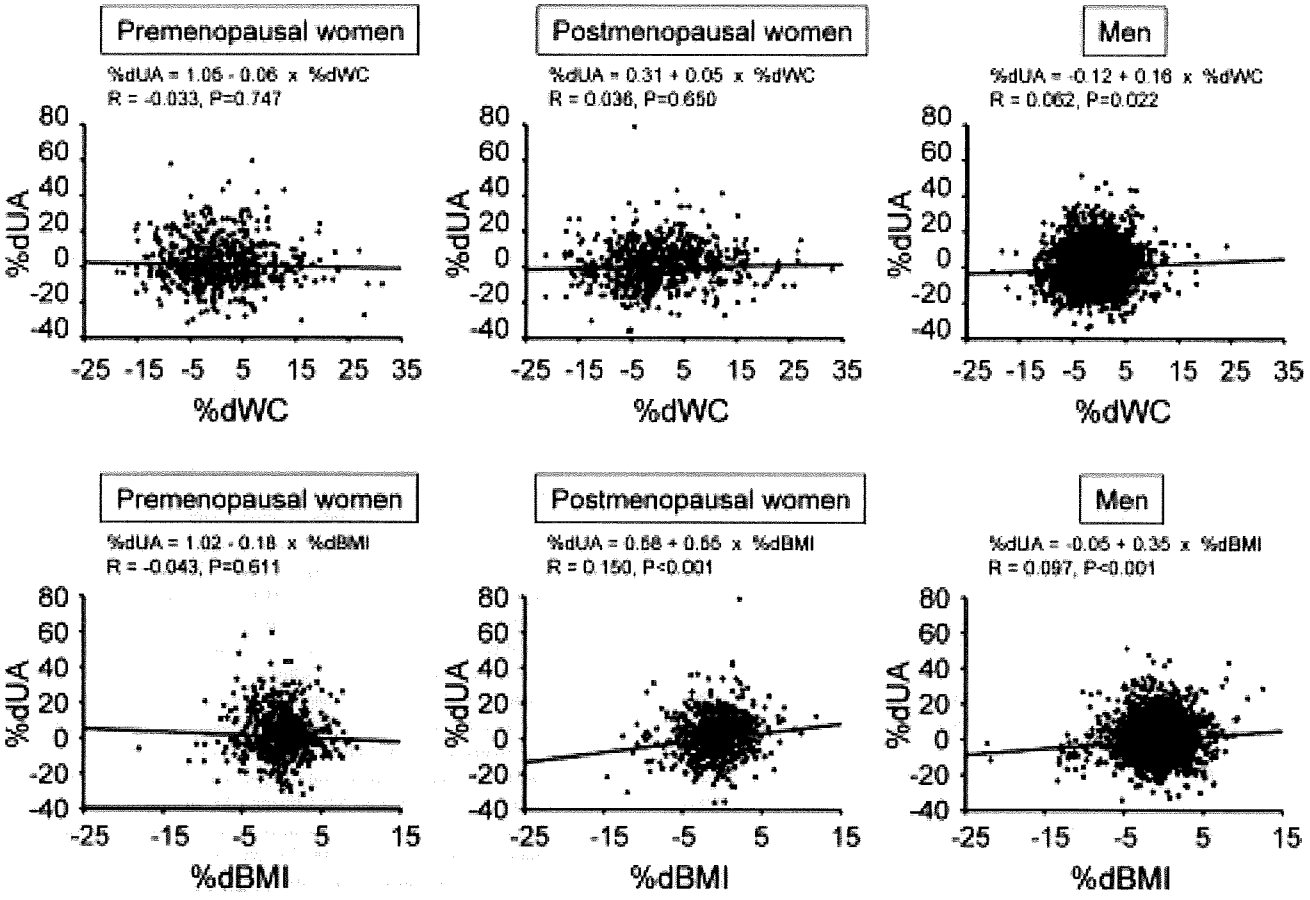

Figure 2. Scatterplot and linear regression between percentage change in waist circumference (%dWC) and percentage change in uric acid (%dUA), and those between percentage change in BMI (%dBMI) and %dUA in premenopausal and postmenopausal women and in men. Serum uric acid values were not adjusted for age or other possible confounders.

general/abdominal obesity, as no program to reduce weight was conducted by our institute. Second, we did not take into account participants' level of alcohol consumption or number of cigarettes smoked; both may affect serum UA levels[29,30]. Third, blood samples were taken from individuals in fasting condition, which may have affected their serum creatinine levels, and thus eGFR.

In summary, during a 1-year period, percentage changes in BMI (%dBMI) were associated positively with percentage changes in serum UA levels (%dUA) in postmenopausal women and men, but not in premenopausal women. This relationship was, at least in part, independent of changes in blood pressure and renal function. Weight loss may represent an effective strategy to decrease serum UA levels without use of antihyperuricemic medications, especially in postmenopausal women and men.

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Table 2. Stepwise multiple regression analysis using %dUA as the dependent variable.

	ß	(95% CI)	Standardized ß	p
Premenopausal women				
Model 1				
UA1	−4.21	(−5.42, −3.00)	−0.28	< 0.001
Model 2				
UA1	−4.21	(−5.42, −3.00)	−0.28	< 0.001
Model 3				
UA1	−4.21	(−5.42, −3.00)	−0.28	< 0.001
Model 4				
%deGFR	−0.43	(−0.53, −0.33)	−0.34	< 0.001
UA1	−3.70	(−4.84, −2.56)	−0.25	< 0.001
Model 5				
%deGFR	−0.43	(−0.53, −0.33)	−0.34	< 0.001
UA1	−3.70	(−4.84, −2.56)	−0.25	< 0.001
Postmenopausal women				
Model 1				
UA1	−3.09	(−4.05, −2.13)	−0.24	< 0.001
Model 2				
UA1	−3.04	(−4.00, −2.09)	−0.24	< 0.001
%dBMI	0.53	(0.26, 0.81)	0.14	< 0.001
Model 3				
UA1	−3.04	(−4.00, −2.09)	−0.24	< 0.001
%dBMI	0.53	(0.26, 0.81)	0.14	< 0.001
Model 4				
%deGFR	−0.33	(−0.41, −0.25)	−0.30	< 0.001
UA1	−2.83	(−3.73, −1.92)	−0.22	< 0.001
%dBMI	0.55	(0.29, 0.81)	0.15	< 0.001
Model 5				
%deGFR	−0.33	(−0.41, −0.25)	−0.30	< 0.001
UA1	−2.83	(−3.73, −1.92)	−0.22	< 0.001
%dBMI	0.55	(0.29, 0.81)	0.15	< 0.001
Men				
Model 1				
UA1	−2.51	(−2.90, −2.12)	−0.27	< 0.001
%dWC	0.14	(0.04, 0.25)	0.06	0.008
Model 2				
UA1	−2.49	(−2.88, −2.10)	−0.27	< 0.001
%dBMI	0.32	(0.17, 0.48)	0.09	< 0.001
Model 3				
UA1	−2.51	(−2.89, −2.12)	−0.27	< 0.001
%dBMI	0.38	(0.22, 0.54)	0.10	< 0.001
%dBPs	−0.06	(−0.10, −0.02)	−0.06	0.006
Model 4				
%deGFR	−0.36	(−0.40, −0.31)	−0.32	< 0.001
UA1	−2.29	(−2.66, −1.92)	−0.25	< 0.001
%dBMI	0.35	(0.21, 0.50)	0.10	< 0.001
Model 5				
%deGFR	−0.36	(−0.40, −0.31)	−0.32	< 0.001
UA1	−2.29	(−2.66, −1.92)	−0.25	< 0.001
%dBMI	0.35	(0.21, 0.50)	0.10	< 0.001

Model 1. Independent variables include age, UA1, WC1, and %dWC. Model 2. Independent variables include Model 1 + BMI1 and %dBMI. Model 3. Independent variables include Model 2 + %dBPs. Model 4. Independent variables include Model 2 + %deGFR. Model 5. Independent variables include Model 2 + %dBPs and %deGFR. UA: uric acid; BMI: body mass index; BPs: systolic blood pressure; eGFR: estimated glomerular filtration rate.

