ABSTRACT

Background: Plasma B-type natriuretic peptide (BNP) levels are confounded by renal dysfunction. The aim of this study was to examine whether plasma BNP might be a reliable biomarker for predicting 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, were determined in participants from a community-based population. Estimated glomerular filtration rate (GFR) was calculated, and chronic kidney disease (CKD) was defined in the following two ways; GFR<60 ml/min/1.73 m^2 and/or proteinuria (CKD definition-1), and GFR<60 ml/min/1.73 m^2 (CKD definition-2). The CV endpoint was surveyed prospectively. The cohorts were followed for 5275 person-years for CKD definition-1, and for 4350 person-years for CKD definition-2. The CV event free survival rate in the highest BNP quartile in either CKD definitions was the lowest among the quartile groups ($p < 0.001$). In multivariate Cox regression models adjusted by traditional cardiovascular 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: Measurement of plasma BNP levels provides strong predictive information about the future onset of CV events in CKD subjects selected from the general population.

KEY WORDS; *heart failure/stroke/renal failure/general population*

Chronic kidney disease (CKD) defined by reduced glomerular filtration rate (GFR) and/or proteinuria increases the risk of cardiovascular (CV) disease and end stage 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 the onset of CV diseases. However, there are no established markers to stratify CV risk in CKD subjects with mild renal dysfunction, such as stage 3 CKD, in mass screening settings.

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 are believed due to the high prevalence of subclinical heart disease in these groups. However, plasma concentrations of BNP and NT-proBNP increased as GFR declined in patients with and without apparent cardiac disorders [7,8]. In view of these facts, it is unclear whether plasma BNP levels might be a reliable biomarker for the prediction of CV

events in the cohort of CKD selected from the community-based population.

CKD is usually defined by two biomarkers of renal function such as urinary protein and reduced GFR. Several community-based studies have applied only the latter definition [9-11]. However, it is uncertain whether the two biomarkers (GFR and urinary protein) provide complementary or overlapping information for CV risk. Cirillo et al. reported that the use of only one of these two biomarkers underscores the potential to misclassify patients as having or lacking CKD, thus misinterpreting the role of CV risk [12]. Therefore, the present study provided two CKD definitions, namely, 1) GFR < 60 ml/min/1.73 m^2 and/or proteinuria; 2) GFR < 60 ml/min/1.73 m^2 , and examined whether plasma BNP might be a reliable biomarker for predicting onset of CV diseases in the CKD cohort selected from the community-based general population.

METHODS

Study Population

The original cohort of the Iwate-KENCO study was recruited from the 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 three 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 cardiovascular 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), and blood pressure data (n = 4); or estimated GFR < 30 ml/min/1.73 m^2 (n = 28). The final statistical analysis was therefore performed on 13,526 subjects (men 4,542; women 8,984). This study protocol was approved by the university ethics committee and by local institutional review committees. All participants gave written informed consent.

Definition of CKD

The estimated GFR 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 multiphasic health examination and urinary protein was semi-quantitatively determined using a dipstick test (Uropaper alpha II, Eiken). Proteinuria was defined as a urine dipstick protein result of trace or more. CKD was defined in the present study in 2 ways; 1) GFR < 60 ml/min/1.73 m^2 and/or proteinuria (CKD definition-1); 2) GFR < 60 ml/min/1.73 m^2 (CKD definition-2).

Measurements

Blood samples were drawn from a peripheral vein in the seated position. When blood samples for routine blood testing were being taken, an additional 2 ml blood sample was collected into a test tube containing EDTA-2Na for plasma BNP measurement. Tubes were stored immediately after sampling in an icebox and transported to our laboratory each afternoon. The samples were then centrifuged at 1,500 g for 10 minutes. 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 inter-assay 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 the medical history including status (yes or 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 a questionnaire.

