Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 50, No. 3, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.03.038

Prognostic Value of B-Type Natriuretic Peptides in Patients With Stable Coronary Artery Disease

The PEACE Trial

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Objectives The purpose of this study was to assess the association between B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the incidence of specific cardiovascular events in low-risk patients with stable coronary disease, the incremental prognostic information obtained from these two biomarkers compared with traditional risk factors, and their ability to identify patients who may benefit from angiotensin-converting enzyme (ACE) inhibition.

Background The prognostic value of BNPs in low-risk patients with stable coronary artery disease remains unclear.

Methods Baseline plasma BNP and NT-proBNP concentrations were measured in 3,761 patients with stable coronary artery disease and preserved left ventricular function participating in the PEACE (Prevention of Events With Angiotensin-Converting Enzyme Inhibition) study, a placebo-controlled trial of trandolapril. Multivariable Cox regression was used to assess the association between natriuretic peptide concentrations and the incidence of cardiovascular mortality, fatal or nonfatal myocardial infarction, heart failure, and stroke.

Results The BNP and NT-proBNP levels were strongly related to the incidence of cardiovascular mortality, heart failure, and stroke but not to myocardial infarction. In multivariable models, BNP remained associated with increased risk of heart failure, whereas NT-proBNP remained associated with increased risk of cardiovascular mortality, heart failure, and stroke. By C-statistic calculations, BNP and NT-proBNP significantly improved the predictive accuracy of the best available model for incident heart failure, and NT-proBNP also improved the model for cardiovascular death. The magnitude of effect of ACE inhibition on the likelihood of experiencing cardiovascular end points was similar, regardless of either BNP or NT-proBNP baseline concentrations.

Conclusions In low-risk patients with stable coronary artery disease and preserved ventricular function, BNPs provide strong and incremental prognostic information to traditional risk factors. (J Am Coll Cardiol 2007;50:205–14)

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Manuscript received December 6, 2006; revised manuscript received March 2, 2007, accepted March 6, 2007.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

BNP = B-type natriuretic peptide

EDTA = ethylenediaminetetraacetic acid

NT-proBNP = N-terminal pro-B-type natriuretic peptide

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B-type natriuretic peptide (BNP) and N-terminal (NT) pro-BNP are peptide fragments derived from a common precursor molecule, proBNP (1). Originally introduced in clinical medicine as diagnostic tools for heart failure (2), BNP and NT-proBNP concentrations have been shown to be strongly predictive of short- and long-term survival in patients with acute coronary syndromes (3–8). Although the association between BNPs and survival has been well documented in a wide spectrum of cardiovascular diseases, some important questions remain unresolved. First, do BNP and NT-proBNP provide independent prognostic information in coronary artery disease patients at low risk? Both BNP and NT-proBNP have recently been identified as strong prognostic indicators in patients with stable coronary artery disease (9–13), but a high rate of clinically suspected heart failure (up to 60%) in those populations suggest that the results may not be generalizable to low-risk stable coronary artery disease patients without clinical heart failure and with preserved systolic ventricular function. Second, can the association between BNPs and cardiovascular mortality be explained mainly by the ability to predict heart failure, or are these peptides also related to the incidence of coronary ischemic events or stroke? Although previous studies have documented strong associations with outcome, they have not had sufficient statistical power to look at specific cardiovascular end points. Third, do BNPs provide clinically important incremental prognostic information to traditional risk factors? Although studies in patients with coronary artery disease have demonstrated that elevated levels of BNPs are statistically significant predictors in multivariable models, that does not necessarily imply better predictive performance (14). Finally, in patients with stable coronary disease and preserved left ventricular systolic function, can BNP and NT-proBNP be used to identify high-risk patients who may benefit from intervention with angiotensin-converting-enzyme (ACE) inhibitors? The ACE inhibitors have proved to be effective in reducing mortality and morbidity in patients at high risk (15,16), but failed to reduce cardiovascular death, myocardial infarction, and coronary revascularization in low-risk patients with stable coronary artery disease (17). Based on the strong prognostic value of BNPs, we hypothesized that measurement of these substances would prove helpful in identifying patients who benefit from ACE inhibition.

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To address these questions, we measured plasma BNP and NT-proBNP concentrations in a subcohort of 3,761 patients with stable coronary disease and preserved systolic function included in the PEACE (Prevention of Events With Angiotensin-Converting Enzyme Inhibition) trial and related peptide concentrations at baseline to the incidence of subsequent fatal and nonfatal cardiovascular events and cardiovascular mortality.

Methods

Study subjects. The design, entry criteria, and main results of the PEACE trial have been described previously (17). In brief, from November 1996 to June 2000, 8,290 patients were randomized to the ACE inhibitor trandolapril or placebo and followed up for a median of 4.8 years. Entry criteria included: age 50 years or more, documented coronary artery disease, and left ventricular ejection fraction >40% by contrast or radionuclide ventriculography or echocardiogram. Exclusion criteria included: serum creatinine >2.0 mg/dl, valvular heart disease requiring surgical intervention, or plans for coronary revascularization. All patients who had baseline ethylenediaminetetraacetic acid (EDTA) plasma samples for measurement of BNP and NT-proBNP were included in this substudy.

