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NT-proBNP has a high negative predictive value to rule-out short-term cardiovascular events in patients with diabetes mellitus

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Aims This study evaluated the predictive value of NT-proBNP for patients with diabetes mellitus and compared the prognostic aptitude of this neurohumoral marker to traditional markers of cardiovascular events.

Methods and results A prospective observational study was conducted in 631 diabetic patients. The composite endpoint consisted of unplanned hospitalization for cardiovascular events or death within the observation period of 12 months. Of all variables analysed (age, gender, history of hypertension, ischaemic heart disease/any cardiac disease, smoking, duration of diabetes, body mass index, blood pressure, New York Heart Association-class, Dyspnoea score, Minnesota Living with Heart Failure Questionnaire, LDL-cholesterol, HbA_{1c}, creatinine, glomerular filtration rate), the logarithm of NT-proBNP gave the most potent information in a stepwise Cox regression analysis ($P < 0.0001$). Bootstrapping with 500 samples supports this result in 95% samples. The negative predictive value of a normal value (<125 pg/mL) of NT-proBNP for short-term cardiovascular events in diabetic patients is 98%.

Conclusion We have demonstrated a strong and independent correlation between NT-proBNP and short-term prognosis of cardiovascular events for patients with diabetes mellitus. With a high negative predictive value it can identify individuals who are not at intermediate risk for cardiovascular events. NT-proBNP proved to be of higher predictive value than traditional cardiovascular markers, in this unselected cohort.

Keywords Natriuretic peptides • Diabetes mellitus • Cardiovascular risk • Prognosis

Introduction

Although is widely recognized that the absolute risk of cardiovascular events varies among individuals with diabetes mellitus, there is a lack of reliable short-term predictors to guide timely and individualized management.

The increased risk of cardiovascular disease in patients with diabetes mellitus is well established since the robust association has been shown by the Framingham heart study,[1] a correlation that has been confirmed in several subsequent trials.[2,3] Many variables, such as HbA_{1c}, blood pressure, several lipid parameters, and markers of kidney function have been put forward to serve as markers for risk stratification to identify individual patients with excessive risk in a timely manner.[4–7] To some extent, all variables are of limited value, as they are good predictors for long-term prognosis; but there is a lack of data on risk estimation for the clinically more relevant short-term prognosis. The need for an individualized and timely risk assessment was also highlighted in a recent statement from the American Heart Association and the American Diabetes Association.[8]

Natriuretic peptides, such as brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), or their inactive N-terminal

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precursors NT-proBNP and NT-proANP are released from myocardial cells in response to volume expansion and increased wall tension.[9] They are well-established rule-out tools for cardiac disease in unselected communities.[10–12] Furthermore, their value for risk stratification in populations with known heart disease has been proven for long-term as well as for short-term outcome.[13]

Data about the prognostic value of NT-proBNP in diabetic patients are limited.[14–18] Again, data for short-term prognosis, which are clinically more relevant, are lacking entirely in this distinct population, as observation periods studied so far lasted from 2 to 15 years. Moreover, there is no direct comparison with the known markers mentioned above.

Early identification of cardiovascular risk is of vital importance in a comprehensive diabetes management, since it allows early, targeted interventions. Although never investigated, it is of great clinical significance for a timely and individualized management to recognize those individuals among the very large population of asymptomatic diabetic patients who might have an increased risk of cardiovascular events in their imminent future, and at the same time identify those individuals who are not at risk for the time being.

We hypothesized that NT-proBNP is superior at providing prognostic information about short-term cardiovascular risk for patients with diabetes mellitus compared with the above-mentioned traditional predictors of cardiovascular events. We proved our hypothesis in an unselected cohort of diabetic patients.

