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ORIGINAL RESEARCH

B-Type Natriuretic Peptide and Long-Term Cardiovascular Mortality in Patients With Coronary Heart Disease

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BACKGROUND: The plasma concentration of B-type natriuretic peptide (BNP) is a strong predictor of adverse cardiovascular events. The aim of this study was to determine whether the association between plasma BNP concentration and cardiovascular mortality is sustained or diminishes with increasing time after BNP is measured.

METHODS AND RESULTS: Six thousand seven hundred forty patients with a history of myocardial infarction or unstable angina who participated in the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) trial had plasma BNP concentration measured at baseline and after 1 year. Associations with cardiovascular mortality were evaluated in landmark analyses 1 to <5, 5 to <10, and 10 to 16 years after randomization. There were 1640 cardiovascular deaths. The cardiovascular mortality rate increased progressively from 10.2 to 19.1 to 26.3/1000 patient-years from 1 to <5, 5 to <10, and 10 to 16 years after baseline, respectively. The average of baseline and 1-year BNP concentration was more strongly associated with cardiovascular mortality compared with baseline or 1-year BNP only. The hazard ratio (HR) for cardiovascular death associated with each doubling of average BNP concentration was similar during years 1 to <5 (HR, 1.53 [95% CI, 1.44–1.63]), years 5 to <10 (HR, 1.52 [95% CI, 1.44–1.60]), and years 10–16 (HR, 1.43 [95% CI, 1.36–1.50]), *P*<0.0001 for all.

CONCLUSIONS: BNP concentration remains an independent predictor of cardiovascular mortality more than a decade after it is measured. Because of random variation in plasma concentrations, the average of >1 BNP measurement improves long-term risk prediction.

Key Words: cardiac biomarkers ■ risk prediction

Plasma concentrations of B-type natriuretic peptide (BNP) and its pro-peptide, N-terminal pro-BNP (NT-pro- BNP) are associated with the risk of cardiovascular death, heart failure, and stroke in diverse populations, including in patients with coronary heart disease (CHD).[1–5] The predictive value of BNP and NT-pro-BNP for adverse cardiovascular events is stronger than for most other biomarkers.[6–8] By identifying patients who have a higher risk of adverse cardiovascular events, measurement of BNP may be useful to better target cardiovascular preventive treatments to patients who have more potential to benefit.

Previous studies of the prognostic importance of BNP have generally evaluated adverse cardiovascular events over <6 years follow-up.[1–5] Some studies have reported longer-term outcomes, but did not specifically evaluate whether and how the association between plasma BNP concentration and cardiovascular

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Nonstandard Abbreviations and Acronyms

LIPID	Long-Term Intervention with Pravastatin in Ischemic Disease Trial
NT-BNP	N-terminal pro BNP

mortality changes with increasing time after BNP is measured.[9] This question is important for determining how useful BNP is for long-term cardiovascular risk prediction.

A related question is the degree to which shorter-term changes in BNP concentration influence long-term cardiovascular risk assessment. Change in plasma BNP concentrations over time could reflect a change in cardiac function, as observed during the months after an acute myocardial infarction (MI),[10,11] or decompensated heart failure,[12,13] or from disease-modifying treatments.[14] However, BNP concentrations also vary in clinically stable patients,[15,16] suggesting there is additional "random" variation in BNP concentrations between assessments beyond that caused by any change in myocardial function.

The aim of this study was to determine the durability of the association between the plasma concentration of BNP and risk of cardiovascular death during 15 years follow-up. In addition, we evaluated the long-term prognostic importance of variation in the plasma BNP concentration over 1 year. The study population included clinically stable patients with a history of previous MI or unstable angina who participated in the LIPID (Long-Term Intervention with Pravastatin for Ischemic Disease) trial.

METHODS
The authors declare that all supporting data are available within the article and its supplemental material.

