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Clinical Features of Japanese Smokers with Initially Diagnosed Coronary Artery Disease : Association of Calcium-channel Blocker Use with Onset of Acute Myocardial Infarction

Hidenori YAGI, Makoto KAWAI, Shinichiro TAKIZAWA, Yasunori INOUE, Toshikazu KUDO, Kunihiko YUMINO, Takatoku AIZAWA, Kenichi YOKOYAMA, Kenichi TOKUTAKE, Akira YOSHII, and Michihiro YOSHIMURA

Division of Cardiology, Department of Internal Medicine, The Jikei University School of Medicine

ABSTRACT

Background : Smoking is an important risk factor for coronary artery disease (CAD). We evaluated the initial clinical presentation of CAD and factors associated with the onset of CAD in smokers.

Methods : Among 2,567 consecutive patients who underwent coronary angiography at our institution, 405 patients in whom CAD was diagnosed for the first time were divided into 140 smokers and 265 nonsmokers (including 108 never smokers and 157 former smokers) and reviewed. The initial clinical presentation of CAD, which was either angina pectoris or acute myocardial infarction (AMI) and unstable angina pectoris ; risk factors ; and previous medications were compared between smokers and nonsmokers. In addition, the initial clinical presentation of CAD was examined according to the use of the medication most strongly associated with preventing CAD among previously administered drugs in each group.

Results : The prevalence of AMI was significantly higher in smokers (47.1%) than in nonsmokers (23.8%, $p<0.001$). The rates of calcium-channel blocker (CCB) use and statin use were lower in smokers. Univariate analysis of patient subgroups based on the use of CCBs or statins revealed that the prevalence of AMI was lower only in smokers using CCB than in smokers not using CCBs. Adjusted multivariate analysis revealed that only CCB use was associated with a reduced risk of AMI in smokers (odds ratio, 0.43 ; 95% CI ; 0.19 to 0.96 ; $p=0.04$).

Conclusion : AMI as the initial clinical presentation of CAD is observed more commonly in smokers than in nonsmokers. While smoking cessation is the primary strategy for preventing CAD, CCB use is associated with a reduced incidence of AMI in Japanese smokers and is, therefore, a potential strategy for preventing CAD. (Jikeikai Med J 2014 ; 61 : 43-51)

Key words : cigarette smoking, acute myocardial infarction, calcium-channel blocker

INTRODUCTION

Coronary artery disease (CAD) is an atherosclerotic heart disease caused by the buildup in the coronary arterial walls of plaques, which narrow the arteries and reduce blood flow to the heart. Usually CAD progresses gradually, and inadequate coronary perfusion may cause regional myocardial ischemia and angina pectoris. However, if an atherosclerotic plaque suddenly ruptures and forms blood clots, it also can completely block the coronary arteries and trigger acute coronary syndrome (ACS), that is, acute myocardial infarction (AMI) and unstable angina pectoris (UAP).

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八木　秀憲，川井　　真，滝沢信一郎，井上　康憲，工藤　敏和，弓野　邦彦，相澤　隆徳，横山　賢一，徳竹　賢一，吉井　　顕，吉村　道博

Mailing address : Hidenori YAGI, Division of Cardiology, Department of Internal Medicine, The Jikei University School of Medicine, 3-25-8 Nishi-shimbashi, Minato-ku, Tokyo 105-8461, Japan.

E-mail : yagi@jikei.ac.jp

Thus, CAD can vary substantially in its clinical presentation.

Smoking is a major risk factor for CAD. The risk of AMI increases with the number of cigarettes smoked per day[1-3]. In addition, smoking cessation decreases the risks of both CAD and recurrent coronary events after AMI[3-6].

Smoking and hypertension were previously reported to be more predictive of ACS than were stable angina pectoris as an initial clinical presentation of CAD[7,8]. In recent years, metabolic syndrome and chronic kidney disease (CKD) have been accepted as new risk factors for cardiovascular disease[9,10]. However, we have previously shown that cigarette smoking is a more important as a risk factor for ACS than are other traditional risk factors, metabolic syndrome, or CKD[11].

