Table 3. Number of deaths, crude and sex- and age-adjusted mortality rates, and relative risks (RRs) for death compared with references by groups according to HCV seropositivity

HCV seropositivity status groups (number of subjects)	group A HCV Ab(−) *n* = 968	group B and C HCV Ab(+) *n* = 109	group B	group C	All subjects *n* = 1077
			HCV Ab(+) Ag(−) *n* = 39	HCV Ab(+) Ag(+) *n* = 70	
all-cause death (crude mortality)	356 (92.7)	50 (127)	14 (94.0)	36 (147)	406 (95.9)
adjusted mortality (95% CI)	71.9 (62.6–81.3)	123 (88.6–158)	80.4 (37.9–123)	156 (104–207)	96.5 (75.5–118)
RR (95% CI)	REF	1.71 (1.27–2.30)	1.12 (0.66–1.91)	2.16 (1.53–3.07)	
cardiovascular (crude mortality)	173 (45.1)	21 (53.4)	4 (26.9)	17 (69.5)	194 (45.8)
adjusted mortality (95% CI)	37.2 (30.5–43.9)	53.0 (30.0–76.0)	24.3 (0.40–48.2)	73.5 (38.0–109)	40.5 (25.3–55.7)
RR (95% CI)	REF	1.42 (0.90–2.44)	0.65 (0.24–1.76)	1.98 (1.19–3.28)	
infectious disease-related (crude mortality)	97 (25.3)	15 (38.1)	5 (33.6)	10 (40.9)	112 (26.5)
adjusted mortality (95% CI)	17.8 (13.1–22.5)	35.6 (17.1–54.1)	25.7 (2.70–48.7)	43.6 (16.3–71.0)	27.1 (16.5–37.7)
RR (95% CI)	REF	1.99 (1.15–3.43)	1.45 (0.50–3.56)	2.46 (1.27–4.76)	
liver disease-related (crude mortality)	2 (0.52)	5 (12.7)	1 (6.71)	4 (16.4)	7 (1.65)
adjusted mortality (95% CI)	0.40 (0.00–1.10)	9.80 (0.00–21.5)	5.70 (0.00–17.4)	12.8 (0.00–29.6)	3.10 (0.00–6.60)
RR (95% CI)	REF	24.2 (4.56–128)	13.7 (1.24–152)	30.8 (5.34–178)	

Crude and sex- and age-adjusted mortality rates (95% confidence intervals) are expressed as /1000 person-years. Adjusted mortalities and relative risks (expressed as relative mortality rate ratios) were estimated by Poisson regression analysis.

Table 4. Relative risks (RRs) for each cause of death compared with references by groups according to HCV seropositivity

HCV seropositivity status groups	group A HCV Ab(−)	group B and C HCV Ab(+)	group B	group C
			HCV Ab(+) Ag(−)	HCV Ab(+) Ag(+)
all-cause death				
model A	Ref	1.62 (1.20–2.18)	1.24 (0.72–2.12)	1.83 (1.29–2.59)
model B		1.48 (1.09–2.00)	1.23 (0.72–2.12)	1.60 (1.13–2.28)
cardiovascular death				
model A	Ref	1.42 (0.89–2.24)	0.75 (0.28–2.04)	1.79 (1.08–2.97)
model B		1.33 (0.84–2.11)	0.75 (0.28–2.02)	1.64 (0.98–2.73)
infectious disease-related death				
model A	Ref	1.83 (1.05–3.19)	1.66 (0.66–4.13)	1.94 (0.99–3.75)
model B		1.60 (0.91–2.80)	1.64 (0.65–4.15)	1.58 (0.81–3.07)
liver disease-related death				
model A	Ref	18.6 (3.51–98.1)	8.55 (0.75–98.1)	26.6 (4.57–155)
model B		22.9 (3.53–149)	15.3 (1.26–186)	28.8 (3.75–221)

Crude and adjusted mortalities (95% confidence intervals) are expressed as /1000 person-years.
Adjusted mortalities were estimated by Poisson regression analysis after adjusting for risk factors.
Adjustment for risk factors
model A: age, male gender, high BMI, dyslipidemia, diabetes, high blood pressure, history of myocardial infarction, stroke, or malignant diseases, smoking habit and regular drinking habit.
model B: model A plus low BMI, low blood pressure, high CRP level, and hypoalbuminemia.

