ORIGINAL RESEARCH

Role of B-Type Natriuretic Peptide and N-Terminal Prohormone BNP as Predictors of Cardiovascular Morbidity and Mortality in Patients With a Recent Coronary Event and Type 2 Diabetes Mellitus

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***Background*—**Natriuretic peptides are recognized as important predictors of cardiovascular events in patients with heart failure, but less is known about their prognostic importance in patients with acute coronary syndrome. We sought to determine whether B-type natriuretic peptide (BNP) and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) could enhance risk prediction of a broad range of cardiovascular outcomes in patients with acute coronary syndrome and type 2 diabetes mellitus.

***Methods and Results*—**Patients with a recent acute coronary syndrome and type 2 diabetes mellitus were prospectively enrolled in the ELIXA trial (n=5525, follow-up time 26 months). Best risk models were constructed from relevant baseline variables with and without BNP/NT-proBNP. C statistics, Net Reclassification Index, and Integrated Discrimination Index were analyzed to estimate the value of adding BNP or NT-proBNP to best risk models. Overall, BNP and NT-proBNP were the most important predictors of all outcomes examined, irrespective of history of heart failure or any prior cardiovascular disease. BNP significantly improved C statistics when added to risk models for each outcome examined, the strongest increments being in death (0.77–0.82, $P<0.001$), cardiovascular death (0.77–0.83, $P<0.001$), and heart failure (0.84–0.87, $P<0.001$). BNP or NT-proBNP alone predicted death as well as all other variables combined (0.77 versus 0.77).

***Conclusions*—**In patients with a recent acute coronary syndrome and type 2 diabetes mellitus, BNP and NT-proBNP were powerful predictors of cardiovascular outcomes beyond heart failure and death, ie, were also predictive of MI and stroke. Natriuretic peptides added as much predictive information about death as all other conventional variables combined.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01147250. **(*J Am Heart Assoc*. 2017;6: e004743. DOI: 10.1161/JAHA.116.004743.)**

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Patients admitted with an acute coronary syndrome (ACS) are at increased risk of subsequent cardiovascular events, especially those with type 2 diabetes mellitus,[1,2] who constitute ≈30% of all ACS patients.[3] Determining the predictors of death, myocardial infarction (MI), heart failure (HF), and stroke among these patients is important as it

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Accompanying Tables S1 through S13 and Figure S1 are available at http://jaha.ahajournals.org/content/6/6/e004743/DC1/embed/inline-supplementary-material-1.pdf

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assists in identifying the individuals at highest risk of these various outcomes. These individuals should be the focus of the most intensive secondary preventive strategies. In the same way, risk stratification may help motivate both patients and clinicians in secondary preventive efforts. Lastly, predictive models can be used to select the highest risk individuals for trials of new secondary preventive therapies.

B-type natriuretic peptide (BNP) and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels are well established predictors of HF hospitalization and mortality in patients with HF.[4–7] However, as the incidences of outcomes differ between patients with HF[8] and patients with a recent ACS[9] in a stable phase, it is less established how natriuretic peptides are associated with cardiovascular outcomes, especially subsequent MI and stroke, in the latter population.[3,10–14] Concentrations of natriuretic peptides may be affected by both asymptomatic myocardial ischemia[15,16] and atrial fibrillation,[17,18] which could make BNP and NT-proBNP relevant as predictors of MI and stroke. However, trials investigating patients at high risk of atherosclerotic events have found conflicting results regarding both the predictive ability of natriuretic peptides and cardiovascular outcomes—including MI and stroke—as well as the predictive strength of BNP versus NT-proBNP.[19–22]

We wanted to expand knowledge of these natriuretic peptides as predictors of death, cardiovascular death, myocardial infarction, heart failure, and stroke in patients with a recent coronary event and type 2 diabetes mellitus enrolled in the Evaluation of Lixisenatide in Acute Coronary Syndrome trial (ELIXA, NCT01147250). Data from the ELIXA trial allowed us to compare the predictive strength of baseline BNP and NT-proBNP in a high risk ACS patient cohort with type 2 diabetes mellitus. In addition, prospective ascertainment during a reasonable follow-up period, and adjudication of a variety of cardiovascular events, ensured detailed and validated data for analyses.

Methods

The ELIXA trial (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial included 6068 patients with type 2 diabetes mellitus and an acute coronary event within 180 days from randomization (index event).[23] The study was approved by the appropriate national and institutional regulatory and ethics boards, and all subjects gave informed consent. The objective of the ELIXA trial was to assess the safety and efficacy of lixisenatide, a glucagon-like peptide-1 receptor agonist, on cardiovascular morbidity and mortality. Details of the trial design and the demographic and clinical characteristics of the included patients have been reported previously.[24] In summary, patients were included in this randomized, double-blind, placebo-controlled, parallel-group study, between 2010 and 2013, from 49 countries, and followed for a median of 25 months. Key exclusion criteria were percutaneous coronary intervention within 15 days of screening or planned percutaneous coronary intervention within 90 days after screening, coronary artery bypass graft treatment at the index event, an estimated glomerular filtration rate of less than 30 mL/min per 1.73 m^2 of body-surface area, a glycated hemoglobin level of less than 5.5% or more than 11.0%, or an inability to provide written informed consent. Patients were randomized to subcutaneous injections of either lixisenatide (maximum 20 μg daily) or placebo (volume matched) in addition to locally determined standards of care. The ELIXA trial showed that lixisenatide had a neutral effect with regard to the occurrence of the primary outcome (cardiovascular death, MI, stroke, or hospitalization for unstable angina) and HF hospitalization.[23]

Covariates and Outcomes

All data pertaining to baseline variables including demographics, anthropometrics, cardiovascular risk factors, 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 who classified events according to prespecified definitions.[24] Data on adjudicated time-to-event for outcomes of all-cause death (death), cardiovascular death (cardiovascular death), heart failure hospitalization (HF), fatal and nonfatal myocardial infarction (MI), and fatal and nonfatal stroke (stroke) were used for analyses.

BNP and NT-proBNP sampling was carried out at baseline. Samples were collected and analyzed at a core laboratory (Covance Central Laboratory Services, Meyrin, Switzerland). The Triage BNP assay was used to analyze BNP. The intra-assay coefficient of variation was 1.1% to 3.1%. The interassay coefficient of variation was 1.8% to 6.6%. The Immulite NT-proBNP assay was used to analyze NT-proBNP. The intra-assay coefficient of variation was 2.3% to 5.4%. The interassay coefficient of variation was 4.0% to 6.4%. BNP and NT-proBNP samples from 5925 patients (98%) were obtained.

Statistical Analyses

Baseline characteristics shown in Table 1 were selected for best risk models. Patients without data on all these relevant variables, including BNP and NT-proBNP measurements, were excluded (n=543, 9%). The distributions of baseline BNP, NT-proBNP, and C-reactive protein were found to be right-skewed and were therefore log-transformed prior to analysis. Continuous variables were included in the models unless there was clear evidence of nonlinearity.

Table 1. Characteristics of All Included Patients

	No Cardiovascular Events (n=4626)	Cardiovascular Events (n=899)	*P* Value
Randomized to lixisenatide	2327 (50.3%)	449 (49.9%)	0.84
Age, y	59.7±9.5	63.3±9.7	<0.001
Male (%)	3238 (70.0%)	627 (69.7%)	0.88
BMI, kg/m^2	30.0±5.6	30.3±6.1	0.24
Race			<0.001
Asian	648 (14.0%)	82 (9.1%)	
Black	14 (3.1%)	47 (5.2%)	
Other	385 (8.3%)	86 (9.6%)	
White	3451 (74.6%)	684 (76.1%)	
Ethnicity—Hispanic	1396 (30.2%)	250 (27.8%)	0.16
Region			<0.001
Africa/Near East	215 (4.6%)	54 (6.0%)	
Asia Pacific	597 (12.9%)	72 (8.0%)	
Eastern Europe	1172 (25.3%)	241 (26.8%)	
North America	563 (12.2%)	153 (17.0%)	
South and Centr. America	1551 (33.5%)	273 (30.4%)	
Western Europe	528 (11.4%)	106 (11.8%)	
Systolic blood pressure, mm Hg	129±17	131±19	0.86
Diastolic blood pressure, mm Hg	77±10	77±11	0.18
Heart rate, bpm	70±10	71±11	0.001
Current smoker	511 (11.0%)	117 (13.0%)	0.09
Former smoker	2113 (45.7%)	409 (45.5%)	0.92
Medical history			
MI	918 (19.8%)	340 (37.7%)	<0.001
HF	905 (19.5%)	330 (36.7%)	<0.001
Atrial fibrillation/flutter	240 (5.2%)	121 (13.5%)	<0.001
PAD	271 (5.9%)	142 (15.8%)	<0.001
TIA	83 (1.8%)	44 (4.9%)	<0.001
Ventricular tachycardia	57 (1.2%)	17 (1.9%)	0.12
Stroke	201 (4.3%)	91 (10.1%)	<0.001
CABG	309 (6.7%)	151 (16.8%)	<0.001
Implanted pacemaker	102 (2.2%)	41 (4.6%)	<0.001
Carotid disease	87 (1.9%)	52 (5.8%)	<0.001
Hypertension	3449 (74.6%)	761 (84.6%)	<0.001
Index event			<0.001
STEMI	2146 (46.4%)	297 (33.0%)	
NSTEMI	1702 (36.8%)	432 (48.1%)	
Unstable angina pectoris	778 (16.8%)	170 (18.9%)	
PCI at index event	2943 (63.6%)	463 (51.5%)	<0.001
Insulin-treated	1699 (36.7%)	460 (51.2%)	<0.001
Duration of diabetes mellitus, y	8.8±7.9	11.9±9.5	<0.001
Retinopathy	452 (9.8%)	139 (15.5%)	<0.001

