Journal of Cardiology (2008) **52**, 212—223

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JOURNAL of CARDIOLOGY
Official Journal of the Japanese College of Cardiology
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ORIGINAL ARTICLE

Plasma brain natriuretic peptide concentrations and the risk of cardiovascular events and death in general practice

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Received 31 March 2008; received in revised form 12 June 2008; accepted 11 July 2008
Available online 26 August 2008

KEYWORDS
Brain natriuretic peptide;
Prognosis;
Cardiovascular events;
Death;
Cohort study;
General practice

Summary
Objectives: The plasma brain natriuretic peptide concentrations (brain natriuretic peptide (BNP) levels) have a prognostic value of mortality and morbidity in patients with chronic heart failure and in a community-based population. However, the prognostic value of BNP levels in outpatients of general practice is not well known. This study investigated the relations of BNP levels to cardiovascular events and death in general practice.
Methods: This study covered 3123 consecutive outpatients (mean age 59.3 ± 15.3 years; 42% men). BNP levels were measured by immunoradiometric assay (Shionogi) in an occasional sample of each person.
Results: During a median follow-up of 5.5 years, 271 patients underwent a cardiovascular event (heart failure 65, coronary heart disease events 63, arrhythmia 26, stroke 96, others 21), 92 died from cardiovascular disease and 227 died from all causes. The patients were stratified into two groups based on a cut-off level of BNP (100 pg/ml). A BNP level ≧100 pg/ml was associated with a hazard ratio (95% confidence interval) of 4.6 (3.5—6.1) for cardiovascular events compared with a BNP <100 pg/ml ($p < 0.0001$), 7.0 (4.5—10.9) for cardiovascular mortality ($p < 0.0001$), 3.2 (2.4—4.2) for all-cause mortality ($p < 0.0001$), 18.8 (11.3—31.1) for heart failure ($p < 0.0001$), 2.5 (1.5—3.9) for stroke ($p = 0.0002$), 5.0 (2.4—11.2) for atrial fibrillation ($p < 0.0001$); however, it was 0.6 (0.2—1.7) for coronary heart disease events ($p = 0.337$). Furthermore, the result of investigation with stratification into six groups based on BNP cut-off levels (20, 40, 100, 200, 500 pg/ml) showed that cardiovascular events, cardiovascular mortality, all-cause mortality, heart failure, stroke, and atrial fibrillation increased stepwise as BNP levels increased ($p < 0.0001$), except for coronary heart disease events ($p = 0.986$).

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doi:10.1016/j.jjcc.2008.07.007

Conclusions: In general practice, BNP levels predicted the risk of cardiovascular events other than coronary heart disease events and of death.

Introduction

Brain natriuretic peptide (BNP) is secreted by the heart, especially from the ventricles [1—3]. The plasma BNP concentrations (BNP levels) are correlated positively with the left ventricular end-diastolic pressure and negatively with the left ventricular ejection fraction [4—7], so BNP levels should be measured to evaluate left ventricular function. BNP levels have proved to be good markers of congestive heart failure. In addition, BNP levels are useful in screening test for left ventricular dysfunction and also heart disease.

Some studies [8—11] have shown that BNP levels have a prognostic value of mortality and morbidity in patients with chronic heart failure. In the Valsartan Heart Failure Trial (Val-HeFT) study in patients with heart failure, BNP in quartiles (<40, 41—96, 97—237, and ≧238 pg/ml) showed significant quartile-dependent increase in mortality and morbid events [8]. The Framingham study for community-based populations showed that BNP levels of 20 pg/ml (for men) and 23.3 pg/ml (for women) were useful thresholds for predicting cardiovascular events [12]. However, the prognostic value of BNP levels in outpatients of general practice is unknown.

This study investigated the relations of BNP levels to cardiovascular events and death in general practice, by stratification into six or two groups based on routinely used cut-off levels of BNP.

Subjects and methods

Subjects

This study included 3123 consecutive outpatients in the Tsuchida Clinic of Internal Medicine and Cardiology, 1307 men and 1816 women (20—98 years with an average age of 59.3 ± 15.3 years), whose BNP levels were measured to evaluate left ventricular function from 1999 to 2002. The patients were treated according to the relevant guidelines and followed up until 31 December 2006. The median follow-up period was 5.5 years (max: 7.5 years). Diagnosis was based on history, physical examination, laboratory findings, chest X-rays, electrocardiograms, and partly echocardiograms (36.2%).

The patient backgrounds are summarized in Table 1. Non-cardiovascular diseases could be demonstrated in 2149 (69%), whereas cardiovascular diseases were found in 974 (31%): congestive heart failure in 89; hypertrophic cardiomyopathy in 67; dilated cardiomyopathy in 15; old myocardial infarction in 67; effort angina in 55; vasospastic angina in 130; valvular disease in 116; chronic atrial fibrillation in 140; paroxysmal atrial fibrillation in 231; paroxysmal supraventricular tachycardia in 116; ventricular tachycardia in 11; pacemaker implantation in 29; congenital heart disease in 17; hypertension in 1550 (hypertension with cardiovascular disease in 622 including 226 with hypertensive heart disease; hypertension without cardiovascular disease in 928); cerebrovascular disease in 89; diabetes mellitus in 340; hyperlipidemia in 1045; hypertension + diabetes mellitus in 238; hypertension + hyperlipidemia in 640; diabetes mellitus + hyperlipidemia in 151, hypertension + diabetes mellitus + hyperlipidemia in 107; chronic obstructive pulmonary disease in 104; gastric and duodenal ulcer in 128; including some patients with more than one disease. As regards hypertension, we classified hypertension into ''non-cardiovascular disease,'' except for ''with cardiovascular disease'' or ''hypertensive heart disease (that is, with the findings of left ventricular hypertrophy in the electrocardiogram).'' The study protocol was approved by the Ethics Committee of Tsuchida Clinic of Internal Medicine and Cardiology.