HCV infection increased mortality among hemodialysis patients: the multivariate-adjusted RR for all-cause death attributable to chronic HCV infection was 2.0.[23] Other studies reported a multivariate-adjusted RR of death attributable to HCV infection (including past HCV infection) between 1.2 and 1.6.[27] The lower relative risks in studies that assessed HCV status using antibody-based techniques may be due to underestimation related to the inclusion of patients with past HCV infection only. In our study, the RR of all-cause death due to chronic HCV infection, as determined by quantitative estimation of HCV core antigen, was 1.83 after traditional risk factor adjustment, which is similar to the RR of 2.0 reported by Stehman-Breen et al. Taken together, both previous studies and the present study suggest that it is mainly chronic HCV infection that increases the risks of all-cause and cause-specific death.

The causes of death that contribute to increased mortality among hemodialysis patients with chronic HCV infection were not fully identified in previous studies. In a meta-analysis, Fabrizi et al showed that HCV-seropositive hemodialysis patients had higher rates of liver disease-related death than their seronegative counterparts, but that

cardiovascular and infectious disease-related morality rates were similar.[27] The studies included in their meta-analysis all cited cardiovascular death as the most common cause of death in dialysis patients. Excess deaths attributable to HCV infection cannot be explained by an increase in the number of HCV-attributable liver disease-related deaths. Whether cardiovascular death (the most common cause of death) and infectious disease-related death (the second most common cause of death) increase mortality among hemodialysis patients is also important, as is the contribution of liver disease-related death.

We are unable to explain the increased risks of cardiovascular death and infectious disease-related death among hemodialysis patients who were positive for anti-HCV core antigen antibodies in the present study. Cross-sectional analysis of baseline data provides some clues regarding possible mechanisms that might explain the association between anti-HCV core antigen positivity and increased cardiovascular and infectious disease-related mortality risk. Despite being younger, patients who were positive on the anti-HCV core antigen test had lower levels of serum lipids and albumin as compared with patients who were negative on the HCV antibody test. These findings suggest that hemodialysis patients who were positive for anti-HCV core antigen antibodies had hypocholesterolemia and hypoalbuminemia. Thus, insufficient levels of serum cholesterol and albumin might be associated with a malnutrition-inflammation syndrome activated by chronic HCV infection. Such a syndrome might lead to immune dysfunction, resulting in an increased risk of cardiovascular and infectious disease-related death.[19–31]

Several limitations in our study should be noted. Because we enrolled only 70 patients who were positive for anti-HCV core antigen, we were not able to perform an accurate sex-stratified risk assessment of cause-specific death. Sex differences in the risk of each cause of death might exist, and the relationships should therefore be re-examined in larger cohort studies or in meta-analyses using data from patients whose chronic HCV infection status is precisely defined. Lack of high-sensitivity, quantitative HCV-RNA data from patients who were positive for HCV antibody and negative for HCV core antigen is a major limitation of this study. It is possible that hemodialysis patients who are negative for HCV core antigen nevertheless have very low levels of HCV-RNA; however, the possibility of missing such cases is very low because none of the population-based controls in our previous study were simultaneously positive for HCV-RNA and HCV antibody and negative for HCV core antigen.[21] Therefore, we believe that the results of the current study are not distorted by the lack of HCV-RNA data.

Because second-generation ELISA became available as a clinical diagnostic tool in 1992, patients who began hemodialysis treatment before 1992 might have had more exposures to infection and a higher incidence of HCV infection. It remains to be clarified whether HCV infection, and a long history of hemodialysis treatment, independently increase the risk of death. In a separate analysis, we estimated the risk of each cause of death attributable to HCV infection only in patients who started hemodialysis treatment after 1992. The results were similar to those from analyses of all subjects (data not shown).

We determined HCV infection status based on baseline information only. Changes in HCV infection status (eg, incident HCV infection during the observation period) were not considered. Previous studies showed that the incidence of HCV infection in hemodialysis patients was lower than 0.5% per year.[11,32] The risk of death attributable to HCV infection may have been underestimated, and putative underestimation of relative risks of death is not negligible.

Despite its limitations, our simple and economic method of determining HCV infection status provided sufficient results to discern a difference in mortality between patients with past versus chronic HCV infection. Furthermore, limiting the analysis to patients with chronic HCV infection enabled us to show that an increased risk of death among hemodialysis patients with HCV infection was due to an increased risk of cardiovascular and infectious disease-related deaths, as well as the increased risk of liver disease-related death. We conclude that more attention should be paid to chronic HCV infection in hemodialysis patients.

