慢性維持透析患者を対象とした大規模コホート研究

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背景と目的

欧米で行われた透析患者の疫学調査によると、死亡率は一般人の約10倍高率で主要死因の半数を心臓疾患が占めると報告されている。また透析患者の死亡や循環器疾患発症リスクを高めている予後因子として栄養状態、貧血、骨ミネラル代謝異常、透析効率などの関与が挙げられている[1~3)]。

日本人透析患者における疫学研究としては日本透析医学会が実施しているJSDT調査（透析学会報告）、沖縄県の井関らの研究グループによるOKIDS研究、わが国も参加している各国共同研究のDOPPS研究などがある。JSDT調査は日本人透析患者の98％（2007年版）の情報を収集したものであり、現在の日本人透析患者の概況を知るうえで貴重な資料である。しかし、縦断研究ではないため正確な死亡率や疾患罹患率、死亡や疾患発症に影響するリスク要因の検討はできない。

井関らのOKIDS研究は日本人透析患者の疫学研究としてこれまで多くの知見を公表してきたが、研究から10年以上が経過し、現在の日本人透析患者と患者属性が大きく異なってきている。DOPPS研究は各国共同研究であり、一地域を網羅した悉皆調査ではない。よって、現在の日本で透析患者の死亡・死因・死亡のリスク要因について明らかにするためには、透析患者を対象とした地域悉皆性のある前向きコホート研究を行う必要がある。

我々は平成15年度に岩手県中央部から北部地域にかけてのすべての透析施設を対象とした前向きコホート研究を開始した[4)]。本論文では、追跡調査データを用いて透析患者の粗死亡率を求め、死亡原因の内訳を示すとともに総死亡に影響するリスク要因について検討した。

対象と方法

対象は岩手県北部から県中央部の成人透析患者である。透析施設は全部で26施設あり患者総数は1,506名。登録調査は2003年6月から2004年3月の期間で行った。25施設の1,447名に面会し、1,260名から書面による同意を得た（同意受容率87.0％）。血液検査を含めたすべての調査を実施できたのは1,214名（80.6％）であった。本研究では、3年間の追跡調査データを収集し終えた1,150例を解析対象とした。本研究は岩手医科大学倫理審査委員会の承認を得て、ヘルシンキガイドラインに従って実施された。

登録調査

登録調査の内容は、調査員の面談による生活問診、血圧測定、身長測定、患者診療録閲覧による患者医療情報収集、透析治療開始直前採血による血液検査である。

追跡調査

毎年透析施設を訪問し、患者診療記録ならびに死亡診断書を閲覧して死亡の有無・死亡原因・循環器疾患発症（心不全、冠動脈疾患、脳血管疾患、その他）の有無・悪性新生物発症の有無について登録した。登録に際しては、本研究疾患定義に基づいて行った[4]。

統計ならびに解析手法

性別、腎不全原因疾患別に死亡数を求めて1,000人年あたりの粗死亡率を算出した。日本透析医学会の死亡内訳に準じて[1]、心不全、感染症、脳血管疾患、悪性腫瘍、心筋梗塞、その他（突然死を含む）に分けて1,000人年あたりの死亡率を求めるとともに60歳未満、60歳から70歳、70歳以上の年齢階級別に3群に分けて死因割合を比較した。

生存群と死亡群で死亡に影響すると考えられたリスク要因の比較を行った。連続変数はT検定を、カテゴリー変数はカイ二乗検定を行った（表1）。リスク要因の死亡に影響する相対危険度を求めるため、上記比較により有意差のみられた各因子を説明変数としてCox回帰分析を用いて多変量調整ハザード比と95％信頼区間を算出した（表2）。P値は両側で5％未満を有意とした。統計解析にはSPSS. Version 14を用いた。

表1●生存群 vs. 死亡群の患者背景の比較

	生存群（912人）	死亡群（302人）	P値
年齢	58.8 ± 12.6	68.5 ± 11.3	＜0.05
男性割合	63.71％	65.6％	0.56
BMI	21.0 ± 3.0	20.8 ± 3.0	0.93
ヘモグロビン値（g/dL）	10.2 ± 1.4	10.0 ± 1.4	0.56
アルブミン値（mg/dL）	3.8 ± 0.33	3.5 ± 0.4	＜0.001
高感度CRP（mg/dL）	0.31 ± 0.76	0.68 ± 1.26	＜0.001
透析前収縮期血圧（mmHg）	154.0 ± 22.7	157.2 ± 27.8	＜0.001
糖尿病の有無	25.9％	33.4％	＜0.05
心筋梗塞	4.3％	7.9％	＜0.05
脳卒中	11.8％	20.2％	＜0.05
末梢動脈疾患	14.6％	20.9％	＜0.05

表2●Cox比例回帰分析（死亡に寄与する因子の検討）

	ハザード比	（95％CI）	P値
年齢（歳）	1.05	（1.04-1.06）	＜0.001
透析前収縮期血圧（per 1mmHg）	1.00	（1.00-1.01）	0.100
アルブミン（per 1mg/dl）	0.21	（0.15-0.29）	＜0.001
高感度CRP（per 1mg/dl）	1.19	（1.09-1.30）	＜0.001
糖尿病	0.84	（0.65-1.09）	0.200
末梢動脈疾患	0.90	（0.67-1.20）	0.460
脳卒中	1.33	（0.99-1.79）	0.060

結　果

研究対象者の平均年齢は61.9 ± 12.6歳で男性が63.2％を占めた。平均透析期間は6.9 ± 6.6年であった。3年間の追跡期間中の総死亡者数は302名で、感染症死亡79名、脳血管死亡44名、突然死37名、心不全死33名、冠動脈疾患死33名、悪性新生物死亡11名、その他の心疾患死9名、血管疾患死7名（大動脈瘤破裂など）が観察された。

粗死亡率は91.8（/1,000人年）で男性は94.2、女性は87.4であった。原因疾患別死亡率は、慢性糸球体腎炎で68.0、糖尿病性腎症で121.3、その他の腎

