

THE PROGNOSTIC VALUE OF B-TYPE NATRIURETIC PEPTIDE IN PATIENTS WITH ACUTE CORONARY SYNDROMES

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ABSTRACT

Background Brain (B-type) natriuretic peptide is a neurohormone synthesized predominantly in ventricular myocardium. Although the circulating level of this neurohormone has been shown to provide independent prognostic information in patients with transmural myocardial infarction, few data are available for patients with acute coronary syndromes in the absence of ST-segment elevation.

Methods We measured B-type natriuretic peptide in plasma specimens obtained a mean (\pm SD) of 40 ± 20 hours after the onset of ischemic symptoms in 2525 patients from the Orbofiban in Patients with Unstable Coronary Syndromes–Thrombolysis in Myocardial Infarction 16 study.

Results The base-line level of B-type natriuretic peptide was correlated with the risk of death, heart failure, and myocardial infarction at 30 days and 10 months. The unadjusted rate of death increased in a stepwise fashion among patients in increasing quartiles of base-line B-type natriuretic peptide levels ($P < 0.001$). This association remained significant in subgroups of patients who had myocardial infarction with ST-segment elevation ($P = 0.02$), patients who had myocardial infarction without ST-segment elevation ($P < 0.001$), and patients who had unstable angina ($P < 0.001$). After adjustment for independent predictors of the long-term risk of death, the odds ratios for death at 10 months in the second, third, and fourth quartiles of B-type natriuretic peptide were 3.8 (95 percent confidence interval, 1.1 to 13.3), 4.0 (95 percent confidence interval, 1.2 to 13.7), and 5.8 (95 percent confidence interval, 1.7 to 19.7). The level of B-type natriuretic peptide was also associated with the risk of new or recurrent myocardial infarction ($P = 0.01$) and new or worsening heart failure ($P < 0.001$) at 10 months.

Conclusions A single measurement of B-type natriuretic peptide, obtained in the first few days after the onset of ischemic symptoms, provides predictive information for use in risk stratification across the spectrum of acute coronary syndromes. Cardiac neurohormonal activation may be a unifying feature among patients at high risk for death after acute coronary syndromes. (N Engl J Med 2001;345:1014-21.)

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BRAIN (B-type) natriuretic peptide is a 32-amino-acid neurohormone synthesized in ventricular myocardium and released into the circulation in response to ventricular dilatation and pressure overload.¹⁻³ The actions of this peptide, like those of atrial (A-type) natriuretic peptide, include natriuresis, vasodilatation, inhibition of the renin–angiotensin–aldosterone axis, and inhibition of sympathetic nerve activity.⁴ The plasma level of B-type natriuretic peptide is elevated in patients with congestive heart failure and increases in proportion to the degree of left ventricular dysfunction and the severity of symptoms of heart failure.^{2,5} After acute myocardial infarction, levels of B-type natriuretic peptide rise rapidly during the first 24 hours and then tend to stabilize.⁶⁻⁹ Measurement of the level of B-type natriuretic peptide between one and four days after a transmural infarction provides prognostic information that is independent of the left ventricular ejection fraction and other important base-line variables.^{8,10-14}

Studies evaluating the prognostic implications of B-type natriuretic peptide have been limited to patients with myocardial infarction with ST-segment elevation, and few data are available on patients who have acute coronary syndromes in the absence of ST-segment elevation. Patients with acute coronary syndromes are a heterogeneous group, with differences in pathophysiology, clinical presentation, and the risk of adverse events. We sought to evaluate the prognostic implications of cardiac neurohormonal activation, as reflected by the plasma level of B-type natriuretic peptide, across the entire spectrum of acute coronary syndromes.