Methods

BNP levels were measured by the immunoradiometric assay method (IRMA) using a Shionoria BNP assay kit (Shionogi, Osaka, Japan) for the one-point blood sample taken in a sitting position.

We selected useful cut-off levels of BNP (20, 40, 100, 200, 500 pg/ml), drawing on many studies [8—27]. Patients were stratified into six groups based on these cut-off levels of BNP (<20, 20—40,

Table 1 Characteristics of the study population

Number of patients	3123
Age, years (mean ± S.D.)	59.3 ± 15.3
Sex	
Male	1307 (42%)
Female	1816 (58%)
Underlying disease[a]	
Cardiovascular disease	974 (31%)
Non-cardiovascular disease	2149 (69%)
Congestive heart failure	89 (2.8%)
Hypertrophic cardiomyopathy	67 (2.1%)
Dilated cardiomyopathy	15 (0.5%)
Coronary heart disease	252 (8.1%)
Old myocardial infarction	67 (2.1%)
Angina pectoris	55 (1.8%)
Vasospastic effort	130 (4.2%)
Valvular disease	116 (3.7%)
Chronic atrial fibrillation	140 (4.5%)
Paroxysmal atrial fibrillation	231 (7.4%)
Paroxysmal supraventricular tachycardia	116 (3.7%)
Ventricular tachycardia	11 (0.4%)
Pacemaker implantation, post-op.	29 (0.9%)
Congenital heart disease	17 (0.5%)
Cerebrovascular disease	89 (2.8%)
Hypertension (HT)	1550 (49.6%)
Hypertension with cardiovascular disease (including hypertensive heart disease: 226)	622 (19.9%)
Hypertension without cardiovascular disease	928 (29.7%)
Diabetes mellitus (DM)	340 (10.9%)
Hyperlipidemia (HL)	1045 (33.5%)
HT + DM	238 (7.6%)
HT + HL	640 (20.5%)
DM + HL	151 (4.8%)
HT + DM + HL	107 (3.4%)
Chronic obstructive pulmonary disease	104 (3.3%)
Gastric and duodenal ulcer	128 (4.1%)
Echocardiography	1132 (36.2%)
Medication	
Calcium-channel blockers	1211 (38.8%)
ACEI/ARB	364 (11.6%)
Beta blockers	141 (4.5%)
Digitalis	419 (13.4%)
Thiazide	137 (4.4%)
Antialdosterone agents	103 (3.3%)
Nitrates	99 (3.2%)
Statins	807 (25.8%)
Warfarin	127 (4.1%)
Antiplatelet drugs	430 (13.8%)

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers.
[a] Some patients with more than one disease.

40—100, 100—200, 200—500, ≧500 pg/ml). Furthermore, some studies of patients with heart failure [10,23] showed that BNP levels more than about 100 pg/ml were significantly related to mortality and morbidity, so the patients were otherwise stratified into two groups based on cut-off levels of BNP (<100 and ≧100 pg/ml).

The primary endpoint was a composite of cardiovascular events (hospitalization and death). Components of the endpoints included the follow-

ing: heart failure, coronary heart disease events (acute myocardial infarction, unstable angina), stroke (infarction, hemorrhage), arrhythmia, dissecting aneurysm, peripheral arterial disease, infective endocarditis, acute myocarditis, renal infarction, pulmonary infarction, embolism of the superior mesenteric artery, and sudden cardiac death. The first of these events was noted as the primary event. Any component of a composite primary endpoint for which a patient could be counted once in each category was treated as a second endpoint. Death from any cause was also designated a secondary endpoint. Furthermore, patients were followed for the development of chronic atrial fibrillation.

Statistical analysis

Values are shown as mean ± standard deviation. Time-to-event curves for the endpoints were estimated by the Kaplan—Meier method for the entire follow-up period. The log-rank test was used to examine the association of BNP levels. Hazard ratio (HR) and 95% confidence interval (CI) were calculated and adjusted for age, sex, the presence or absence of hypertension, diabetes mellitus, and hyperlipidemia with the Cox's proportional hazards model. All analyses were performed with the use of StatView (version 5.0). Significance levels were $p < 0.05$ in these analyses.

Results

Kaplan—Meier curves for the endpoints

Kaplan—Meier analyses were performed on the cumulative event-free rates in patients stratified into six groups based on cut-off levels (20, 40, 100, 200, 500 pg/ml) (Fig. 1). Using the six-group classification, the number of patients with a BNP <20 pg/ml was 1950/3123 (62%); with a BNP of 20—40 pg/ml 600 (19%); of 40—100 pg/ml 377 (12%); of 100—200 pg/ml 122 (4%); of 200—500 pg/ml 59 (2%); of ≧500 pg/ml 15 (0.5%). Otherwise they were stratified into two groups based on cut-off level (100 pg/ml). The number with a BNP <100 pg/ml in the two-group classification was 2927/3123 (94%), and with a BNP ≧100 pg/ml, 196 (6%).

