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Plasma N-terminal pro-brain natriuretic peptide as a major risk marker for cardiovascular disease in patients with type 2 diabetes and microalbuminuria

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Abstract *Aims/hypothesis:* We examined whether plasma N-terminal probrain natriuretic peptide (NT-proBNP) predicts cardiovascular outcome in patients with type 2 diabetes. *Methods:* A total of 160 microalbuminuric type 2 diabetic patients (mean age 55.1 years [SD 7.2], 119 men) were enrolled in the Steno-2 Study examining the effect of multifactorial treatment, and were divided into two groups according to baseline levels of plasma NT-proBNP below or above the median for the cohort, which was followed for an average of 7.8 years. Cardiovascular outcome was a composite of cardiovascular mortality, myocardial infarction, stroke, revascularisation procedures in the heart or legs, and amputations. *Results:* In the whole group, plasma NT-proBNP being above the median was associated with an increased risk of cardiovascular disease during follow-up, with an unadjusted hazard ratio of 4.4 (95% CI 2.3–8.4; $p<0.0001$). A decrease in plasma NT-proBNP of 10 pg/ml during the first 2 years of intervention was associated with a 1% relative reduction in the primary endpoint ($p<0.001$). Despite polypharmacological treatment targeting cardiovascular disease, the mean plasma NT-proBNP level increased during follow-up. *Conclusions/interpretation:* We conclude that high plasma NT-proBNP is a major risk marker for cardiovascular disease in patients with type 2 diabetes and microalbuminuria.

Keywords Cardiovascular disease · Heart failure · Microalbuminuria · Multifactorial intervention trial · Natriuretic peptide · Risk factors · Type 2 diabetes

Abbreviations BNP: brain natriuretic peptide · CVD: cardiovascular disease · NT-proBNP: N-terminal probrain natriuretic peptide

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Introduction

It is well documented that patients with type 2 diabetes have an increased risk of cardiovascular disease (CVD) [1]. Several independent risk markers for the development of CVD in patients with diabetes have been identified, e.g., hyperglycaemia, hypertension, hypercholesterolaemia, smoking and microalbuminuria. However, these markers do not explain all of the increased CVD risk in type 2 diabetic patients.

Brain natriuretic peptide (BNP) is synthesised by cardiocytes as a response to increased cardiac wall stress, and mediates natriuresis, diuresis and vasodilatation [2]. BNP is synthesised as a prohormone that is cleaved into BNP and N-terminal proBNP (NT-proBNP), the latter being more stable in vitro with a longer half-life. The role of BNP as a prognostic risk marker for CVD has been investigated in patients with chronic heart failure and acute myocardial infarction, showing increased risk of future CVD morbidity or mortality with elevated plasma levels of BNP. Measurement of plasma NT-proBNP seems to provide the same information as that of plasma BNP [3].

Since knowledge about the roles of plasma BNP and NT-proBNP as prognostic risk markers for CVD events in patients with type 2 diabetes is sparse, we investigated this aspect in 160 type 2 diabetic patients with microalbumin-

uria who were enrolled in the Steno-2 Study and followed up for an average of 7.8 years.

In nondiabetic subjects with known congestive heart failure, treatment with ACE inhibitors [4] and angiotensin II receptor antagonists [5] as well as aggressive treatment with diuretics and vasodilators [6] reduce plasma BNP concentrations. However, there are few intervention studies demonstrating beneficial effects of a prospectively assessed use of plasma BNP to guide the intensity of pharmacotherapy [7, 8]. Therefore, we studied the effect of a multifactorial risk factor treatment on plasma NT-proBNP level in patients with type 2 diabetes, and assessed whether changes in the plasma NT-proBNP level during treatment correlated with changes in the risk of cardiovascular disease.

