Circ J 2009; **73:** 885–891

Elevated Serum Uric Acid is an Independent Predictor for Cardiovascular Events in Patients With Severe Coronary Artery Stenosis

—— Subanalysis of the Japanese Coronary Artery Disease (JCAD) Study ——

Takafumi Okura, MD; Jitsuo Higaki, MD; Mie Kurata, MD; Jun Irita, MD; Ken-ichi Miyoshi, MD; Tsutomu Yamazaki, MD*; Doubun Hayashi, MD**; Takahide Kohro, MD**; Ryozo Nagai, MD† for the JCAD Study Investigators

Background: The association of elevated serum uric acid (UA) with cardiovascular events in patients with severe coronary artery stenosis was examined.

Methods and Results: Patients with stenosis ≥75% (n=8,832) were followed for "all events" (cardiovascular events and all-cause mortality) for 3 years. The group was divided into quartiles based on baseline UA level. The incidence rate of all events was significantly different among quartiles (58.3, 56.5, 61.2, 76.3/1,000 patients-year, P<0.001). Cox's proportional hazard regression analysis showed that the hazard ratio (HR) for all events was 1.25 [95% confidence interval (CI): 1.07–1.45, P<0.01] in the highest quartile (UA ≥6.8 mg/dl). The group in which UA increased ≥1.0 mg/dl after 6 months had significantly higher cardiovascular events rate than the group in which UA did not change (70.6 vs 58.8/1,000 patients-year, P=0.042). Propensity score matching was performed and 4,206 patients were divided into the highest quartile and the rest. High UA remained an independent predictor of all events (HR 1.25, 95%CI 1.06–1.43). However, no significant difference was observed between the group with increased UA ≥1.0 mg/dl and the group with unchanged UA level.

Conclusions: Elevated UA is an independent predictor of cardiovascular events and all-cause mortality combined in patients with coronary artery stenosis. (*Circ J* 2009; **73:** 885–891)

Key Words: Cardiovascular events; JCAD study; Uric acid

Since Klein et al reported the relation between uric acid (UA) level and coronary artery disease (CAD) in 1973[1] the question of whether high UA is a risk factor for arteriosclerosis and CAD has remained controversial. Although a correlation between UA level and cardiovascular events was not observed in the Framingham study[2] it has been demonstrated in studies of hypertensive patients in the worksite[3] in the PIUMA[4] and SHEP studies[5] and in the Syst-China Trial[6] Moreover, it was recently reported that UA level may be a new predictor of atherosclerosis[7,8] In Japan, a study of an employee cohort[9] and a long-term follow-up survey of atomic bomb survivors[10] demonstrated that high UA was an independent predictor for cardiovascular disease. However, no study has been conducted on the correlation in patients with higher cardiovascular risk, such as CAD.

(Received August 28, 2008; revised manuscript received January 5, 2009; accepted January 6, 2009; released online March 31, 2009)
*Department of Integrated Medicine and Informatics, Ehime University Graduate School of Medicine, Ehime, *Department of Clinical Epidemiology and Systems, **Translational Research for Health Care and Clinical Science and †Cardiovascular Medicine, Graduate School of Medicine, Faculty of Medicine, The University of Tokyo, Tokyo, Japan*
Mailing address: Takafumi Okura, MD, Department of Integrated Medicine and Informatics, Ehime University Graduate School of Medicine, Toon, Ehime 791-0295, Japan. E-mail: okura@m.ehime-u.ac.jp

This study was a subanalysis of data from the Japanese Coronary Artery Disease Study[11] to examine whether elevated UA is an independent predictor of all events including cardiovascular events and all-cause mortality. The study was a 3-year follow-up of high-risk patients who had coronary artery stenosis ≥75% according to the classification of the American Heart Association.

Methods

Study Patients

A total of 13,812 patients who were diagnosed as having stenosis ≥75% (American Heart Association classification) by coronary angiography in at least 1 branch of the coronary arteries were enrolled in the Japanese Coronary Artery Disease Study between April, 2000 and March, 2001.

This subanalysis targeted 8,832 patients (6,781 men, 2,051 women; mean age 65.5±9.7 years) whose UA data were available at registration and after 6 months.

Study Design

The details of the Japanese Coronary Artery Disease Study have been published![11,12] Briefly, all follow-up data were collected in a database over the internet and all the information was entered by the study investigators. The information collected at registration consisted of medication, established CAD risk factors, the underlying condition,