Study Population
The LIPID trial was designed to evaluate the effects of pravastatin 40 mg daily compared with placebo on the risk of fatal CHD and nonfatal MI.[17–19] A total of 9014 patients with a MI or hospital admission for unstable angina 3 to 36 months previously, and with total cholesterol of 155 to 271 mg/dL (4.0–7.0 mmol/L) and triglyceride levels <445 mg/dL (5.0 mmol/L) were enrolled. Left ventricular ejection fraction was not measured as part of the trial protocol, but patients with a known ejection fraction <35% or in New York Heart Association class 3 or 4 were excluded. The trial was terminated early after median follow-up of 6 years after advice from the independent Data and Safety Monitoring Committee that the prespecified boundary for reduction in CHD mortality had been crossed. The primary outcome of death from CHD or nonfatal MI was significantly lower in patients randomized to pravastatin. At trial closure, randomized therapy was stopped and all patients were offered pravastatin or another clinically available statin. Long-term medication was prescribed by the patient's usual doctors with ≈85% in both groups continuing to take statins long term.[20] The current study included all 6740 participants who consented to an additional blood sample for measurement of biomarkers, and who had BNP measurements available from samples at both baseline and 1 year. The study was approved by institutional or regional ethics committees for the participating sites, and all patients provided written informed consent.

Biomarker Analysis
A venous blood sample was obtained after a 12-hour fast into EDTA tubes, and plasma samples were stored in freezers at –70 °C until analysis. BNP was analyzed centrally in the MONICA Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MORGAM) biomarker laboratory, as previously reported.[21] BNP was measured with a chemiluminescent immunoassay (ADVIA Centaur, Semiens Healthcare Diagnostics, Germany) with assay range <5000 pg/nL and cardiovascular interassay of 5.2%.[7]

Outcomes During Follow-Up
The prespecified primary outcome for this analysis was cardiovascular death during 1 to 16 years from randomization. Secondary outcomes were all-cause mortality, cancer mortality, and noncancer, noncardiovascular mortality. Data related to death and cause

of death were obtained by direct follow-up during the trial, and from National Death Registers in Australia and New Zealand, and from Australian state cancer registries as previously reported.[20,22]

Nonfatal outcomes were only available during the randomized trial period, which had a mean follow-up of 6 years. Nonfatal MI and strokes were reviewed by blinded outcome-assessment committees. MI was defined as the definite development of new pathological Q-waves of at least 0.03 seconds in width in at least 2 ECG leads, or the presence of at least 2 of the following: (1) A history of typical ischemic pain lasting for 15 minutes and unresponsive to sublingual nitrates; (2) Elevation of creatine kinase myocardial band over twice the upper limit of normal; and (3) Evolution of electrocardiographic changes. Heart failure hospitalization was not part of the primary end point for the LIPID trial, but because BNP concentration is known to be associated with heart failure hospitalization, it was included as an outcome in the present analysis. It was recorded via discharge records and identified using *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes (428-congestive heart failure, 428.1-left ventricular heart failure and pulmonary edema, or 428.9-heart failure unspecified).

Statistical Analysis

Associations between quartiles of baseline BNP concentration and cardiovascular events during the first 5 years of follow-up in the LIPID study have been reported previously.[7] In the current analysis, BNP categories were defined based on groups representing approximate doubling of BNP; <6.25, 6 to 25 to <12.5, 12.5 to <25, 25 to <50, 50 to <100, and ≥100 pg/mL. Associations between baseline BNP group and baseline characteristics were assessed using ANOVA or a Wilcoxon rank sum test. For the binary variables, the analysis used was a general linear model with a logit link. The *P* values are a test for trend over the 6 levels where possible and a test over all 6 groups otherwise. Distributions of BNP and Log(2) BNP, where a 1-unit change indicates a doubling or halving of BNP, were also evaluated. Associations with the primary outcomes were evaluated for BNP concentration measured at baseline and 1 year, and for the average BNP concentrations at these 2 times. Separate models, each of which includes either baseline BNP, year 1 BNP, the average of baseline and year 1 BNP, or the change in BNP from baseline to year 1, are presented for comparison. Associations were investigated with time-to-event models for each analysis. Log(2) BNP was used because the association with cardiovascular death was approximately linear and the distributions more normal.

