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ORIGINAL RESEARCH

NT-proBNP by Itself Predicts Death and Cardiovascular Events in High-Risk Patients With Type 2 Diabetes Mellitus

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BACKGROUND: NT-proBNP (N-terminal pro-B-type natriuretic peptide) improves the discriminatory ability of risk-prediction models in type 2 diabetes mellitus (T2DM) but is not yet used in clinical practice. We assessed the discriminatory strength of NT-proBNP by itself for death and cardiovascular events in high-risk patients with T2DM.

METHODS AND RESULTS: Cox proportional hazards were used to create a base model formed by 20 variables. The discriminatory ability of the base model was compared with that of NT-proBNP alone and with NT-proBNP added, using C-statistics. We studied 5509 patients (with complete data) of 8561 patients with T2DM and cardiovascular and/or chronic kidney disease who were enrolled in the ALTITUDE (Aliskiren in Type 2 Diabetes Using Cardiorenal Endpoints) trial. During a median 2.6-year follow-up period, 469 patients died and 768 had a cardiovascular composite outcome (cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction, stroke, or heart failure hospitalization). NT-proBNP alone was as discriminatory as the base model for predicting death (C-statistic, 0.745 versus 0.744, P=0.95) and the cardiovascular composite outcome (C-statistic, 0.723 versus 0.731, P=0.37). When NT-proBNP was added, it increased the predictive ability of the base model for death (C-statistic, 0.779 versus 0.744, P<0.001) and for cardiovascular composite outcome (C-statistic, 0.763 versus 0.731, P<0.001).

CONCLUSIONS: In high-risk patients with T2DM, NT-proBNP by itself demonstrated discriminatory ability similar to a multivariable model in predicting both death and cardiovascular events and should be considered for risk stratification.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00549757.

Key Words: cardiovascular diseases ■ diabetes complications ■ diabetes mellitus ■ type 2 ■ pro-B-type natriuretic peptide ■ proportional hazards models

Individuals with type 2 diabetes mellitus (T2DM) have a higher risk of dying than people of comparable age and sex without diabetes mellitus. Cardiovascular disease (CVD) affects approximately one-third of all people with T2DM and accounts for half of all deaths in this population despite major advances in the treatment of the disease.[1,2]

Comorbidities associated with T2DM are important contributors to this increased risk.[3] Multivariable proportional hazards models to predict the risk of death and cardiovascular events incorporate factors known to influence survival such as demographic variables, cardiovascular conditions, and laboratory markers of disease severity and organ involvement.[4] Meanwhile,

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CLINICAL PERSPECTIVE

What Is New?

- In high-risk patients with type 2 diabetes mellitus, NT-proBNP (N-terminal pro-B-type natriuretic peptide) was the major predictor of death and cardiovascular events and, by itself, demonstrated a discriminatory ability similar to a model formed by 20 important clinical variables.
- When added to the multivariable model, NT-proBNP significantly increased the model's ability to predict risk.

What Are the Clinical Implications?

- Our findings underscore the ability of NT-proBNP by itself to be as discriminatory as multiple variables combined, not as a suggestion to replace their use but rather to demonstrate the strength of the information encapsulated in this biomarker and its potential to improve risk-stratification models in patients with type 2 diabetes mellitus and cardiovascular disease, chronic kidney disease, or both.

Nonstandard Abbreviations and Acronyms

CKD	chronic kidney disease
CVCO	cardiovascular composite outcome
CVD	cardiovascular disease
HF	heart failure
hs-TnT	high-sensitivity cardiac troponin
MI	myocardial infarction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
T2DM	type 2 diabetes mellitus

some existing risk-prediction scores based on the use of these traditional variables were considered inaccurate in patients with T2DM.[5]

BNPs (B-type natriuretic peptides), biomarkers of myocardial stress, are well-established predictors of outcomes in heart failure (HF).[6,7] They have also been shown to incrementally improve predictive discrimination of death and cardiovascular events when incorporated into multivariable models in the general population of individuals with T2DM,[8–11] especially in the presence of HF,[12,13] chronic kidney disease (CKD),[14–16] and recent acute coronary syndrome.[17,18] Despite the evidence, in clinical practice, the use of natriuretic peptides is not yet consolidated in the risk assessment of patients with T2DM.

A recent study quantitating the relative contributions of clinical variables and biomarkers in the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial found that the BNPs were the most important predictors of death and of having a nonfatal cardiovascular event. For death, natriuretic peptides levels alone provided predictive ability that was comparable to the use of all other conventional factors combined in a multivariable model.[17]

In this study, we assessed the discriminatory ability provided by NT-proBNP (N-terminal pro-BNP) by itself for the prediction of both death and a cardiovascular composite outcome (CVCO) compared with a multivariable model in patients with T2DM and CVD or/and CKD who were enrolled in the ALTITUDE (Aliskiren in Type 2 Diabetes Using Cardiorenal Points; NCT00549757) trial.[19]

METHODS

We performed an analysis of 5509 people (with complete data) of 8561 individuals screened at 838 centers in 36 countries and randomly enrolled in the ALTITUDE trial.[20]

Male or female individuals ≥35 years of age were included if they used antidiabetic drugs or had documented fasting plasma glucose ≥126 mg/dL or 2-hour plasma glucose ≥200 mg/dL; concomitant use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers without any adjustments to antihypertensive therapy for at least 4 weeks before randomization; and at least one of the following conditions: persistent macroalbuminuria (urine albumin-to-creatinine ratio ≥200 mg/g) and estimated glomerular filtration rate ≥30 mL/min per 1.73 m^2; persistent microalbuminuria (urine albumin-to-creatinine ratio ≥20 mg/g) or/and a history of CVD (myocardial infarction, stroke, HF, or coronary heart disease, and a mean estimated glomerular filtration rate ≥30 mL/min per 1.73 m^2). Patients were excluded if they had serum potassium >5.0 mmol/L directly preceding randomization, type 1 diabetes mellitus, unstable serum creatinine (≥20% difference between 2 consecutive serum creatinine measurements), New York Heart Association class III or IV HF, stroke, acute coronary syndrome, revascularization, HF hospitalization in the prior 3 months, history of cancer, renal transplant, uncontrolled hypertension, treatment with >2 agents blocking the renin–angiotensin aldosterone system, or use of potassium-sparing diuretics.[20]

The study was approved by the ethics committee or institutional review board at each participating center, and all participants signed informed consent before enrollment.[19,20]

Participants were randomized to receive aliskiren or placebo.[20] The intervention had no effect on the primary and secondary end points but was associated with more adverse drug effects.[20]

Demographic information and clinical data were recorded in an electronic case report form. All data pertaining to baseline variables including demographics, anthropometrics, clinical information, laboratory tests, and prior medical history were obtained at the time of randomization in the study. All events were reported to a centralized and independent adjudication committee at Brigham and Women's Hospital (Boston, MA) that classified events according to prespecified definitions (Data S1).[19,20]

The study end points were defined as death from any cause and a CVCO (prespecified as a secondary cardiovascular end point in the ALTITUDE trial, as previously published, and defined as cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction, nonfatal stroke, or unplanned hospitalization for HF).[19,20]

All laboratory variables were centrally measured.[20] NT-proBNP and hs-TnT (high-sensitivity cardiac troponin) values <25 pg/mL and 13 ng/L were converted to 12.5 pg/mL and 6.5 ng/L, respectively (Data S2).

Statistical Analysis

Baseline characteristics shown in Table 1 were selected to create the risk models. We examined all variables collected in the electronic case report form. The most statistically significant or clinically relevant baseline variables were added to the model. Nonsignificant variables were removed ($P>0.05$) unless considered clinically important. The distributions of baseline NT-proBNP, hs-TnT, and other variables that were found to be right-skewed were log-transformed before analysis. Continuous variables were included in the model unless there was clear evidence of nonlinearity. Between-group differences were tested for statistical significance with Student *t* test or Wilcoxon rank sum test for continuous variables; the χ^2 test was used for categorical variables.

