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Plasma B-Type Natriuretic Peptide Level and Cardiovascular Events in Chronic Kidney Disease in a Community-Based Population
Masafumi Sakuma, MD; Motoyuki Nakamura, MD; Fumitaka Tanaka, MD; Toshiyuki Onoda, MD*; Kazuyoshi Itai, PhD*; Kozo Tanno, MD*; Masaki Ohswa, MD*; Kiyomi Sakata, MD*; Yuki Yoshida, MD**; Kazuko Kawamura, MS†; Shinji Makita, MD; Akira Okayama, MD††

Background: Plasma B-type natriuretic peptide (BNP) levels are confounded by renal dysfunction, so this study examined whether plasma BNP might be a reliable biomarker of the onset of cardiovascular (CV) events in a population-based cohort with impaired renal function.

Methods and Results: Baseline data, including plasma BNP, serum creatinine, and urinary protein levels, were determined in participants from a community-based population. Estimated glomerular filtration rate (eGFR) was calculated, and chronic kidney disease (CKD) was defined as either: eGFR <60 ml·min⁻¹·1.73 m⁻² and/or proteinuria (CKD definition-1) or GFR <60 ml·min⁻¹·1.73 m⁻² (CKD definition-2). The CV endpoint was surveyed prospectively. The cohorts were followed for 5,275 person-years for CKD definition-1, and for 4,350 person-years for CKD definition-2. The CV event-free survival rate in the highest BNP quartile in either CKD definition was the lowest among the quartile groups (P<0.001). In multivariate Cox regression models adjusted by traditional CV risk factors and atrial fibrillation, relative risk (RR) for CV events was significantly higher in the highest BNP quartile compared with the lowest BNP quartile (CKD definition-1, RR 3.51, P<0.01; CKD definition-2, RR 4.67, both P<0.01).

Conclusions: Plasma BNP level provides strong predictive information about the future onset of CV events in CKD subjects selected from the general population. (Circ J 2010; 74: 792–797)

Key Words: General population; Heart failure; Renal failure; Stroke

Chronic kidney disease (CKD), defined as reduced glomerular filtration rate (GFR) and/or proteinuria, increases the risk of cardiovascular (CV) disease and endstage renal disease. In population-based studies, the prevalence of CKD has been shown to be 7% in persons aged more than 30 years and to be increased 23–36% in persons aged more than 65 years. The trend in the prevalence of CKD has been speculated to increase over time in line with the recent increasing prevalence of diabetes, obesity, and hypertension. Several reports have emphasized that early identification and treatment of CKD is necessary to prevent serious outcomes in this disorder. However, considering the large number of persons with CKD in the general population, it may not be easy to provide pharmacological and non-pharmacological interventions for all stages of CKD. In view of these limitations, it may be practical to select CKD subjects at relatively high risk for CV diseases from the general population, and then provide treatment to prevent their onset. However, there are no established markers to stratify CV risk in CKD subjects with mild renal dysfunction, such as stage 3 CKD, in the mass screening setting.

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Natriuretic peptide family proteins, including B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-pro BNP), are released from the heart in response to increased intracardiac pressure, cardiac pump dysfunction, hypertensive ventricular hypertrophy, and myocardial ischemia. In community-based studies, increased circulating levels of BNP and NT-pro BNP have been reported to relate to a high risk of CV events and mortality. The high prevalence of CV events in the group with elevated plasma levels of BNP and NT-proBNP is believed related to the high prevalence of subclinical heart disease. However, plasma concentrations of BNP and NT-proBNP increase as GFR declines in patients.
with and without apparent cardiac disorders.\textsuperscript{7,8} In view of these facts, it is unclear whether plasma BNP levels would be a reliable biomarker for predicting CV events in the cohort of CKD selected from a community-based population.