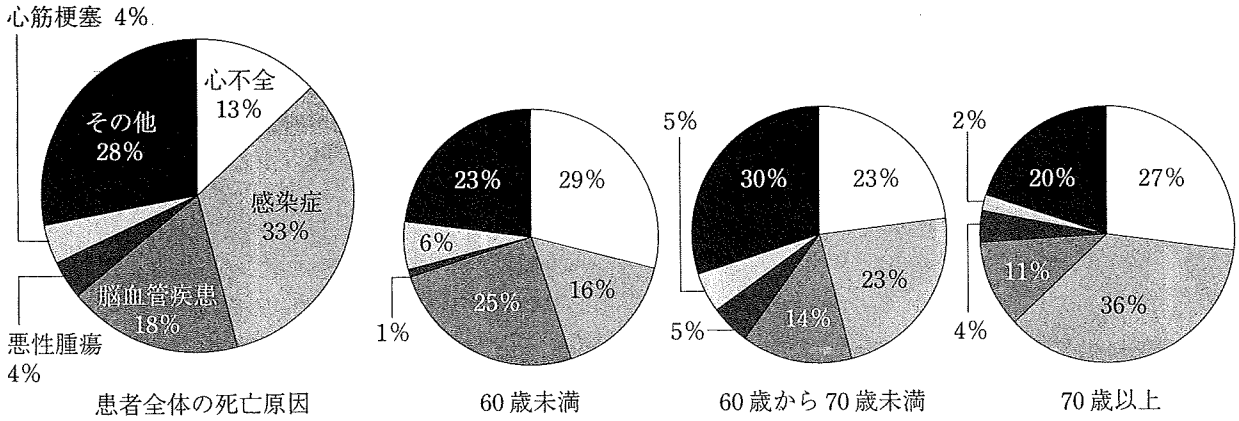

図1●年齢別死亡原因の比較

不全は102.9であった。死因の内訳をみると感染症が27.4％（25.6/1,000人年）、脳血管疾患が14.5％（13.7）、心不全が10.9％（10.3）であった。突然死は12.3％（11.5）であった。突然死と脳血管疾患死亡を合わせた循環器疾患死亡は全体の46.7％を占めた。年齢階級別の死亡原因内訳をみると60歳未満では脳血管疾患（25.4％）による死亡が多く、70歳以上の高齢群では感染症（34.2％）による死亡が多くみられた（図1）。

生存群と死亡群のリスク要因を比較すると、死亡群で年齢が高く、アルブミン値が低く、高感度CRP値と透析前収縮期血圧が高く、糖尿病・心筋梗塞・脳卒中・末梢動脈疾患を高率に合併していた（表1）。これらが死亡リスクを上げているのかを検討した多変量解析では、死亡リスクを有意に上げていた要因として年齢、CRP高値、アルブミン低値が挙げられた（表2）。

考　察

本研究に参加した透析患者の死亡率はおよそ90/1,000人年であり、JSDTサーベイの年間粗死亡率の9％にほぼ一致していた。

欧米では心疾患死亡が約半数を占め、その多くは冠動脈疾患によるものである。一方本調査では、感染症死亡が多いことが特徴的であった。脳卒中を含めた循環器疾患死亡はおよそ4割を占めたものの、心不全死亡は10.9％、心筋梗塞症死亡がわずかに3.6％と欧米との死因の違いが観察された。JSDTサーベイでは、心不全死亡が25.8％、感染症死亡が19.2％と報告され、本研究と同様に循環器疾患、特に心疾患で死亡する患者が欧米透析患者と比べて少ないのが特徴である。

年齢階級別の死亡原因の比較では60歳未満で脳血管疾患死亡が多く、高齢者では感染症死亡が多かった。60歳未満では血圧コントロールを厳重に行う必要が示唆された。

死亡に寄与する因子の検討では欧米の研究と同様に透析患者では古典的危険因子が強いリスク要因とはならず、炎症反応亢進と低栄養状態が死亡リスクを強く上げていることが示された。

結　語

岩手県透析患者コホート研究では欧米と異なり、心疾患死亡、特に冠動脈疾患死亡が少ないことが観察された。60歳未満の透析患者では脳血管疾患死亡が多く、70歳以上の透析患者では感染症死亡が多かった。日本人透析患者の死亡率と死因の内訳は欧米とは大きく異なっており、欧米とは別に日本人透析患者の特徴に合わせた対策が必要と考えられた。

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Predictive value of plasma B-type natriuretic peptide for ischemic stroke: A community-based longitudinal study

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ABSTRACT

Objective: Structural heart diseases including atrial fibrillation are precursors for ischemic stroke. Plasma B-type natriuretic peptide (BNP) has been reported to be increased in patients with several types of structural heart diseases. However, the predictive value of plasma BNP for ischemic stroke remains unknown. We have studied the predictive ability of plasma BNP for future development of stroke in community dwelling adults.

Methods: Subjects of this community-based study were recruited from the general population (n = 13,466). Plasma BNP levels and cardiovascular risk factors were determined at baseline. The incidence of ischemic stroke in the cohort was identified from regional stroke registry data. A multivariate Cox regression analysis was performed to analyze the relationship between plasma BNP levels and the risk of stroke.

Results: During a mean follow-up period of 2.8 years, 102 participants (65 males, 37 females) experienced a first ischemic stroke. In men, after adjustment for classical cardiovascular risk factors and atrial fibrillation, the hazard ratio (HR) for ischemic stroke was significantly elevated in the highest plasma BNP quartile (HR = 2.38; 95% CI = 1.07–5.29). In women, the relationship between plasma BNP levels and risk of ischemic stroke was of marginal significance after adjusting for the presence or absence of atrial fibrillation (HR = 3.03; 95% CI = 0.84–10.92, P = 0.09).

Conclusion: Elevated plasma BNP levels predict the risk of ischemic stroke within men from the general population.

1. Introduction

B-type natriuretic peptide (BNP) is a cardiac hormone secreted from the myocardium in response to changes in intracardiac volume and pressure [1,2]. Plasma BNP levels are known to be elevated in patients with symptomatic left ventricular systolic dysfunction [3,4] and correlate to New York Heart Association (NYHA) class as well as prognosis [5,6]. In addition, irrespective of the degree of left ventricular dysfunction, plasma BNP levels have been shown to be elevated in patients with various structural heart diseases including previous myocardial infarction, cardiomyopathy, valvular heart disease, hypertensive heart disease, and atrial fibrillation [3,7–13].

These structural heart diseases are precursors not only for heart failure, but also for ischemic stroke, and especially cardioembolic stroke [14]. However, there have been very few reports on the association between plasma BNP levels and the risk of stroke. The Framingham Heart Study [15] has described a 4.9-fold increase in the crude incidence of stroke or transient ischemic attack in the highest tertile of BNP levels compared to the lowest tertile. Kistorp et al. [16] reported that plasma levels of N-amino terminal fragment of the prohormone BNP (NT-proBNP) predicted the risk of stroke or transient ischemic attack, with a 3.6-fold increase in risk of stroke for participants with values above the 80th percentile vs those with values equal to or below the 80th percentile in the general population. However, the association between plasma BNP levels and risk of stroke subtypes remains unclear. The predictive value of plasma BNP measurement for ischemic stroke remains unknown.

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We have studied the predictive ability of plasma BNP for future development of ischemic stroke in community dwelling adults.

2. Methods

2.1. Study population

The Iwate-Kenpoku Cohort (Iwate-KENCO) study was designed to prospectively investigate the risk of cardiovascular diseases including stroke and malignant tumor in the general Japanese adult population as described previously [17,18]. Subjects consisted of residents of the Ninohe, Kuji and Miyako districts in the northern Iwate prefecture, Japan. Between April 2002 and January 2005, 26,469 of these residents (men = 9161, women = 17,308) who were participating voluntarily in a multiphasic health checkup agreed to join the study (original cohort). The baseline survey included routine anthropometrical measurement, blood pressure measurement, ECG, routine laboratory assessment, a self-administered lifestyle questionnaire, and a food-frequency 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 (men = 5288, women = 10,106) underwent BNP measurement (BNP cohort). Subjects were excluded from this cohort on the basis of the following characteristics: age under 40 years (n = 575), history of cardiovascular or cerebrovascular events (n = 507), non-measurement of adjustment factors (n = 846). The final statistical analysis was therefore performed in 13,466 subjects (men = 4527, women = 8939, mean age = 62.7 years).