Subjects and methods

The study design and main results of the Steno-2 Study have previously been reported in detail [9]. In brief, 160 microalbuminuric type 2 diabetic patients were randomised to conventional (n=80) or intensified multifactorial treatment targeting several concomitant risk factors. Patients in the conventional group were treated with a multifactorial approach by their general practitioners following national guidelines for the treatment of diabetes. Patients in the intensive therapy group were treated with a stepwise introduction of lifestyle and pharmacological interventions intended to maintain HbA_1c values of below 6.5%, blood pressure values of below 130/80 mm Hg, fasting serum total cholesterol levels of below 4.5 mmol/l, and fasting serum triglyceride levels of below 1.7 mmol/l. Recommended lifestyle interventions included reduced intake of animal fat but increased intake of vegetables and fish, regular participation in light or moderate exercise, and cessation of smoking. All participants in the intensive therapy group were also advised to take a low dose of aspirin and an ACE inhibitor regardless of blood pressure level. Mean follow-up was 7.8 years. Throughout the study period, the intensive group had significantly lower values of HbA_1c, fasting serum levels of total cholesterol, LDL cholesterol and triglycerides, systolic and diastolic blood pressure, and urinary AER [9]. These changes were associated with significant reductions in the risk of macrovascular and microvascular disease (relative risk reduction 53% for cardiovascular disease, 61% for progression to nephropathy, 58% for progression in retinopathy, and 63% for progression in autonomic neuropathy) [9].

All 160 participating patients were recruited from the Steno Diabetes Center during 1992 and 1993. Microalbuminuria was defined as a urinary AER of 30 to 300 mg/24 h in four of six 24-h urine samples. Diabetes was defined according to 1985 WHO criteria. Exclusion criteria included the following: (1) being older than 65 or younger than 40 years; (2) a stimulated serum C-peptide concentration of less than 600 pmol/l 6 min after intravenous injection of 1 mg glucagon; (3) pancreatic insufficiency or diabetes secondary to pancreatitis; (4) alcohol abuse; (5) nondiabetic kidney disease; (6) malignancy; or (7) life-threatening disease with death probable within 4 years. Informed consent was obtained from all participants. The protocol was in accordance with the Helsinki declaration and was approved by the ethics committee of Copenhagen County. All patients gave written informed consent.

In the present analysis patients were stratified into two groups according to baseline plasma NT-proBNP level. One group had levels below the median of the cohort and the other had levels above the median.

Endpoints The primary endpoint in the study was a combined endpoint for cardiovascular disease comprising cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, percutaneous coronary interventions, coronary artery bypass graft, vascular surgery, and amputations. A secondary endpoint comprising cardiovascular mortality and hospitalisation for congestive heart failure was also examined.

Assays All blood samples were drawn at 08.00 hours after an overnight fast. Patients did not take their drugs in the morning of the day of blood sampling.

After the patients had been at rest for at least 20 min in the supine position, blood samples (EDTA plasma) for analysis of plasma NT-proBNP were collected, centrifuged and plasma was stored at −80°C until analysis. Plasma concentrations of NT-proBNP were measured by a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Germany). The analytical range extended from 5 to 35,000 pg/ml, and the total coefficient of variation was below 0.061 in pooled human plasma samples [10]. To convert from picograms per milliliter to picomoles per liter, multiply by 0.118. Blood samples were taken at baseline and after 2, 4 and 8 years of follow-up. The maximum storage time for blood samples prior to analysis was 10 years. Although the Roche NT-proBNP assay used has been extensively evaluated, no data exist on the stability of NT-proBNP in blood samples stored for this time period [10].

Measurements Blood pressure was measured twice after 20 min of rest (with patients in the supine position) using a Hawksley random-zero sphygmomanometer with an appropriate cuff size.

Left ventricular mass index was determined by echocardiography and calculated as previously described [11].

GFR was measured after a single intravenous injection of 3.7 MBq ^{51}Cr-EDTA by determination of the radioactivity in venous blood samples taken 180, 200, 220 and 240 min after the injection [12]. Results were standardised per 1.73 m^2 body surface.

All measurements and blood samples were carried out by persons unaware of treatment allocation.

Statistical analysis Comparison of groups at baseline was by one-way analysis of variance or Mann–Whitney test whenever appropriate for numerical variables. Chi-square

test or Fisher's exact test was used to compare categorical variables. A p value of less than 0.05 was considered significant.

No significant interaction between randomisation and the baseline plasma NT-proBNP level for the prediction of outcome was found. However, since the two original treatment groups differed significantly in the risk for cardiovascular disease, the role of plasma NT-proBNP as a risk marker for cardiovascular disease was analysed in each of these groups separately, using the median value within each of the original treatment arms as cutoff for the below- or above-median group as well as in a combined group.

