Hypertension Research (2012) 35, 1087–1092

www.nature.com/hr

ORIGINAL ARTICLE

Serum uric acid is an independent risk factor for cardiovascular disease and mortality in hypertensive patients

Tatsuo Kawai, Mitsuru Ohishi, Yasushi Takeya, Miyuki Onishi, Norihisa Ito, Koichi Yamamoto, Kei Kamide and Hiromi Rakugi

The purpose of the study was to investigate the association of serum uric acid (UA) levels in hypertensive patients with the prognosis for cardiovascular disease (CVD) and mortality. This hospital-based cohort study included 669 patients with essential hypertension. A questionnaire was used to identify patients in whom hypertensive complications had occurred, as well as causes of death. The primary end point of this study was new onset of stroke or CVD (new onset of angina pectoris, myocardial infarction or heart failure). We evaluated the baseline characteristics of patients, including UA levels, and assessed whether UA levels could be used to predict stroke and CVD. We also classified subjects into four groups according to the serum UA levels. During a mean follow-up period of 7.1 ± 0.1 years, 71 strokes, 58 cases of CVD and 64 deaths were recorded. Kaplan–Meier analysis revealed that subjects in the high UA group had a higher frequency of stroke and CVD ($P = 0.0120$) and total mortality ($P = 0.0021$). A Cox proportional hazard model determined that, after adjusting for traditional risk factors, serum UA levels were predictive of CVD (relative risk = 1.30; $P = 0.0073$), stroke and CVD (relative risk = 1.19; $P = 0.0141$), mortality (relative risk = 1.23; $P = 0.0353$) and stroke CVD and mortality (relative risk = 1.19; $P = 0.0083$), but not stroke ($P = 0.4268$). The significant correlations were particularly marked in women. Serum UA levels may be an independent risk factor for stroke and CVD in patients with essential hypertension, particularly women.
Hypertension Research (2012) **35,** 1087–1092; doi:10.1038/hr.2012.99; published online 28 June 2012

Keywords: cardiovascular disease; mortality; prognosis; uric acid

INTRODUCTION

Cardiovascular disease (CVD) is one of the most severe complications of hypertension,[1–5] and many risk factors are reported to be associated with cardiovascular events in hypertensive patients. Uric acid (UA) is one of the risk factors for CVD in hypertensive patients.[6,7] Previous meta-analyses revealed that hyperuricemia may marginally increase the risk of coronary heart disease events, independent of traditional coronary heart disease risk factors,[8] and that hyperuricemia may modestly increase the risks of both stroke incidence and mortality.[9] In addition, the results of several studies indicate that a higher incidence of CVD occurs not only in patients with 'hyperuricemia' but also in patients with normal-to-high serum UA levels.[10–12]

In contrast, some multivariate analyses have not shown that the serum UA level is a significant risk factor for CVD, independent of traditional risk factors.[13–15] One of the reasons proposed for this finding is that subjects with high CVD risk often also have conditions that affect the serum UA level, such as renal dysfunction, hyperinsulinemia, oxidative stress, tissue ischemia and taking diuretics for hypertension.[16,17] Moreover, UA can act as an antioxidant; thus, some studies have indicated that UA might have a beneficial effect on CVD.[18,19] These factors could affect the correlation between serum UA levels and CVD, which is therefore not fully understood and still controversial.

In this study, to investigate whether the possible confounding effects described above have an effect on the association between UA and CVD, we performed a longitudinal and prospective analysis of a cohort of essential hypertension patients and evaluated various factors, including biochemical and physiological measurements, usage of antihypertensive agents, complicating disorders and lifestyle. We then assessed the hypothesis that serum UA levels are an independent predictor of CVD and mortality in hypertensive patients.

METHODS

Study subjects and study design

The present hospital-based cohort study was designed as part of the Non-invasive Atherosclerotic evaluation in Hypertension study.[20] In this study, a total of 774 serial outpatients who had been diagnosed with essential hypertension were sequentially recruited between January 1998 and June 2004 at Osaka University Medical Hospital. Out of the 774 patients, 34 were

Department of Geriatric Medicine and Nephrology, Osaka University Graduate School of Medicine, Suita, Japan
Correspondence: Dr M Ohishi, Department of Geriatric Medicine and Nephrology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka (B6), Suita 565-0871, Japan.
E-mail: ohishi@geriat.med.osaka-u.ac.jp
Received 23 March 2012; revised 16 April 2012; accepted 1 May 2012; published online 28 June 2012

excluded because of arterial fibrillation, 6 were excluded because of malignant disease and 23 were excluded because of incomplete evaluation for UA. A clinical survey was conducted for each patient, and 42 were excluded because of lack of follow-up. Thus, a total of 669 patients were included in the analysis (Figure 1). The study protocol was approved by the hospital ethics committee, and written informed consent was obtained from all participants.