Risk Factor Definitions

Systemic blood pressure was measured by well-trained persons. All subjects were seated for at least 5 minutes 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 mm Hg and/or diastolic blood pressure $\geq$ 90 mm Hg 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 detection of a non-fasting glucose concentration $\geq$ 200 mg/dl and/or HbA1c value $\geq$ 6.5 % and/or use of anti-diabetic agents including insulin. Hypercholesterolemia was defined as a serum concentration $\geq$ 240 mg/dl and/or the use of anti-lipidemic 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 migration 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 the hospital registration survey data. The diagnosis of acute myocardial infarction was based on the Monica study criteria [18]. Sudden cardiac death within one hour after the onset of acute illness was examined using the death records and then checked 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 of >= 24 hours' 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 end point 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 (HRs) for plasma BNP with CV events were assessed. In this multivariable proportional-hazards regression model, adjustments were made for 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 analysis was performed using SPSS software. A significant difference was defined as $p < 0.05$.

RESULTS

As shown in Table 1, the number of cases of CKD definition-1 was 1901 (727 in men, 1174 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 old, and the mean GFR was 57.4 ml/min/1.73 m^2. The 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 level of plasma BNP was 22.7 pg/ml.

The number of cases of CKD definition-2 was 1578 (552 in men, 1026 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 level of plasma BNP was 23.5 pg/ml in CKD definition-2 cases (Table 1).

The cohorts were followed for 5275 person-years in CKD definition-1, and for 4350 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) were found 62 cases in the CKD definition-1 group and 43 cases in the CKD definition-2 group. The number of the CV events per 1000 person-years was 11.7 and 9.9 in the CKD definition-1 and the CKD definition-2 groups, respectively.

Kaplan-Meier curves for CV event free rate according to the BNP quartiles in both CKD

cohorts are shown in Figure 1. The CV event free rate was significantly lower in the highest quartile of BNP (> 43 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 per 1000 person-years among BNP quartiles (Q) was 5.7 in Q1, 8.6 in Q2, 7.1 in Q3, and 25.9 in Q4, respectively. Similarly, in the CKD definition-2 group, the number was 3.5 in Q1, 8.4 in Q2, 7.7 in Q3, and 20.3 in Q4, respectively. CV events occurred in the highest quartile group in either 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 levels and the risk of CV events (Table 2). The hazard ratio (HR) obtained from a 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% CI=2.04 to 10.9; $p < 0.001$) and for CKD definition-2 (HR=5.56; 95% CI=1.83 to 16.9; $p < 0.003$). In addition, after multivariate adjustment of the models (age, sex, BMI, smoking, hypertension, diabetes, hypercholesterolemia, atrial fibrillation, and GFR), 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 the CKD definition-1 group, $p < 0.001$; HR = 5.54 in the CKD definition-2 group, $p < 0.003$).

DISCUSSION

The present study demonstrated that for the first time in the CKD cohorts defined by different criteria selected from the community-based population, the subgroup with the highest plasma BNP quartile had 4 to 5 times 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. These observations suggested that plasma BNP measurement is a useful tool to stratify CV risk within a CKD cohort selected from the general population.

In cohort studies without renal dysfunction, Wang et al. reported that the subgroup with elevated plasma levels of BNP over the 80 percentile had a three times higher risk of new onset of heart failure and a two times higher risk of brain transient ischemic attack than subjects showing plasma levels below the 80 percentile [5]. Similarly, in the general population without subjects with elevated serum creatinine levels, Kistorp et al. demonstrated that subjects who had higher plasma NT-proBNP levels above the 80 percentile had a three times higher risk of CV diseases than the subjects who had plasma NT-proBNP levels below the 80 percentile [6]. However, no studies have yet examined whether plasma levels of natriuretic peptide might be effective to stratify the CV risk within a large number of CKD subjects selected from the general population. This may be due to concerns that plasma natriuretic peptide levels might increase without organic cardiac disorders, and thus confound the relationship between the plasma levels and CV events in this setting, as the important clearance site of natriuretic peptide family protein is the kidney [20].