Blood sampling procedures and biochemical assays. Samples of EDTA-anticoagulated venous blood were obtained before randomization. The test tube was centrifuged at room temperature, and plasma was aspirated and frozen at −20°C at individual centers. Within 3 months of collection, plasma samples were shipped on dry ice to the central laboratory for storage at −70°C or colder pending analysis. For natriuretic peptide analyses, samples were shipped on dry ice to the University of Oslo, where samples were thawed and analyzed for BNP and NT-proBNP on the same day. Plasma samples were kept on ice throughout the day, avoiding refreezing and rethawing. The stability of samples during long-term storage was assessed by plotting the duration of storage versus peptide concentration, and no indication of degradation during long-term storage of either BNP or NT-proBNP was observed (data not shown).

The BNP concentrations in plasma were determined using a 2-step microparticle enzyme immunoassay on an Abbott Ax Sym analyzer (Abbott Laboratories, Abbott Park, Illinois). The interassay coefficient of variation was 12.7% at a concentration of 32 pg/ml (n = 142), 8.7% at a concentration of 146 pg/ml (n = 128), and 8.6% at a concentration of 480 pg/ml (n = 87). The measuring range for the assay was 15 to 4,000 pg/ml. The Food and Drug Administration (FDA)-approved BNP decision threshold for heart failure is 100 pg/ml.

The NT-proBNP concentrations in plasma were determined with an electrochemiluminescence immunoassay on a Modular platform (Roche Diagnostics, Basel, Switzerland). The interassay coefficient of variation was 4.5% at a concentration of 21 pg/ml (n = 100) and 2.2% at a concentration of 9,120 pg/ml (n = 100). The measuring range for the assay was 5 to 34,000 pg/ml. The FDA-approved NT-

proBNP decision threshold for heart failure is 125 pg/ml for those age <75 years and 450 pg/ml for those age ≥75 years.

For the measurement of C-reactive protein, aliquots were shipped frozen on dry ice to the TIMI (Thrombolysis in Myocardial Infarction) Biomarker Laboratory (Boston, Massachusetts), where they were thawed and analyzed in batch. High-sensitivity testing for C-reactive protein was performed using the CRP-Latex (II) immunoturbidimetric assay (Denka Seiken, Tokyo, Japan) on a Hitachi 911 immunoanalyzer (Roche Diagnostics, Indianapolis, Indiana). This assay has a minimal detectable concentration of 0.03 mg/l and a total imprecision of 5.1% and 2.5% at concentrations of 0.2 and 1.9 mg/l, respectively (18). Creatinine and total cholesterol concentrations in serum were determined by routine laboratory methods. Glomerular filtration rate was estimated using the 4-variable Modification of Diet in Renal Disease equation (19). All biochemical testing was performed by personnel blinded to clinical outcomes and treatment allocation.

Statistical analysis. We used analysis of variance and chi-square tests to test for differences in continuous and categoric baseline characteristics between quartiles of BNP and NT-proBNP. The overall F-test is reported for the analysis of variance models.

In separate models, we used Cox proportional hazards models to examine the association between BNP and NT-proBNP and the following prospectively defined outcome variables: cardiovascular mortality, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, and fatal or nonfatal new congestive heart failure requiring hospitalization. All events were confirmed by review of medical records, with blinded review by an end points committee for cardiovascular death, fatal and nonfatal myocardial infarction, and fatal and nonfatal stroke.

Patients were censored at their last visit. A test of the interaction between BNP and treatment and between NT-proBNP and treatment assignment was included. Subsequent models were adjusted for treatment assignment and baseline variables known to be important predictors of cardiovascular events: age, gender, body mass index, ejection fraction <50%, estimated glomerular filtration rate, current smoking, history of hypertension or measured hypertension, history of myocardial infarction, history of diabetes, history of stroke, history of percutaneous coronary intervention, history of coronary artery bypass grafting, total cholesterol, C-reactive protein, use of a beta-blocker, use of a lipid-lowering drug, use of aspirin or an antiplatelet medication, and use of a diuretic. To examine the potential influence of interim heart failure events on cardiovascular death, additional models were adjusted for interim heart failure as a time-dependent variable and censored patients at the time of their heart failure event. Both BNP and NT-proBNP were examined as continuous variables (per 1 standard deviation of the logarithmic transformation). To determine if there was a gradient effect, BNP and NT-proBNP were also examined using gender-specific quartiles. Kaplan-Meier curves were generated to show the cumulative incidence for each of the end points. Residual analysis was used to assess model fit. The collinearity index was used to check for linear combinations among covariates (20). To assess the discriminative ability of BNP and NT-proBNP, we computed the c-index for each outcome and compared them between BNP and NT-proBNP (21,22).

Pearson correlation was used to describe the association between log BNP, log NT-proBNP, and risk factors. The SAS analysis system version 9.1 was used for all analyses (SAS Institute, Cary, North Carolina).

Results

Characteristics at baseline. Characteristics at baseline in patients included in this biomarker substudy (n = 3,761) did not differ markedly from those of patients not included in this analysis (n = 4,529; data not shown).