The number of cardiovascular events was 271/3123 (9%): heart failure 65, coronary heart disease events 63 (acute myocardial infarction 31, unstable angina 32), arrhythmia 24 (sick sinus syndrome 7, atrioventricular block 3, ventricular tachycardia 2, supraventricular tachycardia 6, others 6), stroke 96 (infarction 83, intracranial hemorrhage 6, subarachnoidal hemorrhage 7), dissecting aneurysm 5, peripheral arterial disease 6, infective endocarditis 3, acute myocarditis 1, renal infarction 1, pulmonary infarction 1, and cardiac sudden death 4. The patients were stratified into six groups based on cut-off levels (20, 40, 100, 200, 500 pg/ml), and a cumulative cardiovascular event-free curve was constructed according to Kaplan—Meier analysis. Based on Kaplan—Meier analysis of a six-group stratification, it was found that as BNP levels increased, the cumulative cardiovascular event-free rate decreased significantly ($p < 0.0001$). Furthermore, patients were stratified into two groups based on cut-off level of BNP (100 pg/ml), and a cumulative cardiovascular event-free curve was constructed according to Kaplan—Meier analysis. Cumulative cardiovascular event-free rate, as evaluated by Kaplan—Meier analysis, was significantly lower with BNP ≧100 pg/ml ($p < 0.0001$).

The number of deaths from cardiovascular disease was 92/3123 (3%): heart failure 35, arrhythmia 3, coronary heart disease events 6 (acute myocardial infarction 6), stroke 35 (infarction 31, intracranial hemorrhage 1, subarachnoidal hemorrhage 3), dissecting aneurysm 5, peripheral artery disease 1, pulmonary infarction 1, embolism of the superior mesenteric artery 2, and cardiac sudden death 4. Based on Kaplan—Meier analysis of the 6-groups stratification, it was found that, as BNP levels increased, the cumulative survival rate decreased significantly ($p < 0.0001$). Furthermore, patients were stratified into two groups based on cut-off level of BNP (100 pg/ml), and cumulative survival curve was constructed according to Kaplan—Meier analysis. Cumulative survival rate, as evaluated by Kaplan—Meier analysis, was significantly lower with BNP ≧100 ($p < 0.0001$).

The number of deaths from all causes were 227/3123 (7%): from cardiovascular disease, 92 (as was stated above); malignant tumors, 70 (lung 18, stomach 12, colon 13, pancreas 4, esophagus 2, liver 2, gallbladder 2, malignant lymphoma 4, others 13); pneumonia and chronic obstructive pulmonary disease, 16; pulmonary tuberculosis 1, bronchial asthma 1, renal failure 5, ileus 4, liver cirrhosis 2, gastro-intestinal bleeding 3, Parkinson syndrome 2, senile dementia 1, senility 2, traffic accident 1, suicide 5, and unknown causes 18. Based on a Kaplan—Meier analysis of 6-group stratification, it was found that, as BNP levels increased, the cumulative survival rate decreased significantly ($p < 0.0001$). Patients were also strat-

