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Predictive value of plasma B-type natriuretic peptide for ischemic stroke: A community-based longitudinal study

Tomohiro Takahashi[a,*], Motoyuki Nakamura[a], Toshiyuki Onoda[b], Masaki Ohsawa[b], Kozo Tanno[b], Kazuyoshi Itai[b], Kiyomi Sakata[b], Masafumi Sakuma[a], Fumitaka Tanaka[a], Shinji Makita[a], Yuki Yoshida[c], Akira Ogawa[c], Kazuko Kawamura[d], Akira Okayama[e]

[a] Division of Cardiology, Department of Internal Medicine, Iwate Medical University, Morioka, Japan
[b] Department of Hygiene and Preventive Medicine, Iwate Medical University, Morioka, Japan
[c] Department of Neurosurgery, Iwate Medical University, Morioka, Japan
[d] Iwate Health Service Association, Morioka, Japan
[e] Japan Anti-Tuberculosis Association, Tokyo, Japan

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ABSTRACT

Objective: Structural heart diseases including atrial fibrillation are precursors for ischemic stroke. Plasma B-type natriuretic peptide (BNP) has been reported to be increased in patients with several types of structural heart diseases. However, the predictive value of plasma BNP for ischemic stroke remains unknown. We have studied the predictive ability of plasma BNP for future development of stroke in community dwelling adults.

Methods: Subjects of this community-based study were recruited from the general population (n = 13,466). Plasma BNP levels and cardiovascular risk factors were determined at baseline. The incidence of ischemic stroke in the cohort was identified from regional stroke registry data. A multivariate Cox regression analysis was performed to analyze the relationship between plasma BNP levels and the risk of stroke.

Results: During a mean follow-up period of 2.8 years, 102 participants (65 males, 37 females) experienced a first ischemic stroke. In men, after adjustment for classical cardiovascular risk factors and atrial fibrillation, the hazard ratio (HR) for ischemic stroke was significantly elevated in the highest plasma BNP quartile (HR = 2.38; 95% CI = 1.07–5.29). In women, the relationship between plasma BNP levels and risk of ischemic stroke was of marginal significance after adjusting for the presence or absence of atrial fibrillation (HR = 3.03; 95% CI = 0.84–10.92, P = 0.09).

Conclusion: Elevated plasma BNP levels predict the risk of ischemic stroke within men from the general population.

1. Introduction

B-type natriuretic peptide (BNP) is a cardiac hormone secreted from the myocardium in response to changes in intracardiac volume and pressure [1,2]. Plasma BNP levels are known to be elevated in patients with symptomatic left ventricular systolic dysfunction [3,4] and correlate to New York Heart Association (NYHA) class as well as prognosis [5,6]. In addition, irrespective of the degree of left ventricular dysfunction, plasma BNP levels have been shown to be elevated in patients with various structural heart diseases including previous myocardial infarction, cardiomyopathy, valvular heart disease, hypertensive heart disease, and atrial fibrillation [3,7–13].

These structural heart diseases are precursors not only for heart failure, but also for ischemic stroke, and especially cardioembolic stroke [14]. However, there have been very few reports on the association between plasma BNP levels and the risk of stroke. The Framingham Heart Study [15] has described a 4.9-fold increase in the crude incidence of stroke or transient ischemic attack in the highest tertile of BNP levels compared to the lowest tertile. Kistorp et al. [16] reported that plasma levels of N-amino terminal fragment of the prohormone BNP (NT-proBNP) predicted the risk of stroke or transient ischemic attack, with a 3.6-fold increase in risk of stroke for participants with values above the 80th percentile vs those with values equal to or below the 80th percentile in the general population. However, the association between plasma BNP levels and risk of stroke subtypes remains unclear. The predictive value of plasma BNP measurement for ischemic stroke remains unknown.

* Corresponding author at: Division of Cardiology, Department of Internal Medicine, Iwate Medical University School of Medicine, 19-1 Uchimaru, Morioka 0208505, Japan. Tel.: +81 19 651 5111x2324; fax: +81 19 651 0401.
E-mail address: ttomo@ruby.ocn.ne.jp (T. Takahashi).

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We have studied the predictive ability of plasma BNP for future development of ischemic stroke in community dwelling adults.

2. Methods

2.1. Study population

The Iwate-Kenpoku Cohort (Iwate-KENCO) study was designed to prospectively investigate the risk of cardiovascular diseases including stroke and malignant tumor in the general Japanese adult population as described previously [17,18]. Subjects consisted of residents of the Ninohe, Kuji and Miyako districts in the northern Iwate prefecture, Japan. Between April 2002 and January 2005, 26,469 of these residents (men = 9161, women = 17,308) who were participating voluntarily in a multiphasic health checkup agreed to join the study (original cohort). The baseline survey included routine anthropometrical measurement, blood pressure measurement, ECG, routine laboratory assessment, a self-administered lifestyle questionnaire, and a food-frequency questionnaire. This study protocol was approved by our institutional ethics committee. All participants gave written informed consent.