Continued

Table 1. Continued

	No Cardiovascular Events (n=4626)	Cardiovascular Events (n=899)	*P* Value
Neuropathy	714 (15.4%)	205 (22.8%)	<0.001
Asthma	114 (2.5%)	40 (4.4%)	<0.001
COPD	173 (3.7%)	76 (8.5%)	<0.001
HbA1c, %	7.6±1.3	7.9±1.3	<0.001
HDL, mg/dL	43±11	43±11	0.65
LDL, mg/dL	77±34	83±39	<0.001
eGFR, mL/min per 1.73 m^2	77.5±21.1	68.1±20.6	<0.001
Albuminuria			<0.001
Normoalbuminuria	3558 (76.9%)	544 (60.5%)	
Microalbuminuria	829 (17.9%)	234 (26.0%)	
Macroalbuminuria	239 (5.2%)	121 (13.5%)	
Hemoglobin, g/dL	13.8±1.4	13.5±1.5	<0.001
Na, mmol/L	140.4±2.9	140.3±3.1	0.75
Albumin, g/dL	4.1±0.3	3.9±0.4	<0.001
CRP, mg/dL	2.0 (1.9–2.0)	2.7 (2.4–2.9)	<0.001
BNP, pg/mL	95 (92–98)	198 (184–213)	<0.001
NT-proBNP, pg/mL	285 (274–295)	703 (644–766)	<0.001

BMI indicates body mass index; bpm, beats per minute; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoproteins; HF, heart failure; LDL, low-density lipoproteins; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIA, transient ischemic attack.

Cox proportional hazard modeling was used to create best risk models without BNP or NT-proBNP using forward selection with a cut-off value of 0.05. Separate base risk models were created for the following outcomes; death, cardiovascular death, fatal or nonfatal MI, fatal or nonfatal HF hospitalization, as well as fatal or nonfatal stroke. The variables selected were ordered according to their χ^2 value and sorted in descending order for each outcome. The predictive ability of base risk models were assessed using Harrell's C statistics. Selected 30-day models were made for comparison with previous studies. Using the selected variables from the base model, comparison between the predictive ability of the base model compared to the base model with $\log_2$BNP/$\log_2$NT-proBNP was assessed for all outcomes. Changes in C statistics, Net Reclassification Index (NRI), and Integrated Discrimination Index (IDI) were estimated to evaluate the incremental value of adding BNP or NT-proBNP to best risk models using a set time of 2 years comparable to the average follow-up time (*somersd* package, STATA 13. *survIDINRI* package, R 2.3.2).

Identification of baseline variables independently associated with BNP/NT-proBNP were obtained using forward selection regression models with $P<0.001$ as a cut-off. The 5 variables with the highest χ^2 value were listed along with the r^2 values.

To identify the most significant predictive threshold of BNP/NT-proBNP values, we divided the continuous BNP/NT-proBNP concentrations into arbitrary threshold concentrations (ie, 35, 100, 125, 200, 300...1000, 2000, 5000). Then using HF hospitalization as an outcome, a fully adjusted Cox model with forward selection identified the BNP threshold concentration that most significantly separated patients into a lower versus a higher risk group. A univariate approach was also carried out using receiver operating characteristic analysis (*SENSPEC* package, STATA 13) with binary outcome of HF hospitalization to determine the optimal cut-off value with respect to Youden index (ie, sensitivity+specificity−1). Interaction analyses between natriuretic peptides and timing of the baseline sample in temporal relation to the index ACS event for outcome of death was also performed, as was interaction between natriuretic peptides and type of ACS index event (ST-elevation MI [STEMI], Non-ST elevation MI [NSTEMI], Unstable Angina Pectoris [UAP]).

To assess whether the relationship between baseline BNP/NT-proBNP and hazard was linear, fully adjusted Cox spline models for each outcome with transformed BNP/NT-proBNP were analyzed. Concentrations below 35 pg/mL (BNP) or 125 pg/mL (NT-proBNP) were considered normal, as these concentrations are commonly referenced as diagnostic

thresholds for excluding HF in patients presenting in a nonacute manner.[25] Hence, the risk of death in patients with these levels were used as references. Both unadjusted and adjusted models were used to confirm findings. Risk modeling, including interaction analyses (history of HF and log_2BNP/log_2NT-proBNP), discriminatory statistics, and Cox spline models were also analyzed in patients stratified according to medical history of HF for BNP.

All BNP/NT-proBNP values were summarized as geometric mean±95% CI. A significance level of 0.05 was considered statistically significant.

Results

Baseline Characteristics

Our study included 5525 patients comprising 91% of the included patients in the ELIXA trial. The median follow-up time was 26 months. In our population, 4626 (84%) patients did not experience any cardiovascular event confirmed by adjudication. Baseline characteristics of patients with or without a cardiovascular event are listed in Table 1 (Baseline characteristics according BNP quartiles and as linear covariates are listed in Tables S1 and S2). Compared with patients not experiencing a cardiovascular event, those that did were in general older and more burdened with comorbidity, and were more likely to have micro- or macroalbuminuria, and a lower estimated glomerular filtration rate. Blood pressure was similar in both groups. Baseline BNP and NT-proBNP were elevated in those subsequently experiencing any cardiovascular event.

Predictive Variables

In separate models, BNP and NT-proBNP were the most significant predictors for each of death from any cause, death from a cardiovascular cause, HF, and stroke among the studied variables. The natriuretic peptides were the second most significant predictors for MI (Tables 2 and 3). Apart from BNP/NT-proBNP, the 14 other variables that conferred the greatest information were the following: Prior MI, body mass index, NSTEMI (index event), heart rate (HR), glycated hemoglobin, percutaneous coronary intervention at the index event (percutaneous coronary intervention), cerebrovascular disease (prior stroke/transient ischemic attack), atrial fibrillation, prior HF, sodium concentration, macroalbuminuria, peripheral artery disease (PAD), age, and LDL concentration. Fifteen and 16 variables were independently associated with concentrations of BNP/NT-proBNP at the α=0.001 level and accounted for 26% and 34% of patient-level variability, respectively. The 5 strongest associated variables are listed in Tables S3 through S5.

Table 2. Predictors of Outcomes Ranked 1 to 5 According to χ^2 Value Using Base Variables and BNP (n=5525)

Outcome	1st	2nd	3rd	4th	5th
Death (397 events)	log_2BNP (χ^2:203, HR 1.67)	AF (χ^2:11, HR 1.60)	NSTEMI (χ^2:11, HR 1.41)	Na* (χ^2:10, HR 1.08)	HR per 10 (χ^2:10, HR 1.17)
Cardiovascular death (286 events)	log_2BNP (χ^2:201, HR 1.82)	HbA1c (χ^2:13, HR 1.18)	AF (χ^2:13, HR 1.79)	NSTEMI (χ^2:9, HR 1.46)	HR per 10 (χ^2:9, HR 1.19)
MI (473 events)	Prior MI (χ^2:46, HR 1.96)	log_2BNP (χ^2:44, HR 1.23)	NSTEMI (χ^2:29, HR 1.66)	Prior stroke (χ^2:13, HR 1.69)	PAD (χ^2:10, HR 1.52)
HF (221 events)	log_2BNP (χ^2:135, HR 1.80)	BMI per 5 (χ^2:34, HR 1.33)	HR per 10 (χ^2:17, HR 1.30)	Prior HF (χ^2:13, HR 1.82)	Prior MI (χ^2:12, HR 1.67)
Stroke (115 events)	log_2BNP (χ^2:23, HR 1.35)	Prior TIA (χ^2:13, HR 3.12)	Macroalbuminuria (χ^2:11, HR 2.35)	Age per 10 (χ^2:9, HR 1.36)	LDL per 10 (χ^2:4, HR 1.06)

Hazard ratios reflect 1 unit changes if nothing else is stated. For log_2BNP that translates into a doubling of the untransformed BNP concentrations. Macroalbuminuria: >300 mg albumin excretion/24 hours. All variables are significant, P<0.05. AF indicates atrial fibrillation/flutter; BNP, B-type natriuretic peptide; HbA1c, glycated hemoglobin; HR, heart rate; LDL, low-density lipoproteins; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction at index event; PAD, peripheral artery disease; TIA, transient ischemic attack.
*1 mmol/L decreases below 140 mmol/L.

Enhanced Prediction With BNP and NT-proBNP

To estimate the predictive strength of BNP alone, C statistics were compared between base models without BNP versus BNP alone. This showed that the discriminatory ability of base models without BNP versus BNP was similar in outcomes of death (Harrell's C statistics: 0.77 both models [0–30 days: 0.82 versus 0.88, P=0.26]) and in cardiovascular death (Harrell's C statistics: 0.77 versus 0.79, P=0.17).

In contrast, BNP was significantly less discriminatory compared with best risk models without BNP for the outcomes of MI (Harrell's C statistics: 0.71 versus 0.62), HF (Harrell's C statistics: 0.84 versus 0.77) and stroke (Harrell's C statistics: 0.75 versus 0.67) (all $P\leq$0.01). Similar estimates and trends were evident for NT-proBNP.

The strength of BNP and NT-proBNP as contributors to risk prediction translated into augmented predictive ability of risk models for all outcomes, as summarized in the increases in C statistics, NRI, and Integrated Discrimination Index (Table 4). Although BNP and NT-proBNP did not increase the C statistics for the risk model for stroke, both peptides improved NRI significantly.