2.2. Outcome

In this cohort study, the primary endpoint was all-cause death, in addition to any nonfatal cardiovascular events such as myocardial infarction, cerebral infarction, or other strokes. Information about death and emigration was obtained from local government records. Stroke events were identified by accessing the Iwate prefecture stroke registration programme, which has been conducted since 1991 by the Iwate Medical Association with the support of the government of the Iwate prefecture [19]. Registration forms were submitted to the registration office of the Iwate Medical Association by mail when a patient with stroke was discharged from a medical facility. Diagnostic criteria for stroke used by the registry correspond with those published by the World Health Organization, based on a definition of sudden onset of neurological symptoms [20]. For diagnosis of stroke subtypes, computed tomography and/or magnetic resonance imaging were performed within each hospital. In order to improve accuracy of registration, trained research nurses checked medical charts in all hospitals located within these districts. Follow-up was conducted until August 2007.

2.3. Measurement

At the time of baseline survey, participants underwent anthropometrical measurement, ECG, blood pressure measurement, and routine laboratory assessment. In addition, a self-administered questionnaire was used to ascertain family history, symptoms, and lifestyle factors such as smoking habits, alcohol consumption, and exercise habits. A medical history including the status of drugs prescribed for hypertension, hyperlipidemia, diabetes, angina, myocardial infarction, congestive heart failure, and stroke was recorded by trained research staff. Using a 3-channel device, a standard 12-lead ECG was recorded in a supine position. Atrial fibrillation was defined by this 12-lead ECG at the time of baseline survey. Systolic and diastolic blood pressures were determined with an automatic device placed on the right arm of seated subjects who had rested in a sitting position for at least 5 min before measurement. Measurement was performed twice, with the mean value used for statistical analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and/or current anti-hypertensive therapy. Hyperlipidemia was defined as total cholesterol level ≥240 mg/dL, and/or current lipid lowering therapy. Diabetes was defined as nonfasting glucose concentration ≥200 mg/dL, and/or glycosylated hemoglobin (HbA1c) value ≥6.5%, and/or current anti-diabetic therapy. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Smoking was defined as current smoker. Regular alcohol consumption was defined as drinking alcohol 5 days or more per week. Regular exercise was defined as exercising (at least 60 min) 8 days or more per month.

Venous blood samples for plasma BNP measurement were drawn from the antecubital vein of seated participants with minimal tourniquet use. Samples were collected into vacuum tubes containing ethylenediaminetetraacetic acid sodium. Tubes were stored in an icebox immediately after sampling and were transported to our laboratory within 8 h of collection. These were then centrifuged at 1500 × g for 10 min. After separation, 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 (ShionoRIA BNP, Shionogi, Japan) within 4 months of separation. The intraassay and interassay coefficients of variation were 5% and 6%, respectively. The lower detection limit of the assay was 0.05 pg/mL. Enzymatic methods were used to measure serum total cholesterol levels, serum creatinine, and blood glucose. HbA1c was measured quantitatively with an HPLC method.

2.4. Statistical analysis

Participants were divided into quartiles according to their baseline plasma BNP levels. Continuous variables were expressed as mean ± SD. Group comparisons were based on the unpaired t-test and multiple group comparisons across BNP quartiles were based on the one-way analysis of variance. Because BNP values were not normally distributed, these were expressed as median and the Mann–Whitney U-test was used for comparison. Categorical parameters were expressed as proportions (percentage) and group comparisons were based on the chi-square test.

The ischemic stroke event free rates according BNP quartiles were estimated using the Kaplan–Meier method, followed by Log-rank test. A multivariate Cox regression analysis was performed to analyze the relationship between plasma BNP levels and risk of stroke. For all models, the hazard ratios were adjusted for age, BMI, blood hemoglobin levels, serum creatinine levels, presence or absence of hypertension, hyperlipidemia, diabetes, smoking, regular alcohol consumption, and regular exercise. The analysis was not adjusted for presence or absence of atrial fibrillation in Model 1 and was adjusted in Model 2. Additional multivariate Cox regression analysis using covariates in Model 1 was performed using 1 SD increments in natural logarithm-transformed BNP values. For the analysis of stroke incidence, person-years were censored at the date of stroke diagnosis, 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, version 11.0. A significant difference was defined as $P < 0.05$.

3. Results

Baseline characteristics of participants by sex are shown in Table 1. The mean age of men was higher than that of women. The percentages of hypertension, diabetes, atrial fibrillation, smoking, regular alcohol consumption, regular exercise, and mean values for

Table 1
Comparison of baseline characteristics between men and women.

Characteristic	Men (N=4527)	Women (N=8939)	P-value
Age (years)	64.1 ± 10.3	62.0 ± 10.0	<0.001
Hypertension (%)	44.4	38.8	<0.001
Hyperlipidemia (%)	10.3	20.3	<0.001
Diabetes (%)	8.0	4.3	<0.001
Body mass index (kg/m^2)	23.9 ± 2.9	24.2 ± 3.4	<0.001
Smoking (%)	33.4	2.5	<0.001
Regular alcohol consumption (%)	47.4	4.2	<0.001
Regular exercise (%)	17.0	10.5	<0.001
Atrial fibrillation (%)	3.0	0.6	<0.001
Hemoglobin (g/dL)	14.6 ± 1.3	13.0 ± 1.1	<0.001
Creatinine (mg/dL)	0.82 ± 0.19	0.63 ± 0.12	<0.001
BNP (median) (pg/mL)	14.8	17.1	<0.001

Continuous variables are expressed as mean ± SD.
Comparison of BNP data are performed using a Mann-Whitney U test.

hemoglobin and serum creatinine were significantly higher in men. The percentage of hyperlipidemia and mean BMI were significantly higher in women. The median value for plasma BNP was higher in women.

Table 2 shows baseline characteristics among the BNP quartiles. In men, mean age and BMI and mean levels of hemoglobin, and serum creatinine were different among the BNP quartiles (P<0.001). Although the percentages of hypertension, hyperlipidemia, current smoking, and regular exercise were different (P<0.001), the percentages of diabetes and regular alcohol consumption did not differ among the BNP quartiles. In women, although mean age and mean levels of hemoglobin, and serum creatinine were different among the BNP quartiles (P<0.001), the mean BMI did not differ among the BNP quartiles. Although the percentages of hypertension, hyperlipidemia, diabetes, current smoking, and regular alcohol consumption were different (P<0.05), the percentage undertaking regular exercise did not differ among the BNP quartiles. Subjects with atrial fibrillation were concentrated in the highest BNP quartile in both men and women.

