Comparison of Natriuretic Peptides as Risk Markers for All-Cause Mortality and Cardiovascular and Renal Complications in Individuals With Type 1 Diabetes

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OBJECTIVE

Few studies have compared midregional proatrial natriuretic peptide (MR-proANP) and N-terminal probrain natriuretic peptide (NT-proBNP). We compared their value as risk markers for all-cause mortality and cardiovascular (CV) and renal complications in individuals with type 1 diabetes.

RESEARCH DESIGN AND METHODS

MR-proANP and NT-proBNP were measured in 664 individuals. Hazard ratios (HRs) were assessed per doubling of NT-proBNP or MR-proANP for risk of a composite of ischemic events, heart failure (HF), a combined renal end point of end-stage kidney disease (ESKD), decline in estimated glomerular filtration rate (eGFR) ≥30%, and all-cause mortality or individual end points. Adjustments included CV risk factors and addition of MR-proANP or NT-proBNP.

RESULTS

Median follow-up was 5.1–6.2 years. MR-proANP was associated with higher risk of all-cause mortality ($n = 57$; HR 1.7, 95% CI 1.1–2.7), combined CV end point ($n = 94$; 1.6, 1.1–2.2), HF ($n = 27$; 2.8, 1.5–5.2), combined renal end point ($n = 123$; 1.6, 1.2–2.1), and ESKD ($n = 21$; 3.1, 1.2–7.8) independent of CV risk factors ($P \leq 0.02$). After addition of NT-proBNP, significance for all end points was lost. A doubling of NT-proBNP was associated with higher risk of all-cause mortality (HR 1.5, 95% CI 1.2–1.8), the combined CV end point (1.3, 1.1–1.5), HF (1.7, 1.3–2.1), and the combined renal end point (1.3, 1.1–1.4) independent of CV risk factors (model 2 [$P < 0.001$]) and MR-proANP (model 3 [$P \leq 0.03$]). There was no association with decline in eGFR ≥30% ($n = 93$).

CONCLUSIONS

Higher NT-proBNP was independently associated with all-cause mortality, CV disease, HF, and the combined renal end point. MR-proANP was associated with all end points but decline in eGFR, although not independent of NT-proBNP. MR-proANP may contribute to the predictive value of NT-proBNP for risk stratification in type 1 diabetes.

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People with diabetes have significantly increased risk of micro- and macrovascular complications. Despite ample reductions in incidence of atherosclerotic cardiovascular disease (CVD), heart failure (HF), and renal complications through improved management of cardiovascular (CV) risk factors, CVD and renal complications still contribute significantly to morbidity and mortality in populations with diabetes (1,2). Current risk prediction is based on established risk factors; however, assessment of other biomarkers is key for moving toward more personalized treatment and prevention.

Among the family of biologically active natriuretic peptides are atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Inactive precursors are cleaved into the active peptides and inactive fragments midregional proANP (MR-proANP) and N-terminal proBNP (NT-proBNP). The inactive fragments have longer half-lives in plasma and therefore serve better as biomarkers. The natriuretic peptides are mainly secreted by the cardiomyocytes in response to stretching of the cardiac wall (3). MR-proANP and NT-proBNP both have numerous effects on the CV and renal systems through reduced vascular tone and increased renal electrolyte and water excretion and possibly by exerting antifibrotic and antihypertrophic effects in the heart (4).

Assessment of the circulating biomarkers MR-proANP and NT-proBNP has mainly been performed in relation to diagnosing and staging of HF; however, these peptides may represent a useful addition for evaluating risk of a broader range of CV and renal complications in people with diabetes. Higher MR-proANP was associated with a combined end point ($n = 35$) comprising end-stage kidney disease (ESKD) and all-cause mortality in a previous evaluation of the current study population of 667 individuals with type 1 diabetes after a median of 3.5 years (5). Furthermore, MR-proANP was positively associated with hospitalization for CV events and death in 781 individuals with type 2 diabetes (6) and with CVD and mortality in individuals undergoing dialysis (7). NT-proBNP has previously been shown to be positively associated with vascular and renal complications and mortality in both type 1 diabetes (8,9) and type 2 diabetes (10,11). Former studies mutually including both natriuretic peptides for comparison of their value as risk markers have primarily been performed in people without diabetes or including only a smaller fraction of people with diabetes.