Follow-up evaluation

Clinical follow-up was conducted by clinical visits, mailed questionnaires and telephone contacts every September from 2003 to 2010. The questionnaire included events related to hypertensive complications and cause of death. We also confirmed the responses of each patient in detail by checking them against patient medical sheets. The primary end point of this study was new onset of stroke (paralysis and diagnosis with computed tomography and/or magnetic resonance imaging), new onset of CVD, including angina pectoris (typical chest pain with ST segment changes on electrocardiograms), myocardial infarction (ST segmental elevation with more than two-fold elevation of creatinine kinase), heart failure (diagnosed using American Heart Association criteria) and rupture of an aortic aneurysm (diagnosed employing ultrasound echography or computed tomography). The follow-up duration was considered to encompass the interval from the initial evaluation to the time of event onset or September 2010. The average follow-up period was 7.1 ± 0.1 years and the follow-up ratio was 93.5%.

Blood pressure (BP) measurements

Conventional BP measurements were performed by trained observers with an electronic sphygmomanometer (HEM-705IT or HEM-711; OMRON, Tokyo, Japan). Following the guidelines for the management of hypertension in Japanese Society of Hypertension 2009, clinic BP was measured at least two times in a sitting position after 5 min of rest; we used the average of the two readings as the official BP if the difference in the measured values was <5 mmHg. When the difference in the measured values was >5 mmHg, additional measurements were conducted to obtain stable BP readings, and we adopted the average of the two stable readings as the official BP.

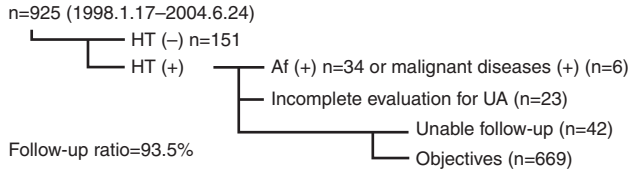

Figure 1 Flow chart of the selection process of study participants.

Renal function. Estimated glomerular filtration rate was calculated using the following equation:

$$\mathrm{eGFR}\left(\mathrm{ml\,min^{-1}1.73\,m^{-2}}\right) = 194\times\mathrm{creatinine}-1.094 \times\mathrm{age}-0.287\ (\times 0.739 \text{ if female}).$$

Pulse wave velocity (PWV) measurement

We evaluated carotid–femoral PWV (cfPWV) as a representative PWV to evaluate arterial stiffness. For the cfPWV measurements, participants visited the hospital in the morning; they were instructed not to take any antihypertensive drugs, nitrate or aspirin for 8 h preceding their visit. Measurements were performed in the morning with each patient in the supine position after 30 min of rest. cfPWV measurement was performed in a controlled environment at 22 ± 2 °C. Three measurements taken 2 min apart were averaged. The intra-observer coefficient of variation was calculated using three measurements from each of seven healthy men. The intra-observer coefficient of variation for cfPWV was 2.8 ± 1.2%.

We determined cfPWV using a model FCP-4731 (Fukuda Denshi, Tokyo, Japan), which allows on-line pulse wave recording and automatic calculation, using a previously reported method.[21]

Statistical analysis

Data were analyzed using JMP ver. 9.0.1 (SAS, Cary, NC, USA) and are presented as the mean ± s.e.m. An event-free curve was estimated employing the Kaplan–Meier method. The log-rank test was used to compare the differences in event-free rates among subjects who were placed into four groups according to their UA level. Cox proportional hazard models were used to detect the relative risk of UA with regard to the prognoses. Analysis of variance and Student's *t*-test were used to test for significant differences between patients with higher and lower variability in systolic BP. A value of $P<0.05$ was regarded as statistically significant.