During a mean follow-up period of 2.8 years, 102 participants (65 males, 37 females) had a first ischemic stroke event. Ranges of BNP levels in men and women are shown in Table 2. The crude incidences of ischemic stroke (per 1000 person-years) among BNP quartiles in men and women are shown in Tables 3 and 4. The crude incidence of ischemic stroke in men was 2.76 per 1000 person-years in Q1 (the lowest quartile) and 12.51 per 1000 person-years in Q4 (the highest quartile). The crude incidence of ischemic stroke in women was 0.44 per 1000 person-years in Q1 and 2.95 per 1000 person-years in Q4. The crude incidence of ischemic stroke elevated in the highest quartile in both men and women.

The Kaplan–Meier curves for ischemic stroke event free rates according to BNP quartiles in men and women are shown in Fig. 1. The ischemic stroke event free rates differed significantly among the BNP quartiles in both men and women (men: P<0.001; women: P<0.001 by log-rank test).

Several studies have demonstrated that blood hemoglobin levels [21], renal function [22] and BMI [23] influence plasma BNP levels. For that reason, after adjustment for classical cardiovascular risk

Table 2
Comparisons of baseline characteristics among BNP quartiles.

BNP quartiles	Q1	Q2	Q3	Q4	P-value
Men					
Number of subjects	1131	1134	1129	1133	
Range of BNP levels (pg/mL)	<6.5	6.5–14.8	14.9–29.9	30.0<	
Age (years)	57.4 ± 10.1	61.9 ± 9.8	66.7 ± 8.3	70.3 ± 7.8	<0.001
Hypertension (%)	33.3	40.0	47.5	56.8	<0.001
Hyperlipidemia (%)	16.5	9.8	7.9	7.1	<0.001
Diabetes (%)	7.6	8.2	8.4	7.6	0.846
Body mass index (kg/m^2)	24.1 ±2.9	24.1 ±2.9	23.8 ± 2.9	23.6 ± 3.0	<0.001
Smoking (%)	40.4	34.9	31.6	26.6	<0.001
Regular alcohol consumption (%)	48.2	45.7	47.3	48.3	0.576
Regular exercise (%)	11.6	17.1	20.0	19.3	<0.001
Atrial fibrillation (%)	0.53	0.00	0.71	10.59	<0.001
Hemoglobin (g/dL)	15.0 ± 1.1	14.8 ± 1.1	14.5 ± 1.2	14.2 ± 1.4	<0.001
Creatinine (mg/dL)	0.80 ± 0.14	0.81 ± 0.16	0.83 ± 0.24	0.84 ± 0.19	<0.001
Women					
Number of subjects	2235	2228	2242	2234	
Range of BNP levels (pg/mL)	<8.9	8.9–17.0	17.1–30.4	30.5<	
Age (years)	57.6 ± 9.5	60.0 ± 9.8	62.8 ± 9.4	67.4 ± 8.7	<0.001
Hypertension (%)	28.6	33.4	40.7	52.4	<0.001
Hyperlipidemia (%)	24.3	20.4	20.2	16.3	<0.001
Diabetes (%)	5.0	3.1	4.1	4.9	0.006
Body mass index (kg/m^2)	24.3 ± 3.4	24.2 ± 3.3	24.0 ± 3.3	24.1 ± 3.5	0.206
Smoking (%)	3.9	2.4	2.2	1.5	<0.001
Regular alcohol consumption (%)	5.0	4.6	3.8	3.4	0.027
Regular exercise (%)	10.2	10.2	10.9	10.9	0.756
Atrial fibrillation (%)	0.09	0.05	0.04	2.24	<0.001
Hemoglobin (g/dL)	13.2 ± 1.1	13.1 ± 1.1	13.0 ± 1.1	12.8 ± 1.1	<0.001
Creatinine (mg/dL)	0.61 ± 0.10	0.63 ± 0.11	0.63 ± 0.10	0.66 ± 0.15	<0.001

Continuous variables are expressed as mean ± SD.

Table 3
The crude incidence and multivariate hazard ratio of ischemic stroke among BNP quartiles in men.

BNP quartiles	Q1	Q2	Q3	Q4	*P* for trend
Observed person-years	3619	3198	3116	3036	
Ischemic stroke					
Crude incidence (/1000 person-years)	2.76	2.19	3.21	12.51	
Multivariate HR (95%CI)					
Model 1	1.0 (ref.)	0.71 (0.27–1.89)	0.85 (0.34–2.12)	2.83 (1.29–6.20)	<0.001
Model 2	1.0 (ref.)	0.71 (0.27–1.88)	0.81 (0.33–2.03)	2.38 (1.07–5.29)	<0.005

For all models, the hazard ratios were adjusted for age, presence or absence of hypertension, hyperlipidemia, diabetes, smoking, regular alcohol consumption, and regular exercise. BMI, blood hemoglobin levels, and serum creatinine levels.
Model 1: The analysis was not adjusted for presence or absence of atrial fibrillation.
Model 2: The analysis was adjusted for presence or absence of atrial fibrillation.

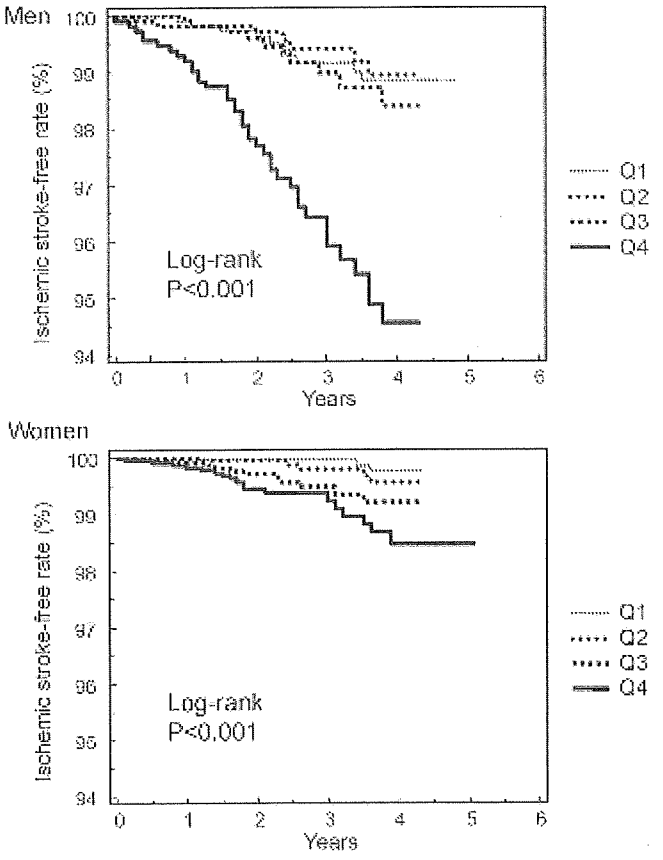

Fig. 1. Kaplan–Meier curves for ischemic stroke event free rate according to BNP quartiles by sex.

factors, blood hemoglobin levels, serum creatinine levels, and BMI, a multivariate Cox regression analysis was performed to analyze the relationship between plasma BNP levels and the risk of stroke. In men, the hazard ratio (HR) obtained from a Cox proportional model for ischemic stroke in the highest BNP quartile was significantly elevated in Model 1 (HR = 2.83; 95% CI = 1.29–6.20; Table 3). After also adjusting for the presence or absence of atrial fibrillation (Model 2), HR in the highest BNP quartile was still significantly elevated (HR = 2.38; 95% CI = 1.07–5.29; Table 3). The risk of incidence of ischemic stroke increased in association with BNP levels ($P < 0.01$). In women, HR for ischemic stroke in the highest BNP quartile was significantly elevated in Model 1 (HR = 3.61; 95% CI = 1.01–12.93; Table 4). After adjusting for the presence or absence of atrial fibrillation (Model 2), the relationship between plasma BNP levels and the risk of ischemic stroke was of marginal significance (HR = 3.03; 95% CI = 0.84–10.92, $P = 0.09$; Table 4).