There are several possible explanations for the fact that elevated plasma BNP 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 [21] and may be related increases in homocysteine, inflammation, oxidative stress, and thrombogenic factors [1,4]. These factors may impair endothelial function, lead to the progression of atherosclerosis, and thus increase the risk of CV events in CKD subjects. Second, plasma BNP level has been reported to be increased with the progression of anemia, which is independent of the degree of cardiac dysfunction [22,23]. In this regard, elevated plasma BNP level may indicate advanced anemia, and thus be a marker at 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 overlord, and myocardial ischemia, and thus prone to CV disorders.

In the present study, although there were no significant differences in the levels of GFR and blood hemoglobin between the third and the fourth BNP quartiles, the incidence of CV events was clearly prevalent in the highest quartile group. These findings indicate that the first and the second possibilities may be unlikely, and thus the third hypothesis may be 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 fourth quartile than those in the lower quartiles. In previous studies dealing with 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 tends to hold subclinical structural cardiac disorders and

is associated with high risk for heart failure, ischemic stroke, and coronary artery diseases. In accordance with this hypothesis, several reports have suggested that 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 versus 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 two biomarkers (GFR and urinary protein) should therefore be recommended for the selection of CKD subjects within apparent healthy populations.

Limitations

Although the present study with a large sample size is a prospective community-based study including 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 levels in our subjects (Table 1). This 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 levels and CV events. The urine dipstick test applied 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 in the dipstick test had good reproducibility and high sensitivity and

specificity for detection of micro-albuminuria in the elderly population [33]. In this regard, the inclusion criteria of CKD definition-1 was the trace result of the dipstick test in the present study.

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

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Figure Legend

Figure 1. Kaplan-Meier curves of CV events free probability according to quartile (Q) of plasma BNP in the CKD definition-1 (left) and the CKD definition-2 (right).

Table 1

Table 1. Clinical characteristics by BNP quartile in each CKD definitions

BNP quartile and range	CKD (definition 1) Total	Q1 =<11.2	Q2 11.3-22.7	Q3 22.8-42.9	Q4 >=43.1	*p value*	CKD (definition 2) Total	Q1 =<11.9	Q2 12.0-23.5	Q3 23.6-43.4	Q4 >=43.6	*p value*
Number	1901	478	473	475	475		1578	395	394	395	394	
Age (yrs)	67.9±9.0	62.7±9.4	67.0±8.1	69.0±7.8	72.8±7.3	<0.001	68.7±8.4	64.4±8.9	67.7±7.8	69.7±7.4	72.9±7.1	<0.001
Women / Men	1174/727	220/258	161/312	155/320	191/284	<0.001	1026/552	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	<0.001	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/1.73m?)	57.4±12.7	61.8±16.5	57.2±11.4	55.1±10.6	55.4±10.6	<0.001	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	<0.001	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	<0.001	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	<0.001	52.8	45.8	51.5	48.6	65.2	<0.001
Antihypertensive drugs (%)	37	27	36	35	49	<0.001	38	29	37	34	50	<0.001
Hyperlipidemia (%)	19	28.5	18.4	15.8	13.3	<0.001	19.1	28.1	19.3	14.4	14.5	<0.001
Diabetes (%)	7.5	9.2	8	4.6	8.2	<0.05	5.3	3.5	6.6	3.5	7.6	<0.02
Smoking (%)	11.8	16.7	9.3	8.8	12.2	<0.001	9.1	10.6	8.1	7.6	9.9	0.396
Atrial fibrillation (%)	3.1	0.4	0.2	1.1	10.5	<0.001	2.9	0.5	0.3	1.0	9.9	<0.001

Table 2

Table 2. Events rates and hazards ratios for CVD by BNP quartile levels in CKD.

BNP quartile (pg/ml)	All CVD events / 1000 person-	Age-sex adjusted hazard ratio (95%CI)	*p value*	Multivariate adjusted hazard ratio* (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

*The hazard ratios were adjusted for age, sex, BMI, current smoking, hypertension, diabetes, hypercholesterolemia, eGFR, and atrial fibrillation.