Natriuretic Peptides and Mortality After Stroke

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Background and Purpose—Measurement of natriuretic peptides provides prognostic information in various patient populations. The prognostic value of natriuretic peptides among patients with acute stroke is not known, although elevated peptide levels have been observed.

Methods—A series of 51 patients (mean age, 68±11 years) with first-ever ischemic stroke underwent a comprehensive clinical examination and measurements of plasma atrial natriuretic peptides (N-ANP) and brain natriuretic peptides (N-BNP) in the acute phase of stroke. The patients were followed-up for 44±21 months. Risk factors for all-cause mortality were assessed. Control populations, matched for gender and age, consisted of 51 patients with acute myocardial infarction (AMI) and 25 healthy subjects.

Results—Plasma concentrations of N-ANP (mean±SD, 988±993 pmol/L) and N-BNP (751±1608 pmol/L) in the stroke patients were at the same level as those in the AMI patients (NS for both), but significantly higher than those of the healthy subjects (358±103 pmol/L, P<0.001 and 54±26 pmol/L, P<0.01, respectively). Elevated levels of N-ANP and N-BNP predicted mortality after stroke (risk ratio [RR] 4.3, P<0.01 and RR 3.9, P<0.01, respectively) and after AMI (P<0.05), and remained independent predictors of death after stroke even after adjustment for age, diabetes, coronary artery disease, and medication (RR 3.9, P<0.05 and RR 3.7, P<0.05, respectively).

Conclusion—Plasma levels of natriuretic peptides are elevated in the acute phase of stroke and predict poststroke mortality. (Stroke. 2005;36:1016-1020.)

Key Words: natriuretic peptides | outcome | stroke

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are vasoactive peptide hormones with natriuretic, diuretic, and vasodilator activity.1–3 They have emerged as important candidates in the development of diagnostic and prognostic tools for cardiovascular diseases.3,4 An association between elevated levels of natriuretic peptides (NPs) and increased mortality has been established in patients with heart failure,5,6 as well as in patients with acute coronary syndromes.7,8 Moreover, previous studies have further extended the role of BNP measurements to risk stratification of the general population.9–11 The current information concerning the role of NPs in cerebrovascular diseases is limited. Polymorphisms of the gene for ANP12 and elevated plasma levels of ANP were recently reported to predict the risk of stroke.11 In the acute phase of stroke, the plasma levels of ANP have been reported to be elevated,13 and the levels of BNP have been shown to correlate with blood pressure levels.14 Immunohistochemical studies suggest that cerebral ischemia induces ANP secretion in brain tissue.15,16 A similar association of NPs with the progression of cerebral ischemia was also reported in a study on the development of delayed neurological deficits in patients with gradually increasing BNP levels after subarachnoid hemorrhage.17

The origin of NP secretion in acute cerebrovascular diseases is still unsettled, although some evidence exists to suggest both a cerebral15,16 and a cardiac origin. We compared the levels of NPs in the acute phase of acute myocardial and brain infarctions and designed this prospective case-control follow-up study to evaluate the prognostic role of NPs after ischemic stroke.

Patients and Methods

Study Population

The study population consisted of 237 stroke patients treated in the stroke unit of our hospital between December 1997 and May 1999. Ischemic stroke patients admitted within the first 24 hours of symptom onset were recruited into the study. We excluded patients older than age 80 years and patients with previous strokes, transient ischemic attacks, head trauma, other cerebral disease, severe psychiatric illness, alcoholism, or malignancy in their medical history. Patients with unstable angina at recruitment or nonsinus rhythm on ECG, as well as patients unable or unwilling to give informed consent, for whom a family member was not available to give consent, were excluded. After the exclusions, the eligible stroke patients were at the same level as those in the AMI patients (NS for both), but significantly higher than those of the healthy subjects (358±103 pmol/L, P<0.001 and 54±26 pmol/L, P<0.01, respectively). Elevated levels of N-ANP and N-BNP predicted mortality after stroke (risk ratio [RR] 4.3, P<0.01 and RR 3.9, P<0.01, respectively) and after AMI (P<0.05), and remained independent predictors of death after stroke even after adjustment for age, diabetes, coronary artery disease, and medication (RR 3.9, P<0.05 and RR 3.7, P<0.05, respectively).

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The blood samples for the analysis of NPs were taken on day 2 after admission through an intravenous cannula into EDTA vacuum tubes. The samples were placed on ice and centrifuged at 4°C for 10 minutes, and the plasma was stored at −70°C. The amino-terminal fragments of natriuretic peptides (N-ANP and N-BNP) were analyzed. The assay was performed as described previously.19

The patients were followed-up for nearly 4 years (mean, 44±21 months). After the follow-up, their clinical outcome was assessed by reviewing their medical records supplemented by an interview of the patient or a family member to make sure that the patient was alive. In the case of death, the hospital records and death certificates were reviewed to verify death. The local ethics committee approved the study protocol, and informed consent was obtained from each patient or family member.