To the best of our knowledge, no studies have investigated the association between MR-proANP and CVD in people with type 1 diabetes or compared the two natriuretic peptides in a population with diabetes. The aim of this study was therefore to evaluate, combine, and compare the value of MR-proANP and NT-proBNP as risk markers for all-cause mortality and development of CV and renal complications in individuals with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Study Population

In 2009–2011, a cohort of 676 persons with type 1 diabetes followed at the Steno Diabetes Center Copenhagen was included in a study with the primary aim to assess the association between arterial stiffness and diabetes complications. The details of the study have previously been published (12). In brief, the main inclusion criterion was type 1 diabetes and main exclusion criterion was prior or present ESKD, defined as chronic dialysis, renal transplantation, or estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2. The study included a research biobank with plasma samples kept at -80°C for future evaluation of biomarkers. There was inadequate plasma for biomarker measurement in 12 subjects; thus, in the current study population 664 individuals with type 1 diabetes were included. The research protocol was approved by the local ethics committee (Copenhagen, Denmark), the study complied with the Declaration of Helsinki, and all participants gave written informed consent to the original study and the research biobank.

Baseline Biochemical and Other Analyses

Plasma MR-proANP was measured in 2014 with use of the Kryptor platform (Thermo Fisher, Schwerte, Germany) as previously described (5). Plasma NT-proBNP was measured in 2019 by immunoradiometric assays with a commercial kit for cobas 6000 (Roche Diagnostics). Values of NT-proBNP below the detection limit (<5 pg/mL) were assigned a value of 2.5 pg/mL. At baseline, urinary albumin excretion rate (UAER) was measured in three 24-h urine samples with an enzyme immunoassay (VITROS, Ortho Clinical Diagnostics, Raritan, NJ). HbA_{1c} and LDL cholesterol level were measured by standardized methods in the routine laboratory, and eGFR was calculated from serum creatinine by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (13). Blood pressure was measured by the investigator after a minimum of 10 min rest with a suitably sized cuff using an automatic device. BMI was calculated in as weight in kilograms divided by the square of height in meters. Current users of one or more cigarettes, cigars, or pipes per day were classified as smokers, and all others were classified as nonsmokers. Information on medication and medical history was collected through questionnaires and checked in electronic medical records by the investigator.

Follow-up

For obtaining information on hospital admission and related ICD-10 diagnoses, procedural codes (Nordic Classification of Surgical Procedures), and date of death, all participants were traced on 31 December 2016 through the Danish National Health Register (14). Information concerning causes of death was available from the Danish National Death Register (15) until 31 December 2015. Plasma creatinine measurements during follow-up were obtained from electronic laboratory records. No participants were lost to follow-up.

The CV end points included the following: *1*) a combined CV end point comprising CV-related death, ischemic heart disease including nonfatal myocardial infarction (ICD-10 codes I20–I25), nonfatal stroke (ICD10 codes I61–I66), coronary interventions (percutaneous arterial intervention or coronary bypass grafting [procedural codes KFNA–KFNG]), or peripheral arterial interventions including amputations (Supplementary Table 1) and *2*) hospitalization due to HF (ICD-10 code I50). Unless an explicit non-CV cause was reported, all deaths were classified as CV related, a formerly applied approach (16). Cause of death was undocumented in only three participants.

The renal end points included *1*) ESKD (defined as chronic kidney disease [CKD] stage 5 [ICD-10 code N18.5], chronic dialysis [procedural code BJFD2], kidney transplantation [procedural codes KKAS 00, 10, and 20], or eGFR <15 mL/min/

1.73 m^2), *2*) decline in eGFR ≥30% assessed as time to the first occurrence of ≥30% decrease in eGFR from baseline, and *3*) a combined renal end point comprising all-cause mortality, ESKD, and decline in eGFR ≥30%.

The analyses for the combined end points included only the first end point for participants who experienced multiple end points. Information on changes in medication during follow-up was not available.

Statistical Analyses

Nonnormally distributed variables are reported as median and interquartile range (IQR), other continuous variables are reported as means (SD), and categorical variables are summarized as total numbers with corresponding percentages. Nonnormally distributed variables, including MR-proANP and NT-proBNP, were log2 transformed before analyses. Correlations between baseline variables and the log2-transformed measures of MR-proANP and NT-proBNP were examined with use of Pearson correlation.

