N-Terminal Pro-B–Type Natriuretic Peptide and Long-Term Mortality in Acute Coronary Syndromes

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Background—B-type natriuretic peptide (BNP) is a predictor of short- and medium-term prognosis across the spectrum of acute coronary syndromes (ACS). The N-terminal fragment of the BNP prohormone, N-BNP, may be an even stronger prognostic marker. We assessed the relation between subacute plasma N-BNP levels and long-term, all-cause mortality in a large, contemporary cohort of patients with ACS.

Methods and Results—Blood samples for N-BNP determination were obtained in the subacute phase in 204 patients with ST-elevation myocardial infarction (MI): 220 with non-ST segment elevation MI and 185 with unstable angina in the subacute phase. After a median follow-up of 51 months, 86 patients (14%) had died. Median N-BNP levels were significantly lower in long-term survivors than in patients dying (442 versus 1306 pmol/L; $P<0.0001$). The unadjusted risk ratio of patients with supramedian N-BNP levels was 3.9 (95% confidence interval, 2.4 to 6.5). In a multivariate Cox regression model, N-BNP (risk ratio 2.1 [95% confidence interval, 1.1 to 3.9]) added prognostic information above and beyond Killip class, patient age, and left ventricular ejection fraction. Adjustment for peak troponin T levels did not markedly alter the relation between N-BNP and mortality. In patients with no evidence of clinical heart failure, N-BNP remained a significant predictor of mortality after adjustment for age and ejection fraction (risk ratio, 2.4 [95% confidence interval, 1.1 to 5.4]).

Conclusions—N-BNP is a powerful indicator of long-term mortality in patients with ACS and provides prognostic information above and beyond conventional risk markers. **(*Circulation*. 2002;106:2913-2918.)**

Key Words: angina ■ myocardial infarction ■ natriuretic peptides ■ prognosis ■ risk factors

Acute coronary syndromes (ACS) encompass a continuum of cardiac ischemic events, ranging from unstable angina pectoris with no biochemical evidence of myocardial necrosis to ST-elevation acute myocardial infarction (AMI). The common denominator of ACS is a pathophysiologic process characterized by rupture of an atherosclerotic plaque, altered coronary vasomotor tone, platelet aggregation, and thrombosis.[1,2] The prognosis of patients with ACS varies widely, and clinical, electrocardiographic, and biochemical markers of adverse prognosis have been used to identify high-risk individuals in need of aggressive intervention. Recently, B-type natriuretic peptide (BNP) has been shown to provide valuable prognostic information in patients with ACS.[3–5] One previous study of 122 patients with predominantly ST-segment elevation AMI suggested that the N-terminal fragment of the BNP prohormone, N-BNP, may provide prognostic information superior to that obtained from BNP.[6] Sparse information exists regarding N-BNP in the setting of non–ST-segment elevation ACS. In one small-scale, cross-sectional study, N-BNP levels were higher in patients with unstable than in those with stable angina.[7] In a recent pilot study, N-BNP levels were predictive of short-term survival after adjustment for conventional contemporary risk markers, including troponin I.[8] The objective of the present study was to assess the long-term, prognostic value of N-BNP in an unselected, consecutive series of patients admitted to a Scandinavian teaching hospital with ACS. Because the presence of clinical heart failure during hospitalization after AMI is known to be associated with adverse prognosis as well as with high natriuretic peptide levels,[3,6,9] we were particularly interested in assessing the relation between N-BNP and all-cause mortality in patients with no signs of heart failure (ie, Killip class I) on admission and during the primary hospitalization, a group of patients commonly considered to be at low risk.

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Methods

Study Design and Patient Population

Patients with ACS, defined as a diagnosis of unstable angina pectoris or AMI, admitted to the coronary care unit of the Sahlgrenska

