
HbA_1c (%)	9.7 (1.6)	9.4 (1.4)	0.11
Urinary albumin excretion (mg 24 h^{-1})	1,273 (35–14 545)	543 (16–5653)	0.002
S-creatinine (μmol l^{-1})	118 (54–684)	89 (56–203)	<0.001
GFR (ml min^{-1} 1.73 m^{-2})	58 (29)	91 (29)	<0.001
Systolic blood pressure (mm Hg)	162 (21)	140 (18)	<0.001
Diastolic blood pressure (mm Hg)	88 (13)	85 (12)	0.11
Antihypertensive drugs at sampling (%)	39	29	0.18
Diuretic treatment prescribed (%)	75	54	0.003
S-cholesterol (mmol l^{-1})	5.8 (1.3)	5.5 (1.1)	0.11
Haemoglobin (mmol l^{-1})	7.7 (1.1)	8.7 (0.9)	<0.001
S-sodium (mmol l^{-1})	138 (4)	138 (3)	0.84
Smokers (%)	43	56	0.09
NT-proBNP (ng l^{-1})	296 (111–79,640)	43 (5–110)	–

Data are *n*, means (SD), medians (range)

symptoms of heart failure. The predictive value persisted after adjustment for kidney function and conventional cardiovascular risk factors including left ventricular hypertrophy. Type 1 nephropathic patients with an NT-proBNP level below the median value of 110 ng l^{-1} had a survival rate comparable to that of type 1 diabetic patients with long-standing normoalbuminuria. The prognosis for patients with diabetic nephropathy has improved during the last decade in comparison with the results of previous studies [1, 17, 18].

BNP is synthesised predominantly in the ventricular wall in response to increased myocyte stretch following volume expansion, pressure overload or increased cardiac chamber wall stress.

Although the present study of patients without symptoms of heart failure was not designed to study possible biological mechanisms for increased BNP levels, other

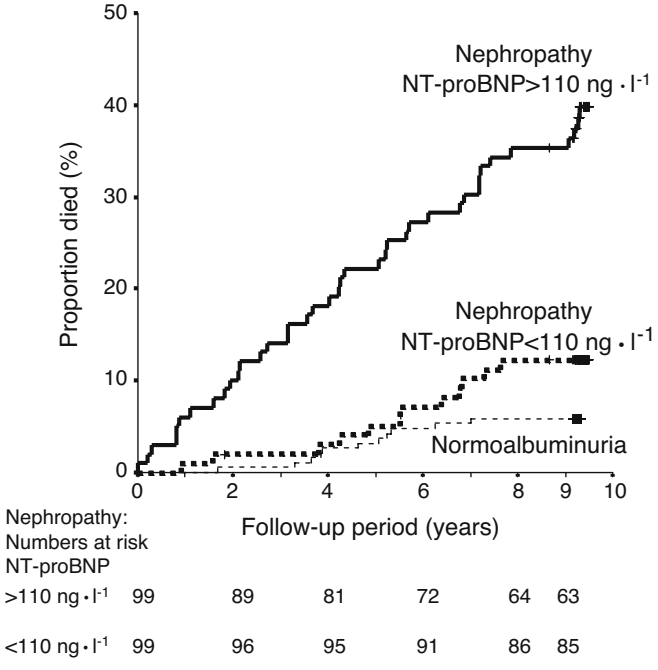

Fig. 2 Kaplan–Meier curves of all-cause mortality in patients with diabetic nephropathy and NT-proBNP concentration above vs. below the median value (110 ng l^{-1}). Log rank test, $p<0.0001$. For comparison, the curve for normoalbuminuric patients is shown by a *thin line*