Event curves for time to first event for the primary and secondary endpoints were based on Kaplan–Meier analysis, and the two groups were compared using the log-rank test. Hazard ratios with 95% CIs were calculated using a Cox regression model. Results are presented as unadjusted values and as values based upon two models with adjustments for risk factors for cardiovascular disease in patients with type 2 diabetes. Model 1 was adjusted for known diabetes duration, known cardiovascular disease at baseline, sex and age, as previously reported [9], and model 2 was adjusted as in model 1 but also for systolic and diastolic blood pressure, HbA_1c, fasting serum levels of total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides, and urinary AER. Results for the combined cohort were also adjusted for original treatment allocation. Changes in the plasma NT-proBNP level during the time within each of the two treatment groups were compared by the Wilcoxon test. The effect of a 10 pg/ml decrease in plasma NT-proBNP during the first 2 years of the study on the primary and secondary outcome was based on a Cox proportional hazards model.

Results

The range of fasting plasma levels of NT-proBNP at baseline was 5 (lowest detectable value) to 1290 pg/ml with a median value of 33.5 pg/ml in the entire Steno-2 cohort. Values in the original intensive therapy group varied from 5 to 1290 (median 35.3) pg/ml and those in the conventional therapy group from 5 to 1134 (median 32.0) pg/ml. Baseline characteristics of the two groups are shown in Table 1. High baseline plasma NT-proBNP level was associated with longer diabetes duration, higher age, higher systolic blood pressure and impaired kidney function. Similarly, a higher proportion of patients in the above-median group were treated with calcium antagonists at baseline (Table 1).

During a mean follow-up time of 7.8 years, 12 first cardiovascular events, as defined, occurred in the group with baseline plasma NT-proBNP below the median value

Table 1 Baseline characteristics of 160 type 2 diabetic patients according to baseline plasma N-terminal proBNP level below or above the median of the entire cohort

	Below-median group (n=80)	Above-median group (n=80)	p value
NT-proBNP (pg/ml)[a]	13.0 (<5–32.8)	69.7 (33.5–1,290)	<0.0001
HbA_1c (%)[b]	8.7 (0.2)	8.4 (0.2)	0.29
Systolic BP (mm Hg)[b]	143 (1.9)	153 (2.2)	0.002
Diastolic BP (mm Hg)[b]	86 (1.0)	85 (1.3)	0.39
Fasting serum total cholesterol (mmol/l)[b]	5.8 (0.1)	5.4 (0.1)	0.048
Fasting serum HDL cholesterol (mmol/l)[b]	1.03 (0.03)	1.01 (0.03)	0.62
Fasting serum triglycerides (mmol/l)[a]	2.1 (0.7–11.2)	1.9 (0.5–22.5)	0.09
Known diabetes duration (years)[a]	5 (0–26)	7 (0–30)	0.003
Sex (M/F)	59/21	60/20	0.96
Smokers (n)	28	32	0.55
Weight (kg)[b]	92.8 (1.7)	89.1 (1.8)	0.13
Known CVD (n)	7	14	0.11
Left ventricular mass index (g/m^2)[b]	110 (2.9)	126 (4.2)	0.001
Age (years)[b]	52 (0.8)	58 (0.7)	<0.0001
Serum creatinine (μmol/l)[b]	74 (1.5)	80 (2.1)	0.015
GFR (ml min^{-1} per 1.73 m)[b]	125 (2.4)	109 (2.8)	<0.0001
Urinary albumin excretion (mg/24 h)[a]	70 (32–286)	80 (33–265)	0.11
Urinary sodium excretion (mmol/24 h)[a]	213 (46–577)	176 (25–449)	0.19
Medication			
ACE inhibitors (n)	13	18	0.42
Diuretics (n)	14	25	0.07
Beta blockers (n)	4	5	1.00
Calcium blockers (n)	3	13	0.02
Treatment allocation in the Steno-2 Study	41 intensive	39 intensive	0.69

[a]Median (range)
[b]Mean (SE). To convert values for NT-proBNP to picomoles per liter, multiply by 0.118

