A comparison of NT-proBNP and Albuminuria for predicting cardiac events

in patients with diabetes mellitus

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Running Title: Cardiac risk stratification in diabetes mellitus

Word Count: 2387

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Abstract:

Background: Cardiovascular events are the most relevant events in patients with diabetes mellitus. We aimed to compare the upcoming marker N-terminal pro-BNP (NT-proBNP) and the state-of-the-art marker, albuminuria, for predicting cardiac events in diabetic patients.

Methods: In this prospective observational study we recruited 1071 patients with diabetes mellitus. NT-proBNP and albuminuria – defined as a urinary albumin/creatinine ratio > 30 mg/g – were measured at baseline. Patients were followed during a mean observation period of 33.1 months. 103 patients reached the defined endpoint (unplanned hospitalization due to a cardiac event).

Results: The mean duration of diabetes was 15 ± 12 years and the mean HbA1c was $7.5 \pm 3.1\%$. At baseline, 23.7% of the patients presented with albuminuria, and 36.6% had plasma NT-proBNP values above 125 pg/ml. Multiple Cox regression analysis including age, gender, duration of diabetes HbA1c, albuminuria, and NT-proBNP revealed that NT-proBNP(Hazard ratio 1.0009; CI1.0007-1.0012 p< 0.001) was a better predictor than albuminuria (HR 1.901; CI 1.252-2.887 p=0.003) or age (HR 1.047; CI 1.025-1.070 p=0.001). Calculating different Cox-models with (A) albuminuria, (B) NT-proBNP, or (C) both in the model revealed that the C-index was best if NT-proBNP was entered in the model (C-index for a 0.735, for B 0.781, and for C 0.786). Kaplan Meier analysis demonstrated that albuminuria does not add substantial information if NT-proBNP is entered into the model.

Conclusion: NT-proBNP was superior to albuminuria for predicting cardiac events.

Introduction

Patients with diabetes mellitus have a two to four-fold increased risk of developing cardiovascular disease compared to the general population. Moreover, it is the leading cause of death in patients suffering from diabetes [1]. Whether this risk is equally distributed in this population is unclear and a subject of debate even in current guidelines [2]. Identifying a subpopulation that is more at risk is challenging, but this subpopulation would probably benefit the most from preventive therapeutic strategies.

Albuminuria is present in about 30% of middle-aged patients with either type 1 or type 2 diabetes mellitus [3]. Numerous studies have dealt with the importance of albuminuria in predicting long term (5-12 years) cardiovascular risk in patients with diabetes mellitus, [4-7] and since the early nineteen-eighties albuminuria has been considered the gold standard for predicting cardiovascular events [4, 5]. Recent data even demonstrate its importance in patients with established cardiac disease [8].

A better understanding of the pathophysiological mechanisms underlying cardiovascular diseases has led to the discovery of numerous relevant markers [9]. Of those, NT-proBNP is regarded as the most important risk-marker in cardiac disease [10]. The predictive value of neurohormones and especially NT-proBNP in patients with diabetes mellitus has been the subject of a limited number of studies [11-15]. Both markers – albuminuria and NT-proBNP – remarkably reflect cardiac risk in their distinct cohorts, but were never directly compared.
In contrast to albuminuria, which reflects renovascular damage, NT-proBNP directly mirrors cardiac stress. Therefore, we hypothesize that NT-proBNP is not only equipotent, but even more powerful than albuminuria for predicting cardiac events in patients with diabetes mellitus.

Methods

Design

This prospective observational study included patients regularly visiting the diabetic outpatient clinic of the Vienna General Hospital and Hietzing Hospital Vienna between December 2005 and November 2007. All patients gave written informed consent according to the Helsinki II declaration. The study was approved by the ethics committees of the Medical University of Vienna and Hietzing Hospital Vienna. As these data are the results of an ongoing project, we have already described this population in detail elsewhere [13].

A comprehensive medical history included data on the history of diabetes, the presence of accompanying cardiovascular and other diseases, and the current therapy. All patients underwent an electrocardiogram (ECG), which was further analyzed for the presence of atrial fibrillation, left bundle branch block, or other cardiac disease. Blood was drawn from an antecubital vein.

Analytic Methods

Plasma glucose, lipid values, liver enzymes, urea, and creatinine were measured using routine tests in a certified laboratory. Long-term glucose metabolism was evaluated by HbA1c.

NT-proBNP was determined using a commercially available kit (Elecsys Essay, Roche Diagnostics).NT-proBNP of 125 pg/ml was used as a cut-point as recommended by the manufacturer. Kidney function (estimated glomerular filtration rate GFR) was calculated using the MDRD formula. First-morning-void urine was collected for measuring the urinary albumin excretion (Immunoturbitometric analysis by Olympus). Albuminuria was determined as the urinary albumin to creatinine ratio. Values above 30mg/g were considered abnormal [16, 17].