CKD is usually defined by 2 biomarkers of renal function: urinary protein and reduced GFR. Several community-based studies have applied only the latter definition.\textsuperscript{9-13} However, it is uncertain whether these biomarkers (GFR and urinary protein) provide complementary or overlapping information for CV risk. Cirillo et al reported that the use of only 1 of the biomarkers underscores the potential to misclassify patients as having or lacking CKD, thus misinterpreting the CV risk.\textsuperscript{12} Therefore, the present study used 2 definitions of CKD to examine whether plasma BNP might be a reliable biomarker for predicting onset of CV diseases in a CKD cohort selected from a community-based general population.

Methods

Study Population

The original cohort of the Iwate-KENCO study was recruited from a community-based population living in Ninohe, Kují, and Miyako districts of northern Iwate prefecture, Japan. The details of the recruitment and measurements of the cohort were shown in previous reports.\textsuperscript{13,14} The total number of participants who agreed to join the Iwate-KENCO study in the 3 districts was 26,469 (original cohort). Of the original cohort living in Ninohe and Kují districts (n=15,927), 15,394 subjects (97%) had BNP measurements (BNP cohort: men 5,288; women 10,106).

Subjects were excluded from the present analysis for the following reasons: age under 40 (n=575); history of CV events, such as myocardial infarction, stroke or heart failure (n=507); missing data of serum creatinine level (n=28), body mass index (n=47), ECG tracing (n=717), or blood pressure (n=4); estimated GFR <30 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2} (n=28). The final statistical analysis included 13,526 subjects (men 4,542; women 8,984). The study protocol was approved by the university ethics committee and local institutional review committees. All participants gave written informed consent.

Definition of CKD

The eGFR was calculated using an equation from the Modification Diet in Renal Disease Study (MDRD) for the Japanese population.\textsuperscript{15} A urine sample was obtained during a multiphase health examination and urinary protein was semi-quantitatively determined using a dipstick test (Uropaper alpha II, Eiken): proteinuria was defined as trace or more. CKD was defined in the present study in 2 ways: (1) eGFR <60 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2} and/or proteinuria (CKD definition-1); (2) eGFR <40 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2} (CKD definition-2).

Measurements

Blood samples were drawn from a peripheral vein while the subject was seated. When blood samples for routine blood testing were being taken, an additional 2 ml was collected into a test tube containing EDTA-2Na for plasma BNP measurement. Tubes were stored immediately in an icebox after sampling and transported to the laboratory each afternoon where they were centrifuged at 1,500 g for 10 min. After separation, plasma samples were stored frozen at −20°C until transportation to the Shionogi central laboratory for assaying (Osaka, Japan). Plasma BNP levels were measured by direct radioimmunoassay using monoclonal antibodies specific for human BNP (Shiono RIA BNP kit, Shionogi). Cross-reactivity of the antibody was 100% for human BNP and 0.001% for human atrial natriuretic peptide. Intra- and interassay coefficients of variation were 5% and 6%, respectively. Serum creatinine level was determined by an enzymatic method using an auto-analyzer (Hitachi 7700).

All subjects used a self-reported questionnaire to confirm their medical history, including status (yes/no) of prescribed drugs for hypertension, diabetes, hypercholesterolemia, stroke, angina, heart failure and myocardial infarction. Smoking status (current, past smoker or non-smoker) was also assessed by questionnaire.

Risk Factor Definitions

Systemic blood pressure was measured by experienced technicians. All subjects were seated for at least 5 min before measurement using an automatic device (BP-103i II, model 513000, Nippon Colin). Measurement was performed twice, with the mean value used for statistical analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of antihypertensive medication. Body mass index was calculated as weight (kg) divided by the square of height (m\textsuperscript{2}). Diabetes was ascertained by non-fasting glucose concentration ≥200 mg/dl and/or hemoglobin A\textsubscript{1c} value ≥6.5% and/or use of antidiabetic agents including insulin. Hypercholesterolemia was defined as a serum concentration ≥240 mg/dl and/or the use of antilipidemic medications.