BNP and NT-proBNP were the most predictive variables in risk models of type of cardiovascular death; however, when added to best risk models, BNP and NT-proBNP only significantly improved the predictive ability (Harrel's C statistics) in outcomes of fatal HF and sudden death; fatal HF (n=39) (Base model: 0.850, BNP: +0.085, NT-proBNP: +0.086, both P<0.001), and sudden death (n=116) (Base model: 0.773, BNP: +0.024, NT-proBNP: +0.037, P=0.20 and 0.046, respectively), but not in outcome of fatal MI (n=52) (Base model: 0.827, BNP: +0.025, NT-proBNP: +0.016, P=0.24 and 0.37, respectively).

In univariate analysis, a BNP concentration of 228 pg/mL best separated patients into a lower versus higher group at risk of subsequent HF (sensitivity: 0.62, specificity: 0.77, Youden index: 0.39), with a corresponding threshold for NT-proBNP of 751 pg/mL (sensitivity: 0.67, specificity: 0.74, Youden index: 0.41). In adjusted Cox models, a BNP concentration of 500 pg/mL provided the most significant threshold by which to further identify patients at lower versus higher risk of subsequent HF (HR 3.0 [2.1–4.1], P<0.0001), with a corresponding threshold for NT-proBNP of 700 pg/mL (HR 2.5 [1.7–3.5], P<0.0001).

Predictive Strength of BNP Compared to NT-proBNP

There was no significant increase in C statistics when BNP was included in the best risk models compared to NT-proBNP in outcomes of death +0.002 (P=0.55), cardiovascular death +0.0002 (P=0.97), MI +0.002 (P=0.50), HF +0.0001 (P=0.98),

Table 3. Predictors of Outcomes Ranked 1 to 5 According to χ^2 Value Using Base Variables and NT-proBNP (n=5525)

Outcome	1st	2nd	3rd	4th	5th
Death (397 events)	log_2NT-proBNP (χ^2:215, HR 1.52)	NSTEMI (χ^2:10, HR 1.40)	PCI (χ^2:10, HR 0.71)	DBP* (χ^2:8, HR 1.02)	Na† (χ^2:8, HR 1.04)
Cardiovascular death (286 events)	log_2NT-proBNP (χ^2:226, HR 1.65)	HbA1c (χ^2:14, HR 1.20)	NSTEMI (χ^2:10, HR 1.47)	AF (χ^2:9, HR 1.62)	Prior HF (χ^2:8, HR 1.44)
MI (473 events)	Prior MI (χ^2:49, HR 2.00)	log_2NT-proBNP (χ^2:37, HR 1.17)	NSTEMI (χ^2:29, HR 1.66)	Prior stroke (χ^2:13, HR 1.71)	PAD (χ^2:9, HR 1.48)
HF (221 events)	log_2NT-proBNP (χ^2:132, HR 1.61)	BMI per 5 (χ^2:31, HR 1.31)	NSTEMI (χ^2:14, HR 1.90)	Prior HF (χ^2:14, HR 1.73)	Prior MI (χ^2:12, HR 1.69)
Stroke (115 events)	log_2NT-proBNP (χ^2:19, HR 1.25)	Prior TIA (χ^2:13, HR 3.09)	Macroalbuminuria (χ^2:10, HR 2.34)	Age per 10 (χ^2:7, HR 1.32)	LDL per 10 (χ^2:4, HR 1.05)

Hazard ratios reflect 1 unit changes if nothing else is stated. For log_2NT-proBNP that translates into a doubling of the untransformed NT-proBNP concentrations. Macroalbuminuria: >300 mg albumin excretion/24 hours. All variables are significant, P<0.05. AF indicates atrial fibrillation/flutter; BMI, body mass index; HbA1c, glycated hemoglobin; HF, heart failure; HR, heart rate; LDL, low-density lipoproteins; MI, myocardial infarction; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; NSTEMI, non-ST elevation myocardial infarction at index event; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

*1 mm Hg decreases below 70 mm Hg.

†1 mmol/L decreases below 140 mmol/L.

Table 4. Discriminatory Changes in Best Risk Models With and Without BNP and NT-proBNP

	C Statistics in Each Model (n=5525)			
	Base Model	BNP/NT-proBNP in Model	NRI	IDI
Death (397 events)				
BNP	0.77 (74–0.79)	0.82 (0.80–0.84)*	30.6% (25.2–36.8)*	5.0% (3.5–7.2)*
NT-proBNP		0.81 (0.79–0.83)*	24.3% (17.4–29.3)*	3.3% (2.1–5.0)*
Cardiovascular death (286 events)				
BNP	0.77 (0.74–0.80)	0.83 (0.81–0.86)*	36.0% (27.4–41.4)*	5.6% (3.4–8.6)*
NT-proBNP		0.83 (0.80–0.86)*	30.9% (21.7–36.9)*	4.0% (2.4–6.3)*
MI (473 events)				
BNP	0.71 (0.68–0.73)	0.72 (0.70–0.75)*	14.3% (9.3–19.5)*	1.2% (0.6–2.1)*
NT-proBNP		0.72 (0.67–0.74)*	10.6% (5.7–16.6)*	0.8% (0.3–1.6)*
HF (221 events)				
BNP	0.84 (0.81–0.86)	0.87 (0.85–0.89)*	35.4% (24.7–40.6)*	5.0% (3.0–7.6)*
NT-proBNP		0.87 (0.84–0.89)*	29.9% (21.8–36.6)*	3.8% (2.2–5.8)*
Stroke (115 events)				
BNP	0.74 (0.70–0.79)	0.76 (0.72–0.80)	19.3% (8.8–29.9)*	0.4% (0–1.2)
NT-proBNP		0.76 (0.72–0.80)	17.2% (6.3–28.1)*	0.2% (0–0.8)

NRI and IDI summarized as mean percent improvement ±95% CI. BNP indicates B-type natriuretic peptide; HF, heart failure; IDI, Integrated Discrimination Index; MI, myocardial infarction; NRI, Net Reclassification Index; NT-proBNP, N-terminal prohormone B-type natriuretic peptide.
*$P<0.05$, comparison between base model and BNP/NT-proBNP model.

stroke +0.002 ($P=0.88$). The comparable estimates were confounded by a significant correlation between BNP and NT-proBNP (Spearman's rho 0.86, $P<0.0001$).

Subgroup and Sensitivity Analyses

In our population, 22% had a history of HF. As sensitivity analysis, patients were stratified according to history of HF at baseline to provide ranking and estimates of important risk factors, although there was no significant interaction with natriuretic peptides and history of HF (death; BNP, $P=0.57$. NT-proBNP, $P=0.21$, Figure S1). BNP was the strongest prognostic variable for all outcomes examined in both groups (±prior HF; Tables S6 through S8). Sensitivity analysis was also done in the subset of patients (52%) without any prior cardiovascular disease at baseline (HF, atrial fibrillation, peripheral artery disease, transient ischemic attack/stroke, ventricular tachycardia, coronary artery bypass graft or MI apart from index event). The same trends were also evident in this subset (Tables S9 and S10).

Analysis in the subset of patients that had information on left ventricular ejection fraction present at their index ACS was performed (n=3390). Left ventricular ejection fraction was not among the 3 most significant predictors across all outcomes when added to the variable list. The predictive ability of BNP and NT-proBNP was comparable in this subset compared to the entire cohort (Tables S11 through S13).

The timing of the sampling in relation to the index ACS event did not affect the risk estimates for death for BNP ($P=0.63$) or NT-proBNP ($P=0.46$), nor did the type of ACS (BNP, $P=0.30$; NT-proBNP, $P=0.32$).

There was no significant interaction between sex and concentrations of BNP ($P=0.17$) or NT-proBNP ($P=0.58$) when tested in a fully adjusted model.

Discussion

Our goal was to examine the strength of BNP and NT-proBNP in predicting a range of cardiovascular outcomes in high risk ACS patients with type 2 diabetes mellitus. We found that baseline levels of these natriuretic peptides were elevated in patients with a subsequent cardiovascular event during follow-up compared with those not having an event. The levels of natriuretic peptides most likely reflect that all patients recently suffered a coronary event and on average had a high comorbid burden.

The significance of elevated natriuretic peptides was reiterated when BNP and NT-proBNP were added to risk models of major cardiovascular outcomes. Ranked according to the strength of prediction, BNP and NT-proBNP were the primary predictive variables in all outcomes examined, except

MI, where they were the second most predictive variable. The predictive strength of BNP and NT-proBNP was also evident when viewing the χ^2 values, which were magnitudes higher than other significant variables in death, cardiovascular death and HF, moderately higher in stroke, and comparable to having had a prior MI in outcome of MI. This was also mirrored in the ability of BNP and NT-proBNP to predict causes of death, where a significant predictive contribution of BNP and NT-proBNP was present when added to risk models in outcome of sudden death and HF death, whereas none was found for fatal MI. The cut-off point that most significantly divided patients into a higher versus lower risk group of subsequent HF hospitalization was 500 and 700 pg/mL for BNP and NT-proBNP, in multivariate analysis.

Natriuretic peptides are primarily recognized as predictors of mortality and HF hospitalization, whereas our finding of a strong predictive ability of natriuretic peptide levels in outcomes of MI and stroke is less validated, especially in ACS patients. This ability could be attributed to higher levels of natriuretic peptides in patients with asymptomatic myocardial ischemia[15,16] and paroxysmal atrial fibrillation,[17,18] which could predispose to both MI and stroke.

Our risk models also identified other important predictors apart from BNP and NT-proBNP. Risk models in other diabetic populations (TREAT [Trial to Reduce Cardiovascular Events with Aranesp (darbepoetin-alfa) Therapy]),[26] UKPDS [UK Prospective Diabetes Study][27]) have yielded results that also highlight the importance of the risk factors we identified, such as prior HF, glycated hemoglobin, age, heart rate, albuminuria, and cardiac arrhythmias.[28,29] Important differences were that these studies either used composite end points[28] or only single outcomes[29] when examining predictors. Furthermore, the diabetic patients on which these risk models were based were either at higher risk (TREAT: 81.1 deaths per 1000 PY) or lower risk of death (UKPDS: 18.9 deaths per 1000 PY) than in the present study (32.3 deaths per 1000 PY). Nonetheless, traditional cardiovascular risk factors combined with markers of chronic dysglycemia seem to persist as predictors of adverse cardiovascular events despite the differences in the diabetic populations studied.