Outcome Analysis

Landmark analyses were performed from 1 year, and included all subjects with baseline and 1 year BNP measurements. To evaluate how the association between BNP and cardiovascular death changed with increasing length of follow-up, landmark analyses were performed for the periods 1 to <5 years, 5 to <10 years, and 10 to 16 years after randomization.

All hazard ratios (HRs) were adjusted for age, sex, and randomized assignment to treatment with pravastatin or placebo. Variables included in the fully adjusted model were prespecified, and based on previous analyses from the LIPID trial.[23,24] They included age, sex, study treatment, prior stroke, diabetes, current smoking, hypertension, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, nature of qualifying prior acute coronary syndrome, timing of coronary revascularization, systolic blood pressure, atrial fibrillation, estimated glomerular filtration rate, body mass index, dyspnea class, angina grade, white blood cell count, peripheral vascular disease, and use of aspirin at baseline. All analyses used SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics

Table 1 shows the characteristics of the study population at baseline for groups defined by ≈2-fold differences of baseline plasma BNP concentration. Higher BNP concentration was associated with older age, female sex, history of hypertension, diabetes, and lower estimated glomerular filtration rate. Patients with higher BNP concentrations were more likely to report dyspnea or angina on exertion, history of stroke, myocardial infarction before the index event, and to have a higher LIPID risk score.[23,24] Obese subjects had on average a lower BNP concentration.

BNP Concentrations at Baseline, 1 Year, and Associations With Cardiovascular Mortality

The median BNP for the study population at baseline was 23, interquartile range 10 to 50 pg/mL, and at 1 year median 20, interquartile range 7 to 45 pg/mL. The mean difference between baseline and 1 year BP was −4 pg/mL and the SD of differences was 52 pg/mL. When expressed as Log(2) BNP, differences in BNP concentrations between baseline and 1 year were normally distributed (Figure S1). Patients in lower BNP categories at baseline had slightly higher BNP concentrations at 1 year, and vice versa, consistent with regression to the mean (Table 1).

Table 1. Baseline Risk Factors by BNP Groups

Demographic or clinical variable	BNP at baseline (pg/mL)						P value trend or global*
	<6.25	6.25 to <12.5	12.5 to <25	25 to <50	50 to <100	≥100	
BNP baseline, mean±SD	3±1	9±2	18±4	36±7	69±14	192±138	<0.001
BNP at 1 y, mean±SD	13±29	14±20	22±27	34±27	59±55	130±151	<0.001
Clinical variables							
Randomized to pravastatin	701 (53%)	546 (49%)	818 (49%)	872 (50%)	622 (49%)	382 (53%)	0.10†
Age (y) mean±SD	58±9	58±8	60±8	62±8	64±7	66±6	<0.001
Female	193 (15%)	150 (14%)	277 (16%)	303 (17%)	249 (20%)	161 (22%)	<0.001
Current smoker	171 (13%)	131 (12%)	154 (9%)	146 (8%)	81 (6%)	52 (7%)	<0.001
Hypertension	522 (39%)	427 (39%)	639 (38%)	717 (41%)	605 (48%)	381 (53%)	<0.001
Diabetes	120 (9%)	86 (8%)	115 (7%)	148 (8%)	125 (10%)	82 (11%)	0.025
Obese	295 (22%)	238 (22%)	289 (17%)	279 (16%)	198 (16%)	98 (14%)	<0.001
Dyspnea NYHA Class >1	120 (9%)	84 (8%)	146 (9%)	160 (9%)	152 (12%)	99 (14%)	<0.001
Angina CCVS Grade >0	455 (34%)	431 (39%)	589 (35%)	624 (36%)	517 (41%)	311 (43%)	<0.001
LDL mean±SD	3.9±0.8	3.9±0.8	3.9±0.7	3.9±0.7	3.9±0.7	3.9±0.8	0.052†
PCI only	233 (18%)	171 (15%)	213 (13%)	131 (8%)	88 (7%)	34 (5%)	<0.001
CABG only	285 (22%)	282 (26%)	520 (31%)	606 (35%)	430 (34%)	260 (36%)	<0.001
PTCA or CABG	518 (39%)	453 (41%)	733 (44%)	737 (42%)	518 (41%)	294 (41%)	0.48
Single MI	664 (50%)	555 (50%)	886 (53%)	932 (53%)	694 (55%)	384 (53%)	0.011
Multiple MIs	98 (7.4%)	86 (7.8%)	165 (9.8%)	214 (12.2%)	182 (14.3%)	160 (22.2%)	<0.001
Previous stroke	39 (2.9%)	36 (3.2%)	68 (4.0%)	67 (3.8%)	72 (5.7%)	40 (5.5%)	<0.001
ACE inhibitors	176 (13%)	116 (11%)	227 (14%)	249 (14%)	249 (20%)	237 (33%)	<0.001
β-Blockers	525 (39.6%)	467 (42.1%)	769 (45.7%)	841 (47.9%)	700 (55.1%)	389 (53.9%)	<0.001
eGFR mL/min per 1.72 m², median (IQR)	74 (64–84)	74 (64–84)	70 (61–81)	69 (60–79)	66 (57–77)	61 (52–70)	<0.001†
Risk score, mean±SD	5.4±3.3	5.3±3.3	5.4±3.4	5.8±3.4	6.5±3.6	7.3±3.8	<0.001