Cox proportional hazards modeling was used to create the multivariable base risk model, which was formed using selected clinical and laboratory variables without NT-proBNP. The discriminatory ability of the base model was compared with that of NT-proBNP alone and with that of the base model after addition of NT-pro BNP, using Harrell C-statistics.

The base model was formed by 20 clinical variables: age (per 10 years), sex, smoking, history of coronary heart disease (previous hospitalizations due to percutaneous coronary intervention, coronary artery bypass grafting, angina, or myocardial infarction), history of stroke, history of prior HF, history of atrial fibrillation, insulin use, systolic blood pressure (per 10 mmHg), diastolic blood pressure (per 10 mmHg), heart rate (per 10 beats/min), left ventricular hypertrophy on ECG, Q wave on ECG, any bundle-branch block on ECG, log-transformed hs-TnT (per 1 log unit), estimated glomerular filtration rate (per 10 mL/min per 1.73 m^2), log-transformed urine albumin-to-creatinine ratio (per 1 log unit), glycosylated hemoglobin (per 1%), low-density lipoprotein cholesterol (per 1 mg/dL), and serum albumin (per 1 mg/dL).

We also performed an additional statistical analysis by dividing the study population into independent sets of training (patients randomized from 2007–2008, n=1969) and validation (patients randomized from 2009–2011, n=3540). We tested the base model of 20 clinical and laboratory variables, NT-proBNP alone, and NT-proBNP added to the base model in predicting death and the CVCO in the training data set. Then we evaluated the performance of these predictive models in the validation data set.

A significance level of 0.05 was considered statistically significant. Analyses were performed using Stata 14 (StataCorp).

RESULTS

During median follow-up of 2.6 years (interquartile range, 2.0–3.2), 469 patients (8.5%) died and 768 (13.9%) experienced a CVCO (cardiovascular death, 294 [5.3%]; myocardial infarction, 201 [3.6%]; HF unplanned hospitalization, 285 [5.2%]; stroke, 201 [3.6%]; resuscitated cardiac arrest, 21 [0.4%]) (Figure S1). Baseline characteristics of patients, classified by end points, death, and cardiovascular events, are presented in Table 1. In this analysis, 2763 patients were randomized to placebo and 2746 were randomized to aliskiren.

Compared with patients who survived, nonsurvivors were older, on average, with higher systolic blood pressure and glycosylated hemoglobin but lower levels of hemoglobin and albumin and lower estimated glomerular filtration rate, in addition to a higher previous load of diseases. Considering patients who had cardiovascular events, higher low-density lipoprotein cholesterol and albuminuria were observed. Baseline levels of NT-proBNP were higher in the nonsurvivor group and among those who developed cardiovascular events. There was no difference in aliskiren use between the groups.

Table 2 shows the composition of the base model, with 20 variables for the prediction of death, the univariable model of log-transformed NT-proBNP (log–NT-proBNP), and the model containing the addition of log–NT-proBNP to the model (21 variables). Table 3 shows the same models for the prediction of CVCO.

Table 1. Baseline Characteristics of Patients Classified by Outcome Status (N=5509)

	Death			CVCO		
	No	Yes		No	Yes	
	n=5040	n=469	*P* Value	n=4741	n=768	*P* Value
Age, y	64.1±9.8	68.1±9.3	<0.001	64.0±9.8	67.0±9.2	<0.001
Female sex	1569 (31.1)	129 (27.5)	0.1	1466 (30.9)	232 (30.2)	0.69
Race			0.002			0.014
White	2755 (54.7)	267 (56.9)		2565 (54.1)	457 (59.5)	
Black	121 (2.4)	12 (2.6)		113 (2.4)	20 (2.6)	
Asian	1876 (37.2)	143 (30.5)		1775 (37.4)	244 (31.8)	
Native American	1 (0.0)	0 (0.0)		1 (0.0)	0 (0.0)	
Pacific Islander	9 (0.2)	2 (0.4)		7 (0.1)	4 (0.5)	
Other	278 (5.5)	45 (9.6)		280 (5.9)	43 (5.6)	
BMI, kg/m^2	29.7±5.9	29.3±6.0	0.09	29.7±5.9	29.9±6.0	0.35
SBP, mm Hg	137.4±16.2	140.4±17.0	<0.001	137.2±16.1	140.9±16.8	<0.001
DBP, mm Hg	74.4±9.7	73.8±10.5	0.2	74.5±9.7	73.8±10.1	0.07
Heart rate, bpm	72.3±12.4	72.6±13.1	0.61	72.5±12.4	71.8±12.8	0.21
Smoking status			0.08			0.08
No smoker	2498 (49.6)	210 (44.8)		2359 (49.8)	349 (45.4)	
Former	1822 (36.2)	193 (41.2)		1715 (36.2)	300 (39.1)	
Current	720 (14.3)	66 (14.1)		667 (14.1)	119 (15.5)	
Hemoglobin, g/dL	13.2±1.7	12.8±1.8	<0.001	13.2±1.7	13.0±1.8	0.004
Serum albumin, mg/dL	4.3±0.4	4.1±0.5	<0.001	4.3±0.4	4.1±0.4	<0.001
HDL-C, mg/dL	46.2±12.7	46.9±13.9	0.25	46.2±12.7	46.6±13.3	0.43
LDL-C, mg/dL	98.4±36.9	100.4±38.1	0.25	97.7±36.6	103.5±39.3	<0.001
Potassium, mEq/L	4.5±0.5	4.5±0.5	0.65	4.5±0.5	4.5±0.5	0.26
HbA_{1c}, %	7.7±1.5	7.9±1.7	0.015	7.7±1.5	7.9±1.7	<0.001
HbA_{1c}, mmol/mol	60.8±16.7	62.8±18.9	0.015	60.6±16.5	63.2±18.7	<0.001
eGFR, mL/min/1.73 m^2	58.0±23.0	51.2±20.1	<0.001	58.1±23.0	53.0±20.8	<0.001
eGFR category			<0.001			<0.001
<30	111 (2.2)	21 (4.5)		108 (2.3)	24 (3.1)	
30 to <45	1431 (28.4)	192 (40.9)		1331 (28.1)	292 (38.0)	
45 to <60	1779 (35.3)	152 (32.4)		1682 (35.5)	249 (32.4)	
≥60	1719 (34.1)	104 (22.2)		1620 (34.2)	203 (26.4)	
UACR geometric mean, mg/g	209.2 (198.1–220.9)	228.1 (188.1–276.5)	0.37	206.4 (195.2–218.3)	239.6 (205.9–278.9)	0.05
UACR, median (IQR)	301.9 (62.8–894.9)	284.6 (53.9–1272.1)	0.31	297.9 (64.5–863.7)	320.9 (52.8–1340.1)	0.015
UACR category			0.59			0.67
<20	708 (14.0)	69 (14.7)		661 (13.9)	116 (15.1)	
20 to <200	1245 (24.7)	124 (26.4)		1183 (25.0)	186 (24.2)	
≥200	3087 (61.3)	276 (58.8)		2897 (61.1)	466 (60.7)	
BB on ECG	480 (9.5)	86 (18.3)	<0.001	438 (9.2)	128 (16.7)	<0.001
LVH on ECG	340 (6.7)	51 (10.9)	<0.001	319 (6.7)	72 (9.4)	0.008
Q wave on ECG	315 (6.3)	53 (11.3)	<0.001	296 (6.2)	72 (9.4)	0.001
T2DM diagnosis time, y			0.29			0.16
>5	4124 (81.8)	395 (84.2)		3870 (81.6)	649 (84.5)	
1–5	738 (14.6)	63 (13.4)		705 (14.9)	96 (12.5)	
<1	178 (3.5)	11 (2.3)		166 (3.5)	23 (3.0)	
Insulin use	2912 (57.8)	300 (64.0)	0.009	2712 (57.2)	500 (65.1)	0.001
Statin use	3220 (63.9)	293 (62.5)	0.54	2996 (63.2)	517 (67.3)	0.027