Of the original cohort living in the Ninohe and Kuji districts (n = 15,927), 15,394 subjects (men = 5288, women = 10,106) underwent BNP measurement (BNP cohort). Subjects were excluded from this cohort on the basis of the following characteristics: age under 40 years (n = 575), history of cardiovascular or cerebrovascular events (n = 507), non-measurement of adjustment factors (n = 846). The final statistical analysis was therefore performed in 13,466 subjects (men = 4527, women = 8939, mean age = 62.7 years).

2.2. Outcome

In this cohort study, the primary endpoint was all-cause death, in addition to any nonfatal cardiovascular events such as myocardial infarction, cerebral infarction, or other strokes. Information about death and emigration was obtained from local government records. Stroke events were identified by accessing the Iwate prefecture stroke registration programme, which has been conducted since 1991 by the Iwate Medical Association with the support of the government of the Iwate prefecture [19]. Registration forms were submitted to the registration office of the Iwate Medical Association by mail when a patient with stroke was discharged from a medical facility. Diagnostic criteria for stroke used by the registry correspond with those published by the World Health Organization, based on a definition of sudden onset of neurological symptoms [20]. For diagnosis of stroke subtypes, computed tomography and/or magnetic resonance imaging were performed within each hospital. In order to improve accuracy of registration, trained research nurses checked medical charts in all hospitals located within these districts. Follow-up was conducted until August 2007.

2.3. Measurement

At the time of baseline survey, participants underwent anthropometrical measurement, ECG, blood pressure measurement, and routine laboratory assessment. In addition, a self-administered questionnaire was used to ascertain family history, symptoms, and lifestyle factors such as smoking habits, alcohol consumption, and exercise habits. A medical history including the status of drugs prescribed for hypertension, hyperlipidemia, diabetes, angina, myocardial infarction, congestive heart failure, and stroke was recorded by trained research staff. Using a 3-channel device, a standard 12-lead ECG was recorded in a supine position. Atrial fibrillation was defined by this 12-lead ECG at the time of baseline survey. Systolic and diastolic blood pressures were determined with an automatic device placed on the right arm of seated subjects who had rested in a sitting position for at least 5 min before measurement. Measurement was performed twice, with the mean value used for statistical analysis. Hypertension was defined as systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg, and/or current anti-hypertensive therapy. Hyperlipidemia was defined as total cholesterol level $\geq$240 mg/dL, and/or current lipid lowering therapy. Diabetes was defined as nonfasting glucose concentration $\geq$200 mg/dL, and/or glycosylated hemoglobin (HbA1c) value $\geq$6.5%, and/or current anti-diabetic therapy. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Smoking was defined as current smoker. Regular alcohol consumption was defined as drinking alcohol 5 days or more per week. Regular exercise was defined as exercising (at least 60 min) 8 days or more per month.

Venous blood samples for plasma BNP measurement were drawn from the antecubital vein of seated participants with minimal tourniquet use. Samples were collected into vacuum tubes containing ethylenediaminetetraacetic acid sodium. Tubes were stored in an icebox immediately after sampling and were transported to our laboratory within 8 h of collection. These were then centrifuged at 1500 $\times$ g for 10 min. After separation, plasma samples were stored frozen at $-20\,^{\circ}C$ until the time of assay. Plasma BNP levels were measured by direct radioimmunoassay using monoclonal antibodies specific for human BNP (ShionoRIA BNP, Shionogi, Japan) within 4 months of separation. The intraassay and interassay coefficients of variation were 5% and 6%, respectively. The lower detection limit of the assay was 0.05 pg/mL. Enzymatic methods were used to measure serum total cholesterol levels, serum creatinine, and blood glucose. HbA1c was measured quantitatively with an HPLC method.

2.4. Statistical analysis

Participants were divided into quartiles according to their baseline plasma BNP levels. Continuous variables were expressed as mean $\pm$ SD. Group comparisons were based on the unpaired t-test and multiple group comparisons across BNP quartiles were based on the one-way analysis of variance. Because BNP values were not normally distributed, these were expressed as median and the Mann–Whitney U-test was used for comparison. Categorical parameters were expressed as proportions (percentage) and group comparisons were based on the chi-square test.

The ischemic stroke event free rates according BNP quartiles were estimated using the Kaplan–Meier method, followed by Log-rank test. A multivariate Cox regression analysis was performed to analyze the relationship between plasma BNP levels and risk of stroke. For all models, the hazard ratios were adjusted for age, BMI, blood hemoglobin levels, serum creatinine levels, presence or absence of hypertension, hyperlipidemia, diabetes, smoking, regular alcohol consumption, and regular exercise. The analysis was not adjusted for presence or absence of atrial fibrillation in Model 1 and was adjusted in Model 2. Additional multivariate Cox regression analysis using covariates in Model 1 was performed using 1 SD increments in natural logarithm-transformed BNP values. For the analysis of stroke incidence, person-years were censored at the date of stroke diagnosis, the date of emigration from the study area, the date of death, or the end of the follow-up period, whichever came first. All statistical analysis was performed using SPSS software, version 11.0. A significant difference was defined as $P < 0.05$.

3. Results

Baseline characteristics of participants by sex are shown in Table 1. The mean age of men was higher than that of women. The percentages of hypertension, diabetes, atrial fibrillation, smoking, regular alcohol consumption, regular exercise, and mean values for