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Sex-Specific Threshold Levels of Plasma B-Type Natriuretic Peptide for Prediction of Cardiovascular Event Risk in a Japanese Population Initially Free of Cardiovascular Disease

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Elevated plasma B-type natriuretic peptide (BNP) levels have been reported to be related to a high risk for cardiovascular (CV) disease in the general population. However, there has been no accurate determination of the threshold levels of plasma BNP that indicate an increased potential for the development of general CV events (i.e., heart failure, stroke, and myocardial infarction) and the validity of these levels for predicting CV events compared to classic risk markers. To establish gender-specific thresholds of plasma BNP levels associated with increased risk for CV disease in the general population, baseline BNP levels were determined in community-dwelling adults (n = 13,209, mean age 62 ± 10 years,) and CV events in the cohort were captured prospectively. The cohort was divided by deciles of plasma BNP level in each gender. A Cox proportional-hazards model was used to determine the relative hazard ratios among the deciles. In addition, to compare the utility of plasma BNP to the Framingham 10-year risk score for predicting general CV events, receiver-operating characteristic analysis was performed. During follow-up, CV events were identified in 429 patients in the cohort. Compared to the reference decile level (first to fourth), the hazard ratio was significantly increased from the ninth decile in men (greater than approximately 37 pg/ml) and the highest decile in women (greater than approximately 55 pg/ml). The area under the curve generated on receiver-operating characteristic analysis of plasma BNP testing was comparable to that for the Framingham risk scoring system (0.67 vs 0.68 in men, 0.63 vs 0.68 in women; p = NS for both). In conclusion, within a community-based general population with no CV history, plasma BNP levels higher than defined thresholds show increased risk for general CV events, and the predictive ability for CV events occurring within several years may be comparable to that of an established long-standing risk score. © 2011 Elsevier Inc. All rights reserved. (Am J Cardiol 2011;108:1564–1569)

In the present study, we measured plasma B-type natriuretic peptide (BNP) in a large-scale population-based sample of >13,000 men and women. This cohort was followed prospectively for >5 years to ascertain the incidence of cardiovascular (CV) events, including heart failure, stroke, and myocardial infarction. To determine gender-specific threshold levels of plasma BNP, the relation between plasma BNP deciles and risk for CV events was determined. In addition, to validate plasma BNP testing for the prediction of general CV events, its predictive ability was compared to an established CV risk scoring system.

Methods

This study is part of the Iwate-KENCO study, a population-based prospective cohort study to investigate heath status and CV risks in Japanese residents living in the Iwate prefecture, northeast Honsyu, Japan. Details about this cohort are provided elsewhere.[1] In brief, the original cohort (n = 26,469) was recruited from April 2002 and January 2005 in 3 districts (Ninohe, Kuji, and Miyako in the Iwate prefecture). The baseline survey included routine anthropometric measurements, blood pressure measurement, electrocardiography, routine laboratory assessment, and a self-administered lifestyle 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 (96.6%) agreed to provide additional blood samples for the measurement of

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plasma BNP levels, and these are designated as the BNP cohort in the present study. Subjects were excluded from this cohort on the basis of the following characteristics: age <40 years (n = 575) or >80 years (n = 330), serum creatinine level ≥2.0 mg/dl (n = 10), and missing data for blood pressure (n = 3), anthropometrics (n = 47), and/or routine blood tests (n = 4). The final statistical analysis was therefore performed on 13,209 subjects (4,365 men, 8,844 women; mean age 62.1 years).

A follow-up survey assessing mortality, migration, and the incidence of CV events was carried out after the baseline study. We defined CV events as stroke, congestive heart failure, and myocardial infarction requiring hospitalization. Hospital admissions for congestive heart failure and myocardial infarction in the cohort were identified by accessing data from the Northern Iwate Heart Disease Registry Consortium, which has been collecting data since 2002. Heart failure was defined by Framingham criteria,[2] and registration of myocardial infarction was based on criteria used in the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study.[3] Stroke events were identified by accessing the prefecture stroke registration program conducted by the Iwate Medical Association. Stroke diagnostic criteria in this registry are based on those published by the World Health Organization and defined as the sudden onset of neurologic symptoms.[4] To ensure that nearly all appropriate cases had been identified, researchers in each registration study periodically retrieved and reviewed medical charts and/or discharge summaries for patients admitted to the cardiology, neurology, neurosurgery, and internal medicine wards of all hospitals located within the study district.

