Performance of NT-proBNP as a single biomarker in comparison to SCORE and the recommended ESC/EASD cardiovascular risk stratification model for risk prediction in type 2 diabetes mellitus

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Abstract

Background. Recently, the European Society of Cardiology (ESC) and European Association for the Society of Diabetes (EASD) introduced a new cardiovascular (CV) risk stratification model to aid further treatment decisions in individuals with diabetes. Our study aimed to investigate the prognostic performance of NT-proBNP and the Systematic COronary Risk Evaluation (SCORE) compared to the ESC/EASD risk model in an unselected cohort of type 2 diabetes mellitus (T2DM).

Methods & Results. A total of 1690 T2DM patients with a 10-year follow up for fatal CV and all-cause death and a 5-year follow up for CV and all-cause hospitalizations were analyzed. According to ESC/EASD risk criteria 25 (1.5%) patients were classified as moderate, 252 (14.9%) high, 1125 (66.6%) very high risk and 288 (17.0%) were not classifiable. NT-proBNP, the ESC/EASD and SCORE risk model were all associated with 10-year CV and all-cause death and 5-year CV and all-cause hospitalizations. NT-proBNP showed significantly higher C-indices than the ESC/EASD and SCORE risk model for CV death [0.80 vs 0.53 vs 0.64, p<0.001] and all-cause death [0.73 vs 0.52 vs 0.66, p<0.001]. The performance of SCORE improved in a subgroup without CV disease aged 40-64 years compared to the unselected cohort, whilst performance of NT-proBNP was robust across all groups.

Conclusion. NT-proBNP is a high-performing biomarker for CV risk assessment in T2DM. Single NT-proBNP is superior compared to SCORE and the multiparameter ESC/EASD risk stratification model for predicting 10-year CV and all-cause fatal events.

Introduction

About 422 million people worldwide suffer from diabetes with prevalence rising most rapidly in middle and low-income countries.[1] Diabetes is associated with a substantially increased risk to develop cardiovascular (CV) disease;[2] however, as individuals with diabetes represent a highly heterogeneous population incremental CV risk is not equally distributed among diabetic patients.[3] Therefore, the development of individualized CV risk assessment tools is essential to warrant a personalized therapy approach.

Recently, the European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) published new guidelines on diabetes, pre-diabetes and cardiovascular disease (CVD).[4] For the first time, the use of a CV risk stratification model is recommended for further treatment decisions in individuals with diabetes. The ESC/EASD risk model stratifies diabetic patients into three different risk categories based on the 10-year risk estimate for fatal CVD adapted from the 2016 European Guidelines on CVD prevention in clinical practice.[5] To the best of our knowledge, the predictive performance of the newly introduced risk stratification model has not been verified in individuals with diabetes.

The Systematic COronary Risk Evaluation (SCORE) equation is commonly used for estimating the 10-year risk of fatal CVD in the general population.[6] Since the predictive performance of SCORE has never been tested in patients with long-standing diabetes specifically, its application for risk estimation in individuals with diabetes cannot be recommended.[5] However, it was suggested that SCORE could be used for a rough assessment of CV risk in diabetic patients.[6] Notably, the application of SCORE on the UKPDS cohort showed that the SCORE equation does not provide a reasonable estimate for 10-years CV death events in patients with newly diagnosed type 2 diabetes mellitus (T2DM).[7]

The prognostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for CV outcomes in patients with diabetes has been demonstrated and was confirmed in numerous studies.[8–12] Nonetheless, the new guidelines do not recommend routine assessment of circulating biomarkers for CV risk estimation in diabetic patients.[4]

This study aimed to perform a head-to-head comparison of the predictive performance of NT-proBNP against SCORE and the ESC/EASD model for risk assessment of 10-year CV death and all-cause death i) in an unselected T2DM cohort, ii) in selected patients with T2DM with characteristics similar to the SCORE derivation cohort and iii) to investigate outcome-specific performance of the different risk estimates. Additionally, the prognostic utility of the risk assessments for 5-year CV and all-cause hospitalization was evaluated.

Methods

Study population

From December 2005 through January 2010 a total of 2186 patients with T2DM from 4 diabetes outpatient clinics were included in a prospective registry. Medical history including comorbidities, diabetes duration, medical therapy and assessment of risk factors was recorded at enrolment. Patients were followed up as clinically appropriate. All patients gave written informed consent. The study was approved by the local Ethics Committee of the Medical University of Vienna and complies with the principles of the Declaration of Helsinki.