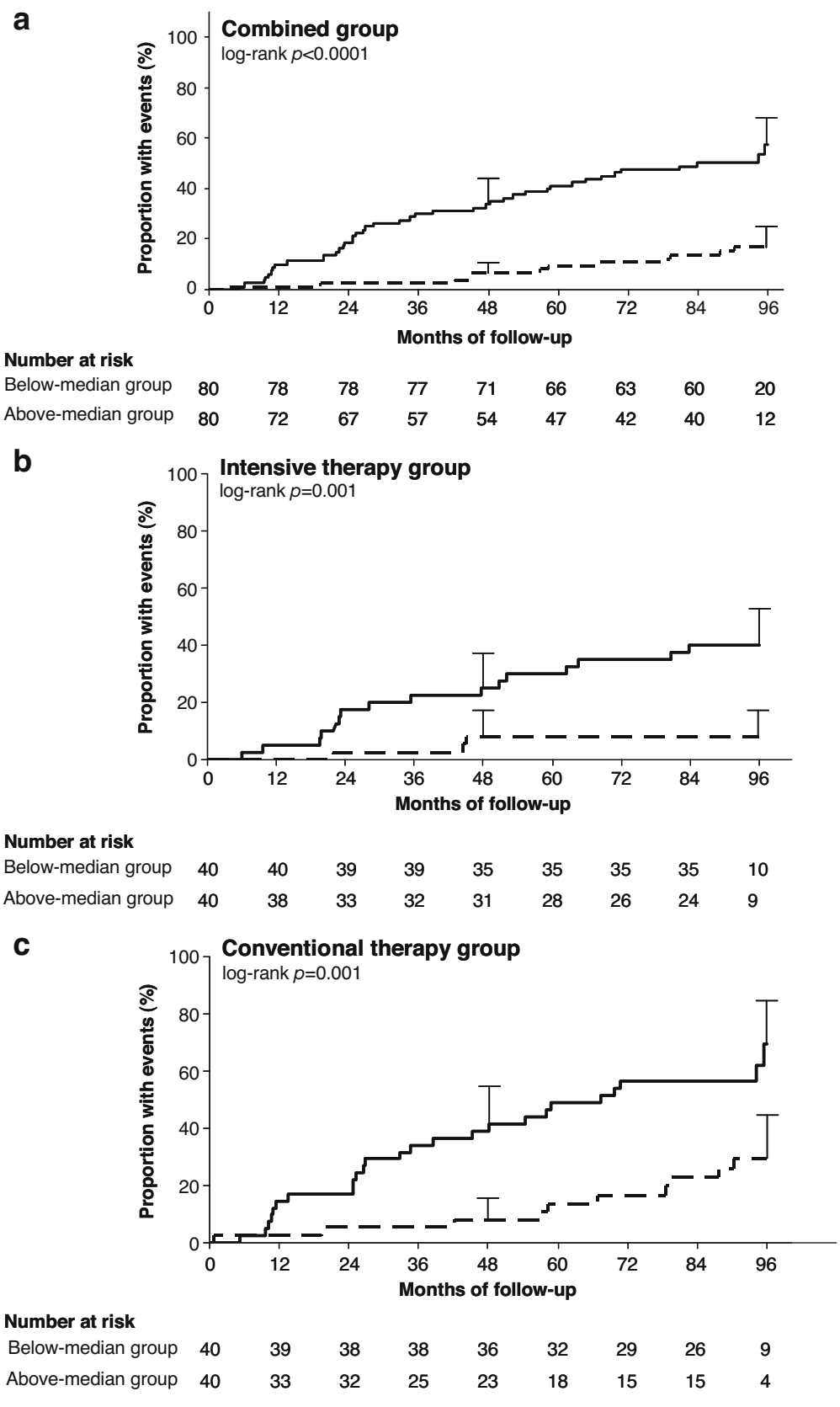

Fig. 1 Kaplan–Meier plot of time to first cardiovascular event in type 2 diabetic patients with baseline plasma NT-proBNP concentrations below (dashed line) or above the median in the entire cohort of 160 patients (**a**) in the original intensive therapy group (**b**) and in the original conventional therapy group (**c**). *p* values were calculated with log-rank test. Error bars show 95% CIs

Table 2 Hazard ratio (95% CI) for the primary and secondary endpoints in type 2 diabetic patients with plasma NT-proBNP levels above the median compared with patients with plasma levels below the median

	Intensive group	Conventional group	Combined group
Primary endpoint			
Unadjusted	6.1 (1.8–20.9), p=0.004	3.1 (1.5–6.5), p=0.002	4.4 (2.3–8.4), p<0.0001
Model 1	4.7 (1.2–17.7), p=0.022	2.3 (1.0–5.0), p=0.038	3.3 (1.7–6.5), p=0.001
Model 2	4.1 (1.0–16.7), p=0.048	3.0 (1.2–7.6), p=0.021	3.6 (1.7–7.5), p=0.001
Secondary endpoint			
Unadjusted	7.3 (0.9–59.3), p=0.06	3.3 (1.1–10.2), p=0.036	5.8 (2.0–16.9), p=0.001
Model 1	4.4 (0.4–48.2), p=0.23	3.3 (0.9–12.3), p=0.08	4.4 (1.3–14.3), p=0.015
Model 2	3.0 (0.3–32.7), p=0.38	5.2 (1.0–26.1), p=0.044	8.4 (2.0–36.3), p=0.004