Table 1 Baseline clinical characteristics of the study participants

		UA				
	Total	*Low*	*Middle-Low*	*Middle-High*	*High*	P-*value*
Number	669	440	142	60	27	
Sex (M/F)	369/300	203/237	93/49	53/7	20/7	<0.0001
Age (year)	61.9 ± 0.5	62.4 ± 0.6	61.2 ± 1.0	60.1 ± 1.6	62.3 ± 2.6	0.4500
BMI ($kg\,m^{-2}$)	24.2 ± 0.1	23.9 ± 0.2	24.5 ± 0.3	24.9 ± 0.5	26.4 ± 0.8	0.0004
Diabetes mellitus (*n*, %)	147 (22.0%)	103 (23.4%)	34 (23.9%)	5 (8.3%)	5 (18.5%)	0.0563
Dyslipidemia (*n*, %)	354 (53.0%)	237 (54.0%)	71 (50.0%)	32 (53.3%)	14 (51.9%)	0.8729
Current smoker (*n*, %)	163 (24.9%)	100 (23.2%)	36 (26.1%)	18 (30.5%)	9 (34.6%)	0.2728
Systolic blood pressure (mmHg)	140.1 ± 0.7	140.0 ± 0.9	140.0 ± 1.4	142.5 ± 2.6	141.5 ± 3.9	0.7163
Diastolic blood pressure (mmHg)	82.5 ± 0.5	81.9 ± 0.6	82.6 ± 1.0	86.9 ± 1.5	81.7 ± 2.7	0.0258
Total cholesterol ($mg\,dl^{-1}$)	204.8 ± 1.3	204.9 ± 1.7	204.6 ± 2.7	204.6 ± 4.4	206.4 ± 6.4	0.9955
Triglyceride ($mg\,dl^{-1}$)	146.5 ± 3.6	134.1 ± 3.8	173.8 ± 8.6	154.5 ± 16.0	186.4 ± 18.7	<0.0001
HDL cholesterol ($mg\,dl^{-1}$)	56.3 ± 0.7	58.0 ± 0.8	52.8 ± 1.3	53.0 ± 2.3	53.9 ± 3.3	0.0045
Creatinine ($mg\,dl^{-1}$)	0.87 ± 0.02	0.82 ± 0.03	0.90 ± 0.02	1.00 ± 0.03	1.20 ± 0.18	0.0008
eGFR ($ml\,min^{-1}\,1.73m^{-2}$)	70.3 ± 0.9	73.2 ± 1.1	66.5 ± 1.7	62.6 ± 2.3	59.6 ± 4.8	<0.0001
UA ($mg\,dl^{-1}$)	5.5 ± 0.1	4.7 ± 0.0	6.4 ± 0.0	7.4 ± 0.0	9.0 ± 0.2	<0.0001
Fasting blood sugar ($mg\,dl^{-1}$)	108.4 ± 1.4	109.2 ± 1.9	106.7 ± 2.3	104.6 ± 3.3	111.3 ± 6.1	0.7285
HbA1c (%)	5.6 ± 0.1	5.7 ± 0.1	5.5 ± 0.1	5.2 ± 0.1	5.3 ± 0.2	0.0493
PWV ($m\,sec^{-1}$)	9.0 ± 0.1	9.0 ± 0.1	9.1 ± 0.2	9.1 ± 0.2	9.4 ± 0.3	0.7010

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; F, female; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; M, male; PWV, pulse wave velocity; UA, uric acid.
Values are expressed as mean ± s.e.m. or numbers.

RESULTS

During a mean follow-up period of 7.1 ± 0.1 years, 71 strokes, 58 cases of CVD, 117 cases of stroke + CVD, 64 deaths and 156 cases of stroke + CVD + death were recorded. Baseline clinical characteristics are shown in Table 1. We classified the subjects into four groups according to serum UA levels: $>8.0\,mg\,dl^{-1}$, high ($n=27$); 7.0–8.0 $mg\,dl^{-1}$, middle-high ($n=60$); 6.0–7.0 $mg\,dl^{-1}$, middle-low ($n=142$); and $<6.0\,mg\,dl^{-1}$, low ($n=440$). We then compared various parameters among these four groups. Subjects with higher UA levels showed significantly higher male-to-female ratio; to have a