Characteristics of the patients according to their BNP and NT-proBNP concentrations at baseline are shown in Tables 1 and 2, respectively. The median value of BNP was 52.6 pg/ml (interquartile range 24.9 to 101.4 pg/ml; normal value <100 pg/ml), and the median value of NT-proBNP was 139.3 pg/ml (interquartile range 71.3 to 272.1 pg/ml; normal value: age <75 years: <125 pg/ml; age ≥75 years: <450 pg/ml). B-type natriuretic peptide and NT-proBNP correlated significantly ($r = 0.62$; $p < 0.001$). Modest correlations were observed between natriuretic peptides and ejection fraction (BNP: $r = -0.09$; $p < 0.001$; NT-proBNP: $r = -0.18$; $p < 0.001$), estimated glomerular filtration rate (BNP: $r = -0.14$; $p < 0.001$; NT-proBNP: $r = -0.22$; $p < 0.001$), body mass index (BNP: $r = -0.09$; $p < 0.001$; NT-proBNP: $r = -0.12$; $p < 0.001$), and systolic blood pressure (BNP: $r = 0.11$; $p < 0.001$; NT-proBNP: $r = 0.15$; $p < 0.001$). Both BNP ($r = 0.27$; $p < 0.001$) and NT-proBNP ($r = 0.39$; $p < 0.001$) correlated more closely with patient age.

Relation to fatal and nonfatal cardiovascular events. During a median of 4.8 years of follow-up there were 127 cardiovascular deaths, 104 fatal or first nonfatal congestive heart failure events, 241 fatal or first nonfatal acute myocardial infarction events and 86 fatal or first nonfatal stroke events. By univariable analyses, both BNP and NT-proBNP were significant predictors of cardiovascular mortality, fatal or nonfatal stroke, and fatal or nonfatal congestive heart failure but not fatal or nonfatal acute myocardial infarction (Table 3).

By multivariable analyses, after adjustment for risk factors, NT-proBNP remained a significant independent predictor of cardiovascular mortality (Fig. 1), fatal or nonfatal congestive heart failure (Fig. 2), and fatal or nonfatal stroke (Fig. 3, Table 4). Consistent results were obtained regardless of whether the peptides were treated as logarithmically transformed continuous variable (Table 4) or as categoric variables (Table 5). Adjustment or censoring for interim congestive heart failure had only minor impact on the

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Table 1 Characteristics of Patients According to BNP Concentrations at Baseline

Baseline Characteristics	1st Quartile (n = 936); Men = 15–24 pg/ml; Women = 15–32 pg/ml	2nd Quartile (n = 941); Men = 24–51 pg/ml; Women = 32–61 pg/ml	3rd Quartile (n = 939); Men = 51–98 pg/ml; Women = 61–115 pg/ml	4th Quartile (n = 938); Men = 98–2,660 pg/ml; Women = 115–2,427 pg/ml	p Value*
Age, mean ± SD, yrs	60.7 ± 7.4	62.9 ± 7.7	64.5 ± 8.1	66.6 ± 8.2	<0.001
Female gender, n (% of patients)	176 (18.8)	179 (19.0)	178 (19.0)	177 (18.9)	1.00
Caucasian race, n (% of patients)	878 (93.8)	865 (91.9)	855 (91.1)	844 (90.0)	0.02
Body mass index, mean ± SD, kg/m^2	29.0 ± 4.9	28.7 ± 4.8	28.4 ± 4.7	27.9 ± 4.5	<0.001
Medical history, n (% of patients)					
Documented myocardial infarction	512 (54.7)	504 (53.6)	545 (58.0)	547 (58.4)	0.09
Angina pectoris	689 (73.6)	691 (73.4)	681 (72.5)	684 (73.0)	0.95
PCI	487 (52.0)	439 (46.7)	432 (46.1)	357 (38.1)	<0.001
CABG	214 (22.9)	315 (33.5)	372 (39.6)	437 (46.6)	<0.001
Diabetes	134 (14.3)	161 (17.1)	161 (17.1)	159 (17.0)	0.27
Hypertension	379 (40.5)	406 (43.1)	423 (45.0)	467 (49.8)	<0.001
Stroke	24 (2.6)	36 (3.8)	42 (4.5)	55 (5.9)	0.004
Current smoker	171 (18.3)	152 (16.2)	117 (12.5)	125 (13.3)	0.01
Mean blood pressure, mean ± SD, mm Hg					
Systolic	132 ± 15.5	132 ± 16.1	133 ± 17.0	137 ± 18.1	<0.001
Diastolic	79.1 ± 9.7	78.1 ± 9.9	77.6 ± 9.3	77.3 ± 10.3	<0.001
Laboratory determinations, mean ± SD					
eGFR, ml/min	81.1 ± 21.6	79.3 ± 18.7	76.6 ± 17.5	74.7 ± 18.8	<0.001
Serum cholesterol, mg/dl	196 ± 39.9	191 ± 37.8	191 ± 38.2	190 ± 39.5	0.002
C-reactive protein	3.69 ± 8.17	3.04 ± 5.21	3.61 ± 11.6	3.54 ± 5.89	0.28
LV ejection fraction >40% and <50%, n (% of patients)	106 (11.3)	108 (11.5)	148 (15.8)	178 (19.0)	<0.001
Medications, n (% of patients)					
Allocation to trandolapril	465 (49.7)	471 (50.2)	483 (51.4)	452 (48.2)	0.57
Calcium-channel blocker	328 (35.0)	319 (33.9)	306 (32.6)	297 (31.7)	0.44
Beta-blocker	481 (51.4)	593 (63.0)	586 (62.4)	670 (71.6)	<0.001
Aspirin/antiplatelet medication	854 (91.2)	875 (93.0)	861 (91.7)	832 (88.9)	0.02
Lipid-lowering drug	722 (77.1)	699 (74.4)	651 (69.3)	629 (67.2)	<0.001
Nonpotassium-sparing diuretic	76 (8.1)	71 (7.5)	86 (9.2)	109 (11.6)	0.01
Digitalis	13 (1.4)	25 (2.7)	30 (3.2)	55 (5.9)	<0.001