METHODS

Study Population

The Oral Glycoprotein IIb/IIIa Inhibition with Orbofiban in Patients with Unstable Coronary Syndromes–Thrombolysis in Myocardial Infarction 16 trial was a randomized, multicenter trial comparing an oral platelet glycoprotein IIb/IIIa receptor inhibitor, or-

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bofiban, with placebo in 10,288 patients with acute coronary syndromes. The study protocol was approved by the institutional review board of each participating hospital, and all patients provided written informed consent. Patients were included if they presented within 72 hours after the onset of ischemic discomfort and met one or more of the following criteria: electrocardiographic changes (ST-segment depression or elevation of at least 0.5 mm, T-wave inversion of at least 3 mm in at least three leads, or left bundle-branch block), elevated levels of cardiac markers, a history of coronary disease, or an age of at least 65 years in patients with diabetes or vascular disease.¹⁵ Patients received 150 to 162 mg of aspirin daily and were randomly assigned to receive 50 mg of orbofiban twice daily; 50 mg of orbofiban twice daily for one month, followed by 30 mg of orbofiban twice daily; or placebo. The study was terminated prematurely because of an increase in mortality in the group assigned to receive 50 mg twice daily initially and then 30 mg twice daily.¹⁵ The present substudy included all 2525 patients who were assigned to the group given 50 mg of orbofiban twice daily and who provided a base-line plasma specimen suitable for analysis. The data were collected and retained by the study investigators, who also performed the analyses.

Blood Sampling

At the time of enrollment, blood specimens were collected in citrate-treated tubes and centrifuged for at least 12 minutes. The plasma component was frozen and shipped on dry ice to Children's Hospital (Boston), where samples were stored at -70°C . In 925 patients, C-reactive protein was measured with use of a high-sensitivity assay (N Latex CRP assay, Dade Behring, Newark, Del.) and fibrinogen was measured with use of a commercial assay on a BN II analyzer (Dade Behring). After the trial was completed, all available plasma specimens from the group given 50 mg of orbofiban twice daily were shipped to Biosite Diagnostics (San Diego, Calif.), where they were thawed and analyzed.

Biochemical Analyses

Sequential sandwich immunoassays for the quantification of B-type natriuretic peptide and troponin I were performed in 384-well microtiter plates with use of an automated system (Tecan Genesis robotic sample processor 200/8, Durham, N.C.). The amount of analyte was quantified on the basis of the level of binding of alkaline phosphatase-conjugated antibody. The analytic sensitivity of the B-type natriuretic peptide and troponin I immunoassays were approximately 5 pg per milliliter and 50 pg per milliliter, respectively.

End Points

The end points of death from any cause and nonfatal myocardial infarction were evaluated at 30 days and the end of the follow-up period (10 months). Myocardial infarction was defined according to previously reported criteria,¹⁶ and all cases of suspected infarction were adjudicated by a clinical-events committee. Information on the end point of new or worsening heart failure or cardiogenic shock was collected from the case-record forms.

Statistical Analysis

Patients were divided into quartiles on the basis of their B-type natriuretic peptide level at the time of enrollment. The mean values and proportions of base-line variables were compared among quartiles with the use of linear regression for continuous variables and log-linear analysis for categorical variables. The correlation between B-type natriuretic peptide levels and other continuous base-line variables was assessed with the use of Pearson's product-moment correlation coefficient. B-type natriuretic peptide levels were not adjusted for age.

To evaluate its association with clinical outcomes, B-type natriuretic peptide was considered as both a continuous and a categorical variable. The level of B-type natriuretic peptide was compared between patients who met a study end point and those who did not with use of the Wilcoxon rank-sum test. Cox regression analy-

sis was used to evaluate the association between the quartile of B-type natriuretic peptide and the risk of adverse outcomes for the first 30 days after randomization and at 10 months. Stratified analyses were performed among patients with various troponin I levels, as well as those with and those without a clinical diagnosis of heart failure. Analyses were performed in subgroups defined according to the index diagnosis. The quartile ranges were recalculated for each of these subgroups.

For the end point of death from any cause through the end of follow-up (10 months), we constructed a logistic-regression model using forward stepwise selection. Clinical variables for which data were available from more than 75 percent of patients were entered into the model if they had a univariate P value of less than 0.1; variables were removed if they had a multivariate P value greater than or equal to 0.1. Base-line levels of troponin I and B-type natriuretic peptide were then added to the completed model. The final model included only the 2280 patients for whom data were available for all variables. Finally, we performed analyses using the B-type natriuretic peptide threshold of 80 pg per milliliter that has been established for the diagnosis of congestive heart failure.¹⁷

RESULTS

The study population consisted of 2525 patients: 825 were enrolled after a myocardial infarction with ST-segment elevation, 565 after a myocardial infarction without ST-segment elevation, and 1133 after an episode of unstable angina. In two patients, the index diagnosis was not specified. The B-type natriuretic peptide level ranged from 5 to 1456 pg per milliliter, with a mean (\pm SD) of 114 ± 126 pg per milliliter, a median of 81 pg per milliliter, and 25th and 75th percentile values of 44 and 138 pg per milliliter, respectively. The mean time from the onset of ischemic symptoms to enrollment was 40 ± 20 hours (median, 40).