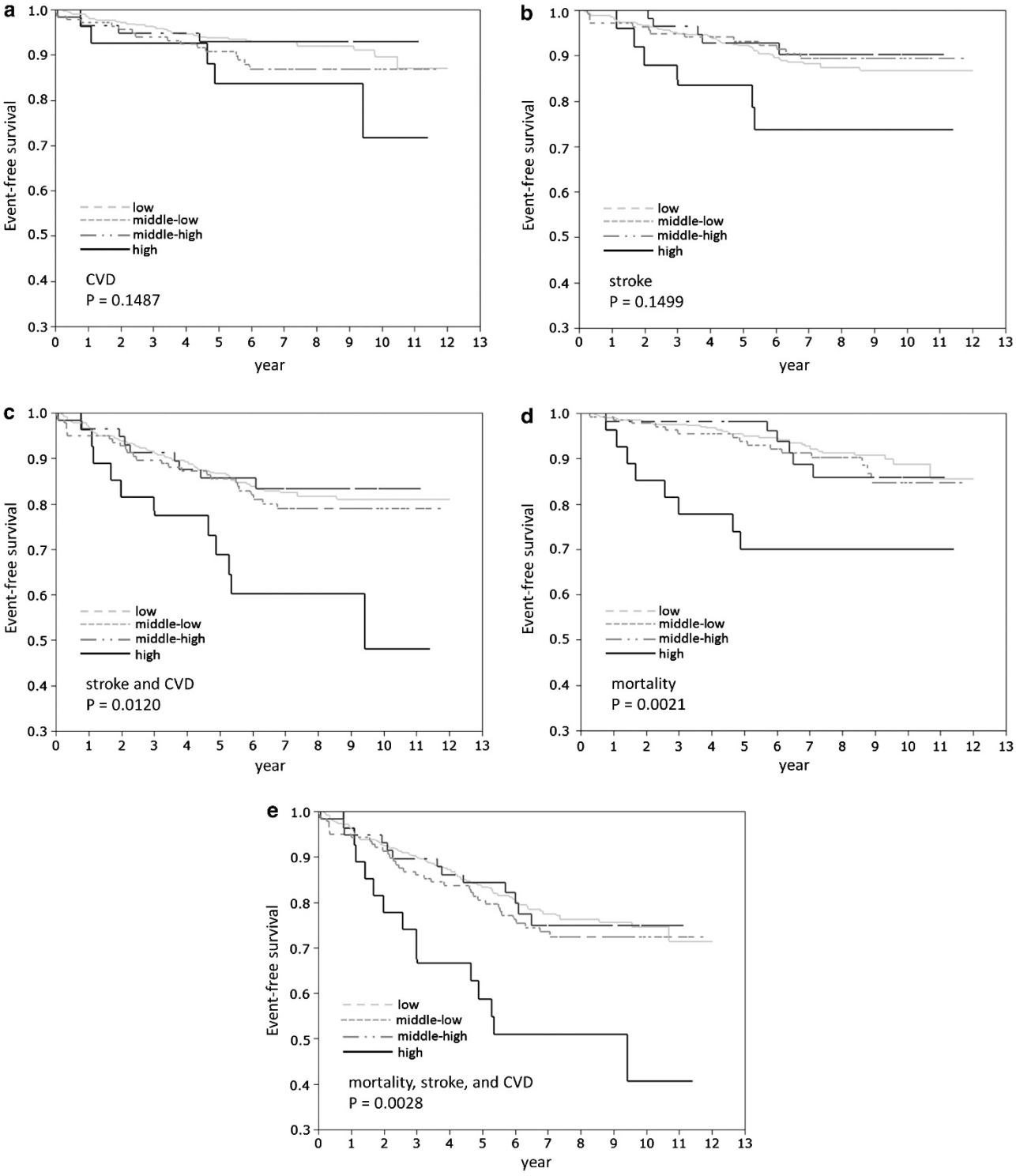

Figure 2 Kaplan–Meier analysis of occurrence of CVD (**a**); stroke (**b**); stroke and CVD (**c**); mortality (**d**); and mortality, stroke and CVD (**e**) among the four groups of patients sorted by UA level (low, middle-low, middle-high and high).

Table 2 Cox proportional hazard models adjusted for gender, BMI, DBP, creatinine, HDL cholesterol, triglyceride and HbA1c