N(%) is presented unless otherwise stated. ACE indicates angiotensin-converting enzyme inhibitor; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CCVS, Canadian Cardiovascular Society; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; NYHA, New York Heart Association Class symptoms; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; and Risk Score, LIPID Risk Score.

*P values are a test for trend, if appropriate, or test over all 6 groups. P values may be highly significant with small differences between groups because of the large sample size.

†P value is over all the groups rather than a test of a trend.

The average of baseline and 12-month Log(2) BNP was more strongly associated with the risk of cardiovascular death compared with Log(2) BNP measured at either baseline or 1 year only (Table 2). The HR for cardiovascular death associated with doubling of the average of baseline and 1 year BNP was 1.51; 95% CI, 1.46–1.56. For baseline BNP alone the HR was 1.37; 95% CI, 1.33–1.41, and for 1 year BNP alone the HR was 1.38; 95% CI, 1.33–1.41. Models that used the average Log(2) BNP had predictive value similar to those that included baseline and 1 year Log(2) BNP separately, and both average Log(2) BNP and change in Log(2) BNP concentration between baseline and 1 year (Table 2).

Association Between Average BNP and Specific Clinical Outcomes

The average of baseline and 1-year BNP was more strongly associated with cardiovascular death than with all-cause mortality. Average BNP was more weakly associated with noncancer, noncardiovascular death, and with cancer mortality after adjusting for all covariates (Table 3). During the randomized treatment phase of the LIPID trial, average BNP was associated with risk of hospitalization for heart failure and stroke, and weakly with the risk of nonfatal MI (Table 3).

Association Between BNP and Mortality Stratified by Duration of Follow-Up

Landmark analyses for the association between average BNP concentration and cardiovascular and all-cause mortality, stratified by duration of follow-up, are presented in Table 4, and shown in the Figure for cardiovascular mortality. The cardiovascular mortality rate increased progressively during long-term follow-up (Table 4). HRs for cardiovascular death associated

Table 2. Associations Between Different Plasma BNP Measurements at Baseline and 1 Year and Cardiovascular Mortality (N=1640) During 1 to 16 Years After Randomization

Form of BNP in the model, log₂ (BNP)	Effect of a 2-fold difference in BNP HR (95% CI)	Likelihood ratio χ^2 (4 degrees of freedom)
Average of baseline+1 y	1.51 (1.46–1.56)*	587
Baseline	1.37 (1.33–1.41)*	421
1 y	1.38 (1.34–1.42)*	494
Change in BNP between baseline and 1 y	1.25 (1.20–1.30)*	146

All analyses are Landmark analyses from 1 year. All analyses are for Log(2) BNP. A 1-unit increase in Log(2) BNP is therefore equivalent to doubling of plasma BNP concentration. HR, hazard ratios for change in BNP. Other covariates are the same for each model (age, sex, and treatment group). A higher likelihood ratio χ^2 indicates an improved model. BNP indicates B-type natriuretic peptide; and cardiovascular mortality, cardiovascular deaths assessed over a mean of 15 years.