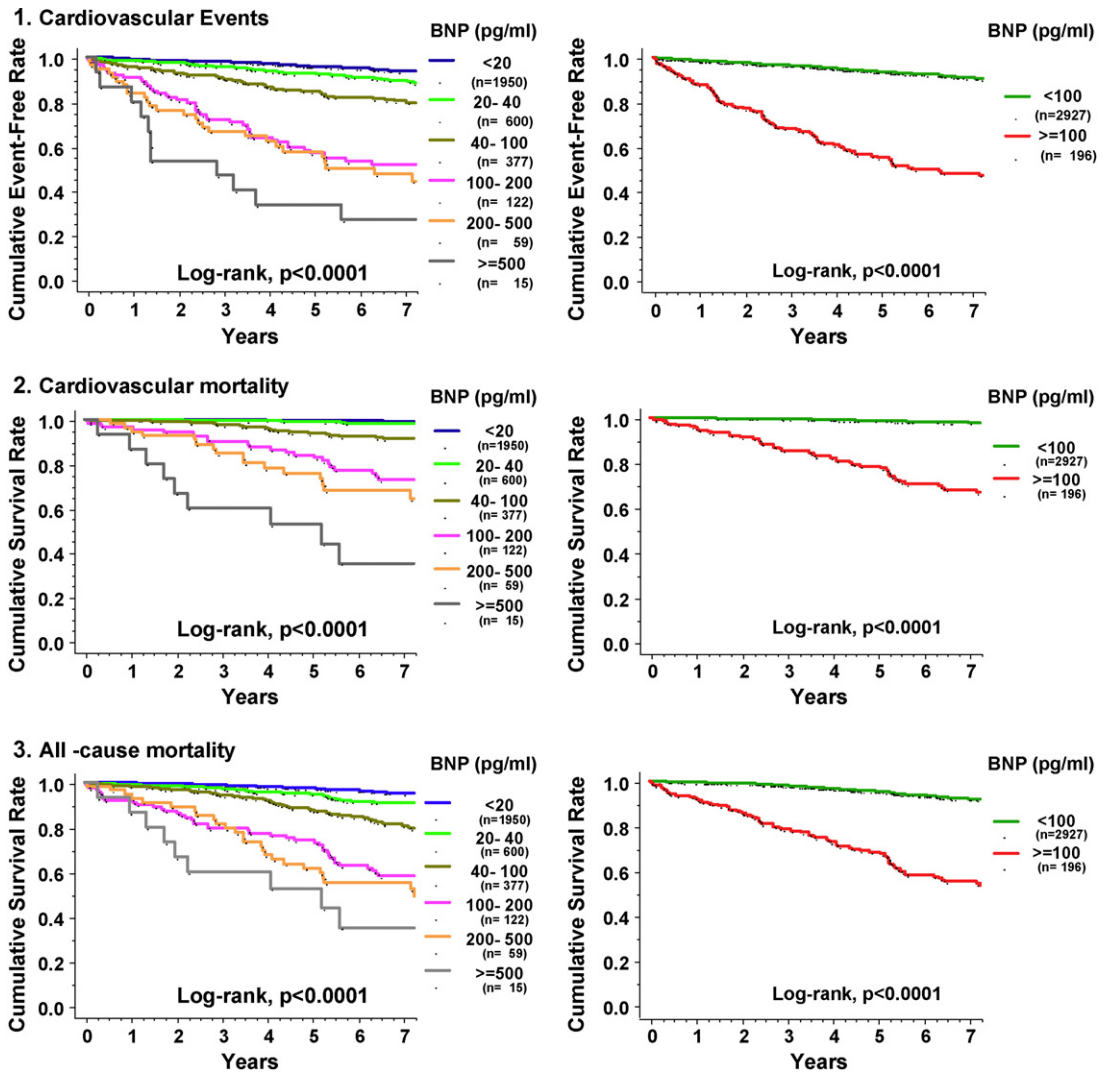

Figure 1 Kaplan—Meier curves for cardiovascular events, cardiovascular mortality and all-cause mortality. Patients were stratified into six groups based on cut-off levels of brain natriuretic peptide (BNP) (20, 40, 100 200, 500 pg/ml), and were otherwise stratified into two groups based on cut-off levels of BNP (100 pg/ml). The cumulative cardiovascular event-free rate and survival rate decreased significantly, as BNP levels increased ($p < 0.0001$).

ified into two groups based on a cut-off level of BNP (100 pg/ml), and a cumulative survival curve was constructed according to Kaplan—Meier analysis. The cumulative survival rate, as evaluated by Kaplan—Meier analysis, was significantly lower with a BNP ≧100 pg/ml ($p < 0.0001$).

In other secondary analyses (Fig. 2), as evaluated by Kaplan—Meier analysis for heart failure, stroke, and atrial fibrillation, it was found that, as BNP levels increased, the cumulative cardiovascular event-free rate decreased significantly ($p < 0.0001$). But only with regard to coronary heart disease events, the cumulative event-free rate was not significantly associated with the BNP level ($p = 0.1144$).

Incidence of death or cardiovascular events

Fig. 3 shows the incidence of cardiovascular events and death during a median follow-up of 5.5 years. The incidence of cardiovascular events, death from cardiovascular disease, death from any cause, heart failure, stroke, and atrial fibrillation were significantly higher with a BNP ≧100 pg/ml than a BNP < 100 pg/ml: HR 4.63 (95%CI 3.52—6.08) for cardiovascular events ($p < 0.0001$), 6.99 (4.49—10.88) for cardiovascular mortality ($p < 0.0001$), 3.15 (2.35—4.21) for all-cause mortality ($p < 0.0001$), 18.77 (11.33—31.08) for heart failure ($p < 0.0001$), 2.45 (1.54—3.89) for stroke ($p = 0.0002$), and 4.96 (2.41—11.22) for atrial fib-