(Continues)

Table 1. Continued

	Death			CVCO		
	No	Yes		No	Yes	
	n=5040	n=469	*P* Value	n=4741	n=768	*P* Value
β-Blocker use	2453 (48.7)	261 (55.7)	0.004	2258 (47.6)	456 (59.4)	<0.001
ACEi use	2143 (43.5)	230 (50.1)	0.006	1989 (43.0)	384 (50.9)	<0.001
ARB use	2904 (58.6)	241 (52.4)	0.01	2757 (59.1)	388 (51.5)	<0.001
Aliskiren use	2509 (49.8)	237 (50.5)	0.76	2346 (49.5)	400 (52.1)	0.18
History of HF	467 (9.3)	113 (24.1)	<0.001	396 (8.4)	184 (24.0)	<0.001
History of CABG	578 (11.5)	64 (13.6)	0.16	517 (10.9)	125 (16.3)	<0.001
History of PCI	715 (14.2)	72 (15.4)	0.49	659 (13.9)	128 (16.7)	0.042
History of MI	735 (14.6)	108 (23.0)	<0.001	662 (14.0)	181 (23.6)	<0.001
History of unstable angina	443 (8.8)	60 (12.8)	0.004	394 (8.3)	109 (14.2)	<0.001
History of stroke	476 (9.4)	66 (14.1)	0.001	434 (9.2)	108 (14.1)	<0.001
History of TIA	211 (4.2)	27 (5.8)	0.11	183 (3.9)	55 (7.2)	<0.001
History of amputation	160 (3.2)	34 (7.2)	<0.001	158 (3.3)	36 (4.7)	0.06
History of ulcer	147 (2.9)	29 (6.2)	<0.001	145 (3.1)	31 (4.0)	0.15
History of AF	381 (7.6)	79 (16.8)	<0.001	336 (7.1)	124 (16.1)	<0.001
History of atrial flutter	20 (0.4)	3 (0.6)	0.44	19 (0.4)	4 (0.5)	0.63
Pacemaker	114 (2.3)	18 (3.8)	0.033	99 (2.1)	33 (4.3)	<0.001
NT-proBNP, pg/mL	389.5±1091.9	1267.9±2611.8	<0.001	357.1±1040.3	1126.1±2286.5	<0.001
hs-TnT, ng/L	18.2±17.9	39.1±124.9	<0.001	17.9±17.7	32.9±98.6	<0.001

Data are shown as mean±SD or n (%) except as noted. ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; BB, any bundle branch block; BMI, body mass index; CABG, coronary artery bypass grafting; CVCO, cardiovascular composite outcome; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; hs-TnT, high-sensitivity cardiac troponin; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack; and UACR, urine albumin-to-creatinine ratio.

In prediction of death, the C-statistic of base model was 0.744 (95% CI, 0.722–0.767), and the mortality rates per 100 person-years were 0.7 (95% CI, 0.4–1.2) in the 1st decile and 11.6 (9.9–13.7) in the 10th decile of predicted risk (Figure 1). The C-statistic for NT-proBNP as a single variable was 0.745 (95% CI, 0.723–0.768; *P*=0.95 versus model), and the mortality rates per 100 person-years were 0.7 (95% CI, 0.4–1.2) in the 1st decile and 11.6 (95% CI, 9.9–13.6) in the 10th decile of NT-proBNP (Figure 1).

In prediction of the CVCO, the C-statistic for the 20-variable model was 0.731 (95% CI, 0.714–0.749), and the incidence rates per 100 person-years were 0.9 (95% CI, 0.5–1.5) in the 1st decile and 19.2 (95% CI, 16.8–22.0) in the 10th decile of predicted risk (Figure 2). The C-statistic for NT-proBNP alone was 0.723 (95% CI, 0.704–0.741; *P*=0.37 versus model), and the incidence rates per 100 person-years were 1.3 (95% CI, 0.8–2.0) in the 1st decile and 19.4 (95% CI, 16.9–22.1) in the 10th decile of NT-proBNP (Figure 2).

The C-statistic for predicting death in the base model (0.744) was improved by adding NT-proBNP (0.779, *P*<0.001 versus model). Similarly, the model ability for predicting the CVCO (0.731) was augmented by including NT-proBNP in the model (0.763, *P*<0.001 versus model). C-statistics for NT-pro BNP alone were also improved by use of the base model plus NT-proBNP in the prediction of both death (0.745 versus 0.779, *P*<0.001) and CVCO (0.723 versus 0.763, *P*<0.001) (Figures 1 and 2).

In the independent training and validation data sets, we reached the same conclusion—that NT-proBNP by itself had discriminatory capacity similar to the 20-variable clinical model for death and the CVCO (Tables S1 through S3).

Sensitivity Analyses

We also performed a sensitivity analysis of 4929 individuals, excluding 580 patients with a previous history of HF. For the prediction of death, once again, NT-proBNP alone was as good as the model (C-statistic, 0.726 versus 0.733, *P*=0.68) and enhanced its ability when added to the model (0.733 versus 0.768, *P*<0.001).

The same type of sensitivity analysis, excluding individuals with a previous history of HF, was performed for the CVCO, for which NT-proBNP as a single variable

Table 2. Death Prediction Models

Variables	Base Model (20 Variables; C-Statistic, 0.744 [95% CI, 0.722–0.767])				Base Model+N-TproBNP (21 Variables; C-Statistic, 0.779 [95% CI, 0.758–0.800])				NT-proBNP by Itself (1 Variable; C-Statistic, 0.745 [95% CI, 0.723–0.768])			
	HR	95% CI	*P* Value	χ^2	HR	95% CI	*P* Value	χ^2	HR	95% CI	*P* Value	χ^2
Log NT-proBNP, per 1 log unit	…	…	…	…	1.62	1.49–1.77	<0.001	118.6	1.94	1.81–2.07	<0.001	383.4
Log hs-TnT, per 1 log unit	1.85	1.63–2.11	<0.001	85.0	1.49	1.29–1.71	<0.001	30.8				
Age, per 10 y	1.57	1.39–1.77	<0.001	54.0	1.43	1.26–1.61	<0.001	32.8				
Albumin, per 1 mg/dL	0.55	0.43–0.69	<0.001	25.2	0.77	0.6–0.98	0.035	4,.5				
History of HF	1.79	1.41–2.28	<0.001	22.7	1.42	1.11–1.81	0.005	7.9				
Heart rate, per 10 beats/min	1.10	1.02–1.19	0.015	5.9	1.13	1.05–1.22	0.002	9.5				
History of stroke	1.38	1.06–1.80	0.02	5.8	1.43	1.10–1.87	0.008	7.1				
HbA_{1c}, per 1%	1.08	1.01–1.14	0.02	5.7	1.09	1.02–1.15	0.007	7.2				
Smoking	1.17	1.02–1.35	0.03	4.9	1.17	1.01–1.34	0.03	4.6				
LVH on ECG	1.38	1.03–1.86	0.03	4.6	1.17	0.87–1.57	0.30	1.1				
Q wave on ECG	1.38	1.02–1.87	0.04	4.3	1.12	0.82–1.53	0.47	0.5				
History of AF	1.31	1.00–1.71	0.05	3.8	0.99	0.76–1.29	0.93	0.0				
BB on ECG	1.27	1.00–1.62	0.05	3.7	1.07	0.84–1.38	0.57	0.3				
Log UACR, per 1 log unit	1.05	0.99–1.11	0.10	2.7	1.03	0.98–1.10	0.24	1.4				
SBP, per 10 mmHg	1.05	0.98–1.12	0.15	2.0	1.03	0.97–1.10	0.33	0.9				
Female sex	1.16	0.92–1.46	0.22	1.5	0.95	0.75–1.21	0.67	0.2				
History of CHD	1.14	0.92–1.42	0.22	1.5	0.97	0.79–1.20	0.79	0.1				
LDL-C, 1 mg/dL	1.00	1.00–1.00	0.24	1.4	1.00	1.00–1.01	0.02	5.9				
eGFR, per 10 mL/min/1.73 m^2	0.97	0.92–1.03	0.34	0.9	1.01	0.96–1.07	0.67	0.2				
Insulin use	1.05	0.85–1.28	0.66	0.2	1.13	0.92–1.39	0.26	1.3				
DBP, per 10 mm Hg	1.01	0.90–1.13	0.86	0.0	0.98	0.87–1.09	0.70	0.2				