Table 1. Baseline Characteristics of the Study Population

	0.5–4.7 mg/dl	4.8–5.7 mg/dl	5.8–6.7 mg/dl	6.8– mg/dl	All	P value
n	2,267	2,231	2,091	2,243	8,832	
Age (years)	66.4±9.4	65.8±9.5	64.9±10.0	64.8±10.1	65.5±9.7	<0.001
Sex, male (%)	1,367 (60.3%)	1,685 (75.5%)	1,755 (78.7%)	1,974 (88.5%)	6,781 (76.8%)	<0.001
Hypertension (%)	1,241 (54.7%)	1,290 (57.8%)	1,229 (55.1%)	1,400 (62.8%)	5,160 (58.4%)	<0.001
Hyperlipidemia (%)	1,197 (52.8%)	1,196 (53.6%)	1,212 (54.3%)	1,351 (60.6%)	4,956 (56.1%)	<0.001
IGT (%)	1,040 (45.9%)	915 (41.0%)	800 (35.9%)	924 (41.4%)	3,679 (41.7%)	<0.001
Obesity (%)	595 (26.2%)	691 (31.0%)	733 (32.9%)	861 (38.6%)	2,880 (32.6%)	<0.001
Smoking (%)	775 (34.2%)	861 (38.6%)	867 (38.9%)	985 (44.2%)	3,488 (39.5%)	<0.001
Drinking (%)	721 (31.8%)	862 (38.6%)	917 (41.1%)	985 (44.2%)	3,485 (39.5%)	<0.001
Familial history (%)	357 (15.7%)	369 (16.5%)	382 (17.1%)	408 (18.3%)	1,516 (17.2%)	0.0639
CHF (%)	175 (7.7%)	194 (8.7%)	180 (8.1%)	349 (15.6%)	898 (10.2%)	<0.001
LMT (%)	89 (3.9%)	101 (4.5%)	98 (4.4%)	112 (5.0%)	400 (4.5%)	0.3697
No. of stenoses (%)	1.76±0.79	1.77±0.79	1.81±0.81	1.85±0.80	1.80±0.80	0.0017
Statin (%)	889 (39.2%)	817 (36.6%)	775 (34.7%)	816 (36.6%)	3,297 (37.3%)	0.1830
Fibrates	52 (2.3%)	69 (3.1%)	86 (3.9%)	113 (5.1%)	320 (3.6%)	<0.001
α-1 blockers	36 (1.6%)	48 (2.2%)	61 (2.7%)	68 (3.0%)	213 (2.4%)	0.0044
α-β-blockers	237 (10.5%)	241 (10.8%)	254 (11.4%)	282 (12.6%)	1,014 (11.5%)	0.0750
Diuretics	250 (11.0%)	312 (14.0%)	323 (14.5%)	529 (23.7%)	1,414 (16.0%)	<0.001
CCB	1,152 (50.8%)	1,131 (50.7%)	1,094 (49.0%)	1,180 (52.9%)	4,557 (51.6%)	0.4512
β-blockers	431 (19.0%)	445 (19.9%)	432 (19.4%)	495 (22.2%)	1,803 (20.4%)	0.0751
ACEI	733 (32.3%)	674 (30.2%)	640 (28.7%)	742 (33.3%)	2,789 (31.6%)	0.1225
ARB	329 (14.5%)	318 (14.3%)	261 (11.7%)	316 (14.2%)	1,224 (13.9%)	0.2103
Uricosuric drugs	75 (3.3%)	31 (1.4%)	24 (1.1%)	31 (1.4%)	161 (1.8%)	<0.001
UA synthesis inhibitors	70 (3.1%)	99 (4.4%)	140 (6.3%)	303 (13.6%)	612 (6.9%)	<0.001
Warfarin	238 (10.5%)	222 (10.0%)	205 (9.2%)	247 (11.1%)	912 (10.3%)	0.5383
Nitrates	1,413 (62.3%)	1,403 (62.9%)	1,338 (60.0%)	1,419 (63.6%)	5,573 (63.1%)	0.7156
Aspirin	1,802 (79.5%)	1,740 (78.0%)	1,650 (74.0%)	1,751 (78.5%)	6,943 (78.6%)	0.5611
Anti-thrombotics	2,011 (88.7%)	1,954 (87.6%)	1,839 (82.4%)	1,969 (88.3%)	7,773 (88.0%)	0.6720

IGT, impaired glucose tolerance; CHF, congestive heart failure; LMT, left main trunk; CCB, calcium-channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; UA, uric acid.

Table 2. Incidence of Events

	UA (mg/dl)	Male incident rate /1,000 patients-year	P value	Female incident rate /1,000 patients-year	P value	Total incident rate /1,000 patients-year	P value
All events	–4.7	60.1	0.0456	55.6	<0.001	58.3	<0.001
	4.8–5.7	58.2		51.4		56.5	
	5.8–6.7	59.9		68.3		61.2	
	6.8–	72.2		108.3		76.3	
Cardiac mortality	–4.7	5.4	0.1250	5.7	0.0251	5.5	0.0253
	4.8–5.7	7.5		5.5		7.0	
	5.8–6.7	6.5		12.2		7.4	
	6.8–	9.6		15.7		10.3	
Ischemic/CAD mortality	–4.7	2.1	0.9520	2.5	0.6965	2.3	0.9669
	4.8–5.7	2.6		1.4		2.3	
	5.8–6.7	2.7		2.2		2.7	
	6.8–	2.5		4.3		2.7	
Other mortality	–4.7	3.2	0.0355	3.3	0.0179	3.2	0.0072
	4.8–5.7	4.8		4.1		4.7	
	5.8–6.7	3.8		10.0		4.8	
	6.8–	7.2		11.4		7.7	
Cerebral mortality	–4.7	0.5	0.2714	0.8	0.6298	0.6	0.1816
	4.8–5.7	0.7		0.0		0.5	
	5.8–6.7	1.7		0.0		1.4	
	6.8–	1.5		1.4		1.5	
Cardiac events	–4.7	45.1	0.3544	41.1	<0.001	43.5	0.0256
	4.8–5.7	43.3		41.0		42.8	
	5.8–6.7	43.4		54.8		45.2	
	6.8–	50.7		82.1		54.2	
Ischemic/CAD events	–4.7	35.4	0.8697	32.1	0.1504	34.1	0.9178
	4.8–5.7	34.3		34.1		34.2	
	5.8–6.7	32.6		31.4		32.4	
	6.8–	32.9		51.5		35.0	
Other events	–4.7	9.5	0.0004	10.8	<0.001	10.0	<0.001
	4.8–5.7	10.0		9.0		9.7	
	5.8–6.7	12.6		23.8		14.4	
	6.8–	18.6		31.0		20.1	
Cerebral events	–4.7	5.4	0.8904	9.1	0.1240	6.9	0.8436
	4.8–5.7	6.2		3.4		5.5	
	5.8–6.7	6.8		4.5		6.4	
	6.8–	6.5		4.3		6.2	