In the baseline survey, all participants underwent routine anthropometric measurements, electrocardiography, blood pressure measurements, and laboratory assessments. In addition, a self-administered questionnaire was used to ascertain lifestyle factors such as smoking habits and medical history, including stroke, congestive heart failure, and myocardial infarction. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Systolic and diastolic blood pressure were determined with an automatic device with the subject in a sitting position for ≥5 minutes before measurement. Measurement was performed twice, with the mean value used for statistical analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or current antihypertensive therapy. Diabetes was defined as a nonfasting glucose concentration ≥200 mg/dl, and/or a glycosylated hemoglobin value ≥6.5%, and/or current antidiabetic therapy. Hypercholesterolemia was defined as total cholesterol level ≥240 mg/dl and/or current lipid-lowering therapy. Enzymatic methods were used to measure serum total cholesterol levels, serum creatinine, and blood glucose. Glycosylated hemoglobin was measured quantitatively using high-performance liquid chromatography. Smoking was defined as current smoking. Estimated glomerular filtration rate was calculated using an equation (estimated glomerular filtration rate [ml/min/1.73 m^2] = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$) from the Modification of Diet in Renal Disease (MDRD) study for the Japanese population.[5] The 10-year risk for general CV disease was calculated using the Framingham 10-year risk

Table 1
Baseline characteristics according to plasma B-type natriuretic peptide deciles in men

Variable	Total	D1–D4	D5	D6	D7	D8	D9	D10
Number	4,365	1,741	441	441	434	436	436	436
BNP (pg/ml)	14.2 (6.3–28.3)	5 (2.1–7.6)	12.3 (11.4–13.2)	16.3 (15.3–17.5)	21.3 (19.8–22.8)	28.3 (26.5–30.5)	41.4 (37.5–46.5)	76.5 (63.4–116.7)
Age (years)	63.3 ± 9.8	58.3 ± 10.0	62.9 ± 9.0	65.5 ± 8.4	65.8 ± 8.1	67.6 ± 7.2	68.1 ± 7.4	69.7 ± 6.2
BMI (kg/m^2)	23.9 ± 2.9	24.1 ± 2.9	24.0 ± 3.0	23.9 ± 2.8	23.7 ± 2.9	23.6 ± 2.8	23.5 ± 2.9	23.7 ± 3.0
Hypertension	43.8%	35.1%	41.0%	46.5%	45.6%	49.8%	56.6%	57.6%
Diabetes mellitus	9.6%	9.8%	8.2%	11.6%	9.0%	10.1%	8.9%	9.2%
Smoker	33.9%	39.1%	33.1%	30.2%	32.7%	31.7%	28.0%	27.1%
Hypercholesterolemia	10.5%	14.5%	9.1%	9.3%	7.1%	8.5%	7.6%	5.7%
eGFR (ml/min/1.73 m^2)	77.2 ± 15.3	80.0 ± 15.3	77.3 ± 15.1	76.4 ± 15.6	76.5 ± 15.0	74.8 ± 14.7	75.8 ± 15.2	71.3 ± 13.3
Antihypertensive drugs	23.3%	15.8%	21.8%	25.9%	26.0%	27.5%	32.8%	35.3%
Framingham risk score	13.8 ± 4.4	12.8 ± 4.5	13.7 ± 4.3	14.5 ± 4.3	14.5 ± 4.1	14.8 ± 4.1	14.9 ± 4.2	15.1 ± 4.1

Data are expressed as median (interquartile range), as mean ± SD, or as percentages.
D = decile; eGFR = estimated glomerular filtration rate.