Research design and methods

The study population consisted of diabetic patients treated at the diabetes outpatient clinic of the Vienna General Hospital. All patients attending this tertiary care centre between January 1, 2006 and February 17, 2007 were invited to participate in our prospective observational study. The only exclusion criterion was refusal to participate. The refusal rate was $<10\%$. A total of 631 consecutive patients were recruited. A certified nurse took a compiled medical history for each patient, with a special focus on cardiovascular disease, in order to obtain information about concomitant diseases and current treatment. All patients were asked to complete the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Dyspnoea score chart. An electrocardiogram was recorded and later analysed for the presence of atrial fibrillation, bundle branch block, or any cardiovascular disease by a cardiologist. Blood pressure was measured in every patient. Blood was drawn from an antecubital vein. Kidney function was determined by measurement of serum-creatinine and glomerular filtration rate (GFR) was calculated by the Cockroft–Gault formula. To obtain risk markers for cardiovascular disease, cholesterol (especially LDL) from fasting samples was measured and NTpro-BNP was determined by a commercially available kit (Roche Diagnostics). Moreover, HbA_{1c}, as a marker of glucose metabolism was determined.

Endpoints

Based on the short observation period, a composite endpoint consisting of unplanned hospitalization for cardiovascular disease or death was chosen as the primary endpoint in this study. Secondary endpoints were death, unplanned cardiovascular hospitalization, hospitalization due to heart failure, and all-cause hospitalization. All patients were traced through the national registry during 2007. All patients were monitored for a fixed time period of 12 months for outcome. Mortality data were obtained from the Austrian Central Office of Civil Registration (Zentrales Melderegister). If a patient had died before February 17, 2008 the date of death was recorded. Hospital reports about hospitalization were obtained from the regional hospital data network (Krankenanstaltenverbund). Information about hospitalizations for cardiovascular disease was obtained from hospital files by a cardiologist, unaware of the results at index time. As this was a one-point analysis, no patient was lost of follow-up.

The study was conducted in accordance with the Helsinki II declaration and was approved by the ethics committee of our institution. All participants gave a written informed consent.

Statistical analysis

Continuous variables are expressed as means $\pm$ standard deviation; categorical variables are presented as frequencies and percentages.

Sample size calculation was based on an expected log hazard ratio of 0.5 and an expected event rate of 10%. For alpha $= 0.05$ and power >0.9 sample size of 600 patients was obtained.

Two stepwise Cox regression models were calculated to identify independent variables in order to predict the combined endpoint of unplanned hospitalization for cardiovascular events and death over time. *P*-value for entering the stepwise model was set at 0.05 and 0.10 for exclusion. A stepwise approach was used to determine the most potent single predictor independent of the number of events out of a large number of variables. All results of the regression model are presented using hazard ratios. Hazard ratios are given for increase per unit. Five hundred bootstrap repetitions are done for both Cox regression models, repeating the variable selection for each sample using the same entering and exclusion rules. It was counted how often a variable was entered into the Cox regression models. The overall predictive accuracy (D) of the Cox regression models was calculated for each model by correlating the prognostic index of each patient with the observed survival time. The prognostic index is defined as the linear combination of regression coefficients and the values of the covariables. The accuracy of a bootstrap model is calculated for the prediction within the actual bootstrap sample (D_{boot}) and for its usefulness for prediction using the whole original data set (D_{orig}). The difference between the two predictive accuracies is called optimism in the fit from the bootstrap sample; and it is averaged over the 500 samples. The described procedure was done for two different sets of variables. One model uses all 17 variables available from our study. One smaller model (8 variables) is based on all variables with a significant predictive influence in the single variable Cox regression models. Proportional hazards assumption was assessed and satisfied for all variables based on partial residual plots and on time interaction tests. For all continuous variables squared values and the logarithm were calculated. Only for NT-proBNP and serum-creatinine the logarithm outperforms the untreated data within single variable Cox regression models. Therefore, the logarithms of NT-proBNP and serum-creatinine were added as two additional variables into both variable sets.