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Table 3. Logistic regression analysis using the highest or lowest %dUA quartile as the dependent variable.

	Independent Variable			
	%dUA ≥ 7.2%		%dUA < –7.5%	
	OR (95% CI)	p	OR (95% CI)	p
Premenopausal women				
Model 1				
%dBMI quartile				
First			1.19 (0.73, 1.94)	0.474
2 and 3	1 Reference			
4	0.65 (0.42, 0.99)	0.046	1.00 Reference	
Model 2				
%dBMI quartile				
First			1.41 (0.85, 2.34)	0.181
2 and 3	1.00 Reference			
4	0.71 (0.45, 1.10)	0.126	1.00 Reference	
%deGFR	0.93 (0.91, 0.95)	< 0.001	1.06 (1.04, 1.08)	< 0.001
%dBPs	0.99 (0.97, 1.01)	0.225	1.00 (0.98, 1.02)	0.804
Postmenopausal women				
Model 1				
%dBMI quartile				
First			2.04 (1.37, 3.03)	< 0.001
2 and 3	1.00 Reference			
4	1.60 (1.06, 2.41)	0.025	1.00 Reference	
Model 2				
%dBMI				
First			2.04 (1.35, 3.07)	0.001
2 and 3	1.00 Reference			
4	1.72 (1.12, 2.63)	0.013	1.00 Reference	
%deGFR	0.95 (0.93, 0.97)	< 0.001	1.05 (1.03, 1.07)	< 0.001
%dBPs	0.98 (0.97, 1.00)	0.039	1.00 (0.98, 1.01)	0.684
Men				
Model 1				
%dBMI quartile				
First			1.35 (1.07, 1.69)	0.011
2 and 3	1.00 Reference			
4	1.38 (1.08, 1.76)	0.010	1.00 Reference	
Model 2				
%dBMI quartile				
First			1.46 (1.14, 1.86)	0.002
2 and 3	1.00 Reference			
4	1.49 (1.15, 1.92)	0.002	1.00 Reference	
%deGFR	0.94 (0.92, 0.95)	< 0.001	1.07 (1.06, 1.08)	< 0.001
%dBPs	1.00 (0.99, 1.01)	0.300	1.00 (0.99, 1.01)	0.715

Model 1. Independent variables include age, UA1, BMI1, and %dBMI quartiles. Model 2. Independent variables include Model 1 + %dBPs and %deGFR. UA: uric acid; BMI: body mass index; BPs: systolic blood pressure; eGFR: estimated glomerular filtration rate.

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ACD

Detecting occult coronary artery disease followed by early coronary artery bypass surgery in patients with diabetic retinopathy: Report from a diabetic retinocoronary clinic

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Objectives: We hypothesized that a large number of patients with diabetic retinopathy who could benefit greatly from early coronary artery bypass grafting would not be identified.

Methods: Patients with diabetic retinopathy receiving ophthalmologic care as outpatients in our hospital in whom coronary artery disease was not previously suspected were referred randomly to the diabetic retinocoronary clinic and were asked to participate in diagnostic tests, including an exercise treadmill test and exercise thallium scintigraphy or coronary computed tomography. Patients who had type 1 diabetes mellitus, required hemodialysis, or both were excluded from this study. A definitive diagnosis of coronary artery disease was confirmed by means of coronary angiography.

Results: Of 214 patients with diabetic retinopathy, 55 (25.7%) were confirmed as having significant stenotic coronary artery disease. Patients with angiographically confirmed coronary disease were older than those with negative results on diagnostic tests (62.2 ± 9.8 vs 57.9 ± 10.3 years, $P = .01$). Fifteen had 1-vessel disease, 17 had 2-vessel disease, 14 had 3-vessel disease, 1 had left main trunk plus 1-vessel disease, 2 had left main trunk plus 2-vessel disease, and 5 had left main trunk plus 3-vessel disease. Eight patients had left main trunk disease, and 18 patients with non–left main trunk disease had proximal left anterior descending coronary artery (LAD) disease. Forty-two patients showed indications of coronary revascularization (coronary artery bypass grafting in 17 and percutaneous coronary intervention in 25). During the entire follow-up (287.6 ± 183.2 days) of 39 patients undergoing coronary revascularization, all were alive without myocardial infarction, but 8 experienced vitreous hemorrhage.

Conclusions: Approximately 25% of patients with diabetic retinopathy receiving ophthalmologic care as outpatients have a significant stenotic coronary artery disease. Of the total diabetic population, a large number of patients with diabetic retinopathy who show strong indications for early coronary artery bypass grafting might well go unrecognized. (J Thorac Cardiovasc Surg 2010;139:92-7)

Coronary artery disease (CAD) is the leading cause of death in diabetic patients, accounting for 75% of deaths.[1] The risk of CAD events varies widely from patient to patient and even within a diabetic patient as the disease progresses. Diabetic retinopathy (DR) is an early sign of microvascular complication of diabetes, its severity being directly related to the duration of the diabetes and to the amount of increase in blood glucose concentration.[2] Evidence demonstrates that the severity of DR is associated with a graded increased risk of myocardial infarction and death from CAD.[3-11] We reviewed the literature regarding the association between DR and CAD and hypothesized that a large number of patients with DR and CAD who could benefit greatly from early coronary artery bypass grafting (CABG) would not be identified until the occurrence of a catastrophic event, such as overt heart failure or sudden death.[12] In this regard we opened a novel clinic named the diabetic retinocoronary clinic for the purpose of identification and treatment of occult CAD in patients with DR, and this article reports our experience in this clinic.

MATERIALS AND METHODS

Study Patients

The concept of a diabetic retinocoronary clinic was approved by the University of Tokyo Institutional Board for Outpatients in December 2006, and the clinic was opened in April 2007. Patients with DR receiving ophthalmologic care as outpatients in our hospital in whom CAD had not previously been suspected were referred randomly to the clinic by ophthalmologists or endocrinologists. Patients who had type 1 diabetes mellitus, required hemodialysis, or both were excluded from this study. All patients provided informed consent

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CAD = coronary artery disease
CT = computed tomography
DES = drug-eluting stent
DR = diabetic retinopathy
ECG = electrocardiography
ETT = exercise treadmill test
LAD = left anterior descending coronary artery
LMT = left main trunk
NPDR = nonproliferative diabetic retinopathy
PCI = percutaneous coronary intervention
PDR = proliferative diabetic retinopathy

and were asked to participate in a screening that included a cardiovascular history and a physical examination, risk factor assessment, resting electrocardiography (ECG), and an exercise treadmill test (ETT). The positivity of the ETT was determined by using conventional criteria (≥1 mm of horizontal or downsloping ST-segment depressions at 80 ms after the end of the QRS complex [from the J points]). The results of the ETT were classified as negative, positive (if ST-segment depression exceeded 2 mm), or nondiagnostic.[13] If patients had limitations that precluded the ETT, such as limitation of physical activity associated with severely impaired vision, peripheral arterial disease, or an abnormal resting ECG result or if the results of ETT were nondiagnostic, they were approached for exercise thallium scintigraphy or coronary computed tomography (CT). Patients with positive ETT results, abnormal scintigraphic results, or CT results indicating CAD were approached for coronary angiography. A significant stenotic CAD was confirmed by means of coronary angiography. The findings reported in this study were documented for all patients as of November 15, 2008.