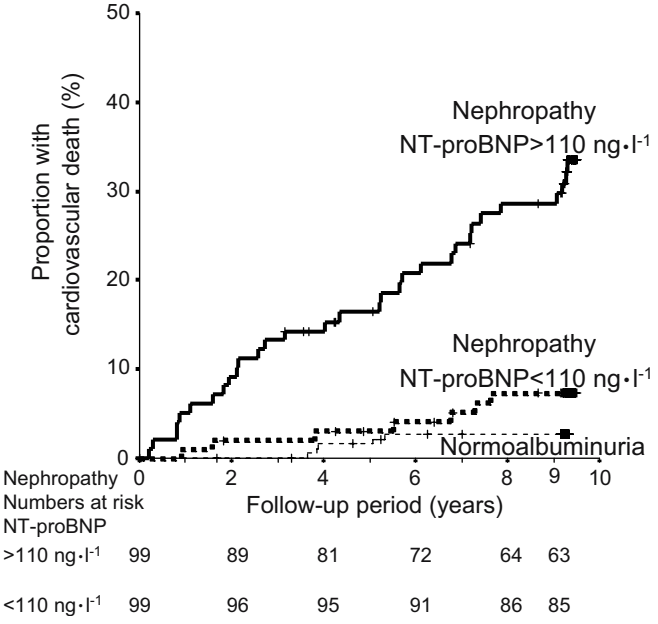

Fig. 3 Kaplan–Meier curves of cardiovascular mortality in patients with diabetic nephropathy and NT-proBNP concentration above vs. below the median value (110 ng l^{-1}). Log rank test, $p<0.0001$. For comparison, the curve for normoalbuminuric patients is shown by a *thin line*

studies have shown fluid retention to occur frequently and early in the course of diabetic kidney disease [12]. In addition, blood pressures are elevated early in type 1 diabetic patients with elevated urinary albumin excretion (microalbuminuria) [12], and the prevalence of hypertension (JNC-V criteria ≥140/90 mm Hg) increases with albuminuria, being 42%, 52% and 79% in subjects with normo-, micro- and macroalbuminuria respectively [19]. NT-proBNP has been shown to be elevated in patients with hypertension and moderate left ventricular hypertrophy despite preserved global systolic function, presumably due to subclinical left ventricular dysfunction [20]. Furthermore, plasma BNP levels correlate with left ventricular systolic and diastolic dysfunction and left ventricular hypertrophy, all of which are more prevalent in the presence of diabetes and particularly in the presence of diabetic nephropathy [21]. Recently, associations between plasma BNP and ventricular dysfunction were reported from cross-sectional studies of mixed populations of type 1 and type 2 diabetic patients with and without symptoms of congestive heart failure [22, 23]. However, the diagnostic role of BNP in diabetic heart disease needs further investigation, and no data are available on the impact on prognosis.

In nondiabetic populations, BNP levels have been shown to increase with reduced cardiac performance due to postexercise ischaemia, temporary coronary occlusion during coronary intervention or ongoing myocardial damage in non-ST segment elevation acute coronary syndromes [24–26]. This is presumably due to ischaemia-induced wall motion abnormalities and increased wall stress. Another possible explanation for the observed NT-proBNP in our study is therefore the presence of asymptomatic cardiac ischaemia, since cardiac autonomic neuropathy is a frequent complication in type 1 diabetic patients with nephropathy.

Finally, the possibility remains that genetic loci that regulate plasma BNP levels might play a role, as suggested by a recent observation from the Framingham study reporting that a substantial proportion of the variation in plasma natriuretic peptide levels was attributable to additive genetic effects [27]. Recently, cardiac BNP gene expression was reported to be increased and to improve by intervention with a breaker of advanced glycation endproducts in streptozotocin diabetic rats [28].

The above-mentioned considerations regarding possible biological mechanisms involved in the rise in NT-proBNP in diabetic nephropathy in our study suggest a multifactorial origin compounded of haemodynamic and non-haemodynamic risk factors.

First studied in nondiabetic populations as a diagnostic and prognostic marker in patients with congestive heart failure [4], BNP was subsequently found to predict outcome in patients with hypertension [20] and a broad range of acute coronary syndromes, including patients without myocardial necrosis or evidence of heart failure [9, 25, 26].