AF indicates atrial fibrillation; BB, any bundle-branch block; CHD, coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HF, heart failure; HR, hazard ratio; hs-TnT, high-sensitivity cardiac troponin; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio.

proved to be as discriminatory as the model (0.705 versus 0.714, *P*=0.42) and improved its strength when added to the model (0.714 versus 0.749, *P*<0.001).

Regardless of whether the inclusion criteria was CVD (n=2237) or CKD (n=3368), the finding of NT-proBNP being as discriminatory as the model was confirmed for predicting death (C-statistic, 0.711 versus 0.732 [*P*=0.18] among patients with CVD and 0.743 versus 0.746 [*P*=0.82] in those with CKD) and the CVCO (0.692 versus 0.711 [*P*=0.16] among patients with CVD and 0.722 versus 0.732 [*P*=0.40] in those with CKD). Only 96 patients (1.7%) met both criteria and were not assessed separately.

Sensitivity analyses considering body mass index and use of aliskiren are shown in Table S4.

DISCUSSION

Our goal was to evaluate the discriminatory ability of NT-proBNP by itself in high-risk patients with T2DM and CVD, CKD, or both. We demonstrated that NT-proBNP alone was able to predict both death and a CVCO as accurately as the multivariable model composed of the 20 most significant and relevant clinical variables.

Patients with T2DM are at 2 to 4 times greater risk of death and cardiovascular events than the general population.[2] Validated models, such as the Framingham risk score and the UKPDS (United Kingdom Prospective Diabetes Study) model, have shown limited ability to accurately estimate the cardiovascular risk of individuals with T2DM.[4,5] Several studies have proposed improvements for risk stratification of patients with T2DM, especially those in secondary prevention; suggested improvements include the incorporation of clinical information[21] and the addition of cardiac biomarkers.[8–18]

The importance of BNPs in improving the prediction of cardiovascular events has been well established when added to multivariable models. An analysis of 42 protein biomarkers in the SUMMIT (Surrogate Markers for Micro- and Macrovascular Hard Endpoints for Innovative Diabetes Tools) consortium involving individuals with T2DM and without apparent CVD and controls, NT-proBNP, followed by hs-TnT and 4 other proteins, revealed the ability to increase cardiovascular

Table 3. CVCO Prediction Models

Variables	Base Model (20 Variables; C-Statistic, 0.731 [95% CI, 0.714–0.749])				Base Model+NT-proBNP (21 Variables; C-Statistic, 0.763 [95% CI, 0.746–0.780])				NT-proBNP by Itself (1 Variable; C-Statistic, 0.723 [95% CI, 0.704–0.741])			
	HR	95% CI	*P* Value	χ^2	HR	95% CI	*P* Value	χ^2	HR	95% CI	*P* Value	χ^2
Log NT-proBNP, per 1 log unit	…	…	…	…	1.63	1.52–1.75	<0.001	189.9	1.88	1.78–1.98	<0.001	545.2
Log hs-TnT, per 1 log unit	1.63	1.47–1.81	<0.001	86.5	1.31	1.18–1.47	<0.001	23.3				
History of HF	2.11	1.75–2.55	<0.001	60.7	1.69	1.40–2.05	<0.001	29.6				
Age, per 10 y	1.32	1.21–1.45	<0.001	34.8	1.21	1.10–1.33	<0.001	15.4				
Albumin, per 1 mg/dL	0.58	0.48–0.70	<0.001	34.1	0.80	0.66–0.96	0.02	5.4				
LDL-C, 1 mg/dL	1.00	1.00–1.01	<0.001	17.3	1.01	1.00–1.01	<0.001	30.1				
History of AF	1.49	1.21–1.85	<0.001	13.5	1.12	0.9–1.38	0.32	1.0				
History of stroke	1.46	1.19–1.80	<0.001	13.0	1.51	1.23–1.86	<0.001	15.4				
SBP, per 10 mmHg	1.09	1.04–1.15	0.001	11.8	1.07	1.02–1.12	0.01	6.7				
HbA_{1c}, per 1%	1.08	1.03–1.14	0.001	11.4	1.10	1.05–1.15	<0.001	15.5				
Smoking	1.19	1.07–1.33	0.002	9.9	1.18	1.06–1.31	0.003	8.8				
History of CHD	1.29	1.09–1.53	0.003	8.8	1.10	0.93–1.30	0.25	1.3				
Female sex	1.26	1.05–1.51	0.01	6.5	1.04	0.87–1.25	0.65	0.2				
Log UACR, per 1 log unit	1.06	1.01–1.11	0.012	6.4	1.04	1.00–1.09	0.057	3.6				
BB on ECG	1.26	1.04–1.54	0.02	5.4	1.09	0.89–1.33	0.39	0.7				
DBP, per 10 mm Hg	0.94	0.86–1.03	0.16	2.0	0.92	0.85–1.01	0.07	3.3				
Insulin use	1.12	0.95–1.31	0.18	1.8	1.19	1.01–1.40	0.04	4.2				
Q wave on ECG	1.16	0.90–1.49	0.26	1.3	0.93	0.71–1.20	0.57	0.3				
Heart rate, per 10 bpm	1.03	0.97–1.10	0.32	1.0	1.06	1.00–1.13	0.06	3.6				
LVH on ECG	1.10	0.86–1.42	0.43	0.6	0.94	0.73–1.20	0.60	0.3				
eGFR, per 10 mL/min/1.73 m^2	0.99	0.95–1.03	0.76	0.1	1.03	0.99–1.08	0.10	2.7				

AF indicates atrial fibrillation; BB, any bundle-branch block; CHD, coronary heart disease; CVCO, cardiovascular composite outcome; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HF, heart failure; HR, hazard ratio; hs-TnT, high-sensitivity cardiac troponin; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; and UACR, urine albumin-to-creatinine ratio.

outcome prediction.[22] Abnormal NT-proBNP and hs-TnT levels were able to distinguish individuals with T2DM at high cardiovascular risk from those at low risk in the ARIC (Atherosclerosis Risk in Communities) study.[8] Another study that evaluated 237 biomarkers in 8401 individuals with dysglycemia (59% with previous CVD) who were enrolled in the ORIGIN (Outcome Reduction With Initial Glargine Intervention) trial also identified NT-proBNP as the major predictor of cardiovascular events and death.[23] In patients with T2DM involved in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Evaluation) trial, the accuracy of 5-year cardiovascular risk prediction was increased by 39% with NT-proBNP and 46% with hs-TnT in net reclassification index when added to the base model.[9] Among patients with T2DM and microalbuminuria enrolled in the Steno-2 (Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria) study, NT-proBNP above the median was associated with an increased risk of CVD.[14] In the Sun-MACRO (Sulodexide Macroalbuminuria) trial, the addition of NT-proBNP to a multivariable model improved prediction of cardiovascular end points in patients with T2DM and macroalbuminuria.[15] Furthermore, in patients with T2DM and predialytic CKD and anemia who were evaluated in TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy), the addition of NT-proBNP and TnT to the multivariable model was associated with net improvement of 17.8% in predicting cardiovascular outcome.[16] A previous analysis of the ALTITUDE trial showed that the response to treatment with aliskiren in cardiorenal outcomes was related to baseline levels of NT-proBNP.[24]