Multiple risk factors promote atherosclerosis[12,13]. However, these risk factors may vary in the degree to which they promote CAD. Furthermore, neither the clinical features of CAD caused by smoking nor how smokers develop CAD is clearly understood. We wanted to know what factors promote the onset of CAD in smokers. Therefore, in the present study, we evaluated the initial clinical presentation of CAD and the factors associated with its onset in smokers.

Preventing the onset of CAD involves treating multiple risk factors. Some medications are reportedly associated with the initial clinical presentation of CAD[14]. We previously found calcium-channel blockers (CCBs) to have a preventive effect on ACS in the Japanese population[11]. Therefore, we also evaluated the potential of certain medications in the primary prevention of CAD to affect the initial clinical presentation of CAD in smokers.

PATIENTS AND METHODS

Subjects and design

From November 2004 through March 2008, 2,567 consecutive patients underwent coronary angiography at The Jikei University Hospital in Tokyo, Japan. From among these patients, 405 in whom CAD was diagnosed for the first time were selected as subjects of the present study. CAD was defined, with the American Heart Association classification, as stenosis of 75% or more, visually assessed with coronary angiography, in at least 1 epicardial coronary artery. Among the patients with initially diagnosed CAD, 55 patients who had had a myocardial infarction were excluded. In addition, patients who had coronary artery spasm or had coronary artery stenosis of less than 75% or both were excluded.

The patients were divided into 2 groups based on whether they had smoked when the symptoms or findings of CAD appeared : those who smoked (Smoker group) and those who did not smoke (Nonsmoker group). Smoking status was assessed at the time of the first medical examination at our hospital using information obtained from hospital medical records, a questionnaire, and direct patient interviews. Smokers were defined as patients who had smoked cigarettes for at least 1 year before the appearance of symptoms or other findings of CAD. However, smoking cessation just after the appearance of symptoms or findings of CAD was not taken into consideration. In addition, former smokers who had quit smoking before the appearance of symptoms or other findings of CAD were included in the Nonsmoker group along with patients who had never smoked cigarettes (never smokers). In each group we examined the initial clinical presentation of CAD, which was either angina pectoris or ACS ; the presence of other risk factors, including traditional coronary risk factors (age, hypertension, dyslipidemia, type 2 diabetes, and obesity), metabolic syndrome, and CKD ; and any previous medications for the primary prevention of CAD.

The initial clinical presentation of CAD was examined in each group according to the use of the medication most strongly associated with preventing CAD among previously administered drugs.

The study protocol [22-039 (6216)] was approved by the ethics committee of The Jikei University School of Medicine.

Definition of ACS

ACS was defined as the presence of AMI or UAP. The diagnosis of AMI was based on the "Universal definition of myocardial infarction" and required the presence of any 2 of the following 3 criteria : 1) a history of chest pain, oppression, or discomfort over 20 minutes ; 2) typical electrocardiographic changes (namely, ST segment elevation of 0.1 mV or greater in at least 1 standard lead or 2 precordial leads, ST segment depressions of 0.1 mV or greater in at least 2 leads, and abnormal Q waves or T wave inversions in at least 2 leads) ; and 3) an increased serum level of the

MB fraction of creatine kinase to at least twice the upper limit of the normal range[15]. All patients were hospitalized within 1 week of the onset of AMI. A diagnosis of UAP was made when patients had chest pain, oppression, or discomfort at rest within 72 hours before hospitalization without an increase in the serum level of the MB fraction of creatine kinase that satisfied the above criteria.

Definitions of traditional risk factors

When patients received a diagnosis of CAD, each known risk factor was examined. Hypertension was defined as the presence of any of the following : systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive agents. Dyslipidemia was diagnosed when any lipid-lowering agent was used, and/or by the presence of 1 or more of the following 3 lipid disorders at the first fasting blood sampling : low-density lipoprotein (LDL) cholesterol ≥140 mg/dL, triglycerides ≥150 mg/dL, and high-density lipoprotein (HDL) cholesterol <40 mg/dL. Type 2 diabetes was diagnosed on the basis of the presence of any of the following : fasting plasma glucose level ≥126 mg/dL, casual plasma glucose level ≥200 mg/dL, or a history of type 2 diabetes. However, the fasting plasma glucose level in patients with ACS was determined after the inflammatory reaction had resolved. The value for HbA1c (%) was estimated as a National Glycohemoglobin Standardization Program equivalent value (%). Obesity was defined as body-mass index ≥25 kg/m^2.