Severity of DR

The severity in the more affected eye was used, and the patients with retinopathy were grouped into 2 categories: those with nonproliferative diabetic retinopathy (NPDR; only microaneurysms or microaneurysms plus 1 or more the following: retinal hemorrhages, soft exudates, hard exudates, intraretinal microvascular abnormalities, or venous beading) and those with proliferative diabetic retinopathy (PDR; the presence of new vessels, preretinal or vitreous hemorrhages, panretinal photocoagulation scarring, and a history of vitreous surgery).[2]

Coronary Angiography

Angiographic analysis was performed and evaluated by experienced cardiologists. The severity of CAD was determined based on stenosis of the left main trunk (LMT; defined as lesions causing lumen narrowing by ≥50%) and the number of vessels with 70% or greater stenosis. The proximal LAD was defined as the vessel between the circumflex takeoff and the first major septal or diagonal branch.

RESULTS

Between April 2007 and October 2008, 286 consecutive patients with DR were referred to the diabetic retinocoronary clinic. Thirty-four patients refused to undergo diagnostic tests, and 38 did not have a definitive diagnosis by November 15, 2008. The remaining 214 patients were included in this study. Of them, 59 patients had NPDR, and 155 had PDR.

One hundred seventy-six (82.2%) patients were completely asymptomatic; 25 (11.7%) were revealed during history taking by cardiac surgeons and cardiologists to have chest discomfort, but their symptoms were not typical of angina pectoris. Furthermore, limited physical activity prevented a precise evaluation of angina pectoris in 11 (5.1%) patients with severely impaired vision and in 2 (0.9%) patients with peripheral arterial disease. Of the study group, normal resting ECG results were seen in 159 (74.3%), Q waves were seen in 4 (1.9%), nonspecific ST-T changes were seen in 39 (18.2%), right bundle branch block was seen in 9 (4.2%), atrial fibrillation was seen in 2 (0.9%), and second-degree atrioventricular block was seen in 1 (0.5%).

Of the 172 patients undergoing ETT, 50 (29.1%) had a positive ETT result, 106 (61.7%) had a negative ETT result, and 15 (8.7%) had nondiagnostic results. The patients who had limitations that precluded the ETT (n = 42) or had nondiagnostic results on the ETT were approached for exercise thallium scintigraphic analysis or coronary CT scanning. Thirty-three patients underwent exercise thallium scintigraphy, and 8 (24.2%) had abnormal results. Twenty-four patients underwent coronary CT, which revealed atherosclerotic CAD in 7 (29.2%).

Sixty-five patients underwent coronary angiography. Overall, of 214 study patients, 55 (25.7%) were confirmed as having significant stenotic CAD (Figure 1). The baseline characteristics of the patients with an angiographically confirmed CAD were compared with those of patients with negative results on diagnostic tests (Table 1). Patients with angiographically confirmed CAD were older (62.2 ± 9.8 vs 57.9 ± 10.3 years, $P = .01$). Twenty (46.5%) of 43 patients with Q-wave or ST-T changes on resting ECGs had CAD, whereas 35 (20.5%) of 171 patients without these abnormalities had CAD ($P = .001$). The serum creatinine level, estimated glomerular filtration rate, hemoglobin A1c level, low-density lipoprotein level, and high-density lipoprotein level were similar in the 2 groups. Neither the severity of DR nor treatment with insulin was associated with angiographically confirmed CAD.

Of the 55 patients with CAD, 8 (14.5%) had LMT disease, 18 (32.7%) patients without LMT disease had proximal LAD disease, and 29 patients had non-LMT, nonproximal LAD disease (Figure 1). One-vessel disease was seen in 15 (27.3%), 2-vessel disease was seen in 17 (30.9%), 3-vessel disease was seen in 14 (25.5%), LMT plus 1-vessel disease was seen in 1 (1.8%), LMT plus 2-vessel disease was seen in 2 (3.6%), and LMT plus 3-vessel disease was seen in 5 (9.1%) patients. In a daily coronary conference held within our institution, CABG was recommended for 17 patients, percutaneous coronary intervention (PCI) was recommended for 25 patients, and aggressive medical therapy alone was recommended for 13 patients. For all patients with LMT disease, coronary revascularization was indicated. Of 18 patients without LMT

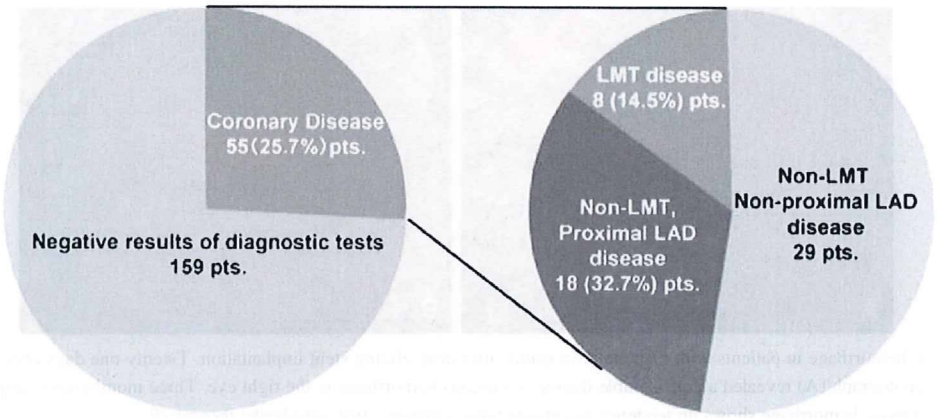

FIGURE 1. Incidence of occult coronary artery disease in 214 patients with diabetic retinopathy who were referred to the diabetic retinocoronary clinic. Fifty-five (25.7%) patients had angiographically confirmed coronary artery disease. Eight (14.5%) of them had left main trunk *(LMT)* disease, and 18 (32.7%) had proximal left anterior descending coronary artery *(LAD)* disease.

disease but with proximal LAD disease, 15 were considered to have indications for revascularization. Thus far, 12 have undergone CABG, and 27 have undergone PCI. Three patients for whom CABG was recommended consented to undergo only PCI. Three refused coronary revascularization by means of either CABG or PCI. During the entire follow-up (287.6 ± 183.2 days), from the initial coronary revascularization, all patients have remained alive without myocardial infarction. However, vitreous hemorrhage occurred in 4 patients with PDR receiving CABG and in 4 patients with PDR receiving PCI (Figure 2). No patients with NPDR experienced vitreous hemorrhage. The mean interval between the initial revascularization and the occurrence of vitreous hemorrhage was 118 days (range, 6–387 days). Six patients experienced vitreous hemorrhage within 6 months after the initial revascularization and 7 within 1 year after revascularization.

