

ORIGINAL ARTICLE

# N-Terminal Pro-B-Type Natriuretic Peptide and Long-Term Mortality in Stable Coronary Heart Disease

Charlotte Kragelund, M.D., Bjørn Grønning, M.D., Lars Køber, D.M.Sc., Per Hildebrandt, D.M.Sc., and Rolf Steffensen, M.D.

ABSTRACT

**BACKGROUND**

The level of the inactive N-terminal fragment of pro-brain (B-type) natriuretic peptide (BNP) is a strong predictor of mortality among patients with acute coronary syndromes and may be a strong prognostic marker in patients with chronic coronary heart disease as well. We assessed the relationship between N-terminal pro-BNP (NT-pro-BNP) levels and long-term mortality from all causes in a large cohort of patients with stable coronary heart disease.

**METHODS**

NT-pro-BNP was measured in baseline serum samples from 1034 patients referred for angiography because of symptoms or signs of coronary heart disease. The rate of death from all causes was determined after a median follow-up of nine years.

**RESULTS**

At follow-up, 288 patients had died. The median NT-pro-BNP level was significantly lower among patients who survived than among those who died (120 pg per milliliter [interquartile range, 50 to 318] vs. 386 pg per milliliter [interquartile range, 146 to 897],  $P < 0.001$ ). Patients with NT-pro-BNP levels in the highest quartile were older, had a lower left ventricular ejection fraction (LVEF) and a lower creatinine clearance rate, and were more likely to have a history of myocardial infarction, clinically significant coronary artery disease, and diabetes than patients with NT-pro-BNP levels in the lowest quartile. In a multivariable Cox regression model, the hazard ratio for death from any cause for the patients with NT-pro-BNP levels in the fourth quartile as compared with those in the first quartile was 2.4 (95 percent confidence interval, 1.5 to 4.0;  $P < 0.001$ ); the NT-pro-BNP level added prognostic information beyond that provided by conventional risk factors, including the patient's age; sex; family history with respect to ischemic heart disease; the presence or absence of a history of myocardial infarction, angina, hypertension, diabetes, or chronic heart failure; creatinine clearance rate; body-mass index; smoking status; plasma lipid levels; LVEF; and the presence or absence of clinically significant coronary artery disease on angiography.

**CONCLUSIONS**

NT-pro-BNP is a marker of long-term mortality in patients with stable coronary disease and provides prognostic information above and beyond that provided by conventional cardiovascular risk factors and the degree of left ventricular systolic dysfunction.

From the Department of Cardiology and Endocrinology, Frederiksberg Hospital, Frederiksberg (C.K., B.G., P.H.); the Department of Cardiology, Rigshospitalet, Copenhagen (L.K.); and the Department of Cardiology, Hillerød University Hospital, Copenhagen (R.S.) — all in Denmark. Address reprint requests to Dr. Kragelund at the Department of Cardiology and Endocrinology, Frederiksberg Hospital, University of Copenhagen, Nordre Fasanvej 57, DK-2000 Frederiksberg, Denmark, or at kragelund@dadlnet.dk.

N Engl J Med 2005;352:666-75.  
Copyright © 2005 Massachusetts Medical Society.

**B**RAIN (B-TYPE) NATRIURETIC PEPTIDE (BNP) is a peptide hormone released primarily from the cardiac ventricles in response to myocyte stretch. It is synthesized as an inactive prohormone that is split into the active hormone BNP and the inactive N-terminal fragment (NT-pro-BNP). BNP has a number of systemic effects, including vasodilation, increases in urinary volume and sodium output, and inhibition of the sympathetic nervous system and the renin–angiotensin–aldosterone system.<sup>1,2</sup>

It is widely believed that the predominant pathophysiological process underlying increased circulating levels of BNP and NT-pro-BNP is regional or global impairment of left ventricular systolic or diastolic function leading to increased left ventricular wall stretch. In addition, elevated BNP and NT-pro-BNP levels may not only reflect increased left ventricular wall stress but may also result directly from cardiac ischemia.<sup>3</sup>

The prognostic importance of BNP and NT-pro-BNP has been extensively studied in patients with heart failure as well as in patients with acute coronary syndromes, and both markers have been shown to be strong predictors of morbidity and mortality.<sup>4–6</sup> Recently, data from the Framingham Heart Study identified BNP as a strong predictor of morbidity and mortality in the general population even when BNP levels were below the threshold of 100 pg per milliliter normally used to identify patients with heart failure.<sup>7</sup>

However, the prognostic importance of natriuretic peptides in patients with chronic coronary artery disease is unknown. Therefore, we undertook the present study to evaluate the effect of the level of NT-pro-BNP on long-term mortality from all causes in a large cohort of patients with stable coronary artery disease; our emphasis was on patients with angiographic evidence of coronary disease and normal left ventricular systolic function.