### Statistical Analysis

The end-point of this study was all-cause mortality. A sample size of 50 patients with an average follow-up of 3.5 years was based on the assumption that the annual incidence of death in this type of population is ~10% in the current treatment era. A minimal number of 15 end-points was evaluated to be needed to accomplish a valid analysis for 1 powerful risk predictor.20

The data were analyzed using the SPSS software (SPSS 11.0; SPSS Inc.). Univariate comparisons of the baseline characteristics between the different study groups as well as between the stroke patients who died and those who survived were performed with the t test for the continuous variables and with the 2-sample t test for the categorical variables. To find the best cutoff points for all predictive variables, the dichotomous cutoff points that maximized the risk ratio obtained from the Cox regression model were sought, with all-cause mortality as the end-point. Risk ratio (RR) and 95% confidence intervals (CI) were calculated for each variable. After adjustment for age, clinical variables, and medication, the risk variables were included in a Cox proportional hazards regression analysis to estimate their independent predictive powers. Kaplan–Meier estimates of the distribution of times from baseline to death were computed, and log-rank analysis was performed to compare the survival curves between the groups. P<0.05 was considered significant.

### Results

The baseline clinical characteristics of the patient and control populations are presented in Table 1. Twenty-two (43%) stroke and 6 (12%) AMI patients died during the follow-up. Among the stroke patients, 9 (41%) cerebrovascular deaths, 7 (32%) cardiac deaths, and 6 (27%) other causes of death were observed. During the

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Laboratory values are means±SD. ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ASA, acetylsalicylic acid; CAD, coronary artery disease; N-ANP, N-terminal ANP; N-BNP, N-terminal BNP.

*P<0.01 between patients and healthy persons.
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The plasma concentration of N-ANP averaged (mean ± SD) 988 ± 993 pmol/L and that of N-BNP averaged 751 ± 1608 pmol/L in the stroke patients. The values were equally high as the values in the AMI patients (706 ± 418 pmol/L for N-ANP and 502 ± 468 pmol/L for N-BNP), with a tendency toward higher N-ANP values in the stroke patients (P = 0.07). The healthy controls had significantly lower N-ANP (358 ± 103 pmol/L, P < 0.001) and N-BNP (54 ± 26 pmol/L, P < 0.01) values than the stroke or AMI patients.

The N-ANP and N-BNP plasma concentrations were significantly higher among the stroke patients who died during the follow-up than among the survivors (1501.4 ± 26 pmol/L, P < 0.05) and older age (RR, 7.5; CI, 1.0 to 56.3; P < 0.05) also predicted death. In multivariate analysis, after adjustment for age, diabetes, coronary artery disease, and usage of angiotensin-converting enzyme inhibitors and β-blockers, N-ANP and N-BNP showed independent prognostic values for mortality (RR, 3.9; CI, 1.2 to 12.6; P < 0.05 and RR, 3.7; CI, 1.4 to 10.0; P < 0.05, respectively), whereas SSS did not (Table 4). Among the AMI patients, N-ANP (RR, 5.2; CI, 1.0 to 31.0; P < 0.05) and older age (RR, 7.5; CI, 1.6 to 9.4; P < 0.05) had significant prognostic value. A low SSS score (RR, 2.5; CI, 1.1 to 6.1; P < 0.05) and older age (RR, 7.5; CI, 1.0 to 56.3; P < 0.05) also predicted death. In multivariate analysis, after adjustment for age, diabetes, coronary artery disease, and usage of angiotensin-converting enzyme inhibitors and β-blockers, N-ANP and N-BNP showed independent prognostic values for mortality (RR, 3.9; CI, 1.2 to 12.6; P < 0.05 and RR, 3.7; CI, 1.4 to 10.0; P < 0.05, respectively), whereas SSS did not (Table 4). Among the AMI patients, N-ANP (RR, 5.2; CI, 1.0 to 31.0; P < 0.05) was also significantly prognostic, whereas N-BNP did not reach statistical significance (RR, 3.5; CI, 0.7 to 19.2; P < 0.1) because of the small sample size. The Kaplan–Meier survival curves showed poor survival for the stroke and AMI patients with N-ANP >850 pmol/L. The cumulative survival rate was 80% for the stroke patients with N-ANP <850 pmol/L and 20% for those with higher values, estimated over the 4-year follow-up period. Similarly, the AMI patients with high N-ANP values had poorer survival than those with lower N-ANP levels (Figure).