Variables as follows were included in the 17 variables model: age (years), gender (1/0), body mass index (kg/m^2), history of any heart disease (0/1), ischaemic heart disease (IHD) (0/1), hypertension (0/1), history of smoking (0/1), systolic blood pressure (mmHg), HbA_{1c} (%), LDL-cholesterol (mg/dL), serum-creatinine (mg/dL), GFR (mL/min), NT-proBNP (pg/mL), New York Heart Association (NYHA)-class (1–4), MLHFQ (0–100), Self-assessment Dyspnoea score (1–10), and duration of diabetes (years).

Variables in the reduced model: age (years), history of any heart disease (0/1), IHD (0/1), serum-creatinine (mg/dL), GFR (mL/min), NT-proBNP (pg/mL), NYHA-class (1–4), and MLHFQ (0–100).

Survival was calculated using the Kaplan–Meier method, where patients were divided into those with NT-proBNP values above or below the cut-point of 125 pg/mL.

Receiver operating characteristic (ROC) analysis was calculated to assess the predictive power of NT-proBNP.

A $P < 0.05$ was considered significant in all analysis. SPSS 15.0 software (SPSS, Chicago, IL) and GChaos 13.2 statistical software written in C++ by one of the authors were used for all statistical analysis.

Results

Description of the total study population

Demographics and outcome

The total study population comprised 631 patients with diabetes mellitus, which were included consecutively into the study. Characteristics of this population correspond to a usual collective of unscreened diabetic patients, mean age being 58 ± 14 years, mean duration of diabetes being 9 ± 10 years (*Table 1*).

A total of 42% of patients were treated with insulin, 60% with oral antidiabetics, 15% of patients were receiving both drugs. The mean value of HbA_{1c} was 8.0 ± 1.6%. 23% of patients had a history of cardiovascular disease. Mean blood pressure values were 143 ± 22 mmHg systolic and 85 ± 13 diastolic. Twenty-five per cent of patients were treated with a beta-blocker, 54% with a RAAS antagonist, 20% with a calcium channel blocker. Mean LDL-cholesterol values were 112 ± 38 mg/dL, 34% of patients were treated with statins. The gender ratio (male/female) was 55/45%. Only <5% of patients were defined as type I diabetes patients.

Of the entire collective, 44 (7.0%) patients reached the composite endpoint (39 unplanned hospitalizations for cardiovascular disease and 7 deaths—2 deaths occurring after an unplanned CV hospitalization) during the observation period of 12 months.

The reasons for hospitalization were classified as follows: chronic heart failure 13; coronary artery disease 8; atrial fibrillation 4, carotid artery disease 6; peripheral artery occlusive disease 8.

Stepwise Cox regression model

Both stepwise Cox regression models demonstrate that the logarithm of NT-proBNP gives the most potent information to predict future events (*Table 2*). Both models are finally based on the logarithm of NT-proBNP (best Wald statistic) and on the MLHFQ (second best Wald statistic). The model initially started with 17 variables plus the logarithms of serum-creatinine and NT-proBNP and adds at last the duration of diabetes. The small variable set includes the age as third best predictor. Bootstrap testing supports the importance and robustness of the logarithm of the NT-proBNP (*Table 3*). For the large variable set 92% of the bootstrap samples include the logarithm of the NT-proBNP. In the small variable set it is included in >95% of the 500 models.

Optimism for the model based on the large variable set is 0.05, resulting in a corrected predicted accuracy of $D = 0.31$. Optimism for the model from the small data set is 0.02 also resulting in a corrected predicted accuracy of $D = 0.31$.

Table 1 Baseline clinical and laboratory characteristics

Number of unplanned cardiovascular hospitalization or death %	44 (7.00%)
Age (years)	58.70 ± 13.86
Gender (female), *n* (%)	282 (44.70)
Body mass index (kg/m^2)	30.21 ± 11.80
History of any cardiac disease (%)	144 (22.82)
History of ischaemic heart disease (%)	108 (17.12)
History of hypertension (%)	513 (81.30)
History of smoking (%)	274 (56.57)
RR sys (mmHg)	142.52 ± 22.34
HbA_{1c} (%)	8.00 ± 1.63
LDL-cholesterol (mg/dL)	112.16 ± 37.93
Serum-creatinine (mg/dL)	1.05 ± .45
GFR (mL/min)	92.73 ± 39.98
NT-proBNP (pg/mL)	285.55 ± 489.43
NYHA-class (I/II/III/IV) (%)	428(67.8)/145 (23.00)/ 55(8.7)/3 (0.5)
MLHFQ (0–100)	11.22 ± 11.01
Dyspnoe score (1–10)	1.39 ± 6.60
Duration of diabetes (years)	9.28 ± 10.13
Serum-creatinine (log)	1.67E-3 ± .29
NT-proBNP (log)	4.95 ± 1.03