Laboratory analysis

Blood samples were collected under fasting conditions and immediately sent to the local laboratory. Estimated glomerular filtration rate (eGFR) was assessed by the Modified Diet for Renal Disease Study equation. NT-proBNP determination was performed directly using a commercial point of care system (Roche Diagnostics, Basel, Switzerland) with a lower detection limit of 59 pg/ml. Urine albumin creatinine ratio was assessed quantitively in fresh spot urine samples according to the local laboratory standards.

Calculating risk estimates

a) ESC/EASD risk stratification model

Patients were categorized as moderate, high and very high risk based on the predicted 10-year risk estimates for CVD death <5%, 5-10 and >10%, respectively, according to the ESC/EASD cardiovascular risk categories as indicated in Additional file 1: Table S1.[4] Except for renal impairment no precise definition on the rating of the respective risk factors used within the ESC/EASD stratification model was given. Thus, we defined age, obesity and proteinuria as being at risk at >50years, ≥30kg/m^2 and a urinary albumin/creatinine ratio >30mg/mmol, respectively. High blood pressure and dyslipidemia were defined according to the criteria of the respective current European guidelines,[13,14] as documented in medical charts or on specific therapy. Smoking status was assessed based on hospital charts and by self-report. CVD was considered as coronary artery disease, cerebrovascular disease (CeVD), peripheral artery disease (PAD), documented electrocardiographic alterations as atrial fibrillation/flutter and complete bundle branch block and abnormal echocardiographic findings, i.e. reduced ejection fraction, qualitative left ventricular hypertrophy/wall motion abnormalities and significant valve disease (i.e. grade>1). PAD was defined as a history of claudication or documented vascular procedures, i.e. percutaneous transluminal angioplasty and bypass of the lower/thoracic limbs and abdominal aorta or amputation. CeVD was considered as documented history of stroke or transient ischemic attack. As retinopathy and left ventricular hypertrophy were not systematically assessed, these variables were not included in the analysis. Additional file 1: Table S2 provides an overview about the specific cut-offs and definitions used for risk stratification of the ESC/EASD model.

b) SCORE risk model

SCORE risk estimation is recommended for individuals without CVD and aged 40-64 years in accordance to the selection criteria of SCORE.[5,6] The 10-year fatal CVD risk was calculated using the low SCORE risk chart based on the risk variables age, sex, smoking status, total cholesterol and systolic blood pressure.[6] As indicated in the reference publication, we multiplied the SCORE risk estimates by 2 for men and 4 for women to account for the increased CV risk in individuals with diabetes.[6] Risk estimation for individuals aged <40 and >65 years was performed referring to the risk estimates provided for individuals aged 40 and 65 years, respectively.

Endpoints

The primary outcome measure was CV death at 10 years and secondary outcome measures were all-cause death at 10 years and unplanned CVD as well as all-cause hospitalization at 5 years. Time at risk was calculated as time between enrolment and event or end of follow-up period whichever came first. Data on final death diagnosis was obtained from the Austrian Death Registry including cause of death based on the International Statistical Classification of Disease and Related Health Problem 10th revision. CV events resulting in death or hospitalization were defined as atherosclerotic CVD, valvular heart disease, heart failure, malignant arrhythmia, PAD and CeVD. If given diagnosis was unclear, hospital charts were studied to give a final diagnosis of cause of death.

Statistical analysis

Continuous data are presented as median and interquartile range (IQR) and discrete data as frequency and percentages. Continuous variables were compared by the Kruskal-Wallis and Mann-Whitney-U-test, counts by the Fisher's exact test.

For the comparison between the risk estimators, i.e. NT-proBNP, ESC/EASD risk estimate and SCORE, both NT-proBNP and SCORE were entered as continuous as well as categorical variables (NT-proBNP: tertiles and two groups with cut-off at 125 pg/ml; SCORE: 3 risk groups with cut-off: <5%, 5-10%, >10%). All comparisons were made for the total cohort and two subgroups similar to the characteristics of the original derivation cohort of SCORE. Subgroup A consisted of patients without CVD and subgroup B without CVD aged 40-64 years. Cox regression analysis was performed to evaluate the association of the risk assessments with 10-year fatal CVD events and secondary outcome measures. Hazard ratios (HRs) of continuous NT-proBNP refer to ln-transformed NT-proBNP. In addition to the univariate analysis, adjustments for potential confounders were conducted to demonstrate the robustness of NT-proBNP. Proportional hazard assumption was assessed and satisfied for all variables based on time interaction tests. Kaplan-Meier curves were plotted and log-rank test used to demonstrate the time-dependent discriminative power of the various risk assessment tools for CV and all-cause death.