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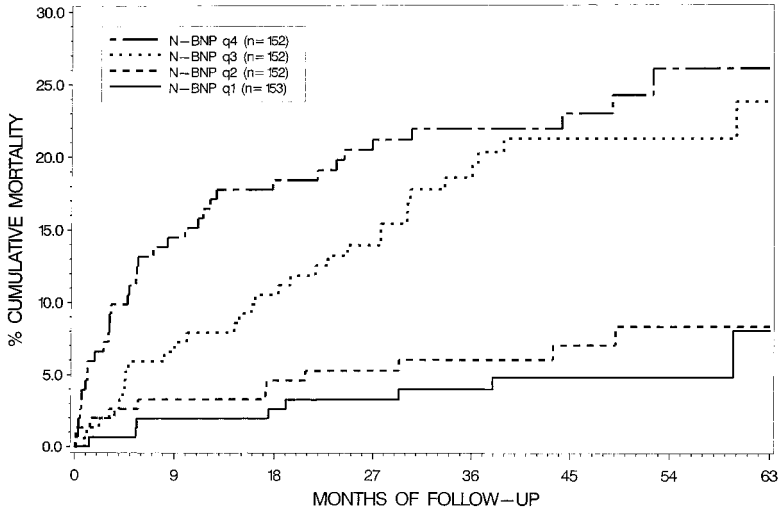

Figure 1. Kaplan-Meier survival curves for patients with acute coronary syndromes according to N-BNP quartile at baseline ($P<0.0001$ for difference between the two groups, q1+q2 vs q3+q4).

University Hospital, Gothenburg, Sweden from September 1995 to February 2000 were eligible for participation in an ongoing risk-stratification program. Patients who consented to blood sampling were included consecutively in the present study. The main exclusion criteria were age <18 or >80 years, noncoronary artery disease associated with a life expectancy <1 year, unwillingness or incapacity to provide informed consent, residence outside the city of Gothenburg, and prior admission resulting in inclusion in the study. The primary outcome measure of the study was all-cause mortality from the time of inclusion in the study to September 15, 2001. Survival status and date of death were obtained from the Death Registry of Western Sweden. The patients were prospectively classified according to maximum Killip class[10] on admission and during primary hospitalization. Electrocardiographic findings on admission were classified according to the presence of ST-segment elevation and ST-segment depression. Based on hospital records and personal interview, the patients were classified as having or not having a medical history of AMI, angina pectoris, congestive heart failure, diabetes mellitus, and arterial hypertension. The study protocol was approved by the Regional Ethics Committee before the initiation of the study. Informed consent was obtained from all participating patients.

Blood Sampling Procedures and Echocardiography

Peripheral blood samples for plasma N-BNP determination were obtained in the subacute phase (median 3 days) after hospital admission by direct venipuncture of an antecubital vein after the patient had been resting in the supine position for >30 minutes. Blood samples were immediately immersed in ice water and centrifuged within 1 hour, and EDTA plasma was aspirated. Plasma samples were stored at −70°C pending analysis. Echocardiographic investigation was performed by an experienced operator within 5 days of hospital admission. Biplane left ventricular ejection fraction (LVEF) was calculated by the disc sum method, and tracings were checked in motion mode for accuracy, as described previously.[11]

Assay of N-BNP

Our assay for N-BNP was based on the noncompetitive N-BNP assay described by Karl et al.[12] Peptides corresponding to the N-terminal (amino acids 1 to 12) and C-terminal (amino acids 65 to 76) of the human N-BNP were used to raise rabbit polyclonal antibodies.[13] IgG from the sera was purified on protein A sepharose columns. The C-terminal–directed antibody (0.5 μg in 100 μL for each well) was immobilized onto ELISA plates. The N-terminal antibody was affinity purified and biotinylated using biotin-X-N-hydroxysuccinimide ester (Calbiochem). Aliquots (20 μL) of samples or N-BNP standards were incubated in the C-terminal antibody coated wells with the biotinylated antibody for 24 hours at 4°C. ELISA plates were washed with 0.1% Tween in PBS, and streptavidin (Chemicon International Ltd) labeled with methyl-acridinium ester (5×10^6 relative light units/mL)[14] was added to each well. Plates were read on a Dynatech MLX Luminometer, with sequential injections of 100 μL of 0.1 mol/L nitric acid (with H_2O_2) and then 100 μL of NaOH (with cetyl ammonium bromide).[13] The lower limit of detection was 14.4 fmol/mL of unextracted plasma. Within and between assays, coefficients of variation were acceptable at 2.3% and 4.8%, respectively. There was no cross-reactivity with ANP, BNP, or CNP.