Life insurance companies have recognized the predictive strength of NT-proBNP and use it to assess risk of death.[25] For death, some previous studies also demonstrated the ability of BNPs to improve prediction of the multivariable models in patients with T2DM with or without CVD.[9–11,15–17] Pfister et al showed that NT-proBNP measured at discharge predicts death and cardiovascular events in patients with T2DM hospitalized for a broad spectrum of CVDs.[26] Studying older adults with T2DM, Bruno et al demonstrated that

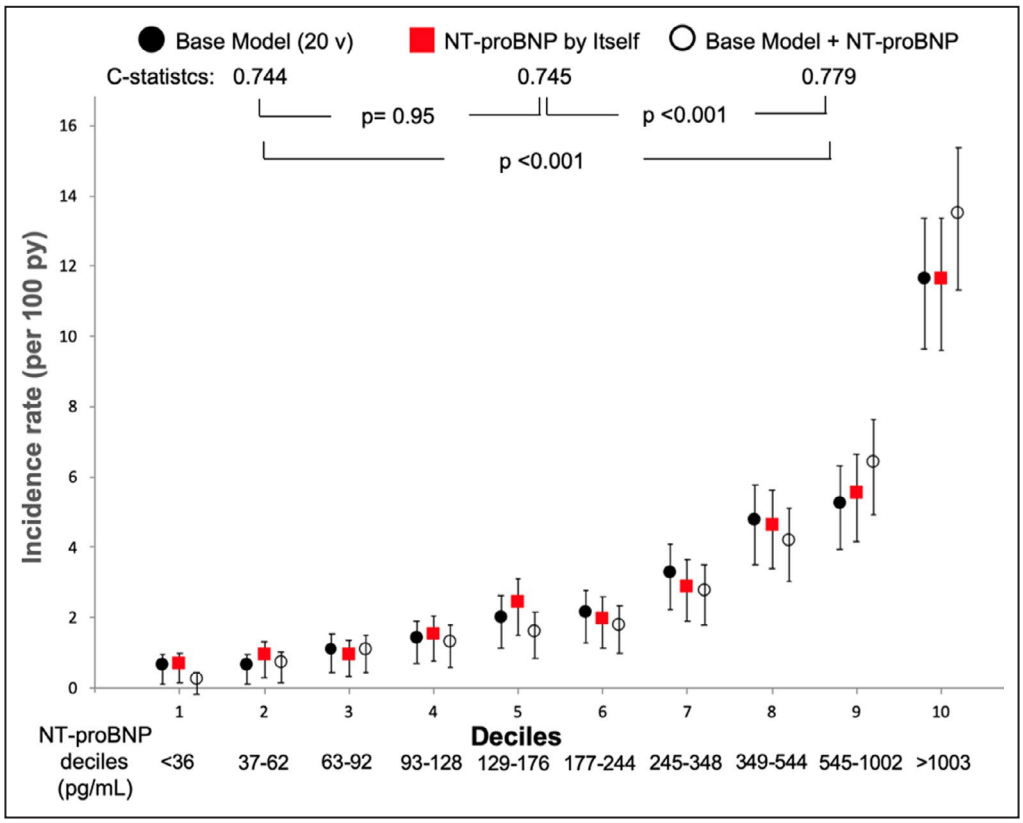

Figure 1. Death prediction models by deciles of predicted risk/deciles of NT-proBNP.
NT-proBNP indicates N-terminal pro-B-type natriuretic peptide; and py, person/years. Base Model: formed by high sensitivity cardiac troponin, age, albumin, history of heart failure, heart rate, history of stroke, HbA_{1c}, smoking, left ventricular hypertrophy on ECG, Q wave on ECG, history of atrial fibrillation, any bundle branch block on ECG, urine albumin-to-creatinine ratio, systolic blood pressure, sex, history of coronary heart disease, low density lipoprotein cholesterol, estimated glomerular filtration rate, insulin use, and diastolic blood pressure, in decreasing order of χ^2; v=variables. Error bars represent 95% CIs.

NT-proBNP, adjusted for covariates, was the strongest predictor of cardiovascular mortality.[27]

Notably, in an analysis of the ELIXA trial, BNPs alone were as predictive as the multivariable model for death but not for other outcomes in patients with T2DM ≤180 days after acute coronary syndrome.[17] We expanded knowledge about the discriminatory ability of NT-proBNP by itself, demonstrating that it was as predictive as the base model not only for death but also for CVCO and in a clinical population of patients with T2DM and CVD, CKD, or both. In addition, we showed that these results were maintained even in sensitivity analyses, excluding patients with a history of HF or considering the 2 main inclusion criteria of the study, CVD or CKD. Furthermore, NT-proBNP demonstrated incremental discriminatory strength when added to the model.

This study is a post hoc analysis of a large cohort of patients previously enrolled in a neutral clinical trial, with the possible limitations of secondary interpretations. In our data set, there was no information on left ventricular function, imaging exams, or social variables such as income and educational level, which could provide additional contribution to risk prediction.

The mechanisms by which NT-proBNP as a single variable has been shown to be such a strong predictor of risk of death and cardiovascular events have not yet been fully elucidated. It is known that the concentrations of natriuretic peptides may change in relation to different variables such as race/ethnicity,[28] heart rate,[29] obesity,[30] volume overload,[24] left ventricular hypertrophy,[29] HF,[6,7,12,13] myocardial ischemia[17,18,31] atrial fibrillation,[32] CKD,[14–16] stroke,[33] and treatments.[7,34] BNPs are released from the heart as a counterregulatory response to increased stress on the wall, sympathetic tone, and vasoconstriction, but they are also associated with the regulation of numerous physiologic functions that control energy metabolism.[35] It is plausible that NT-proBNP is sensitive to different influences that expand its potential discriminatory capacity when integrating cardiovascular and hemodynamic stress from several sources.

Our results underscore the ability of a single biomarker to be as discriminatory as multiple variables