Model 1 is adjusted for known cardiovascular disease at baseline, known diabetes duration, age and sex. Model 2 is adjusted for the variables in model 1 as well as for systolic and diastolic blood pressure, HbA_1c, fasting serum lipids, and urinary AER

compared with 54 events in the above-median group (p<0.0001; Fig. 1). Similarly, the significant correlation between cardiovascular disease during follow-up and the baseline plasma NT-proBNP level was also observed in each of the two original treatment groups in the Steno-2 Study, as shown in Table 1. Adjustment for conventional risk factors for cardiovascular disease in type 2 diabetes did not change the significance of the correlation in any of the adjustment models (Table 2).

The hazard ratio for the secondary endpoint was also significantly correlated with the baseline level of plasma NT-proBNP, both unadjusted and adjusted for classical risk factors (Fig. 2). However, although hazard ratios of a similar magnitude were observed when analysed in each of the two original treatment groups, adjustment diluted the significance of plasma NT-proBNP as a risk marker (Table 2).

When measured 2 years after the start of the study, levels of plasma NT-proBNP increased significantly in the combined cohort (14.9 pg/ml, p<0.0001) and a similar result was seen in the intensive and the conventional therapy groups (11.7 pg/ml, p=0.001, and 18.2 pg/ml, p<0.0001, respectively). Median plasma NT-proBNP level continued to increase in both the original intensified therapy and the conventional therapy groups during follow-up, as shown in Fig. 3.

Changes in plasma NT-proBNP during the first 2 years of intervention were significantly correlated with the risk of cardiovascular events during the rest of the follow-up period. A 10-pg/ml reduction in the plasma NT-proBNP level during the first 2 years of follow-up was associated with a significant 1% relative risk reduction in the intensive, conventional and combined cohorts for the primary and the secondary endpoints (p<0.001 in all cases). A total of 42 patients of the 160 patients included in the study had reduced plasma NT-proBNP level during the first 2 years of follow-up, with a median decrease of 12 pg/ml. Eighteen patients from the baseline classification above the median reached the below-median level after 2 years of intervention. Reaching this level, however, was not associated with a decreased risk of cardiovascular disease compared with patients not reaching the level (hazard ratio 0.45 [0.12–1.65], p=0.23). Analysing the original intensive group separately demonstrated a similar negative result (p=0.60).

The correlation between the plasma NT-proBNP level and risk of cardiovascular disease during the remaining follow-up period remained significant after 2 years for both the primary and the secondary endpoints.

Discussion

In the present long-term study of patients with type 2 diabetes and microalbuminuria we have demonstrated a significant and independent correlation between plasma NT-proBNP levels and the future risk of cardiovascular disease (primary endpoint) and cardiovascular mortality and hospitalisation for congestive heart failure (secondary endpoint). Previous studies in nondiabetic populations have shown that plasma levels of both BNP and NT-proBNP facilitate the diagnosis of heart failure. Moreover, these novel risk factors are correlated with functional status in patients with congestive heart failure [13]. Plasma levels of BNP and NT-proBNP also correlate with left ventricular dilatation, remodelling and dysfunction [13–15].

Intriguingly, compared with these studies, the level of plasma NT-proBNP is low in the type 2 diabetic patients with microalbuminuria included in the Steno-2 Study, thereby expanding the use of NT-proBNP as a risk marker for future cardiovascular disease to levels seen in the general population [16]. This observation is consistent with a recent publication from the Framingham Heart Study concerning the prognostic value of natriuretic peptides in more than 3000 subjects without heart failure [17]. Plasma natriuretic peptides predicted the risk of death and cardiovascular events after adjustment for traditional risk factors, although the circulating peptide levels, in contrast to in the present study, were not significantly correlated to the risk of coronary heart disease events. In this respect it should be emphasised that even though the type 2 diabetic patients enrolled in the Steno-2 Study had relatively low levels of plasma NT-proBNP, all had microalbuminuria as a sign of generalised vascular damage.