CAD, coronary artery disease. Other abbreviation see in Table 1.

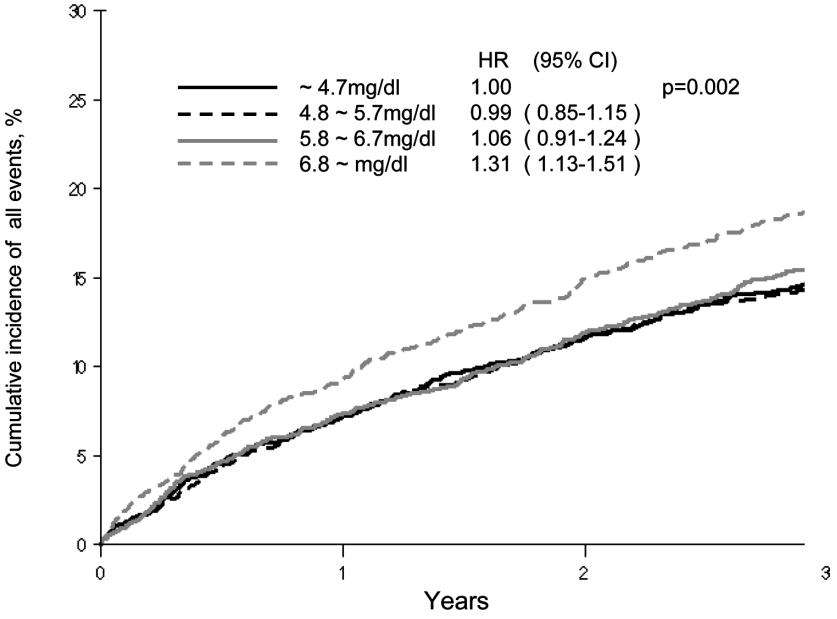

Figure 1. Comparison of cumulative incidence of cardio-and cerebrovascular events including all-cause death among quartiles with uric acid ≥6.8 mg/dl (gray broken line), 5.8–6.7 mg/dl (gray solid line), 4.8–5.7 mg/dl (black broken line), and <4.7 mg/dl (black solid line). HR, hazard ratio; CI, confidence interval.

the medical history (disease and treatment), the site and degree of stenosis, and medical procedures undertaken after coronary angiography. The information on CAD risk factors and clinical laboratory values was collected at registration and every 6 months thereafter for 3 years.

The primary endpoint was "all events", defined as cardiovascular events and all-cause mortality. Detailed information was collected regarding cardiovascular events, all-cause mortality, treatment, and outcome. All events registered in the database were defined by all-cause mortality and cardio- and cerebrovascular events. Angiographic restenosis found during routine coronary angiography without symptoms was excluded.

We divided the 8,832 patients into quartiles based on baseline UA level and compared the incidence of all events and cardiac events among the 4 groups. Study patients were placed in a quartiles regardless of hyperuricemic medication. The group was also divided into 2 subgroups according to the changes in UA at 6 months after registration. The increased UA group included patients with a UA increasing by more than 1.0 mg/dl and the non-increased UA group included those whose UA did not change or increased by <1.0 mg/dl.

To reduce the effect of medications that directly affect serum UA level, we also conducted propensity score matching. A propensity score for each patient was calculated by multivariate logistic regression analysis, taking into account the CAD risk factors and medications that directly affect the serum UA level, including α1-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, diuretics, losartan, uricosuric drugs, and UA synthesis inhibitors. We then divided 4,206 patients into the highest quartile (UA ≥6.8 mg/dl) and the rest, and compared the results.

Statistical Analysis

For patient baseline characteristics, the difference in percentage was evaluated among the 4 groups by χ^2 test. Continuous variables are expressed as mean±standard deviation, and the difference among the 4 groups was evaluated by Kruscal-Wallis test. Cumulative incidence of events was estimated by the Kaplan-Meier product-limit method and compared by log-rank test in the events. The multivariate analysis was performed using the Cox hazard ratio (HR) model, and expressed with 95% confidence intervals (CI). Statistical analysis was performed with SAS version 8.02 (SAS Institute Inc, Cary, NC, USA).