## METHODS

Dr. Kragelund, Dr. Steffensen, and Dr. Hildebrandt designed the study. Dr. Kragelund and Dr. Steffensen gathered the data. Dr. Kragelund, Dr. Køber, and Dr. Grønning analyzed the data. Dr. Kragelund wrote the article, and vouches for the data and the analyses. All authors critically reviewed the manuscript. Roche Diagnostics provided the assay kits and measured NT-pro-BNP but had no other role in the study.

## STUDY PATIENTS

We conducted a prospective observational study of the prognostic value of NT-pro-BNP in a large consecutive series of patients with symptoms or signs of coronary artery disease who were referred to the Rigshospitalet in Copenhagen for elective coronary angiography from February 1, 1991, through February 1, 1993. If patients underwent angiography more than once, our analysis was based only on data obtained at the time of the first angiographic study. Patients with valve disease or a congenital disorder were excluded. A total of 1078 consenting patients who had angina pectoris or had evidence of ischemia on exercise electrocardiography or myocardial radionuclide imaging were enrolled. In 44 patients, no serum samples were available for subsequent measurement of NT-pro-BNP. Consequently, the remaining 1034 patients were included in the analysis. The Danish Health Authorities and the Regional Ethics Committee approved the study, and written informed consent was obtained from all participating subjects.

## CORONARY ANGIOGRAPHY AND LEFT VENTRICULOGRAPHY

At baseline, selective coronary angiography and left ventriculography were performed, with recording on cineangiographic film. Two experienced invasive cardiologists, who were blinded to the patients' NT-pro-BNP measurements, evaluated the angiograms. The left ventricular ejection fraction (LVEF) was calculated from a single view (right anterior oblique, 30 degrees) by the area–length method.<sup>8</sup> Left ventricular end-diastolic pressure was registered in a subgroup of 288 patients. The number of stenotic vessels was recorded, and patients were classified as having one-, two-, or three-vessel disease or stenosis of the left main coronary artery. A narrowing of the lumen by more than 70 percent of the prestenotic diameter was considered to indicate clinically significant stenosis, except for the left main artery, in which a narrowing of more than 50 percent was considered clinically significant.

## BASELINE MEASUREMENTS

In all patients, a thorough medical history was recorded, including details of any previous myocardial infarction, previous revascularization, angina pectoris, arterial hypertension, suspected congestive heart failure (defined by symptoms of shortness of breath or leg edema), previous stroke or transient ischemic attacks, diabetes, intermittent claudication,

**Table 1. Baseline Clinical Characteristics According to Quartiles of NT-pro-BNP.\***

Characteristic	1st Quartile (N=258)	2nd Quartile (N=259)	3rd Quartile (N=259)	4th Quartile (N=258)	P Value
NT-pro-BNP level (pg/ml)	5–63	64–169	170–455	456–13,889	
Age (yr)					<0.001
Median	54	58	59	64	
Interquartile range	48–60	52–63	53–68	57–69	
Male sex (%)	72	70	74	75	0.51
Family history of ischemic heart disease (%)	40	37	38	24	<0.001
Medical history (%)					
Suspected heart failure†	57	56	61	67	0.08
NYHA functional class					
I	22	19	20	12	
II	59	58	61	58	
III	16	19	17	26	
IV	4	4	3	3	
Hypertension	26	32	29	36	0.10
Diabetes	16	18	16	26	0.01
Previous myocardial infarction	33	49	61	70	<0.001
Peripheral vascular disease	9	14	13	16	0.26
Cerebrovascular disease	3	8	5	6	0.13
Hypercholesterolemia	38	48	37	26	<0.001
Angina pectoris	93	94	87	85	0.001
CCS class					
I	27	28	20	12	
II	47	42	40	44	
III	21	26	36	38	
IV	5	4	4	6	
Positive exercise test (%)	15	16	17	16	0.25
Positive radionuclide scan (%)	3	2	2	2	0.36
Previous PTCA (%)	2	2	1	1	0.47
Previous CABG (%)	3	9	7	5	0.05

and smoking status; information came from medical records, directly from patients, or both.

In the morning of the day that angiography was performed with the patient in the supine position, fasting blood samples were drawn for measurement of plasma glucose, lipids, and creatinine. One sample was allowed to stand for 30 minutes for coagulation; the remaining serum was immediately frozen in plastic containers at  $-80^{\circ}\text{C}$ . NT-pro-BNP was measured in January 2004 with use of a commercially available immunoassay based on the sandwich technique (Elecsys proBNP, Roche Diagnostics). The lower limit of detection was 5 pg per milliliter. Intraassay and interassay coefficients of variation

at different concentrations of NT-pro-BNP relevant to this study were as follows: at 175 pg per milliliter, 2.7 percent and 3.2 percent, respectively; at 355 pg per milliliter, 2.4 percent and 2.9 percent; at 1068 pg per milliliter, 1.9 percent and 2.6 percent; and at 4962 pg per milliliter, 1.8 percent and 2.3 percent.