Cox regression models were applied to estimate the hazard ratio (HR) with 95% CI for all-cause mortality, the combined CV end point, HF, the combined renal end point, ESKD, and decline in eGFR ≥30% per doubling of MR-proANP and NT-proBNP. First, we investigated whether an association existed between MR-proANP and NT-proBNP and all end points in unadjusted models (model 1). Subsequent adjustment for potential confounders included sex, age, systolic blood pressure, LDL cholesterol, smoking, HbA_{1c}, BMI, eGFR, and UAER at baseline (model 2). Lastly, MR-proANP and NT-proBNP were mutually included in the model (model 3). The assumption of proportional hazards and the linearity of the log of MR-proANP and NT-proBNP were tested for all outcomes. A nonlinear association was demonstrated for both biomarkers and ESKD and for NT-proBNP and decline in eGFR ≥30%. Therefore, in those analyses, the risk was calculated for participants in the highest quartile (Q4) compared with participants in the three lowest quartiles (Q1–Q3). We performed collinearity diagnostics assessing the variance inflation factor and tolerance values in model 3. The variance inflation factors were within the range 1.06–2.16, and the tolerance was 0.46–0.94 and therefore not considered to infer problems with collinearity.

For sensitivity we investigated the association of MR-proANP and NT-proBNP with all end points including potential confounders as in model 2 and with addition of either previous CVD or diabetes duration. For end points with <90 events, a minimally adjusted model including age, sex, and eGFR was tested. Furthermore, the area under the curve was calculated for logistic regression models including conventional CV risk factors (base model) and after addition of MR-proANP, NT-proBNP, or both markers. In addition, an end point of eGFR decline ≥40% from baseline was tested.

Survival functions (presented as Kaplan-Meier plots) and the log-rank test were applied for comparison of risk in the population categorized according to levels below or above the median for MR-proANP and for NT-proBNP.

A two-tailed *P* value of <0.05 was considered significant. Statistical analyses were performed with SAS Enterprise Guide 7.1.

Data and Resource Availability

The data sets generated during and/or analyzed in this study are not publicly available due to aspects of data protection but are available in an anonymized fashion upon reasonable request. Requests to access the data sets should be directed to P.R., peter.rossing@regionh.dk.

RESULTS

Baseline Characteristics

Of the 664 included participants, 55% were male; mean (SD) age was 55 (13) years and eGFR 81 (26) mL/min/1.73 m^2. The median concentration was 74 pmol/L (IQR 49–116) for MR-proANP and 70 pg/L (29–162) for NT-proBNP. Table 1 displays the baseline characteristics for all participants as well as Pearson correlation coefficients between each baseline variable and MR-proANP or NT-proBNP. Several clinical variables were significantly correlated with both MR-proANP and NT-proBNP; the strongest correlations were demonstrated for age, diabetes duration, and eGFR. The positive correlation between the log2-transformed measures of MR-proANP and NT-proBNP was 0.80 ($P < 0.0001$) (Fig. 1).

Median follow-up for each end point was 6.2 years (IQR 5.8–6.7) for all-cause mortality ($n = 57$), 5.1 years (4.7–5.6) for the combined CV end point ($n = 94$), 5.2 years (4.8–5.7) for HF ($n = 27$), 5.2 years (4.7–5.7) for the combined renal end point ($n = 123$), 5.2 years (4.8–5.7) for ESKD ($n = 21$), and 5.3 years (2.7–6.2) for a decline in eGFR ≥30% ($n = 93$). The combined renal end point included only the first end point for participants who experienced multiple end points and comprised all-cause mortality ($n = 30$), ESKD ($n = 10$), and decline in eGFR ≥30% ($n = 76$).

MR-proANP and NT-proBNP as Risk Markers

A doubling of MR-proANP was associated with higher risk of all-cause mortality, the combined CV end point, HF, the combined renal end point, and ESKD independent of CV risk factors ($P \leq 0.02$, model 2); however, after addition of NT-proBNP, significance for all end points was lost ($P \geq 0.30$ [model 3]) (Table 2). Higher MR-proANP was associated with decline in eGFR ≥30% in the unadjusted model ($P < 0.001$) but not after adjustment ($P \geq 0.08$ [model 2 and 3]).