*Based on F-tests for continuous data and chi-square statistics for categoric data.
BNP = B-type natriuretic peptide; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; LV = left ventricular; PCI = percutaneous coronary intervention.

association between NT-proBNP and risk of cardiovascular death. For example, adjustment for interim congestive heart failure reduced the hazard ratio for the fourth versus first quartile of NT-proBNP marginally from 4.9 (95% confidence interval 2.2 to 10.7) to 4.5 (95% confidence interval 2.0 to 9.8).

Calculation of the c-index as a measure of overall prognostic accuracy demonstrated that in univariable analysis NT-proBNP performed significantly better than BNP as a predictor of cardiovascular mortality, fatal or nonfatal stroke, and fatal or nonfatal congestive heart failure; neither predicted fatal or nonfatal myocardial infarction (Table 6). For the end point of fatal and nonfatal congestive heart failure, addition of either BNP or NT-proBNP to the multivariable model resulted in statistically significant improved prognostic accuracy, as evaluated by the c-index, compared with the conventional risk factor model. For cardiovascular mortality, NT-proBNP, but not BNP, resulted in statistically significant improved prognostic accuracy (Table 7).

In the main PEACE trial the incidence of the primary end point—death from cardiovascular causes, myocardial infarction, or coronary revascularization—was not significantly different between the ACE inhibitor or placebo group. However, significantly fewer patients in the ACE inhibitor group than in the placebo group were hospitalized with or died of congestive heart failure. No interaction was observed between BNP or NT-proBNP and randomized treatment group. That is, the association between treatment group (ACE inhibition or placebo) and each outcome did not vary according to BNP or NT-proBNP concentration (data not shown).

Discussion

The salient findings of this large-scale study of low-risk patients with stable coronary artery disease and preserved left ventricular function are: 1) both BNP and NT-proBNP are predictive of the incidence of cardiovascular death, congestive heart failure, and stroke, but neither peptide

Table 2 Characteristics of Patients According to NT-ProBNP Concentrations at Baseline

Baseline Characteristics	1st Quartile (n = 943); Men = 5–66 pg/ml; Women = 5–105 pg/ml	2nd Quartile (n = 938); Men = 66–127 pg/ml; Women = 105–196 pg/ml	3rd Quartile (n = 939); Men = 127–253 pg/ml; Women = 196–372pg/ml	4th Quartile (n = 941); Men = 253–5,590 pg/ml; Women = 372–4,593 pg/ml	p Value*
Age, mean ± SD, yrs	59.9 ± 7.1	62.8 ± 7.6	64.1 ± 7.9	67.8 ± 8.0	<0.001
Female gender, n (% of patients)	178 (18.9)	178 (19.0)	178 (19.0)	179 (19.0)	1.00
Caucasian race, n (% of patients)	847 (89.8)	863 (92.0)	867 (92.3)	871 (92.6)	0.12
Body mass index, mean ± SD, kg/m^2	29.1 ± 4.9	28.8 ± 4.7	28.5 ± 4.7	27.6 ± 4.5	<0.001
Medical history, n (% of patients)					
Documented myocardial infarction	462 (49.0)	507 (54.1)	559 (59.6)	584 (62.1)	<0.001
Angina pectoris	693 (73.5)	692 (73.8)	694 (74.0)	673 (71.5)	0.60
PCI	523 (55.5)	443 (47.2)	400 (42.6)	352 (37.4)	<0.001
CABG	178 (18.9)	307 (32.7)	408 (43.5)	447 (47.5)	<0.001
Diabetes	161 (17.1)	151 (16.1)	143 (15.2)	161 (17.1)	0.65
Hypertension	390 (41.4)	402 (42.9)	416 (44.3)	474 (50.4)	<0.001
Stroke	24 (2.5)	29 (3.1)	42 (4.5)	64 (6.8)	<0.001
Current smoker	155 (16.5)	156 (16.6)	133 (14.2)	122 (13.0)	0.23
Mean blood pressure, mean ± SD, mm Hg					
Systolic	131 ± 15.0	132 ± 16.4	133 ± 16.5	137 ± 18.5	<0.001
Diastolic	79.1 ± 9.8	78.1 ± 9.3	77.7 ± 9.8	77.1 ± 10.1	<0.001
Laboratory determinations, mean ± SD					
eGFR, ml/min	82.2 ± 18.7	79.5 ± 20.6	77.7 ± 18.7	72.1 ± 18.0	<0.001
Serum cholesterol, mg/dl	196 ± 38.6	194 ± 39.2	189 ± 37.4	190 ± 40.0	<0.001
C-reactive protein	3.10 ± 5.44	3.11 ± 7.06	3.59 ± 7.42	4.08 ± 11.12	0.02
LV ejection fraction >40% and <50%, n (% of patients)	76 (8.1)	107 (11.4)	136 (14.5)	223 (23.7)	<0.001
Medications, n (% of patients)					
Allocation to trandolapril	492 (52.2)	454 (48.4)	456 (48.6)	473 (50.3)	0.32
Calcium-channel blocker	352 (37.3)	333 (35.5)	290 (30.9)	278 (29.5)	<0.001
Beta-blocker	452 (47.9)	558 (59.6)	663 (70.7)	662 (70.4)	<0.001
Aspirin/antiplatelet medication	873 (92.6)	868 (92.6)	862 (91.9)	825 (87.7)	<0.001
Lipid-lowering drug	697 (74.0)	690 (73.6)	693 (73.9)	624 (66.3)	<0.001
Nonpotassium-sparing diuretic	62 (6.6)	67 (7.2)	86 (9.2)	130 (13.8)	<0.001
Digitalis	13 (1.4)	22 (2.3)	26 (2.8)	62 (6.6)	<0.001