Results

Baseline Patient Characteristics

Baseline patient characteristics were compared among the 4 groups (**Table 1**): there were significant differences among the quartiles in age, sex, the number of stenoses, hypertension, hyperlipidemia, impaired glucose tolerance, obesity, smokers, alcohol users, and congestive heart failure (CHF). However, there was no difference in the rate of CAD familial history and left main CAD (LMT).

Incidence Rates of Events

Table 2 shows the association between baseline UA and subsequent events by sex and each endpoint. The total incidence rates of all events were significantly different among the 4 groups (58.3, 56.5, 61.2, 76.3/1,000 patients-year, P< 0.001). Cardiac mortality and morbidity for total and female patients were significantly different among quartiles, but not for male patients. When the cardiac events were divided into CAD events (ie, acute myocardial infarction, unstable angina pectoris, and coronary artery bypass graft) and other events (ie, arrhythmia, CHF, and cardiopulmonary arrest on arrival), the incidence of CAD events was not significantly different among quartiles. However, other events were significantly different. On the other hand, the incidence rate of cerebral death and events did not differ among the 4 groups.

Cumulative Incidence of Events

The cumulative incidence of all events and cardiac events that occurred during the 3 years in the quartiles was compared with a Kaplan-Meier curve (**Figure 1**). The HRs were significantly different among quartiles (1.00, 0.99, 1.06, 1.31, P<0.001). The results by sex showed a similar trend (**Figures 2a**, **b**).

The cumulative incidence of all events in the patients

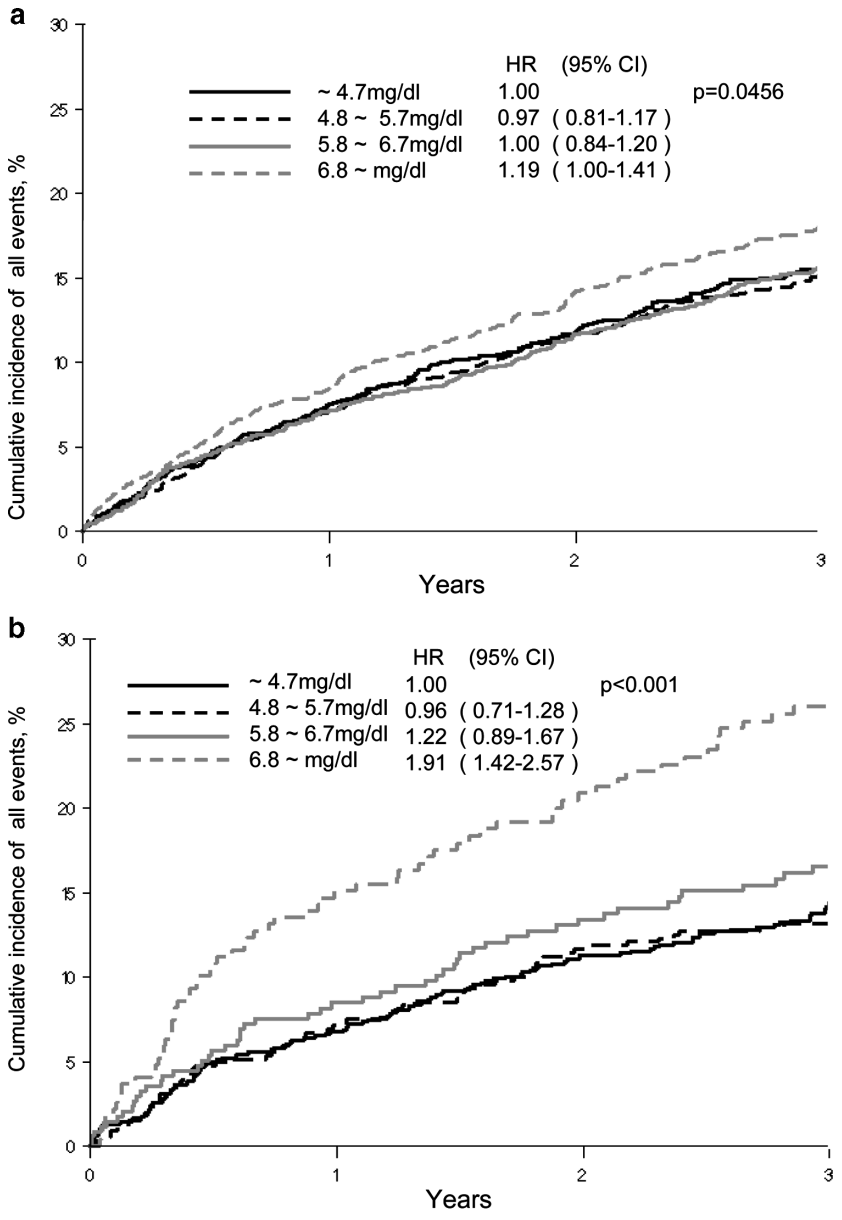

Figure 2. Comparison of cumulative incidence of cardio- and cerebrovascular events including all-cause death by quartiles of uric acid ≥6.8 mg/dl (gray broken line), 5.8–6.7 mg/dl (gray solid line), 4.8–5.7 mg/dl (black broken line), and <4.7 mg/dl (black solid line) in (**a**) male and (**b**) female patients. HR, hazard ratio; CI, confidence interval.

with UA increasing by ≥1.0 mg/dl after 6 months compared with those with unchanged UA is shown by Kaplan-Meier curve (**Figure 3a**). The event rate in the increased UA group was 70.6, vs 58.8/1,000 patient-years in the group with no increase (P=0.042).