The creatinine clearance rate, expressed in milliliters per minute, was calculated from the equation of Cockcroft and Gault, as follows:  $[(140 - \text{age}) \times \text{weight in kilograms}] \div \text{serum creatinine in micromoles per liter}$ , multiplied by a constant of 1.25 for men and 1.03 for women.

Information on vital status was obtained from

**Table 1. (Continued.)**

Characteristic	1st Quartile (N=258)	2nd Quartile (N=259)	3rd Quartile (N=259)	4th Quartile (N=258)	P Value
Low-fat or low-cholesterol diet (%)	53	58	47	44	0.02
Regular exercise (%)	38	41	39	35	0.60
Current smoker (%)	42	41	39	37	0.44
Angiographic findings (%)					<0.001
No coronary artery disease	31	19	14	16	
1-Vessel disease	28	21	13	18	
2-Vessel disease	19	24	23	19	
3-Vessel disease	15	26	40	36	
Left main coronary artery disease	7	10	10	11	
LVEF (%)					<0.001
≥60	80	61	34	25	
45–59	18	29	42	27	
30–44	2	9	22	34	
<30	0	0.4	2	14	
Body-mass index‡					0.001
Median	26	26	26	25	
Interquartile range	24–28	24–29	24–28	23–28	
LVEDP (mm Hg)					<0.001
Median	14	15	16	18	
Interquartile range	10–18	12–17	13–19	15–24	
Creatinine clearance (ml/min)					<0.001
Median	85	78	74	65	
Interquartile range	69–102	65–92	60–90	52–78	

\* NYHA denotes New York Heart Association, CCS Canadian Cardiovascular Society, PTCA percutaneous transluminal coronary angioplasty, CABG coronary-artery bypass grafting, LVEF left ventricular ejection fraction, and LVEDP left ventricular end-diastolic pressure. Percentages may not total 100 because of rounding. P values are for the overall comparison among the groups.

† Suspected heart failure includes patients with any symptoms of shortness of breath, leg edema, or both.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

the Danish Central Person Registry by means of a computerized search performed on August 1, 2001. No patients were lost to follow-up.

#### STATISTICAL ANALYSIS

Baseline characteristics of the study patients, grouped according to quartiles of NT-pro-BNP, are presented as percentages for dichotomous variables and medians with interquartile ranges for continuous variables. Baseline characteristics were compared among quartiles with use of the chi-square test for discrete variables and the Wilcoxon or Kruskal–Wallis rank-sum test for continuous variables, as appropriate. Additional NT-pro-BNP analyses were performed in subgroups defined ac-

ording to LVEF and the results of angiography. Survival curves were generated by means of Kaplan–Meier estimates, and differences in survival were compared with use of the log-rank test. To evaluate the effect of different levels of NT-pro-BNP on mortality, relative risks and 95 percent confidence intervals were calculated as hazard ratios derived from the Cox proportional-hazards regression model. Multivariable models were fitted with use of the available clinical covariates. The assumptions underlying the proportional-hazards model (proportional hazards, lack of interaction, and linearity of continuous variables) were tested and found valid unless otherwise indicated.

The patients were classified according to the se-

**Table 2. Baseline Clinical Characteristics According to the Left Ventricular Ejection Fraction (LVEF) and the Presence or Absence of Clinically Significant Coronary Artery Disease (CAD).\***

Characteristic	LVEF $\geq$ 60%			LVEF <60%		
	No CAD (N=152)	CAD (N=354)	P Value	No CAD (N=55)	CAD (N=473)	P Value
Age (yr)			<0.001			0.02
Median	56	59		54	59	
Interquartile range	47–63	52–65		46–67	54–66	
Male sex (%)	33	76	<0.001	62	84	<0.001
Family history of ischemic heart disease (%)	38	40	0.62	16	33	0.01
Medical history (%)						
Suspected heart failure†	69	52	<0.001	67	63	0.61
NYHA functional class						
I	13	22		17	17	
II	64	60		35	58	
III	17	15		48	21	
IV	6	3		0	3	
Hypertension	26	34	0.08	20	32	0.07
Diabetes	13	19	0.13	15	22	0.21
Previous myocardial infarction	17	43	<0.001	43	73	<0.001
Peripheral vascular disease	11	11	0.61	11	15	0.76
Cerebrovascular disease	8	6	0.26	2	5	0.33
Hypercholesterolemia	31	41	0.03	27	38	0.13
Angina pectoris	89	93	0.11	63	90	<0.001
CCS class						
I	26	23		20	20	
II	45	45		45	41	
III	24	28		25	36	
IV	5	4		10	6	
Previous PTCA (%)	0.7	1.4	0.50	0	1.5	0.38
Previous CABG (%)	0.7	6	0.01	2	9	0.10