When BNP or NT-proBNP was used to predict death or cardiovascular death alone compared to using all variables available excluding these natriuretic peptides, estimates of C statistics were comparable, but the stand-alone natriuretic peptide receiver operating characteristic area under the curve values exceeded those reported earlier in patients with HF or coronary artery disease.[19,30] Thus, a single measurement of BNP or NT-proBNP contains the same predictive information about risk of death as all other variables listed in Table 1. Of note, the reverse was seen in cardiovascular morbidity

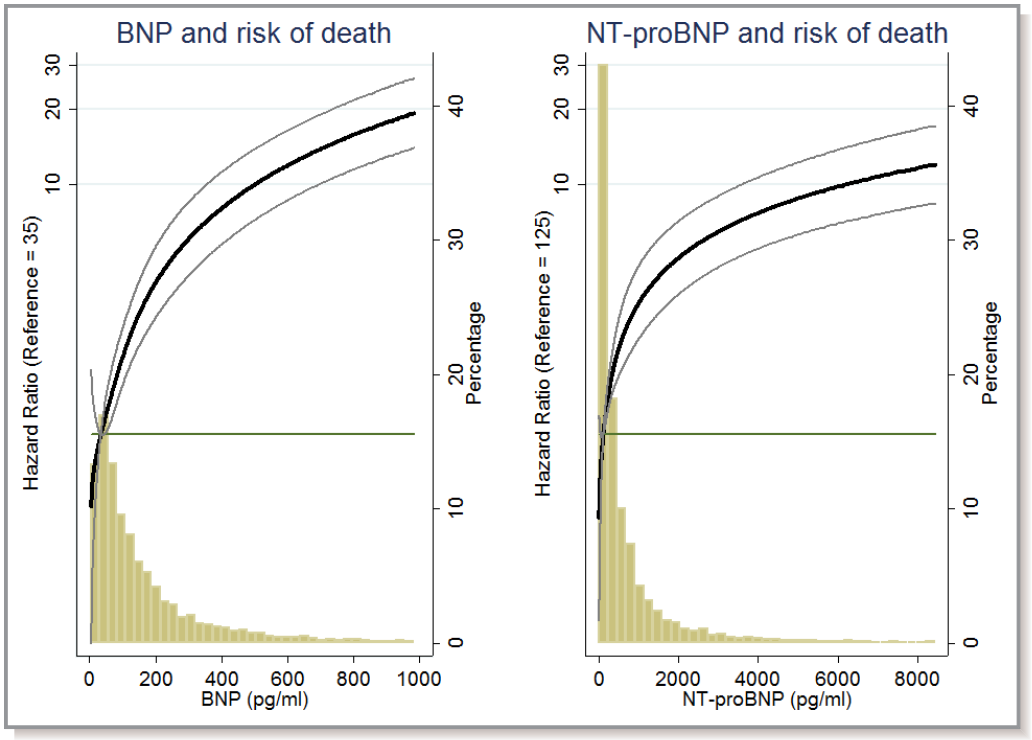

Figure. The association of BNP and NT-proBNP concentrations and risk of all-cause death. The hazard of death is depicted with 95% CIs. The reference of hazard ratio=1.0 corresponds to a BNP concentration of 35 pg/mL, and a NT-proBNP concentration of 125 pg/mL. BNP indicates B-type natriuretic peptide; NT-proBNP, N-terminal prohormone BNP.

(MI, HF, stroke) where best risk models outperformed a single BNP or NT-proBNP measurement. As visually depicted in the figure, differences in natriuretic peptides conferred ≈20-fold changes in risk of death. This large risk gradient enables easier identification of patients at higher versus lower risk and reinforces the prognostic information contained in BNP and NT-proBNP levels.

The addition of either natriuretic peptide to best risk models improved the discriminatory ability significantly. This was evident in the changes in C statistics, NRI, and Integrated Discrimination Index. C statistics increased 0.01 to 0.06 depending on outcome, which was reflected in NRI increases of 10.6% to 35.4%. These changes make both BNP and NT-proBNP valuable prognostic determinants that should be considered in future risk determination in a comparable population. Furthermore, history of HF did not influence the predictive ability of BNP or NT-proBNP across all outcomes, including MI and stroke.

Having diabetes mellitus seems to influence levels of natriuretic peptides in both the absence and presence of cardiovascular disease,[31,32] which potentially could change the relationship between levels of natriuretic peptides and risk of cardiovascular events. Whether natriuretic peptides predict outcomes differently in ACS patients with type 2 diabetes mellitus compared to similar patients without diabetes mellitus is not known. The stand-alone discriminatory strength of BNP and NT-proBNP in cardiovascular death was somewhat lower (receiver operating characteristic area under the curve: BNP 0.58; NT-proBNP 0.68) in patients with coronary artery disease from the Prevention of Events With Angiotensin Converting Enzyme (PEACE) trial (≈16% patients had diabetes mellitus). In comparison, when BNP was sampled 2 to 4 days after the infarct in STEMI patients included in the Enoxaparin Tenecteplase-Tissue-Type Plasminogen Activator With or Without Glycoprotein IIb/IIIa Inhibitor as Reperfusion Strategy in ST-Segment Elevation Myocardial Infarction-Thrombolysis In Myocardial Infarction-23 (ENTIRE-TIMI-23) trial (≈13% patients had diabetes mellitus), the receiver operating characteristic area under the curve for death after 30 days was 0.81,[11] which is comparable to our results (area under the curve$_{30\ days}$: 0.88). This could suggest that the severity of the coronary pathology influences the predictive strength of natriuretic peptides and/or the timing of the sample used for risk determination is important, as shown by Lindahl et al.[33] Earlier studies have shown that levels of natriuretic peptides are dynamic in the subacute phase following an MI,[34] and smaller studies suggest that patients are at higher risk of death and left ventricular remodeling if natriuretic peptides continue to be elevated after the MI, compared with those with decreasing levels.[35,36] In our study, patients were randomized within 180 days from their ACS. The timing of the baseline sample in relation to their index ACS did not affect the risk estimates of BNP or NT-proBNP, nor did the type of index event (STEMI, NSTEMI, or UAP). This suggests that the predictive value of natriuretic peptides is retained from shortly after the event until at least 6 months after the ACS in patients with type 2 diabetes mellitus, irrespective of coronary pathology.

As the availability of BNP and NT-proBNP analyses differs between institutions and regions, we also assessed the predictive value of BNP compared to NT-proBNP. In the PEACE trial, BNP was only a predictor of HF, while NT-proBNP was a predictor of cardiovascular death, HF, and stroke in coronary artery disease patients.[19] Neither biomarker predicted MI. In the Valsartan Heart Failure Trial (Val-Heft), NT-proBNP proved superior to BNP in predicting a composite of morbidity and mortality and HF hospitalization in chronic HF patients; however, the incremental discriminatory value of NT-proBNP versus BNP was small.[30] In our study of ACS patients with type 2 diabetes mellitus, both natriuretic peptides had comparable predictive strength in all outcomes studied (death, cardiovascular death, MI, HF, and stroke), albeit NRI and Integrated Discrimination Index values increased slightly more with BNP across all outcomes.

Our results expand knowledge of earlier findings of enhanced risk prediction using natriuretic peptides in patients with a recent ACS[3,10–12] to also include patients with a recent ACS and type 2 diabetes mellitus. This prevalent population has only marginally been studied in this context.[37–40] The use of BNP or NT-proBNP for risk prediction in all ACS patients, irrespective of diabetes mellitus status, is now further substantiated. Whether drugs that directly influence natriuretic peptide concentrations (eg, sacubitril[41]) can modify the incidence of the cardiovascular outcomes examined in this study remains speculative.

Limitations

To learn more about how diabetes mellitus per se affects the predictive ability of natriuretic peptides, a similar study design with ACS patients with and without type 2 diabetes mellitus would have been optimal. Furthermore, our average follow-up time of ≈2 years precludes any estimates on the long-term predictive ability of BNP and NT-proBNP. Data on the severity of the index ACS were not obtained (eg, troponin), which as a marker of myocardial damage could have attenuated the prognostic ability of BNP/NT-proBNP. Extrapolating from the present study to other ACS patients with type 2 diabetes mellitus should be done cautiously, as inclusion criteria may have led to selection bias compared to patients not included in this trial. Importantly, patients with estimated glomerular filtration rate <30 mL/min per 1.73 m^2 were excluded from this study, and renal function is shown to affect levels of natriuretic peptides.[42]

Conclusion

In a population of patients with a recent ACS and type 2 diabetes mellitus, BNP and NT-proBNP are important and comparable predictors of death, cardiovascular death, MI, HF, as well as stroke. Both natriuretic peptides improve the discriminatory ability significantly when added to best risk models with known predictors of adverse cardiovascular outcomes, irrespective of prior history of HF or prior cardiovascular disease.