An additional multivariate Cox regression analysis was performed using 1 SD increments in natural logarithm-transformed BNP values. Elevated plasma BNP levels were associated with an elevated risk of ischemic stroke in both men and women (HR = 1.70; 95% CI = 1.17–2.45 in men: HR = 1.69; 95% CI = 1.04–2.75 in women).

4. Discussion

There have been very few reports on the association between plasma BNP levels and the risk of stroke, [15,16] and the relationship with risk of stroke subtypes therefore remains unclear. The present study suggests that high plasma BNP levels predict the risk of ischemic stroke within the general Japanese population. Ischemic stroke is classified into atherothrombotic infarction, cardiogenic embolic infarction, and lacunar infarction. Several types of structural heart diseases including atrial fibrillation, which are associated with elevated plasma BNP levels, may be an important cause of ischemic stroke, especially cardioembolic stroke. In view of this, elevated plasma BNP levels may be a biomarker for high risk of ischemic stroke.

Cardiac disorders linked with ischemic stroke, especially cardioembolic stroke, are nonvalvular atrial fibrillation, acute

Table 4
The crude incidence and multivariate hazard ratio of ischemic stroke among BNP quartiles in women.

BNP quartiles	Q1	Q2	Q3	Q4	*P* for trend
Observed person-years	6794	6283	6188	6099	
Ischemic stroke					
Crude incidence (/1000 person-years)	0.44	0.80	1.78	2.95	
Multivariate HR (95%CI)					
Model 1	1.0 (ref.)	1.72 (0.41–7.25)	3.07 (0.84–11.16)	3.61 (1.01–12.93)	0.168
Model 2	1.0 (ref.)	1.79 (0.43–7.55)	3.15 (0.87–11.44)	3.03 (0.84–10.92)	0.269

For all models, the hazard ratios were adjusted for age, presence or absence of hypertension, hyperlipidemia, diabetes, smoking, regular alcohol consumption, and regular exercise. BMI, blood hemoglobin levels, and serum creatinine levels.
Model 1: The analysis was not adjusted for presence or absence of atrial fibrillation.
Model 2:The analysis was adjusted for presence or absence of atrial fibrillation.

myocardial infarction, ventricular aneurysm, and valvular heart disease. According to the Cerebral Embolism Task Force [14], nonvalvular atrial fibrillation is the most common cardiac disorder associated with embolic stroke, accounting for 45% of embolic strokes. Several previous studies have suggested that plasma BNP levels were significantly higher in patients with atrial fibrillation than in those without atrial fibrillation [11,13]. The Framingham Heart Study [15] has indicated that higher plasma BNP levels predict risk of atrial fibrillation. It is therefore possible that atrial fibrillation-related high plasma BNP levels are associated with increased risk of ischemic stroke. We therefore analyzed the relationship between plasma BNP levels and risk of ischemic stroke after adjusting for the presence or absence of atrial fibrillation. Even after this adjustment, HR was still significant in men. This suggests that there may be factors other than atrial fibrillation underlying the apparent relationship between plasma BNP levels and risk of ischemic stroke. As the present study did not perform echocardiography as a baseline examination, some subjects may have had asymptomatic structural heart disease (i.e. left ventricular dysfunction, valvular heart disease, or left ventricular hypertrophy) characterized by elevated plasma BNP [12] which would account for the significant relationship between plasma BNP levels and risk of ischemic stroke. This study was therefore unable to show a correlation between plasma BNP levels and risk of stroke independent of the presence of heart disease. However, it is difficult to perform echocardiography routinely for participants in a community-based multiphasic health checkup. A simple blood test for BNP is an ideal approach for selecting males at high risk for ischemic stroke within the general population. In addition, a previous study examining the relationship between traditional and nontraditional risk factors and the incidence of ischemic stroke subtypes has reported that left ventricular hypertrophy increases the risk not only of cardioembolic stroke but also of atherothrombotic stroke [24]. It follows that high plasma BNP levels may be associated with both cardioembolic and atherothrombotic stroke.

The present study has shown a median plasma BNP level of 14.8 pg/mL and the threshold plasma BNP levels associated with elevated risk of ischemic stroke of 30.0 pg/mL in men. The Framingham Heart Study [15] found a median plasma BNP level of 6.2 pg/mL and the threshold plasma BNP levels associated with elevated risk of stroke or transient ischemic attack of 20.0 pg/mL in a community-based male sample. Both studies have shown that excess risk is apparent at plasma BNP levels well below the thresholds currently used to diagnose heart failure [25].

A possible reason for the marginal significance of the relationship between plasma BNP levels and risk of ischemic stroke in women after adjusting for the presence or absence of atrial fibrillation may be the low incidence of stroke in the female cohort. The crude incidences of stroke in women were clearly lower than those in men, and thus, the statistical power to show any relationship between risk and incidence of stroke might be limited in women. As the statistical results concerning the relationship between plasma BNP levels and risk of stroke in women were not so robust, more events should be gathered to investigate the predictive power of plasma BNP with regard to stroke in women.

Although our study was a large, prospective community-based longitudinal study, several limitations must be considered when interpreting the results. Since ECG testing was performed only at the time of baseline survey, paroxysmal atrial fibrillation had not been detected and new incidence of atrial fibrillation was not captured after the baseline survey. Hence the impact of atrial fibrillation on the association between plasma BNP levels and risk of ischemic stroke may not have been accurately estimated. In addition, since the attending physicians participating in the registration survey were not all neurological specialists, the diagnosis of stroke subtypes was occasionally carried out by general physicians. However, since most of the patients registered were diagnosed using computed tomography or magnetic resonance imaging, the differential diagnosis between ischemic stroke and hemorrhagic stroke was made correctly.

In conclusion, this community-based study has shown that elevated plasma BNP levels predict the risk of ischemic stroke within Japanese men from the general population. This suggests that a simple blood test for BNP is an ideal approach for selecting men at high risk for ischemic stroke within the general population.