Baseline clinical and laboratory characteristics of 631 diabetic patients with and without an unplanned cardiovascular hospitalization or death.

Table 2 Model based on initially 17 and 8 variables plus logarithm of serum-creatinine and NT-proBNP

Variable	Hazard ratio	SEM	Wald	Sig
17 variables				
logarithm of NT-proBNP	2.117	0.122	38.09	<0.0001
MLHFQ	1.037	0.010	12.78	0.0004
Duration of diabetes	1.026	0.012	4.51	0.0338
Predictive accuracy	0.357			
Optimism	0.047			
Corrected predictive accuracy	0.310			
8 variables				
logarithm of NT-proBNP	1.963	0.134	25.398	<0.0001
MLHFQ	1.036	0.010	11.807	0.0006
Age	1.031	0.015	4.371	0.0375
Predictive accuracy	0.329			
Optimism	0.021			
Corrected predictive accuracy	0.308			

Table 3 Results from stepwise Cox regression for 500 Bootstrap samples. Frequencies of variables within the regression model after stepwise selection

Initially 17 variables	Per cent	Initially 8 variables	Per cent
Logarithm of NT-proBNP	91.8	Logarithm of NT-proBNP	95.2
Duration of diabetes	59.6	MLHFQ	46.4
MLHFQ	48.0	Age	43.2
NYHA-class	46.0	NYHA-class	42.6
History of smoking	32.4	History of any heart disease	21.8
History of any heart disease	31.8	GFR	17.2
Age	31.6	Ischaemic heart disease	10.2
Gender	18.4	Logarithm of serum-creatinine	7.0
Ischaemic heart disease	17.0	NT-proBNP	6.2
Self-assessment Dyspnoe score	15.6	Serum-creatinine	6.0
GFR	15.2		
Hypertension	12.0		
LDL-cholesterol	11.4		
NT-proBNP	11.2		
HbA_{1c}	10.4		
Systolic blood pressure	9.8		
Logarithm of serum-creatinine	5.4		
Serum-creatinine	5.2		
Body mass index	2.6		

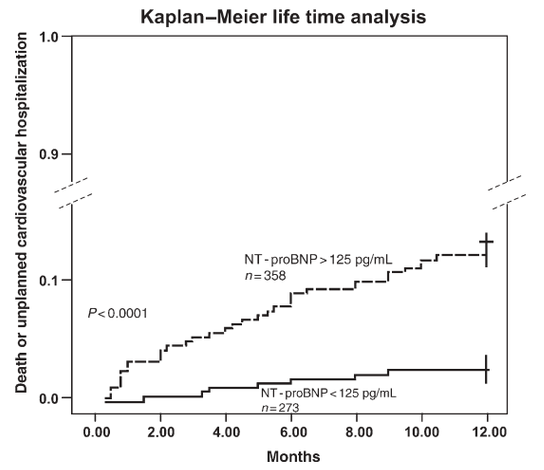


Figure 1 Kaplan–Meier curves of all-cause mortality or unplanned cardiovascular hospitalization in 631 diabetic patients according to plasma-levels of NT-proBNP at baseline. Solid line: patients with NT-proBNP levels below cut-off (<125 pg/mL). Dashed line: patients with NT-proBNP levels above cut-off (>125 pg/mL). Log-rank test for overall difference, $P < 0.0001$.