DISCUSSION

The present study revealed that of 214 patients with DR receiving ophthalmologic outpatient care, 55 (25.7%) had angiographically confirmed significant stenotic CAD, and 26 (12.1%) had LMT disease, proximal LAD disease, or both. In 42 (19.6%) patients coronary revascularization was indicated. These findings suggest that a large number of patients with DR and CAD could go unrecognized until the arrival of a catastrophic event, such as overt heart failure or sudden death.

Of the 214 study patients, 87 (40.7%) were receiving insulin treatment, a proportion that seems high for patients with type 2 diabetes. All the study patients had DR, 59 diabetic patients had nonproliferative retinopathy, and 155 diabetic patients had proliferative retinopathy. Therefore our patients, especially those with proliferative retinopathy,

TABLE 1. Baseline characteristics of patients with diabetic retinopathy who were referred to the diabetic retinocoronary clinic*

Characteristic	Patients with angiographically confirmed CAD (n = 55)	Patients with negative results on diagnostic tests (n = 159)	*P* value
Mean age (y)	62.2 ± 9.8	57.9 ± 10.3	.01
Female sex, no. (%)	11 (20.0)	53 (33.3)	.09
Height (cm)	163.0 ± 8.2	162.7 ± 8.5	.87
Body weight (kg)	65.9 ± 14.4	66.3 ± 13.9	.88
Body mass index	24.8 ± 4.8	24.9 ± 4.3	.94
NPDR, no. (%)	17 (30.9)	42 (26.4)	.64
PDR, no. (%)	38 (69.1)	117 (73.6)	.64
Treatment with insulin, no. (%)	21 (38.2)	66 (41.5)	.75
Q-wave/ST-T change, no. (%)	20 (36.4)	23 (14.5)	.001
Hemoglobin A1c (%)	7.3 ± 1.7	7.4 ± 1.4	.56
Mean serum creatinine (mg/dL)	0.94 ± 0.52	1.0 ± 0.82	.58
eGFR (mL/min)	69.0 ± 19.8	69.7 ± 25.1	.86
BNP (pg/mL)	43.7 ± 79.2	30.0 ± 38.5	.10
Mean serum LDL (mg/dL)	107.6 ± 30.4	109.2 ± 33.6	.77
Mean serum HDL (mg/dL)	55.8 ± 26.3	57.7 ± 15.9	.59
Mean serum triglycerides (mg/dL)	134.2 ± 74.6	135.2 ± 81.8	.94

Values are presented as means ± standard deviations, where shown. *CAD*, Coronary artery disease; *NPDR*, nonproliferative diabetic retinopathy; *PDR*, proliferative diabetic retinopathy; *eGFR*, estimated glomerular filtration rate; *BNP*, B-type natriuretic peptide; *LDL*, low-density lipoprotein; *HDL*, high-density lipoprotein.

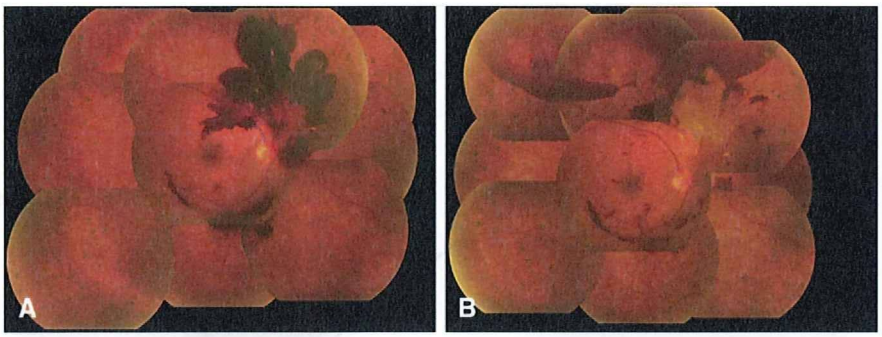

FIGURE 2. Vitreous hemorrhage in patients with diabetic retinopathy after drug-eluting stent implantation. Twenty-one days after drug-eluting stent implantation, a fundus photograph (A) revealed a considerable degree of vitreous hemorrhage in the right eye. Three months after drug-eluting stent implantation, the patient's vitreous hemorrhage shows no tendency to subside with continued dual-antiplatelet therapy (B).

were at severe stages of diabetes mellitus, and therefore the high prevalence of insulin treatment can be expected.

Most patients with DR who were referred to our diabetic retinocoronary clinic were asymptomatic. Few studies assessed the incidence of CAD in asymptomatic patients with DR with normal ECG results and indicated that approximately 20% of these patients had CAD.[14-16] In the present study 20.5% of patients with DR without Q-wave or ST-T changes had angiographically confirmed CAD. The results of previous studies and our results correspond closely. One important issue is that identification of CAD is sometimes difficult, especially in patients with sight-threatening DR. Many patients with this condition have limited physical activity because of impaired vision.[17-19] Limited physical activity clearly reduces the appreciation of ischemic pain and is attributed to the difficulty of evaluation of chest pain. In this study 11 patients had severely impaired vision, and therefore we could not evaluate their symptoms. One patient with PDR had previously had typical angina pectoris, but he said that his angina disappeared after vitreous hemorrhage. Furthermore, 4 patients in whom coronary revascularization was indicated refused it because they were completely free of angina pectoris.

In patients with DR and CAD, the main treatment effect of coronary revascularization should be to prevent myocardial infarction and death from CAD. Evidence indicates that PCI does not reduce the risk of death or myocardial infarction in patients with stable CAD.[20,21] In contrast, CABG confers survival benefit to high-risk patients, such as those with extensive coronary disease or diabetes mellitus.[22,23] In addition, our previous study demonstrated that the survival benefit of CABG over PCI is more apparent in patients with DR than in diabetic patients without retinopathy.[24] Overall consideration suggests that CABG should be the first choice for revascularization of patients with DR and CAD.

Previously, we demonstrated that long-term survival after CABG is closely related to the severity of DR and that patients with advanced DR have a poor prognosis.[25,26] Furthermore, we showed that patients with NPDR have a greater risk of target-vessel failure (defined as a composite of cardiac death, myocardial infarction, and target-vessel revascularization) after drug-eluting stent (DES) implantation.[27] In this study the prevalence of angiographically confirmed CAD was similar in patients with NPDR (28.8%) and in those with PDR (24.5%). However, the association between the severity of DR and the extent of CAD were not evaluated in this study. Nargaz and colleagues[28] demonstrated that the diffuse nature of CAD is associated with the severity of DR. We postulate that detecting occult CAD followed by CABG would confer survival benefit effectively in patients with DR, especially in the early stage.

Vitreous hemorrhage is a sight-threatening complication in patients with DR and requires vitreous surgery in persistent cases. Progression of DR involving vitreous hemorrhage can take place spontaneously in diabetic patients after coronary revascularization with either PCI or CABG, but little about the prevalence of vitreous hemorrhage after coronary revascularization is known.[29-31] A large number of patients with DR who are at risk of vitreous hemorrhage appear to undergo coronary revascularization. Therefore the issue of postrevascularization vitreous hemorrhage is an important one for both cardiologists and cardiac surgeons. This study revealed that vitreous hemorrhage after coronary revascularization was unexpectedly high in patients with PDR. Of 24 patients with PDR undergoing coronary revascularization, 6 (25%) had vitreous hemorrhage within 6 months after the initial revascularization. Our experience indicates that careful postoperative eye care is required. Figure 2 presents one case. The difficulty in treating vitreous hemorrhage after PCI with DES implantation is that prolonged dual-antiplatelet therapy is mandatory because of further potential risk for stent thrombosis. Therefore the future risk of vitreous hemorrhage might influence the choice of revascularization strategy for patients with DR, and DES implantation might not be indicated in patients with PDR.