Endpoint

The endpoint was defined as unplanned hospitalization due to a cardiac event which was a combination of ischemic heart disease, chronic heart failure, and heart rhythm disturbances.

Data concerning hospitalization were collected from the regional hospital data network. Information about hospitalization for cardiac events was obtained from hospital files by a cardiologist who was unaware of the results at index time.

Statistical Analysis

We present continuous variables as means ± standard deviation; categorical variables are shown as frequencies and percentages. Differences between continuous variables were tested with the T-test; for categorical data, Fisher's exact test was used. At first we evaluated the predictive values of albuminuria and NT-proBNP separately to show that both parameters were significant predictors of cardiac events in our study group. Two Cox regression models were run to determine the variables that predict the defined endpoint. P-value for entering the stepwise model was set at .05; for exclusion it was set at .10. 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. Variables included were age, gender, duration of diabetes mellitus, HbA1c (factors known to affect either the endpoint or the NT-proBNP levels), as well as albuminuria in the first model and NT-proBNP in the second model. A third model included both NT-proBNP and albuminuria along with age, gender, duration of diabetes, and HbA1c. Hazard ratios were calculated per unit increase. Proportional hazards assumption was assessed and satisfied for all variables based on the time interaction test. Harrell's concordance index (c-index) was

used as a measurement of the overall performance of the Cox regression models. The c-index can be interpreted similarly to the well-known area under the curve (AUC) of the ROC-curve. 500 bootstrap repetitions were done for the third Cox regression Model, repeating the variable selection for each sample using the same entering and exclusion rules. The number of times a variable was entered into the Cox regression models was counted. Receiver operating characteristic (ROC) calculations were performed to compare NT-proBNP and albuminuria as predictors of the defined endpoint.

After splitting our collective into four groups (no albuminuria/NT-proBNP < 125pg/ml; albuminuria/NT-proBNP<125 pg/ml; no albuminuria/NT-proBNP > 125pg/ml, and albuminuria/NT-proBNP> 125), Kaplan Meier lifetime analysis curves were drawn. All models were run in SPSS 14.0 software (SPSS, Chicago, IL), and bootstrapping was done with GChaos 17.3 statistical software written in C++ by one of the authors. A $p< 0.05$ was considered statistically significant.

Results:

Patient Characteristics

The study population consisted of 1071 consecutive patients (613 male; 458 female (42.8%)) enrolled between April 2005 and November 2007 (Table 1). The mean age was 61 ± 13 years, the mean duration of diabetes was 15 ± 12 years, and the mean HbA1c was 7.5 ± 3.1%. 147 patients (13.8%) had a medical history of ischemic heart disease, 38 patients (3.5%) had undergone a percutaneous coronary intervention, 46 patients (4.3%) had a coronary artery bypass, and 23 patients (2.2%) were presenting with atrial fibrillation.

Hypertension was present in 723 patients (67.8%). Mean systolic BP was 144 ± 23 mmHg and mean diastolic BP was 82 ± 12 mmHg. Plasma NT-proBNP levels were 236 ± 425 pg/ml and mean plasma LDL levels were 105.8 ± 30.4 mg/dl. 254

subjects (23.7%) had albuminuria; the albumin-creatinine ratio was between 30-300 mg/g in 170 patients and ≥300 mg/g in 58 patients.

Patients were followed during a mean observation period of 33.1 ± 10 months. 103 patients reached the primary endpoint defined as hospitalization due to a cardiac event.

20.9% of patients with NT-proBNP above 125 pg/ml were hospitalized due to a cardiac event, and 30.5% of the hospitalized patients died.

Cox-regression model

Cox-regression was performed in three models. The first model clearly showed that albuminuria (Hazard ratio 2.360, CI 1.563 – 3.564, p<0.001) together with age (Hazard ratio 1.066, CI 1.045 – 1.088, p<0.001) was a significant predictor for cardiac events in this cohort. The c-index was 0.735 for this model. A second Cox-regression was run in which the parameter albuminuria was replaced by NT-proBNP. This time NT-proBNP (Hazard ratio 1.001, CI 1.0008 – 1.0012, p<0.001) and age (Hazard ratio 1.049, CI 1.027 – 1.071, p<0.001) were significant for predicting the endpoint. This model revealed a higher c-index of 0.781 than the first model. Finally, we combined albuminuria and NT-proBNP in a third model to determine the best predictor of the defined endpoint. In this model NT-proBNP was the most potent single predictor of cardiac events (Hazard ratio 1.0009, CI 1.0007 – 1.0012, p<0.001, Wald coefficient 67.746). In this model age (Hazard ratio 1.047, CI 1.025 – 1.070, p<0.001) and albuminuria (Hazard ratio 1.901, CI 1.252 – 2.887, p=0.003) provided additional information. Here we find only a slight advantage over the second model; the c-index is 0.786.