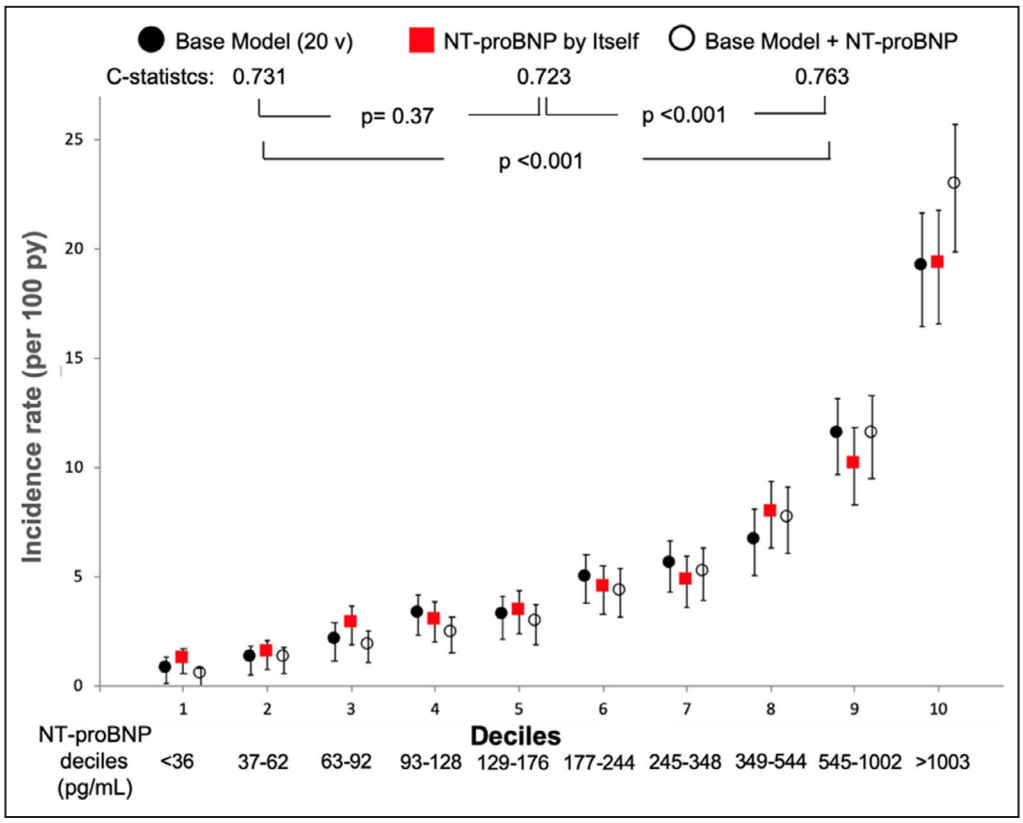

Figure 2. Cardiovascular composite outcome prediction models by deciles of predicted risk/ deciles of NT-proBNP.
NT-proBNP indicates N-terminal pro-B-type natriuretic peptide; and py, person/years. Base Model: formed by high sensitivity cardiac troponin, history of heart failure, age, albumin, low density lipoprotein cholesterol, history of atrial fibrillation, history of stroke, systolic blood pressure, HbA_{1c}, smoking, history of coronary heart disease, sex, urine albumin-to-creatinine ratio, any bundle branch block on ECG, diastolic blood pressure, insulin use, Q wave on ECG, heart rate, left ventricular hypertrophy on ECG, and estimated glomerular filtration rate, in decreasing order of χ^2; v=variables. Error bars represent 95% CIs.

combined, not as a suggestion to replace their use but to demonstrate the strength of the information encapsulated in NT-proBNP and its potential to improve models of risk stratification in high-risk patients with T2DM.

CONCLUSIONS

In high-risk patients with T2DM, NT-proBNP by itself was as discriminatory as the model of 20 traditional clinical and laboratory variables in prediction of both death and cardiovascular events. This finding does not minimize the influence of multiple other factors in the prognosis but emphasizes the importance of this biomarker as a sensitive integrator of different variables and its potential role in risk stratification.

DATA SHARING

The sponsor of this trial is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Trial data are available according to the criteria and process described.[36]

ARTICLE INFORMATION

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Supplementary Materials

Data S1–S2
Tables S1–S4
Figure S1

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods: Adjudication of endpoints and definition of outcomes.

Definitions of death were: cardiovascular (CV) death, including sudden death, death during a CV procedure or as a result of procedure-related complications, presumed sudden and presumed CV death, or death resulting from a documented CV cause; non-CV death as an unequivocal and documented non-CV primary cause of death; and death unknown when insufficient data were available to make an reasonable differentiation of CV or non-CV cause of death. Resuscitated cardiac arrest was defined as an experience of sudden death or cardiac arrest successfully resuscitated by cardioversion, defibrillation or cardiopulmonary resuscitation with a meaningful recovery of consciousness. A myocardial infarction (MI) was defined by the criteria adopted at the time of the study by a troponin or creatinine kinase-MB > 2 × upper reference limit (>3 × post-percutaneous coronary intervention [PCI] or >5 × post-coronary artery bypass grafting [CABG]) and either ischaemic symptoms or new ischemic electrocardiogram (ECG) changes. A heart failure (HF) hospitalization was defined as presentation to an acute care facility requiring an overnight hospitalization with an unexpected exacerbation of HF (one or more symptoms and two or more signs), which required treatment with either intravenous diuretics, vasodilators, inotropes, mechanical fluid removal, or insertion of an intra-aortic balloon pump for haemodynamic compromise, initiation of standing oral diuretics, or intensification of the maintenance diuretic. A stroke was defined by a focal neurological deficit of central origin lasting >24 hour, with or without imaging confirmation of cerebral infarction or intracerebral hemorrhage. Data

on adjudicated time-to-event for death and a CV composite outcome were used for analyses (19).

Data S2.

Supplemental Methods: Laboratory Analysis of Cardiac Biomarkers

Biological samples were analyzed in central laboratories in the USA and Europe. Samples were analyzed in complete patient sets by laboratory personnel blinded to treatment allocation and clinical outcomes. NT-proBNP and hs-TnT analyses were performed by CRL.Medinet laboratories in Cambridgeshire, UK and Breda, NL. NT-proBNP was measured in EDTA plasma using an electrochemiluminescence immunoassay (proBNP II; Roche Diagnostics GmbH, Penzberg, Germany), with a reporting range of 25-35,000 pg/mL. Intra-day and inter-day assay variation coefficients were $\leq$ 2.5% and $\leq$ 4 %, respectively. NT-proBNP values below 25 pg/mL (lower limit of quantification [LLOQ]), observed in 320 (5,8 %) patients, were automatically converted to half the minimum value, 12.5 pg/mL. Hs-TnT was measured in EDTA plasma using a high sensitivity immunoassay (Troponin T hs; Roche Diagnostics, Roche Diagnostics GmbH, Penzberg, Germany) with a reporting range of 5 – 10,000 ng/L. Intra-day and inter-day assay variation coefficients were < 3%. Although the LLOQ for the hs-TnT used in this analysis has been reported to be 5 ng/L, based on the manufacturer-determined 99th percentile equal to 14 ng/L and coefficient of variation < 10% at 13 ng/L, hs-TnT values found below 13 ng/L, observed in 2,167 (39,3%), were automatically converted to 6.5 ng/L. Results prior to these conversions of cardiac biomarkers values were not available.

Table S1. Baseline characteristics in training and validation datasets.

	Training dataset Randomization year ≤ 2008 n= 1,969	Validation dataset Randomization year > 2008 n= 3,540
Age, y	65.2 ± 9.6	64.0 ± 9.9
Female sex	548 (27.8%)	1150 (32.5%)
Race		
Caucasian	1228 (62.4%)	1794 (50.7%)
Black	70 (3.6%)	63 (1.8%)
Asian	526 (26.7%)	1493 (42.2%)
Native American	0	1 (0.0%)
Pacific Islander	8 (0.4%)	3 (0.1%)
Other	137 (7.0%)	186 (5.3%)
BMI, kg/m2	30.3 ± 6.0	29.4 ± 5.8
SBP, mmHg	138.4 ± 16.0	137.3 ± 16.4
DBP, mmHg	74.5 ± 9.7	74.3 ± 9.8
Heart rate (bpm)	71.4 ± 12.5	72.9 ± 12.4
Smoking status		
No smoker	867 (44.0%)	1841 (52.0%)
Former	821 (41.7%)	1194 (33.7%)
Current	281 (14.3%)	505 (14.3%)
Hemoglobin, g/dL	13.2 ± 1.7	13.1 ± 1.8
Albumin, mg/L	4.3 ± 0.4	4.3 ± 0.4
HDLc, mg/L	46.0 ± 12.6	46.4 ± 12.9
LDLc, mg/L	96.4 ± 35.8	99.7 ± 37.6
Potassium, mEq/L	4.5 ± 0.5	4.5 ± 0.5
HbA1c, %	7.6 ± 1.5	7.8 ± 1.6
HbA1c, mmol/mol	60.0 ± 16.5	61.5 ± 17.1
eGFR, ml/min/1.73m²	56.1 ± 21.5	58.1 ± 23.5
eGFR category		
< 30	41 (2.1%)	91 (2.6%)
30 - < 45	603 (30.6%)	1020 (28.8%)
45 - < 60	723 (36.7%)	1208 (34.1%)
60 or more	602 (30.6%)	1221 (34.5%)
UACR [IQR]	249.3 [41.5 - 711.6]	333.8 [80.4 - 1013.1]
UACR category		
< 20	330 (16.8%)	447 (12.6%)
20 - < 200	538 (27.3%)	831 (23.5%)
200 or more	1101 (55.9%)	2262 (63.9%)
BB on ECG	235 (11.9%)	331 (9.4%)
LVH on ECG	147 (7.5%)	244 (6.9%)
Q wave on ECG	136 (6.9%)	232 (6.6%)
Insulin use	1116 (56.7%)	2096 (59.2%)
Statin use	1353 (68.7%)	2160 (61.0%)
Betablocker use	1003 (50.9%)	1711 (48.3%)
History of HF	221 (11.2%)	359 (10.1%)
History of CABG	289 (14.7%)	353 (10.0%)
History of PCI	315 (16.0%)	472 (13.3%)
History of MI	320 (16.3%)	523 (14.8%)
History of angina	212 (10.8%)	291 (8.2%)
History of stroke	213 (10.8%)	329 (9.3%)
History of TIA	116 (5.9%)	122 (3.4%)