A doubling of NT-proBNP was associated with higher risk of all-cause mortality, the combined CV end point, HF, and the combined renal end point independent of CV risk factors ($P < 0.001$ [model 2]) and MR-proANP ($P \leq 0.03$ [model 3]) (Table 2). There were no significant associations with ESKD or decline in eGFR ≥30% in the adjusted models ($P \geq 0.22$ [models 2 and 3]); however, higher NT-proBNP was associated with ESKD in the unadjusted model ($P = 0.02$).

The cumulative survival probability for all end points was lower for participants with concentrations of both MR-proANP and NT-proBNP above the median as compared with participants with concentrations of either MR-proANP or NT-proBNP above the median or participants with both MR-proANP and NT-proBNP below the median (log-rank $P < 0.001$) (Fig. 2*A*–*C*).

Sensitivity Analyses

The significant association between MR-proANP and the combined CV end point was lost when previous CVD was added to model 2 ($P = 0.06$), Supplementary Table 2. All other significant associations between MR-proANP and end points persisted after addition of previous CVD, and none of the associations were significantly affected when diabetes duration

Table 1—Baseline clinical characteristics of the study population (n = 664) and Pearson correlation coefficients between baseline variables and MR-proANP or NT-proBNP

	All participants (n = 664)	Pearson correlation with MR-proANP (r)	P	Pearson correlation with NT-proBNP (r)	P
Male, n (%)	368 (55)	0.03	0.50	0.20	<0.001
Age (years)	55 (13)	0.50	<0.001	0.41	<0.001
Diabetes duration (years)	33 (16)	0.39	<0.001	0.37	<0.001
BMI (kg/m^2)	25 (6)	0.005	0.90	−0.04	0.30
HbA_{1c} (%)	8.0 (1.2)	−0.12	0.002	−0.02	0.60
HbA_{1c} (mmol/mol)	64 (13)	−0.12	0.002	−0.02	0.60
UAER (mg/24 h)	18 [8–64]	0.31	<0.001	0.26	<0.001
eGFR (mL/min/1.73 m^2)	82 (25)	−0.67	<0.001	−0.50	<0.001
Systolic blood pressure (mmHg)	132 (17)	0.26	<0.001	0.24	<0.001
Diastolic blood pressure (mmHg)	74 (9)	−0.15	<0.001	−0.11	0.006
LDL cholesterol (mmol/L)	2.5 (0.8)	−0.14	<0.001	−0.10	0.01
Current smoker, n (%)	136 (20)	0.09	0.02	−0.005	0.90
History of CVD, n (%)	142 (21)	0.33	<0.001	0.33	<0.001
Treatment					
Antihypertensive drugs, n (%)	477 (72)	0.34	<0.001	0.28	<0.001
Diuretics, n (%)	335 (50)	0.33	<0.001	0.25	<0.001
Statins, n (%)	398 (60)	0.18	<0.001	0.10	0.009
Aspirin/clopidogrel, n (%)	352 (53)	0.32	<0.001	0.23	<0.001

Data are n (%, rounded), mean (SD), or median [IQR].

was added to model 2. None of the significant associations between NT-proBNP and end points were affected by inclusion of previous CVD or diabetes duration in model 2. For end points with few events (all-cause mortality, HF, and ESKD), a minimally adjusted model including only age, sex, and eGFR was tested. The results of these analyses were consistent with the results from the analyses including all clinical variables, as shown in the Supplementary Table 3. Testing development of eGFR decline ≥40% (n = 54) did not alter the significance of the findings reported (Supplementary Table 2).

The area under the curve for prediction of the combined CV end point or ESKD did not significantly improve with the addition of MR-proANP, NT-proBNP, or both markers to a base model including sex, age, systolic blood pressure, LDL cholesterol, smoking, HbA_{1c}, BMI, eGFR, and UAER ($P \geq 0.07$), Supplementary Table 4.