Statistical Analysis

Continuous data are presented as median and interquartile range. To test for differences between patients with supramedian versus inframedian N-BNP levels, the Mann-Whitney U and Fisher exact tests were used for ordered/continuous and categorical variables, as appropriate. For survival analysis, continuous and ordered variables were dichotomized using the 25th, 50th, or 75th percentile as the cut off. The cut-off value giving optimal discrimination with regard to all-cause mortality was selected for additional analysis. To visualize the relation between N-BNP levels and all-cause mortality, patients were subdivided according to the median value (545 pmol/L), Kaplan-Meier plots were generated, and the log rank test was used for comparison of the resulting survival curves. Cox proportional hazards regression was used to assess the prognostic value of N-BNP after adjustment for confounders, defined as the variables that separately decreased the risk ratio of supramedian N-BNP levels by at least 10%. The confounders identified were included simultaneously in 2 separate final models, one encompassing the complete patients sample with ejection fraction data and another comprising patients without clinical signs of heart failure (ie, Killip class I) on admission and during the index hospitalization. The optimal prognostic thresholds in the subgroups of patients with unstable angina, non–ST-segment elevation AMI, and ST-segment elevation AMI as index diagnosis were derived from receiver-operating characteristics plots. All probability values are two-tailed and were considered significant when <0.05. Risk ratios (RRs) are given with 95% confidence intervals.

Results

The study population consisted of 609 patients, 204 with ST-elevation AMI, 220 with non-ST segment elevation AMI, and 185 with unstable angina. Thrombolytic therapy or primary percutaneous coronary intervention was performed in 147 patients (24%), whereas rescue/planned percutaneous coronary intervention or coronary artery bypass grafting was performed in 153 patients (25%) during the primary hospitalization. The characteristics of the patients, subdivided according to the median level of plasma N-BNP, are listed in

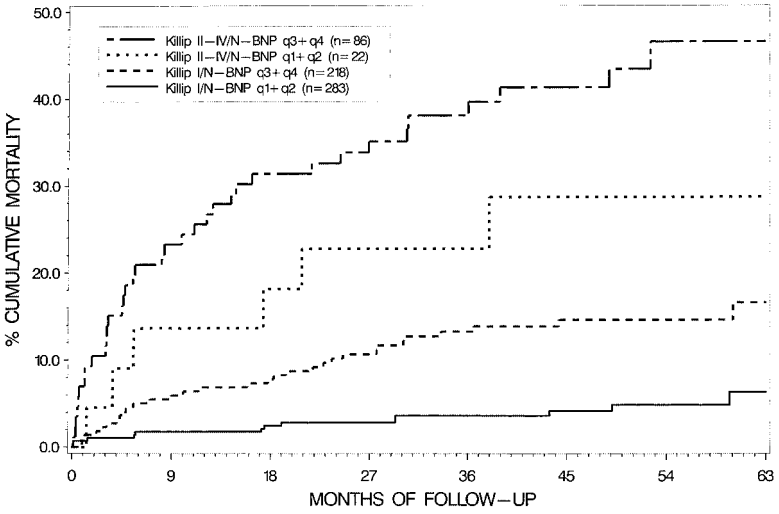

Figure 2. Kaplan-Meier survival curves for patients with acute coronary syndromes according to maximum Killip class during index hospitalization (I versus II through IV) and N-BNP levels below and above median ($P=0.0001$ for difference between N-BNP groups in maximum Killip class I patients and $P=0.18$ in maximum Killip class II through IV patients).

Table 1. The median N-BNP concentration in plasma was 545 pmol/L (interquartile range, 157 to 1435 pmol/L). As expected, the median plasma N-BNP concentrations differed according to the patients' index diagnosis (ST-segment elevation AMI, 1034 [390 to 2076] pmol/L; non-ST-segment elevation AMI, 644 [217 to 1507] pmol/L; unstable angina, 179 [62 to 477] pmol/L). Patients with supramedian N-BNP levels were significantly older and had higher serum creatinine, peak troponin T, and creatine kinase MB levels than those with inframedian N-BNP concentrations. Moreover, supramedian N-BNP values were associated with higher Killip class, lower LVEF, and a higher proportion of patients with ST-segment deviation, Q-wave changes, and anterior wall ECG changes.

