Cardiovascular prognostic value of echocardiography and N terminal pro B-type natriuretic peptide in type 1 diabetes: the Thousand & 1 Study

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Abstract

Aims: Patients with type 1 diabetes have a high risk of cardiovascular disease. Yet, the importance of routine assessment of myocardial function in patients with type 1 diabetes is not known. Thus, we examined the prognostic importance of NT-proBNP and E/e', an echocardiographic measure of diastolic function, in type 1 diabetes patients with preserved left ventricular ejection fraction (LVEF) and without known heart disease.

Methods and results: Type 1 diabetes patients without known heart disease and LVEF $\geq 45\%$ enrolled in the *Thousand and 1 study* were included and followed through nationwide registries. The risk of major cardiovascular events (MACE) and death associated with levels of NT-proBNP and E/e' was examined. Of 960 patients, median follow-up of 6.3 years (Q1–Q3: 5.7–7.0), 121 (12%) experienced MACE and 51 (5%) died. Increased levels of both NT-proBNP and E/e' were associated with worse outcomes (adjusted hazard ratios for MACE = 1.56 (1.23–1.98) and 4.29 (2.25–8.16) per Log_e increase for NT-proBNP and E/e', respectively). NT-proBNP and E/e' combined significantly improved the discrimination power of the Steno T1D risk engine (MACE, C-index: 0.813 (0.779–0.847) vs 0.779 (0.742–0.816); $P = 0.0001$; All-cause mortality, C-index 0.855 (0.806–0.903) vs 0.828 (0.776–0.880); $P = 0.03$).

Conclusion: In patients with type 1 diabetes, preserved ejection fraction, and no known heart disease, NT-proBNP and E/e' were associated with increased risk of MACE and all-cause mortality. The risks associated with NT-proBNP and E/e' combined identified patients at remarkably high risk.

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Introduction

Cardiovascular disease is common and the leading cause of death in patients with type 1 diabetes (1, 2). Several parameters have been identified as independent predictors of cardiovascular disease in patients with type 1 diabetes, including age, sex, diabetes duration, haemoglobin A1c (HbA1c), blood pressure, renal function, smoking status

and physical activity (3, 4). However, none of these models have included metrics of myocardial function. Thus, no routine assessment of myocardial function is performed in the clinical control of type 1 diabetes and the importance of such is not known. Levels of natriuretic peptides increase in response to myocardial wall stretch,

and by inhibition of the renin–angiotensin–aldosterone system, natriuresis and reduced vascular tone they are believed to exert a protective function (5). N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been shown to be an independent predictor of cardiovascular and all-cause mortality in type 1 diabetes patients with diabetic nephropathy (6). In patients with heart failure, it is well established that levels of the NT-proBNP are predictive of adverse clinical outcomes. For this reason, NT-proBNP is now measured routinely in these patients (7, 8, 9).

In echocardiography, E/e' is the ratio between early mitral inflow into the left ventricle (E) and the early diastolic filling velocity of the left ventricular mitral annulus (e'). E/e' is a marker of left ventricular filling pressure and diastolic function (10). E/e' is used routinely in the clinical setting for the assessment of diastolic dysfunction and can predict events across different populations (11, 12, 13, 14, 15, 16). Diastolic dysfunction is a hallmark of diabetic cardiomyopathy and therefore has particular relevance in the assessment of myocardial function in patients with type 1 diabetes (17).

We do not know whether the individual and combined value of echocardiographic and hormonal indices of diastolic dysfunction and increased filling pressure improve the prognostic accuracy in patients with type 1 diabetes. We examined the prognostic importance of NT-proBNP and E/e' in type 1 diabetes patients with preserved ejection fraction and without known heart disease in the *Thousand and 1 Study*.

Methods

Study design and patients

The background and design of the Thousand & 1 Study have been described previously (17, 18, 19, 20). In brief, the Thousand & 1 Study was a cross-sectional cohort study with planned longitudinal follow-up. The study included 1093 patients aged 18 or older, with a diagnosis of type 1 diabetes and without known heart disease from April 1st, 2010 to April 1st, 2012 at the Steno Diabetes Center Copenhagen, Denmark, and echocardiography was performed at Department of Cardiology, Copenhagen University Hospital Herlev-Gentofte. All patients provided written informed consent. In this study, only patients with preserved ejection fraction, $LVEF \geq 45\%$, were included. The study was approved by by the regional ethics committee (*H-3-2009-139*) and the Danish Data Protection Agency (*00934-Geh-2010-003*)

and performed in accordance with the second Helsinki declaration.