Furthermore, BNP was found to be a significant independent predictor of cardiac death in haemodialysis patients with and without diabetes [29]. In the present study, for the first time, NT-proBNP was shown to be a strong predictor of mortality and cardiovascular mortality in type 1 diabetic patients with early diabetic nephropathy.

That patients with diabetic nephropathy are at increased risk of cardiovascular death is well known; however, further risk stratification of this heterogeneous population without cardiac symptoms has so far not been possible based on conventional cardiovascular risk factors. A recent community-based study [30] found a single determination of BNP to provide additional prognostic information and suggested that BNP is elevated before the onset of clinical apparent cardiovascular disease in a predominantly (90%) nondiabetic population. In accordance and also based on one measurement, our study of type 1 diabetic patients suggests that in clinical practice, NT-proBNP could be useful for the identification of nephropathy patients with a hitherto unknown very high risk of death, who would benefit from even more aggressive management of established cardiovascular risk factors and referral for further cardiology follow-up.

Furthermore, NT-proBNP measurements might prove valuable for enrichment of diabetic patient populations in future intervention trials, including studies of cardioprotective treatment aiming to demonstrate that specific modification of this marker will translate into improved outcome, as suggested in patients with heart failure [31] and emergency patients with dyspnoea [32]. In addition, determination of plasma NT-proBNP concentration will enable the identification of type 1 diabetic patients with nephropathy with a relatively low 10-year mortality rate, a rate approaching the risk in diabetic patients with persistent normoalbuminuria. The value of such an approach, however, remains to be proven in clinical trials.

In conclusion, elevated circulating NT-proBNP is an independent predictor of the excess overall and cardiovascular mortality in diabetic nephropathy. The measurement of NT-proBNP adds prognostic information to available methods and thus could help to guide the management of type 1 diabetic patients with diabetic nephropathy.

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References

1. Andersen AR, Christiansen JS, Andersen JK, Kreiner S, Deckert T (1983) Diabetic nephropathy in Type 1 (insulin-dependent) diabetes: an epidemiological study. Diabetologia 25:496–501
2. Borch-Johnsen K, Andersen PK, Deckert T (1985) The effect of proteinuria on relative mortality in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 28:590–596
3. Jensen T, Borch-Johnsen K, Kofoed-Enevoldsen A, Deckert T (1987) Coronary heart disease in young type 1 (insulin-dependent) diabetic patients with and without diabetic nephropathy: incidence and risk-factors. Diabetologia 30:144–148