*Based on F-tests for continuous data and chi-square statistics for categoric data.
NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Table 1.

predicts the incidence of myocardial infarction; 2) after adjustment for conventional risk factors, both BNP and NT-proBNP remained significant predictors of congestive heart failure, but only NT-proBNP remained a predictor of cardiovascular death and stroke; 3) adjustment for the incidence of heart failure did not diminish the merit of NT-proBNP as a predictor of cardiovascular mortality, suggesting that mechanisms other than prediction of congestive heart failure are responsible for this relationship; 4) addition of a single NT-proBNP measurement provides improved overall prognostic accuracy for the end points of cardiovascular mortality and heart failure compared with that obtained from a model consisting of conventional risk factors, whereas BNP provided improved prognostic accuracy for the end point of heart failure; and 5) natriuretic peptide determination did not identify a subset of patients who experienced a greater degree of benefit with ACE inhibition. These observations may have important impli-

Table 3 Association Between BNPs as Continuous Variables and Cardiovascular Outcomes Adjusted for Randomization Status

	BNP		NT-ProBNP	
Outcome	HR (95% CI)*	p Value	HR (95% CI)*	p Value
Cardiovascular mortality	1.28 (1.08–1.51)	0.004	2.00 (1.69–2.36)	<0.001
Fatal/nonfatal MI	0.95 (0.83–1.08)	0.43	1.05 (0.93–1.18)	0.43
Fatal/nonfatal CHF	1.92 (1.61–2.27)	<0.001	2.81 (2.33–3.38)	<0.001
Fatal/nonfatal stroke	1.35 (1.10–1.65)	0.003	1.93 (1.58–2.36)	<0.001

*Per 1 SD pg/ml in log BNP and log NT-proBNP.
CHF = congestive heart failure; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; other abbreviations as in Tables 1 and 2.

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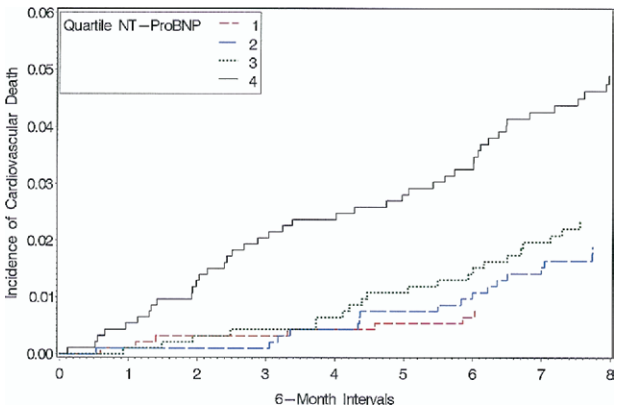

Figure 1 NT-ProBNP and Cardiovascular Death

Kaplan-Meier curves showing the cumulative incidence of death due to a cardiovascular cause in patients according to quartiles of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations.

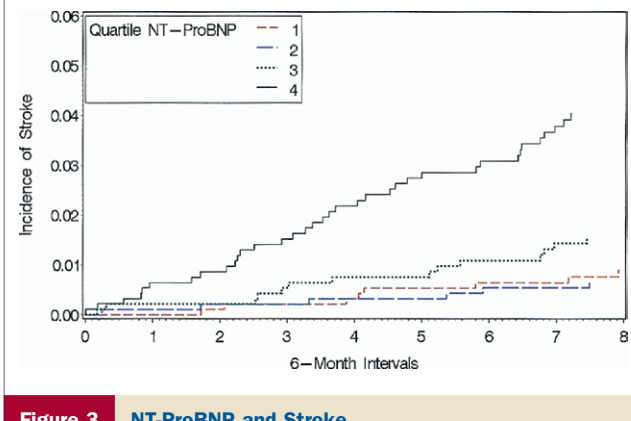

Figure 3 NT-ProBNP and Stroke

Kaplan-Meier curves showing the cumulative incidence of fatal or nonfatal stroke in patients according to quartiles of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations.

cations for the clinical use of BNPs in the large group of patients with stable coronary artery disease.