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Supplemental material

Table S1. Characteristics of all included patients grouped according to quartiles of BNP

	BNP (5-49 pg/ml) n=1381	BNP (50-105 pg/ml) n=1383	BNP (106-218 pg/ml) n=1378	BNP (218-4231 pg/ml) n=1383	P value
randomized to lixisenatide	666 (48.2%)	745 (53.9%)	696 (50.5%)	669 (48.4%)	0.009
age (yrs)	56.7 ± 9.3	59.5 ± 9.1	61.3 ± 9.2	63.5 ± 9.7	<0.001
male (%)	1019 (73.8%)	968 (70.0%)	982 (71.3%)	896 (64.8%)	<0.001
BMI (kg/m2)	30.8 ± 5.7	30.3 ± 5.8	29.9 ± 5.6	29.3 ± 5.6	<0.001
Race					0.020
Asian	204 (14.8%)	186 (13.4%)	183 (13.3%)	157 (11.4%)	
Black	57 (4.1%)	44 (3.2%)	33 (2.4%)	55 (4.0%)	
Other	102 (7.4%)	115 (8.3%)	117 (8.5%)	137 (9.9%)	
White	1018 (73.7%)	1038 (75.1%)	1045 (75.8%)	1034 (74.8%)	
ethnicity – hispanic	375 (27.2%)	407 (29.4%)	413 (30.0%)	451 (32.6%)	0.019
Region					<0.001
Africa/Near East	86 (6.2%)	71 (5.1%)	58 (4.2%)	54 (3.9%)	
Asia Pacific	184 (13.3%)	175 (12.7%)	172 (12.5%)	138 (10.0%)	
Eastern Europe	290 (21.0%)	332 (24.0%)	377 (27.4%)	414 (29.9%)	
North America	219 (15.9%)	181 (13.1%)	181 (13.1%)	135 (9.8%)	
South and Centr. America	421 (30.5%)	438 (31.7%)	449 (32.6%)	516 (37.3%)	
Western Europe	181 (13.1%)	186 (13.4%)	141 (10.2%)	126 (9.1%)	
Systolic blood pressure (mmHg)	128.4 ± 15.1	129.9 ± 17.0	130.0 ± 17.8	129.9 ± 19.3	0.035
Diastolic blood pressure (mmHg)	78.0 ± 9.2	77.0 ± 9.6	77.2 ± 10.5	76.5 ± 10.8	0.003
heart rate (bpm)	70.5 ± 9.9	69.0 ± 10.3	69.5 ± 10.5	71.3 ± 10.9	<0.001
current smoker	194 (14.0%)	174 (12.6%)	134 (9.7%)	125 (9.0%)	<0.001
former smoker	656 (47.5%)	614 (44.4%)	640 (46.4%)	612 (44.3%)	0.24
Medical history					
MI	252 (18.2%)	299 (21.6%)	314 (22.8%)	393 (28.4%)	<0.001
HF	172 (12.5%)	245 (17.7%)	304 (22.1%)	514 (37.2%)	<0.001
atrial fibrillation/flutter	30 (2.2%)	63 (4.6%)	96 (7.0%)	172 (12.4%)	<0.001
PAD	65 (4.7%)	86 (6.2%)	111 (8.1%)	151 (10.9%)	<0.001
TIA	29 (2.1%)	33 (2.4%)	23 (1.7%)	42 (3.0%)	0.11
ventricular tachycardia	13 (0.9%)	14 (1.0%)	21 (1.5%)	26 (1.9%)	0.10
stroke	45 (3.3%)	68 (4.9%)	67 (4.9%)	112 (8.1%)	<0.001
CABG	51 (3.7%)	101 (7.3%)	157 (11.4%)	151 (10.9%)	<0.001
implanted pacemaker	17 (1.2%)	23 (1.7%)	43 (3.1%)	60 (4.3%)	<0.001
carotid disease	28 (2.0%)	28 (2.0%)	39 (2.8%)	44 (3.2%)	0.12
hypertension	1001 (72.5%)	1068 (77.2%)	1062 (77.1%)	1079 (78.0%)	0.002
Index event					<0.001
STEMI	458 (33.2%)	591 (42.7%)	684 (49.6%)	710 (51.3%)	
NSTEMI	591 (42.8%)	559 (40.4%)	505 (36.6%)	479 (34.6%)	
UAP	332 (24.0%)	233 (16.8%)	189 (13.7%)	194 (14.0%)	
PCI treatment at index ACS	903 (65.4%)	906 (65.5%)	870 (63.1%)	727 (52.6%)	<0.001
insulin-treated	463 (33.5%)	539 (39.0%)	555 (40.3%)	602 (43.5%)	<0.001
duration of diabetes (yrs)	7.8 ± 7.2	9.2 ± 8.2	9.4 ± 8.3	10.7 ± 9.0	<0.001
retinopathy	122 (8.8%)	134 (9.7%)	141 (10.2%)	194 (14.0%)	<0.001
neuropathy	215 (15.6%)	224 (16.2%)	209 (15.2%)	271 (19.6%)	0.007
asthma	33 (2.4%)	53 (3.8%)	36 (2.6%)	32 (2.3%)	0.05
COPD	42 (3.0%)	59 (4.3%)	79 (5.7%)	69 (5.0%)	0.005
HbA1c (%)	7.7 ± 1.3	7.7 ± 1.3	7.7 ± 1.3	7.7 ± 1.2	0.64
HDL(mg/dl)	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.58
LDL (mg/dl)	2.1 ± 0.9	2.0 ± 1.0	2.0 ± 0.9	2.0 ± 0.9	0.17
eGFR (ml/min/1.73m^2)	82.6 ± 20.4	78.6 ± 20.8	74.4 ± 21.0	68.1 ± 20.2	<0.001
Albuminuria					<0.001
normoalbuminuria	1134 (82.1%)	1074 (77.7%)	1019 (73.9%)	875 (63.3%)	
microalbuminura	200 (14.5%)	249 (18.0%)	269 (19.5%)	345 (24.9%)	
macroalbuminuria	47 (3.4%)	60 (4.3%)	90 (6.5%)	163 (11.8%)	
Hemoglobin (g/dL)	14.1 ± 1.4	13.9 ± 1.3	13.8 ± 1.4	13.3 ± 1.5	<0.001
Na (mmol/l)	140.2 ± 2.7	140.3 ± 2.8	140.5 ± 3.0	140.5 ± 3.2	0.033
albumin (g/dl)	41.6 ± 3.2	40.9 ± 3.1	40.4 ± 3.5	39.3 ± 4.0	<0.001
CRP (mg/dl)	1.9 (1.8-2.0)	1.9 (1.8-2.0)	2.1 (2.0-2.3)	2.4 (2.3-2.6)	<0.001
BNP (pg/ml)	28 (27-28)	73 (72-74)	150 (148-152)	431 (419-443)	
NT-proBNP (pg/ml)	78 (74-81)	208 (200-215)	470 (453-487)	1541 (1468-1618)	

Table S2. Linear regression of BNP and NT-proBNP with all variables listed in the model

	BNP	P value	NT-proBNP	P value
randomized to lixisenatide	0.0 (-14.0, 14.0)	0.996	16.2 (-66.4, 98.8)	0.701
age (yrs)	1.9 (1.0, 2.9)	<0.001	7.2 (1.6, 12.8)	0.012
male (%)	15.0 (-3.6, 33.6)	0.113	8.2 (-101.4, 117.9)	0.883
BMI (kg/m2)	-7.0 (-8.4, -5.6)	<0.001	-46.8 (-55.2, -38.4)	<0.001
Race				
Black vs. white	19.4 (-20.4, 59.2)	0.340	27.7 (-207.3, 262.8)	0.817
Asian vs. white	-37.9 (-64.6, -11.2)	0.005	-225.1 (-382.7, -67.4)	0.005
other vs. white	-1.0 (-27.3, 25.4)	0.943	127.4 (-28.3, 283.2)	0.109
ethnicity – hispanic	19.8 (0.7, 38.9)	0.042	169.9 (57.0, 282.8)	0.003
Systolic blood pressure (mmHg)	-1.0 (-1.6, -0.5)	<0.001	-5.3 (-8.6, -2.0)	0.002
Diastolic blood pressure (mmHg)	1.3 (0.4, 2.2)	0.007	6.6 (1.1, 12.2)	0.019
heart rate (bpm)	2.1 (1.4, 2.8)	<0.001	13.8 (9.7, 18.0)	<0.001
current smoker	-5.0 (-29.9, 19.8)	0.692	-78.0 (-224.8, 68.8)	0.298
former smoker	3.0 (-13.0, 18.9)	0.717	-31.9 (-126.2, 62.5)	0.508
Medical history				
MI	28.5 (10.4, 46.5)	0.002	35.3 (-71.3, 141.9)	0.516
HF	114.2 (95.7, 132.7)	<0.001	648.8 (539.4, 758.2)	<0.001
atrial fibrillation/flutter	34.2 (4.4., 64.0)	0.024	232.8 (57.0, 408.7)	0.009
PAD	27.7 (-0.5, 56.0)	0.054	290.0 (123.2, 456.7)	0.001
TIA	2.5(-44.8, 49.9)	0.916	-48.3 (-327.7, 231.2)	0.735
ventricular tachycardia	82.3 (20.9, 143.6)	0.009	182.8 (-179.4, 545.0)	0.323
stroke	42.7 (10.6, 74.7)	0.009	105.2 (-84.0, 294.4)	0.276
CABG	-5.0 (-32.3, 22.4)	0.722	-166.9 (-328.3, -5.5)	0.043
implanted pacemaker	6.5 (-39.1, 52.1)	0.781	-20.6 (-289.9, 248.8)	0.881
carotid disease	-28.1 (-74.8, 18.6)	0.239	-120.8 (-396.6, 154.9)	0.390
hypertension	-20.6 (-38.8, -2.3)	0.027	-95.5 (-203.4, 12.4)	0.083
Index event				
STEMI	103.0 (81.2, 124.8)	<0.001	579.6 (451.0, 708.3)	<0.001
NSTEMI	50.0 (28.8, 71.2)	<0.001	294.5 (169.3, 419.6)	<0.001
PCI treatment at index ACS	-41.0 (-56.7, -25.3)	<0.001	-179.6 (-272.2, -86.9)	<0.001
insulin-treated	-12.7 (-29.1, 3.7)	0.130	-17.6 (-114.5, 79.3)	0.722
duration of diabetes (yrs)	-0.1 (-1.1, 1.0)	0.900	-4.6 (-10.7, 1.5)	0.137
Retinopathy	-12.1 (-37.1, 12.9)	0.343	-68.3 (-215.9, 79.2)	0.364
neuropathy	-19.3 (-40.0, 1.4)	0.068	-12.6 (-135.0, 109.8)	0.840
asthma	0.8 (-42.7, 44.4)	0.970	-46.0 (-303.1, 211.1)	0.726
COPD	-2.1 (-32.2, 32.9)	0.905	-67.4 (-274.5, 139.7)	0.523
HbA1c (%)	-3.6 (-9.7, 2.6)	0.254	-51.8 (-88.1, -15.5)	0.005
HDL(mg/dl)	-10.5 (-37.7, 16.7)	0.449	-91.0 (-251.5, 69.5)	0.267
LDL (mg/dl)	1.4 (7.0, 9.7)	0.750	2.0 (-47.3, 51.2)	0.938
eGFR (ml/min/1.73m^2)	-1.8 (-2.1, -1.4)	<0.001	-14.4 (-16.7, -12.2)	<0.001
micro vs. Normoalbuminuria	67.3 (48.7, 85.9)	<0.001	443.7 (334, 553.4)	<0.001
macro vs. Normoalbuminuria	89.6 (57.6, 121.6)	<0.001	661.0 (472.2, 849.9)	<0.001
Hemoglobin (g/dL)	-21.4 (-27.4, -15.4)	<0.001	-98.3 (-133.6, -63.1)	<0.001
Na (mmol/l)	2.4 (-0.2, 4.9)	0.072	-5.1 (-20.3, 10.0)	0.506
albumin (g/dl)	-13.8 (-16.1, -11.5)	<0.001	-85.4 (-99.1, -71.8)	<0.001