Association with Base-Line Clinical Variables

In univariate analyses, higher base-line levels of B-type natriuretic peptide were associated with older age, female sex, white race, and a history of hypertension, heart failure, and vascular disease; the level of B-type natriuretic peptide was inversely associated with a history of hypercholesterolemia and current smoking (Table 1). Patients with higher B-type natriuretic peptide levels were more likely than those with lower levels to present in Killip class II, III, or IV and to have electrocardiographic changes at base line, elevated levels of creatine kinase MB, and renal insufficiency (Table 1). There was no consistent relation between the level of B-type natriuretic peptide and the time from the onset of ischemic symptoms: the median levels were 72, 87, and 81 pg per milliliter for patients presenting less than 24 hours, 24 to 48 hours, and more than 48 hours after the onset of symptoms, respectively.

Although statistically significant, the associations between levels of B-type natriuretic peptide and C-reactive protein levels ($r=0.2$, $P<0.001$), fibrinogen levels ($r=0.18$, $P<0.001$), peak levels of the MB isoform of creatine kinase ($r=0.09$, $P<0.001$), and the ejection fraction ($r=0.23$, $P<0.001$) were only moderately strong. Patients with higher B-type natriuretic peptide levels had a greater number of coronary ar-

TABLE 1. BASE-LINE CLINICAL CHARACTERISTICS ACCORDING TO THE QUARTILE OF B-TYPE NATRIURETIC PEPTIDE LEVEL.*

CHARACTERISTIC†	QUARTILE 1 (5.0–43.6 pg/ml)	QUARTILE 2 (43.7–81.2 pg/ml)	QUARTILE 3 (81.3–137.8 pg/ml)	QUARTILE 4 (137.9–1456.6 pg/ml)	P VALUE FOR TREND
No. of patients	631	632	632	630	
Age — yr	57±10	59±11	61±12	66±11	<0.001
Male sex — no. (%)	474 (75)	465 (74)	472 (75)	405 (64)	<0.001
White race — no. (%)	575 (91)	592 (94)	605 (96)	603 (96)	<0.001
Medical history — no. (%)					
Hypertension	246 (39)	254 (40)	263 (42)	298 (47)	0.003
Congestive heart failure	26 (4)	28 (4)	26 (4)	56 (9)	<0.001
Coronary artery disease	329 (52)	312 (49)	294 (47)	327 (52)	0.7
Peripheral vascular disease	33 (5)	43 (7)	48 (8)	57 (9)	0.008
Cerebrovascular disease	24 (4)	32 (5)	39 (6)	60 (10)	<0.001
Diabetes	138 (22)	133 (21)	132 (21)	152 (24)	0.4
Hypercholesterolemia	199 (32)	191 (30)	173 (27)	149 (24)	<0.001
Smoking status — no. (%)					<0.001
Current smoker	233 (37)	263 (42)	236 (37)	189 (30)	
Never smoked	193 (31)	161 (26)	185 (29)	254 (40)	
Former smoker	204 (32)	205 (33)	209 (33)	186 (30)	
Index diagnosis — no. (%)					<0.001
Myocardial infarction with ST-segment elevation	141 (22)	189 (30)	231 (37)	264 (42)	
Myocardial infarction without ST-segment elevation	87 (14)	137 (22)	159 (25)	182 (29)	
Unstable angina	402 (64)	306 (48)	241 (38)	184 (29)	
Physical findings					
Systolic blood pressure — mm Hg	130±20	129±19	128±22	129±21	0.3
Killip class II, III, or IV — no. (%)	31 (5)	36 (6)	56 (9)	109 (18)	<0.001
Results of diagnostic tests — no. (%)					
Creatinine clearance ≤90 ml/min	146 (24)	185 (31)	229 (38)	350 (58)	<0.001
Creatine kinase MB >upper limit of normal	212 (58)	308 (72)	349 (79)	388 (86)	<0.001
ST-segment depression ≥0.5 mm	270 (43)	297 (47)	311 (49)	356 (57)	<0.001

*Plus-minus values are means ±SD.