Table 2
Baseline characteristics according to plasma B-type natriuretic peptide deciles in women

Variable	Total	D1–D4	D5	D6	D7	D8	D9	D10
Number	8,844	3,539	880	880	893	882	885	885
BNP (pg/ml)	16.9 (8.8–29.8)	7.3 (3.8–10.4)	15.0 (14.1–15.9)	18.7 (17.8–19.7)	23.5 (22.2–25.0)	29.8 (28.0–31.9)	40.4 (37.1–43.8)	66.1 (55.1–88.0)
Age (years)	61.6 ± 9.7	58.1 ± 9.5	60.7 ± 9.4	60.9 ± 9.6	63.2 ± 9.0	64.3 ± 8.7	65.3 ± 8.3	68.7 ± 7.2
BMI (kg/m^2)	24.2 ± 3.4	24.2 ± 3.4	24.0 ± 3.3	24.0 ± 3.4	24.1 ± 3.4	24.0 ± 3.3	24.0 ± 3.5	24.4 ± 3.7
Hypertension	38.2%	29.5%	35.1%	36.0%	43.8%	43.2%	47.2%	59.0%
Diabetes mellitus	5.4%	5.3%	4.7%	4.8%	5.0%	6.2%	5.2%	7.2%
Smoker	2.5%	3.5%	1.7%	2.5%	1.9%	2.0%	2.3%	0.8%
Hypercholesterolemia	20.3%	23.3%	18.0%	18.9%	21.2%	19.7%	14.5%	17.2%
eGFR (ml/min/1.73 m^2)	75.8 ± 15.0	78.6 ± 14.9	76.5 ± 14.8	76 ± 13.9	74.7 ± 14.1	73.9 ± 15.2	73.2 ± 14.7	69.5 ± 14.8
Antihypertensive drugs	23.8%	16.8%	22.8%	21.5%	28.4%	27.4%	29.9%	41.2%
Framingham risk score	11.9 ± 4.6	10.8 ± 4.6	11.2 ± 4.5	11.7 ± 4.5	12.4 ± 4.5	12.6 ± 4.4	13.1 ± 4.4	14.3 ± 4.0

Data are expressed as median (interquartile range), as mean ± SD, or as percentages.
D = decile; eGFR = estimated glomerular filtration rate.

Figure 1. Crude incidence of CV events per 1,000 person-years among baseline plasma BNP deciles in men *(closed bars)* and women *(open bars)*.

score, including age, gender-specific cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diabetes, and cigarette smoking.[6]

Blood samples for routine laboratory testing were drawn from the antecubital vein with the subject in a sitting position. While blood samples were being collected into vacuum tubes, an additional 2-ml sample of venous blood was collected into a test tube containing ethylenediaminetetraacetic acid sodium. Tubes were stored immediately after sampling in an icebox and were transported to the laboratory <8 hours after collection. They were then centrifuged at 1,500g for 10 minutes. After separation, the plasma samples were stored frozen at −20°C until the time of assay. Plasma BNP levels were measured by direct radioimmunoassay using monoclonal antibodies specific for human BNP (Shionogi, Osaka, Japan) <4 months after blood sampling. Cross-reactivity of the antibodies was 100% for human BNP and 0.001% for human atrial natriuretic peptide. Intra- and interassay coefficients of variation were 5% and 6%, respectively. The lower detection limit of the assay was 0.05 pg/ml.

Continuous variables are expressed as mean ± SD. The cohort was divided into deciles according to baseline plasma BNP levels. To compare baseline data among the BNP deciles, 1-way analysis of variance and chi-square tests were used as appropriate. Differences in clinical characteristics between men and women were tested using unpaired Student's *t* test or Mann-Whitney U tests. We defined the end point as general CV events (i.e., a composite of stroke, heart failure, and myocardial infarction). The association between baseline plasma BNP levels and the end point was evaluated using a Cox proportional-hazards regression model. The gender-specific hazard ratios (HR) for each BNP decile's end point were assessed. In this multivariate regression model, adjustments were made in the analysis for age, BMI, diabetes, hypertension, hypercholesterolemia, atrial fibrillation, estimated glomerular filtration rate, and current smoking. 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. To compare the predictive abilities of plasma BNP testing to the Framingham 10-year risk scoring system, receiver-operating-characteristic curves were constructed. The area under the curve (AUC) and 95% confidence interval (CI) for each ROC curve were calculated to provide a measure of the overall diagnostic accu-