Predictive performance was expressed as discrimination (receiver operating characteristic [ROC] curve, C-index) and calibration using Hosmer-Lemeshow goodness-of-fit test (H-L). Observed 10-year risk for fatal CVD is presented using the Kaplan-Meier estimates. An improvement in individual risk prediction for the risk assessments was examined by the continuous net reclassification improvement (NRI) as described by Pencina et al.[15] Differences in outcomes were assessed by non-overlapping confidence intervals (CI 95%) between C-indices.

A two-tailed p-value lower than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (IBM SPSS, Chicago, Illinois, USA) version 24 and STATA software (StataCorp, College Station, Texas, USA) version 13.

Results

Study population

A total of 2,186 T2DM patients were enrolled in the study, 496 patients were excluded from the analysis as survival status (n=460) or diabetes duration (n=36) was not available, thus a total of 1,690 T2DM patients were analyzed. Detailed description of the baseline characteristics is displayed in Table 1.

Table 1. Baseline characteristics of the overall study cohort.

Characteristics	Overall cohort (n=1690)
Demographics	
Age, years (IQR)	63 [54-69]
Female, n (%)	783 (46)
Diabetes duration, years (IQR)	10 [5-19]
Hypertension, n (%)	1135 (67)
Dyslipidaemia, n (%)	1152 (68)
Smoking, n (%)	339 (20)
BMI, kg/m² (IQR)	28.7 [25.4-32.7]
Cardiovascular disease	
PCI, n (%)	66 (4)
PAD, n (%)	173 (10)
CeVD, n (%)	99 (6)
CABG, n (%)	62 (4)
Medications	
Statins, n (%)	764 (45)
Acetylsalicylic acid, n (%)	634 (38)
Insulin, n (%)	888 (53)
Oral antidiabetics, n (%)	984 (58)
Laboratory parameters	
NT-proBNP, pg/ml (IQR)	122 [59-266]
Albumin/creatinine ratio, mg/mmol (IQR)	0.87 [0.35-2.94]
eGFR, ml/min (IQR)	72.7 [60.3-85.3]
LDL cholesterol, mg/dl (IQR)	102 [82-123]
HbA1c, % (IQR)	7.2 [6.5-8.1]

BMI, body mass index; PCI, percutaneous coronary intervention; PAD. peripheral artery disease; CeVD, cerebrovascular disease; CABG, coronary artery bypass graft; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein

Median age of the total study population was 63 years (IQR 54-69), 783 (46%) of the patients were female. CVD was present in 311 (18.4%) patients. According to the ESC/EASD risk model criteria, 25 (1.5%) were classified as moderate, 252 (14.9%) as high and 1125 (66.6%) as very high risk. A total of 288 patients (17.0%) were not classifiable based on the stated ESC/EASD criteria, as 280 patients had diabetes duration less than 10 years with 1 or 2 (but < 3) established CV risk factors and 8 patients presented with a diabetes duration longer than 10 years without any risk factors. Detailed characteristics for the ESC/EASD risk strata are presented in Additional file 1: Table S3. In the overall cohort, 654 patients (39%) had a calculated SCORE risk estimate below 5%, 525 patients (31%) between 5 and 10% and 511 patients (30%) above 10%. The calculated SCORE risk estimates for 10-year fatal CVD increased with ESC/EASD risk category (0% [IQR 0-0] vs 6% [IQR 2-10] vs 8% [IQR 4-12], p<0.001 for the moderate, high and very-high risk category).

Distribution of patients in the ESC/EASD and SCORE risk strata as well as proportion of patients with normal (n=871) and elevated (n=819) NT-proBNP levels at a cut-off 125 pg/ml within these groups are illustrated in Figure 1 (p<0.001 for both models).

Association of NT-proBNP, ESC/EASD risk strata and SCORE with CV and all-cause death at 10 years

During 10 years of follow-up, 448 (26.5%) patients died, CV death accounted to 44.9% (n=201) of all deaths. Kaplan Meier analysis for all risk models stratified into three groups with regards to both endpoints are shown in Figure 2. The ESC/EASD risk model, SCORE and NT-proBNP were all significantly associated with CV death (ESC/EASD: p=0.013; SCORE and NT-proBNP: p<0.001) and all-cause death (ESC/EASD: p=0.022; SCORE and NT-proBNP: p<0.001). Table 2 shows the results of the univariate Cox regression analysis.

Table 2. Association of NT-proBNP, the ESC/EASD and SCORE risk model with outcome in unselected patients with T2DM (n=1690).