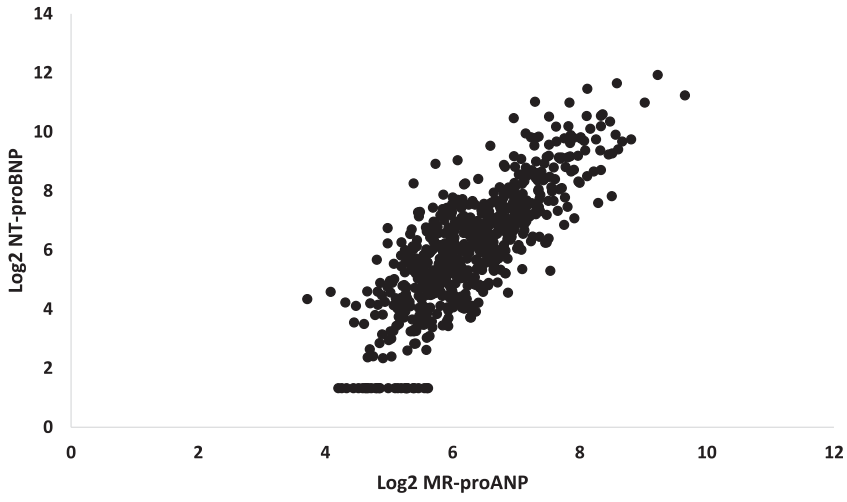

Figure 1—Correlation between the log2-transformed measures of MR-proANP and NT-proBNP (R = 0.80, P < 0.0001).

CONCLUSIONS

In this study, we evaluated and compared the value of MR-proANP and NT-proBNP as risk markers for all-cause mortality and development of CV and renal complications in individuals with type 1 diabetes. We demonstrated that *1*) higher MR-proANP was associated with several CV and renal end points independent of conventional CV risk factors although not independent of NT-proBNP and *2*) higher NT-proBNP was independently associated with all-cause mortality, the combined CV end point, and HF.

MR-proANP was previously demonstrated to be a risk marker for a combined end point comprising ESKD and all-cause mortality in the current study population after a shorter follow-up (5). In the present investigation, we expanded the follow-up, extended the end points (to include, among others, also CV events), and, importantly, investigated both MR-proANP and NT-proBNP.

Relation to All-Cause Mortality and CV End Points

MR-proANP has previously been shown to be associated with all-cause mortality and CVD, although not in a population with type 1 diabetes. In this study, we demonstrated that MR-proANP was associated with all-cause mortality, a combined CV end point, and hospitalization

Table 2—MR-proANP and NT-proBNP in relation to all-cause mortality, the combined CV end point, HF, and the combined renal end point, ESKD, and decline in eGFR ≥30%

	Model	All-cause mortality	Combined CV end point	HF	Combined renal end point	ESKD	Decline in eGFR ≥30%
Events, *n* (%)		57 (9)	94 (14)	27 (4)	123 (19)	21 (3)	93 (14)
MR-proANP	1	2.7 (2.1–3.5), <0.001	2.1 (1.7–2.6), <0.001	2.9 (2.0–4.2), <0.001	2.5 (2.1–3.0), <0.001	3.5 (2.0–6.3), <0.001	2.1 (1.7–2.6), <0.001
	2	1.7 (1.1–2.7), 0.01	1.6 (1.1–2.2), 0.01	2.8 (1.5–5.2), 0.001	1.6 (1.2–2.1), 0.002	3.1 (1.2–7.8), 0.02	1.3 (1.0–1.9), 0.08
	3	0.7 (0.4–1.3), 0.30	0.9 (0.5–1.4), 0.58	1.1 (0.4–2.8), 0.84	1.1 (0.7–1.7), 0.81	2.0 (0.5–7.7), 0.30	1.4 (0.8–2.3), 0.21
NT-proBNP	1	1.8 (1.6–2.1), <0.001	1.5 (1.4–1.7), <0.001	1.8 (1.5–2.1), <0.001	1.6 (1.4–1.7), <0.001	1.5 (1.1–2.2), 0.02	1.2 (0.9–1.5), 0.21
	2	1.5 (1.2–1.8), <0.001	1.3 (1.1–1.5), <0.001	1.7 (1.3–2.1), <0.001	1.3 (1.1–1.4), <0.001	1.4 (0.8–2.2), 0.22	0.9 (0.7–1.2), 0.62
	3	1.6 (1.3–2.2), <0.001	1.4 (1.1–1.7), 0.003	1.7 (1.1–2.4), 0.01	1.2 (1.0–1.5), 0.03	1.1 (0.6–2.0), 0.84	0.8 (0.6–1.2), 0.29

Data are HR (95% CI), *P* value, unless otherwise indicated. Model 1, unadjusted; model 2, adjustment for sex, age, systolic blood pressure, LDL cholesterol, smoking, HbA_{1c}, BMI, eGFR, and UAER; model 3, model adjustments plus MR-proANP or NT-proBNP.