	CVD		*Stroke*		*CVD and stroke*		*Mortality*		*Mortality, CVD and stroke*	
	Relative risk	P-*value*	*Relative risk*	P-*value*	*Relative risk*	P-*value*	*Relative risk*	P-*value*	*Relative risk*	P-*value*
(a)										
Model 1										
Gender (male)	0.4409	0.0281	1.3876	0.3494	0.7977	0.3985	2.4058	0.0172	1.0676	0.7758
BMI ($kg\,m^{-2}$)	1.0111	0.8390	1.0066	0.8949	1.0009	0.9818	0.8800	0.0088	0.9522	0.1315
DBP (mmHg)	0.9699	0.0588	1.0090	0.5450	0.9883	0.3068	0.9864	0.3618	0.9892	0.2674
Triglyceride ($mg\,dl^{-1}$)	1.0001	0.9638	0.9983	0.4558	0.9994	0.7225	0.9982	0.4485	0.9988	0.4162
HDL cholesterol ($mg\,dl^{-1}$)	0.9739	0.0760	0.9889	0.3746	0.9809	0.0566	0.9835	0.1433	0.9801	0.0156
Creatinine ($mg\,dl^{-1}$)	1.1398	0.6482	0.9127	0.7531	0.9617	0.8570	1.3956	0.0150	1.2652	0.0434
HbA1c (%)	1.3269	0.0291	1.1385	0.2901	1.2252	0.0308	1.1101	0.4190	1.1262	0.1607
UA group	1	0.0570	1	0.2978	1	0.0420	1	0.0581	1	0.0096
Middle-low/low	2.6179		0.8599		1.6202		1.2259		1.4773	
Middle-high/low	2.3497		0.5437		1.2709		1.0649		1.0352	
High/low	4.3191		3.1884		4.3871		5.4835		4.5181	
(b)										
Model 2										
Gender (male)	0.4311	0.0244	1.1312	0.4482	0.7647	0.2788	2.2690	0.0274	0.9897	0.9644
BMI ($kg\,m^{-2}$)	0.9946	0.9206	1.0240	0.6414	1.0036	0.9258	0.8852	0.0160	0.9560	0.1739
DBP (mmHg)	0.9694	0.0541	1.0069	0.6444	0.9864	0.2321	0.9846	0.3099	0.9869	0.1786
Triglyceride ($mg\,dl^{-1}$)	1.0005	0.8433	0.9985	0.5105	0.9997	0.8463	0.9988	0.5926	0.9992	0.5611
HDL chol ($mg\,dl^{-1}$)	0.9737	0.0700	0.9918	0.5104	0.9820	0.0703	0.9859	0.2128	0.9818	0.0274
Creatinine ($mg\,dl^{-1}$)	1.1064	0.7020	0.9938	0.9837	0.9975	0.9905	1.4276	0.0092	1.2712	0.0384
HbA1c (%)	1.3437	0.0222	1.1367	0.3095	1.2300	0.0288	1.0963	0.4883	1.1336	0.1450
UA ($mg\,dl^{-1}$)	1.3581	0.0149	1.0078	0.9555	1.2258	0.0332	1.1853	0.1768	1.2002	0.0315

Abbreviations:BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; UA, uric acid.
Model 1: UA treated as a group variable and Model 2: UA treated as a continuous variable.

higher body mass index (BMI) and triglyceride and serum creatinine levels; and to have lower high-density lipoprotein cholesterol levels and diastolic BP. Subjects with lower UA levels had significantly higher concentrations of hemoglobin A1c and a higher estimated glomerular filtration rate (Table 1). There was no correlation between UA levels and systolic BP or cfPWV representing arterial stiffness. Chi-square analysis also revealed that patients in the high UA group were significantly more likely to be taking diuretics (high UA group: $n=5$, 19.2%; middle-high UA group: $n=6$, 10.0%; middle-low UA group: $n=16$, 11.4%; and low UA group: $n=25$, 5.69%; $P=0.0162$). There was no significant correlation between the serum UA level and other classes of antihypertensive agents.

Kaplan–Meier analysis revealed that subjects in the high UA group had a higher frequency of stroke and CVD ($P=0.0120$; Figure 2c), total mortality ($P=0.0021$; Figure 2d) and mortality, stroke and CVD ($P=0.0028$; Figure 2e). On the other hand, there was no significant difference in CVD ($P=0.1487$; Figure 2a) and stroke ($P=0.1499$; Figure 2b) among the subjects in the four UA groups.

To further investigate, we used a Cox proportional hazard model to reveal whether the serum UA level could predict the onset of cardiovascular events or mortality, independent of other risk factors. First, we adjusted for gender, BMI, diastolic BP, serum creatinine, high-density lipoprotein cholesterol, tryglyceride and hemoglobin A1c, because these parameters were significantly correlated with UA in this cohort. Table 2a shows the results of the Cox proportional hazard model in which the UA level was treated as a group variable; the serum UA level was significantly and independently predictive of CVD and stroke ($P=0.0420$) and mortality, CVD and stroke ($P=0.0096$). Table 2b shows the results of the Cox proportional hazard model in which UA was treated as a continuous variable; the serum UA level was significantly and independently predictive of CVD (relative risk $=1.36$; $P=0.0149$), CVD and stroke (relative risk $=1.23$; $P=0.0332$), and mortality, CVD and stroke (relative risk $=1.20$; $P=0.0315$). Additionally, in a Cox proportional hazard model that adjusted for the usage of diuretics instead of diastolic BP, the serum UA level was significantly and independently predictive of cardiovascular events. A gender-segregated Cox proportional hazard model in which UA was treated as a continuous value revealed that in female subjects, the serum UA level was significantly and independently predictive of CVD (relative risk $=1.74$; $P=0.0043$), CVD and stroke (relative risk $=1.52$; $P=0.0055$), and mortality, CVD and stroke (relative risk $=1.46$; $P=0.0077$). However, in male subjects, the serum UA level was not predictive of CVD ($P=0.5507$), CVD and stroke ($P=0.5385$) or mortality, CVD and stroke ($P=0.9807$).