N-BNP and All-Cause Mortality

No patient was lost to follow-up. After a median duration of follow-up of 51 months (range, 19 to 72 months), 86 patients (14%) had died. Ten deaths (2%) occurred during the first 30 days after hospital admission. Kaplan-Meier survival curves according to N-BNP quartile at baseline are presented in Figure 1. Median baseline N-BNP levels were significantly lower in long-term survivors than in patients dying (442 versus 1306 pmol/L; $P<0.0001$). The unadjusted RR of patients with supramedian N-BNP levels at baseline was 3.9 (95% confidence interval, 2.4 to 6.5) compared with those with inframedian values. No significant statistical interaction between index diagnosis and N-BNP regarding all-cause mortality was observed. The unadjusted RR of patients with supramedian N-BNP levels at baseline (ie, >545 pmol/L) compared with those with inframedian values was 4.7 (95% confidence interval, 1.4 to 15.6) in the subgroup with ST-segment elevation AMI, 5.6 (95% confidence interval, 2.2 to 14.5) in the subgroup with non–ST-segment elevation AMI, and 3.0 (95% confidence interval, 1.3 to 7.0) in the subgroup with unstable angina. Moreover, there was no significant interaction between thrombolytic therapy/primary percutaneous coronary intervention and N-BNP or between rescue/planned percutaneous coronary interventions/coronary artery bypass grafting and N-BNP with regard to all-cause mortality.

The association between potential confounders and long-term mortality is summarized in Table 2. Although several variables were univariate predictors of long-term mortality, only patient age, Killip class, and LVEF decreased the RR of N-BNP with >10%, suggesting that these factors were true confounders. Of note, although troponin T >25th percentile (ie, >0.05 μg/L) was related to mortality (RR 2.1 [95% confidence interval, 1.1 to 4.0]), the risk ratio of N-BNP was only slightly altered when adjusting for troponin T (unadjusted RR, 3.5 for supramedian N-BNP in patients with troponin T available, 3.3 after adjustment). The following potential confounder variables were tested in a series of 3-factor analyses but did not decrease the relative risk of N-BNP with more than the prespecified criterion for inclusion in the multivariate model (ie, 10%): patient sex (<1%), previous AMI (−2%), previous angina (3%), previous congestive heart failure (−4%), previous diabetes (1%), previous arterial hypertension (<1%), previous hyperlipidemia (−2%), current smoking (<1%), peak serum creatine kinase MB greater than lower quartile (7%), peak serum troponin T greater than lower quartile (−8%), serum creatinine greater than third quartile (−9%), ST-segment elevation on admission ECG (9%), ST-segment depression on admission ECG (−4%), T-wave changes on admission ECG (<1%), pathological Q-wave changes on admission ECG (−2%), anterior wall ST-segment deviation (3%), ST-segment elevation AMI as index diagnosis (5%), non–ST-segment elevation AMI as index diagnosis (−1%), and unstable angina as index diagnosis (4%).

In a multivariate model, adjusting for patient age, Killip class, and LVEF (ie, variables decreasing the RR of N-BNP with >10%), N-BNP remained significantly associated with mortality (Table 3). The adjusted RR of patients with supramedian N-BNP levels at baseline (ie, >545 pmol/L) compared with those with inframedian values was 2.6 (95% confidence interval, 0.7 to 8.9) in the subgroup with ST-segment elevation AMI, 2.3 (95% confidence interval, 0.8 to 6.6) in the subgroup with non–ST-segment elevation AMI, and 2.0 (95% confidence interval, 0.6 to 6.7) in the subgroup with unstable angina. The optimal prognostic thresholds in these 3 diagnostic subgroups, as assessed by receiver-operating characteristics analysis, was 1147 pmol/L in patients with ST-segment elevation AMI, 1284 pmol/L in

TABLE 1. Characteristics of Patients With N-BNP Levels Greater or Less Than the Median