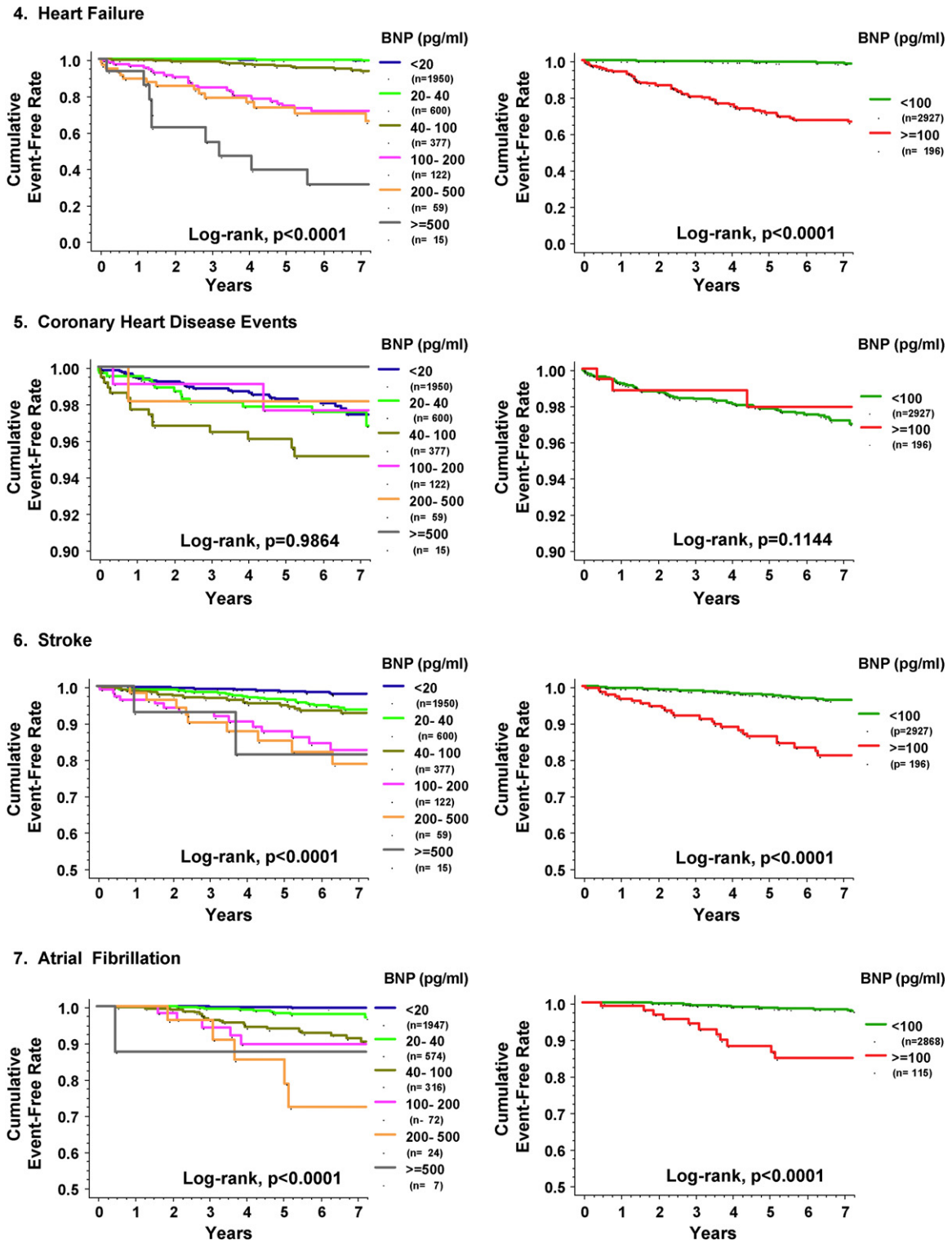

Figure 2 Kaplan—Meier curves for heart failure, coronary heart disease events, stroke and atrial fibrillation. Patients were stratified into six groups based on cut-off levels of brain natriuretic peptide (BNP) (20, 40, 100, 200, 500 pg/ml), and were otherwise stratified into two groups based on cut-off levels of BNP (100 pg/ml). As brain natriuretic peptide (BNP) levels increased, the cumulative cardiovascular event-free rate for heart failure, stroke and atrial fibrillation decreased significantly ($p < 0.0001$), but only with regard to coronary heart disease events, it was not significantly associated with the BNP level ($p = 0.1144$).

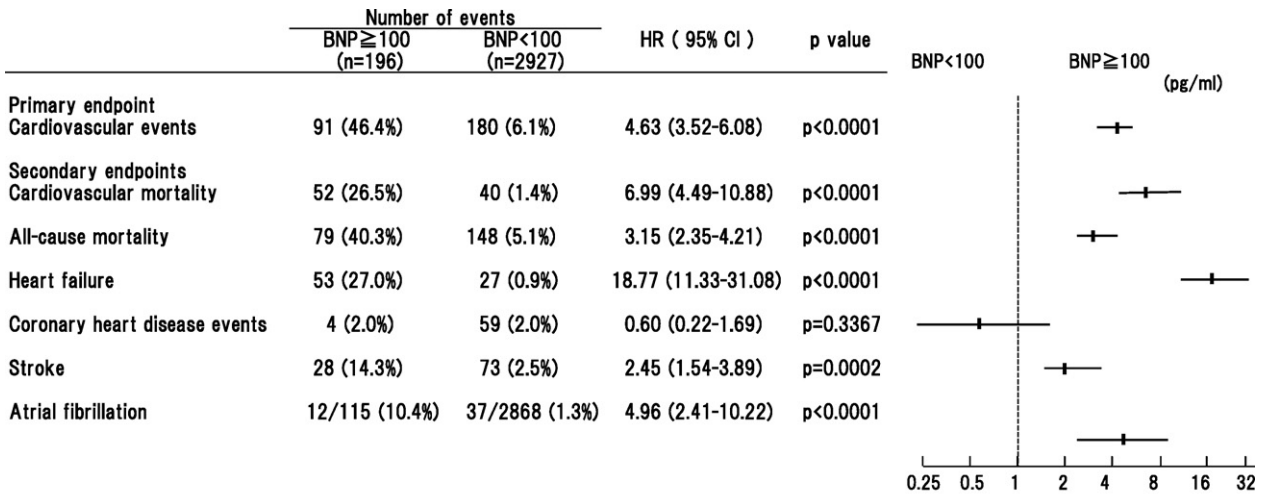

Figure 3 The incidence of cardiovascular events, cardiovascular mortality, all-cause mortality, heart failure, stroke and atrial fibrillation were significantly higher with a brain natriuretic peptide (BNP) ≧100 pg/ml than a BNP <100 pg/ml ($p < 0.0001$). However the incidence of coronary heart disease events was not significantly associated with BNP levels ($p = 0.3367$). Hazard ratios are adjusted for sex (male), age, hypertension, diabetes and hyperlipidemia.