verity of coronary artery disease as having no clinically significant disease, one-, two-, or three-vessel disease, or disease of the left main coronary artery. Patients with three-vessel and left main coronary artery disease had similar mortality rates and were therefore combined into one group in the regression analysis. Analyses were performed with NT-pro-BNP, in quartiles, as a categorical variable with the lowest quartile serving as reference for the other three quartiles. A backward-elimination model was applied. Tests were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. All calculations were generated by SAS software, version 8.2.

## RESULTS

### DEMOGRAPHIC CHARACTERISTICS

After a median follow-up of 9.2 years, 288 of the 1034 patients (28 percent) had died. The median NT-pro-BNP level for all subjects was elevated (169 pg per milliliter; interquartile range, 63 to 456) and was significantly lower among patients who survived than among those who died (120 pg per milliliter [interquartile range, 50 to 318] vs. 386 pg per milliliter [146 to 897],  $P < 0.001$ ). The patients were divided into subgroups according to quartiles of NT-pro-BNP. Patients with NT-pro-BNP in the upper quartile were older, had a higher left ventricular

**Table 2. (Continued.)**

Characteristic	LVEF $\geq$ 60%			LVEF <60%		
	No CAD (N=152)	CAD (N=354)	P Value	No CAD (N=55)	CAD (N=473)	P Value
Low-fat or low-cholesterol diet (%)	42	53	0.03	58	51	0.42
Regular exercise (%)	34	41	0.20	34	38	0.68
Current smoker (%)	35	40	0.32	49	41	0.33
Angiographic findings (%)						<0.001‡
No CAD	100	0		100	0	
1-Vessel disease	0	33		0	18	
2-Vessel disease	0	30		0	24	
3-Vessel disease	0	26		0	45	
Left main coronary artery disease	0	11		0	13	
NT-pro-BNP (pg/ml)			0.02			0.28
Median	65	83		343	305	
Interquartile range	31–159	45–232		164–1085	147–738	
Creatinine clearance (ml/min)			0.31			0.99
Median	75	79		74	74	
Interquartile range	62–94	65–93		60–91	60–90	

\* NYHA denotes New York Heart Association, CCS Canadian Cardiovascular Society, PTCA percutaneous transluminal coronary angioplasty, and CABG coronary-artery bypass grafting. Percentages may not total 100 because of rounding.

† Suspected heart failure includes patients with any symptoms of shortness of breath, leg edema, or both.

‡ The P value is for the comparison between the groups with normal LVEF and those with reduced LVEF.

end-diastolic pressure, and were more likely to have a history of myocardial infarction, clinically significant coronary artery disease, and diabetes; the LVEF, body-mass index (the weight in kilograms divided by the square of the height in meters), and creatinine clearance rate were lower than among patients with NT-pro-BNP levels in the lowest quartile. Table 1 shows the baseline characteristics according to quartiles of NT-pro-BNP.

#### RELATION OF NT-PRO-BNP LEVELS TO ANGIOGRAPHIC STATUS AND LVEF

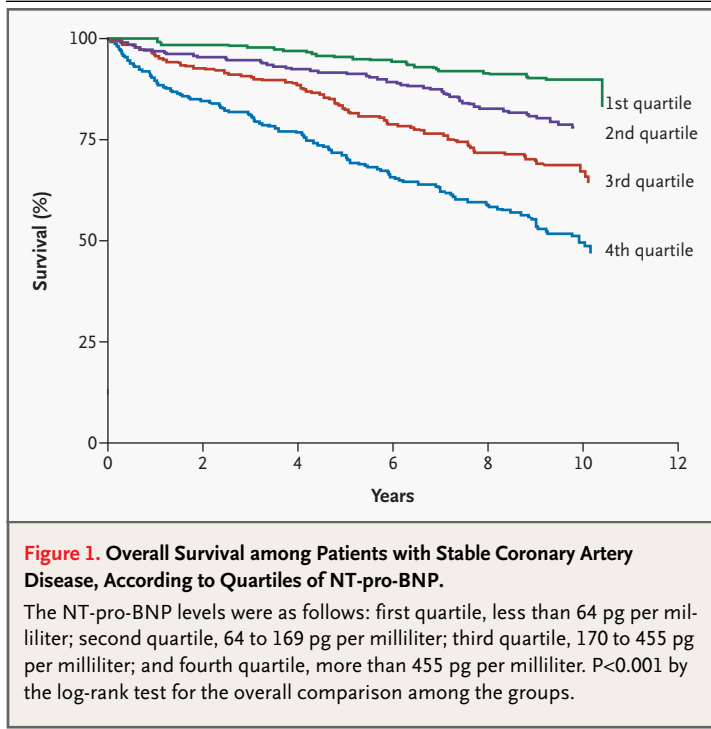
The NT-pro-BNP level increased with the severity of angiographic disease and of left ventricular systolic dysfunction. In the subgroup of the population with normal LVEF (i.e.,  $\geq$ 60 percent; 506 patients), the level of NT-pro-BNP was significantly higher in patients with than in those without coronary artery disease. Table 2 shows the baseline characteristics of patients according to LVEF and the presence or absence of coronary artery disease.