		10-y Cardiovascular death		
		HR [95% CI]	P	C-index [95% CI]
risk model	**ESC/EASD**	1.65 [1.11 to 2.45]	0.013	0.5 [0.50 to 0.56]
	SCORE, %	1.05 [1.04 to 1.07]	<0.001	0.6 [0.60 to 0.67]
proBNP, pg/ml*	**NT-**	5.72 [4.68 to 7.00]	<0.001	0.8 [0.77 to 0.83]
proBNP, tertiles	**NT-**	4.11 [3.23 to 5.22]	<0.001	0.7 [0.73 to 0.78]
proBNP, > 125 pg/ml	**NT-**	7.15 [4.85 to 10.53]	<0.001	0.7 [0.68 to 0.74]

*Hazard ratio (HR) refers to ln-transformed NT-proBNP per 1-IQR increase

NT-proBNP remained a strong predictor of risk independently from traditional confounders as age, eGFR, sex, hypertension, smoking and albuminuria for both CV death (ln[NT-proBNP]: adjusted HR: 3.92 [2.92-5.27], p<0.001) and all-cause death (ln[NT-proBNP]: adjusted HR: 2.29 [1.89-2.78], p<0.001). Patients with NT-proBNP >125pg/ml had a 7.2-fold and 3.1-fold risk to suffer from death from CV causes or all-causes at 10 years, respectively, compared to individuals with NT-proBNP within the range considered as normal (p<0.001).

Discriminatory performance of NT-proBNP, the ESC/EASD risk strata and SCORE in in unselected T2DM patients

ROC curves for all risk models and the endpoints 10-year CV and all-cause death are shown in Figure 3. The best discriminatory power to predict 10-year CV and all-cause death was observed for NT-proBNP indicated by highest C-indices compared to both the ESC/EASD and SCORE risk model (C-index: CV death: 0.80 vs 0.53 vs 0.64; all-cause death: 0.73 vs 0.52 vs 0.66, p<0.001 for all comparisons).

When NT-proBNP was entered as a categorical variable based on tertiles (1st tertile: 59 [IQR 59 - 59], 2nd tertile: 122 [IQR 90 - 156], 3rd tertile: 376 [IQR 267 - 648] pg/mL) the results remained virtually unchanged (C-index: CV death: 0.75 vs 0.53 vs 0.64, p<0.001 for all comparisons; all-cause death: 0.70 vs 0.52 vs 0.66, p<0.001 for comparison NT-proBNP vs ESC/EASD, p=0.014 for NT-proBNP vs SCORE).

Net individual risk prediction was significantly improved when assessing NT-proBNP confirmed by a significant improvement of the NRI with 81% for CV death and 58% for all-cause death (P<0.001 for both) compared with the ESC/EASD risk model. Comparable results were observed for NT-proBNP compared with the SCORE model with a significant improvement of the NRI with 83% for CV death and 63% for all-cause death (P<0.001 for both).

Predictive performance of NT-proBNP, the ESC/EASD risk strata and SCORE in distinct subgroups

The following subgroups were investigated: Subgroup A including patients without CVD and subgroup B including patients without CVD and aged 40-64 years according to SCORE derivation cohort.

Cox regression analysis for the subgroups regarding 10-year fatal outcome are shown in Additional file 1: Table S4. NT-proBNP and SCORE were equally associated with 10-year CV and all-cause death in subgroup A and B (p<0.001 for all). The ESC/EASD risk model was only associated with 10-year CV death in subgroup B (p=0.050).

Figure 4 displays C-statistics of the risk assessments according to the T2DM population studied, the respective ROC graphics are shown in Additional file 1: Figure S1. NT-proBNP was characterized by robustly highest C-indices across both subgroups comparable to the unselected cohort for both endpoints. The ESC/EASD model was characterized by poor C-indices in all groups. The performance of the SCORE risk prediction model improved with progressing exclusivity of patient criteria, performing best in the cohort closest to its derivation population, i.e. subgroup B. NT-proBNP outperformed SCORE with regards to CV death in subgroup A and was statistically comparable whereas with numerically higher C-indices in subgroup B.

Observed vs predicted risk estimate for 10-year fatal CVD by SCORE

The SCORE risk algorithm underestimated the actual risk of CV death in unselected T2DM patients (observed vs predicted CVD fatal risk: 13% vs 8% [IQR 4-12]; X^2 =70.1, p<0.001) and in subgroup A (observed vs predicted CVD fatal risk: 10% vs 8% [IQR 4-12]; X^2=19.8, p<0.001). In subgroup B observed risk was 6% compared with a median predicted risk of 4% [IQR 2-8]. Here, goodness-of-fit for SCORE risk estimate was good with a X^2 of 4.3 (p = 0.234).