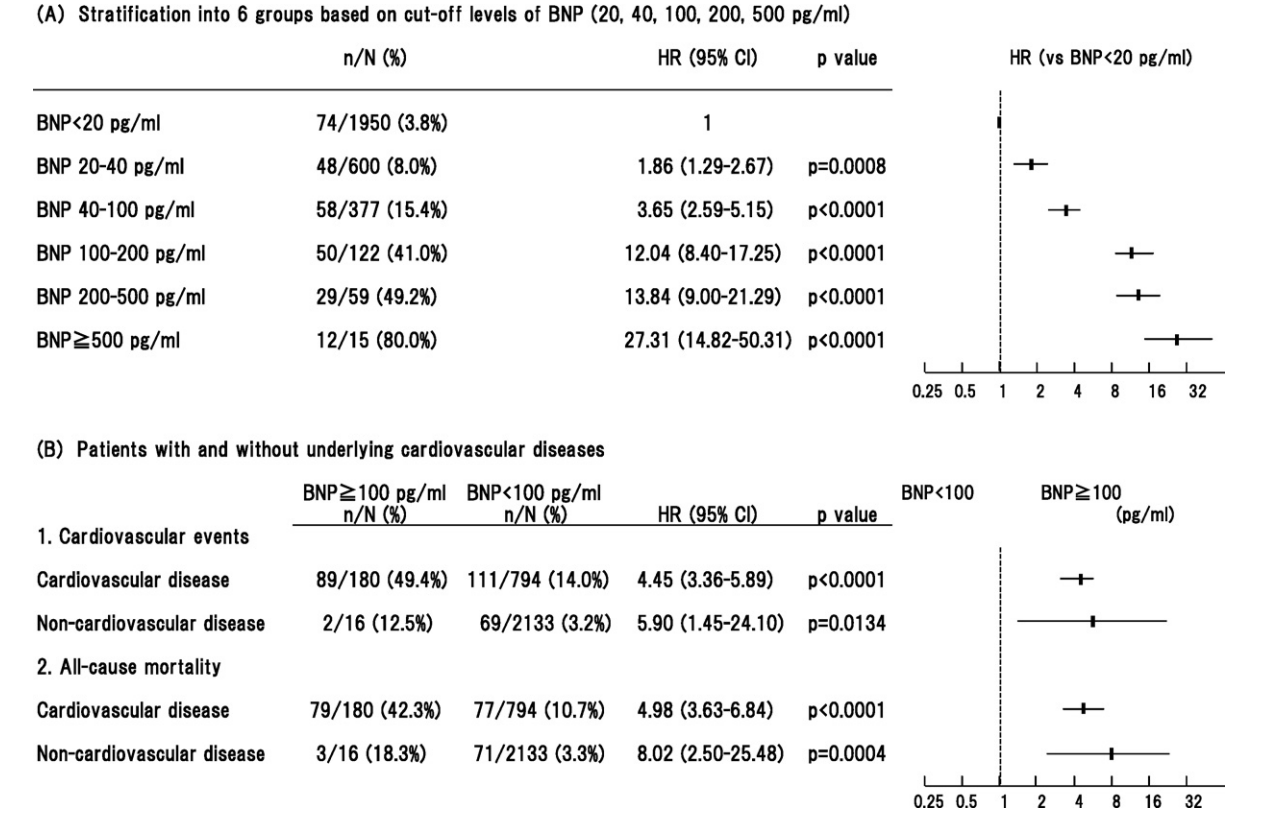

Figure 4 (A) Using six-group classification based on cut-off levels of brain natriuretic peptide (BNP) (20, 40, 100, 200, 500 pg/ml), the hazard ratio (HR) (versus BNP <20 pg/ml) for cardiovascular events increased stepwise as the BNP levels increased, significantly ($p < 0.0001$), by univariate analysis. (B) The incidence of cardiovascular events was significantly higher with BNP ≧100 pg/ml than with BNP <100 pg/ml, not only in the patients with cardiovascular diseases ($p < 0.0001$), but also with non-cardiovascular diseases ($p = 0.0134$). The incidence of all-cause mortality was also significantly higher with BNP ≧100 pg/ml than with BNP <100 pg/ml, not only in the patients with cardiovascular diseases ($p < 0.0001$), but also with non-cardiovascular diseases ($p = 0.0004$), by univariate analysis.

rillation ($p < 0.0001$). However the incidence of coronary heart disease events was not significantly associated with BNP levels (HR 0.60, 95%CI 0.22—1.69, $p = 0.3367$).

Furthermore, as a result of investigation with stratification into six groups based on cut-off levels of BNP (20, 40, 100, 200, 500 pg/ml), it was seen that cardiovascular events, cardiovascular mortality, all-cause mortality, heart failure, stroke, and atrial fibrillation increased stepwise as the BNP levels increased ($p < 0.0001$), except in the case of coronary heart disease events ($p = 0.986$).

Fig. 4(A) shows that the HR (95%CI) (versus a BNP <20 pg/ml) for cardiovascular events increased significantly: a BNP of 20—40 pg/ml 1.86 (1.29—2.67); a BNP of 40—100 pg/ml 3.65 (2.59—5.15); a BNP of 100—200 pg/ml 12.04 (8.40—17.25); a BNP of 200—500 pg/ml 13.84 (9.00—21.29); a BNP ≧500 pg/ml 27.31 (14.82—50.31).

In patients with cardiovascular diseases, the incidence of cardiovascular events was