*$P<0.001$.

with a 2-fold difference in average BNP concentration were similar during years 1 to <5, 5 to <10, and 10 to 16 years (Table 4). This graded association is illustrated for all groups according to BNP concentrations in the Figure, with corresponding data provided in Table S1. There was a graded association between average BNP concentration and risk of cardiovascular death

across the 3 time strata and across the full range of BNP concentrations (Figure).

There was a modest decrease in the HRs for the association between average BNP concentration and all-cause mortality with increasing duration of follow-up (Table 4). The proportion of deaths from noncardiovascular causes increased from 34% during years 1 to <5, to 41% during years 5 to <10, and 48% during years 10 to 16 (Table 4).

DISCUSSION

BNP and Long-Term Cardiovascular Risk

In this study, the plasma concentration of BNP was strongly and durably associated with the risk of cardiovascular death during 15 years follow-up, and this association was graded throughout the range of BNP concentrations. These observations are consistent with previous studies that have evaluated the prognostic importance of BNP and/or NT-pro-BNP during shorter durations of follow-up.[2–4,9,25]

For all patients, there was a progressive increase in both the cardiovascular and all-cause mortality rate with increasing years of follow-up. Compared with the first 4 to 5 years follow-up, cardiovascular mortality was more than twice as high 10 to 16 years after the last

Table 3. Associations Between Plasma Average BNP Concentration and Different Clinical Outcomes During the Randomized Trial, and During Long-Term Follow-Up

End point	Number	Adjusted for age, sex, treatment group		Fully adjusted model	
		HR for 2-fold difference in BNP (95% CI)	P value	HR for 2-fold difference in BNP (95% CI)	P value
Number of subjects	6740				
Randomized trial phase*					
Cardiovascular death	451	1.60 (1.50–1.70)	<0.001	1.44 (1.34–1.55)	<0.001
Nonfatal MI	410	1.06 (1.00–1.13)	0.05	1.03 (0.97–1.11)	0.33
Stroke	259	1.27 (1.18–1.38)	<0.001	1.18 (1.08–1.29)	<0.001
Heart failure	466	1.67 (1.57–1.78)	<0.001	1.54 (1.43–1.65)	<0.001
Any cardiovascular event	1161	1.34 (1.29–1.39)	<0.001	1.26 (1.21–1.31)	<0.001
Long-term follow-up†					
Cardiovascular death	1640	1.51 (1.46–1.56)	<0.001	1.33 (1.28–1.38)	<0.001
Cancer death	706	1.16 (1.11–1.22)	<0.001	1.07 (1.01–1.13)	0.02
Noncardiovascular/cancer death	559	1.28 (1.21–1.36)	<0.001	1.09 (1.03–1.16)	0.005
All-cause mortality	2905	1.37 (1.33–1.40)	<0.001	1.21 (1.18–1.25)	<0.001