Predictive performance of NT-proBNP, the ESC/EASD risk strata and SCORE for 5-year CV and all-cause hospitalization

Over a follow-up of 5 years, 1053 (62.3%) patients were hospitalized due to any causes and 367 (21.7%) patients due to unplanned CV events. Risk for all-cause hospitalization increased by 7% and for CV hospitalization by 12% per 100pg/ml increase in NT-proBNP (p<0.001 for both). Similarly, the ESC/EASD and SCORE were associated with increased risk for CV and all-cause hospitalizations (p<0.001 for both). Cox regression analysis is presented in Additional file 1: Table S5.

Figure 5 presents cumulative incidence of 5-year hospitalizations for NT-proBNP. In terms of discriminatory accuracy NT-proBNP was superior to the ESC/EASD risk model for both outcomes (C-index: CV hospitalization: 0.74 vs 0.54; all-cause hospitalization: 0.62 vs 0.55; p<0.001 for all comparisons). When comparing NT-proBNP with SCORE, NT-proBNP showed superior discrimination for CV hospitalization (C-index: 0.74 vs 0.62, p<0.001) but not for all-cause hospitalization (C-index: 0.62 vs 0.59, p=0.09).

Outcome specifity of NT-proBNP, the ESC/EASD risk strata and SCORE

As indicated by C-statistics, NT-proBNP yielded better discrimination for CV than for all-cause death (0.80 vs 0.73, p<0.05) and for CV than for all-cause hospitalization (0.74 vs 0.62, p<0.05). No difference for the ESC/EASD risk strata (CV vs all-cause death: 0.53 vs 0.52, p>0.05; CV vs all-cause hospitalization: 0.54 vs 0.55, p>0.05) or the SCORE risk estimation (CV vs all-cause death: 0.64 vs 0.66, p>0.05; CV vs all-cause hospitalization: 0.62 vs 0.59, p>0.05) could be observed.

Discussion

Accurate CV death risk estimation in individuals with T2DM is of particular interest, given their 2-4-fold increased risk for CV death compared with the non-diabetic population.[16] Subsequently, early identification of patients being at high CV risk is crucial in order to merit close surveillance and to facilitate early interventions and treatment.[17,18] To date, however, large-scale randomized trials are missing to prove the concept whether measurement of biomarkers but also assessment of risk stratification models could improve treatment decisions and, subsequently, lead to better outcomes.

This is the first study evaluating the predictive performance of the recently published ESC/EASD risk stratification model and the SCORE risk estimation in a reasonably large real-world cohort of patients with T2DM and directly comparing these risk models with the biomarker NT-proBNP. Our results demonstrate that i) in an unselected cohort of T2DM patients all three risk assessments are associated with 10-year CV and all-cause mortality and 5-years hospitalizations, ii) NT-proBNP is a robust predictor in both unselected and selected T2DM patients, iii) NT-proBNP is superior to the ESC/EASD and SCORE risk estimates in terms of discriminatory accuracy and that iv) contrary to the ESC/EASD and SCORE risk model, NT-proBNP showed outcome specifity for future CVD events in T2DM individuals.

The ESC/EASD model and individual risk for 10-years CV death

The recently published ESC/EASD guidelines on diabetes, pre-diabetes and CVD recommend for the first time the use of a risk stratification model based on an individual 10-year fatal CV death risk estimate to guide further treatment decisions in individuals with diabetes.[4] However, the predictive performance of this model has neither been derived nor tested in patients with diabetes. When applying the ESC/EASD risk criteria to our cohort, most patients with 67% were stratified to the very high risk category, 15% met the ESC/EASD criteria for the high risk category whereas the moderate risk category was poorly represented with 1.5%. Notably, also a substantial number of patients (17%) could not be categorized into either of the ESC/EASD CV risk categories based on the model's stratification criteria. An increase in risk category of the ESC/EASD was associated with risk for 10-year CV death, however the overall model showed poor discriminatory power with a C-index of 0.53 in the unselected population.

Apparently, the moderate risk category as defined by short diabetes duration and no risk factors at all is poorly represented in a typical cohort of patients with T2DM. The original risk model from the prevention guidelines considered diabetic patients as either at high or very high risk, thus the moderate risk category introduced in the ESC/EASD diabetic 2019 guidelines has been newly defined for individuals with diabetes. From a clinical perspective, the question arises, how many T2DM patients with short diabetes duration and no risk factors are truly seen in daily practice. Our findings suggest that the ESC/EASD model indeed acknowledges the overall higher CV risk in diabetic patients but adds limited information to the individual risk for long-term fatal CV events in patients with T2DM.