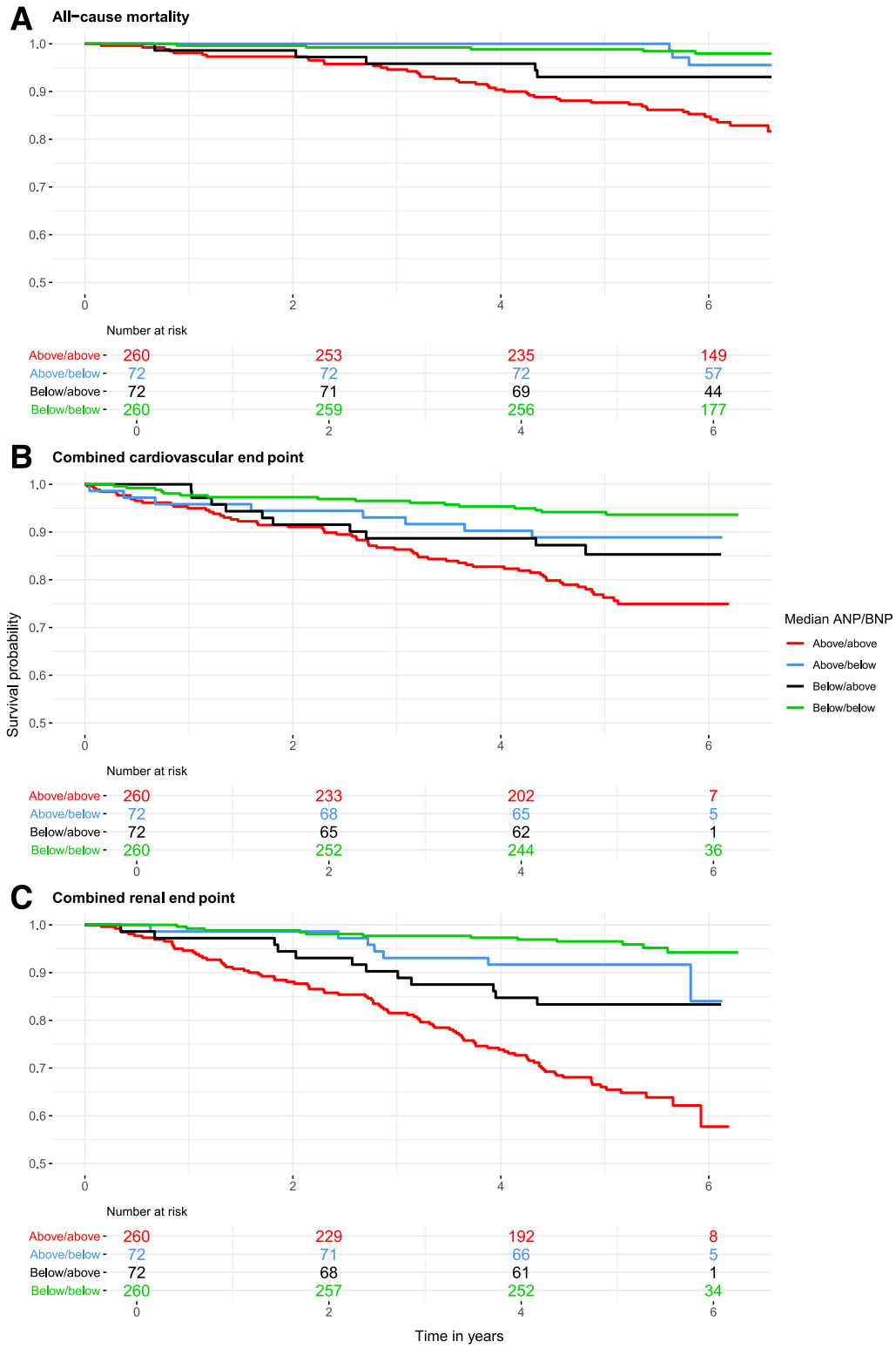

Figure 2—Kaplan-Meier plots for all-cause mortality (*A*), the combined CV end point (*B*), and the combined renal end point (*C*) for levels below or above the median for MR-proANP and for NT-proBNP. ANP denotes MR-proANP, and BNP denotes NT-proBNP.