In 2005, the Japanese Ophthalmologists Association announced that approximately 3 million Japanese people between the ages of 50 and 69 years have DR. In the present

study 12.1% of patients with DR in whom CAD was not suspected had LMT, proximal LAD disease, or both. Theoretically, CABG with an internal thoracic artery graft confers the survival benefit effectively in patients with LMT disease, proximal LAD disease, or both. Therefore 363,000 patients in Japan can be expected to benefit greatly from early CABG. On the other hand, annually, approximately 20,000 patients in Japan undergo CABG; in other words, 4000 patients with DR undergo CABG per year. These estimates suggest that a large number of patients with DR in whom the survival chances can be improved by CABG would remain without diagnoses until a fatal coronary event. We think that this specialized clinic might become the new model of an institution for identifying occult CAD in patients with DR requiring CABG.

The present study has some caveats. First, this study did not include diabetic patients without retinopathy. Therefore we did not estimate the relative risk of occult CAD in patients with DR compared with that in seen diabetic patients without retinopathy. Previous studies have demonstrated that the incidence of occult CAD in diabetic patients without retinopathy has ranged from 1.5% to 8.5%.[14-16] In addition, the previous studies have shown that the risk of cardiac events in diabetic patients without retinopathy is lower than that seen in patients with DR.[3-11]

Second, we used ETT as a diagnostic test for CAD screening in patients in whom ETT was not precluded. Therefore, some patients with negative results on diagnostic tests might have a significant stenotic CAD.

Third, in this study the survival data of patients with negative diagnostic test results were not obtained. The mean follow-up duration of patients with CAD since the initial admission to our clinic was 415 days, and no one died during this period. Therefore, long-term follow-up might be required to evaluate the survival benefit of early CABG.

Finally, in Japan medical costs are 3200 yen for ETT, 33,000 yen for coronary CT, and 94,000 yen for exercise thallium scintigraphy. Further study is needed regarding cost-effective analysis of our proactive strategy.

While acknowledging these caveats, we believe that the incidence of CAD in patients with DR seems very high, and we believe that targeting patients with DR among the general population of diabetic patients would be a useful strategy for improving the life expectancy of the overall diabetic population.

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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 ——

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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.

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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.

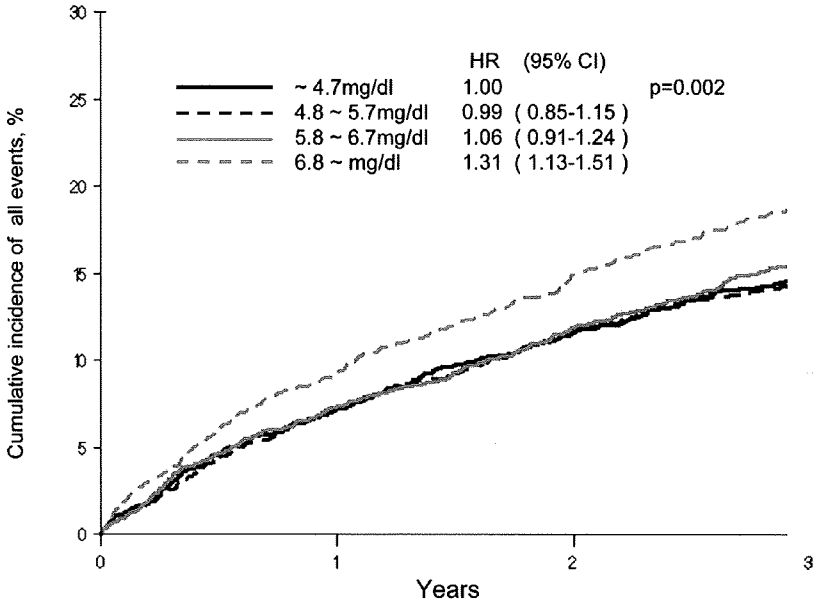

Figure 1. Comparison of cumulative incidence of cardio-and cerebrovascular events including all-cause death among quartiles with uric acid ≥6.8 mg/dl (gray broken line), 5.8–6.7 mg/dl (gray solid line), 4.8–5.7 mg/dl (black broken line), and <4.7 mg/dl (black solid line). HR, hazard ratio; CI, confidence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

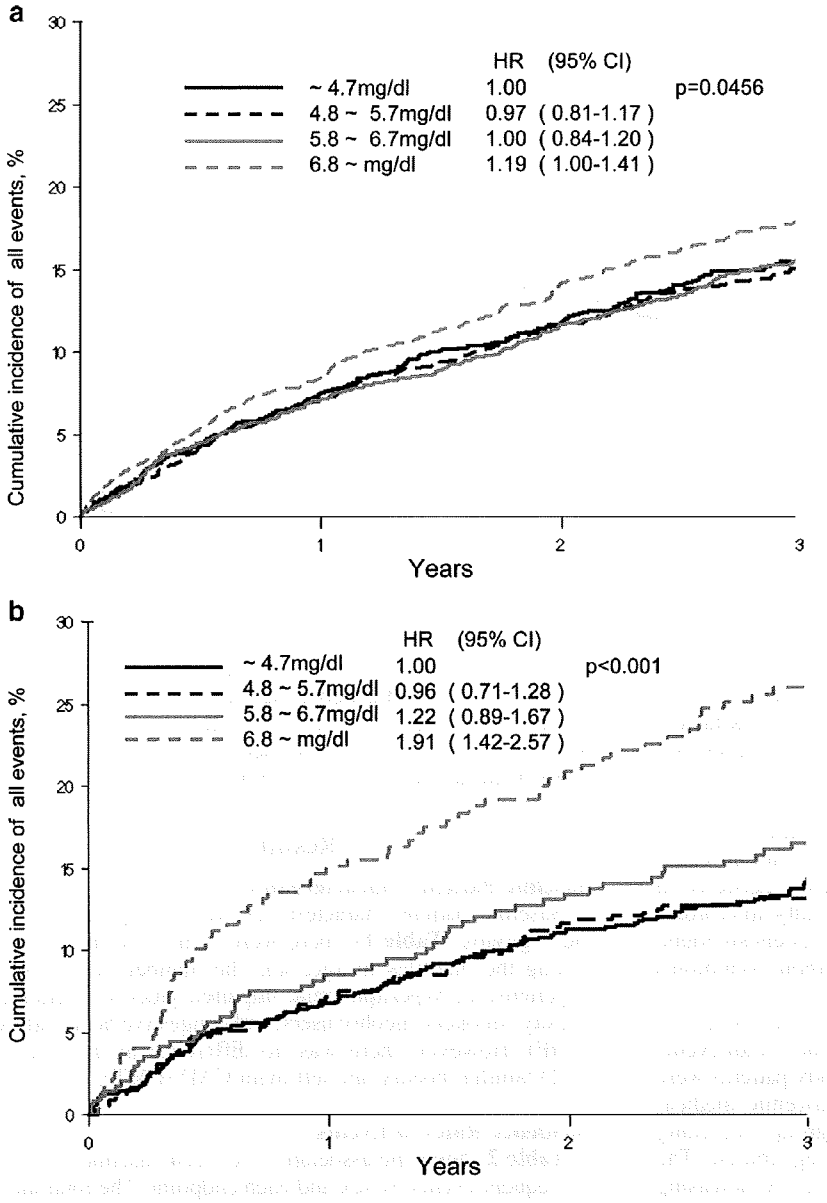

Figure 2. Comparison of cumulative incidence of cardio- and cerebrovascular events including all-cause death by quartiles of uric acid ≥6.8 mg/dl (gray broken line), 5.8–6.7 mg/dl (gray solid line), 4.8–5.7 mg/dl (black broken line), and <4.7 mg/dl (black solid line) in (**a**) male and (**b**) female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