#### RELATION OF NT-PRO-BNP AND MORTALITY FROM ALL CAUSES

Kaplan–Meier estimates of survival for all subjects according to quartiles of NT-pro-BNP are shown in

Figure 1. In a Cox regression analysis with the NT-pro-BNP level as a categorical variable, the unadjusted hazard ratios for death of patients with NT-pro-BNP levels in the second, third, and fourth quartiles, as compared with those in the first quartile, were 2.1 (95 percent confidence interval, 1.3 to 3.3;  $P=0.002$ ), 3.5 (95 percent confidence interval, 2.3 to 5.4;  $P<0.001$ ), and 6.1 (95 percent confidence interval, 4.0 to 9.2;  $P<0.001$ ), respectively. In a multivariable Cox regression model, the hazard ratio for death among patients in the second quartile of NT-pro-BNP, as compared with those in the first quartile, was 1.5 (95 percent confidence interval, 0.94 to 2.6;  $P=0.09$ ), that for the third quartile was 1.9 (95 percent confidence interval, 1.2 to 3.0;  $P=0.007$ ), and that for the fourth quartile was 2.4 (95 percent confidence interval, 1.5 to 4.0;  $P<0.001$ ).

NT-pro-BNP added prognostic information above and beyond that provided by age; sex; family history with respect to ischemic heart disease; presence or absence of previous and recent myocardial infarction; presence or absence of angina; Canadian Cardiovascular Society (CCS) class; presence or absence of hypertension, diabetes, suspected heart failure, and prior revascularization; smoking status; results of stress testing; body-mass index; creatinine



clearance rate; plasma lipid level; LVEF; left ventricular end-diastolic pressure; and severity of coronary artery disease at angiography. Excluding the 41 patients with CCS class 4 angina did not significantly change the results (hazard ratio for the fourth quartile as compared with the first, 1.8 [95 percent confidence interval, 1.3 to 2.6];  $P < 0.001$ ). Hazard ratios after the backward elimination of the non-significant variables are shown in Table 3. Adjusted Kaplan-Meier estimates of survival according to quartiles of NT-pro-BNP are shown in Figure 2.

Further analyses of subgroups of patients with LVEF values of 60 percent or more and less than 60 percent yielded the same results. In patients with LVEF values of less than 60 percent, the adjusted hazard ratio for death in the fourth quartile of NT-pro-BNP, as compared with the first quartile, was 3.1 (95 percent confidence interval, 1.2 to 8.1;  $P < 0.001$ ). Among patients with an LVEF above 60 percent and clinically significant coronary artery disease on angiography, NT-pro-BNP remained a strong prognostic marker, with an adjusted hazard ratio of 1.9 (95 percent confidence interval, 1.2 to 3.3;  $P = 0.01$ ) for the fourth versus the first quartile of NT-pro-BNP. Among patients with an LVEF of 60 percent or more but without angiographic evidence of coronary artery disease, the same trend

was observed, but was not significant, presumably because of the lower number of patients.

## DISCUSSION

Our study demonstrates that NT-pro-BNP measured immediately before coronary angiography in patients with stable coronary heart disease provides prognostic information on mortality from all causes that is independent of invasive measurements of left ventricular function and the severity of coronary artery disease. These results extend currently available information about the value of NT-pro-BNP and BNP as markers of risk in the general population and among patients with acute coronary syndromes to a new population of patients with stable coronary disease who are at “intermediate” risk, thereby widening the spectrum of clinical usefulness of NT-pro-BNP as a prognostic marker.