SCORE and 10-year CV death in patients with diabetes

The SCORE risk estimation has been developed from the general population, but notably the original derivation cohort also included diabetic patients.[6] Since data on diabetes has not been collected uniformly, the presence of diabetes has not been included as a predictor variable in the SCORE risk algorithm. However, it has been suggested to multiply the risk calculated with SCORE by two in diabetic men and by four in diabetic women to get a rough estimate of the increased CV risk in diabetic patients. In the current report, SCORE was significantly associated with 10-year risk of fatal CVD and all-cause mortality but underestimated the risk for fatal CVD events in patients with T2DM with a median predicted risk of 8% [IQR 4-12] compared with an actual risk of 13%. This also applied for the most preselected subgroup closest to the derivation cohort of SCORE, i.e. patients without CVD and aged between 40 and 64 years, albeit agreement between observed and predicted risk improved (observed vs predicted risk: 6% vs 4% [IQR 2-8]). SCORE provided modest discriminatory ability for 10-yaers CV death with a C-index of 0.64 in the unselected population showing improvement in the subgroups up to 0.69, which is similar to SCORE in non-diabetics.[6] Previous studies reported that CVD risk scores developed in the general population underestimate risk in individuals with T2DM.[19] In contrast, a brief report by Coleman et al. investigating SCORE in 3,898 individuals with newly diagnosed T2DM from the UKPDS cohort reported that SCORE risk equation overestimates the 10-year risk for fatal CVD in individuals with T2DM by 18%, but provides good discriminatory accuracy with a C-index of 0.77 for fatal CVD events.[7] The direct comparison of these results with our data might be limited, as the UKPDS included only individuals with newly diagnosed T2DM and treatment has been fundamentally changed within the study period. As mentioned above, SCORE performed best when applied in the cohort closest to its derivation cohort, i.e. in middle aged individuals without known CVD. However, using these criteria resulted in the exclusion of more than half of the study population (58%). Since T2DM is in particular a disease of the elderly, age restrictions as given by SCORE limits its utility in clinical practice.

NT-proBNP in the context of the ESC/EASD model and SCORE

Although there are numerous studies providing evidence that NT-proBNP performs well for CVD risk prediction in individuals with T2DM,[8–12,18,20] the current guidelines do not recommend the application of NT-proBNP for risk stratification in T2DM. Generally, NT-proBNP is widely available in industrialized countries and is a well-established CV risk parameter. In the current report, NT-proBNP was consistently and independently associated with long term (CV) outcome in individuals with T2DM with highest C-indices of 0.80 for fatal CVD death and 0.73 for all-cause death at 10 years in unselected patients. NT-proBNP performed better in identifying T2DM individuals at increased risk for fatal (CVD) events than the ESC/EASD risk model for risk stratification in diabetes as indicated by significantly higher C-indices for unselected patients as well as subgroups without CVD with or without age restriction. NT-proBNP similarly outperformed SCORE, whilst the discriminatory accuracy of SCORE for future fatal (CVD) events was comparable with NT-proBNP when investigated in a small subgroup of middle-aged individuals without known CVD.

Previous studies have demonstrated that NT-proBNP levels below 125 pg/mL have a high negative predictive value for CV outcome in patients with T2DM.[8,11,20] In line, our data confirmed that NT-proBNP concentrations above 125 pg/ml are strongly associated with adverse outcomes in T2DM patients. Furthermore, this report demonstrates that NT-proBNP is significantly associated with future CV hospitalization and performs superior in identifying patients at increased risk for CV hospitalization compared to the ESC/EASD and SCORE models. By predicting future hospital admissions, NT-proBNP-guided risk stratification might also have the potential for overall cost reductions, as it has already been demonstrated for heart failure.[21] Contrary to both risk models, NT-proBNP was even more specific for increased CV risk than all-cause risk in T2DM, emphasizing its clinical relevance as an outcome specific marker.

As demonstrated by our data, NT-proBNP measurement allows identification of T2DM individuals at increased CV risk independent of traditional confounders and shows potential benefits over traditional scores. The use of NT-proBNP as single risk stratificator would omit the need for an extensive assessment of risk factors, calculation of scores as well as the problem of non- or misclassification or overfitting. Moreover, our data support the relevance of NT-proBNP as a single marker for risk stratification in a broad range of T2DM patients from CV risk to advanced CV stages. NT-proBNP meaurement could improve identifying T2DM at increased risk for future CVD events disclosing the possibilities for personalized medicine as targeting preventive treatments, which have been shown promising by previous natriuretic peptide-guided trials in patients with heart failure but also diabetes.[18,22,23] Future studies are needed to investigate the cost-effectiveness and feasibility of NT-proBNP based screening for prediction of adverse CV outcome in individuals with T2DM.