Finally, we conducted a Cox proportional hazard model in which we adjusted for gender, age, presence or absence of diabetes mellitus, presence or absence of dyslipidemia and systolic BP, because these parameters are widely recognized as traditional risk factors for cardiovascular events and mortality. Table 3a shows the results of the Cox proportional hazard model in which UA was treated as a group variable; the serum UA level was significantly and independently predictive of mortality ($P=0.0285$) and mortality, CVD and stroke ($P=0.0316$). Table 3b shows the results of the Cox proportional hazard model in which UA was treated as a continuous variable; the serum UA level was significantly and independently predictive of

Table 3 Cox proportional hazard models adjusted for traditional risk factors

	CVD		*Stroke*		*CVD and stroke*		*Mortality*		*Mortality, CVD and stroke*	
	Relative risk	P-*value*	*Relative risk*	P-*value*	*Relative risk*	P-*value*	*Relative risk*	P-*value*	*Relative risk*	P-*value*
(a)										
Model 1										
Gender (male)	0.8560	0.5855	1.4622	0.1432	1.1910	0.3897	3.1691	<0.0001	1.4830	0.0259
Age (year)	1.0685	<0.0001	1.0426	0.0003	1.0450	<0.0001	1.1084	<0.0001	1.0573	<0.0001
Diabetes mellitus	1.7963	0.0600	1.1353	0.6675	1.5104	0.0654	2.0935	0.0115	1.6077	0.0138
Dyslipidemia	1.0526	0.8507	1.6484	0.0482	1.3336	0.1369	0.7168	0.2048	1.1450	0.4175
SBP (mmHg)	1.0079	0.2878	1.0093	0.1678	1.0084	0.1063	1.0102	0.1315	1.0116	0.0087
UA group	1	0.1437	1	0.4352	1	0.1165	1	0.0285	1	0.0316
Middle-low/low	1.8063		0.8756		1.2402		1.3179		1.2387	
Middle-high/low	1.2492		0.7916		1.0807		0.9756		1.0225	
High/low	2.8248		2.1078		2.5959		5.4835		4.5181	
(b)										
Model 2										
Gender (male)	0.7689	0.3575	1.3627	0.2399	1.0888	0.6775	2.9534	0.0003	1.3646	0.0808
Age (year)	1.0687	<0.0001	1.0433	0.0003	1.0461	<0.0001	1.1077	<0.0001	1.0583	<0.0001
Diabetes mellitus	1.8982	0.0388	1.1561	0.6212	1.5407	0.0515	2.1963	0.0064	1.6453	0.0092
Dyslipidemia	1.0102	0.9703	1.6341	0.0521	1.2969	0.1795	0.7200	0.2082	1.1214	0.4929
SBP (mmHg)	1.0073	0.3213	1.0090	0.1815	1.0078	0.1342	1.0099	0.1412	1.0111	0.0121
UA ($mg\,dl^{-1}$)	1.3008	0.0073	1.0784	0.4268	1.1910	0.0141	1.2336	0.0353	1.1797	0.0083

Abbreviations: CVD, cardiovascular disease; SBP, systolic blood pressure; UA, uric acid.
Model 1: UA treated as a group variable and Model 2: UA treated as a continuous variable.

CVD (relative risk = 1.30; $P = 0.0073$); CVD and stroke (relative risk = 1.19; $P = 0.0141$), mortality (relative risk = 1.23; $P = 0.0353$), and mortality, CVD and stroke (relative risk = 1.18; $P = 0.0083$), but not stroke ($P = 0.4268$), after adjustment for traditional risk factors. A gender-segregated Cox proportional hazard model in which UA was treated as a continuous value revealed that in female subjects, serum UA levels were significantly and independently predictive of CVD (relative risk = 1.65; $P = 0.0002$), CVD and stroke (relative risk = 1.40; $P = 0.0023$), total mortality (relative risk = 1.71; $P = 0.0028$) and mortality, CVD and stroke (relative risk = 1.44; $P = 0.0002$). However, in male subjects, the serum UA level was not predictive of CVD ($P = 0.9950$), CVD and stroke ($P = 0.5773$), total mortality ($P = 0.6480$) or mortality, CVD and stroke ($P = 0.7342$).

DISCUSSION

Many studies have investigated the correlation between serum UA levels and CVDs such as coronary heart disease,[8] stroke[9] and chronic kidney disease.[22–24] Serum UA levels have also been reported to be correlated with metabolic syndrome[25] and diabetes mellitus.[26] However, various clinical conditions in subjects at high risk of CVD, such as renal dysfunction, hyperinsulinemia, oxidative stress and taking diuretics for hypertension, can have an effect on serum UA levels. Moreover, many studies have reported that elevated serum UA levels could cause hypertension.[27–29] The complex interactions between CVD risk and serum UA levels have made it difficult to interpret the results of previous studies.