Metabolic syndrome was diagnosed by applying the definition of the International Diabetes Federation[16]. We determined the estimated glomerular filtration rate (eGFR) from serum creatinine values using the Modification of Diet in Renal Disease equation with coefficients modified for Japanese patients[17]. We defined proteinuria as a urine protein level of 1+ or greater by dipstick analysis and defined microalbuminuria as a spot urine albumin-to-creatinine ratio of 30 to 300 mg albumin/g creatinine. The diagnosis of CKD was based on the presence of proteinuria or microalbuminuria, an eGFR <60 mL/min/1.73 m^2, or both.

Information about the treatment of risk factors at the time of the first examination at our hospital was obtained from hospital medical records, questionnaires, and direct patient interviews. Medications started just after the onset of CAD symptoms were excluded.

Statistical analysis

Continuous variables were compared by means of unpaired *t*-tests, the Mann-Whitney U-test, or one-way analysis of variance and are expressed as means±SD. Categorical variables were compared by means of the chi-square test or Fisher's exact test and are expressed as percentages. Multivariate analysis for the associations with AMI was performed with multiple regression tests.

Differences with *p*-values of less than 0.05 were considered to be statistically significant. All data were statistically analyzed using the SPSS software package, version 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of smokers at initial diagnosis of coronary artery disease

Of the 405 subjects in whom CAD was diagnosed for the first time, 140 were placed in the Smoker group and 265 in the Nonsmoker group.

The smoking status of smokers in the Smoker group and that of former smokers in the Nonsmoker group (n=157) were as follows. The number of cigarettes smoked per day did not differ significantly between current smokers of the Smoker group (25.6±12.5/day) and former smokers in the Nonsmoker group (26.9±15.0/day). However, smoking duration was longer for smokers in the Smoker group (35.9±9.9 years) than for former smokers in the Nonsmoker group (29.6±14.4 years, p<0.001). In addition, the mean period after smoking cessation in former smokers was 15.4±12.8 years.

Compared with patients in the Nonsmoker group, those in the Smoker group were younger and had higher triglyceride levels, lower HDL cholesterol levels, and higher eGFR (Table 1).

A comparison of risk factors (Table 2) showed that the rate of hypertriglyceridemia was significantly higher in the Smoker group than in the Nonsmoker group. However, the prevalence of other risk factors, including metabolic syndrome and CKD, did not differ significantly between the groups.

The prevalence of ACS was significantly higher in the Smoker group (60.0%) than in the Nonsmoker group (36.6%, p<0.001, Table 3). Most notably, the prevalence of AMI in the Smoker group (47.1%) was approximately

Table 1. Clinical and laboratory characteristics

	Smoker (n=140)	Nonsmoker (n=265)	p value
Age (years)	58.4 ± 9.6	66.5 ± 10.7	<0.001
Male (%)	123 (87.9%)	216 (81.5%)	0.100
Body-mass index (kg/m^2)	24.4 ± 3.7	24.4 ± 3.0	0.856
Waist circumference (cm)	88.7 ± 9.6	88.1 ± 9.3	0.522
Systolic blood pressure (mm Hg)	139.4 ± 25.5	139.6 ± 19.0	0.942
Diastolic blood pressure (mm Hg)	82.8 ± 15.3	81.0 ± 13.0	0.229
Triglycerides (mg/dL)	146.6 ± 112.4	123.2 ± 62.6	0.023
High-density lipoprotein cholesterol (mg/dL)	44.0 ± 10.9	48.0 ± 13.2	0.001
Low-density lipoprotein cholesterol (mg/dL)	132.3 ± 35.6	125.1 ± 35.2	0.053
Fasting plasma glucose (mg/dL)	107.1 ± 27.9	107.4 ± 27.1	0.914
Hemoglobin A1c (%)	6.3 ± 1.7	6.1 ± 1.4	0.288
Serum creatinine (mg/dL)	1.4 ± 2.3	1.5 ± 2.2	0.840
Estimated glomerular filtration rate (mL/min/1.73 m^2)	70.8 ± 27.3	65.0 ± 27.1	0.041
Urine protein level	0.5 ± 1.3	0.5 ± 1.3	0.597
Urine albumin-to-creatinine ratio (mg/g Cr)	25.1 ± 41.9	24.9 ± 50.8	0.977
C-reactive protein (mg/dL)	0.84 ± 2.29	0.65 ± 1.89	0.380