Laboratory analyses

All samples were collected at baseline. NT-proBNP was measured by use of MAGLUMI™ 800 Chemiluminescence Immunoassay (Snibe Diagnostics). A cut-off for NT-proBNP of 150 pg/mL was chosen based on data from the general population, showing that individuals with levels ≥ 150 pg/mL had significantly higher risks of cardiovascular events and death (21). Furthermore a cut-off of 150 pg/mL has a high negative predictive value of heart failure in a primary care setting (22). A cut-off of 300 pg/mL was chosen as this is the best documented level of NT-proBNP for exclusion of acutely decompensated heart failure (23, 24, 25). Albuminuria was measured in 24-h sterile urine collections by use of enzymes immunoassays and micro- and macroalbuminuria were defined as urinary albumin excretion rates of 30 to 299 mg/24 h and ≥ 300 mg/24 h, respectively. HbA_{1c} was measured by HPLC (normal range: 21–46 mmol/mol, (4.1–6.4%); Variant; Bio-Rad Laboratories) and serum creatinine concentration by an enzymatic method (Hitachi 912; Roche Diagnostics).

Echocardiography

Echocardiography was performed with a General Electric, Vivid 7 Dimension imaging system device (GE Vingmed Ultrasound AS, Horten, Norway). Pulsed-wave Doppler was performed in the apical four-chamber view with the sample volume placed between the mitral leaflet tips to obtain diastolic mitral early (E) velocity wave. Pulsed-wave early diastolic tissue Doppler velocity (e') was determined from the apical four-chamber view at the lateral region of the mitral annulus. E/e' , as a measure of diastolic dysfunction, was categorized into three groups, no/low: $E/e' < 8$, discrete/moderate: $E/e' 8–12$, and gross/high: $E/e' \geq 12$ (26). Left ventricular ejection fraction (LVEF) was determined by Simpson's biplane method. Global left ventricular longitudinal strain (GLS) was measured by use of 2D speckle-tracking. GLS was stratified into sex-specific quartiles and the highest quartile defined as impaired; that is, $> -17\%$ in women and $> -16.1\%$ in men.

Prognostic variables

The Steno T1D Risk Engine has been shown to be superior to other models in predicting risk of cardiovascular outcomes in patients with type 1 diabetes without

known heart disease (3). In the present study, the model was therefore used as the baseline risk model. The Steno T1D Risk Engine includes the following factors: age, sex, duration of diabetes, systolic blood pressure, LDL cholesterol, HbA_{1c}, albuminuria (normo-, micro- and macroalbuminuria), estimated glomerular filtration rate, smoking (ever smoker) and physical activity (light, moderate and high).

Outcomes

We investigated the association between NT-proBNP and E/e', alone and in combination, and a composite outcome of major cardiovascular adverse events (MACE) and all-cause mortality. MACE included hospital admissions for acute coronary syndromes (ICD-10: DI20–22), heart failure (ICD-10: DI50; DI42; DI11), stroke (ICD-10: DI60–68; DG45), cardiac revascularization (ICD-10: KFN) and death. Hospital admissions and procedures were obtained from The Danish National Patient Register. Information on vital status was obtained from The Danish National Population Register.

Statistical analysis

Baseline characteristics are described by use of proportions for categorical variables and means, with standard deviations, or medians, with quartiles, for continuous variables. Differences in baseline characteristics according to levels of NT-proBNP were tested using a χ^2 -test for categorical variables and ANOVA or Kruskal–Wallis's test for continuous variables. Kaplan–Meier curves for all-cause mortality and cumulative incidence curves for MACE were estimated and differences between groups were compared by use of Log rank and Gray's test respectively. Cox proportional hazard models were used to compare the risk of MACE and all-cause mortality according to levels of NT-proBNP, E/e' and GLS. The Cox regression models were adjusted for all variables included in the Steno T1D risk engine, that is, age, sex, duration of diabetes, systolic blood pressure, LDL cholesterol, HbA_{1c}, albuminuria (normo-, micro- and macroalbuminuria), estimated glomerular filtration rate, smoking (ever smoker) and physical activity (light, moderate and high). The assumption of linearity was tested for age, E/e', NT-proBNP and GLS. Log (–log(survival)) curves were used to evaluate the proportional hazard assumption. Tests for interactions of age and sex with NT-proBNP, E/e' and GLS in relation to all outcomes were performed and reported if significant. Model discrimination was tested by

use of Harrell's c-statistic (27). NT-proBNP and E/e' were examined as continuous variables in adjusted models using restricted cubic splines. *P*-values of <0.05 were considered significant. Analyses were performed by use of Stata version 15 and R version 3.3.2.