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Serum C-reactive protein levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population

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ABSTRACT

Background: High C-reactive protein (CRP) levels have been reported to be associated with an increased risk of atherosclerotic cardiovascular events. The relationship of CRP levels to the risk of cerebrovascular events in the Japanese population, which has a lower prevalence of coronary artery disease and a lower CRP level than Western populations, has not been fully clarified. The present study examined the predictive value of serum high sensitivity CRP (hs-CRP) levels for future cerebrovascular events and mortality in the general Japanese population.

Methods: The subjects for this community-based, prospective cohort study were recruited from the general population ($n = 7901$, male only, mean age = 64.0 years). Serum hs-CRP levels and cardiovascular risk factors were determined at baseline. The mean follow-up period was 2.7 years. After excluding subjects with a cardiovascular history, the relationships between hs-CRP levels and cerebrovascular events and mortality were assessed.

Results: During follow-up, 130 participants had a first stroke (95 ischemic strokes), and 161 participants died. The hs-CRP tertile level was a significant predictor for a first ischemic stroke (3rd tertile, HR = 1.77: 95% CI, 1.04–3.03, compared with the 1st tertile), after adjustment for age and classical cardiovascular risk factors. Similar trends were observed for the prediction of all-cause mortality (3rd tertile, HR = 2.26: 95% CI, 1.49–3.42, compared with the 1st tertile).

Conclusion: CRP levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population, independently from traditional cardiovascular risk factors.

1. Introduction

The degree of systemic inflammation that is represented by elevated high sensitivity C-reactive protein (hs-CRP) levels has been associated with an increased risk of cardiovascular events in studies conducted in the United States and Europe [1–3]. In the prospective Physicians' Health Study (PHS), elevated hs-CRP levels were associated with an approximately twofold increase in the risk of stroke [1].

We previously reported that, in apparently healthy males living in Japan, hs-CRP levels were closely associated with atherosclerotic changes as measured by carotid plaque formation [4]. Thus, the extent of inflammation may reflect the propensity of atherosclerotic lesions to precipitate clinical vascular events. However, the serum hs-CRP levels of the general Japanese population have been reported to be lower than those of other ethnic groups [5,6]. One must clarify whether associations between a future risk of cerebrovascular diseases and elevated hs-CRP levels also exist in a population that has a relatively lower hs-CRP level. Only one study has reported the association between hs-CRP and ischemic stroke in a rural area of Japan [7]. Therefore, we evaluated the ability of hs-CRP levels to predict future cerebrovascular events and mortality in a larger cohort of the general Japanese population.

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2. Methods

2.1. Study subjects

The study subjects were recruited from the community-dwelling population living in the Ninohe, Kuji, and Miyako districts of Iwate in northern Japan (the Iwate-Kenpoku Cohort study). This study was conducted as part of a government-sponsored, multiphasic health checkup program aimed at the general population. Between April 2002 and January 2005, invitations to participate in this health checkup program were issued by government offices in 17 rural municipalities located in these districts; 26,469 individuals (9161 males) took part in the program and agreed to join the present study. Of these, 25,925 subjects (8957 males) had hs-CRP measurements. Subjects aged over 80 years (280 males) and those under 40 years (300 males), as well as those with a history of cardiovascular disease or stroke (527 males), were excluded. Thus, the data of 7901 males (mean age, 64.0 ± 9.7 years) were analyzed. Baseline clinical examinations included a standard 12-lead electrocardiogram, and a self-reported questionnaire was administered to document subjects' medical history and lifestyle. Hospital inpatients, persons who could not walk independently, and persons with recent inflammatory conditions, such as major trauma, surgery, or obvious acute infectious disease, were not included in the present study.

The study was approved by our institutional ethics committee, and all of the participants provided their written informed consent.

2.2. Risk factor definitions

The presence of baseline cardiovascular risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, obesity, and smoking, was determined. Hypertension was defined as at least one of: systolic blood pressure ≥140 mmHg; a diastolic blood pressure ≥90 mmHg; or current antihypertensive therapy. Diabetes mellitus was defined as a history of a random blood glucose level ≥200 mg/dL or an HbA1c level ≥6.5% or current anti-diabetic therapy. Dyslipidemia was defined as a total cholesterol level ≥240 mg/dL or high density lipoprotein cholesterol level <40 mg/dL or current cholesterol-lowering therapy. Obesity was defined as a body mass index ≥25.0 kg/m^2. The estimated glomerular filtration rate (eGFR) was calculated using the modified equation of the Modification of Diet in Renal Disease (MDRD) study [8].

An electrocardiogram was not done in 225 males (2.8%). Body height or body weight was missing in 10 males, and blood pressure data were missing in 2 males. These participants were considered to have no risk factors such as atrial fibrillation, obesity, or hypertension if they had no history of atrial fibrillation or hypertension.

2.3. Blood samples and hs-CRP measurement

Blood samples were collected from an antecubital vein. The samples were collected into vacuum tubes containing EDTA or a serum separator gel (CRP, lipids). After sampling, tubes were stored immediately in an icebox and centrifuged at 1500 × *g* for 10 min within 8 h of collection. Aliquots of serum were stored at −20 °C, and routine hematology and biochemistry tests, including hs-CRP, were done within a few days after blood sampling. hs-CRP levels were determined using a highly sensitive immunonephelometric method with a coefficient of variation <5% (N Latex CRP, Dade Behring). The detection limit of CRP assay is 0.1 mg/L, and cases with levels below the limit of detection were considered as 0.1 mg/L.

2.4. Outcome measures

In this cohort study, the primary endpoint was all-cause death, as well as any non-fatal cardiovascular events, such as myocardial infarction, cerebral infarction, or other strokes. The dates of death and move-out were confirmed by the investigators reviewing population-register sheets in each local government. Persons who were known to be alive at the end of follow-up and those who had moved away from the study area were treated as censored cases.

Stroke events were identified by accessing the Iwate prefecture stroke registration program, which included the entire area where the subjects lived; details of this registry have been described previously [9]. Since 1991, the stroke registration program has been coordinated by the Iwate prefecture government and the Iwate Medical Association; the medical records of all medical facilities within the survey area are verified to ensure complete capture of all data. Incidents of acute myocardial infarction were identified by accessing data from the Northern Iwate Heart Disease Registry Consortium, which has been collecting data since 2002. The registration of acute myocardial infarction and sudden death was based on the criteria of the MONICA study [10]. To verify the accuracy of the data, a physician or trained research nurse visited and checked the medical records of the referral hospitals.

Females were excluded from the analysis due to a low incidence of ischemic stroke events (59 events in 15,457 females; 0.4%). For the same reason, coronary heart disease events (non-fatal myocardial infarction, 34 events in 7901 males; 0.4%) were also not analyzed.