†For each variable, the percentages reflect the total number of patients for whom data were available. In some instances, this number was less than the total number of patients in the quartile.

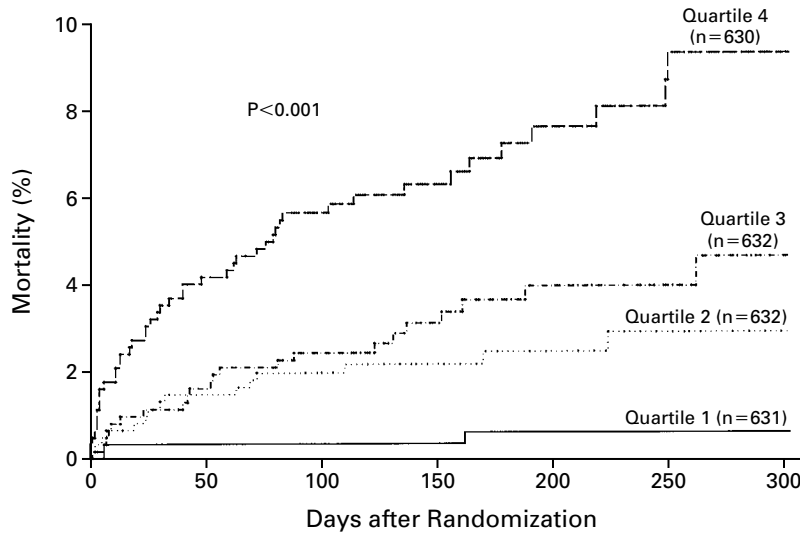
teries with stenosis of at least 50 percent ($P<0.001$) and a greater likelihood of a positive stress test ($P<0.01$) than patients with lower levels (data not shown).

Clinical Outcomes

The base-line level of B-type natriuretic peptide was higher among patients who died than among those who were alive at 30 days (median, 153 vs. 80 pg per milliliter; $P<0.001$) and at 10 months (median, 143 vs. 79 pg per milliliter; $P<0.001$). These differences remained significant in subgroups of patients who had myocardial infarction with ST-segment elevation ($P=0.002$ at 30 days and $P=0.008$ at 10 months), patients who had myocardial infarction in the absence of ST-segment elevation ($P<0.001$ at both 30 days and 10 months), and patients who had unstable angina ($P=0.002$ at 30 days and $P<0.001$ at 10 months). The level of B-type natriuretic peptide was higher among patients who had new or recurrent myocardial infarction within 30 days ($P=0.02$) or 10 months ($P=0.01$) than among patients who were free of infarction. Finally, the level of B-type natriuretic peptide was higher among patients who

had new or worsening heart failure within 30 days ($P<0.001$) or 10 months ($P<0.001$) than among those in whom heart failure did not develop.

The unadjusted mortality rate increased in a step-wise fashion across increasing quartiles of base-line B-type natriuretic peptide levels ($P<0.001$) (Fig. 1). This association remained significant in subgroups of patients who had myocardial infarction with ST-segment elevation, patients who had myocardial infarction in the absence of ST-segment elevation, and patients who had unstable angina (Fig. 2). In addition, the association between the level of B-type natriuretic peptide and the 10-month mortality rate remained graded and significant both among 327 patients with a history of heart failure or a finding of Killip class II, III, or IV at presentation ($P=0.007$) and among 2165 patients without such findings ($P<0.001$). When stratification was based on the level of troponin I at the time of enrollment, increasing levels of B-type natriuretic peptide remained associated with a higher 10-month mortality rate, among both 882 patients with a troponin I level of 0.1 ng per milliliter or less ($P=0.01$) and 1630 patients with a troponin I level



No. AT RISK							
Quartile 1	631	615	550	431	321	218	104
Quartile 2	632	603	525	390	283	159	64
Quartile 3	632	615	529	384	266	168	72
Quartile 4	630	594	487	345	227	146	58
Total	2525	2427	2091	1550	1097	691	298

Figure 1. Kaplan–Meier Curves Showing the Cumulative Incidence of Death at 10 Months, According to the Quartile of B-Type Natriuretic Peptide Level at Enrollment.