Association of UA With Risk for All Events

The HR for all events, including cardiac and cerebrovascular events, and all-cause mortality was 1.25 (1.07–1.45, P<0.01) in the highest quartile when adjusted for sex, age, hyperlipidemia, impaired glucose tolerance, hypertension, obesity, smoking, drinking, CAD familial history, CHF, LMT, and the number of stenoses, suggesting that elevated serum UA was an independent predictor for cardiovascular events (**Table 3**).

Propensity Score Analysis

Baseline patient characteristics adjusted by propensity score analysis were compared between the 2 groups (**Table 4**). Even after adjustment for CAD risk factors and medications directly affecting serum UA level, the incidence rate of all events was significantly higher in the highest quartile than in the others (**Table 5**). When analyzed by each endpoint, results were similar to that of all events, except for mortality. The HR calculated by the Cox HR model was 1.23 (95%CI 1.06–1.43, P<0.01), which was similar to that of all patients (**Table 6**). However, the cumulative incidence of all events in the patients with UA increased ≥1.0 mg/dl after 6 months was not significantly different from that of patients with unchanged UA (**Figure 3b**).

Discussion

The Japanese Coronary Artery Disease Study[11] targeted patients who had a severe stenosis in their coronary arteries diagnosed by coronary angiography, which conferred an equivalent risk of CAD as in Western patients. We performed a subanalysis of cardio- and cerebrovascular events and all-cause mortality among quartiles based on baseline UA. The UA of the highest quartile was >6.8 mg/dl. The

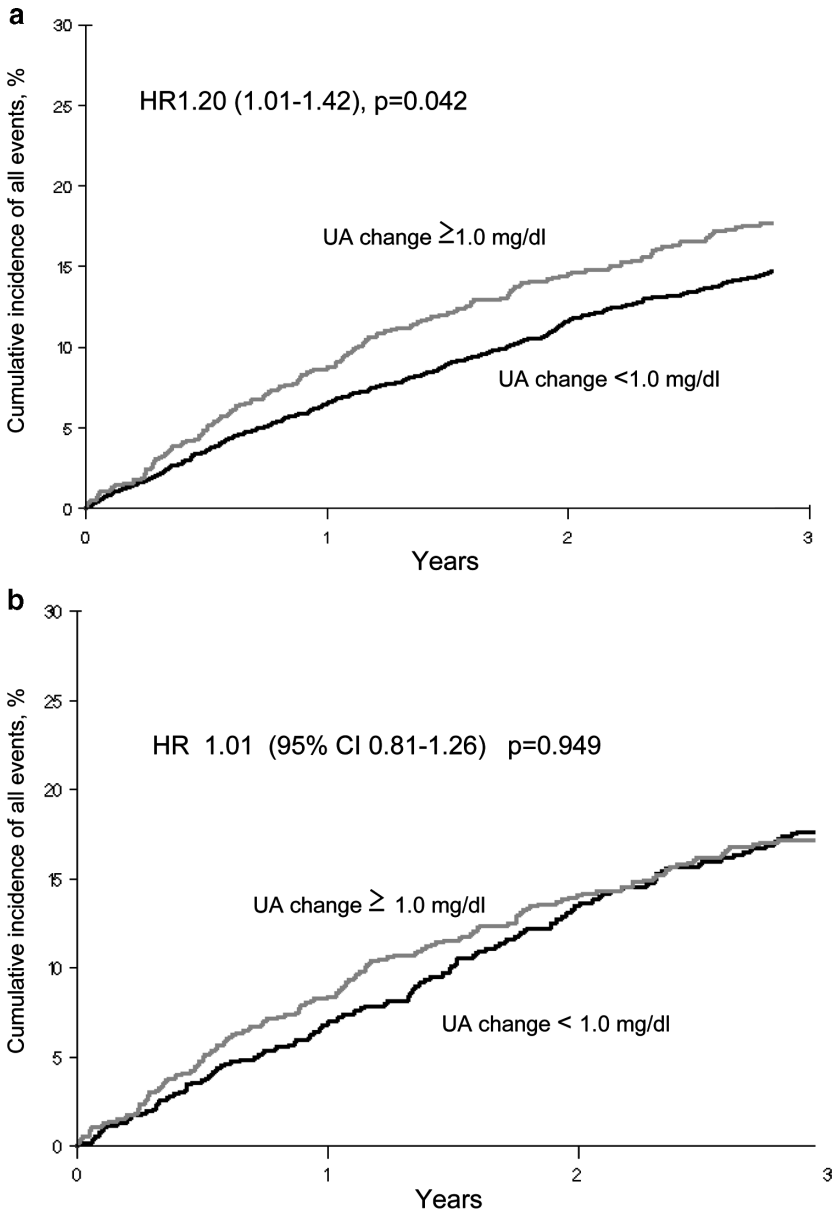

Figure 3. Comparison of cumulative incidence of cardio- and cerebrovascular events including all-cause death in patients with change in uric acid (UA) level ≥1.0 mg/dl (gray line) and <1.0 mg/dl (black line) before (**a**) and after (**b**) propensity score matching. HR, hazard ratio; CI, confidence interval.

incidence of cardio- and cerebrovascular events and all-cause mortality was higher in the highest quartile than in the others. The results demonstrate that elevated UA was an important risk factor for cardio- and cerebrovascular events and all-cause mortality combined in patients who had severe coronary artery stenosis. Cox's proportional hazard regression analysis showed that the HR for all events was 1.25 (95%CI 1.07–1.45, P<0.01) in the highest quartile (UA ≥6.8 mg/dl). It showed that UA was still an independent predictor for all events, including all-cause death and cardio–cerebrovascular events.