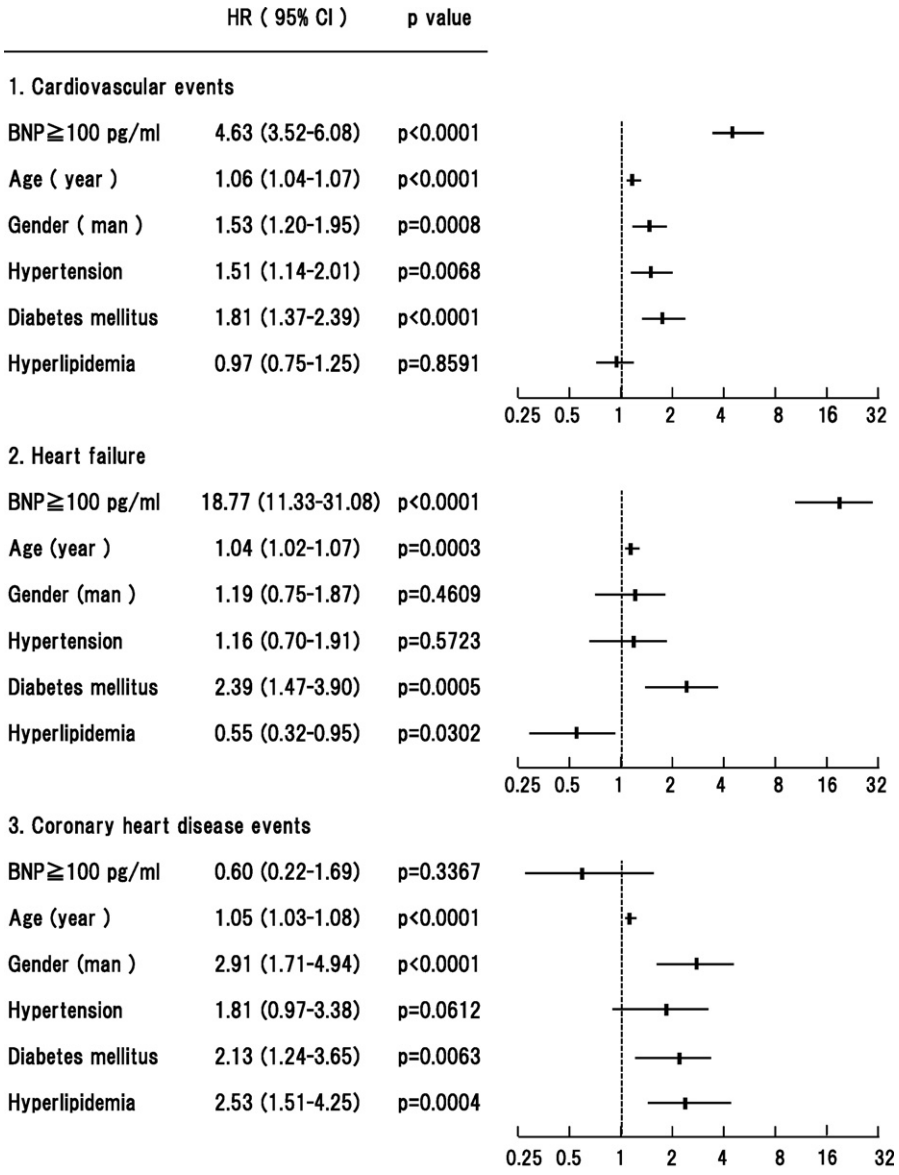

Figure 5 Multivariate analysis for endpoints (cardiovascular events, heart failure, coronary heart disease events) using Cox's proportional hazards model. The incidence of cardiovascular events was significantly associated with brain natriuretic peptide (BNP) ≧100 pg/ml, age, gender (men), hypertension and diabetes; heart failure was associated with BNP ≧100 pg/ml, age and diabetes; and coronary heart disease events, with age, gender (men), diabetes and hyperlipidemia.

significantly higher with BNP ≧100 pg/ml than with BNP <100 pg/ml (HR of 4.45, 95%CI 3.36—5.89; $p < 0.0001$). Also in patients with non-cardiovascular diseases, the incidence of cardiovascular events was significantly higher with BNP ≧100 pg/ml than a BNP < 100 pg/ml (HR 5.90, 95%CI 1.45—24.10; $p = 0.0134$). The incidence of all-cause mortality was also significantly higher with BNP ≧100 pg/ml than with BNP < 100 pg/ml, not only in patients with cardiovascular diseases (HR 4.98, 95%CI 3.63—6.84; $p < 0.0001$), but also in patients with non-cardiovascular diseases (HR 8.02, 95%CI 2.50—25.48; $p = 0.0004$), as shown in Fig. 4(B).

Factors affecting prognosis of cardiovascular diseases

We assessed the effects of BNP ≧100 pg/ml, age, gender (men), hypertension, diabetes mellitus, and hyperlipidemia on the endpoints using Cox's proportional hazards model (Figs. 5 and 6). The incidence of cardiovascular events was significantly associated with BNP ≧100 pg/ml, age, gender (men), hypertension, and diabetes, and heart failure was associated with BNP 100 pg/ml, age, and diabetes. Coronary heart disease events were associated with age, gender (men), diabetes, and hyperlipidemia; stroke was associated with BNP ≧100 pg/ml, age, and hypertension; and atrial fibrillation, with BNP ≧100 pg/ml and age. Finally, cardiovascular mortality was associated with BNP ≧100 pg/ml, age, and diabetes, and all-cause mortality was associated with BNP ≧100 pg/ml, age, gender (men), and diabetes.

Discussion

This study shows that BNP is an important prognostic marker of cardiovascular events and death in outpatients of general practice. The stratification into six groups based on routinely used cut-off levels of BNP demonstrated that the incidence of cardiovascular events increased stepwise as BNP levels increased [8]. In addition, BNP levels had