Kaplan–Meyer analysis

The Kaplan–Meyer analysis for NT-proBNP showed differences between patients with values above and below the cut-points of 125 pg/mL. The difference was statistically significant ($P < 0.0001$), through the observation period (*Figure 1*).

Receiver operating characteristic curve

The area under the ROC curve with respect to the combined endpoint unplanned cardiovascular hospitalization and death was 0.785 for NT-proBNP in our study population. Sensitivity, specificity, negative predictive value, positive predictive value, and accuracy for different values of NT-proBNP are depicted in *Figure 2*.

Discussion

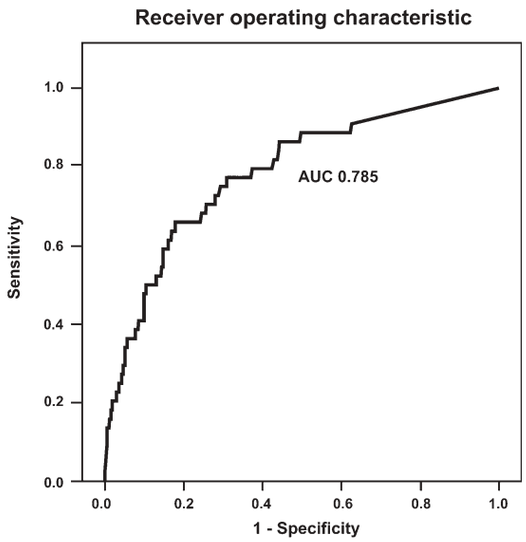
In the present study, we have demonstrated a strong and independent correlation between plasma NT-proBNP levels and short-term prognosis of cardiovascular events for patients with diabetes mellitus. Patients with low levels of NT-proBNP (<125 pg/mL) had an excellent short-time prognosis. This was true despite the fact that they had less background therapy (data not shown). At the same time, NT-proBNP provided more concise information about cardiovascular risk in this diabetic population compared with traditional markers.

Traditional predictors of increased risk

Many variables such as HbA_{1c}, glucose management, blood pressure, LDL-cholesterol, and kidney function have been evaluated for their potential to predict outcome in diabetic patients and to identify those that need more aggressive management. All of these markers have proved valuable for long-term prognosis, but not for the assessment of imminent threat of major cardiovascular events for diabetic patients. The American Heart Association and the American Diabetes Association recently extensively discussed and questioned the individual predictive role of blood pressure, lipids, or glucose management on outcome.[8]

The reason for the limited aptitude of these traditional markers to predict short-term events might be that they are not functional markers of cardiovascular health but mediators of cardiovascular injury. There is a well-studied dose–effect relationship over time for these modifiable risk factors for large cohorts, and targeted, multifactorial interventions should be undertaken to reduce cardiovascular long-term risk as outlined, for example, in the Steno-2 Study.[19] Notwithstanding this important role, the information about the current, immediate risk for the individual patient is uncertain.

An additional explanation for the shortcomings of cardiovascular markers to predict outcome in this setting might be attributed to the 'heart failure paradox'. Several studies have linked obesity, hypercholesterolaemia, higher blood pressure, and even higher HbA_{1c} levels, which are well-known risk factors for coronary artery disease, to improved survival of patients with heart failure.[20–24] The mechanisms of this 'reverse epidemiology' are not quite clear.[25] However, traditional risk markers of cardiovascular disease might be



NT-proBNP pg/ml	Sensitivity	Specificity	PPV	NPV	Accuracy
125	0.795	0.6	12.9	97.6	61.4
200	0.727	0.72	16.2	97.2	72.0
300	0.659	0.82	21.5	96.9	80.8
400	0.523	0.858	21.6	96.0	83.5
500	0.5	0.889	25.2	95.5	86.2
600	0.409	0.901	23.6	95.3	86.7

Figure 2 Receiver operating characteristic curve of the ability of NT-proBNP to predict the combined endpoint of unplanned hospitalizations for cardiovascular events or death. The area under the receiver operating characteristic curve was 0.785.

understood as risk modifiers in advanced heart failure, which is the endgame of cardiac disease and a metabolically taxing condition. Given that heart failure patients make up a relevant part of any population of diabetic patients,[26] clinical trials trying to assess the prognostic accuracy of these markers should get mixed results.