All analyses are for Log(2) BNP. A 1-unit increase in Log(2) BNP is therefore equivalent to doubling of plasma BNP concentration. BNP is the average of baseline and 1-year measurements. Fatal and nonfatal cardiovascular events are reported during the randomized trial phase only, with average follow-up of 5 years from year 1. Cause-specific mortality is reported over 16 years. HR+hazard ratios are for each doubling of average BNP level (Ln2 BNP=+1). Data are restricted to patients who have BNP known at both baseline and 1 year. Model 1 includes age, sex, and randomized treatment (pravastatin or placebo) stratified by randomized trial and long-term follow-up phases. Model 2 also adjusted for age, history of stroke, diabetes, current smoker, hypertension, total cholesterol, HDL cholesterol, index acute coronary syndrome type type, history of coronary revascularization, systolic blood pressure, atrial fibrillation, estimated glomerular filtration rate, body mass index, NYHA dyspnea grade, presence of angina, white blood cell count, peripheral vascular disease, aspirin, fasting glucose, and triglycerides. Hazard ratios were similar in models that additionally included other prognostic biomarkers. BNP indicates B-type natriuretic peptide; HR, hazard ratio; HDL, high-density lipoprotein; MI, myocardial infarction; and NYHA, New York Heart Association.

*A participant can have >1 event type. The number of patients removed because of an event in the first year is different for different nonfatal events.

†Rates are calculated at the end of 5 years for the randomized clinical trial and 16 years for the long-term follow-up from a Kaplan–Meier curve. First-year events have been removed for the landmark analysis.

Table 4. Associations Between the Average of Baseline and 1-Year Plasma BNP Concentration and Cardiovascular and All-Cause Mortality, Stratified by Number of Years After Randomization

Outcome	1–5 y	>5–10 y	>10–16 y
Number of subjects at risk	6740	6214	5185
Cardiovascular death			
Number of events	342	541	757
HR (95% CI)	1.57 (1.46–1.69)	1.52 (1.43–1.61)	1.46 (1.39–1.54)
HR, fully adjusted	1.36 (1.27–1.46)	1.35 (1.27–1.43)	1.31 (1.24–1.38)
Rate/1000 pt-y	10.2	19.1	26.3
All deaths			
Number of events	517	920	1468
HR (95% CI)	1.47 (1.39–1.56)	1.36 (1.30–1.42)	1.33 (1.28–1.38)
HR, fully adjusted	1.29 (1.22–1.37)	1.21 (1.16–.27)	1.19 (1.15–1.24)
Rate/1000 pt-y	15.3	32.4	50.9

To evaluate cardiovascular and all-cause mortality during different periods of follow-up, a landmark analysis was performed at the end of 5 and 10 years from randomization. All analyses use Log(2) BNP. Hazard ratios are for each 2-fold change in average BNP (baseline and 1 year) in a model adjusting for age, sex, and treatment group, and in the fully adjusted model. For all HRs $P<0.0001$. The 95% CIs were overlapping for cardiovascular deaths for each time period. For all-cause mortality the HR decreased with long-term follow-up and the 95% CI for the unadjusted analysis did not overlap for 1 to <5 years compared with >10 years. BNP indicates B-type natriuretic peptide; and HR, hazard ratio.