The findings of the present study support previous studies suggesting that the elevation of NT-pro-BNP is associated with coronary heart disease.<sup>9,10</sup> However, unlike previous investigators, we used angiographically diagnosed coronary artery disease to define existing coronary heart disease. Patients with high NT-pro-BNP levels had a significantly higher prevalence of coronary disease at angiography than patients with low concentrations of NT-pro-BNP. Interestingly, this association was also seen in the group of patients with normal left ventricular systolic function.

In this study, NT-pro-BNP was elevated in patients with stable angina, a condition characterized by transient ischemic episodes. It was also elevated in patients with angiographically verified coronary atherosclerosis, regardless of left ventricular systolic function. Recent studies have suggested that ischemia itself, rather than changes in left ventricular wall stress secondary to ischemia, promotes the release of BNP,<sup>11</sup> but the responsible mechanisms still remain to be fully elucidated.

In support of this notion, it is well known that acute myocardial infarction is associated with activation of the neurohormonal system that causes increases in levels of natriuretic peptides,<sup>12</sup> in particular NT-pro-BNP,<sup>13</sup> which predicts poor short-term and long-term outcome, independently of ventricular function.<sup>5,14-16</sup> Nevertheless, only a few studies have examined the association between BNP and NT-pro-BNP and ischemia, and the results have been conflicting.<sup>17-19</sup>

The study by Bibbins-Domingo and colleagues,<sup>19</sup>

**Table 3 Hazard Ratios for Death from Any Cause in the Multivariable Model.\***

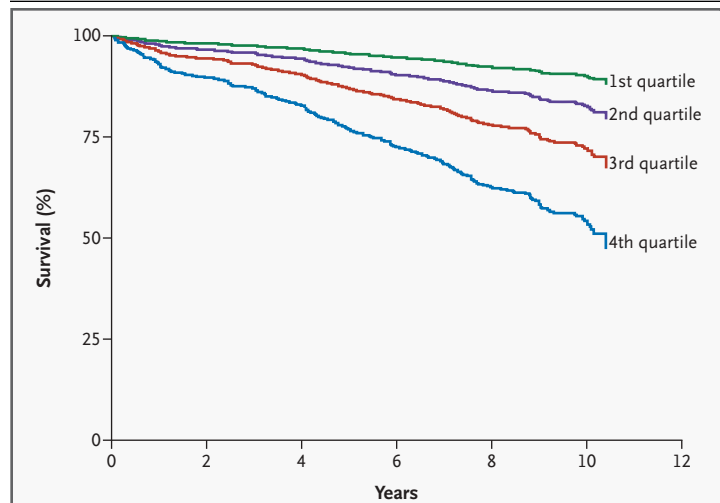
Variable	Hazard Ratio (95% CI)	P Value
NT-pro-BNP (4th vs. 1st quartile)	2.4 (1.5–4.0)	<0.001
Age (per 10-yr increase)	1.6 (1.4–1.9)	<0.001
Diabetes	1.7 (1.3–2.2)	<0.001
Cigarette smoking	1.6 (1.2–2.0)	<0.001
CAD (severe vs. none)†	1.8 (1.2–2.6)	0.002
LVEF (per 10% decrease)	1.2 (1.1–1.4)	<0.001
Suspected heart failure	1.8 (1.4–2.4)	<0.001

\* Relative risk and 95 percent confidence interval (CI) were calculated as hazard ratios derived from the Cox proportional-hazards regression model for overall mortality after backward elimination of the nonsignificant variables. Covariates included in the initial model were age, sex, NT-pro-BNP level, family history with respect to ischemic heart disease, presence or absence of previous and recent myocardial infarction, presence or absence of angina, Canadian Cardiovascular Society class, results of exercise testing, presence or absence of previous revascularization, hypertension, diabetes, suspected heart failure, creatinine clearance rate, smoking status, lipid levels, body-mass index, left ventricular ejection fraction (LVEF), and severity of coronary disease at angiography.

† The hazard ratio is for three-vessel and left main coronary artery disease (CAD) as compared with no clinically significant coronary artery disease on angiography.

which included 355 patients with stable coronary disease, showed that elevated levels of BNP were associated with inducible ischemia, suggesting an explanation for the increased risk of subsequent coronary events in patients with elevated BNP. Furthermore, BNP is associated with the occurrence of transient ischemic episodes during percutaneous transluminal coronary angioplasty. In a study by Tateishi and colleagues,<sup>20</sup> the transient increase in BNP during balloon inflation was independent of hemodynamic variables. However, there was no correlation between BNP and the volume of ischemic myocardium or the duration of ischemia. The mechanism involved remains unclear, but two studies have demonstrated increased cardiac BNP gene expression in the ischemic left ventricle, suggesting that elevated levels of BNP and NT-pro-BNP may result from cardiac ischemia.<sup>3,21</sup>