Variable	N-BNP ≤545 pmol/L	N-BNP >545 pmol/L	*P*
Demographics			
Median age, y	62	69	<0.0001
Female sex, %	27	30	0.42
Previous medical history			
Myocardial infarction, %	23	28	0.14
Angina pectoris, %	55	46	0.04
Congestive heart failure, %	7	12	0.05
Diabetes mellitus, %	18	19	0.84
Arterial hypertension, %	40	43	0.41
Index diagnosis			<0.0001
ST-elevation myocardial infarction, %	20	45	
Non–ST-elevation myocardial infarction, %	33	39	
Unstable angina, %	47	16	
ECG findings			
ST-elevation, %	20	42	<0.0001
ST-depression, %	21	35	0.0002
Q-wave changes, %	5	21	<0.0001
Anterior wall location, %	20	42	<0.0001
Biochemical markers			
Median peak creatine kinase MB fraction, μg/L	14	78	<0.0001
Median peak troponin T, μg/L	0.1	1.9	<0.0001
Median creatinine, μmol/L	97	104	<0.0001
Clinical data			
Killip class II through IV on admission, %	4	11	0.0005
Maximum Killip class II through IV, %	7	28	<0.0001
Thrombolytic therapy/primary PCI, %	20	29	0.01
Rescue/planned PCI/CABG, %	31	19	0.001
Left ventricular function			
Median LVEF, %	60	50	<0.0001

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass grafting.

patients with non–ST-segment elevation AMI, and 238 pmol/L in patients with unstable angina.

N-BNP and All-Cause Mortality in Killip Class I Patients

In the subgroup of patients with no clinical signs of heart failure on admission or during the primary hospitalization (n=501), 44 patients died during follow-up. The unadjusted RR for patients with supramedian N-BNP levels was 3.3 (95% confidence interval, 1.7 to 6.3) compared with those with inframedian values. In the subgroup of patients with LVEF measurements (n=403), the unadjusted RR for supramedian N-BNP was 3.7 (95% confidence interval, 1.8 to 7.9). In a multivariate model, adjusting for patient age and LVEF (ie, variables decreasing the RR for supramedian N-BNP >10%), N-BNP was still associated with long-term, all-cause mortality (risk ratio, 2.4 [95% confidence interval, 1.1 to 5.4]) (Table 3). Kaplan-Meier survival curves in patients stratified according to N-BNP levels and maximum Killip class during index hospitalization are presented in Figure 2.

Discussion

In a large, unselected, contemporary cohort of patients with ACS, we have demonstrated that N-BNP is a powerful indicator of long-term mortality. The relation seemed to be equally strong across the spectrum of ACS as well as in patients with and without evidence of clinical heart failure during the primary hospitalization.

N-BNP and Long-Term Mortality

Our results for N-BNP confirm and extend observations made in an important, recent, large-scale study of the prognostic value of BNP in patients with ACS.[5] In that study, which included patients from one of the treatment arms of the OPUS-TIMI 16 trial, BNP obtained during the first few days after the onset of ischemic symptoms was strongly and independently predictive of mortality at 1 and 10 months. In contrast to the OPUS-TIMI 16 BNP substudy, the present investigation was not a substudy of a multicenter, clinical drug trial but prospectively and primarily designed for evaluation of risk indicators in ACS. Although both studies included patients across the spectrum of ACS, from

TABLE 2. Prediction of All-Cause Mortality: Univariate Analyses

	Risk Ratio (95% Confidence Interval)	
Variable	All Patients	Max Killip Class I
N-BNP >545 pmol/L	3.9 (2.4 to 6.5)	3.3 (1.7 to 6.3)
Demographics		
Patient age >66 y	4.5 (2.7 to 7.5)	3.8 (2.0 to 7.3)
Female vs male sex	1.0 (0.6 to 1.6)	0.9 (0.5 to 1.9)
Previous medical history		
Myocardial infarction	2.0 (1.3 to 3.1)	1.6 (0.9 to 3.0)
Angina pectoris	1.2 (0.8 to 1.8)	1.1 (0.6 to 2.0)
Congestive heart failure	3.2 (1.9 to 5.3)	2.4 (1.0 to 5.6)
Diabetes mellitus	1.7 (1.1 to 2.8)	1.7 (0.8 to 3.3)
Arterial hypertension	1.0 (0.7 to 1.5)	1.1 (0.6 to 2.0)
ECG findings		
ST elevation	1.0 (0.6 to 1.5)	1.2 (0.6 to 2.2)
ST depression	1.7 (1.1 to 2.6)	1.8 (1.0 to 3.4)
Q-wave changes	1.6 (1.0 to 2.8)	1.4 (0.6 to 3.2)
Anterior wall location	1.2 (0.8 to 1.9)	1.3 (0.7 to 2.5)
Biochemical markers		
Peak creatine kinase MB >4 μg/L	1.4 (0.8 to 2.3)	0.9 (0.5 to 1.8)
Troponin T >0.5 μg/L	2.1 (1.1 to 4.0)	1.4 (0.6 to 3.1)
Creatinine >114 μmol/L	2.2 (1.4 to 3.4)	1.5 (0.7 to 2.8)
Clinical data		
Killip class on admission (II through IV vs I)	6.5 (4.0 to 10.4)	NA
Maximum Killip class (II through IV vs I)	5.6 (3.6 to 8.5)	NA
Left ventricular function		
LVEF <47%	3.4 (2.1 to 5.3)	3.8 (2.0 to 7.3)