LIMITATIONS

We are aware of the following limitations of our study: First, retinopathy was not generally documented in this registry and could therefore not be implemented in the risk score which could have led to misclassification. Hypothetically, the eventual identification of these individuals would have led to even more patients being stratified into the very high-risk group, resulting in an even greater weighting of the very high-risk category. Notably, a study by Klein et al. demonstrated that retinopathy occurs more frequently in patients with long-term diabetes, CVD and proteinuria,[24] thus it seems conceivable that these patients may also have been captured in the very high-risk category. Second, as this registry included mainly outpatients followed in hospital, T2DM individuals at lower risk who are more often treated by general practitioners might be underrepresented. The ESC/EASD model might have performed different with an altered cohort including these patients.

Conclusion

The current report demonstrates that NT-proBNP is a high-performing biomarker for CV risk assessment in T2DM better allocating 10-year risk for CV death but also all-cause death and hospitalizations than the ESC/EASD model recommended by current guidelines. NT-proBNP measurement might be a simple and independent screening tool applicable for a broad spectrum of T2DM patients in order to identify an increased risk for specifically adverse CV outcome. Future studies need to investigate the cost-effectiveness and feasibility of NT-proBNP-based screening.

List Of Abbreviations

CeVD	Cerebrovascular disease
CV	Cardiovascular risk
CVD	Cardiovascular disease
EASD	European Association for the Society of Diabetes
eGFR	Glomerular filtration rate
ESC	European Society of Cardiology
IQR	Interquartile range
NRI	Net reclassification improvement
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAD	Peripheral artery disease
ROC	Receiver operating characteristic
SCORE	Systemic COronary Risk Evaluation
T2DM	Type 2 diabetes mellitus

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All patients gave written informed consent and the study protocol was approved by the Ethics Committee of the Medical University of Vienna.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the article and its supplementary information files.

COMPETING INTEREST

None declared.

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AUTHORS' CONTRIBUTIONS

HA, MC, MR, SP, NP, GG, RW, MH and PEB contributed to the conception or design of the work. GS, MC, MR, SN, SP, GG, NP and MH contributed to the acquisition, analysis, or interpretation of data for the work. HA, MC, MR, SN, SP, GG, NP, RW, MH and PEB drafted the manuscript. MR, SP, NP, GG, RW and MH critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Not applicable.

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Figures

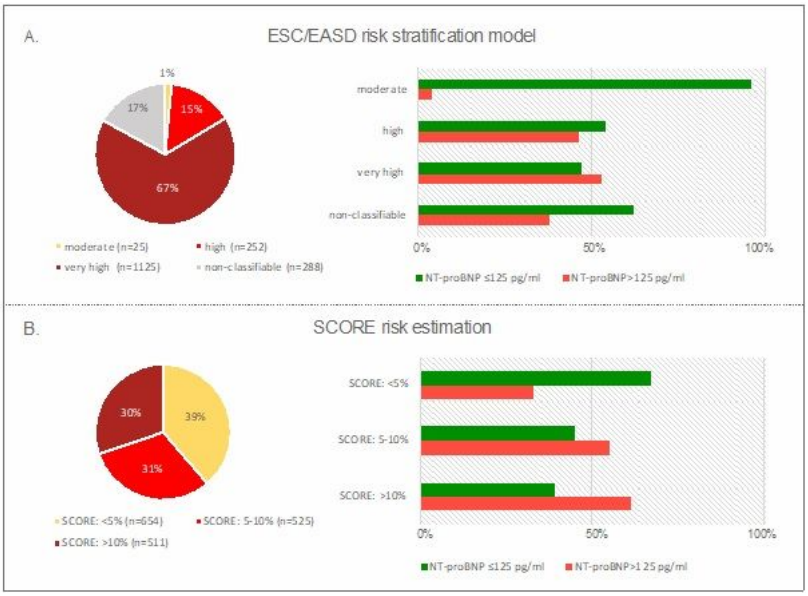

Figure 1

Distribution of the risk estimate as well as the proportion of patients with normal and elevated NT-proBNP (cut-off: 125pg/ml) for A. the ESC/EASD and B. SCORE risk model.