Outcome

A follow-up survey assessing mortality, migration, and the incidence of heart failure, acute myocardial infarction and sudden death, and stroke was carried out after the baseline study. All deaths and migrations were confirmed by the official resident registration data issued by the local government offices. Admission cases of heart failure in the cohort were checked by the regional registration survey data, which records primary hospital discharge diagnoses in the study area. The cases of heart failure were objectively defined by the Framingham criteria.\textsuperscript{16} Details of this register have been described previously.\textsuperscript{17} The event of non-sudden fatal myocardial infarction was also based on hospital registration survey data. The diagnosis of acute myocardial infarction was based on the Monica study criteria.\textsuperscript{18} Sudden cardiac death within 1 h of the onset of acute illness was examined using death records and then checked against medical records of the hospitals within the survey areas. Stroke registry was used for the outcome study.\textsuperscript{19} Stroke was defined as a sudden onset of focal neurological deficit ≥24 h duration and confirmed by brain computed tomography or magnetic resonance imaging.

Statistical Analysis

Continuous variables are shown as mean±SD. CKD subjects were divided into quartiles according to their baseline plasma BNP levels. To compare results among quartiles, ANOVA or chi-square test was used as appropriate. Survival from entry into the study was estimated using the Kaplan-Meier method, followed by a trend test (log rank). The association between baseline plasma BNP levels and endpoint CV diseases (new onset of heart failure, acute myocardial infarction/sudden cardiac death, and stroke) was evaluated. Using a Cox proportional hazards regression model, hazard ratios (HR) for plasma BNP with CV events were assessed. In this multivariable proportional-hazards regression model,
adjustments were made in the analyses for age, body mass index, and the presence or absence of hypertension, diabetes, hypercholesterolemia, current smoking, and atrial fibrillation. For analyses of CV incidence, person-years were censored at the date of CV events, 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 analyses were performed using SPSS software (Chicago, IL, USA). A significant difference was defined as P<0.05.

Results

As shown in Table 1, the number of cases of CKD definition-1 was 1,901 (727 in men, 1,174 in women) in this type of CKD, the prevalence within the community-based population was 14% (16% in men, 13% in women). The mean age was 67.9 years and the mean eGFR was 57.4 ml·min⁻¹·1.73 m⁻².

Table 1. Clinical Characteristics by BNP Quartile in Each CKD Definition

<table>
<thead>
<tr>
<th></th>
<th>CKD (definition-1), BNP quartile and range</th>
<th>P value</th>
<th>CKD (definition-2), BNP quartile and range</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Q1 ≤11.2</td>
<td>Q2 11.3–22.7</td>
<td>Q3 22.8–42.9</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>Q1 ≤11.9</td>
<td>Q2 12.0–23.5</td>
<td>Q3 23.6–43.4</td>
</tr>
<tr>
<td>n</td>
<td>1,901</td>
<td>478</td>
<td>473</td>
<td>475</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.9±9.0</td>
<td>62.7±9.4</td>
<td>67.8±8.1</td>
<td>69.0±7.8</td>
</tr>
<tr>
<td>M/F</td>
<td>727/1,174</td>
<td>220/256</td>
<td>161/312</td>
<td>155/261</td>
</tr>
<tr>
<td>BMI</td>
<td>25.4±3.4</td>
<td>25.0±3.3</td>
<td>24.6±3.4</td>
<td>24.0±3.3</td>
</tr>
<tr>
<td>eGFR (ml·min⁻¹·1.73 m⁻²)</td>
<td>57.4±12.7</td>
<td>61.8±16.5</td>
<td>57.2±11.4</td>
<td>55.1±10.6</td>
</tr>
<tr>
<td>Proteinuria (%)</td>
<td>22.7</td>
<td>28.2</td>
<td>20.9</td>
<td>17.1</td>
</tr>
<tr>
<td>Blood hemoglobin (g/dl)</td>
<td>13.6±1.5</td>
<td>14.2±1.4</td>
<td>13.6±1.3</td>
<td>13.3±1.3</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>53.8</td>
<td>47.1</td>
<td>50.7</td>
<td>50.7</td>
</tr>
<tr>
<td>Antihypertensive drugs (%)</td>
<td>37</td>
<td>27</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>19</td>
<td>28.5</td>
<td>18.4</td>
<td>15.8</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>7.5</td>
<td>9.2</td>
<td>8</td>
<td>4.6</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>11.8</td>
<td>16.7</td>
<td>9.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>3.1</td>
<td>0.4</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

BNP, B-type natriuretic peptide; CKD, chronic kidney disease; BMI, body mass index; eGFR, estimated glomerular filtration rate.