History of amputation	76 (3.9%)	118 (3.3%)
History of ulcer	62 (3.1%)	114 (3.2%)
History of AF	173 (8.8%)	287 (8.1%)
History of atrial flutter	10 (0.5%)	13 (0.4%)
History of pace	54 (2.7%)	78 (2.2%)
ACEi use	881 (44.8%)	1492 (43.7%)
ARB use	1093 (55.5%)	2052 (59.5%)
Aliskiren use	994 (50.5%)	1752 (49.5%)
T2DM diagnosis time, y		
> 5 y	1654 (84.0%)	2865 (80.9%)
1 - 5 y	260 (13.2%)	541 (15.3%)
< 1 y	55 (2.8%)	134 (3.8%)
NT-proBNP, pg/ml	449.9 ± 1232.7	472.3 ± 1359.4
hs-TnT, ng/L	19.3 ± 19.5	20.4 ± 48.6
Death	207 (10.5%)	262 (7.4%)
CV Composite Outcome	330 (16.8%)	438 (12.4%)

CV: cardiovascular; BMI= body mass index, SBP= systolic blood pressure, DBP= diastolic blood pressure, HDLc= high-density lipoprotein cholesterol, LDLc= low-density lipoprotein cholesterol, HbA1c= glycated haemoglobin, eGFR= estimated glomerular filtration rate, UACR= urine albumin-to-creatinine ratio, IQR= interquartile range; ECG: electrocardiogram; BB = any bundle branch block, LVH= left ventricular hypertrophy, HF= heart failure, CABG= coronary artery bypass grafting, PCI= percutaneous coronary intervention MI= myocardial infarction, TIA= transient ischemic attack, AF= atrial fibrillation, T2D= type 2 diabetes; y= years; ACEi= angiotensin-converting enzyme inhibitors, ARB= angiotensin II receptor blockers, NT-proBNP= N-Terminal pro-B-type natriuretic peptide, hs-TnT= high sensitivity cardiac troponin, CV: cardiovascular.

Table S2. Prediction of Death in Training and Validation Datasets.

	Base Model (M1) (20 variables)					Base Model + NT-proBNP (M2) (21 variables)					NT-proBNP by Itself (M3) (1 variable)				
C-statistics training dataset n= 1969	0.742 (0.708 - 0.776) M1 vs M2, p <0.001					0.778 (0.746 - 0.810) M2 vs M3, p <0.001					0.738 (0.705 - 0.772) M3 vs M1, p= 0.85				
C-statistics validation dataset n= 3540	0.732 (0.702 – 0.762) M1 vs M2, p= 0.001					0.760 (0.732 – 0.789) M2 vs M3, p= 0.073					0.742 (0.712 – 0.772) M3 vs M1, p= 0.54				
Variables	**HR**	**95% CI**		**P**	**X^2**	**HR**	**95% CI**		**P**	**X^2**	**HR**	**95% CI**		**P**	**X^2**
Log-NT-proBNP, per 1 log unit						1.68	1.47	1.93	<0.001	55.06	1.96	1.77	2.17	<0.001	165.63
Log-hs-TnT, per 1 log unit	1.83	1.48	2.26	<0.001	31.47	1.44	1.16	1.80	0,001	10.56					
Age, per 10 years	1.68	1.39	2.02	<0.001	29.16	1.48	1.23	1.79	<0.001	16.56					
History of HF	1.93	1.35	2.75	<0.001	12.96	1.44	1.00	2.07	0.048	3.92					
LVH on ECG	2.01	1.33	3.04	0,001	11.02	1.69	1.12	2.54	0.013	6.15					
History of Stroke	1.58	1.07	2.34	0.021	5.34	1.65	1.12	2.43	0.012	6.35					
BB on ECG	1.46	1.04	2.06	0.031	4.67	1.17	0.82	1.67	0.40	0.72					
Albumin, per 1 mg/dL	0.69	0.46	1.02	0.06	3.46	1.05	0.69	1.59	0.83	0.048					
HbA1c, per 1 %	1.08	0.99	1.19	0.09	2.89	1.09	0.99	1.19	0.09	2.96					
LDLc, per 1 mg/dL	1.00	1.00	1.01	0.10	2.66	1.00	1.00	1.01	0.020	5.43					
Q wave on ECG	1.43	0.91	2.24	0.12	2.37	1.18	0.73	1.88	0.50	0.45					
Log-UACR, per 1 log unit	1.06	0.97	1.16	0.19	1.74	1.05	0.97	1.15	0.25	1.32					
Smoking	1.15	0.93	1.43	0.21	1.61	1.12	0.90	1.39	0.31	1.04					
Heart rate, per 10 bpm	1.07	0.94	1.22	0.29	1.14	1.09	0.96	1.23	0.20	1.66					
Female sex	1.14	0.80	1.63	0.47	0.52	0.93	0.64	1.34	0.68	0.17					
History of CHD	1.11	0.81	1.53	0.52	0.42	0.92	0.67	1.27	0.62	0.24					
SBP, per 10 mm Hg	0.98	0.88	1.08	0.63	0.23	0.95	0.86	1.06	0.37	0.81					
Insulin use	0.96	0.70	1.30	0.78	0.08	1.03	0.75	1.40	0.87	0.03					
History of AF	0.95	0.62	1.45	0.82	0.05	0.76	0.50	1.15	0.19	1.72					
eGFR, per 10 ml/min/1.73 m^2	1.01	0.93	1.10	0.87	0.03	1.05	0.96	1.14	0.30	1.08					
DBP, per 10 mm Hg	1.01	0.85	1.21	0.92	0.01	0.98	0.83	1.17	0.84	0.04					

Log-NT-proBNP= log-transformed N-Terminal pro-B-type natriuretic peptide, Log-hs-TnT= log-transformed high sensitivity cardiac troponin, HF= heart failure, LVH= left ventricular hypertrophy, ECG= electrocardiogram, BB= any bundle branch block, HbA1c= glycated haemoglobin, LDLc= low-density lipoprotein cholesterol, Log-UACR= log-transformed urine albumin-to-creatinine ratio, CHD= coronary heart disease, SBP= systolic blood pressure, AF= atrial fibrillation, eGFR= estimated glomerular filtration rate, LDL= low density lipoprotein, eGFR= estimated glomerular filtration rate, DBP= diastolic blood pressure, X^2= chi square. Hazard ratios were calculated in the training dataset. Comparisons between models were made within datasets.

Table S3. Prediction of Cardiovascular Composite Outcome in Training and Validation Datasets.