BNPs and specific cardiovascular events. In contrast to earlier studies in patients with stable coronary artery disease (9–13), the present study provides data on a range of specific cardiovascular end points, which also permits analysis of the association between these end points and cardiovascular death. The observation that neither BNP nor NT-proBNP predicted fatal and nonfatal myocardial infarction suggests that the association between NT-proBNP and cardiovascular death is unlikely to be explained by prediction of myocardial infarction. These results are in line with those of 3 large acute coronary syndrome studies that failed to demonstrate an independent association between BNPs and the incidence of coronary events (4,6,8), Not unexpectedly, both BNP and NT-proBNP were powerful and independent predictors of heart failure. However, in the present low-risk population, prediction of heart failure appeared to be of modest importance for prediction of cardiovascular mortality, because BNP failed to independently predict cardiovascular mortality despite a strong association with the incidence of heart failure. Interestingly, a similar lack of association between BNP and cardiovascular mortality, after adjustment for echocardiographic indices of ventricular function, was observed in the Framingham Heart Study population that also excluded subjects with heart failure at baseline (23). Moreover, adjustment for or censoring of incident heart failure in the present study did not impact on the merit of NT-proBNP as a predictor of cardiovascular mortality. The association between NT-proBNP and cardiovascular mortality may therefore be ascribed to prediction of neither heart failure nor myocardial infarction.

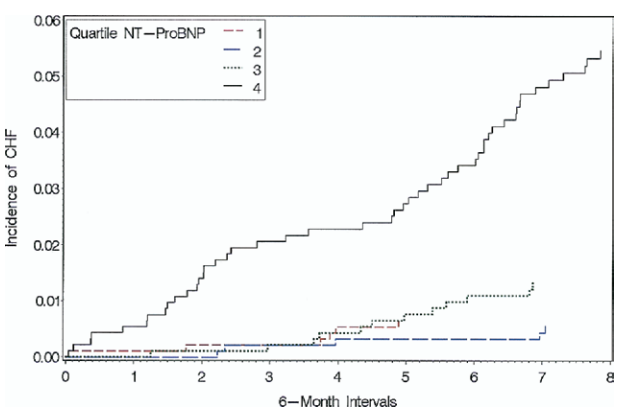

Figure 2 NT-ProBNP and Heart Failure

Kaplan-Meier curves showing the cumulative incidence of fatal or nonfatal congestive heart failure (CHF) in patients according to quartiles of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations.

BNP and NT-proBNP as prognostic indicators. Existing data on the relative prognostic value of BNP and NT-proBNP are still scarce. One recent publication of patients with coronary artery disease suggested that the two are comparable as predictors of all-cause mortality and heart failure hospitalizations, but the study included a large proportion of patients with chronic heart failure and impaired systolic function and the results may not be generalizable to low-risk patients with stable coronary artery disease (13). Moreover, that study restricted their analysis to the end points of all-cause mortality or all-cause mortality and heart failure. The study also included a substantially lower number of study subjects than the present investigation and may as a consequence have had less statistical power to detect differences between BNP and NT-proBNP. The use of in-house biochemical assays for analysis of BNP and NT-proBNP also make direct comparisons with the present data and other studies using commercially available assays somewhat difficult. Moreover, the duration of time between blood sampling and determination of circulating

Table 4 Multivariable* Analysis of the Association Between BNPs as Continuous Variables and Cardiovascular Outcomes

	BNP		NT-ProBNP	
Outcome	HR (95% CI)†	p Value	HR (95% CI)†	p Value
Cardiovascular mortality	1.06 (0.87–1.28)	0.57	1.69 (1.38–2.07)	<0.001
Fatal/nonfatal MI	0.91 (0.77–1.07)	0.24	1.02 (0.87–1.19)	0.84
Fatal/nonfatal CHF	1.62 (1.32–1.97)	<0.001	2.35 (1.86–2.98)	<0.001
Fatal/nonfatal stroke	1.15 (0.91–1.45)	0.24	1.63 (1.26–2.12)	<0.001

*Adjusted for treatment assignment, age, gender, body mass index, ejection fraction <50%, estimated glomerular filtration rate, current smoking, history of hypertension or measured hypertension, history of myocardial infarction, history of diabetes, history of stroke, history of percutaneous coronary intervention, history of coronary artery bypass grafting, total cholesterol, C-reactive protein, use of a beta-blocker, use of a lipid-lowering drug, use of aspirin or an antiplatelet medication, and use of a diuretic. †Per 1 SD pg/ml in log BNP and NT-proBNP.

Abbreviations as in Tables 1 to 3.

peptide concentrations was substantially longer for NT-proBNP than for BNP, which may have introduced bias in favor of BNP in that study.

The relative prognostic value of BNP and NT-proBNP has also been evaluated in 2 other recent studies. The association between BNP and NT-proBNP and all-cause mortality was assessed in a community-based cohort of subjects free of heart failure at baseline (24). In a model containing both peptides, only NT-proBNP was predictive of outcome. However, because no overall index of prognostic value was provided, the clinical significance of the statistical difference is somewhat difficult to assess. Moreover, end points other than mortality were not examined. The relative value of BNP and NT-proBNP has also been examined in a large population of patients with symptomatic chronic heart failure (25). The predictive ability of BNP and NT-proBNP did not differ concerning the end point of all-cause mortality, but NT-proBNP provided superior prognostic information concerning the combined mortality and morbidity end point and concerning heart failure hospitalizations.