### TABLE 4. Clinical Risk Variables as Predictors of Death After Stroke

| Risk Variable | Death (n=22) | P  
<table>
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<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td>Risk Ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>7.5 (1.0–56.3)</td>
<td>0.0489</td>
</tr>
<tr>
<td>SSS (&lt;30)</td>
<td>2.5 (1.1–6.1)</td>
<td>0.0392</td>
</tr>
<tr>
<td>N-ANP (&gt;850 pmol/l)</td>
<td>4.3 (1.6–11.2)</td>
<td>0.0029</td>
</tr>
<tr>
<td>N-BNP (&gt;500 pmol/l)</td>
<td>3.9 (1.6–9.4)</td>
<td>0.0028</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td>Risk Ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td>SSS (&lt;30)</td>
<td>1.2 (0.5–3.3)</td>
<td>0.6221</td>
</tr>
<tr>
<td>N-ANP (&gt;850 pmol/l)</td>
<td>3.9 (1.2–12.6)</td>
<td>0.0207</td>
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<td>N-BNP (&gt;500 pmol/l)</td>
<td>3.7 (1.4–10.0)</td>
<td>0.0103</td>
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CAD indicates coronary artery disease; CI, confidence interval. *Risk ratio assessed by Cox regression analysis.
Discussion

The present findings demonstrate that elevated values of plasma NPs in the acute phase of stroke indicate an increased risk of future mortality. High plasma levels of NPs predicted mortality after stroke better than any other risk variable, with the risk of death being 4-fold among the patients with high NP values. This is the first study to our knowledge to report an association between elevated NP values and an increased risk of death after acute ischemic stroke.

NPs in Stroke

NPs are synthesized mainly in the atrial (ANP) and ventricular (BNP) myocardium.1,2 They are also known to be released from brain tissue, mainly from the hypothalamus,22 and their release is suggested to be induced by cerebral ischemia.15,16 Our findings are in concordance with a previous study13 reporting markedly elevated levels of ANP in the acute phase of stroke. We also found high BNP levels in stroke patients. When the NP values in the acute phases of stroke and AMI were compared, we found the stroke patients to have equally high or even higher NP plasma values than the AMI patients, although an acute cardiac event was ruled out. This suggests that the secretion of NPs from the myocardium or various extracardiac sites, such as the brain and the vascular wall, is increased in ischemic stroke.

NP release has been claimed to be associated with the intensity of brain ischemia, reflecting increased biosynthesis and secretion from ischemic brain tissue.15,16 High concentrations of plasma BNP have been associated with the development of cerebral ischemia and neurological deficits.17 A similar association between NP levels and the clinical manifestations of cerebral ischemia was also found in this population, because the concentrations of NPs correlated significantly with the measures of neurological deficits (SSS, BI, MRS). However, as predictors of poor outcome, NPs surpassed the measures of neurological deficits, indicating that NPs provide prognostic information incremental to that obtained from the measures assessing merely the clinical severity of brain injury.

NPs and Mechanisms of Stroke Mortality

The prognostic value of NPs has previously been demonstrated in patients with heart failure,5,6 patients with acute coronary syndromes,7,8,23 and the general population.9–11 This study suggests a further application of NP measurement to the risk stratification of stroke patients.

It is generally assumed that elevated NP concentrations indicate activation of the neuroendocrine system, and that higher NP levels hence reflect a greater degree of hemodynamic dysfunction and explain the increased mortality in patients with acute cardiac disease. The mechanisms underlying the association of elevated NPs with increased mortality after stroke in patients with no obvious heart diseases are less obvious. The most probable reason for the high NP levels in acute stroke is the severity of brain injury. It is plausible to speculate that the elevated NP levels in the acute phase of stroke reflect the magnitude of brain injury and, by this mechanism, increase the risk of dying after stroke. This assumption is also supported by the association between the clinical deficits and NP values.

In addition, these peptides have a role in the modulation of the autonomic control of the heart.24,25 BNP is known to augment parasympathetic vagal neurotransmission, but high concentrations of NPs can directly stimulate cardiac pacemaking,24 suggesting that the disturbances in autonomic cardiovascular control might be one explanation for the increased risk of death in patients with elevated NP values. Further evidence for this interpretation was obtained in our recent study reporting that autonomic dysfunction in the acute phase of stroke also predicts long-term mortality.26

The NP system is suggested to be involved in atherosclerotic plaque formation in coronary arteries.27 The severity of coronary artery disease is reported to correlate with NP values28 and with
changes in the ANP gene.29 These findings imply that the severity of atherosclerosis underlying the pathologically high plasma values of NPs might also account for the poor long-term survival of stroke patients.

Limitations
The small sample size is an obvious limitation of the present preliminary study and obliges us to be cautious in the generalization of the results. More research with larger populations will be needed to establish the role of NPs in risk stratification after stroke. The long follow-up time ensured the accumulation of sufficient number of deaths for reliable statistical analyses, however. Moreover, several clinical variables were added in the multivariate analysis to reveal the independent prognostic power of NPs. They proved to be the most powerful predictors of mortality in this limited-size population, indicating their strong predictive power. This study was designed to reveal the predictive power of NPs in total mortality, but not in different subgroups. To assess survival in different mortality categories, a larger prospective observational study will be needed.

Clinical Implications
The results of this study show that elevated plasma levels of NPs are not a specific feature of acute cardiac events but are also seen after acute stroke. Furthermore, measurements of NP values seem to be useful in the risk stratification of patients with acute stroke. Preliminary findings on heart failure patients suggest that BNP-guided treatment leads to a better outcome.30 Application of similar procedures to stroke populations would seem tempting.

Acknowledgments
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