Table S3. Variables independently associated with BNP/NT-proBNP concentrations, and corresponding r^2 values for regression models with the 5 listed variables

	1st	**2nd**	**3rd**	**4th**	**5th**
log_2BNP	**Albumin**	**Age (per 10 years)**	**Prior HF**	**STEMI**	**BMI (per 5 kg/m^2)**
(r^2=0.20)	(χ^2:318, coeff:- 0.09)	(χ^2:316, coeff: -0.35)	(χ^2: 312, coeff: 0.78)	(χ^2:227, coeff: 0.57)	(χ^2:80, coeff: -0.15)
log_2NT-proBNP	**eGFR**	**Albumin**	**STEMI**	**BMI (per 5 kg/m^2)**	**prior HF**
(r^2=0.28)	(χ^2:672, coeff: 0.27)	(χ^2:527, coeff: -0.14)	(χ^2: 381, coeff: 0.87)	(χ^2:305, coeff: -0.34)	(χ^2:262, coeff: 0.86)

Table S4. Unadjusted estimates of predictors of outcomes found significant in multivariate models using base variables and BNP (n=5525)

Outcome	1st	2nd	3rd	4th	5th
Death (397 events)	**log_2BNP** HR 1.90 (1.78-2.03)	**AF** HR 2.90 (2.22-3.79)	**NSTEMI** HR 1.53 (1.26-1.86)	**Na*** HR 1.10 (1.05-1.16)	**HR per 10** HR 1.21 (1.11-1.34)
CV death (286 events)	**log_2BNP** HR 2.01 (1.87-2.17)	**HbA1c** HR 1.23 (1.13-1.34)	**AF** HR 3.14 (2.31-4.25)	**NSTEMI** HR 1.61 (1.28-2.04)	**HR per 10** HR 1.25 (1.12-1.40)
MI (473 events)	**prior MI** HR 2.63 (2.19-3.16)	**log_2BNP** HR 1.33 (1.25-1.41)	**NSTEMI** HR 1.90 (1.59-2.28)	**prior stroke** HR 2.50 (1.89-3.33)	**PAD** HR 2.52 (1.94-3.29)
HF (221 events)	**log_2BNP** HR 1.96 (1.80-2.14)	**BMI per 5** HR 1.31 (1.19-1.43)	**HR per 10** HR 1.34 (1.18-1.51)	**prior HF** HR 4.16 (3.19-5.42)	**prior MI** HR 3.09 (2.37-4.03)
Stroke (115 events)	**log_2BNP** HR 1.49 (1.33-1.68)	**prior TIA** HR 4.90 (2.69-8.91)	**macroalbuminuria** HR 3.05 (1.86-4.99)	**Age per 10** HR 1.61 (1.32-1.95)	**LDL per 10** HR 1.07 (1.02-1.12)

Table S5. Unadjusted estimated of predictors of outcomes found significant in multivariate models using base variables and NT-proBNP (n=5525)

Outcome	1st	2nd	3rd	4th	5th
Death (397 events)	**log_2NT-proBNP** HR 1.64 (1.56-1.73)	**NSTEMI** HR 1.53 (1.26-1.86)	**PCI** HR 0.52 (0.42-0.63)	**DBP#** HR 1.04 (1.02-1.06)	**Na*** HR 1.10 (1.05-1.16)
CV death (286 events)	**log_2NT-proBNP** HR 1.72 (1.62-1.83)	**HbA1c** HR 1.23 (1.13-1.34)	**NSTEMI** HR 1.61 (1.28-2.04)	**AF** HR 3.14 (2.31-4.25)	**prior HF** HR 2.87 (2.27-3.62)
MI (473 events)	**prior MI** HR 2.63 (2.19-3.16)	**log_2NT-proBNP** HR 1.23 (1.18-1.29)	**NSTEMI** HR 1.90 (1.59-2.28)	**prior stroke** HR 2.50 (1.89-3.33)	**PAD** HR 2.52 (1.94-3.29)
HF (221 events)	**log_2NT-proBNP** HR 1.68 (1.57-1.80)	**BMI per 5** HR 1.31 (1.19-1.43)	**NSTEMI** HR 1.91 (1.47-2.49)	**prior HF** HR 4.16 (3.19-5.42)	**prior MI** HR 3.09 (2.37-4.03)
Stroke (115 events)	**log_2NT-proBNP** HR 1.34 (1.22-1.48)	**prior TIA** HR 4.90 (2.69-8.91)	**macroalbuminuria** HR 3.05 (1.86-4.99)	**Age per 10** HR 1.61 (1.32-1.95)	**LDL per 10** HR 1.07 (1.02-1.12)

Table S6. Predictors of outcomes ranked according to χ^2 value using base variables and BNP and stratified according to history of heart failure (No prior HF, n=4290; Prior HF, n=1235)

Outcome		1st	2nd	3rd
Death (397 events)	**No prior HF**	**log_2BNP** (χ^2:108, HR 1.68)	**HR per 10** (χ^2:11, HR 1.24)	**Age per 10** (χ^2:9, HR 1.28)
	Prior HF	**log_2BNP** (χ^2:108, HR 1.72)	**AF** (χ^2:13, HR 1.93)	**Race** (χ^2:13, HR 1.42)
CV death (286 events)	**No prior HF**	**log_2BNP** (χ^2:101, HR 1.80)	**AF** (χ^2:12, HR 2.45)	**NSTEMI** (χ^2:9, HR 1.64)
	Prior HF	**log_2BNP** (χ^2:95, HR 1.84)	**CABG** (χ^2:10, HR 2.03)	**PAD** (χ^2:9, HR 1.90)
MI (473 events)	**No prior HF**	**log_2BNP** (χ^2:29, HR 1.23)	**prior MI** (χ^2:27, HR 1.86)	**PAD** (χ^2:21, HR 2.03)
	Prior HF	**log_2BNP** (χ^2:26, HR 1.34)	**prior MI** (χ^2:17, HR 2.10)	**NSTEMI** (χ^2:15, HR 2.00)
HF (221 events)	**No prior HF**	**log_2BNP** (χ^2:52, HR 1.70)	**HR per 10** (χ^2:22, HR 1.53)	**macroalbuminuria** (χ^2:13, HR 2.78)
	Prior HF	**log_2BNP** (χ^2:100, HR 1.94)	**BMI per 5** (χ^2:28, HR 1.39)	**DBP*** (χ^2:12, HR 1.06)
Stroke (115 events)	**No prior HF**	**log_2BNP** (χ^2:15, HR 1.40)	**macroalbuminuria** (χ^2:12, HR 2.98)	**TIA** (χ^2:10, HR 3.98)
	Prior HF	**log_2BNP** (χ^2:8, HR 1.31)	**TIA** (χ^2:6, HR 2.46)	**MI** (χ^2:5, HR 2.20)

Hazard ratio's reflect 1 unit changes if nothing else is stated. For log_2BNP that translates into a doubling of the untransformed BNP concentrations. Macroalbuminuria: >300 mg albumin excretion/24 h. *per 1 mmHg decrease below ≥75 mmHg.. AF- atrial fibrillation/flutter. NSTEMI – non-ST elevation myocardial infarction at index event. HR – heart rate. PAD – peripheral artery disease. TIA – transient ischemic attack. Duration of T2D is per year since diagnosis. All variables are significant, $p<0.05$.