	Base Model (M1) (20 variables)					Base Model + NT-proBNP (M2) (21 variables)					NT-proBNP by Itself (M3) (1 variable)				
C-statistics training dataset n= 1969	0.732 (0.706 – 0.758) M1 vs M2, p= 0.001					0.758 (0.733 – 0.784) M2 vs M3, p <0.001					0.717 (0.688 – 0.745) M3 vs M1, p= 0.27				
C-statistics validation dataset N= 3540	0.720 (0.696 – 0.744) M1 vs M2, p <0.001					0.752 (0.729 – 0.775) M2 vs M3, p= 0.001					0.725 (0.701 – 0.750) M3 vs M1, p= 0.70				
Variables	**HR**	**95% CI**		**P**	**X^2**	**HR**	**95% CI**		**P**	**X^2**	**HR**	**95% CI**		**P**	**X^2**
Log NT-proBNP, per 1 log unit						1.58	1.41	1.76	<0.001	66.59	1.88	1.73	2.04	<0.001	224,10
Log hs-TnT, per 1 log unit	1.83	1.55	2.15	<0.001	51.84	1.52	1.28	1.81	<0.001	22.66					
History of HF	2.08	1.56	2.76	<0.001	25.40	1.64	1.24	2.19	0.001	11.63					
Age, per 10 years	1.34	1.15	1.55	<0.001	14.75	1.20	1.04	1.40	0.015	5.95					
History of Stroke	1.63	1.19	2.24	0.002	9.36	1.68	1.23	2.30	0.001	10.63					
Log UACR, per 1 log unit	1.10	1.03	1.18	0.006	7.45	1.09	1.02	1.17	0.015	5.90					
History of AF	1.50	1.09	2.08	0.014	6.05	1.20	0.87	1.66	0.27	1.21					
SBP, per 10 mm Hg	1.10	1.01	1.19	0.020	5.38	1.08	0.99	1.17	0.08	3.06					
LVH on ECG	1.47	1.04	2.08	0.028	4.80	1.24	0.88	1.75	0.22	1.49					
Albumin, per 1 mg/dL	0.71	0.53	0.97	0.030	4.67	1.01	0.73	1.39	0.96	0.00					
LDLc, per 1 mg/dL	1.00	1.00	1.01	0.027	4.88	1.00	1.00	1.01	0.006	7.45					
DBP, per 10 mm Hg	0.86	0.75	0.99	0.035	4.45	0.86	0.74	0.98	0.027	4.93					
History of CHD	1.27	0.98	1.63	0.07	3.35	1.06	0.83	1.36	0.63	0.23					
Female sex	1.29	0.98	1.70	0.07	3.31	1.10	0.83	1.46	0.51	0.44					
BB on ECG	1.26	0.94	1.68	0.12	2.40	1.08	0.81	1.45	0.60	0.28					
HbA1c, per 1 %	1.06	0.98	1.14	0.15	2.10	1.07	0.99	1.15	0.09	2.92					
Heart rate, per 10 bpm	1.06	0.96	1.18	0.22	1.49	1.08	0.97	1.19	0.15	2.04					
Smoking	1.08	0.91	1.28	0.38	0.77	1.06	0.89	1.25	0.54	0.38					
eGFR, per 10 ml/min/1.73 m^2	1.03	0.97	1.10	0.38	0.76	1.07	1.00	1.14	0.048	3.92					
Insulin use	1.06	0.83	1.35	0.65	0.21	1.12	0.88	1.44	0.35	0.86					
Q wave on ECG	1.07	0.71	1.61	0.74	0.12	0.93	0.61	1.40	0.72	0.12					

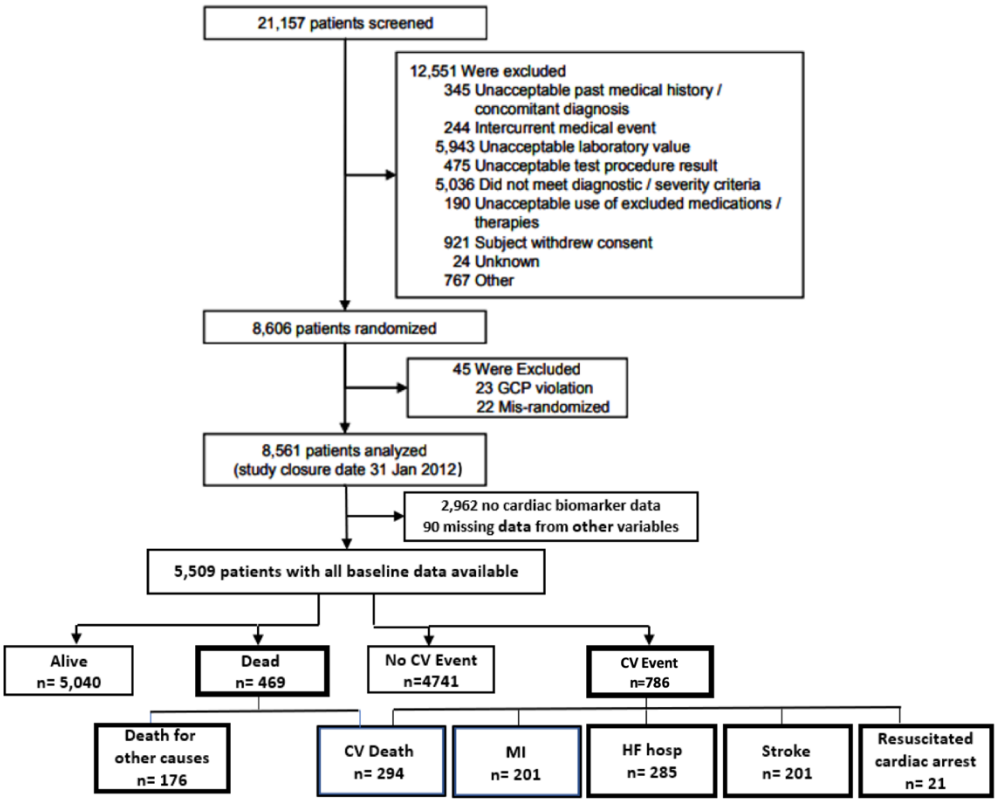
Log-NT-proBNP= log-transformed N-Terminal pro-B-type natriuretic peptide, Log-hs-TnT= log-transformed high sensitivity cardiac troponin, HF= heart failure, Log-UACR= log-transformed urine albumin-to-creatinine ratio, AF= atrial fibrillation, SBP= systolic blood pressure, LVH= left ventricular hypertrophy, ECG= electrocardiogram, LDLc= low-density lipoprotein cholesterol, DBP= diastolic blood pressure, CHD= coronary heart disease, BB= any bundle branch block, HbA1c= glycated haemoglobin, eGFR= estimated glomerular filtration rate, eGFR= estimated glomerular filtration rate, X^2= chi square. Hazard ratios were calculated in the training dataset. Comparisons between models were made within datasets.

Table S4. Other sensitivity analyses, considering BMI and use of Aliskiren.

Death Prediction					Cardiovascular Composite Outcome Prediction			
	Base Model	**NT-proBNP by Itself**	p			**Base Model**	**NT-proBNP by Itself**	p
	C-statistics	C-statistics				C-statistics	C-statistics	
BMI					**BMI**			
< 30 Kg/m²	0.736	0.706	0.89		**< 30 Kg/m²**	0.744	0.727	0.22
>= 30 Kg/m²	0.746	0.748	0.94		**>= 30 Kg/m²**	0.7321	0.719	0.33
Intervention					**Intervention**			
Aliskiren	0.762	0.755	0.64		**Aliskiren**	0.710	0.702	0.58
Placebo	0.741	0.735	0.76		**Placebo**	0.753	0.742	0.77

NT-proBNP: N-terminal pro-B-type natriuretic peptide; BMI: body mass index.

Figure S1. Number of patients who were screened, who underwent randomization, who completed the trail, and who were evaluated in this study.



GCP= good clinical practice, CV= cardiovascular, MI= myocardial infarction, HF hosp= heart failure hospitalization.