As in previous studies, in this cohort study, subjects with higher serum UA levels had significantly higher BMIs, higher levels of triglycerides and serum creatinine and a higher rate of taking diuretics. However, there was no significant correlation between the serum UA level and systolic BP, because 59.3% of the subjects were already under medical treatment for hypertension. A Cox proportional hazard model showed that, after adjustment for confounding factors (that is, serum creatinine, BMI, hemoglobin A1c, dyslipidemia, diastolic BP and using diuretics) that were reported to be affected by serum UA levels in previous reports and were significantly correlated with serum UA levels in this study, serum UA levels were also a significant and independent risk factor for cardiovascular events.

Some studies have reported J-shaped relationships between the serum UA level and CVD or total mortality.[30–32] This was also the case in the present study; when UA was treated as a group variable, the Cox proportional hazard models showed that patients with middle-high UA levels had a lower relative risk than those with middle-low UA levels for cardiovascular events; however, other risk factors, such as BMI and triglyceride and serum creatinine levels, were correlated with the serum UA level in a linear fashion. Previous studies reported that increased UA levels might have a beneficial effect on CVD by serving as an antioxidant;[18,19] our results may support a beneficial effect of UA on CVD. To determine the optimal UA levels for preventing CVD, a larger cohort is required, as well as a longer period of follow-up.

Our findings revealed that the serum UA level was a significant and independent risk factor for cardiovascular events after adjustment for other traditional risk factors or confounding factors in female subjects, but not in male subjects. Females are known to show lower serum UA levels than males because of estrogenic compounds that enhance the renal urate excretion and increase urate clearance.[33] Our results support the findings of previous reports, suggesting that the correlation between hyperuricemia and CVD differs between the sexes.[34,35]

The present study has several limitations. First, the sample size in this study was relatively small; to avoid study bias and confirm the observations of this study, a larger cohort and multi-center trials are needed. Second, the subjects enrolled in this study were receiving medical treatment, such as angiotensin receptor type II blockers,

angiotensin-converting enzyme inhibitors and statins; these drugs may have contributed to better outcomes.

In conclusion, we have presented evidence that in patients with essential hypertension, especially women, the serum UA level is a significant and independent risk factor for cardiovascular events after adjusting for other traditional risk factors and confounding factors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank Ms Takako Baba and Ms Yuki Imaizumi for their excellent technical assistance. This study was funded by the Osaka Medical Research Foundation for Incurable Diseases.