The range of B-type natriuretic peptide levels was as follows: 5.0 to 43.6 pg per milliliter (quartile 1), 43.7 to 81.2 pg per milliliter (quartile 2), 81.3 to 137.8 pg per milliliter (quartile 3), and 137.9 to 1456.6 pg per milliliter (quartile 4). $P < 0.001$ for the trend among the quartiles.

of more than 0.1 ng per milliliter ($P < 0.001$). Similar results were obtained when stratification was based on troponin I thresholds of 0.4 and 1.5 ng per milliliter ($P < 0.001$ for each comparison of patients above and patients at or below each threshold). The association between B-type natriuretic peptide and mortality at 10 months was significant for both men ($P < 0.001$) and women ($P = 0.01$).

In a logistic-regression model in which we adjusted for other independent predictors of the long-term risk of death, including age, troponin I levels, and presence or absence of heart failure, renal insufficiency, and ST-segment deviation, increasing levels of B-type natriuretic peptide remained associated with an increased risk of death at 10 months (Fig. 3). The adjusted odds ratios for death at 10 months in the second, third, and fourth quartiles of B-type natriuretic peptide were 3.8 (95 percent confidence interval, 1.1 to 13.3), 4.0 (95 percent confidence interval, 1.2 to 13.7), and 5.8 (95 percent confidence interval, 1.7 to 19.7), respectively (Fig. 3). When age was entered into the model as a continuous variable, the results were unchanged.

Evaluation of a B-Type Natriuretic Peptide Threshold of 80 pg per Milliliter

Patients with a B-type natriuretic peptide level of more than 80 pg per milliliter were significantly more likely to die, have a new or recurrent myocardial infarction, or have new or progressive heart failure than those with a level of 80 pg per milliliter or less (Fig. 4). After adjustment for other independent predictors of the long-term risk of death, a B-type natriuretic peptide level of more than 80 pg per milliliter remained significantly associated with an increased 10-month mortality rate ($P = 0.04$).

DISCUSSION

We have demonstrated in a large, contemporary cohort of patients that a single measurement of B-type natriuretic peptide, obtained a median of 40 hours after the onset of ischemic symptoms, provides powerful information for use in risk stratification across the entire spectrum of acute coronary syndromes. Despite heterogeneity in pathophysiology, clinical presentation, and risk among patients who had myocardial infarction with ST-segment elevation, patients

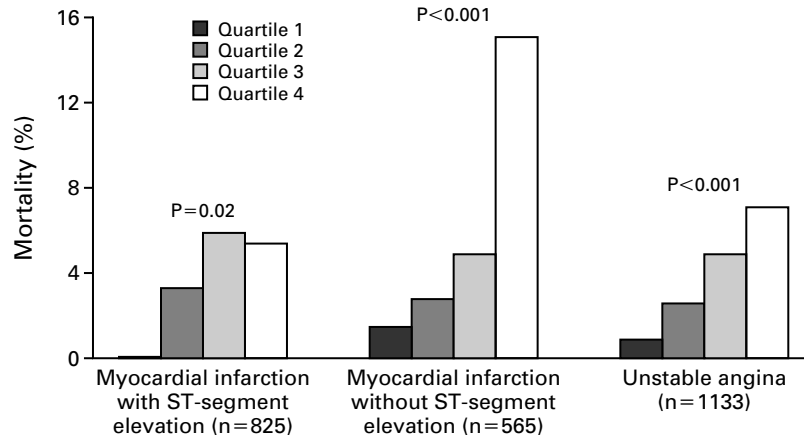


Figure 2. Association between the B-Type Natriuretic Peptide Level and the Mortality Rate at 10 Months, According to the Index Diagnosis.

Quartiles were recalibrated for each of the subgroups. Quartile 1 represents the lowest level of B-type natriuretic peptide, and quartile 4 the highest level. P values are for the trend within each subgroup.