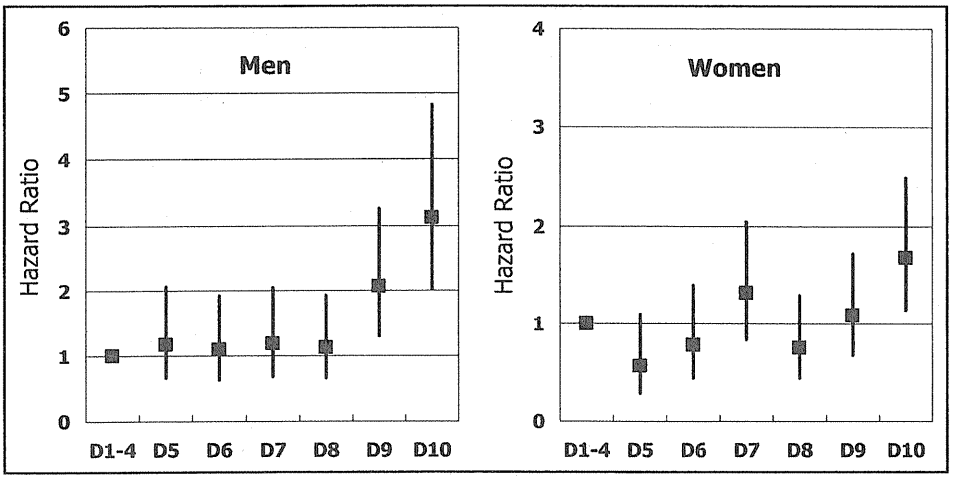

Figure 2. Multivariate-adjusted HRs and 95% CIs for risk for CV events according to plasma BNP decile in men *(left)* and women *(right)*.

racy of the test. The follow-up survey for congestive heart failure, stroke, and myocardial infarction was carried out after the baseline study through to March 2009. Migrations were confirmed by official resident registration data issued by the local government offices (October 2009). All statistical analyses were performed using SPSS version 11.0.1J (SPSS, Inc., Chicago, Illinois). A significant difference was defined as $p < 0.05$.

Results

Mean ages were 63.3 ± 9.8 years in men and 61.6 ± 9.7 years in women (Tables 1 and 2). The number of women was approximately twice the number of men. Plasma BNP levels and BMI were higher in women than in men (median BNP 16.9 vs 14.2 pg/ml, $p < 0.001$; mean BMI 24.2 ± 3.4 vs 23.9 ± 2.9 kg/m^2, $p < 0.001$). The prevalence of hypertension (44% vs 38%), atrial fibrillation (2.9% vs 0.6%), diabetes (9.6% vs 5.4%), and current smoking (33.9% vs 2.5%) was higher in men. The incidence of hypercholesterolemia was higher in women (10.5% vs 20.3%). The administration rates for hypertensive drugs was 23.3% in men and 23.8% in women ($p = 0.232$). The mean Framingham risk score in men was higher than that in women (13.8 ± 4.4 vs 11.9 ± 4.6).

During the mean follow-up period of 5.8 years, 430 CV events (215 in men, 215 in women) were recorded. When the lowest 4 (first to fourth) plasma BNP deciles were set to the reference, the crude incidence of CV events per 1,000 person-years increased with deciles in both genders (Figure 1). As shown in Figure 2, after adjustment for potential confounding factors in the Cox regression model, the relative HR for CV events increased according to deciles (p for trend <0.01 in men, p for trend <0.001 in women). Compared to the reference, the HR was significantly elevated in the ninth (HR 2.06, 95% CI 1.30 to 3.27) and tenth (HR 3.15, 95% CI 2.03 to 4.88) deciles in men and in the tenth decile only in women (HR 1.68, 95% CI 1.13 to 2.50). The thresholds for increased CV risk were greater than approximately 37 pg/ml in men and greater than approximately 55 pg/ml in women.

The overall power for predicting general CV events was comparable between plasma BNP level and Framingham risk score. The areas under the curve for plasma BNP were 0.669 (95% CI 0.629 to 0.710) in men and 0.634 (95% CI 0.593 to 0.676) in women. The areas under the curve did not differ significantly from those for the Framingham risk score (men 0.676, 95% CI 0.640 to 0.712; women 0.681, 95% CI 0.649 to 0.713).

Discussion

The present study has demonstrated that in the general population with no CV history or renal dysfunction, plasma BNP levels signaling increased CV risk are greater than the 80th percentile in men and the 90th percentile in women. The predictive ability of plasma BNP testing for general CV events is similar to that of the established total CV risk scoring system. The present study has therefore shown for the first time that increased plasma BNP levels higher than these gender-specific thresholds are a simple and useful marker for elevated risk for CV events in a community-based middle-aged and elderly population.