Table S7. Discriminatory changes in best risk models with and without BNP stratified according to history of heart failure (No prior HF, n=4290; Prior HF, n=1235)

C statistics in each model (n=5525)

		Base model	BNP in model	NRI	IDI
Death (397 events)	No prior HF	0.77 (0.73-0.80)	0.80 (0.77-0.84)*	25.7% (17.3-34.7)*	4.0% (2.4-6.8)*
	Prior HF	0.69 (0.64-0.73)	0.78 (0.75-0.81)*	38.5% (28.7-45.4)*	7.8% (4.4-11.4)*
CV death (286 events)	No prior HF	0.76 (0.72-0.80)	0.81 (0.77-0.85)*	27.4% (17.7-35.6)*	3.7% (1.9-6.8)*
	Prior HF	0.73 (0.68-0.77)	0.82 (0.79-0.85)*	39.6% (28.6-51.1)*	6.9% (3.6-11.6)*
MI (473 events)	No prior HF	0.72 (0.69-0.75)	0.73 (0.70-0.75)#	13.7% (5.6-19.4)*	0.8% (0.2-1.9)*
	Prior HF	0.71 (0.66-0.76)	0.73 (0.68-0.77)	21.7% (8.4-30.9)*	2.4% (0.9-4.7)*
HF (221 events)	No prior HF	0.83 (0.79-0.87)	0.86 (0.83-0.90)*	29.4% (15.3-39.4)*	3.4% (1.4-6.7)*
	Prior HF	0.75 (0.71-0.80)	0.81 (0.77-0.85)*	38.8% (26.6-46.6)*	9.0% (5.1-13.3)*
Stroke (115 events)	No prior HF	0.76 (0.71-0.82)	0.79 (0.73-0.84)	17.6% (1.8-31.1)*	0.1% (-0.6-1.6)
	Prior HF	0.67 (0.58-0.75)	0.69 (0.61-0.76)	21.3% (0.0-35.2)*	1.0% (0.1-3.9)*

*$p<0.05$, comparison between base model and BNP model. #$p=0.053$, comparison between base model and BNP model. NRI – Net Reclassification Index. IDI – Integrated Discrimination Index. NRI and IDI summarized as mean percent improvement ±95%CI..

Table S8. Discriminatory changes in best risk models without BNP compared to BNP alone, in all patients (n=5525) and stratified according to history of heart failure (No prior HF, n=4290; Prior HF, n=1235).

	All patients		**No prior HF**		**Prior HF**	
Outcome	**Base model**	**BNP**	**Base model**	**BNP**	**Base model**	**BNP**
Death (397 events)	0.77 (0.74-0.79)	0.77 (0.75-0.80)	0.77 (0.74-80)	0.75 (0.71-0.78)	0.71 (0.67-0.74)	**0.76 (0.73-0.80)***
CV death (286 events)	0.77 (0.74-0.80)	0.79 (0.76-0.82)	0.76 (0.72-0.80)	0.76 (0.72-0.81)	0.73 (0.68-0.77)	0.78 (0.74-0.82)
MI (473 events)	**0.71 (0.68-0.73)**	0.63 (0.61-0.66)*	**0.72 (0.69-0.75)**	0.62 (0.59-0.65)*	0.71 (0.66-0.76)	0.66 (0.61-0.70)
HF (221 events)	**0.84 (0.81-0.86)**	0.78 (0.75-0.81)*	**0.83 (0.79-0.87)**	0.76 (0.72-0.80)*	0.75 (0.71-0.80)	0.74 (0.69-0.78)
Stroke (115 events)	**0.75 (0.70-0.79)**	0.67 (0.62-0.72)*	**0.76 (0.71-0.82)**	0.67 (0.60-0.74)*	0.67 (0.58-0.75)	0.61 (0.52-0.70)

*$p<0.05$, significant difference between base model compared to BNP model.

Table S9. Predictors of outcomes ranked according to χ^2 value using base variables and BNP in patients without prior CV disease (n=2899)

Outcome	1st	2nd	3rd
Death (112 events)	**log_2BNP** (χ^2:81, HR 1.78)	**DBP*** (χ^2:14, HR 1.05)	**Na#** (χ^2:7, HR 0.84)
CV death (74 events)	**log_2BNP** (χ^2:81, HR 2.04)	**DBP*** (χ^2:16, HR 1.06)	**duration of T2D** (χ^2:10, HR 1.04)
MI (153 events)	**log_2BNP** (χ^2:18, HR 1.27)	**macroalbuminuria** (χ^2:12, HR 2.34)	**hypertension** (χ^2:10, HR 1.89)
HF (39 events)	**log_2BNP** (χ^2:31, HR 1.87)	**duration of T2D** (χ^2:13, HR 1.06)	**albumin** (χ^2:6, HR 0.91)
Stroke (31 events)	**carotid disease** (χ^2:41, HR 34.79)	**microalbuminuria** (χ^2:16, HR 5.08)	**DBP*** (χ^2:16, HR 1.09)

Hazard ratio's reflect 1 unit changes if nothing else is stated. For log_2BNP that translates into a doubling of the untransformed BNP concentrations. Microalbuminuria ≥30-300 mg albumin excretion/24h. Macroalbuminuria: >300 mg albumin excretion/24h.. *per 1 mmHg decrease below ≥75 mmHg.. T2D – Type 2 diabetes (years). All variables are significant, $p<0.05$.

Table S10. Predictors of outcomes ranked according to χ^2 value using base variables and NT-proBNP in patients without prior CV disease (n=2899)

Outcome	1st	2nd	3rd
Death (112 events)	**log_2proBNP** (χ^2:81, HR 1.61)	**DBP*** (χ^2:16, HR 1.05)	**age per 10** (χ^2:8, HR 1.36)
CV death (74 events)	**log_2proBNP** (χ^2:81, HR 1.81)	**DBP*** (χ^2:16, HR 1.06)	**duration of T2D** (χ^2:10, HR 1.04)
MI (153 events)	**log_2proBNP** (χ^2:18, HR 1.21)	**macroalbuminuria** (χ^2:11, HR 2.23)	**hypertension** (χ^2:10, HR 1.92)
HF (39 events)	**log_2proBNP** (χ^2:53, HR 1.91)	**duration of T2D** (χ^2:14, HR 1.06)	**NSTEMI** (χ^2:5, HR 2.06)
Stroke (31 events)	**carotid disease** (χ^2:37, HR 29.09)	**microalbuminuria** (χ^2:16, HR 5.06)	**DBP*** (χ^2:15, HR 1.08)

Hazard ratio's reflect 1 unit changes if nothing else is stated. For log_2BNP that translates into a doubling of the untransformed BNP concentrations. Microalbuminuria ≥30-300 mg albumin excretion/24h. Macroalbuminuria: >300 mg albumin excretion/24h. DBP* diastolic blood pressure per 1 mmHg decrease below ≥75 mmHg. NSTEMI – non-ST elevation myocardial infarction at index event. T2D – Type 2 diabetes (years). All variables are significant, $p<0.05$.

Table S11. Predictors of outcomes ranked according to χ^2 value using base variables and BNP with and without adding information on LVEF (n=3390)

Outcome		1st	2nd	3rd
Death (236 events)	**Variables**	**log_2BNP** (χ^2:99, HR 1.60)	**Duration of T2D** (χ^2:17, HR 1.03)	**male** (χ^2:9, HR 1.59)
	Variables +LVEF	**log_2BNP** (χ^2:108, HR 1.60)	**Duration of T2D** (χ^2:17, HR 1.03)	**male** (χ^2:9, HR 1.59)
CV death (166 events)	**Variables**	**log_2BNP** (χ^2:131, HR 1.86)	**HbA1c** (χ^2:10, HR 1.22)	**Duration of T2D** (χ^2:10, HR 1.03)
	Variables +LVEF	**log_2BNP** (χ^2:95, HR 1.79)	**HbA1c** (χ^2:11, HR 1.23)	**Duration of T2D** (χ^2:10, HR 1.03)
MI (290 events)	**Variables**	**prior MI** (χ^2:43, HR 2.21)	**NSTEMI** (χ^2:24, HR 1.81)	**log_2BNP** (χ^2:23, HR 1.21)
	Variables +LVEF	**prior MI** (χ^2:43, HR 2.21)	**NSTEMI** (χ^2:24, HR 1.81)	**log_2BNP** (χ^2:23, HR 1.21)
HF (148 events)	**Variables**	**log_2BNP** (χ^2:97, HR 1.80)	**BMI per 5** (χ^2:25, HR 1.33)	**HR per 10** (χ^2:20, HR 1.43)
	Variables +LVEF	**log_2BNP** (χ^2:97, HR 1.80)	**BMI per 5** (χ^2:25, HR 1.33)	**HR per 10** (χ^2:20, HR 1.43)
Stroke (70 events)	**Variables**	**log_2BNP** (χ^2:21, HR 1.42)	**TIA** (χ^2:11, HR 3.59)	**LDL per 10** (χ^2:7, HR 1.08)
	Variables +LVEF	**log_2BNP** (χ^2:21, HR 1.42)	**TIA** (χ^2:11, HR 3.59)	**LDL per 10** (χ^2:7, HR 1.08)

Table S12. Predictors of outcomes ranked according to χ^2 value using base variables and NT-proBNP with and without adding information on LVEF at index ACS (n=3390)