Table 2. Prevalences of risk factors

	Smoker (n=140)	Nonsmoker (n=265)	p value
Hypertension (%)	92 (65.7%)	194 (73.2%)	0.115
Dyslipidemia (%)	115 (82.1%)	202 (76.2%)	0.170
High low-density lipoprotein cholesterol (%)	80 (57.1%)	144 (54.3%)	0.589
High triglycerides (%)	51 (36.4%)	69 (26.0%)	0.029
Low high-density lipoprotein cholesterol (%)	56 (40.0%)	83 (31.3%)	0.800
Diabetes (%)	50 (35.7%)	91 (34.3%)	0.782
Obesity (%)	56 (40.0%)	103 (38.9%)	0.824
Metabolic syndrome (%)	58 (41.4%)	97 (36.6%)	0.342
Chronic kidney disease (%)	56 (40.0%)	121 (45.7%)	0.257
Estimated glomerular filtration rate <60 mL/min/1.73 m^2 (%)	37 (26.4%)	98 (37.0%)	0.032
Proteinuria (%)	17 (13.9%)	28 (11.7%)	0.536
Microalbuminuria (%)	19 (18.1%)	32 (15.2%)	0.505
Dialysis (%)	11 (7.9%)	20 (7.5%)	0.911

Table 3. Initial clinical presentation of coronary artery disease

	Smoker (n=140)	Nonsmoker (n=265)	p value
Acute coronary syndrome (%)	84 (60.0%)	97 (36.6%)	<0.001
Acute myocardial infarction (%)	66 (47.1%)	63 (23.8%)	<0.001
Unstable angina pectoris (%)	18 (12.9%)	34 (12.8%)	0.994
Angina pectoris (%)	56 (40.0%)	168 (63.4%)	<0.001

twice that in the Nonsmoker group (23.8%, p<0.001, Table 3). However, the prevalence of multivessel disease did not differ between the Smoker group (52.1%) and the Nonsmoker group (48.7%).

The rate of medical treatment of hypertension, in particular, the rate of CCB use, was lower in the Smoker group

Table 4. Medications at time of first examination

	Smoker (n=140)	Nonsmoker (n=265)	p value
Antihypertensive agents (%)	65 (46.4%)	169 (63.8%)	0.001
Angiotensin-converting enzyme inhibitor (%)	8 (5.7%)	24 (9.1%)	0.236
Angiotensin receptor blocker (%)	40 (28.6%)	84 (31.7%)	0.516
Beta-blocker (%)	18 (12.9%)	45 (17.0%)	0.276
Ca-channel blocker (%)	45 (32.1%)	126 (47.5%)	0.003
Diuretics (%)	8 (5.7%)	21 (7.9%)	0.412
Lipid-lowering agents (%)	31 (22.1%)	85 (32.1%)	0.035
Statin (%)	21 (15.0%)	68 (25.7%)	0.014
Fibrate (%)	6 (4.3%)	11 (4.2%)	0.949
Antidiabetic agents (%)	29 (20.7%)	71 (26.8%)	0.177
Insulin (%)	10 (7.1%)	23 (8.7%)	0.591
Sulfonylurea (%)	17 (12.1%)	35 (13.2%)	0.761
Biguanide (%)	8 (5.7%)	13 (4.9%)	0.727
Alpha-glucosidase inhibitor (%)	13 (9.3%)	22 (8.3%)	0.738
Glinide (%)	2 (1.4%)	3 (1.1%)	0.797
Thiazolidinedione (%)	8 (5.7%)	6 (2.3%)	0.071
Antiplatelet agents (%)	20 (14.3%)	58 (21.9%)	0.065

(32.1%) than in the Nonsmoker group (47.5%, p=0.003, Table 4). However, the rates of treatment with beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers did not differ between the groups. In addition, lipid-lowering therapy, in particular, the use of statins, was less frequent in the Smoker group (15.0%) than in the Nonsmoker group (25.7%, p=0.01).