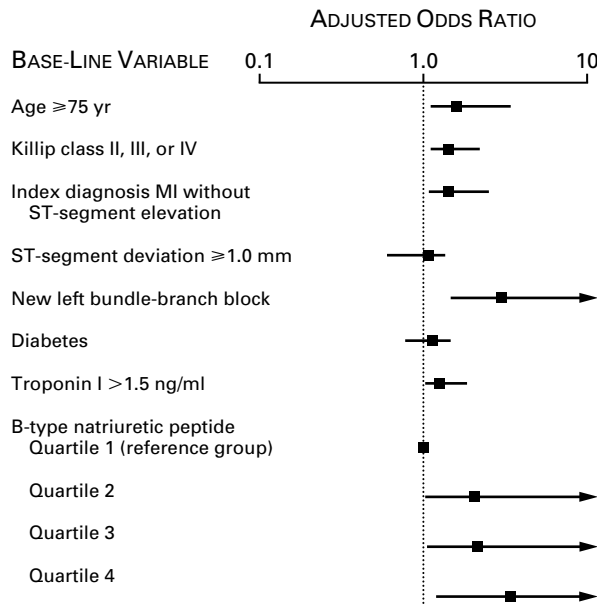


Figure 3. Stepwise Logistic-Regression Model Showing the Association between Selected Base-Line Clinical Variables and the Odds Ratio for Death at 10 Months.

The cardiac troponin I level and B-type natriuretic peptide quartiles were forced into the final model. Horizontal lines are 95 percent confidence intervals. In addition to the variables shown in the figure, the final model included presence or absence of a history of hyperlipidemia, peripheral vascular disease, or heart failure; presence or absence of prior therapy with diuretics, angiotensin-converting-enzyme inhibitors, nitrates, or heparin; heart rate; blood pressure; and creatinine clearance. MI denotes myocardial infarction.

who had myocardial infarction in the absence of ST-segment elevation, and patients who had unstable angina, increasing levels of B-type natriuretic peptide were predictive of an increased risk of death in each of these subgroups. This finding suggests that activation of the cardiac neurohormonal system may be a unifying feature among patients at high risk for death after acute coronary syndromes.

The association between B-type natriuretic peptide and the long-term risk of death was independent of the presence or absence of clinical evidence of heart failure, as well as renal function, the troponin I level, electrocardiographic changes, and other known predictors of the risk of death in patients with acute coronary syndromes. In addition, a high level of B-type natriuretic peptide was associated with an increased risk of nonfatal end points, including new or progressive heart failure and myocardial infarction. Finally, it appears that the previously defined B-type natriuretic peptide threshold of 80 pg per milliliter, indicative of neurohormonal activation in patients with heart failure,¹⁷ is also an appropriate threshold among patients with acute coronary syndromes.

Previous studies have demonstrated that after a myocardial infarction, a higher plasma level of B-type natriuretic peptide is associated with a larger infarct size,^{6,18} an increased likelihood of ventricular remodeling,¹⁹ a lower ejection fraction,^{11,18} and an increased risk of heart failure and death.^{8,10-14} These studies each included fewer than 150 patients and focused on relatively homogeneous groups of patients who had myocardial infarction with ST-segment elevation.

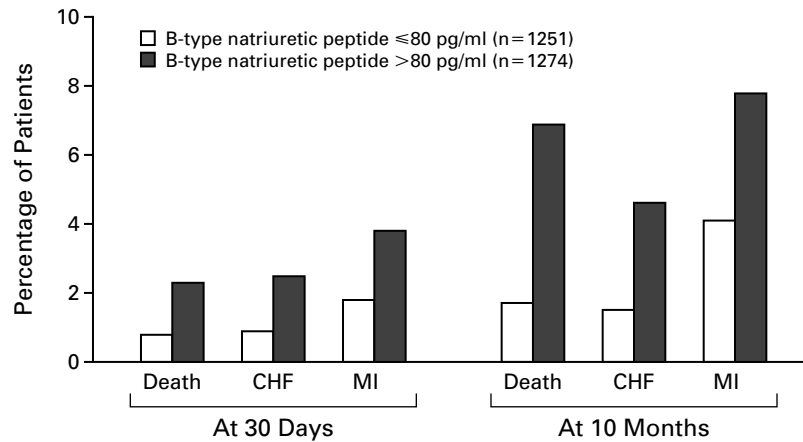


Figure 4. The Incidence of Death, New or Progressive Congestive Heart Failure (CHF), and New or Recurrent Myocardial Infarction (MI) at 30 Days and 10 Months among Patients with B-Type Natriuretic Peptide Levels above or at or below the Prespecified Threshold of 80 pg per Milliliter. $P < 0.005$ for each comparison.