Bootstrap testing supported the importance and robustness of NT-proBNP

 (Table 2). 100.0% of the bootstrap samples included NT-proBNP.

<u>Kaplan Meier Lifetime Analysis</u>

The Kaplan Meier curves underlined the prognostic value of NT-proBNP in comparison with albuminuria. The curve of the albuminuric group with an NT-proBNP below 125pg/ml was nearly similar to the group without albuminuria and NT-proBNP below 125pg/ml (Figure 1).

Discussion

To our knowledge this is the first study directly comparing albuminuria to NT-proBNP in order to predict outcome in an unselected cohort of patients with diabetes. Our results clearly show that NT-proBNP is superior to albuminuria for predicting cardiac events in diabetic patients.

According to the current diabetes guidelines [2] decisions concerning cardiovascular prevention are based on cardiovascular risk factors. There are two issues to consider regarding these guidelines: 1. There is no evidence whether there are disease specific risk markers, and if there were, which among these would be most appropriate
2. No data exist on the question whether patients with low risk profiles need preventive treatment regarding lipid status, antiplatelet treatment, and blood pressure lowering agents [2] [18, 19].

Direct Comparison of Different Markers

There are numerous established CV risk-markers for patients with diabetes mellitus to determine the patient's cardiovascular risk profile. We recently

demonstrated that none of those variables is superior to NT-proBNP for short-term prognosis – a time frame that is of tremendous interest both clinically as well for study purposes [13]. Albuminuria is most commonly used as the predictor of choice for cardiovascular risk [4] but was not included in our former model [13]. Recommendations state that patients with albuminuria or advanced age should be more aggressively treated in regard to CV prevention.

Albuminuria reflects vascular injury in the kidney, and is thereby a marker for secondary morphologic organ damage. Quite differently, NT-proBNP is directly linked to the function of the heart, as it is secreted by the ventricles in response to cardiac stress. Thus, NT-proBNP levels are elevated early in the course of disease at the state of functional impairment of the CV system. NT-proBNP is partly cleared by the kidneys and increases with the severity of renal dysfunction. This implies that peripheral organ damage is also reflected by increased levels of NT-proBNP [20]. The increased cardiac NT-proBNP release and reduced degradation by the kidneys add independent information to risk profiling. Looking at this as a whole, this might explain the superiority of NT-proBNP to albuminuria. In fact, entering albuminuria in a Cox model does not increase the power if NT-proBNP is already entered. The opposite is true; NT-proBNP markedly increases the power of a model when albuminuria is already entered, which confirms previous data [12].

The fact that in our study patients with increased levels of NT-proBNP were not a subset of those with albuminuria, but rather both groups had only a modest overlap is very important in this context. Patients without albuminuria but increased NT-proBNP concentrations were at almost as much risk as patients that presented with both risk markers. (Figure 1)

Therapeutic implications:

Patient selection for intensified treatment appears to be a new challenge in the era of limited resources on one hand and the questionable benefit of these interventions in distinct patient groups on the other [2]. In recent megatrials examining patients with a long duration of diabetes, no beneficial effects of intensified antihyperglycemic therapy on cardiovascular outcome was seen [21-23]. Similar findings were presented for an aggressive lipid modulation [18] or blood pressure control [19]. These findings are quite different from the earlier results of the Steno 2 study, which investigated the influence of an intensive multifactorial therapy on the incidence of cardiovascular events in a high-risk population of diabetic patients [24]. In this study of a highly selected population of albuminuric patients, significant treatment effects were noted despite the small number of patients included.

Since it is possible but unlikely that the therapeutic interventions do not influence outcome per se, other factors that could be relevant for the disappointing findings of recent trials should be examined.

It is possible, as some argue, that beneficial effects of the interventions would have been observed with a longer observation period.

A second possibility – as already discussed by Nilsson[25] – for the less than conclusive results of recent mega-trials is the right patient selection.

It is striking that even though all trials exclusively included patients with cardiovascular risk, event rates were remarkably low, much lower than in the Steno 2 study or in our registry, which suggest that the patients selected may not have been high risk after all. Cardiovascular risk in the megatrials was defined as increased age, a history of cardiovascular disease, or, in some cases, microalbuminuria. As mentioned above, we demonstrated earlier that these surrogate markers used for risk stratification are not relevant for short-term outcome [13].

Gaede et al showed that stratifying the STENO population into those with high or low NT-proBNP unmasks two distinct populations[12]. In the group of patients with low NT-proBNP concentrations no treatment effect could be demonstrated, since this group did not experience significant adverse events, regardless of their randomization into the treatment arm or control arm. In the high NT-proBNP group the event rate showed a five-fold increase. Therefore, treatment effects seem to be relevant only in this population. If NT-proBNP were used as a risk-marker, we could safely focus our attention on a smaller group of high-risk patients.