The reasons for the observed differences in prognostic value between BNP and NT-proBNP remain somewhat unclear. Early reports suggested that NT-proBNP is a more sensitive marker of asymptomatic left ventricular dysfunction than BNP (26,27), and this observation has been confirmed by a recent population-based study (28). A closer relation to renal function may not be fully accounted for by adjustment for estimated glomerular filtration rate and blood pressure and may represent a potential link to adverse outcome. A third possibility is that a longer half-life of NT-proBNP makes this peptide less prone to intraday variability than BNP, making a single measurement of NT-proBNP a more accurate and robust index of cardiovascular function and prognosis than a single measurement of BNP.

Finally, we cannot rule out the possibility that differences in in vitro stability and analytical precision between BNP and NT-proBNP assays may have contributed to the observed differences in prognostic merit. In a substudy of the SAVE (Survival and Ventricular Enlargement) trial, NT-pro-A-type natriuretic peptide (ANP) was found to be a stronger prognostic indicator than ANP (29), and this difference in prognostic value may have been based on the marked in vitro stability difference between ANP and NT-proANP. Data concerning the in vitro stability of BNP have been somewhat conflicting. Early studies suggested that BNP is stable in whole blood and EDTA plasma for at least 24 h (30,31). More recent data suggest that this may depend on the assay used. According to the manufacturer of the BNP assay used in the present study, BNP is stable for 4 h in whole blood and in EDTA plasma, and the recovery of BNP may potentially be diminished if collected in glass tubes. Moreover, long-term storage of frozen samples may also be associated with degradation of BNP. For instance, in one recent study using the Abbott AxSym assay, BNP immunoreactivity in EDTA plasma samples stored at −20°C for 2 to 4 months were reported to be <50% compared with levels measured within 4 h of blood collection (32). On the other hand, no association between the duration of storage and natriuretic peptide concentrations were observed in the present study. The observation of a strong and independent relationship to incident heart failure also argues strongly against significant degradation of BNP in the present study. However, the differences in prognostic merit between BNP and NT-proBNP for other end points may potentially be attributed to differences in in vitro stability, and these findings may not be relevant for samples measured immediately after blood collection in clinical day-to-day testing.

Differences in analytic performance of the assays may also have affected the results. In accordance with a study comparing the assays used in the present analysis (33), the low-range sensitivity and analytic precision of the NT-proBNP assay appeared to be superior to those of the BNP assay. Combined, these factors may have contributed to a lower signal-to-noise ratio for BNP than for NT-proBNP, translating into reduced prognostic power for BNP for non-heart failure end points.

What BNP and NT-proBNP concentrations define increased risk? Identification of threshold concentrations of BNP and NT-proBNP that define increased risk in clinically stable patients would be helpful for the clinician. The approved cut-off for BNP for heart failure is derived from

Table 5 Multivariable* Analysis of the Association Between Quartiles of BNPs and Cardiovascular Outcomes

Outcome	BNP			NT-ProBNP		
	2nd vs. 1st Quartile† Men = 24–51 pg/ml; Women = 32–61 pg/ml	3rd vs. 1st Quartile† Men = 51–98 pg/ml; Women = 61–115 pg/ml	4th vs. 1st Quartile† Men = 98–2,660 pg/ml; Women = 115–2,427 pg/ml	2nd vs. 1st Quartile† Men = 66–127 pg/ml; Women = 105–196 pg/ml	3rd vs. 1st Quartile† Men = 127–253 pg/ml; Women = 196–372 pg/ml	4th vs. 1st Quartile† Men = 253–5,590 pg/ml; Women = 372–4,593 pg/ml
Cardiovascular mortality	1.34 (0.76–2.36)	0.83 (0.45–1.53)	1.23 (0.70–2.18)	2.58 (1.15–5.78)	2.55 (1.13–5.78)	4.89 (2.23–10.72)
Fatal/nonfatal MI	1.05 (0.71–1.55)	1.02 (0.67–1.53)	0.79 (0.50–1.25)	1.14 (0.75–1.75)	1.23 (0.79–1.90)	1.19 (0.77–1.83)
Fatal/nonfatal CHF	2.34 (0.97–5.61)	2.38 (1.01–5.61)	4.04 (1.77–9.24)	1.03 (0.42–2.51)	1.32 (0.56–3.10)	4.37 (2.02–9.43)
Fatal/nonfatal stroke	1.46 (0.67–3.19)	1.55 (0.71–3.38)	1.80 (0.84–3.87)	1.17 (0.47–2.91)	1.68 (0.69–4.10)	4.07 (1.77–9.35)

*Adjusted for treatment assignment, age, gender, body mass index, ejection fraction <50%, estimated glomerular filtration rate, current smoking, history of hypertension or measured hypertension, history of myocardial infarction, history of diabetes, history of stroke, history of percutaneous coronary intervention, history of coronary artery bypass grafting, total cholesterol, C-reactive protein, use of a beta-blocker, use of a lipid-lowering drug, use of aspirin or an antiplatelet medication, and use of a diuretic. †HR (95% CI) between quartiles. Abbreviations as in Tables 1 to 3.