Outcome		1st	2nd	3rd
Death (236 events)	**Variables**	**log_2NT-proBNP** (χ^2:107, HR 1.46)	**COPD** (χ^2:9, HR 1.81)	**Male** (χ^2:9, HR 1.58)
	Variables +LVEF	**log_2NT-proBNP** (χ^2:107, HR 1.46)	**COPD** (χ^2:9, HR 1.81)	**Male** (χ^2:9, HR 1.58)
CV death (166 events)	**Variables**	**log_2NT-proBNP** (χ^2:115, HR 1.57)	**HbA1c** (χ^2:14, HR 1.27)	**Male** (χ^2:9, HR 1.71)
	Variables +LVEF	**log_2NT-proBNP** (χ^2:68, HR 1.49)	**HbA1c** (χ^2:13, HR 1.26)	**AF** (χ^2:10, HR 1.92)
MI (290 events)	**Variables**	**prior MI** (χ^2:44, HR 2.24)	**log_2NT-proBNP** (χ^2:30, HR 1.18)	**NSTEMI** (χ^2:25, HR 1.18)
	Variables +LVEF	**prior MI** (χ^2:44, HR 2.24)	**log_2NT-proBNP** (χ^2:30, HR 1.18)	**NSTEMI** (χ^2:25, HR 1.18)
HF (148 events)	**Variables**	**log_2NT-proBNP** (χ^2:86, HR 1.56)	**BMI per 5** (χ^2:25, HR 1.33)	**CABG** (χ^2:19, HR 2.48)
	Variables +LVEF	**log_2NT-proBNP** (χ^2:86, HR 1.56)	**BMI per 5** (χ^2:25, HR 1.33)	**CABG** (χ^2:19, HR 2.48)
Stroke (70 events)	**Variables**	**log_2NT-proBNP** (χ^2:14, HR 1.26)	**TIA** (χ^2:10, HR 3.36)	**LDL per 10** (χ^2:6, HR 1.07)
	Variables +LVEF	**log_2NT-proBNP** (χ^2:14, HR 1.26)	**TIA** (χ^2:10, HR 3.36)	**LDL per 10** (χ^2:6, HR 1.07)

Table S13. Discriminatory changes in best risk models with and without BNP and NT-proBNP with LVEF and coronary intervention procedure added to base model

C statistics in each model (n=3390)

		Base model	BNP/ NT-proBNP in model	NRI	IDI
Death (236 events)	BNP	0.75 (0.72-0.78)	0.79 (0.76-0.82)*	31.8% (25.1-37.4)*	5.3% (3.5-7.4)*
	NT-proBNP		0.79 (0.75-0.82)*	25.5% (19.4-31.9)*	3.5% (2.3-5.1)*
CV death (166 events)	BNP	0.77 (0.73-0.81)	0.83 (0.80-0.86)*	34.8% (28.0-41.7)*	5.7% (3.7-8.4)*
	NT-proBNP		0.82 (0.79-0.85)*	29.9% (22.4-36.8)*	3.9% (2.3-6.2)*
MI (290 events)	BNP	0.70 (0.67-0.73)	0.71 (0.67-0.74)	14.3% (9.3-19.5)*	1.2% (0.6-2.1)*
	NT-proBNP		0.71 (0.68-0.74)	10.6% (5.7-16.6)*	0.8% (0.3-1.6)*
HF (148 events)	BNP	0.86 (0.83-0.89)	0.88 (0.85-0.90)*	35.4% (24.7-40.6)*	5.0% (3.0-7.6)*
	NT-proBNP		0.88 (0.85-0.90)*	29.9% (21.8-36.6)*	3.8% (2.2-5.8)*
Stroke (70 events)	BNP	0.72 (0.66-0.78)	0.76 (0.70-0.82)	19.3% (8.8-29.9)*	0.4% (0-1.2)
	NT-proBNP		0.75 (0.70-0.81)	17.2% (6.3-28.1)*	0.2% (0-0.8)

*$p<0.05$, comparison between base model and /NT-proBNP model. NRI – Net Reclassification Index. IDI – Integrated Discrimination Index. NRI and IDI summarized as mean percent improvement ±95%CI.

Myocardial infarction summary criteria for positive adjudication:

Spontaneous MI: Elevated cardiac markers (CM) and either new electrocardiographic (ECG) changes or a clinical presentation consistent with an acute MI.
○PCI-related MI: Elevated CM (or other criteria in the absence of elevated CM).
○Coronary artery bypass graft (CABG)–related MI: Elevated CM and new ECG changes (or other criteria).
Detailed criteria for positive adjudication:
a. Spontaneous MI:
Cardiac markers:
○Troponin$_p$>upper limit of normal (ULN) or
○CK-MB>ULN

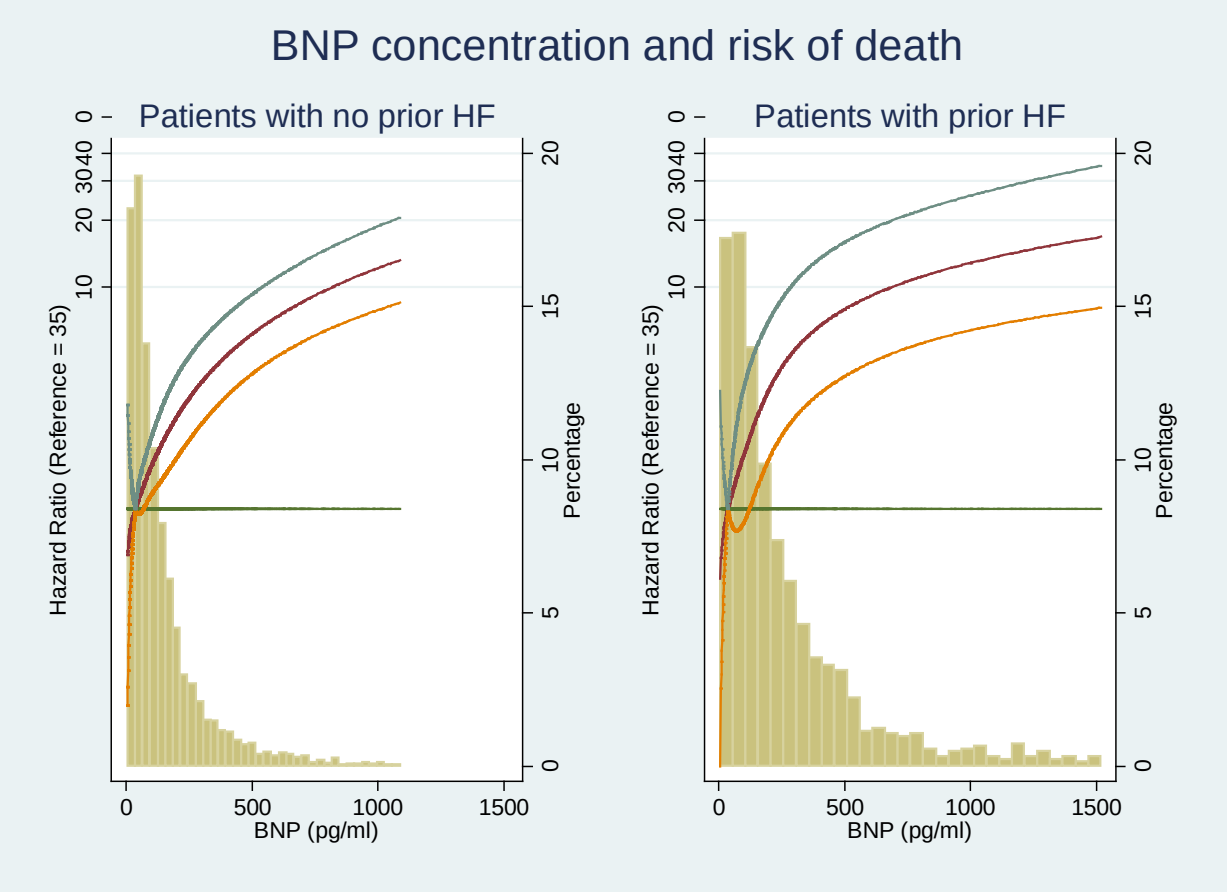
and at least 1 of the following:
○Ischemic symptoms: rest or accelerated symptoms (pain, dyspnea, and pressure) consistent with myocardial ischemia.
○ECG changes consistent with infarction:
•New significant Q waves (or R waves in V_1-V_2)in 2 contiguous leads in absence of previous left ventricular hypertrophy or conduction abnormalities. OR
•Evolving ST-segment to T-wave changes in≥2 contiguous leads.
•Development of new left bundle-branch block.
•ST-segment elevation requiring thrombolytics or PCI.
b. PCI-related MI:
Cardiac markers$_q$:
1. Assuming baseline value>ULN
2. Within 48 hours of procedure
a. Troponin$_p$>3× ULN OR
b. CK-MB>3× ULN
c. CABG-related MI:
Cardiac markers:
1. Assuming baseline value>ULN
2. Within 72 hours of procedure
a. Troponin$_p$>5× ULN OR
b. CK-MB>5× ULN
AND
c. New pathologic Q waves or left bundle-branch block, new native or graft vessel occlusion, or imaging evidence of loss of viable myocardium.
3. Hospitalization for UA
a. Unplanned hospitalization for worsening angina defined as rest or accelerated symptoms (pain, dyspnea, and pressure) consistent with myocardialischemia AND
b. Cardiac markers (CK-MB or troponin) suggestive of myocardial injury but not meeting MI criteria. Note: if abnormal troponin, value must be in the suggestive (middle) range and below the threshold for MI.

Baseline variables used in risk models:

Log_2BNP, Log_2NT-proBNP

Race, ethnicity, region, randomization to lixisenatide, PCI at index ACS, age, gender, BMI, systolic blood pressure, diastolic blood pressure (above/below 70 mmHg), heart rate, smoking (current/never/former), history of MI, history of HF, history of AF, history of PAD, history of TIA, history of stroke, history of ventr. tachycardia, history of CABG, pacemaker implanted, carotid disease, history of hypertension, index ACS (STEMI, NSTEMI, UAP), insulin use (yes/no), duration of T2D, retinopathy, neuropathy, asthma, COPD, albuminuria (no/micro/macro), logCRP, HbA1c, HDL, LDL, eGFR, Hgb, Na (above/below 140 mmol/L), albumin.

Figure S1. The association of BNP concentrations and risk of all-cause death according to history of heart failure



The hazard of death is depicted with 95%CI. The Cox spline model was fully adjusted for all significant variables. The reference of HR=1.0 corresponds to a BNP concentration of 35 pg/ml.