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Table 2. Event Rates and HR for CVD by BNP Quartile in CKD

<table>
<thead>
<tr>
<th>BNP quartile (pg/ml)</th>
<th>All CVD events/1,000 person-years</th>
<th>Age-sex adjusted HR (95%CI)</th>
<th>P value</th>
<th>Multivariate adjusted HR* (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD (definition 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;11.2)</td>
<td>5.7</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 (11.3–22.7)</td>
<td>8.6</td>
<td>1.77 (0.70–4.49)</td>
<td>0.226</td>
<td>1.83 (0.72–4.66)</td>
<td>0.203</td>
</tr>
<tr>
<td>Q3 (22.8–42.9)</td>
<td>7.1</td>
<td>1.47 (0.55–3.93)</td>
<td>0.439</td>
<td>1.62 (0.60–4.37)</td>
<td>0.341</td>
</tr>
<tr>
<td>Q4 (≥43.1)</td>
<td>25.9</td>
<td>4.71 (2.04–10.90)</td>
<td>&lt;0.001</td>
<td>4.59 (1.97–10.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD (definition 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;11.9)</td>
<td>3.5</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 (12.0–23.5)</td>
<td>8.4</td>
<td>2.58 (0.79–8.48)</td>
<td>0.118</td>
<td>2.48 (0.75–8.19)</td>
<td>0.135</td>
</tr>
<tr>
<td>Q3 (23.6–43.4)</td>
<td>7.7</td>
<td>2.39 (0.78–8.12)</td>
<td>0.164</td>
<td>2.56 (0.75–8.73)</td>
<td>0.134</td>
</tr>
<tr>
<td>Q4 (≥43.6)</td>
<td>20.3</td>
<td>5.56 (1.83–16.90)</td>
<td>&lt;0.003</td>
<td>5.54 (1.81–16.97)</td>
<td>&lt;0.003</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, BMI, current smoking, hypertension, diabetes, hypercholesterolemia, eGFR, and atrial fibrillation.

The present study demonstrates that for the first time in CKD cohorts defined by different criteria and selected from a community-based population, the subgroup with the highest plasma BNP quartile had a 4- to 5-fold higher CV risk, including heart failure, stroke, myocardial infarction, and sudden cardiac death compared with the subgroup with the lowest plasma BNP quartile. This relationship was robust even after adjustment for classical CV risk factors. Our observations suggest that the plasma BNP level is a useful tool for stratifying CV risk within a CKD cohort selected from a general population.

In cohort studies without renal dysfunction, Wang et al reported that the subgroup with plasma levels of BNP over the 80th percentile had a 3-fold higher risk of new onset of heart failure and a 2-fold higher risk of brain transient ischemic attack than subjects showing plasma levels below the 80th percentile. Similarly, in a general population without subjects with elevated serum creatinine levels, Kistorp et al demonstrated that subjects who had higher plasma NT-proBNP levels above the 80th percentile had a 3-fold higher risk of CV diseases than the subjects who had plasma NT-proBNP levels below the 80th percentile. However, no studies have yet examined whether plasma levels of natriuretic peptides might be effective for stratifying the CV risk within a large number of CKD subjects selected from the general population. This may have been because of concerns that plasma natriuretic peptide levels might increase in the absence of organic cardiac disorders, and thus confound the relationship between the plasma level and CV events in this setting, as the important clearance site of the natriuretic peptide family protein is the kidney.