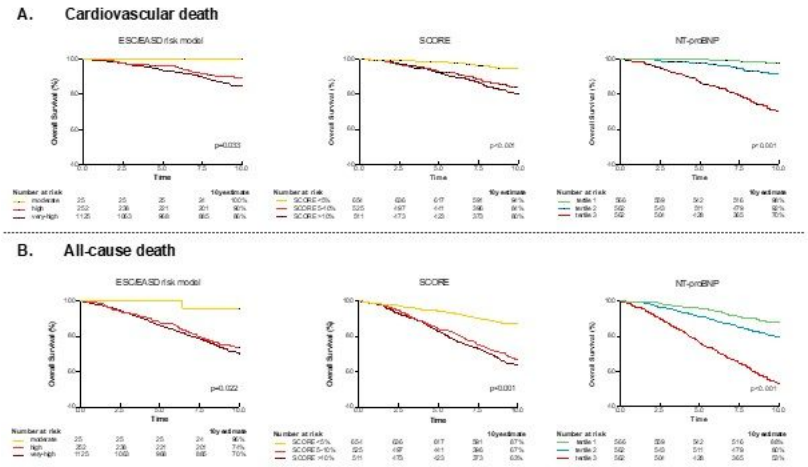

Figure 2

Kaplan-Meier curves for (A) cardiovascular and (B) all-cause death are shown for the ESC/EASD risk model (left), SCORE (cut-off: <5%, 5-10%, >10%) (middle), and NT-proBNP tertiles (right).

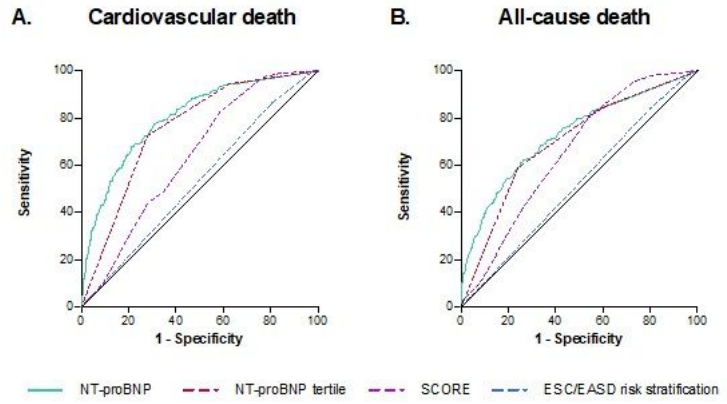

Figure 3

ROC curves of NT-proBNP, the ESC/EASD and SCORE risk model for the outcomes (A) cardiovascular death and (B) all-cause mortality.

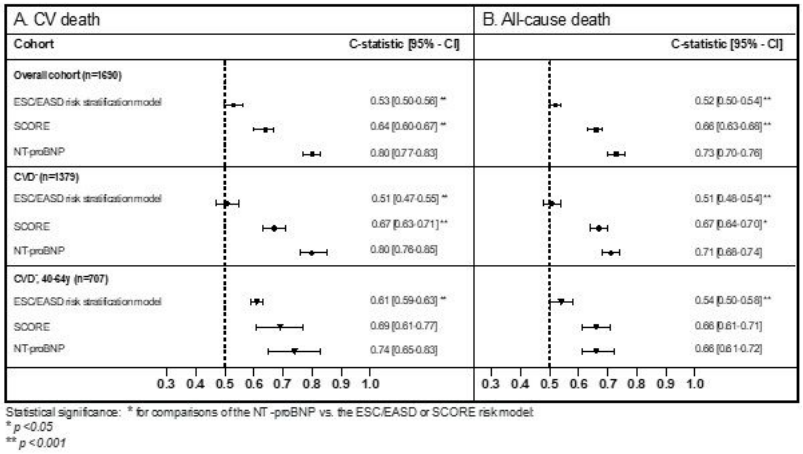

Figure 4

Discriminative performance of NT-proBNP, the ESC/EASD and SCORE risk model in the overall cohort, in T2DM individuals without CVD and without CVD and age 40-64 for the outcome (A) cardiovascular death and (B) all-cause death. The figure displays C-indices and 95%CI.

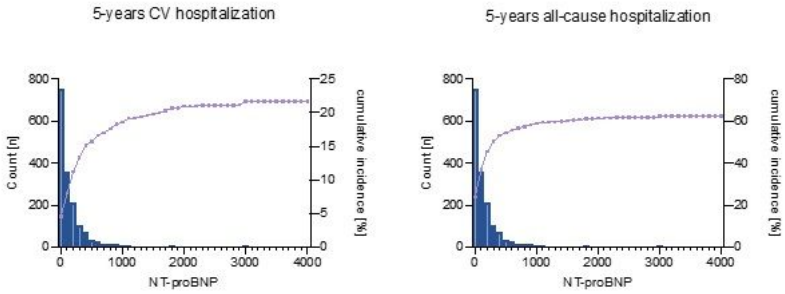

Figure 5

Distribution of NT-proBNP in patients with T2DM and the cumulative incidence of 5-year CV and all-cause hospitalization.

Supplementary Files

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- Additionalfile1.docx