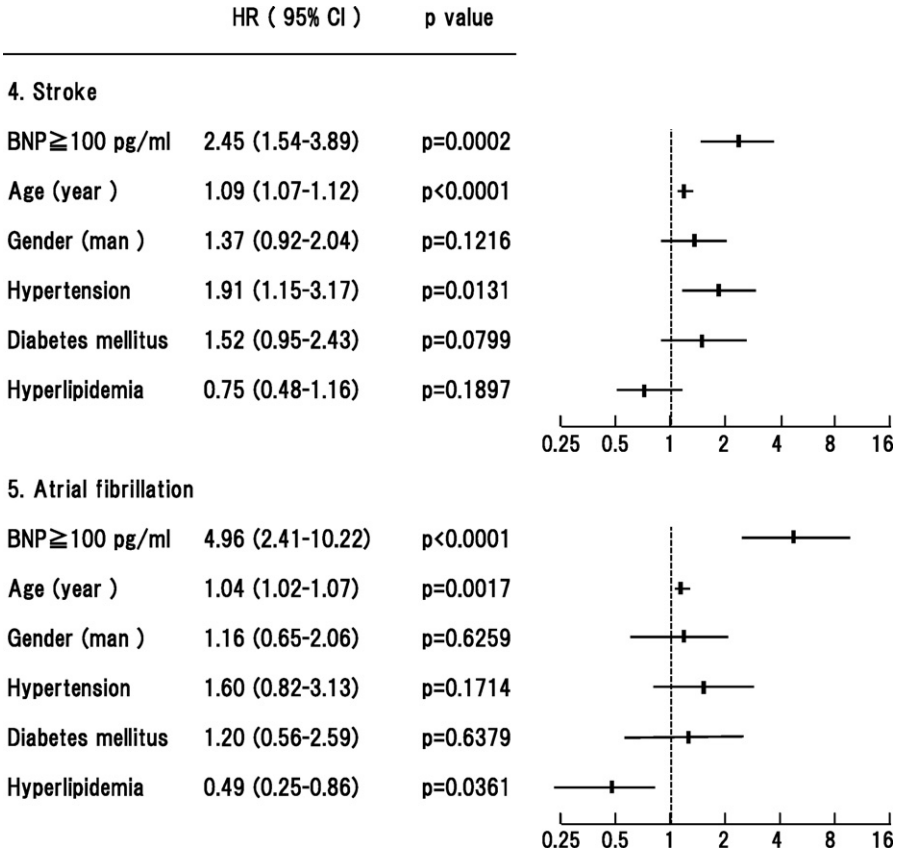

Figure 6 Multivariate analysis for endpoints (stroke, atrial fibrillation) using Cox's proportional hazards model. Stroke was significantly associated with brain natriuretic peptide (BNP) ≧100 pg/ml, age and hypertension, and atrial fibrillation was associated with BNP ≧100 pg/ml and age.

a prognostic value of cardiovascular events and all-cause mortality not only in patients with underlying cardiovascular diseases, but also in those without them, by stratification into two groups based on the cut-off level (100 pg/ml). The Framingham study of a community-based sample of 3346 persons without heart failure showed that BNP levels above the 80th percentile (20 pg/ml for men and 23.3 pg/ml for women) were useful as a threshold for predicting cardiovascular events [12]. In this study, we selected useful cut-off levels of BNP (20, 40, 100, 200, 500 pg/ml) that were seen in many studies. The findings of this study was that these BNP cut-off levels had value in the prognosis of cardiovascular events which reconfirmed that these cut-off levels were useful for diagnosis and screening of cardiovascular diseases.

As regards secondary endpoints, the incidence of cardiovascular death, all-cause death, heart failure, stroke, and atrial fibrillation were significantly higher with BNP $\geqq$100 pg/ml than with BNP < 100 pg/ml. A few studies in community-based samples showed that BNP levels had prognostic value regarding all-cause mortality. The present study in outpatients of general practice demonstrated that death from cardiovascular disease and death from any cause increased as BNP levels increased.

Many studies in patients with heart failure showed that BNP levels had a prognostic value for mortality and morbidity. In the Val-HeFT study [8] in 4284 patients with heart failure, BNP in quartiles (<40, 41—96, 97—237, $\geqq$238 pg/ml) showed a significant quartile-dependent increase in mortality and morbid events. In this study, also in outpatients of general practice, the stratification based on cut-off levels of BNP (<20, 20—40, 40—100, 100—200, 200—500, $\geqq$500 pg/ml) demonstrated that the incidence of heart failure increased stepwise as BNP levels increased.

In patients with coronary heart disease, BNP levels were definitely associated with acute phase and outcome of myocardial infarction [13,21,22,26,27]. However, in this study, we did not find an association between BNP levels and the risk of coronary heart disease events in outpatients of general practice, reflecting a similar finding in the report of the Framingham study in a community-based population [12]. Further, this study showed that the incidence of coronary heart disease events was not associated with BNP levels but with age, gender (men), diabetes, and hyperlipidemia.

In this study, BNP levels were associated with the risk of stroke in outpatients of general practice, again reflecting the finding of the Framingham study in a community-based population [12]. Furthermore, we found that the incidence of stroke was significantly associated not only with BNP levels ($p = 0.0002$), but also with age ($p < 0.0001$) and hypertension ($p < 0.0131$).

As to atrial fibrillation, in this study, BNP levels were also associated with the risk of atrial fibrillation in patients seen in general practice, as the report of the Framingham study also stated [12]. Our previous study in outpatients with paroxysmal atrial fibrillation [28] showed that BNP levels during atrial fibrillation attack (median: 102 pg/ml) was increased by 66 (median) pg/ml (2.4-fold) compared with BNP levels during sinus rhythm (median: 39 pg/ml). In addition, the substantial and significant BNP elevation in asymptomatic cases (median BNP during sinus rhythm: 31 pg/ml, during atrial fibrillation attack: 71 pg/ml) may indicate that BNP elevation of unknown origin may be attributed to the occurrence of asymptomatic atrial fibrillation attack.

Study limitations

The present study has some limitations. First, we could not determine the cause of death of 18 subjects (8.1% of 223 deaths in all) in this study. This may be inevitable in an observation study of outpatients of general practice. Second, the study population consisted of 3123 outpatients of one local clinic in Japan, who were treated according to the accepted guidelines and by BNP-guided therapy [29,30]. Therefore, it was unavoidable that this study showed a certain amount of bias in relation to patient background, diagnosis, and treatment.

Conclusion

In general practice, plasma BNP concentrations predicted the risk of cardiovascular events, cardiovascular mortality, all-cause mortality, heart failure, stroke, and atrial fibrillation, except for coronary heart disease events. In addition, BNP levels had a prognostic value of cardiovascular events and all-cause mortality not only in patients with underlying cardiovascular diseases, but also in those without them.

Acknowledgments

We would like to thank Nobuo Shirahashi (Clinical Epidemiology, Osaka City Graduate School)

for statistical support, and Dr. Joukichi Suzuki (Suzuki Clinic) and Dr. Takashi Tomidokoro (Nagaoka Chuo General Hospital) for helpful discussions, and Sako Narita (George Washington University) for important advice. We also appreciate the staff in the Tsuchida Clinic of Internal Medicine and Cardiology for their important contribution to this study.

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