A similar relationship between elevated UA and cardiovascular events, such as myocardial infarction and stroke, has been demonstrated in numerous large-scale clinical studies. In the NHANES I Study,[13] a high level of UA was an independent predictor for cardiovascular disease in both men and women. The incidence of cardiac death increased in men with UA >7.0 mg/dl, and in women with UA >5.6 mg/dl. Bickel et al reported similar findings to the Japanese Coronary Artery Disease Study in patients with CAD diagnosed

Table 3. Proportional Hazards Cox Regression Model: Incidence of All Events Including Death

Factors	HR (95%CI)	P value
Sex, male	1.08 (0.94–1.25)	0.2914
Age, 10 years	1.02 (1.01–1.03)	<0.001
Hyperlipidemia	0.90 (0.80–1.00)	0.0580
IGT	1.26 (1.13–1.41)	<0.001
Hypertension	1.30 (1.16–1.46)	<0.001
Obesity	0.87 (0.77–0.98)	0.0269
Smoking	1.02 (0.91–1.15)	0.7042
Drinking	0.97 (0.86–1.10)	0.6431
Familial history	0.89 (0.77–1.04)	0.1389
CHF	1.83 (1.59–2.11)	<0.001
LMT	1.36 (1.09–1.69)	0.0064
No. of stenoses	1.24 (1.16–1.32)	<0.001
UA (mg/dl)		
≤4.7	1.00	
4.8–5.7	1.00 (0.85–1.17)	0.9835
5.8–6.7	1.10 (0.93–1.28)	0.2612
≥6.8	1.25 (1.07–1.45)	0.0048

HR, hazard ratio; CI, confidence interval. Other abbreviations see in Table 1.

Table 4. Baseline Characteristics of Patients After Propensity Score Analysis

	≤6.7 mg/dl	≥6.8 mg/dl	All	P value
n	2,103	2,103	4,206	
Age, years	64.4±9.9	64.8±10.1	64.6±10.0	0.0729
Sex, male (%)	1,848 (87.9%)	1,840 (87.5%)	3,688 (87.7%)	0.7074
Hypertension (%)	1,290 (61.3%)	1,302 (61.9%)	2,592 (61.6%)	0.7036
Hyperlipidemia (%)	1,271 (60.4%)	1,255 (59.7%)	2,526 (60.1%)	0.6145
IGT (%)	847 (40.3%)	862 (41.0%)	1,709 (40.6%)	0.6377
Obesity (%)	830 (39.5%)	797 (37.9%)	1,627 (38.7%)	0.2961
Smoking (%)	952 (45.3%)	926 (44.0%)	1,878 (44.7%)	0.4200
Drinking (%)	1,000 (47.6%)	930 (44.2%)	1,930 (45.9%)	0.0303
Familial history (%)	368 (17.5%)	381 (18.1%)	749 (17.8%)	0.6003
CHF (%)	279 (13.3%)	313 (14.9%)	592 (14.1%)	0.1317
LMT (%)	99 (4.7%)	101 (4.8%)	200 (4.8%)	0.8848
No. of stenoses (%)	1.84±0.81	1.84±0.80	1.84±0.80	0.9629
Statins (%)	823 (39.1%)	756 (35.9%)	1,579 (37.5%)	0.0329
Fibrates	88 (4.2%)	106 (5.0%)	194 (4.6%)	0.1858
α-1-blockers	65 (3.1%)	58 (2.8%)	123 (2.9%)	0.5218
α-β-blockers	231 (11.0%)	259 (12.3%)	490 (11.7%)	0.1784
Diuretics	471 (22.4%)	470 (22.3%)	941 (22.4%)	0.9705
CCB	1,116 (53.1%)	1,104 (52.5%)	2,220 (52.8%)	0.7109
β-blockers	456 (21.7%)	466 (22.2%)	922 (21.9%)	0.7094
ACEI	712 (33.9%)	689 (32.8%)	1,401 (33.3%)	0.4518
ARB	300 (14.3%)	293 (13.9%)	593 (14.1%)	0.7564
Uricosuric drugs	27 (1.3%)	31 (1.5%)	58 (1.4%)	0.5969
UA synthesis inhibitors	229 (10.9%)	244 (11.6%)	473 (11.2%)	0.4641
Warfarin	255 (12.1%)	224 (10.7%)	479 (11.4%)	0.1324
Nitrates	1,387 (66.0%)	1,334 (63.4%)	2,721 (64.7%)	0.0873
Aspirin	1,696 (80.6%)	1,647 (78.3%)	3,343 (79.5%)	0.0614
Anti-thrombotics	1,916 (91.1%)	1,847 (87.8%)	3,763 (89.5%)	<0.001

Abbreviations see in Table 1.