Our study extends these findings to patients with acute coronary syndromes in the absence of ST-segment elevation, including those with unstable angina and no evidence of myocardial necrosis.

Unlike traditional cardiac biomarkers used to predict risk among patients with acute coronary syndromes, B-type natriuretic peptide has a putative role in the counterregulatory response to ischemia. Therefore, it may act as an index of the extent or severity of the ischemic insult, as well as the degree of underlying impairment in left ventricular function. In an animal model of transmural infarction, the level of expression of the B-type natriuretic peptide gene in the left ventricle was tripled within four hours after coronary ligation, and tissue levels of B-type natriuretic peptide were increased in noninfarcted as well as infarcted regions.²⁰ The level of B-type natriuretic peptide increases rapidly and transiently after exercise testing in patients with chronic stable angina, and the degree of elevation is correlated with the size of the ischemic territory as measured with the use of nuclear single-photon-emission computed tomography imaging.²¹ Furthermore, the level increases transiently after uncomplicated percutaneous transluminal coronary angioplasty, even in the absence of changes in pulmonary-capillary wedge pressure.^{22,23}

Several small cross-sectional studies have shown that the level of B-type natriuretic peptide is higher among patients with unstable angina than among patients with stable angina or among healthy controls.^{24,25} In one of these studies, a finding of an elevation in B-type natriuretic peptide correlated with echocardiographic findings of regional wall-motion abnormalities, but not with hemodynamic data ob-

tained at the time of simultaneous cardiac catheterization; furthermore, after medical stabilization, wall-motion abnormalities improved and B-type natriuretic peptide levels fell significantly.²⁵

Taken together, these findings suggest that myocardial ischemia augments the synthesis and release of B-type natriuretic peptide, even in the absence of myocardial necrosis or preexisting left ventricular dysfunction. Reversible ischemia may transiently increase left ventricular wall stress, which may be sufficient to cause an elevation in B-type natriuretic peptide levels. Our findings further suggest that the prognostic implications of neurohormonal activation are distinct from those of myocyte necrosis; even among patients with unstable angina and those without troponin I elevation, the degree of elevation in B-type natriuretic peptide is of prognostic importance.

We measured B-type natriuretic peptide once, approximately two days after the index event. It is not possible from a single measurement to determine whether neurohormonal activation is reflective of the acute (index) event or of preexisting left ventricular dysfunction. However, even after adjustment for variables such as the presence or absence of a history of hypertension, heart failure, and use of diuretics or angiotensin-converting-enzyme inhibitors, the level of B-type natriuretic peptide remained predictive of the long-term risk of death. A study in patients hospitalized with heart failure suggests that serial measurements of B-type natriuretic peptide may provide more prognostic information than a single measurement, since the prognosis was better when levels fell after therapy than when they remained the same.²⁶ Future studies should evaluate the use of serial measurements

of B-type natriuretic peptide in patients with acute coronary syndromes.

For a cardiac biomarker to be clinically useful, it must help clinicians select an appropriate therapeutic regimen. For example, patients who have an elevation in troponin T or I levels after acute coronary syndromes appear to derive specific benefit from an early, aggressive strategy that includes potent antiplatelet²⁷ and antithrombotic²⁸ therapy and early revascularization.²⁹ In addition, patients who have elevated C-reactive protein levels after myocardial infarction appear to benefit from statin therapy.³⁰ Patients with elevated levels of B-type natriuretic peptide after an acute coronary syndrome are at high risk for death, a new myocardial infarction, and heart failure and may benefit from intensive antiplatelet and antithrombotic therapies, neurohormonal antagonism with agents such as beta-blockers and angiotensin-converting-enzyme inhibitors, and early revascularization. Equally important, patients who have normal levels of B-type natriuretic peptide after an acute coronary event appear to have a particularly low long-term risk of death and heart failure. In this group of patients, a less intensive management approach may be appropriate, in order to avoid the cost and risk associated with potentially unnecessary therapies. Future studies should directly assess the role of B-type natriuretic peptide in identifying patients who would benefit from various treatment strategies.