NT-pro-BNP has repeatedly been shown to be elevated in patients with left ventricular dysfunction.<sup>4,14,22</sup> We measured the LVEF with single-plane contrast ventriculography, previously regarded as

**Figure 2. Adjusted Estimates of Overall Survival among Patients with Stable Coronary Disease, According to Quartiles of NT-pro-BNP.**

The survival estimates have been adjusted for age, presence or absence of diabetes, smoking status, left ventricular ejection fraction, presence or absence of suspected heart failure, and severity of angiographic coronary disease. The NT-pro-BNP levels were as follows: first quartile, less than 64 pg per milliliter; second quartile, 64 to 169 pg per milliliter; third quartile, 170 to 455 pg per milliliter; and fourth quartile, more than 455 pg per milliliter.  $P < 0.001$  by the log-rank test for the overall comparison among the groups.

the gold standard for LVEF measurements. In our study population, with more than half of patients having had a previous myocardial infarction and therefore likely to have abnormal left ventricular geometry, this technique may have some limitations, as it relies on geometric assumptions and therefore may overestimate LVEF. Despite these limitations, previous studies have found a relatively good correlation between LVEF as determined by echocardiography and as determined by contrast ventriculography.<sup>23</sup> However, the possibility remains that the elevated NT-pro-BNP levels in patients with normal LVEF, as determined by standard imaging methods such as echocardiography, reflect unrecognized left ventricular remodeling that is detectable only by high-definition methods, such as magnetic resonance imaging.<sup>24</sup>

In our study of the prognostic importance of NT-pro-BNP in intermediate-risk patients with stable coronary disease, we found NT-pro-BNP to be a prognostic marker of long-term mortality from all causes. BNP and NT-pro-BNP have previously been shown to be predictors of cardiovascular morbidity and mortality in the general population,<sup>7</sup> among pa-

tients with acute coronary syndromes, and among patients with heart failure.<sup>4,5,25</sup>

The increased risk of death we observed among patients with elevated NT-pro-BNP may be a consequence of a higher frequency of coronary events. The mortality rate among our patients was similar to the rates in other recent studies of patients with angiographic evidence of coronary artery disease.<sup>26</sup> Information on the causes of death was not available in our study, but other studies of patients with stable coronary heart disease and similar mortality rates have demonstrated that the chief causes of death are myocardial infarction and sudden death.<sup>27</sup> Moreover, the association of NT-pro-BNP in our study was independent of both LVEF and left ventricular end-diastolic pressure, thus providing further evidence in support of the hypothesis that ischemia directly promotes the release of NT-pro-BNP, in a manner that is independent of left ventricular wall stress.

To explore this hypothesis further, we adjusted our prognostic models for the severity of coronary artery disease on angiography. Because angiographic measures may not fully account for eccentric atherosclerotic lesions in the coronary vessel wall, the possibility remains that the severity of coronary artery disease on angiography does not fully reflect the functional ischemic burden. One could therefore speculate that including the results of measurements of cardiac ischemia that may be more sensitive, such as radionuclide stress testing, in the multivariable analysis might attenuate the prognostic value of NT-pro-BNP. Unfortunately, only 10 percent of the patients in our study underwent radionuclide stress testing; the data sample was therefore insufficient for any attempts at a meaningful analysis.

Other potential confounders of the association between increasing levels of NT-pro-BNP and mortality include atrial fibrillation and left ventricular systolic dysfunction, which a convincing body of evidence shows is strongly associated with BNP and NT-pro-BNP. Unfortunately, information on atrial fibrillation was not available. We adjusted for left ventricular dysfunction, but the possibility of undetected systolic and diastolic dysfunction remains.

For the purpose of optimal risk stratification and for the targeting of treatment strategies, a multimarker strategy has become increasingly common in the management of acute coronary syndromes.<sup>16,28,29</sup> In stable coronary disease, early identification of specific groups of patients at increased risk or even at very low risk is equally justified. With limited resources, careful risk stratification could potentially identify patients who would benefit the most from specific treatment strategies and make it possible to avoid overtreating patients at low risk. In this study we have identified NT-pro-BNP as a marker of increased risk, one independent of invasive measures of left ventricular dysfunction and the severity of coronary disease. Further studies will show whether treatment strategies guided by NT-pro-BNP levels will decrease morbidity and mortality in patients with stable coronary disease and whether NT-pro-BNP will find a place in the routine clinical stratification of risk among such patients.

Supported by the Danish Pharmacists Foundation. Dr. Kragelund is the recipient of a junior research fellowship from the Danish Heart Foundation (grant no. 00-2-9-10-22011). Roche Diagnostics supplied the assay kits and measured NT-pro-BNP in patients' samples.