Several previously published studies have shown a significant association between plasma BNP and N-terminal pro-BNP (NT-proBNP) levels and CV events in the general population.[7–11] The Framingham study conventionally applied a single cutoff point (the 80th percentile) to examine the association between "high" BNP levels and CV events.[7] Linssen et al[10] recently reported that in a selected population mainly with urinary albumin excretion >10 mg/L, multivariate HRs for the risk for all-cause mortality increased gradually with increasing levels of plasma NT-proBNP, with no clear cut-off level in both genders. However, no studies have explored the threshold levels of BNP that indicate an increased risk for the future development of CV events.

Several studies have shown that median plasma BNP and NT-proBNP levels are higher in women,[12,13] although the incidence of CV events in the general population is usually lower in women than in men. This suggests that a gender-stratified analysis should be incorporated when determining cut-off levels of plasma BNP and NT-proBNP for predicting the future onset of CV events in the general population. However, no reports to date have shown which levels of plasma BNP increase the risk for CV events in either gender.

The present study has shown for the first time in an unselected general population that the adjusted HR was significantly increased from the ninth plasma BNP decile in men and the tenth decile in women. The association between plasma BNP and the future development of CV events may be because elevated plasma BNP is a significant biomarker for asymptomatic structural heart disease such as impaired left ventricular function, left ventricular hypertrophy, atrial dilatation and fibrillation, and myocardial ischemia. In accord with this concept, Struthers and Lang[14] suggested that BNP and NT-proBNP testing could be used to identify "pancardiac" target organ damage and may become to the heart what albuminuria is to the kidneys, that is, a useful biomarker for targeting organ damage in the CV system. In our previous cross-sectional study applying transthoracic echocardiography in the general population, plasma BNP concentrations >50 pg/ml showed sensitivity and specificity for several select phenotypes of structural heart disease that are prone to progress into several types of CV events.[15] The threshold plasma BNP levels that increased the HR (greater than approximately 37 pg/ml in men and greater than approximately 55 pg/ml in women) in the present study are lower compared to the previously reported cut-off level for detection of structural heart disease. This apparent discord may be due to the present study being longitudinal and the cut-off level being gender specific.

The present study suggests that the usefulness in terms of sensitivity and specificity of plasma BNP testing for predicting CV events differs little from the Framingham 10-year risk score for general CV events. This finding may indicate that the predictive ability of BNP testing is equivalent to that of the established risk calculation. However, such a conclusion may be premature, because the mean follow-up period of this study was shorter (<6 years) than the Framingham study (10 years). In fact, the established risk scoring includes lipids, blood pressure, smoking, and diabetes, which are long-standing risk factors for CV events. In contrast, plasma BNP may be unique in that it is instead identifying the end process of several types of cardiac damage itself. In view of this, plasma BNP testing could be useful for identifying subjects at high risk for several types of CV events within a few years. BNP may thus be a direct or novel biomarker for various types of intrinsic cardiac abnormalities rather than an additional biomarker for assessing long-term risk.

The present study had several strengths. This study included the largest general population sample in whom plasma BNP levels have been reported. The plasma BNP measurement was performed in fresh plasma samples without long-term freezing and repeated thawing. CV events were captured prospectively according to previously determined standard epidemiologic criteria and confirmed by the research staff at medical chart review. Baseline data including clinical characteristics and biochemical data were determined well before the start of the follow-up study.

Despite these merits, several limitations must be considered when interpreting the results. First, because echocardiographic evaluation was not included in the baseline data, the utility of the BNP testing could not be compared to that of echocardiography. However, several previous studies have reported that BNP testing remained independently predictive of future CV events after adjusting for echocardiographic variables.[7,11] Second, mean BMI was lower in our study than in previous general population reports.[7,9,10] Plasma BNP levels have been reported to be lower in obese subjects than in the lean population,[16,17] with 1 previous study demonstrating that each standard deviation increase in BMI was associated with a 16% to 18% decrement in plasma BNP.[16] It follows that threshold BNP levels may be slightly lower in predominantly obese populations. Third, according to population-based studies, the Japanese population has a lower incidence of CV events than Western countries. Thus, care must be taken before these data can be generalized to other ethnic groups. Fourth, McKie et al[18] recently demonstrated that the use of NT-proBNP as a CV risk predictor is worthless in healthy subjects, as verified by close clinical examination including echocardiography. This observation may not validate our results, because the present population comprises entirely healthy subjects and may include a substantial part of subjects with CV risk factors, as listed in Tables 1 and 2. Finally, the age range of our population may have been relatively narrow, with no subjects aged <40 years or >80 years.

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