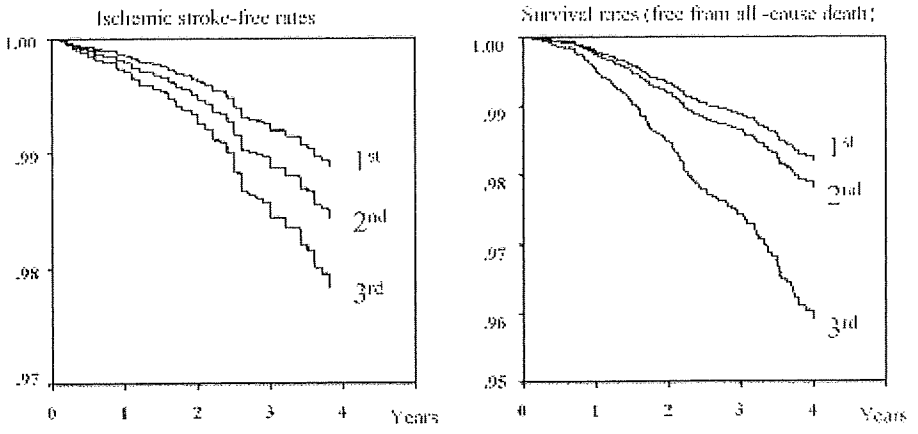

Fig. 1. Cumulative ischemic stroke-free rates and survival rates by age-adjusted Cox regression model for hs-CRP tertiles.

Table 1
Baseline clinical characteristics of all subjects with and without endpoints

	Ischemic stroke			All-cause death		
	(−)	(+)	p	(−)	(+)	p
No. of subjects	7806	95		7740	161	
Age (years)	63.9 ± 9.7	69.6 ± 7.2	<0.001	63.9 ± 9.7	69.8 ± 7.8	<0.001
Body mass index (kg/m^2)	23.9 ± 2.9	23.6 ± 3.0	0.20	24.0 ± 2.9	22.9 ± 3.0	<0.001
Systolic blood pressure (mmHg)	131 ± 19	139 ± 20	<0.001	131 ± 19	132 ± 20	0.31
Diastolic blood pressure (mmHg)	79 ± 11	80 ± 11	0.31	79 ± 11	76 ± 10	0.006
Hemoglobin A1c (%)	5.15 ± 0.74	5.28 ± 0.83	0.09	5.15 ± 0.74	5.30 ± 0.98	0.052
Serum creatinine (mg/dL)	0.82 ± 0.20	0.85 ± 0.16	0.15	0.82 ± 0.19	0.88 ± 0.42	0.18
eGFR (mL/min/1.73 m^2)	73.4 ± 15.1	69.2 ± 13.5	0.006	73.4 ± 15.0	70.2 ± 18.0	0.004
Uric acid (mg/dL)	5.73 ± 1.35	5.45 ± 1.51	0.038	5.72 ± 1.35	5.95 ± 1.59	0.16
Total cholesterol (mg/dL)	191 ± 32	188 ± 35	0.15	192 ± 32	181 ± 35	0.001
Triglyceride (mg/dL)	126 ± 84	123 ± 85	0.41	126 ± 84	121 ± 81	0.39
LDL-cholesterol (mg/dL)	114 ± 29	112 ± 31	0.25	114 ± 29	107 ± 32	0.023
HDL-cholesterol (mg/dL)	56 ± 15	56 ± 16	0.90	56 ± 15	53 ± 17	0.002
hs-CRP (mg/L)	0.54	0.80	<0.001	0.55	1.07	<0.001
Hypertension (%)	45.6	67.4	<0.001	45.7	54.0	0.038
Diabetes mellitus (%)	7.7	11.6	0.17	7.6	14.3	0.004
Dyslipidemia (%)	21.6	18.9	0.61	21.4	26.1	0.17
Obesity (%)	33.3	33.7	0.91	33.5	26.1	0.052
Atrial fibrillation (%)	2.6	15.8	<0.001	2.7	6.2	0.013
Current/past smoking (%)	62.2	75.8	0.007	62.2	68.9	0.085

hs-CRP, high sensitivity C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR: estimated glomerular filtration rate.
Log-transformed values were used for comparisons of CRP levels.
Data are shown as mean ± S.D. hs-CRP are shown as geometric mean.

2.5. Statistical analysis

The cumulative survival curves (free of ischemic stroke or free of all-cause death) by hs-CRP tertile levels were determined according to the age-adjusted Cox model (Fig. 1). The proportionality assumptions of the hazard by hs-CRP tertile were verified by log minus log curves. To determine the relative risks for each hs-CRP tertile level, multivariate Cox proportional hazard models were used. Age and known cardiovascular risk factors were used, and age (10-year increase), systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, uric acid, estimated glomerular filtration rate, body mass index, smoking, and presence of diabetes were forced into the multivariate adjusted model. One rural community (n = 728) was excluded from multivariate analysis because of missing data for serum uric acid, and cases having other missing data as random phenomena were also excluded. This multivariate analysis was finally performed for 7127 subjects. The results are expressed as the hazard ratio (HR) and the corresponding 95% confidence interval (CI). The analyses were performed using the SPSS statistical package, version 11.0.

3. Results

The mean follow-up period was 2.7 years. During follow-up, 130 subjects (1.6%) had a first stroke. Of these, 95 (1.2%) had an ischemic stroke; 161 (2.0%) died due to any cause; and 34 (0.4%) had a new onset, non-fatal myocardial infarction (MI). All of the non-ischemic strokes were the result of intracerebral or subarachnoid hemorrhages.

Baseline characteristics of the participants with and without ischemic stroke or all-cause death are shown in Table 1. Age, systolic and diastolic blood pressures, serum creatinine level, the prevalence of hypertension, atrial fibrillation, and smoking were higher in those with ischemic stroke than in those without. On the other hand, eGFR was lower in those with ischemic stroke than in those without. Similar results were obtained with respect to all-cause death. Some paradoxical relationships were found with respect to the uric acid level in participants with ischemic stroke, and the total cholesterol level and LDL level in those with all-cause death (Table 1).

The median serum hs-CRP level was 0.5 mg/L (95 percentile range: 0.1–4.3 mg/L) in males. This median hs-CRP level was lower than the levels reported in other populations in which hs-CRP levels were measured using the same assay methodology [1–3]. A total of 917 participants showed CRP levels ≤0.1 mg/L. Overall tertile ranges for the hs-CRP levels were: 1st, 0.1–0.3; 2nd, 0.4–0.7; and 3rd, ≥0.8 mg/L. Participants showing CRP > 10.0 mg/L comprised 1.7% of the study population. However, presence of acute infectious condition cannot be judged by CRP level alone, so making a cut-off level for infection is not possible. We therefore ventured to perform analyses without any exclusion criteria for high CRP level.