BNP measurement. Because the relative increase in cardiovascular mortality associated with a higher BNP concentration was similar, or only decreased slightly with increasing duration of follow-up, the absolute risk of cardiovascular death associated with a higher average BNP concentration was greater after 5 and 10 years, compared with <5 years. These observations indicate that plasma BNP concentration continues to
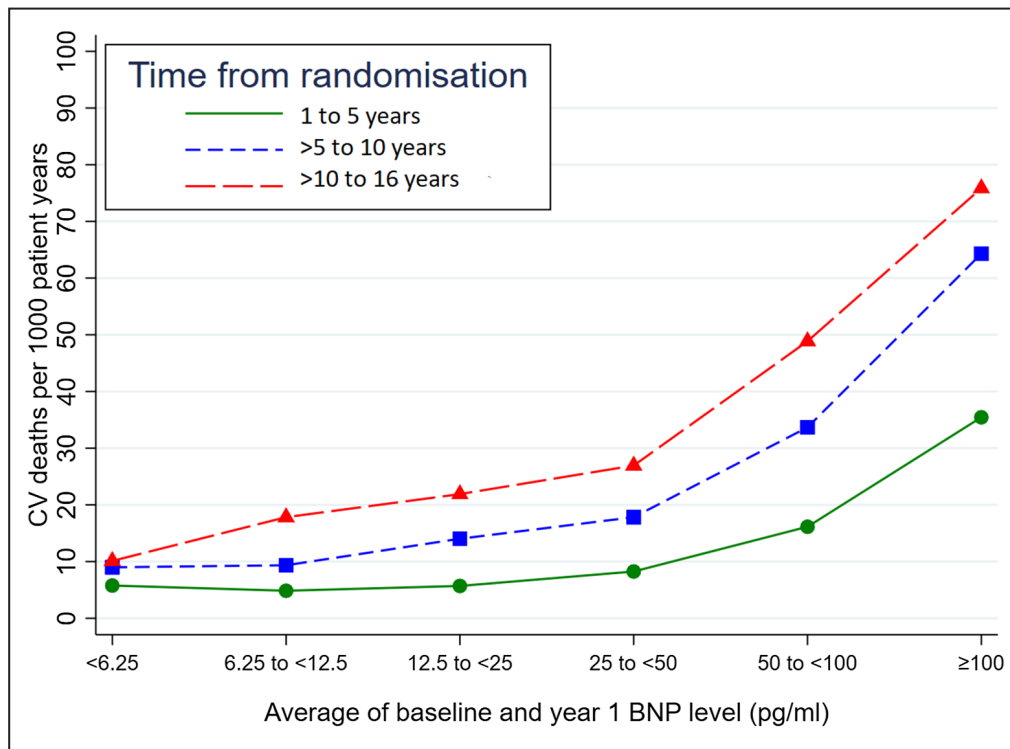
Figure. Cardiovascular death by BNP concentration stratified by length of follow-up.
Data are stratified by time from randomization: 1 to <5, 5 to <10 years, and 10 to 16 years. BNP is the average of baseline and 1 year BNP concentration. The cardiovascular mortality rate increased progressively with increasing duration of follow-up for all BNP groups, and across each of the 3 time strata. The absolute increase in cardiovascular mortality associated with longer durations of follow-up was greater in patients with a higher average BNP concentration. BNP indicates B-type natriuretic peptide; and CV indicates cardiovascular.

predict cardiovascular mortality more than a decade after it is measured, even while the absolute cardiovascular risk progressively increases.

BNP was much more weakly associated with noncardiovascular mortality, which represented an increasing proportion of total deaths during long-term follow-up. This would in part explain why the association between average BNP concentration and all-cause mortality diminished with increasing time after measurement. The reason for the association of BNP with deaths from cancer is unexplained. Other studies have reported higher BNP concentrations in patients with diagnosed cancer, possibly related to associated inflammation.[26,27]

Importance of Biological Variation in BNP Concentrations

We observed large variation of plasma BNP concentrations over 1 year, similar to that observed in studies where BNP was remeasured after several weeks in clinically stable populations.[15,16] If large variations in BNP concentration reflect sustained changes in "myocardial function," the strength of the association between plasma BNP concentration and cardiovascular death would progressively diminish with increasing years after it is measured. Several observations support the conclusion that most variation in plasma BNP concentrations did not reflect a long-term change in myocardial function. Average BNP concentration was a stronger marker of long-term cardiovascular mortality risk compared with the most recent BNP measured at 1 year, and change in BNP concentration provided little additional prognostic information in models that included the average BNP of baseline and 1 year BNP. Also, there was evidence for regression to the mean between baseline and 1 year BNP measurements, which is best explained by random variation. Previous studies have reported that BNP concentration usually decreases during follow-up after an acute MI or episode of acute heart failure, and BNP measured during the convalescent phase is the more reliable indicator of ongoing cardiovascular risk.[10–13] Changes in plasma concentrations of BNP over time could therefore reflect changes in myocardial function related to acute or chronic disease or disease-modifying therapies, as well as random variation.