Table 5. Incidence of Events

	UA (mg/dl)	/1,000 patients-year	P value
All events	–6.7	59.0	0.0024
	6.8–	76.1	
Cardiac mortality	–6.7	8.0	0.2116
	6.8–	10.3	
Ischemic/CAD mortality	–6.7	3.0	0.8169
	6.8–	2.8	
Other mortality	–6.7	4.9	0.0942
	6.8–	7.5	
Cerebral mortality	–6.7	0.5	0.2483
	6.8–	1.2	
Cardiac events	–6.7	43.8	0.0208
	6.8–	54.7	
Ischemic/CAD events	–6.7	32.4	0.4131
	6.8–	35.7	
Other events	–6.7	13.2	0.0122
	6.8–	19.6	
Cerebral events	–6.7	7.7	0.3089
	6.8–	6.3	

Abbreviations see in Tables 1,2.

Table 6. Proportional Hazards Cox Regression Model

Factors	HR (95%CI)	P value
Sex, male	0.94 (0.75–1.18)	0.5966
Age, 10 years	1.02 (1.01–1.03)	<0.001
Hyperlipidemia	0.96 (0.82–1.12)	0.6213
IGT	1.10 (0.94–1.28)	0.2364
Hypertension	1.32 (1.12–1.55)	<0.001
Obesity	0.87 (0.74–1.02)	0.0793
Smoking	1.05 (0.89–1.24)	0.5509
Drinking	1.00 (0.85–1.17)	0.9866
Familial history	0.81 (0.66–1.00)	0.0493
CHF	1.93 (1.61–2.31)	<0.001
LMT	1.27 (0.93–1.73)	0.1344
No. of stenoses	1.30 (1.18–1.43)	<0.001
UA (≥6.8 mg/dl)	1.23 (1.06–1.43)	0.0058

Abbreviations see in Tables 1,3.

by coronary angiography. The HR for death in their report was 1.30 in women and 1.39 in men,[14] suggesting that elevated UA is an independent risk factor for death. According to our study results, the HR for cardiac events of 1.25 (95%CI 1.07–1.45, P<0.01) in Japanese patients was comparable to the HR for death of patients in Western countries.

In Japan, Tomita et al's employee survey[9] found that in patients with UA >8.5 mg/dl, the HR for death from CAD and for cerebrovascular death increased to 1.7 and 2.6, respectively. In our study, the highest quartile showed the same tendency when we focused only on the endpoint of cardiac events. However, the HR did not increase for cerebral events. Although the incidence of cerebral events is greater than that of cardiac events in the Japanese general population, patients with severe coronary stenosis were targeted in the Japanese Coronary Artery Disease Study, which may be reflected in our results that the incidence of cardiac events was much greater than that of cerebral events.

When the cardiac events were divided into CAD events and other events, for other events only there was a significant difference among baseline UA quartiles in terms of both mortality and morbidity. Strasak et al reported similar results in their cohort study of 83,683 male patients.[15] In the present study, CHF accounted for approximately 75% of other events. Recent in vitro and in vivo findings suggest that UA contributes directly to endothelial dysfunction by inducing antiproliferative effects and impairing nitric oxide production,[16] thus causing a deterioration of CHF. Sakai et al[17] recently demonstrated that in patients with mild to

severe CHF, not only high plasma concentrations of B-type natriuretic peptide but also high UA concentrations were likely to be independent predictors of mortality. They concluded that monitoring both of these parameters may be important in the management of CHF patients.

In the present study, the UA level was not significantly associated with the incidence of CAD, which is consistent with the findings of previous studies including the Framingham Heart Study[2] Wannamethee et al[18] and the ARIC study[19] On the other hand, it has been reported that human atherosclerotic plaque contains a considerable amount of UA, and hyperuricemia may promote thrombus formation via purine metabolism[20,21] Strasak et al[22] reported that UA is an independent predictor for acute and subacute forms of CAD, so we cannot conclude that there is no association between UA and CAD. However, UA may have a stronger effect on dysfunction of the heart than CAD.

When analyzed by sex, the association of UA with event risk was higher in female patients than in male patients. In the NHANES I Study[13] and ARIC study[19] the cut-off value increasing CAD risk was higher by approximately 1 mg/dl in male patients compared with female patients. In the present study, we assumed that the incidence rate of female patients was high because we used the UA cut-off value of 6.8 mg/dl to divide patients into quartiles, regardless of sex.

According to the Japanese guidelines, hyperuricemia is defined as UA ≥7.0 mg/dl and the target UA level is <6.0 mg/dl, which may be reasonable, because in the present study the incidence rate of events increased in male patients with UA ≥6.8 mg/dl.

In this analysis, the group in which UA increased more than 1.0 mg/dl after 6 months had more events than the other group, regardless of the UA level. Hakota et al[10] reported that a 1.0 mg/dl increase in UA increased the HR of myocardial infarction to 1.17 in men and 1.23 in women. However, in our propensity score analysis, taking into account CAD risk factors and medications directly affecting serum UA level, no difference was observed between patients with UA change ≥1.0 mg/dl and UA change <1.0 mg/dl after 6 months. We assumed that the presence of complications and medications affecting serum UA level caused cardiovascular events. Because we can only control complications, but not completely cure them, management of serum UA level by medication is important for reducing cardiovascular events.