1 Lloyd-Jones DM, Leip EP, Larson MG, Vasan RS, Levy D. Novel approach to examining first cardiovascular events after hypertension onset. *Hypertension* 2005; **45**: 39–45.
2 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective Studies Collaboration: age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–1913.
3 Pastor-Barriuso R, Banegas JR, Damián J, Appel LJ, Guallar E. Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. *Ann Intern Med* 2003; **139**: 731–739.
4 Pletcher MJ, Bibbins-Domingo K, Lewis CE, Wei GS, Sidney S, Carr JJ, Vittinghoff E, McCulloch CE, Hulley SB. Prehypertension during young adulthood and coronary calcium later in life. *Ann Intern Med* 2008; **149**: 91–99.
5 Lawes CM, Vander Hoorn S, Rodgers A. International Society of Hypertension: global burden of blood-pressure-related disease, 2001. *Lancet* 2008; **371**: 1513–1518.
6 Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008; **359**: 1811–1821.
7 Alderman MH. Serum uric acid as a cardiovascular risk factor for heart disease. *Curr Hypertens Rep* 2001; **3**: 184–189.
8 Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2010; **62**: 170–180.
9 Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. *Arthritis Rheum* 2009; **61**: 885–892.
10 Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. *Hypertension* 2003; **42**: 247–252.
11 Niskanen LK, Laaksonen DE, Nyyssönen K, Alfthan G, Lakka HM, Lakka TA, Salonen JT. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. *Arch Intern Med* 2004; **164**: 1546–1551.
12 Nakagawa T, Tuttle KR, Short RA, Johnson RJ. Fructose-induced hyperuricemia as a casual mechanism for the epidemic of the metabolic syndrome. *Nat Clin Pract Nephrol* 2005; **1**: 80–86.
13 Wannamethee SG, Shaper AG, Whincup PH. Serum urate and the risk of major coronary heart disease events. *Heart* 1997; **78**: 147–153.
14 Moriarity JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol* 2000; **10**: 136–143.
15 Wheeler JG, Juzwishin KD, Eiriksdottir G, Gudnason V, Danesh J. Serum uric acid and coronary heart disease in 9,458 incident cases and 155,084 controls: prospective study and meta-analysis. *PLoS Med* 2005; **2**: e76.
16 Cappuccio FP, Strazzullo P, Farinaro E, Trevisan M. Uric acid metabolism and tubular sodium handling: results from a population-based study. *JAMA* 1993; **270**: 354–359.
17 Quiñones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, Ferrannini E. Effect of insulin on uric acid excretion in humans. *Am J Physiol* 1995; **268**: E1–E5.
18 Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci US A* 1981; **78**: 6858–6862.
19 Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? *Atherosclerosis* 2000; **148**: 131–139.
20 Terai M, Ohishi M, Ito N, Takagi T, Tatara Y, Kaibe M, Komai N, Rakugi H, Ogihara T. Comparison of arterial functional evaluations as a predictor of cardiovascular events in hypertensive patients: the Non-Invasive Atherosclerotic Evaluation in Hypertension (NOAH) study. *Hypertens Res* 2008; **31**: 1135–1145.
21 Komai N, Ohishi M, Morishita R, Moriguchi A, Kaibe M, Matsumoto K, Rakugi H, Higaki J, Ogihara T. Serum hepatocyte growth factor concentration is correlated with the forearm vasodilator response in hypertensive patients. *Am J Hypertens* 2002; **15**: 499–506.
22 Iseki K, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. *Am J Kidney Dis* 2004; **44**: 642–650.
23 Iseki K, Oshiro S, Tozawa M, Iseki C, Ikemiya Y, Takishita S. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. *Hypertens Res* 2001; **24**: 691–697.
24 Tomita M, Mizuno S, Yamanaka H, Hosoda Y, Sakuma K, Matuoka Y, Odaka M, Yamaguchi M, Yosida H, Morisawa H, Murayama T. Does hyperuricemia affect mortality? A prospective cohort study of Japanese male workers. *J Epidemiol* 2000; **10**: 403–409.
25 Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. *Am J Med* 2007; **120**: 442–447.
26 Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. High serum uric acid as a novel risk factor for type 2 diabetes. *Diabetes Care* 2008; **31**: 361–362.
27 Alper Jr AB, Chen W, Yau L, Srinivasan SR, Berenson GS, Hamm LL. Childhood uric acid predicts adult blood pressure: the Bogalusa Heart Study. *Hypertension* 2005; **45**: 34–38.
28 Perlstein TS, Gumieniak O, Williams GH, Sparrow D, Vokonas PS, Gaziano M, Weiss ST, Litonjua AA. Uric acid and the development of hypertension: the Normative Aging Study. *Hypertension* 2006; **48**: 1031–1036.
29 Forman JP, Choi H, Curhan GC. Plasma uric acid level and risk for incident hypertension among men. *J Am Soc Nephrol* 2007; **18**: 287–292.
30 Hsu SP, Pai MF, Peng YS, Chiang CK, Ho TI, Hung KY. Serum uric acid levels show a 'J-shaped' association with all-cause mortality in haemodialysis patients. *Nephrol Dial Transplant* 2004; **19**: 457–462.
31 Mazza A, Zamboni S, Rizzato E, Pessina AC, Tikhonoff V, Schiavon L, Casiglia E. Serum uric acid shows a J-shaped trend with coronary mortality in non-insulin-dependent diabetic elderly people: the CArdiovascular STudy in the Elderly (CASTEL). *Acta Diabetol* 2007; **44**: 99–105.
32 Suliman ME, Johnson RJ, García-López E, Qureshi AR, Molinaei H, Carrero JJ, Heimbürger O, Bárány P, Axelsson J, Lindholm B, Stenvinkel P. J-shaped mortality relationship for uric acid in CKD. *Am J Kidney Dis* 2006; **48**: 761–771.
33 Antón FM, García Puig J, Ramos T, González P, Ordás J. Sex differences in uric acid metabolism in adults: evidence for a lack of influence of estradiol-17 beta (E2) on the renal handling of urate. *Metabolism* 1986; **35**: 343–348.
34 Longo-Mbenza B, Luila E, Mbete P, Vita E. Is hyperuricemia a risk factor of stroke and coronary heart disease among Africans? *Int J Cardiol* 1999; **71**: 17–22.
35 Lin K, Tsai S, Lin H, Chou P. Different progressions of hyperglycemia and diabetes among hyperuricemic men and women in the kinmen study. *J Rheumatol* 2004; **31**: 1159–1165.