Implications for Long-Term Risk Assessment

The duration of exposure to risk factors, such as elevated low-density lipoprotein cholesterol, plasma glucose, and blood pressure, influences long-term cardiovascular risk. For this reason, earlier treatment of risk factors is increasingly recommended in clinical practice guidelines. Secondary analyses from clinical trials have reported greater absolute benefit from preventive therapies for patients with higher plasma BNP concentrations during follow-up of ≤6 years. In the LIPID trial,[7,28] patients with higher compared with lower BNP concentrations had a greater absolute decrease in major CHD events on pravastatin compared with placebo. In the Systolic Blood Pressure Intervention trial,[29] patients with NT-proBNP at baseline ≥ versus <125 pg/mL had a greater absolute decrease in hospitalization for heart failure or death when the blood pressure target was <120 mm Hg compared with <140 mm Hg.

Study Limitations

This study did not evaluate the optimal frequency of BNP measurements for long-term cardiovascular risk assessment, or the importance of time between measurements. Intercurrent cardiac events could influence BNP concentration, but secondary analyses that excluded patients who had an acute cardiovascular event between baseline and 1 year did not change study findings. Because of random variation in BNP concentrations, additional measurements would be expected to provide a more reliable estimate of "long-term average BNP concentration," and would also more reliably identify true changes in cardiac function, if present, over time.

HRs for BNP concentrations and cardiovascular death were lower in fully adjusted models compared with models that only adjusted for age, sex, and treatment group, suggesting that part of this association is mediated by other risk factors. The current analysis did not include evaluation of other biomarkers associated with cardiovascular death in previous analyses, such as troponin, D-dimer, and cystatin C.[7] However, for each patient, baseline clinical and demographic variables and prognostic biomarkers were the same for each of the landmark time periods, and for comparison of baseline, 1 year, and average BNP, and therefore do not bias these comparisons. Associations of BNP with noncardiovascular/noncancer deaths could reflect possible contamination with cardiovascular causes not meeting the study criteria for adjudication as cardiovascular death, but the application of definitions was according to standard practice for most large cardiovascular trials.

Outcomes for patients with CHD have improved with improved treatments during the years since patients were randomized into the LIPID trial. Left ventricular ejection fraction was not assessed routinely as part of the LIPID trial, but patients with a known left ventricular ejection fraction <35% or with New York Heart Association class 3 or 4 symptoms were excluded.[17–19] Despite these limitations, which would be expected to decrease the strength of association between BNP and cardiovascular mortality over time,

BNP retained its predictive power for cardiovascular mortality over at least 16 years. It is therefore unlikely that these factors substantially influenced study results or conclusions.

CONCLUSIONS

In patients with a history of myocardial infarction or unstable angina 3 to 36 months previously, the strength of association between plasma BNP concentration and the risk of cardiovascular death was sustained for at least a decade. Because there is considerable random variation in plasma concentrations of BNP, the average of 2 BNP measurements 1 year apart was a more accurate predictor compared with BNP measured at either baseline or 1 year only.

Supplemental Material

Table S1
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Cardiovascular mortality rate during follow-up by average of baseline and one year BNP level.

Landmark analyses were used to stratify CV mortality during periods of 1-5, 6 to 10 and11 to 16 years after randomisation. This data is presented graphically in Figure 2.

	Number of subjects	CV deaths from 1 to 16 years Number (%)	CV mortality rate per 1000 person years		
			During years 1 to <5 *n*=6740	During years 5 to <10 *n*=6214	During years >10 to 16 *n*=5185
All subjects	6740	1640 (24%)	10.2	19.1	26.3
Average BNP, pg/ml					
≤6.25	937	112 (8%)	5.8	9.0	10.1
6.25 to ≤12.5	1031	156 (11%)	4.9	9.4	17.8
12.5 to ≤25	1544	298 (14%)	5.7	14.0	21.9
25 to ≤50	1649	384 (17%)	8.3	17.8	26.9
50 to ≤100	1054	408 (32%)	16.1	33.7	48.9
>100	525	282 (55%)	35.5	64.3	75.9

Figure S1. Difference between Log(2) BNP measured at baseline and one year in stable patients with coronary heart disease.