q indicates quartile.

unstable angina to ST-segment elevation AMI, the mortality rate in the present study was significantly higher than in the OPUS-TIMI 16 BNP substudy, probably because of higher patient age and a higher proportion of patients with comorbidities. However, we believe that these features are common among contemporary patients with ACS, and our results are generalizable to other unselected patient groups.

TABLE 3. Multivariate Models

Variable	Risk Ratio (95% Confidence Interval)	*P*
All patients with ejection fraction measurements		
Patient age >66 y	2.5 (1.4 to 4.3)	0.001
LVEF <47%	1.9 (1.1 to 3.1)	0.01
Killip class on admission >1	3.2 (1.9 to 5.5)	<0.0001
N-BNP >545 pmol/L	2.1 (1.1 to 3.9)	0.02
Patients with ejection fraction measurements and maximum Killip class I on admission and during primary hospitalization		
Patient age >66 y	2.5 (1.2 to 5.0)	0.01
LVEF <47%	2.6 (1.3 to 5.2)	0.005
N-BNP >545 pmol/L	2.4 (1.1 to 5.4)	0.02

The observation that natriuretic peptides are powerful indicators not only of short-term and medium-term but also long-term prognosis across the spectrum of ACS is a novel one. We and others have previously shown that BNP[3] and N-BNP[6] are related to long-term prognosis in patients with predominantly ST-segment elevation AMI. However, no long-term follow-up data are yet available for patients with non–ST-segment elevation ACS. Moreover, none of the early, long-term studies made adjustments for modern, sensitive biochemical markers of myocardial necrosis. Importantly, as demonstrated both for BNP[5] and for N-BNP in the present investigation, these natriuretic peptides seem to provide complementary prognostic information to that obtained from troponin T.

Prognostic Value of N-BNP in Patients Without Clinical Heart Failure

Clinical heart failure is a poor prognostic sign in patients with ACS and is commonly regarded as a sign of significant ventricular dysfunction. LVEF is a frequently used index of left ventricular systolic function and a powerful prognostic indicator. Interestingly, LVEF and clinical classification of heart failure (ie, Killip classification) provide independent prognostic information, suggesting that factors other than systolic function are of importance for prognosis in these patients. Circulating natriuretic peptide levels are elevated both in patients with low ejection

fractions and in patients with clinical heart failure.[3,6,7] As previously shown for BNP,[5] we were able to demonstrate that N-BNP provides important prognostic information in ACS patients without clinical evidence of heart failure. Moreover, in this important subgroup, N-BNP added prognostic information to LVEF, a variable not adjusted for in the multivariate model of the OPUS-TIMI 16 BNP study.

Why Is N-BNP a Powerful Prognostic Indicator?

The pathophysiologic mechanisms responsible for the strong association between N-BNP and mortality cannot be deduced from the present study. However, our findings are compatible with the theory that BNP and N-BNP release, even in the absence of myocardial necrosis, is augmented by transient or permanent ventricular dysfunction induced by myocardial ischemia. Moreover, the magnitude of the increase in N-BNP may reflect the extent of the ischemic territory. In contrast to the highly sensitive and specific contemporary biochemical markers of myocardial necrosis, N-BNP (and BNP) elevation is associated with several other risk factors for adverse outcome, including advanced patient age, renal impairment, cardiac arrhythmias, and preexisting LV systolic or diastolic dysfunction. Consequently, BNP and N-BNP may in a unique way reflect a sum or integral of different risk markers. Indeed, the prognostic power of N-BNP may be directly related to this lack of specificity.