Table 6 Overall Prognostic Merit of BNP and NT-ProBNP

Outcome	BNP*	NT-ProBNP*	p Value†
Cardiovascular mortality	0.58 (0.53–0.63)	0.68 (0.63–0.73)	<0.001
Fatal and nonfatal MI	0.53 (0.49–0.57)	0.53 (0.49–0.56)	0.84
Fatal and nonfatal CHF	0.69 (0.64–0.73)	0.74 (0.69–0.79)	0.005
Fatal and nonfatal stroke	0.61 (0.55–0.67)	0.70 (0.65–0.75)	<0.001

*C-statistic (95% CI). †Between NT-proBNP and BNP as estimated by the nonparametric approach of DeLong et al. (22).
Abbreviations as in Tables 1 to 3.

trials of acutely dyspneic patients and does not take into account the confounding effects of age and gender. Because it is not based on healthy individuals it should not be regarded as a conventional upper normal value and may be imperfect for defining risk in stable coronary artery disease patients. In fact, this was a main argument for not using those cut-offs in the present analyses. Instead, we analyzed BNP and NT-proBNP as continuous variables and by quartile. Although there is some degree of peptide-specific and end point–specific variations, the current data suggest that the risk associated with increasing BNP and NT-proBNP concentrations is largely monotonic and does not allow definition of a specific threshold value.

Incremental prognostic value of BNPs. Multiple biomarkers have been proposed as prognostic tools in patients with coronary artery disease, but few have been demonstrated to provide clinically relevant incremental prognostic value to conventional risk factors (14). A recent publication from the HOPE (Heart Outcomes Prevention Evaluation) study in patients with cardiovascular risk factors suggests that NT-proBNP provides incremental prognostic information concerning the combined end point of cardiovascular death, stroke, and myocardial infarction above that obtained by models of traditional risk factors (34). The present study extends these findings by showing that, in patients with established coronary artery disease, adding BNP and NT-proBNP to the best available model results in statistically significant improvement in predictive ability for the individual end point of heart failure, as evaluated by the c-index. Moreover, NT-proBNP improved the predictive ability of the model for the end point of cardiovascular death. In

Table 7 Incremental Prognostic Value of BNP and NT-ProBNP to the Best Available Multivariable* Model for Cardiovascular End Points

Outcome	Covariates†	Covariates and BNP†	Covariates and NT-ProBNP†
CV mortality	0.74 (0.70–0.79)	0.75 (0.71–0.80)	0.77 (0.73–0.81)‡
CHF	0.82 (0.78–0.86)	0.84 (0.80–0.87)‡	0.85 (0.81–0.88)‡
Stroke	0.78 (0.73–0.83)	0.78 (0.73–0.83)	0.80 (0.76–0.85)

*Covariates include treatment assignment, age, gender, body mass index, ejection fraction <50%, estimated glomerular filtration rate, current smoking, history of hypertension or measured hypertension, history of myocardial infarction, history of diabetes, history of stroke, history of percutaneous coronary intervention, history of coronary artery bypass grafting, total cholesterol, C-reactive protein, use of a beta-blocker, use of a lipid-lowering drug, use of aspirin or an antiplatelet medication, and use of a diuretic. †C-statistic (95% CI). ‡$p < 0.05$ as estimated by the nonparametric approach of DeLong et al. (22).
CV = cardiovascular; other abbreviations as in Tables 1 to 3.

contrast to the HOPE substudy, the best available model in the present study included an objective measure of ventricular function.

Prediction of the effect of ACE inhibition. In contrast to the HOPE (16) and EUROPA (EURopean trial On Reduction of cardiac events with Perindopril in stable coronary Artery disease) (15) studies, in the PEACE trial, ACE inhibition did not result in any reduction in the primary outcome (i.e., cardiovascular mortality, myocardial infarction, or coronary revascularization) (17). One possible explanation for the discrepant result is the considerably lower risk of the patients included in the PEACE trial than in the HOPE and the EUROPA trials. Because BNP and NT-proBNP strongly relate to mortality in a wide spectrum of cardiovascular disease, including patients with stable coronary artery disease (9–13), it seemed reasonable to hypothesize that measurement of BNP and NT-proBNP might identify patients who benefit from ACE inhibition. The failure of BNP and NT-proBNP to be helpful in this respect may be related to the inability of BNPs to predict coronary ischemic events, which constituted the majority of events in the PEACE trial. It is also conceivable that the neutral overall results of the PEACE trial may have reduced the likelihood of detecting a significant interaction between natriuretic peptide levels and benefit of ACE inhibition.

Study limitations. Limitations of the present study include the selection of patients participating in clinical trials who may not be representative of all stable coronary artery disease patients, as well as the use of biobank specimens obtained at multiple sites and shipped for peptide analysis.

Study strengths. Strengths of the study include the prospective design of the PEACE biomarker substudy, the large and well characterized patient sample, the long duration of follow-up, accuracy of recording of cardiovascular end points, and adjustment for important cardiovascular risk factors.

Clinical implications. In low-risk patients with stable coronary artery disease and preserved left ventricular function, BNPs provide strong and incremental prognostic information to traditional risk factors. The clinical implications of elevated BNPs are less clear. Lack of prediction of myocardial infarction suggests that determination of BNPs may not be useful for selection of anti-ischemic therapies in low-risk patients. Contrary to our expectations, BNP and NT-proBNP failed to identify stable coronary artery disease patients who benefit from ACE inhibition. In conclusion, current data support measurement of BNPs in low-risk populations for prognostic assessment but do not provide a mandate for the use of these peptides for tailoring therapy in individual patients.

Acknowledgements

The authors gratefully acknowledge the efforts of the PEACE investigators, research coordinators, and committee members. A list of those individuals is available at: http://www.bsc.gwu.edu/peace/.

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