Natriuretic peptides as prognostic markers

The use of natriuretic peptides such as ANP and BNP and their precursors NT-proBNP and NT-proANP for the assessment of cardiovascular risk is firmly established in cardiovascular guidelines.[27] Increasing plasma levels of natriuretic hormones are associated with the development of cardiac arrhythmias and increasing haemodynamic instability.[28] Higher NT-proBNP levels have been demonstrated to be associated with advanced patient age, renal impairment, cardiac arrhythmias, and systolic and diastolic dysfunction.[29] Natriuretic peptide may therefore reflect an integral of risk factors resulting in the current functional cardiovascular status of individual patients.

NT-proBNP and diabetes mellitus

Data about the prognostic accuracy of natriuretic peptides for patients with diabetes mellitus are limited. Several studies have examined the relationship between BNP/NT-proBNP and long-term cardiovascular outcome. Christoffersen *et al.*[18] outlines some of the challenges of interpreting natriuretic peptides in diabetic patients. In Tarnows *et al.*[15] study only relatively young (<66 years) type 2 diabetic patients were included. In this observational study, increased NT-proBNP levels were found to be predictive of overall and cardiovascular mortality for a follow-up period of 15 years. An important observation in this population was that the predictive accuracy of NT-proBNP is independent of GFR, and the level of albumin excretion rate. In Gaedes *et al.* study,[16] microalbuminuretic type 2 diabetic patients were enrolled. A NT-proBNP level above the median was associated with an increased risk of cardiovascular disease during a follow-up of ~7.8 years. In Bhallas *et al.* study,[17] some of the predominantly male patients were referred on the basis of clinical suspicion of cardiac dysfunction, and the rest recruited from a diabetic clinic. Follow-up to show an association between increased BNP and cardiac and all-cause mortality was ~2.3 years.

The results of our total study population, which are, unlike the preceding studies, an unselected collective of consecutive patients attending a tertiary care centre, confirm previous observations. It adds new information about NT-proBNP predictive potential, in the clinically more relevant, short-term design. Bootstrapping clearly demonstrate the robustness of this finding. NT-proBNP is the only variable, which provides significant independent information irrespective of the chosen population. All other variables such as history of any heart disease, kidney function, LDL-cholesterol, or HbA_{1c} strongly depend on the predefined study population. Although results of ROC curves have to be interpreted with caution,[30] excellent negative predictive values or accuracies can be achieved, dependent on the chosen cut-point.

Implications of risk stratification with NT-proBNP

In the present study, we have identified a subset of diabetic patients who appear to be at a dramatically increased risk of short-term cardiovascular events. This group, which can be readily recognized by increased NT-proBNP levels, might need a more extensive work up. This rapid determination of increased risk would allow targeted interventions and more aggressive management to prevent hospitalization or death.

Limitations: our study is based on a data set with more than 600 patients, which seems to be sufficiently big enough for robust statistics. As the observation time is limited to 1 year, there is a certain risk of over-fitting the stepwise regression models. We tried to avoid this risk by using bootstrapping methods. Additionally, we limited the number of predictive variables in our second model. The role of NT-proBNP seems to be robust. Additional mechanisms could be relevant but cannot be identified based on the limited observation time.

As already mentioned above, interpretations of results from ROC curves have to take some limitations into account. One of the most important is the rank order statistic on which ROC curves are based, which means that the amount of differences between the risks of patients is not reflected in the area under the curve. Notwithstanding these limitations, the ROC curve is the most widely used statistical tool in cardiovascular literature.[30]

Conclusions

NT-proBNP, a neurohumoral prognostic marker could be part of a comprehensive, timely and individualized cardiovascular risk assessment of patients with diabetes mellitus. With a high negative predictive value it can safely identify those individuals who are not at intermediate risk for cardiovascular events.

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