Results

Baseline characteristics

Patients with a baseline NT-proBNP measurement above 300 pg/mL were older, more were women and a longer duration of diabetes, higher blood pressure and worse renal function compared to those with NT-proBNP <150 pg/mL (Table 1). Use of blood pressure lowering medication was also more common among patients with NT-proBNP >300 pg/mL. Regarding echocardiographic measurements, no significant differences were seen in LVEF and GLS. However, patients with NT-proBNP >300 pg/mL did have a significantly higher proportion of patients with increased E/e'. Patients with NT-proBNP between 150–300 pg/mL were phenotypically intermediate between those with NT-proBNP <150 pg/mL and NT-proBNP >300 pg/mL.

NT-proBNP

During a median of 6.3 years (Q1–Q3: 5.7–7.0) of follow-up, patients with NT-proBNP above 300 pg/mL had a significantly higher risk of the composite outcome of MACE and of all-cause mortality (Fig. 1). Thus, patients with NT-proBNP above 300 pg/mL had a higher crude incidence rate of MACE (41 per 1000 person years) compared to those with NT-proBNP below 150 pg/mL (10 per 1000 person years). The elevated risk related to NT-proBNP persisted in adjusted analyses incorporating NT-proBNP as a categorical- (<150 vs 150–300 vs >300) or as a continuous variable (per Log_e increase in NT-proBNP) (Supplementary Fig. 1 and Supplementary Table 1, see section on [supplementary materials](#) given at the end of this article). Thus, the risk of MACE and all-cause mortality increased with 56% and 67% per log unit increase in NT-proBNP, respectively.

E/e'

Patients with an E/e' >12 had a significantly higher risk of MACE and all-cause mortality (Fig. 2). Consequently, the crude incidence rate of MACE was 88 per 1000 person

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Table 1 Baseline characteristics according to NT-proBNP cut-offs. Data are presented as *n* (%), mean $\pm$ s.d. or as median (Q1, Q3).

	NT pro BNP (pg/mL)			P-value
	<150	150–300	>300	
Patients	433 (45%)	256 (27%)	271 (28%)	
NT-proBNP, pg/mL	87 (63, 112)	213 (176, 252)	466 (370, 652)	–
Age, years	44 $\pm$ 13	50 $\pm$ 13	58 $\pm$ 13	0.0001
Sex, male	257 (59)	130 (51)	104 (38)	0.0001
Diabetes duration, years	22 $\pm$ 13	26 $\pm$ 14	32 $\pm$ 15	0.0001
BMI, kg/m ²	25 (23, 28)	25 (23, 27)	25 (22, 27)	0.004
HbA1c, mmol/mol	66 (57, 75)	63 (55, 73)	64 (55, 73)	0.007
Ever smoker	228 (53)	143 (56)	161 (59)	0.21
Systolic blood pressure, mmHg	131 $\pm$ 15	133 $\pm$ 17	138 $\pm$ 18	0.0001
Diastolic blood pressure, mmHg	74 $\pm$ 9	73 $\pm$ 10	72 $\pm$ 10	0.02
Physical activity				0.39
0–3 h/week	141 (33%)	80 (31.3%)	103 (38.0%)	
3–7 h/week	209 (48%)	126 (49.2%)	127 (46.9%)	
>7 h/week	83 (19%)	50 (19.5%)	41 (15.1%)	
LDL cholesterol, mmol/L	2.6 (2.1, 3.1)	2.5 (2.1, 3.0)	2.4 (2.0, 2.9)	0.01
eGFR, mL/min·1.73 m ²	93 (82, 105)	86 (75, 101)	77 (61, 90)	0.0001
Albuminuria				0.0001
Normoalbuminuria	335 (77%)	178 (70%)	157 (58%)	
Microalbuminuria	76 (18%)	53 (21%)	71 (26%)	
Macroalbuminuria	22 (5%)	25 (10%)	43 (16%)	
Medication				
Statin	170 (39%)	106 (41%)	139 (51%)	0.006
Beta Blockers	4 (1%)	10 (4%)	29 (11%)	0.0001
ACE or ATII inhibitors	165 (38%)	119 (46%)	160 (59%)	0.0001
Diuretics	85 (20%)	64 (25%)	104 (38%)	0.0001
Echocardiography				
LV ejection fraction (LVEF), %	57.5 $\pm$ 4.6	57.8 $\pm$ 5.0	58.3 $\pm$ 5.5	0.14
E/e'	6.8 $\pm$ 2.5	7.4 $\pm$ 2.8	9.1 $\pm$ 3.4	0.0001
E/e' <8	340 (79%)	174 (68%)	125 (46%)	0.0001
E/e' 8–12	78 (18%)	68 (27%)	102 (38%)	
E/e' >12	15 (3%)	14 (5%)	44 (16%)	
Global longitudinal strain (GLS), %	-18.2 $\pm$ 2.5	-18.5 $\pm$ 2.6	-18.6 $\pm$ 2.7	0.15
E/A ratio	1.3 $\pm$ 0.5	1.3 $\pm$ 0.5	1.2 $\pm$ 0.4	0.0001
Dimensions (cm)				
LV internal diameter	4.6 $\pm$ 0.5	4.6 $\pm$ 0.5	4.4 $\pm$ 0.5	0.0001
Septal wall	0.9 $\pm$ 0.2	0.9 $\pm$ 0.2	0.9 $\pm$ 0.2	0.0002
Posterior	0.9 $\pm$ 0.2	0.9 $\pm$ 0.2	1.0 $\pm$ 0.2	0.008
LA volume index (mL/m ²)	29 $\pm$ 6	31 $\pm$ 6	31 $\pm$ 7	0.0001
LV mass index (g/m ²)	70 $\pm$ 14	71 $\pm$ 14	72 $\pm$ 16	0.11