for HF, independent of CV risk factors, in individuals with type 1 diabetes. These associations were, however, not independent of NT-proBNP, which was strongly associated with all CV end points. Both MR-proANP and NT-proBNP were previously shown to be significantly associated with development of HF when mutually investigated in a population of 721 individuals, of whom 16% had diabetes (17). In three studies with investigation of populations with chronic HF, including between 424 and 797 participants and only a smaller fraction with diabetes, both natriuretic peptides were demonstrated to

be independently associated with mortality, although with inconsistency between studies regarding which marker was superior to the other (18–20). Higher BNP was previously shown to be associated with higher risk of all-cause mortality both in individuals with and in individuals without a history of HF (21). In a study of 3,717 individuals with stable coronary artery disease, 16% with diabetes, both MR-proANP and NT-proBNP were independently associated with the primary end point, which consisted of CV mortality and hospitalization for HF (22). In the current study, 21% had a history of CVD; however, adjustment for previous CVD did not alter the results. In one other study of 1,456 individuals with stable CVD, 18% with diabetes, both markers were also associated with development of HF and overall CV events; however, MR-proANP was not associated with HF independent of conventional CV risk factors or with overall CV events after mutual inclusion of three other measured biomarkers (NT-proBNP, homocysteine, and C-reactive protein) (23). This is, to some extent, in line with our findings that the associations between MR-proANP and end points were not independent of NT-proBNP.

Relation to Renal End Points

With the extended follow-up (5), we could confirm the association between MR-proANP and progression to ESKD independent of traditional CV risk factors, but significance was lost after inclusion of NT-proBNP in the model; this may partly be explained by the low number of events. To our knowledge, only one previous study has examined MR-proANP in relation to renal end points in a model also including NT-proBNP (24). In 177 individuals with CKD (none with diabetes), MR-proANP was significantly associated with doubling of creatinine or renal failure ($n = 65$) during a 7-year follow-up, independent of NT-proBNP.

NT-proBNP has previously been shown to be associated with incident nephropathy in type 1 diabetes (4), development of CKD in type 2 diabetes (10), and progression to ESKD in people with CKD and type 2 diabetes (25). MR-proANP was not measured in those studies. In the current study, NT-proBNP was independently associated with the combined renal end point. This may reflect the strong association between NT-proBNP and all-cause mortality, since all-cause mortality accounted for 37 (30%) of the events included in the combined renal end point. NT-proBNP was not associated with any of the other renal end points in adjusted models.

Taken together, these results suggest that MR-proANP may be a better risk marker for renal disease than NT-proBNP; however, this finding needs to be examined in further studies.

Possible Mechanisms

The natriuretic peptides have been demonstrated to be inversely associated with risk of developing obesity and diabetes (26,27). Moreover, a recent meta-analysis has demonstrated an association between higher levels of natriuretic peptides and favorable lipid profiles (28). This to some extent contrasts with the findings of this and other studies demonstrating that higher levels of natriuretic peptides are risk markers for CV and renal complications of diabetes. Genetically determined higher natriuretic peptide levels have previously been shown to be protective in relation to cardiometabolic risk (29,30). At the same time, circulating natriuretic peptide levels rise in response to physiological factors, such as increased stress on cardiomyocytes and volume overload. Thus, the fact that higher natriuretic peptide levels are risk markers for CV and renal complications may reflect appropriate responses to increased stress on cardiomyocytes and volume overload in subclinical CV and renal disease.