The level of B-type natriuretic peptide, measured in the first few days after an acute coronary event, predicts the long-term risk of death and nonfatal cardiac events across the spectrum of acute coronary syndromes. The prognostic usefulness of B-type natriuretic peptide persists after adjustment for the presence or absence of clinical evidence of heart failure, as well as other important predictors of mortality, including clinical characteristics, renal function, electrocardiographic changes, and troponin I levels. These findings suggest that B-type natriuretic peptide should be measured after an acute coronary syndrome in order to identify patients at high and low risk for adverse outcomes and that treatment, including the intensity of surveillance and the use of aggressive pharmacologic and interventional therapy, should be adjusted accordingly.

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REFERENCES

- Wiese S, Breyer T, Dragu A, et al. Gene expression of brain natriuretic peptide in isolated atrial and ventricular human myocardium: influence of angiotensin II and diastolic fiber length. *Circulation* 2000;102:3074-9.
- Yasue H, Yoshimura M, Sumida H, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 1994;90:195-203.
- Yoshimura M, Yasue H, Okumura K, et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. *Circulation* 1993;87:464-9.
- Stein BC, Levin RI. Natriuretic peptides: physiology, therapeutic potential, and risk stratification in ischemic heart disease. *Am Heart J* 1998;135:914-23.
- Omland T, Aakvaag A, Vik-Mo H. Plasma cardiac natriuretic peptide determination as a screening test for the detection of patients with mild left ventricular impairment. *Heart* 1996;76:232-7.
- Arakawa N, Nakamura M, Aoki H, Hiramori K. Relationship between plasma level of brain natriuretic peptide and myocardial infarct size. *Cardiology* 1994;85:334-40.
- Motwani JG, McAlpine H, Kennedy N, Struthers AD. Plasma brain natriuretic peptide as an indicator for angiotensin-converting-enzyme inhibition after myocardial infarction. *Lancet* 1993;341:1109-13.
- Talwar S, Squire IB, Downie PE, 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.
- 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.
- Darbar D, Davidson NC, Gillespie N, et al. Diagnostic value of B-type natriuretic peptide concentrations in patients with acute myocardial infarction. *Am J Cardiol* 1996;78:284-7.
- Richards AM, Nicholls MG, Yandle TG, et al. Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction. *Heart* 1999;81:114-20.
- 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.
- Arakawa N, Nakamura M, Aoki H, Hiramori K. Plasma brain natriuretic peptide concentrations predict survival after acute myocardial infarction. *J Am Coll Cardiol* 1996;27:1656-61.
- 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.
- Cannon CP, McCabe CH, Wilcox RG, et al. Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation* 2000;102:149-56.
- Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 11B trial. *Circulation* 1999;100:1593-601.
- Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol* 2001;37:379-85.
- Horio T, Shimada K, Kohno M, et al. Serial changes in atrial and brain natriuretic peptides in patients with acute myocardial infarction treated with early coronary angioplasty. *Am Heart J* 1993;126:293-9.
- Nagaya N, Nishikimi T, Goto Y, et al. Plasma brain natriuretic peptide is a biochemical marker for the prediction of progressive ventricular remodeling after acute myocardial infarction. *Am Heart J* 1998;135:21-8.
- Hama N, Itoh H, Shirakami G, et al. Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction. *Circulation* 1995;92:1558-64.
- 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 (Colch)* 1995;88:551-6.
- 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.
- Kyriakides ZS, Markianos M, Michalis L, Antoniadis A, Nikolaou NI, Kremastinos DT. Brain natriuretic peptide increases acutely and much more prominently than atrial natriuretic peptide during coronary angioplasty. *Clin Cardiol* 2000;23:285-8.
- Talwar S, Squire IB, Downie PE, Davies JE, Ng LL. Plasma N terminal pro-brain natriuretic peptide and cardiotrophin 1 are raised in unstable angina. *Heart* 2000;84:421-4.
- Kikuta K, Yasue H, Yoshimura M, et al. Increased plasma levels of B-type natriuretic peptide in patients with unstable angina. *Am Heart J* 1996;132:101-7.
- Cheng V, Kazanagra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol* 2001;37:386-91.
- Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in

patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med* 1999;340:1623-9.

28. Morrow DA, Antman EM, Tanasijevic M, et al. Cardiac troponin I for stratification of early outcomes and the efficacy of enoxaparin in unstable angina: a TIMI 11B substudy. *J Am Coll Cardiol* 2000;36:1812-7.

29. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary

syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.

30. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation* 1998;98:839-44.

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