Associations of CCB use and statin use with the onset of AMI in smokers

To examine the association between the use of CCBs or statins and the onset of AMI in smokers, patients in the Smoker and Nonsmoker groups were further subdivided according to the use of CCBs or statins and subjected to univariate analysis. The initial clinical presentation of CAD did not differ between the stain-use subgroups in either the Smoker group or the Nonsmoker group. However, in the Smoker group the prevalence of ACS, in particular, that of AMI, was significantly lower in patients using CCBs than in those not using CCBs (Table 5, 6).

The background clinical characteristics that differed between smokers using CCBs and smokers not using CCBs

Table 5. Characteristics of patients with initially diagnosed coronary artery disease according to use of calcium-channel blockers in smokers and nonsmokers

	Smoker/CCB (+) (n=45)	Smoker/CCB (−) (n=95)	Nonsmoker/CCB (+) (n=126)	Nonsmoker/CCB (−) (n=139)	p value
Age (years)	60.8 ± 8.4	57.2 ± 10.0	69.1 ± 9.6	64.1 ± 11.1	<0.001
Male (%)	42 (93.3%)	81 (85.3%)	103 (81.7%)	113 (81.3%)	0.229
Hypertension (%)	45 (100%)	47 (49.5%)	124 (98.4%)	70 (50.4%)	<0.001
Dyslipidemia (%)	34 (75.6%)	81 (85.3%)	100 (79.4%)	102 (73.4%)	0.174
Diabetes (%)	22 (48.9%)	28 (29.5%)	41 (32.5%)	50 (36.0%)	0.139
Obesity (%)	17 (37.8%)	39 (41.1%)	53 (42.1%)	50 (36.0%)	0.749
Metabolic syndrome (%)	21 (46.7%)	37 (38.9%)	59 (46.8%)	38 (27.3%)	0.006
Chronic kidney disease (%)	27 (60.0%)	29 (30.5%)	68 (54.0%)	53 (38.1%)	<0.0001
Systolic blood pressure (mm Hg)	141.7 ± 19.2	138.3 ± 28.1	139.3 ± 16.8	139.8 ± 20.8	0.449
Diastolic blood pressure (mm Hg)	81.9 ± 14.5	83.2 ± 15.8	79.6 ± 12.0	82.4 ± 13.7	0.221

CCB=calcium-channel blocker

Table 6. Prevalences of initial clinical presentation of coronary artery disease according to use of calcium-channel blockers in smokers and nonsmokers

	Smoker			Nonsmoker		
	CCB (+) (n=45)	CCB (−) (n=95)	p value	CCB (+) (n=126)	CCB (−) (n=139)	p value
Acute coronary syndrome (%)	21 (46.7%)	63 (66.3%)	0.027	41 (32.5%)	56 (40.3%)	0.191
Acute myocardial infarction (%)	15 (33.3%)	51 (53.7%)	0.024	26 (20.6%)	37 (26.6%)	0.253
Unstable angina pectoris (%)	6 (13.3%)	12 (12.6%)	0.908	15 (11.9%)	19 (13.7%)	0.668
Angina pectoris (%)	24 (53.3%)	32 (33.7%)	0.027	85 (67.5%)	83 (59.7%)	0.191

CCB=calcium-channel blocker

Table 7. Characteristics of smokers with initially diagnosed coronary artery disease according to calcium-channel blocker use