Dr. Hildebrandt reports having received consulting and lecture fees from Roche Diagnostics.

#### REFERENCES

- Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med* 1998; 339:321-8.
- Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail* 2004;6:257-60.
- Goetze JP, Christoffersen C, Perko M, et al. Increased cardiac BNP expression associated with myocardial ischemia. *FASEB J* 2003;17:1105-7.
- Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation* 1997;96:509-16.
- Omland T, Persson A, Ng L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation* 2002;106:2913-8.
- de Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001;345:1014-21.
- Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004;350:655-63.
- Dodge HT, Sheehan FH. Quantitative contrast angiography for assessment of ventricular performance in heart disease. *J Am Coll Cardiol* 1983;1:73-81.
- James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation* 2003; 108:275-81.
- Jernberg T, Stridsberg M, Venge P, Lindahl B. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. *J Am Coll Cardiol* 2002; 40:437-45.
- D'Souza SP, Baxter GF. B type natriuretic peptide: a good omen in myocardial ischaemia? *Heart* 2003;89:707-9.
- Morita E, Yasue H, Yoshimura M, et al. Increased plasma levels of brain natriuretic

- peptide in patients with acute myocardial infarction. *Circulation* 1993;88:82-91.
13. Gill D, Seidler T, Troughton RW, et al. Vigorous response in plasma N-terminal pro-brain natriuretic peptide (NT-BNP) to acute myocardial infarction. *Clin Sci (Lond)* 2004;106:135-9.
  14. Omland T, Aakvaag A, Bonarjee VV, et al. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction: comparison with plasma atrial natriuretic peptide and N-terminal proatrial natriuretic peptide. *Circulation* 1996;93:1963-9.
  15. Talwar S, Squire IB, Downie PF, et al. Profile of plasma N-terminal proBNP following acute myocardial infarction: correlation with left ventricular systolic dysfunction. *Eur Heart J* 2000;21:1514-21.
  16. Sabatine MS, Morrow DA, de Lemos JA, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation* 2002;105:1760-3.
  17. Talwar S, Squire IB, Downie PF, Davies JE, Ng LL. Plasma N terminal pro-brain natriuretic peptide and cardiostrophin 1 are raised in unstable angina. *Heart* 2000;84:421-4.
  18. Marumoto K, Hamada M, Hiwada K. Increased secretion of atrial and brain natriuretic peptides during acute myocardial ischaemia induced by dynamic exercise in patients with angina pectoris. *Clin Sci (Lond)* 1995;88:551-6.
  19. Bibbins-Domingo K, Ansari M, Schiller NB, Massie B, Whooley MA. B-type natriuretic peptide and ischemia in patients with stable coronary disease: data from the Heart and Soul study. *Circulation* 2003;108:2987-92.
  20. Tateishi J, Masutani M, Ohyanagi M, Iwasaki T. Transient increase in plasma brain (B-type) natriuretic peptide after percutaneous transluminal coronary angioplasty. *Clin Cardiol* 2000;23:776-80.
  21. D'Souza SP, Davis M, Baxter GF. Autocrine and paracrine actions of natriuretic peptides in the heart. *Pharmacol Ther* 2004;101:113-29.
  22. Richards AM, Nicholls MG, Yandle TG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. *Circulation* 1998;97:1921-9.
  23. McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. *Am Heart J* 2003;146:388-97.
  24. Nilsson JC, Groenning BA, Nielsen G, et al. Left ventricular remodeling in the first year after acute myocardial infarction and the predictive value of N-terminal pro brain natriuretic peptide. *Am Heart J* 2002;143:696-702.
  25. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide: a new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J* 2003;24:1735-43.
  26. Cole JH, Miller JI III, Sperling LS, Weintraub WS. Long-term follow-up of coronary artery disease presenting in young adults. *J Am Coll Cardiol* 2003;41:521-8.
  27. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-8.
  28. Wiviott SD, Cannon CP, Morrow DA, et al. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non-ST-elevation myocardial infarction: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18) substudy. *Circulation* 2004;109:580-6.
  29. Morrow DA, de Lemos JA, Sabatine MS, et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST-elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS-TIMI 18. *J Am Coll Cardiol* 2003;41:1264-72. [Erratum, *J Am Coll Cardiol* 2003;41:1852.]

Copyright © 2005 Massachusetts Medical Society.

#### CLINICAL TRIAL REGISTRATION

The *Journal* encourages investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors plan to consider clinical trials for publication only if they have been registered (see *N Engl J Med* 2004;351:1250-1). The National Library of Medicine's [www.clinicaltrials.gov](http://www.clinicaltrials.gov) is a free registry, open to all investigators, that meets the committee's requirements.