years for patients with E/e' >12 compared with 9 per 1000 person years for patients with E/e' <8. In adjusted models, incorporating E/e' as a categorical- (<8, 8–12, >12) or a continuous variable (per Log_e increase in E/e'), higher levels of E/e' remained associated with an increased risk of outcomes (Supplementary Fig. 2 and Supplementary Table 1).

Combination of NT-proBNP and E/e'

The risk of outcome associated with NT-proBNP and E/e' was additive. Thus, patients with NT-proBNP >300 and an E/e' >12 had a crude incidence MACE rate of 115 per 1000 person years, compared to a rate of 5 per 1000 person years in those with a NT-proBNP <150 and an E/e' <8.

In multivariable adjusted analyses, patients with NT-proBNP levels >300 and E/e' >12 had an 8.9-fold (3.5–22.7) higher risk of MACE compared to those with NT-proBNP levels <150 and E/e' <8 (Fig. 3).

Incremental prognostic value of NT-proBNP and E/e'

The added discriminatory power, that is, the ability to better separate patients at higher risk from those at lower risk of NT-proBNP and E/e' are outlined in Supplementary table 2. NT-proBNP alone did not significantly improve the predictive ability when compared with clinical factors, whereas E/e' did. However, the effect of NT-proBNP and E/e' seemed to be additive, as the highest C-indices were found in models incorporating both NT-proBNP and E/e'.

Figure 1

Cumulative incidences of the risk of MACE (A) and all-cause mortality (B) according to levels of NT pro BNP in type 1 diabetes patients with preserved ejection fraction and without known heart disease ($n = 960$).

Discussion

This study, on the prognostic importance of NTproBNP and E/e' in type 1 diabetes patients with preserved ejection fraction and without known heart disease, has three main findings. First, higher levels of NT-proBNP and E/e' were each associated with worse outcomes.

Figure 2

Cumulative incidences of the risk of MACE (A) and all-cause mortality (B) according to levels of E/e' in type 1 diabetes patients with preserved ejection fraction and without known heart disease ($n = 960$).

Secondly, the risks associated with NT-proBNP and E/e' were additive, making it possible to identify patients at remarkably high risk, that is, patients with NT-proBNP >300 and an E/e' >12 had a MACE outcome rate of 115 per 1000 person years (compared with 5 per 1000 person years in those with NT-proBNP <150 and E/e' <8). Thirdly, NTproBNP and E/e' together significantly improved the

Figure 3

Risk of MACE according to levels of E/e' and NT-proBNP levels in type 1 diabetes patients with preserved ejection fraction and without known heart disease ($n = 960$). Adjusted for age, sex, diabetes duration, systolic blood pressure, LDL cholesterol, HbA1c, albuminuria (normo-, micro- and macroalbuminuria), eGFR, smoking and leisure-time physical activity (low, moderate and high).

discrimination power of the Steno T1D risk engine which includes conventional clinical risk factors.