Discussion

The present study demonstrates that for the first time in CKD cohorts defined by different criteria and selected from a community-based population, the subgroup with the highest plasma BNP quartile had a 4- to 5-fold higher CV risk, including heart failure, stroke, myocardial infarction, and sudden cardiac death compared with the subgroup with the lowest plasma BNP quartile. There are several possible explanations for the fact that an elevated plasma BNP level was associated with a high risk for CV events, as demonstrated in the present study. First, the increased level of plasma BNP might be a marker for more advanced renal dysfunction, and deterioration of renal function is usually associated with an accumulation of traditional CV risk factors and there may be related increases in homocysteine, inflammation, oxidative stress, and thrombogenic factors. These factors may impair endothelial function, lead to progression of atherosclerosis, and thus increase
the risk of CV events in CKD subjects. Second, the plasma BNP level has been reported as increased with progression of anemia, which is independent of the degree of cardiac dysfunction.\textsuperscript{22,23} In this regard, an elevated plasma BNP level may indicate advanced anemia, and thus be a marker at a high risk of CV events in CKD subjects. In fact, several reports have demonstrated that the prevalence of future onset of coronary artery disease and heart failure were significantly elevated in subjects with anemia.\textsuperscript{24–26} Third, elevated levels of plasma BNP denote impaired cardiac function, including latent structural heart diseases, cardiac volume overload, and myocardial ischemia, and thus such patients are prone to CV disorders.

In the present study, although there were no significant differences in the levels of eGFR and blood hemoglobin between the 3\textsuperscript{rd} and the 4\textsuperscript{th} BNP quartiles, CV events were clearly prevalent in the highest quartile group. These findings indicate that the first and the second explanations are unlikely, and thus the third hypothesis may be the more possible. However, left ventricular function and morphological data were unavailable in the present cohort study, and it was unclear whether patients with structural heart disease or impaired cardiac function were more common in the 4\textsuperscript{th} quartile than in the lower quartiles. In previous studies using echocardiography, a plasma level of plasma BNP $>40–50$ pg/ml was a useful marker with high sensitivity and specificity for identifying subjects with latent structural heart disease, including left ventricular dysfunction, valvular heart diseases, cardiomyopathy, and atrial fibrillation.\textsuperscript{27–29} In view of these findings, a CKD subgroup with elevated plasma BNP levels tends to show subclinical structural cardiac disorders and is associated with a high risk for heart failure, ischemic stroke, and coronary artery diseases. In accordance with this hypothesis, several reports have suggested that an increased plasma BNP level in patients with renal dysfunction is mainly caused by cardiac overload and intrinsic organic heart disease rather than renal dysfunction.\textsuperscript{30–32}

Incidentally, the present study found that CKD definition-1 using reduced GFR and/or proteinuria captured a greater number of subjects with CV events than CKD definition-2 using reduced GFR only (62 cases for definition-1 vs 43 cases for definition-2). This observation suggests that definition-1 is more useful for the definition of CKD in terms of CV risk stratification. Measurement of 2 biomarkers (GFR and urinary protein) is therefore be recommended for the selection of CKD subjects within apparent healthy populations.

**Study Limitations**

Although the present study with its large sample size is a prospective community-based study that included routine biochemical data, several limitations must be considered when interpreting the results. More than 35% of the CKD subjects were receiving antihypertensive agents at baseline. Several types of antihypertensive drugs, such as angiotensin-convert- ing enzyme-inhibitors and angiotensin II receptor blockers, reduce the onset of CV events. The present study did not evaluate the effects of these drugs on the incidence of CV events. However, the percentage of subjects receiving antihypertensive drugs increased with the quartiles of plasma BNP level (Table 1), which suggests that the CKD subjects with higher plasma BNP levels were likely to receive these medications. This limitation might have underestimated the association between plasma BNP level and CV events. The urine dipstick test used in the present CKD definition is usually regarded as not being accurate for the diagnosis of persistence proteinuria. However, in a previous population-based study, trace proteinuria on dipstick test had good reproducibility and high sensitivity and specificity for detection of micro-albuminuria in an elderly population.\textsuperscript{33} In this regard, the inclusion criterion for CKD definition-1 in the present study was a trace result for dipstick test.

In conclusion, the plasma BNP level provides strong predictive information about the future onset of CV events in subjects with mildly reduced renal function. This result implies that plasma BNP measurement is a powerful tool for stratifying CV risk in CKD subjects selected from the general population.

**Acknowledgments**

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**References**

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