Beyond its role as a risk marker, the STENO II study also showed that NT-proBNP can reflect the alteration of risk by treatment. In this study every decrease in NT-proBNP concentrations was related to a decrease in future event rates [12]. Therefore, it appears that therapeutic success is mirrored by changes of NT-proBNP concentrations. Similarly, our own unpublished data demonstrate the potency of changes of NT-proBNP as a further surrogate of risk along with absolute levels[26].

Conclusion

Similar to its prognostic power in cardiac disease, NT-proBNP provides excellent prognostic information in patients with diabetes mellitus. Albuminuria, although independent of NT-proBNP, adds only minimal additional information. Our data provide evidence for the shift of paradigm concerning predictors of risk and target populations for CV prevention in patients with diabetes mellitus.

Table 1: Patient characteristics at baseline

|	NT-proBNP < 125 pg/ml (64.3%)	NT-proBNP > 125 pg/ml (35.7%)	p-Value
Age (years)	57,53 ± 12,46	67,17 ± 10,29	<0.001
Gender: (% male)	57,70%	56,55%	0.775
Duration of Diabetes (years)	14,11 ± 11,90	15,78 ± 11,89	0.033
HBA1C (%)	7,50 ± 3,78	7,44 ± 1,40	0.751
BMI	29,10 ± 8,81	30,70 ± 28,73	0.305
GFR	77,49 ± 16,59	64,62 ± 18,58	<0.001
CHOL	198,69 ± 46,52	184,61 ± 42,27	<0.001
LDL (mg/dl)	107,64 ± 29,29	101,26 ± 30,39	0.001
TRIG (mg/dl)	172,56 ± 306,57	148,84 ± 128,59	0.089
Proteinuria (% yes)	16,33%	36,49%	<0.001
Creatinine (mg/dl)	0,98 ± 0,21	1,16 ± 0,38	<0.001
Albumin / Creatinine Ratio	48.60 ± 200.22	142.18 ± 420.46	<0.001
RRS (mm HG)	142,66 ± 22,03	146,96 ± 25,29	0.007
RRD (mm HG)	81,96 ± 11,39	80,64 ± 12,56	0.092

Table 2

Initially 6 variables	Percent
NT-proBNP	100.0
Age	99.4
Proteinuria	76.8
Gender	24.6
HbA$_{1c}$	8.2
Duration of diabetes	7.2

Results from stepwise Cox regression for 500 bootstrap samples. Frequency of variables within the regression model after stepwise selection.

Figure 1:

Kaplan Meier Plot
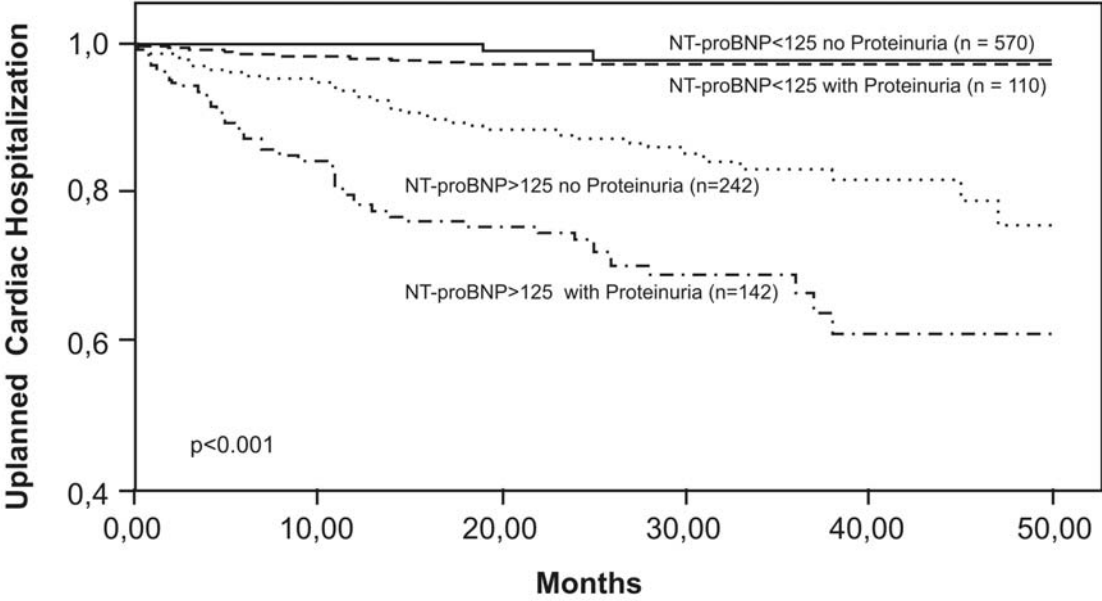
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