Does the Prognostic Value of BNP and N-BNP Differ?

BNP and N-BNP are released in a 1:1 fashion, but circulating concentrations may differ because of differing clearance characteristics. Although some early data suggested that the relative increase in circulating levels from the healthy state to heart failure is more pronounced for N-BNP than BNP[15] and the prognostic value in one early study tended to be slightly better for N-BNP than for BNP,[6] no well-powered study has so far compared the prognostic value in the setting of ACS. However, the OPUS-TIMI 16 BNP study results and data from the present investigation seem remarkably similar, suggesting that the difference, if any, is of limited practical consequence.

Limitations

A limitation of this and all similar studies is the fact that circulating concentrations of the natriuretic peptides before the ischemic event remain unknown. Accordingly, we cannot rule out the possibility that preexistent ventricular dysfunction, hypertrophy, or renal impairment, and not the ischemic injury per se, is the cause of N-BNP elevation and the relation to outcome. By adjusting for history of prior AMI, congestive heart failure, and hypertension, as well as for ejection fraction and serum creatinine, we attempted to minimize this effect. On a practical level, one could also argue that for risk stratification purposes, the main point is first to identify individuals at high risk, regardless of the cause. Assessment of the clinical utility of N-BNP may ultimately have to await clinical trials in which patients with high and low concentrations are randomized to different treatment strategies.

Conclusions

The present data strongly suggest that N-BNP levels in the first few days after the onset of symptoms are predictive of short- and long-term mortality in patients with ACS. Recently, a rapid, qualitative electrochemiluminescence immunoassay for automated determination of N-BNP has become commercially available, permitting the hospital clinician easy access to prognostic information not obtained from conventional risk markers. Whether N-BNP will find an important place in the diagnostic armamentarium of the clinical cardiologists will depend on future studies addressing the value of N-BNP measurements as a guide to different therapeutic strategies in patients with ACS.

Acknowledgments

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References

1. Shah PK. New insights in the pathogenesis and prevention of acute coronary syndromes. *Am J Cardiol*. 1997;79:17–23.
2. Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med*. 1999;340: 115–126.
3. 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. *Circulation*. 1996;93:1963–1969.
4. Arakawa N, Nakamura M, Aoki H, et al. Plasma brain natriuretic peptide predicts survival after acute myocardial infarction. *J Am Coll Cardiol*. 1996; 27:1656–1661.
5. 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;345:1014–1021.
6. 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;97:1921–1929.
7. Talwar S, Squire IB, Downie PF, et al. Plasma N terminal pro-brain natriuretic peptide and cardiotrophin-1 are raised in unstable angina. *Heart*. 2000;84:421–424.
8. Omland T, de Lemos JA, Morrow DA, et al. Prognostic value of N-terminal pro-atrial and pro-brain natriuretic peptide in patients with acute coronary syndromes. *Am J Cardiol*. 2002;89:463–465.
9. Talwar S, Squire IB, Downie PF, et al. Profile of plasma N-terminal proBNP following acute myocardial infarction. Correlation with left ventricular dysfunction. *Eur Heart J*. 2000;21:1514–1521.
10. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit: a two year experience with 250 patients. *Am J Cardiol*. 1967;20: 457–464.
11. Omland T, Samuelsson A, Hartford M, et al. Serum homocysteine concentration as an indicator of survival in patients with acute coronary syndromes. *Arch Intern Med*. 2000;160:1834–1840.
12. Karl J, Borgya A, Galluser A, et al. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. *Scand J Clin Lab Invest Suppl*. 1999;230:177–181.
13. Hughes D, Talwar S, Squire IB, et al. An immunoluminometric assay for N-terminal pro-brain natriuretic peptide: development of a test for left ventricular dysfunction. *Clin Sci*. 1999;96:373–380.
14. Hart RC, Taaffe LR. The use of acridinium ester-labeled streptavidin in immunoassays. *J Immunol Methods*. 1987;101:91–96.
15. Hunt PJ, Yandle TG, Nicholls MG, et al. The amino-terminal portion of pro-brain natriuretic peptide (pro-BNP) circulates in human plasma. *Biochem Biophys Res Commun*. 1995;214:1175–1183.