4. de Lemos JA, McGuire DK, Drazner MH (2003) B-Type natriuretic peptide in cardiovascular disease. Lancet 362:316–322
5. Maisel AS, Krishnaswamy P, Nowak RM et al (2002) Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 347:161–167
6. Gustafsson F, Badskjær J, Hansen FS, Poulsen AH, Hildebrandt P (2003) Value of N-terminal proBNP in the diagnosis of left ventricular systolic dysfunction in primary care patients referred for echocardiography. Heart Drug 3:141–146
7. Groenning BA, Nilsson JC, Sondergaard L et al (2002) Detection of left ventricular enlargement and impaired systolic function with plasma N-terminal pro brain natriuretic peptide concentrations. Am Heart J 143:923–929
8. Gardner RS, Özalp F, Murday AJ, Robb SD, McDonagh TA (2003) N-Terminal pro-brain natriuretic peptide—a new gold standard in predicting mortality in patients with advanced heart failure. Eur Heart J 24:1735–1743
9. de Lemos JA, Morrow DA, Bentley JH et al (2001) The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 345:1014–1021
10. Tarnow L, Cambien F, Rossing P et al (1995) Insertion/deletion polymorphism in the angiotensin-I-converting enzyme gene is associated with coronary heart disease in IDDM patients with diabetic nephropathy. Diabetologia 38:798–803
11. Tarnow L, Cambien F, Rossing P et al (1995) Lack of relationship between an insertion/deletion polymorphism in the angiotensin-I-converting enzyme gene and diabetic nephropathy and proliferative retinopathy in IDDM patients. Diabetes 44:489–494
12. Parving H-H, Østerby R, Ritz E (2003) Diabetic nephropathy. In: Brenner BM (ed) The kidney, 7th edn. WB Saunders, Philadelphia, pp 1777–1818
13. Feldt-Rasmussen B, Dinesen B, Deckert M (1985) Enzyme immunoassay: an improved determination of urinary albumin in diabetics with incipient nephropathy. Scand J Clin Lab Invest 45:539–544
14. Bröchner-Mortensen J, Rödbro P (1976) Selection of routine method for determination of glomerular filtration rate in adult patients. Scand J Clin Lab Invest 36:35–45
15. Levey AS, Bosch JP, Lewis JB et al (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 130:461–470
16. Pfeffer MA, Swedberg K, Granger CP et al (2003) Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-overall programme. Lancet 362:759–766
17. Knowles HC, Guest GM, Lampe J, Kessler M, Skillman TG (1965) The course of juvenile diabetes treated with unmeasured diet. Diabetes 14:239–273
18. Rossing P, Hougaard P, Borch-Johnsen K, Parving H-H (1996) Predictors of mortality in insulin dependent diabetes: 10 year follow-up study. Br Med J 313:779–784
19. Tarnow L, Rossing P, Gall M-A, Nielsen FS, Parving H-H (1994) Prevalence of arterial hypertension in diabetic patients before and after the JNC-V. Diabetes Care 17:1247–1251
20. Hildebrandt P, Boesen M, Olsen MH, Wachtell K, Groenning BA (2004) N-Terminal pro brain natriuretic peptide in arterial hypertension—a marker for left ventricular dimensions and prognosis. Eur J Heart Fail 6:313–317
21. Sato A, Tarnow L, Parving H-H (1999) Prevalence of left ventricular hypertrophy in type 1 diabetic patients with diabetic nephropathy. Diabetologia 42:76–80
22. Epshteyn V, Mudalier S, Morrison K et al (2003) Utility of B-type natriuretic peptide (BNP) as a screen for left ventricular dysfunction in patients with diabetes. Diabetes Care 26:2081–2087
23. Srivastava PM, Calafiore P, Burrell LM (2003) The role of BNP in the diagnosis of cardiac dysfunction in subjects with diabetes mellitus. Diabetologia 46(Suppl 2): A359 (Abstract)
24. de Lemos JA, Morrow DA (2002) Brain natriuretic peptide measurement in acute coronary syndromes: ready for clinical application? Circulation 106:2868–2870
25. Morrow DA, de Lemos JA, Sabatine MS et al (2003) Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST-elevation myocardial infarction. J Am Coll Cardiol 42:1264–1272
26. James SK, Lindahl B, Siegbahn A et al (2003) N-Terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease—a global utilization of strategies to open occluded arteries (GUSTO)-IV substudy. Circulation 108:275–281
27. Wang TJ, Larson MG, Levy D et al (2003) Heritability and genetic linkage of plasma natriuretic peptide levels. Circulation 108:13–16
28. Candido R, Forbes JM, Thomas MC et al (2003) A breaker of advanced glycation end products attenuates diabetes-induced myocardial structural changes. Circ Res 92:785–792
29. Naganuma T, Sugimura K, Wada S et al (2002) The prognostic role of brain natriuretic peptides in hemodialysis patients. Am J Nephrol 22:437–444
30. Wang TJ, Larson MG, Levy D et al (2004) Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 350:655–663
31. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM (2000) Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 355:1126–1130
32. Mueller C, Scholer A, Laule-Kilian K et al (2004) Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 350:647–654