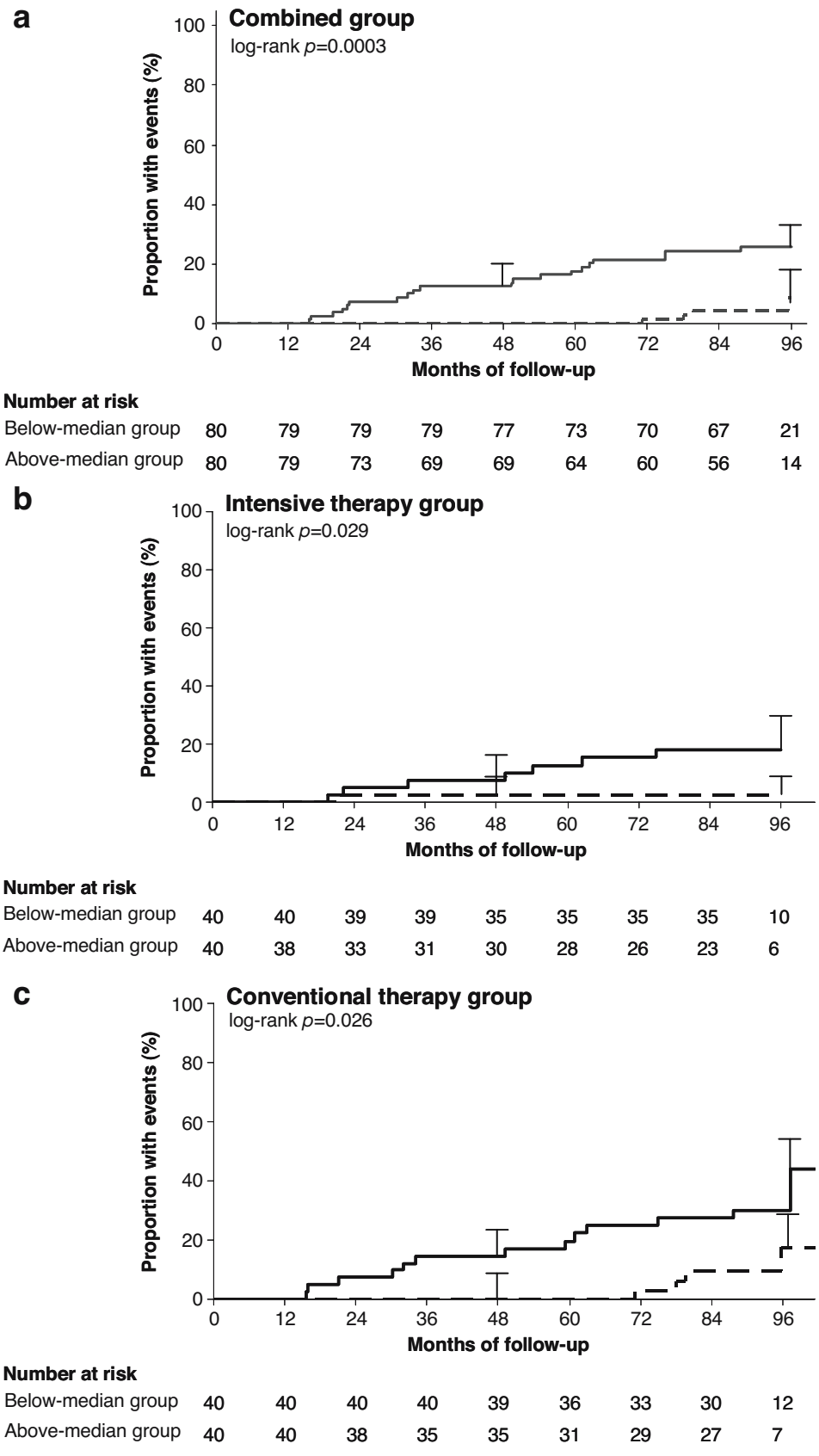

Fig. 2 Kaplan–Meier plot of time to death from cardiovascular disease, or first admission for congestive heart failure in type 2 diabetic patients with baseline plasma NT-proBNP concentrations below (dashed line) or above the median in the entire cohort of 160 patients (**a**) in the original intensive therapy group (**b**) and in the original conventional therapy group (**c**). *p* values were calculated with log-rank test. Error bars show 95% CIs

