Plasma B-Type Natriuretic Peptide Level and Cardiovascular Events in Chronic Kidney Disease in a Community-Based Population

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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 $<60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ and/or proteinuria (CKD definition-1) or GFR $<60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ (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.¹ 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.² 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.³ Several reports have emphasized that early identification and treatment of CKD are necessary to prevent serious outcomes in this disorder.^{1,4} 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.^{5,6} 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

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with and without apparent cardiac disorders.^{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.^{9–11} 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.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, Kuji, and Miyako districts of northern Iwate prefecture, Japan. The details of the recruitment and measurements of the cohort were shown in previous reports.^{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 Kuji 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 $<30 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ($n=28$). 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.¹⁵ A urine sample was obtained during a multi-phase 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 $<60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ and/or proteinuria (CKD definition-1); (2) eGFR $<60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ (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 $\geq 140 \text{ mmHg}$ and/or diastolic blood pressure $\geq 90 \text{ mmHg}$ and/or the use of antihypertensive medication. Body mass index was calculated as weight (kg) divided by the square of height (m^2). Diabetes was ascertained by non-fasting glucose concentration $\geq 200 \text{ mg/dl}$ and/or hemoglobin A_{1c} value $\geq 6.5\%$ and/or use of antidiabetic agents including insulin. Hypercholesterolemia was defined as a serum concentration $\geq 240 \text{ mg/dl}$ 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.¹⁶ Details of this register have been described previously.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.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.¹⁹ Stroke was defined as a sudden onset of focal neurological deficit $\geq 24 \text{ h}$ duration and confirmed by brain computed tomography or magnetic resonance imaging.

Statistical Analysis

Continuous variables are shown as mean $\pm$ 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,

	CKD (definition-1), BNP quartile and range					CKD (definition-2), BNP quartile and range					P value
	Total	Q1 ≤11.2	Q2 11.3–22.7	Q3 22.8–42.9	Q4 ≥43.1	Total	Q1 ≤11.9	Q2 12.0–23.5	Q3 23.6–43.4	Q4 ≥43.6	
n	1,901	478	473	475	475	1,578	395	394	395	394	
Age (years)	67.9±9.0	62.7±9.4	67.0±8.1	69.0±7.8	72.8±7.3	68.7±8.4	64.4±8.9	67.7±7.8	69.7±7.4	72.9±7.1	<0.001
M/F	727/1,174	220/258	161/312	155/320	191/284	552/1,026	159/236	131/263	118/277	144/250	<0.02
BMI	24.5±3.4	25.0±3.3	24.6±3.4	24.0±3.3	24.2±3.4	24.4±3.3	24.8±3.2	24.5±3.2	23.9±3.3	24.2±3.4	<0.002
eGFR (ml·min ⁻¹ ·1.73m ⁻²)	57.4±12.7	61.8±16.5	57.2±11.4	55.1±10.6	55.4±10.6	52.9±5.4	54.0±4.9	53.2±5.0	52.4±5.7	51.8±5.6	<0.001
Proteinuria (%)	22.7	28.2	20.9	17.1	24.6	6.9	4.8	6.6	5.6	10.7	<0.01
Blood hemoglobin (g/dl)	13.6±1.5	14.2±1.4	13.6±1.3	13.3±1.3	13.4±1.6	13.5±1.4	13.9±1.4	13.6±1.3	13.3±1.3	13.3±1.5	<0.001
Hypertension (%)	53.8	47.1	50.7	50.7	66.5	52.8	45.8	51.5	48.6	65.2	<0.001
Antihypertensive drugs (%)	37	27	36	35	49	38	29	37	34	50	<0.001
Hyperlipidemia (%)	19	28.5	18.4	15.8	13.3	19.1	28.1	19.3	14.4	14.5	<0.001
Diabetes (%)	7.5	9.2	8	4.6	8.2	5.3	3.5	6.6	3.5	7.6	<0.02
Smoking (%)	11.8	16.7	9.3	8.8	12.2	9.1	10.6	8.1	7.6	9.9	0.396
Atrial fibrillation (%)	3.1	0.4	0.2	1.1	10.5	2.9	0.5	0.3	1.0	9.9	<0.001

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

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·

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

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

*Adjusted for age, sex, BMI, current smoking, hypertension, diabetes, hypercholesterolemia, eGFR, and atrial fibrillation. HR, hazard ratios; CVD, cardiovascular disease; CI, confidence interval. Other abbreviations see in Table 1.

1.73 m^{-2} . Proteinuria was found in 23% of the subjects. The percentages of cases of hypertension, diabetes, and atrial fibrillation were 54%, 7.5%, and 3.1%, respectively. The median plasma BNP level was 22.7 pg/ml.

The number of cases of CKD definition-2 was 1,578 (552 in men, 1,026 in women), and the prevalence was 12% (12% in men, 11% in women) within the community-based population. The percentages of hypertension, diabetes, and proteinuria were 53%, 5.3%, and 6.9%, respectively. The prevalence of atrial fibrillation was 2.9%. The median plasma BNP level was 23.5 pg/ml (Table 1).

The cohorts were followed for 5,275 person-years in CKD definition-1, and for 4,350 person-years in CKD definition-2, respectively. Composite CV events (heart failure, acute myocardial infarction, sudden cardiac death, stroke) during the follow-up period (mean, 2.8 years) occurred in 62 cases in the CKD definition-1 group and in 43 cases in the CKD definition-2 group. The number of CV events/1,000 person-years was 11.7 and 9.9 in the CKD definition-1 and definition-2 groups, respectively.

Kaplan-Meier curves for the CV event-free rate according to the BNP quartiles in both CKD cohorts are shown in Figure. The CV event-free rate was significantly lower in the highest quartile of BNP ($>43 \text{ pg/ml}$) in both CKD cohorts (CKD definition-1, $P<0.0001$; CKD definition-2, $P<0.0005$ by log-rank test).

As shown in Table 2, in the CKD definition-1 group, the number of CV events/1,000 person-years among BNP quartiles (Q) was 5.7 in Q1, 8.6 in Q2, 7.1 in Q3, and 25.9 in Q4. Similarly, in the CKD definition-2 group, the number was 3.5, 8.4, 7.7, and 20.3, respectively. CV events occurred in the highest quartile group of each CKD cohort ($P<0.001$ for both definitions).

After adjustment for age and sex, Cox regression analysis was performed to analyze the relationship between plasma BNP level and the risk of CV events (Table 2). The HR obtained from the Cox proportional model for the highest quartile of plasma BNP was significantly higher than that for the lowest quartile for CKD definition-1 (HR 4.71; 95% confidence interval (CI) 2.04–10.9; $P<0.001$) and for CKD definition-2 (HR 5.56; 95%CI 1.83–16.9; $P<0.003$). In addition, after multivariate adjustment of the models (age, sex, BMI, smoking, hypertension, diabetes, hypercholesterolemia, atrial fibrillation, and eGFR), similar results were obtained (Table 2). The HR in the highest quartile was significantly higher compared with the lower quartile groups (HR 4.59 in

CKD definition-1 group, $P<0.001$; HR 5.54 in CKD definition-2 group, $P<0.003$).

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. 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.⁵ 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.⁶ 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.²⁰

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 factors²¹ and there may be related increases in homocysteine, inflammation, oxidative stress, and thrombotic factors.^{1,4} 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.^{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.^{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 3rd and the 4th 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 4th 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.^{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.^{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 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-converting 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.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.

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