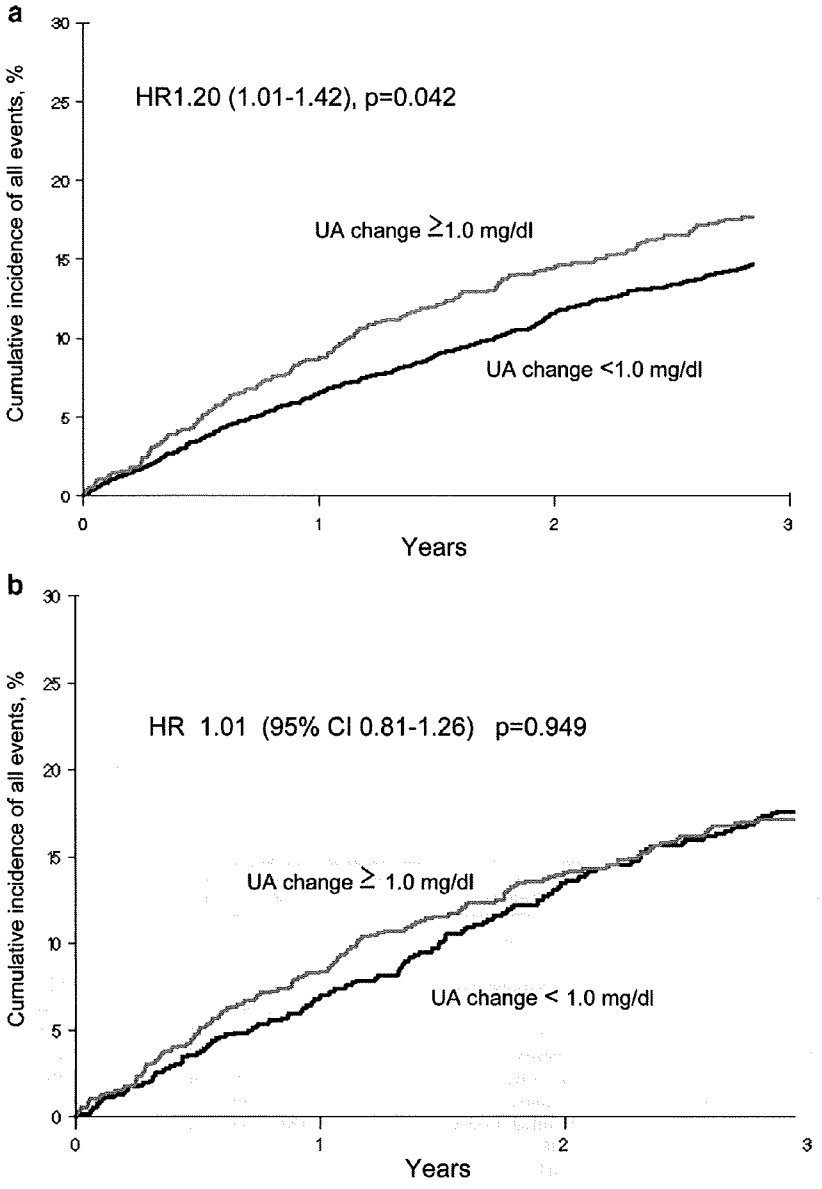

Figure 3. Comparison of cumulative incidence of cardio- and cerebrovascular events including all-cause death in patients with change in uric acid (UA) level ≥1.0 mg/dl (gray line) and <1.0 mg/dl (black line) before (**a**) and after (**b**) propensity score matching. HR, hazard ratio; CI, confidence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

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Circ J 2009; **73:** 912–917

Gender Differences in Patients With Coronary Artery Disease in Japan

—— The Japanese Coronary Artery Disease Study (The JCAD Study) ——

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Background: Gender differences among patients with coronary artery disease vary from study to study. In one of the largest studies, the Japanese Coronary Artery Disease (JCAD) Study, gender differences in patients were investigated.

Methods and Results: Consecutive patients diagnosed with stenosis 75% or more in at least one branch of the coronary arteries were enrolled in the study. The endpoint is a composite of all-cause death and cardiovascular events. Data were collected over the internet. Out of 15,628 patients screened, 13,812 of them met the inclusion criteria and were followed up for a mean period of 2.7 years. The event rate was 62.8 per 1,000 patients-year, all-cause death 17.3 and total cardiac events 47.4. The incident rate of unstable angina was higher in females (27.1) than males (21.8) (P=0.0363). The incidence of all-cause death was lower in females than males (16.9 and 17.8, respectively; P=0.0148). Other than gender, hypertension and number of vessel disease contribute to the event of unstable angina, and age, family history, obesity, impaired fasting glycemia, hyperlipidemia, congestive heart failure and number of vessel disease contribute to the all-cause death.

Conclusions: Gender is an independent contributing factor of unstable angina and of all-cause death. (*Circ J* 2009; **73:** 912–917)

Key Words: Coronary artery disease; JCAD Study; Prognosis; Sex difference

Coronary and cerebrovascular diseases are the leading causes of death in Japan[1] The incidence of coronary artery diseases (CADs) and the prognosis are known to be different between men and women[1,2] The Japanese Coronary Artery Disease (JCAD) Study[3] is one of the largest cohort studies conducted to date in Japan, in which the diagnosis of CAD was confirmed in more than 13,000 of the enrolled patients with coronary angiography (CAG). The aim of the present study is to assess gender difference with regard to prognosis and to evaluate the contributing factors using this large scale database.

Methods

Investigations

The complete protocol of the present study with the purpose, study design, criteria for eligibility and exclusion of patients, clinical measures, events and statistical analyses has been published elsewhere[4] Briefly, the patients underwent CAG for various reasons, such as old and acute myocardial infarction (MI), stable and unstable angina, chronic heart failure and clinical demand to perform the procedure. All CAG was performed after written consent was given, except in emergency cases in which oral agreement was obtained. All consecutive patients diagnosed as having 75% or higher stenosis according to the American Heart Association (AHA) classification in at least one branch of the coronary arteries by cardiac catheterization were registered in the study. Data including background information, risk factors, clinical management, and medication were collected over the internet. When follow-up data of more than 6 months could be obtained or when a cerebro- and cardiovascular event occurred, including death, within 6 months of enrollment, the participants were included in the final analysis. The patients were followed up for 3 years. The endpoint used in this report is a composite of all-cause death and cardiovascular events, defined as the occurrence of fatal and non-fatal MI, fatal and non-fatal stroke, other cardiovascular events and death of any cause.