Study Limitations

This study was observational and although confounding factors were adjusted by multivariate Cox regression analysis, and the results were still consistent after propensity score matching, an interventional study must be conducted to examine the effect of UA lowering treatment on cardiovascular disease.

In conclusion, hyperuricemia is an independent predictor of cardiovascular events and all-cause mortality combined in patients with severe coronary artery stenosis.

Acknowledgment

This study was supported by the Japan Heart Foundation.

References

1. Klein R, Klein BE, Cornoni JC, Maready J, Cassel JC, Tyroler HA. Serum uric acid: Its relationship to coronary heart disease risk factors and cardiovascular disease, Evans County, Georgia. *Arch Intern Med* 1973; **132:** 401–410.
2. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: The Framingham heart study. *Ann Intern Med* 1999; **131:** 7–13.
3. Alderman MH, Cohen H, Madhavan S, Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. *Hypertension* 1999; **34:** 144–150.
4. Verdecchia P, Schillaci G, Reboldi G, Santeusanio F, Porcellati C, Brunetti P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension: The PIUMA study. *Hypertension* 2000; **36:** 1072–1078.
5. Franse LV, Pahor M, Bari MD, Shorr RI, Wan JY, Somes GW, et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the systolic hypertension in the elderly program (SHEP). *J Hypertens* 2000; **18:** 1149–1154.
6. Wang J, Staessen JA, Fagard RH, Birkenhäger WH, Gong L, Liu L. Prognostic significance of serum creatinine and uric acid in older Chinese patients with isolated systolic hypertension. *Hypertension* 2001; **37:** 1069–1074.
7. Tseng CH. Sex difference in the distribution of atherosclerotic risk factors and their association with peripheral arterial disease in Taiwanese type 2 diabetic patients. *Circ J* 2007; **71:** 1131–1136.
8. Song SH, Kwak IS, Kim YJ, Kim SJ, Lee SB, Lee DW, et al. Can γ-glutamyltransferase be an additional marker of arterial stiffness. *Circ J* 2007; **71:** 1715–1720.
9. Tomita M, Mizuno S, Yamanaka H, Hosoda Y, Sakuma K, Matuoka Y, et al. Does hyperuricemia affect mortality? A prospective cohort study of Japanese male workers. *J Epidemiol* 2000; **10:** 403–409.
10. Hakoda M, Masunari N, Yamada M, Fujiwara S, Suzuki G, Kodama K, et al. Serum uric acid concentration as a risk factor for cardiovascular mortality: A long term cohort study of atomic bomb survivors. *J Rheumatol* 2005; **32:** 906–912.
11. Japanese Coronary Artery Disease (JCAD) Study Investigators. Current status of the background of patients with coronary artery disease in Japan: The Japanese coronary artery disease study. *Circ J* 2006; **70:** 1256–1262.
12. Kohro T, Hayashi D, Okada Y, Yamazaki T, Nagai R, JCAD Investigators. Effects of medication on cardiovascular events in the Japanese coronary artery disease (JCAD) study. *Circ J* 2007; **71:** 1835–1840.
13. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality: The NHANES epidemiologic follow-up study. *JAMA* 2000; **283:** 2404–2410.
14. Bickel C, Rupprecht HJ, Blankenberg S, Rippin G, Hafner G, Daunhauer A, et al. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 2002; **89:** 12–17.
15. Strasak A, Ruttmann E, Brant L, Kelleher C, Klenk J, Concin H, et al. Serum uric acid and risk of cardiovascular mortality: A prospective long-term study of 83683 Austrian men. *Clin Chem* 2008; **54:** 273–284.
16. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol* 2005; **25:** 39–42.
17. Sakai H, Tsutamoto T, Tsutsui T, Tanaka T, Ishikawa C, Horie M. Serum level of uric acid, partly secreted from the failing heart, is a prognostic marker in patients with congestive heart failure. *Circ J* 2006; **70:** 1006–1011.
18. Wannamethee SG, Shaper AG, Whincup PH. Serum urate and the risk of major coronary hear disease events. *Heart* 1997; **78:** 147–153.
19. Moriarity JT, Folsom AR, Iribarren C, Javier Nieto F, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis risk in communities (ARIC) study. *Ann Epidemiol* 2000; **10:** 136–143.
20. Suarna C, Dean RT, May J, Stocker R. Human atherosclerotic plaque contains both oxidized lipids and relatively large amounts of alpha-tocopherol and ascorbate. *Arterioscler Thromb Vasc Biol* 1995; **15:** 1616–1624.
21. Visy JM, Le Coa P, Chadefaux B, Fressinaud C, Woimant F, Marquiet J, et al. Homocystinuria due to 5, 10-methylenetetrahydofolate reductase deficiency revealed by stroke in adult siblings. *Neurology* 1991; **41:** 1313–1315.
22. Strasak AM, Kelleher CC, Brant LJ, Rapp K, Ruttmann E, Concin H, et al. Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: A prospective 21-year follow-up study. *Int J Cardiol* 2008; **125:** 232–239.