	Smoker/CCB (+) (n=45)	Smoker/CCB (−) (n=95)	p value
Age (years)	60.8 ± 8.4	57.2 ± 10.0	0.038
Male (%)	42 (93.3%)	81 (85.3%)	0.286
Hypertension (%)	45 (100.0%)	47 (49.5%)	<0.001
Dyslipidemia (%)	34 (75.6%)	81 (85.3%)	0.161
High LDL cholesterol (%)	22 (48.9%)	58 (61.1%)	0.174
High triglycerides (%)	18 (40.0%)	33 (34.7%)	0.546
Low HDL cholesterol (%)	16 (35.6%)	40 (42.1%)	0.460
Diabetes (%)	22 (48.9%)	28 (29.5%)	0.025
Obesity (%)	17 (37.8%)	39 (41.1%)	0.712
Metabolic syndrome (%)	21 (46.7%)	37 (38.9%)	0.387
Chronic kidney disease (%)	27 (60.0%)	29 (30.5%)	0.001
Antihypertensive agents (%)	45 (100.0%)	20 (21.1%)	<0.001
Systolic blood pressure (mm Hg)	141.7 ± 19.2	138.3 ± 28.1	0.409
Diastolic blood pressure (mm Hg)	81.9 ± 14.5	83.2 ± 15.8	0.647
Lipid lowering agents (%)	14 (31.1%)	17 (17.9%)	0.079
Triglycerides (mg/dL)	142.0 ± 85.2	148.8 ± 123.5	0.736
HDL cholesterol (mg/dL)	43.7 ± 10.4	44.1 ± 11.2	0.864
LDL cholesterol (mg/dL)	122.3 ± 33.7	137.0 ± 35.7	0.022
Antidiabetic agents (%)	17 (37.8%)	12 (12.6%)	0.001
Fasting plasma glucose (mg/dL)	108.7 ± 27.7	106.3 ± 28.1	0.646
Hemoglobin A1c (%)	6.3 ± 1.5	6.2 ± 1.7	0.631
Cigarettes/day	23.4 ± 11.0	26.7 ± 13.2	0.154
Smoking duration (years)	39.3 ± 9.5	34.3 ± 9.7	0.004

CCB=calcium-channel blocker ; HDL=high-density lipoprotein ; LDL=low-density lipoprotein

Table 8. Risk factor-adjusted odds ratios of calcium-channel blocker use for acute myocardial infarction in smokers

	Beta coefficient	Odds ratio	95% confidence interval	p value
Calcium-channel blocker	−0.85	0.43	0.19-0.96	0.041
Older age	−0.06	0.94	0.88-1.01	0.090
Low-density lipoprotein cholesterol	0.002	1.00	0.99-1.01	0.672
Smoking duration	0.03	1.03	0.97-1.10	0.309
Diabetes	0.13	1.14	0.54-2.41	0.727
Male sex	0.18	1.19	0.38-3.70	0.762
Chronic kidney disease	0.20	1.22	0.56-2.64	0.616

were age, hypertension, LDL cholesterol levels, type 2 diabetes, CKD, the rate of medical treatment for hypertension, the rate of medical treatment for type 2 diabetes, and smoking duration (Table 7). Systolic and diastolic blood pressures did not differ between these subgroups. After adjustment for age, sex, LDL cholesterol levels, type 2 diabetes, CKD, and smoking duration, multivariate analysis showed that among smokers, only those using CCBs were at lower risk for AMI (odds ratio, 0.43 ; 95% CI, 0.19 to 0.96 ; $p=0.04$; Table 8).

Discussion

In the present study, we evaluated a possible smoker-specific difference in the initial clinical presentation of CAD, the profiles of other risk factors, and their associations with the primary prevention of CAD. In patients with CAD diagnosed for the first time, the initial clinical presentation of CAD differed between smokers and nonsmokers. More than 40% of the smokers studied had had an AMI.

In general, atherosclerosis progresses if 2 or more risk factors are present[18]. Furthermore, metabolic syndrome and CKD have recently been identified as new risk factors for cardiovascular disease[9,10]. However, according to our statistical analysis of risk factors, traditional coronary risk factors, metabolic syndrome, and CKD did not differ significantly between smokers and nonsmokers. Of note, however, smokers with CAD were younger than nonsmokers with CAD. Because smoking duration in current smokers was longer than that in formerly smoking nonsmokers, CAD might have developed at a younger age in smokers than in nonsmokers. Furthermore, smokers had significantly higher triglyceride levels and lower HDL cholesterol levels than did nonsmokers, findings consistent with those of previous reports[19,20]. Although the underlying mechanisms remain unclear, a possible reason for these observations is low-grade inflammation in smokers[20,21].