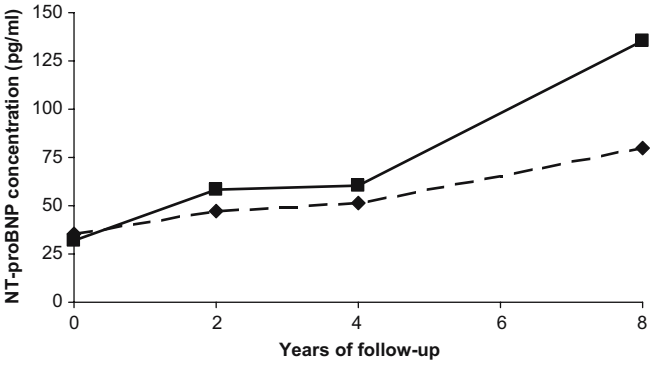

Fig. 3 Median plasma levels of NT-proBNP during follow-up in the cohort of 160 type 2 diabetic patients in the Steno-2 Study according to original treatment allocation (dashed line represents patients in the intensive therapy group)

The plasma levels of brain natriuretic peptides have so far only been examined in a few studies of patients with type 2 diabetes. A Japanese study found plasma BNP levels to be elevated in 16 microalbuminuric type 2 diabetic patients compared with 47 normoalbuminuric patients or healthy control subjects [18], whereas another Japanese study found elevated plasma levels of BNP in 100 normotensive type 2 diabetic patients compared with healthy controls but similar plasma levels in normoalbuminuric and microalbuminuric patients (n=35 and n=65, respectively) [19].

The positive correlation between plasma NT-proBNP levels and the risk of cardiovascular disease was present both at baseline and 2 years after the initiation of a multifactorial treatment approach targeting several concomitant risk factors in type 2 diabetes. These findings underlining the role of plasma NT-proBNP as an important risk marker also in patients without congestive heart failure indicate that plasma NT-proBNP-guided therapy might be a useful tool in the treatment of patients with type 2 diabetes. However, in patients with baseline NT-proBNP levels above the median in the present study, no significant risk reductions in cardiovascular events were seen in patients treated to the below-median level compared with patients remaining above the median level after 2 years of intervention. However, only a few patients obtained the lower levels during treatment and there were few events, thereby decreasing the power.

A few randomised studies in patients with heart failure have also examined the concept of plasma-BNP-guided therapy, but none of these studies have reported results for patients with diabetes. In one study 69 patients with heart failure were randomised to receive treatment guided by plasma NT-proBNP or by symptoms [7]. Mean plasma NT-proBNP levels were 217 and 251 pmol/l in the two groups, respectively. The treatment goal in the plasma-BNP-guided group was 200 pmol/l (1,695 pg/ml). ACE inhibitors and diuretics were used more frequently in the plasma-BNP-guided group during a mean follow-up of 9.5 months, resulting in a decrease in plasma NT-proBNP of 79 pmol/l (669 pg/ml) compared with 3 pmol/l (25 pg/ml) in the symptom-guided group. Significantly fewer events were seen in the guided therapy group [7]. In a second small randomised trial, patients with mild to moderate chronic heart failure had ACE inhibitor doses titrated to achieve the lowest plasma BNP level possible [8]. After 8 weeks of treatment, inhibition of the renin–angiotensin–aldosterone system was more profound and a significant fall in heart rate was seen in the titrated group compared with the group that received empirical therapy.

Thus, a decrease in plasma NT-proBNP might also be expected during intensified treatment of several risk factors in the Steno-2 Study. However, median plasma NT-proBNP levels increased in both the conventional therapy group and the intensive therapy group during follow-up (Fig. 3). In contrast to previous reports, the increase in plasma BNP level in the intensive therapy group was seen despite significant reductions in classical cardiovascular risk factors such as systolic blood pressure and total fasting serum cholesterol. It is characteristic in these studies for plasma BNP levels to be substantially higher than in the present study where the median plasma NT-proBNP level at baseline was 33.5 pg/ml. Since this level is in the normal range for the mean age in the cohort studied, it might explain the lack of a mean reduction in plasma NT-proBNP despite successful risk factor intervention.

In conclusion, plasma NT-proBNP is a strong risk marker for cardiovascular disease and congestive heart failure in patients with type 2 diabetes and generalised vascular damage as estimated from the presence of microalbuminuria.

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