The differences demonstrated for associations between CV and renal events and NT-proBNP as compared with MR-proANP cannot directly be explained by different pathophysiological roles of the two inactive fragments. The influence of renal function on NT-proBNP has previously been described with conflicting results in studies including individuals with manifest HF (20), and the influence of renal function on MR-proANP remains unknown. Moreover, differences in the stability of the assays used may need to be taken into account.

Clinical Implication

Improved risk stratification is crucial for moving toward more personalized prevention and treatment of CV and renal disease. The new treatment option of sodium–glucose cotransporter 2 (SGLT2) inhibitors has demonstrated CV benefit in people with type 2 diabetes and established CVD (31–33), with a reduction in hospitalization for HF. In the DAPA-HF study, the SGLT2 inhibitor dapagliflozin has also been shown to reduce the risk of worsening HF and CV mortality in people with reduced ejection fraction (EF) regardless of presence of diabetes (34). In Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), patients were required to have increased NT-proBNP for inclusion, and NT-proBNP was significantly reduced in participants treated with dapagliflozin compared with placebo; however, whether there is a direct link between lowering of NT-proBNP and improved outcome is unknown. SGLT2 inhibitors have recently also been approved for treatment in people with type 1 diabetes, but CV effects have so far not been studied in larger studies.

Sacubitril-valsartan, an angiotensin receptor–neprilysin inhibitor, has been shown to reduce the rate of a composite end point of hospitalization for HF and CV mortality in people with HF and reduced EF (35). Sacubitril-valsartan did not, however, reduce the rate of hospitalization for HF or CV mortality in people with HF and preserved EF (36). In a study of the natriuretic peptides, sacubitril-valsartan increased the levels of ANP and BNP, while the levels of MR-proANP and NT-proBNP tended to decrease during treatment (37) People with high levels of natriuretic peptides may especially benefit from treatment options that alter the levels of the natriuretic peptides, and these drugs could hold a potential for prevention of CV complications. An ongoing outcome-driven study in people with type 2 diabetes and CKD is investigating the effect of the mineralocorticoid receptor antagonist finerenone for prevention of CV morbidity and mortality (38), while levels of BNP are monitored throughout the study. In a previous study of multifactorial treatment of type 2 diabetes, a decrease in NT-proBNP in the first 2 years of intervention was associated with a better prognosis in relation to CVD (39). There is an ongoing debate as to whether levels of NT-proBNP can guide treatment of HF (40).

Strengths and Limitations

The strengths of our study include the prospective design and the careful assessment of CV risk factors allowing extensive adjustments and examination of both MR-proANP and NT-proBNP.

Follow-up data were obtained from Danish national registers with no participants lost to follow-up and assessment of both major CV and renal events. Limitations include the fact that this is a single-center study including only Caucasian participants, which may impact generalizability. Moreover, history of previous CVD was based on self-reporting and electronic medical records; this may have resulted in an underestimation of previous or incident CVD at baseline. Further, the low number of cases involving hospitalization due to HF and ESKD is a limitation of this study. MR-proANP and NT-proBNP were measured in stored plasma samples after 3.5 years and 8 years, respectively.

In conclusion, higher NT-proBNP was independently associated with all-cause mortality, CVD, HF, and the combined renal end point. Conversely, MR-proANP was associated with all end points except decrease in eGFR >30%, although not after adjustment for NT-proBNP, indicating that NT-proBNP is the stronger risk marker. MR-proANP may contribute to the predictive value of NT-proBNP for risk stratification in type 1 diabetes.

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Duality of Interest. Outside this work, P.R. reports personally holding shares in Novo Nordisk; giving lectures for Mundipharma, Eli Lilly, and Boehringer Ingelheim; being on the advisory board for Novo Nordisk, Merck Sharp & Dohme, Bayer, Astellas, AbbVie, Sanofi, and Boehringer Ingelheim; and being a steering group member for Gilead, AstraZeneca, Bayer, and Novo Nordisk (all honorarium given to institution). S.A.W. was employed by the company Novo Nordisk A/S. S.T. reports personally holding shares in Novo Nordisk and being on the advisory board for Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

None of above represent conflicts of interest associated with this manuscript.

Author Contributions. All authors conceived and designed the research and interpreted the data. N.T. performed the statistical analysis and wrote the manuscript. All authors critically revised the manuscript and approved the final version of the manuscript. P.R. obtained funding and supervised the study. N.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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