Clinical events to be registered in the database were defined as follows: all-cause deaths including cardiac, cerebral, vascular and other deaths and cerebral, cardiac and vascular events. Cerebro-vascular accidents (CVAs) included cerebral hemorrhage, cerebral infarction and transient ischemic attack (TIA). Cardiac events consisted of fatal and non-fatal MI, unstable angina, congestive heart failure

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Table 1. Clinical Profile of Both Genders

	Female	Male	P value	
Number of patients	3,172	10,576		
Age (years)				
Mean±SD	68.8±9.1	64.5±9.8	0.000	*
Height (cm)				
Mean±SD	149.7±6.1	163.4±6.4	0.000	*
Weight (kg)				
Mean±SD	53.1±8.7	63.9±9.8	0.000	*
Body mass index				
Mean±SD	23.7±3.5	23.9±3.0	0.000	*
Smoking				
+	427 (13.5%)	4,988 (47.2%)	0.000	**
−	2,745 (86.5%)	5,588 (52.8%)		
Family history				
+	525 (16.6%)	1,752 (16.6%)	0.984	**
−	2,647 (83.4%)	8,824 (83.4%)		
Past history				
+	1,668 (52.6%)	6,146 (58.1%)	0.000	**
−	1,504 (47.4%)	4,430 (41.9%)		
Myocardial infarction				
+	780 (46.8%)	3,601 (58.6%)	0.000	**
−	888 (53.2%)	2,545 (41.4%)		
Angina pectoris				
+	959 (57.5%)	2,595 (48.1%)	0.000	**
−	709 (42.5%)	3,187 (51.9%)		
Congestive heart failure				
+	64 (3.8%)	173 (2.8%)	0.030	**
−	1,604 (96.2%)	5,973 (97.2%)		
Intervension (history)				
+	1,228 (73.6%)	4,744 (77.2%)	0.002	**
−	440 (26.4%)	1,402 (22.8%)		
PCI				
+	978 (79.6%)	3,887 (81.9%)	0.065	**
−	250 (20.4%)	857 (18.1%)		
Coronary artery bypass graft				
+	278 (22.6%)	963 (20.3%)	0.071	**
−	950 (77.4%)	3,781 (79.7%)		
Intracoronary thrombolysis				
+	19 (1.5%)	115 (2.4%)	0.064	**
−	1,209 (98.5%)	4,629 (97.6%)		
Congestive heart failure				
+	364 (12.0%)	1,021 (10.1%)	0.003	**
−	2,674 (88.0%)	9,055 (89.9%)		
LVEF (%)				
Mean±SD	62.0±14.0	58.5±14.2	0.000	*
Coronary arteriography (number of vessel disease)				
1	1,428 (45.0%)	4,642 (43.9%)	0.258	**
2	1,008 (31.8%)	3,526 (33.3%)		
3	736 (23.2%)	2,408 (22.8%)		
Left main trunk disease				
+	103 (3.2%)	460 (4.3%)	0.006	**
−	3,069 (96.8%)	10,116 (95.7%)		
Impaired fasting glycemia including diabetes mellitus				
+	1,372 (43.3%)	4,178 (39.5%)	0.000	**
−	1,800 (56.7%)	6,398 (60.5%)		
Hemoglobin A_{1c} (%)	6.54±1.60	6.27±1.45	0.000	*
Hyperlipidemia (mg/dl)				
+	1,989 (62.7%)	5,525 (52.2%)	0.000	**
−	1,183 (37.3%)	5,051 (47.8%)		
Low-density lipoprotein-cholesterol	127.8±36.1	120.8±33.3	0.000	*
High-density lipoprotein-cholesterol	51.7±15.1	45.8±14.0	0.000	*
Triglycerides	132.8±71.3	141.9±85.7	0.000	*
Hypertension (mmHg)				
+	2,045 (64.5%)	5,871 (55.5%)	0.000	**
−	1,127 (35.5%)	4,705 (44.5%)		
Systolic blood pressure	136.5±21.9	132.1±20.1	0.000	*
Diastolic blood pressure	73.7±12.5	75.0±12.42	0.000	*
Uric acid (mg/dl)	5.16±1.86	6.02±1.62	0.000	*
Lipoprotein (a) (mg/dl)	29.9±26.5	28.7±25.6	0.474	*
C-reactive protein (mmHg)	0.51±1.69	0.55±1.88	0.014	*
Fibrinogen (mg/dl)	340.6±103.3	333.8±96.8	0.097	*
Smoking guidance				
+	545 (18.5%)	4,959 (48.8%)	0.000	**
−	2,405 (81.5%)	5,205 (51.2%)		
Diet guidance				
+	2,117 (71.6%)	7,139 (72.8%)	0.224	**
−	838 (28.4%)	2,670 (27.2%)		
Exercise training				
+	1,024 (34.8%)	3,561 (36.5%)	0.093	**
−	1,919 (65.2%)	6,198 (63.5%)		

*Wilcoxon analysis; **chi-squared analysis.
LVEF, left ventricular ejection fraction measured with left ventriculography or echocardiography.

Table 2. Cardiac/Non-Cardiac Events in Female and Male Gender (COX Regression Analysis*)

	Patients/ 1,000 patient-years		COX HR	P value
	Female	Male	95%CI for COX HR	Female vs Male
Incidence rate				
AMI	7.22	7.66	0.786–1.493	0.626
Unstable AP	27.1	21.8	0.694–0.988	0.036
Arrhythmia/CPR	0.37	0.44	0.202–3.606	0.829
CPAOA	2.47	2.82	0.717–2.117	0.450
CABG	4.23	4.82	0.803–1.825	0.361
CHF	12.7	9.7	0.808–1.355	0.732
CVA	5.08	5.78	0.772–1.648	0.534
TIA	0.99	1.04	0.338–1.970	0.650
Mortality rate				
Cardiovascular death	7.89	7.63	0.827–1.544	0.442
Cerebro/cardiovascular death	8.51	9.11	0.962–1.736	0.088
All-cause death	16.9	17.8	1.052–1.596	0.014

*Corrected with age, obesity, somoking, alcohol intake, family history, history of CHF, number of vessel disease, left main trunk disease, impaired fasting glycemia, hyperlipidemia and hypertension.
HR, hazard ratio; CI, confidence interval; AMI, acute myocardial infarction; AP, angina pectoris; CPR, cardiopulmonary resuscitation; CPAOA, cardiopulmonary arrest on arrival; CABG, coronary artery bypass graft; CHF, congestive heart failure; CVA, cerebro-vascular accident; TIA, transient ischemic attack.

Table 3. Contributing Factors of Unstable Angina and All-Cause Death (COX Regression Analysis)

	COX HR	95%CI	P value
Unstable AP			
Male	0.828	0.694–0.988	0.036
Hypertension	1.352	1.162–1.571	0.000
VD	1.311	1.199–1.433	0.000
All-cause death			
Male	1.296	1.052–1.596	0.014
Age	1.052	1.041–1.062	0.000
CHF	3.402	2.859–4.048	0.000
VD	1.380	1.247–1.528	0.000
IFG	1.247	1.061–1.466	0.007
Hyperlipidemia	0.721	0.611–0.850	0.000
Obesity (body mass index ≥25)	0.804	0.666–0.971	0.023
Positive family history	0.743	0.580–0.951	0.018

VD, number of vessel disease; IFG, impaired fasting glycemia including diabetes mellitus. Other abbreviations see in Table 2.