We also found that the rates of CCB and statin use were lower in smokers. Our evaluation of the association between these drugs and the initial clinical presentation of CAD showed that statin use was not associated with the prevalence of AMI in either smokers or nonsmokers. On the other hand, CCB use in smokers was associated with a lower prevalence of AMI, which was independent of the blood pressure-lowering effect of this drug. Adjusted multivariate analysis showed that among other risk factors and previous medications for the primary prevention of CAD, only CCB use was associated with a reduced incidence of AMI in smokers.

Although more than 250 of the approximately 4,000 components of cigarette smoke are known to be harmful[21], a possible mechanism of AMI development in Japanese smokers, based on coronary atherosclerosis, is smoking-induced endothelial dysfunction. Furthermore, the most harmful components of cigarette smoke might be extracts of oxygen free radicals, which inactivate nitric oxide and directly damage endothelial cells[21]. In Japanese smokers, endothelial function is thought to be markedly reduced by smoking in conjunction with predisposing genetic factors[22,23]. Endothelial dysfunction can induce vascular hypercontractility or coronary spasm[24]. The presence of vascular hypercontractility or coronary spasm probably accounts for CCB use being associated with CAD prevention in our population of Japanese smokers.

In our previous study, we compared the medications used to treat risk factors between Japanese patients with ACS and those with stable angina pectoris and found that CCB, but not beta-blockers, were useful for preventing ACS[11]. In the present study, our evaluation of risk factors and the medication used for the primary prevention of CAD found that CCB use was associated with a reduced incidence of AMI in Japanese smokers. These findings suggest that hypercontractility of the coronary arteries or coronary spasm is strongly associated with the development of AMI in Japanese smokers, because spasm of major coronary arteries is reportedly common in the Japanese population[25-27]. In fact, cigarette smoking is more important than other known risk factors for coronary artery spasm[27-29].

Other possible mechanisms by which CCBs prevent AMI in Japanese smokers should also be considered. For example, CCBs might prevent AMI through their reported improvement of coronary endothelial function[30,31].

In the present study, smokers more often experienced AMI as the initial clinical presentation of CAD than did nonsmokers. However, the rate of multivessel disease did not differ between smokers and nonsmokers. Although the prevalence of cigarette smoking has been decreasing over the first decade of the 21st century, in our previous study, we found that cigarette smoking is still a more important risk factor for ACS than are other known risks in the Japa-

nese population[11]. On the other hand, we found CKD to be the most important risk factor for multivessel disease[32]. Although treating each risk factor is important for preventing the progression of atherosclerosis, these risk factors may vary in the degree to which they promote CAD.

Although the Ministry of Health, Labour and Welfare of Japan recently reported that the smoking rate in Japan has been decreasing, in 2011 the smoking rate in Japanese men was still 32.4%. Smoking cessation is clearly an effective strategy for the primary prevention of CAD, and, as in many countries, smoking is increasingly prohibited in workplaces, public transport, and restaurants in Japan. Therefore, instructing patients and the general public to quit smoking remains the cornerstone of preventing heart disease in this country.

Study Limitations

Our study had several limitations. Only a small number of patients with initially diagnosed CAD were reviewed. Furthermore, former smokers were included in the Nonsmoker group along with never smokers. Although investigating the effects of CCBs in smokers in a randomized, controlled trial is ethically problematic, a large-scale prospective study in Japan may be required to confirm our observations. In addition, in such a large-scale study, statin use also might be associated with the initial clinical presentation of CAD.

Conclusions

The initial clinical presentation of CAD differs between smokers and nonsmokers, in a population consisting exclusively of patients with initially diagnosed CAD. Smokers more often experience AMI as the initial clinical presentation of CAD than nonsmokers. Furthermore, among the therapeutic agents used for primary prevention of CAD, CCBs are underprescribed for smokers with initially diagnosed CAD. The strong association of CCB use with reduced AMI incidence in Japanese smokers may be attributable to CCB suppressing hypercontractility of the coronary arteries and improving coronary endothelial function. If necessary, Japanese smokers should be treated with CCBs. However, smoking cessation is clearly the primary strategy for preventing CAD. We should encourage smokers, above all, to quit smoking as soon as possible.

Authors have no conflicts of interest.

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