Table 2
Hazard ratios for first ischemic stroke and all-cause death by hs-CRP tertile levels

	hs-CRP tertile	Incidence of events/no. of subjects, n (%)	Age adjusted hazard ratios (95% CI)	p	Multivariate adjusted hazard ratios (95% CI)[a]	p
Ischemic stroke	1	22/2922 (0.75)	1.00 (reference)		1.00 (reference)	
	2	28/2296 (1.22)	1.41 (0.80–2.48)	0.24	1.30 (0.72–2.33)	0.39
	3	45/2683 (1.68)	1.95 (1.17–3.25)	0.010	1.77 (1.04–3.03)	0.037
All-cause death	1	36/2922 (1.23)	1.00 (reference)		1.00 (reference)	
	2	37/2296 (1.61)	1.22 (0.77–1.93)	0.40	1.15 (0.71–1.88)	0.57
	3	88/2683 (3.28)	2.32 (1.57–3.42)	<0.001	2.26 (1.49–3.42)	<0.001

hs-CRP, high sensitivity C-reactive protein; CI, confidence interval.
[a] Age (10-year increase), systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, uric acid, estimated glomerular filtration rate, body mass index, smoking (current and past), and the presence of diabetes were forced into the Cox regression analysis model.

As shown in Fig. 1, first ischemic stroke-free survival was lower in the higher hs-CRP tertile level when adjusted for age ($p = 0.034$). Similar results were observed for all-cause death-free survival rates ($p < 0.001$). The proportionality assumptions of the hazard by hs-CRP tertiles for these outcomes were satisfied.

In the multivariate Cox regression analysis model adjusted by age, a significantly increased hazard ratio of ischemic stroke was found in the 3rd hs-CRP tertile (HR = 1.95, $p = 0.010$) compared to the 1st hs-CRP tertile. After adjustment for age (10-year increase) and other classical cardiovascular risk factors, such as systolic and diastolic blood pressures, total cholesterol, high density lipoprotein cholesterol, uric acid, eGFR, BMI, smoking (current and past), and the presence of diabetes, the estimated HRs were maintained in the 3rd hs-CRP tertiles (HR = 1.77, $p = 0.037$). The results of the analysis of all-cause death were similar (Table 2). When the presence of atrial fibrillation was included in the multivariate adjusted model for ischemic stroke, the statistical significance of the hs-CRP tertiles declined (3rd hs-CRP tertile, HR = 1.56, $p = 0.10$).

On the other hand, there was no significant association between the hs-CRP tertiles and strokes from any causes (trend $p = 0.19$) in the model adjusted by age and other classical cardiovascular risk factors.

4. Discussion

This prospective cohort study found that baseline serum hs-CRP level was an independent predictor for future ischemic stroke and all-cause mortality in an apparently healthy population. It is interesting that these results were obtained in the Japanese population, which has a lower median hs-CRP level than Western populations [4,5].

The major risk factors for stroke and cardiovascular disease, such as smoking, diabetes, and hypertension, are associated with higher hs-CRP levels [11,12]. These relationships could potentially explain the associations that have been found between hs-CRP level and stroke or mortality. However, since adjustment for such risk factors did not have a large effect on the associations, the traditional risk factors cannot completely explain the relationship between the hs-CRP level and ischemic stroke events.

Carotid plaque formation is a well-established predictor for future ischemic stroke in the general population [13,14]. Our previous data showed a close association between the hs-CRP level and the severity of carotid atherosclerosis as demonstrated by plaque formation in men [6]. The present prospective results show that future stroke events were related to elevated baseline hs-CRP levels; this finding appears to substantiate our previous cross-sectional data. Although a significant association between the hs-CRP level and carotid atherosclerosis was only seen in men in our previous data, the present study could not demonstrate a gender difference for the association between hs-CRP level and the study endpoint.

Atrial fibrillation has been known to be closely related with ischemic stroke due to cardiac thromboembolism. In the present study, the presence of atrial fibrillation was the strongest predictor for ischemic stroke in the same model of multivariate Cox regression analysis with various risk factors (HR = 5.13, 95% CI; 2.82–9.35, $p < 0.001$). It is considered natural that the significance of the hs-CRP tertiles declined when the presence of atrial fibrillation was included in the multivariate adjusted model for ischemic stroke.

In the present cohort, the association between elevated hs-CRP level and stroke was only present when the analysis was limited to the ischemic stroke subtype. In the present study's subjects, all non-ischemic strokes were intracranial hemorrhages, which are known to be caused by rupture of cerebral perforating arteries or an intracranial aneurysm. These pathological conditions develop primarily due to hypertension and small artery hyalinosis [15]. The relationship between cerebral aneurysm and atherosclerosis is not considered to be very strong [16]. Few large-scale prospective cohort studies have addressed stroke subtype.

The major results of our study are completely consistent with the findings of the Hisayama Study [7]. Although the novelty of our study may be lacking, we would raise some unique minor points of difference from the findings and design of the Hisayama Study. First, the presence of atrial fibrillation reduced the predictive power of CRP for ischemic stroke in our study. Second, hs-CRP measurement at baseline was planned a priori and the assay was performed immediately, without long-term cryopreservation. Third, registration of our study population was started in 2002. Compared with the survey in 1988 of the Hisayama study, many new anti-atherosclerotic agents such as strong statins, long-acting anti-hypertensive agents and angiotensin-receptor blockers were likely to be in more frequent use in our study population. Furthermore, our study population comprised older, more obese subjects compared with those in Hisayama Study. All of these characteristics are thought to represent a closer fit with modern Japanese society and community population.

It is possible that the hospital-based follow-up used in the present study was not completely reliable for detecting clinical events. However, an attempt was made to retrieve and view all medical charts from all hospitals and clinics located in the survey area, and the study included several remote teaching hospitals and tertiary referral medical centers. Furthermore, the population of the study district has been stable, with an annual variation rate of only 0.2%. Moreover, participants who developed cerebrovascular and cardiovascular diseases or fatal events had access to only a limited number of medical institutes. Therefore, most major clinical adverse events were likely to have been captured in the present study cohort.

Elevated hs-CRP levels did not reflect the presence of imminent diseases from which stroke events or all-cause deaths had not yet occurred, since the interval between baseline hs-CRP measurement and the ischemic stroke event or death was relatively long: a mean of 1.8 years for ischemic stroke events and a mean of 1.9 years for all-cause death.

Some study limitations should be noted. The results of this study are based on one baseline hs-CRP measurement. Subjects who had recent acute inflammatory conditions, other than a mild "common cold", were not included in the study. However, the subjects were not examined to determine whether any chronic infections, including silent infections such as periodontitis, bladder cystitis, and chronic bronchitis, were present. Chronic infections have been known to have a relationship with carotid atherogenesis [17]. The present study did not assess the use of drugs that can lower hs-CRP levels, such as rennin–angiotensin system inhibitors [18,19], statins [20], and thiazolidinedione [21]. However, it was unlikely that the frequency of the use of these medications was higher in event-free participants. Although imaging was used to verify all stroke cases who visited the hospital with typical symptoms of neurological deficit, patients with events who were not hospitalized or those who were hospitalized at hospitals located outside the area could not be captured in this study design. However, this occurred very infrequently. Finally, this study tested several possible outcomes, including stroke and coronary heart disease in each gender, and then reported the significant findings. The possibility thus remains that chance findings were responsible for the present results.

In conclusion, CRP levels can predict future ischemic stroke and mortality in Japanese males from the general population, independently from traditional cardiovascular risk factors other than atrial fibrillation.

Conflict of interest

The authors report no conflicts of interest.

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