(CHF), coronary bypass graft surgery (CABG), resuscitated cardiac arrest and cardiopulmonary arrest on arrival (CPAOA). Aortic dissection and rupture of aortic aneurysm were classified as vascular events.

Statistical Analysis

Continuous variables are expressed as mean±SD (median), and categorical variables are expressed as percentages. Mean values for age, left ventricular ejection fraction (LVEF), lipid concentration, HbA_{1c}, blood pressure, height, weight, body mass index (BMI), cigarettes, uric acid, Lp(a), C-reactive protein (CRP), and fibrinogen were tested with the Wilcoxon test, and the prevalence of baseline characteristics were tested with the chi-square test for comparison between men and women. Relative risks and the 95% confidence intervals were calculated using the Cox proportional hazards model with adjustment for baseline characteristics such as age, obesity, smoking, family history, past history of MI, angina pectoris (AP) and CHF, coronary interventions, CHF, LVEF, number of coronary vessel disease, left main trunk disease, impaired fasting glycemia (IFG) including diabetes mellitus, lipid profile, hypertension and others (**Table 1**). A P-value <0.05 was considered significant.

Ethical Considerations

The protocol of the current study was approved by the Central Institutional Review Board in the University of Tokyo.

Results

Of the recruited 15,628 individuals, 13,748 CAD patients satisfied the criteria for eligibility. The patients consisted of 3,172 females and 10,576 males (**Table 1**). The follow-up rate was 83.5% and the mean follow-up period was 2.7 years. Females were older than males in average (68.8±9.1 years old in females, 64.5±9.8 years old in males). Nearly 50% of the patients had a history of MI; 58.6% in males but 46.8% in females. AP was present in 57.5% in females, and 48.1% in males. With regard to risk factors, 54.6% of the patients had hyperlipidemia (62.7% in females, 52.2% in males), and 57.6% had hypertension (64.5% in females, 55.5% in males). Patients with IFG were 40.3% (43.3% in females, 39.5% in males). More than 65% of the patients bore multiple risk factors of life style-related diseases (smoking, BMI ≥25, hypertension, IFG, hyperlipidemia, regular alcohol consumption); 35.9% had 2 risk factors, 23.5% had 3 and 5.9% had 4 risk factors.

The Incident Rate of Events

The incident rates of events as expressed in events per 1,000 patient-years are shown in **Table 2**. The incidence

Table 4. COX Regression Analysis of Clinical Events in Both Genders

	Female			Male		
	COX HR	95%CI	P value	COX HR	95%CI	P value
AMI						
Smoking	2.534	1.335–4.807	0.004			
CHF (Hx)	2.285	1.245–4.192	0.007	1.660	1.138–2.419	0.008
IFG				1.480	1.120–1.956	0.006
Unstable AP						
Age				1.011	1.001–1.020	0.023
Hypertension				1.355	1.140–1.612	0.001
VD	1.361	1.147–1.615	0.000	1.295	1.166–1.438	0.000
CHF						
Age	1.055	1.028–1.083	0.000	1.045	1.030–1.061	0.000
CHF (Hx)	6.559	4.361–9.864	0.000	8.126	6.341–10.415	0.000
IFG	1.692	1.117–2.564	0.013	1.476	1.150–1.895	0.002
VD				1.249	1.068–1.462	0.005
Cardiovascular death						
Age	1.087	1.051–1.124	0.000	1.038	1.021–1.055	0.000
CHF (Hx)	6.695	3.984–11.25	0.000	6.896	5.214–9.122	0.000
Hyperlipidemia	0.569	0.341–0.95	0.031			
IFG	1.915	1.139–3.221	0.014			
VD	1.609	1.17–2.212	0.003	1.706	1.423–2.046	0.000
LMT disease				1.878	1.218–2.898	0.004
Cerebro-/cardiovascular death						
Age	1.077	1.043–1.113	0.000	1.044	1.028–1.060	0.000
CHF (Hx)	6.682	4.063–10.988	0.000	5.538	4.272–7.180	0.000
Hyperlipidemia	0.514	0.313–0.845	0.009			
IFG	1.785	1.084–2.941	0.023			
VD	1.550	1.140–2.108	0.005	1.556	1.320–1.833	0.000
LMT disease				1.623	1.058–2.491	0.027
All-cause death						
Age	1.051	1.028–1.074	0.000	1.052	1.041–1.064	0.000
Smoking	1.895	1.167–3.077	0.010			
Alcohol	0.401	0.162–0.994	0.049			
CHF (Hx)	3.875	2.716–5.529	0.000	3.236	2.645–3.958	0.000
Hyperlipidemia	0.534	0.377–0.756	0.000	0.786	0.652–0.948	0.012
IFG				1.231	1.024–1.478	0.027
Obesity				0.796	0.642–0.987	0.037
VD	1.487	1.199–1.844	0.000	1.348	1.201–1.513	0.000

Hx, history. Other abbreviations see in Tables 2,3.

of MI was 58 cases (7.22 patients/1,000 patient-years) in females and 205 cases (7.66) in males without a significant difference. The incidence of unstable angina was 210 cases (27.1) in female and 569 cases (21.8) in male, and the rate was higher in females than males (P=0.0363). Other events such as arrhythmia/cardiopulmonary resuscitation (3 cases in female and 12 cases in male), CPAOA (20 and 79 cases, respectively), CABG (34 and 129 cases, respectively), CHF (101 and 260 cases, respectively), CVA (41 and 155 cases, respectively), TIA (8 and 28 cases, respectively), cardiovascular death (64 and 206 cases, respectively) and cerebro/cardiovascular death (69 and 246 cases, respectively) showed no significant difference between genders, whereas an event rate of all-cause of death was lower in females (137 cases, 16.9 patients/1,000 patient-years) than males (481 cases, 17.8) (P=0.014).

Table 3 shows clinical factors contributing to unstable angina and all-cause of death. Female gender, as well as hypertension and number of vessel disease, increase the risk of unstable AP. In all-cause death male gender as well as age, CHF, IFG and number of vessel disease contributed to increase hazard, whereas presence of hyperlipidemia, obesity and family history decrease hazard.

Table 4 shows contributing factors in various clinical events in female and in male. Smoking plays an important role in acute MI and all-cause death, but alcohol consumption is beneficial in the latter in female. Age is contributing to various events except acute MI in both genders and unstable AP in female. A history of CHF plays an important role in cardiac events and cardiovascular death except unstable AP in both genders. Ordinary coronary risk factors (hypertension, hyperlipidemia, IFG) are also closely correlated with various events in this study group. Number of coronary vessel disease is associated with cardio- and cerebro-vascular events, but not in acute MI.

Discussion

Our study is unique to assess gender difference with regard to prognosis and to evaluate the contributing factors using a large number of patients with angiographically confirmed coronary atherosclerosis. Gender is an independent contributing factor in prognosis of unstable angina (worse in females than males) and in all-cause mortality (better in females than males) of this large scale cohort in JCAD patients. Hypertension and number of vessel disease also contribute to the former, and age, CHF, number of vessel disease, IFG, hyperlipidemia, obesity, and family history contribute to the latter.

The incident rate of MI in this study was 7.56 per 1,000 patients-year, which is considerably higher than the numbers in the general population (0.524–1.25 per 1,000 patients-