The development of cardiovascular disease in type 1 diabetes is frequent and associated with an ominous prognosis. The link between type 1 diabetes and cardiovascular disease is not fully elucidated. For example, it is still unclear whether type 1 diabetes *per se* promotes the development of heart failure or whether the relationship is due to comorbidities such as hypertension, microvascular disease and myocardial infarction (28, 29, 30). Initiatives to shed light on factors of importance for the development of cardiovascular disease in patients with type 1 diabetes are therefore warranted (2, 31). Several parameters have been identified as predictors of cardiovascular outcomes in patients with type 1 diabetes (3). However, factors with information on myocardial function have rarely been investigated.

Data on natriuretic peptides' importance and prognostic performance in type 1 diabetes are sparse (6, 32, 33, 34). However, their release from cardiomyocytes in response to stress and their close relationship to both diagnosis and prognosis of heart failure makes them an apparent marker of myocardial function to investigate. In patients with type 1 diabetes and diabetic nephropathy, NT-proBNP has been shown to be a prognostic marker of

cardiovascular- and all-cause mortality (6). Our finding of NT-proBNP being associated with risk of cardiovascular outcomes and death adds a new aspect with importance for the development of cardiovascular disease in patients with type 1 diabetes. Thus NT-proBNP might help to understand how the heart is affected by type 1 diabetes in the early stages and help to identify patients at high risk for poor outcomes. Levels of NT-proBNP are correlated with prognostic factors such as age and renal function, and increased levels of NT-proBNP have been associated with diabetic nephropathy (35). This was also evident in our study, as patients with the highest levels of NT-proBNP were older and had worse renal function and increased albuminuria. However, the association of NT-proBNP and outcome persisted even after adjusting for age and kidney function.

Echocardiography is a non-invasive test and a key clinical examination in the assessment of myocardial function. Data on whether a distinct diabetic cardiomyopathy exists or on the effect of diabetes on cardiac functional and structural changes is mediated through known cardiac diseases, such as hypertension and myocardial infarction, relies mainly on echocardiographic findings (28, 36, 37). Elevated E/e' is a well-established marker of diastolic dysfunction. In the present study, we used E/e' as a marker of diastolic function. E/e' is easy to measure, clinically implemented and not subject to changes in definitions or diagnostic criteria as contemporary classifications of diastolic dysfunction or heart failure with preserved ejection fraction regularly are. The presence and prevalence of diastolic function in patients with type 1 diabetes have previously been investigated and shown to be frequent, but the relationship with NT-proBNP and importance for outcomes have, to our knowledge, not been investigated before (17, 19, 38). We demonstrated a significant association between levels of E/e' and risk of MACE. Furthermore, E/e' added significant discriminatory power to the Steno T1D risk engine, which makes E/e' an interesting candidate for risk stratification in patients with type 1 diabetes and preserved ejection fraction. The strong and better prognostic performance of E/e' than NT-proBNP are most likely linked to a high and often unrecognized presence of diastolic dysfunction in patients with type 1 diabetes. The additive effect of NT-proBNP and E/e' could be of importance for clinical practice. Thus, by the use of relatively inexpensive and already available clinical parameters, we were able to identify a subset of type 1 diabetes patients with remarkably high risk of MACE, despite having preserved ejection fraction and no known heart diseases. Identification of these patients

could lead to intensive treatment strategies, individualized counseling, closer surveillance and potentially improved prognosis. Furthermore, these high-risk individuals may be targets for new treatments.

Limitations

Characteristics of the population including NT-proBNP and E/e' were only obtained at baseline. Thus, we could not account for changes over time in our analyses. All patients were included and followed in outpatient clinics at the Steno Diabetes Center Copenhagen, which might lead to better risk profiles than other type 1 diabetes cohorts. Most patients were of Scandinavian descent and therefore not necessarily representative of all type 1 diabetes patients. The observational nature of the study means that residual confounding cannot be excluded.

Conclusions

In type 1 diabetes patients with preserved ejection fraction and no known heart diseases, high levels of NT-proBNP and E/e' were associated with increased risk of MACE and all-cause mortality. The risks associated with NT-proBNP and E/e' were additive and could, in combination, help to identify patients at very high risk.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-1015>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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