

# Clinical Outcomes of Vasospastic Angina Patients Presenting With Acute Coronary Syndrome

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**Background**—Coronary vasospasm is an important pathogenesis of acute coronary syndrome (ACS). However, the clinical features and prognosis of vasospastic angina (VA) patients presenting with ACS (VAACS) are still unclear. We aimed to evaluate the clinical characteristics and long-term outcomes of VAACS patients without significant coronary artery stenosis.

**Methods and Results**—A total of 986 VA patients confirmed by ergonovine provocation test were analyzed. VAACS was defined as VA patients visiting the emergency room with documented electrocardiographic changes, significant arrhythmias, or elevated cardiac biomarkers. VA patients with elevated cardiac biomarkers were further considered to have myocardial infarction (MI; VAMI). During 4.4 years of median follow-up, we investigated major adverse cardiac events including cardiac death, MI, revascularization, and rehospitalization because of recurrent angina. The VAACS group consisted of 149 patients (15.1%), and VAMI occurred in 81 patients (8.2%). VAACS patients were younger and had a higher prevalence of diabetes mellitus, MI history, and higher levels of inflammatory markers compared with non-VAACS patients. In multivariable Cox regression analyses, VAACS patients were associated with an increased risk of major adverse cardiac events (hazard ratio, 1.65; 95% CI 1.14–2.37;  $P=0.007$ ) and recurrent MI hazard ratio, 2.57; 95% CI, 1.35–4.87;  $P=0.004$ ). In addition, VAMI patients had an increased risk of major adverse cardiac events (hazard ratio, 1.75; 95% CI, 1.11–2.76;  $P=0.016$ ) and recurrent MI (hazard ratio, 2.43; 95% CI, 1.09–5.40;  $P=0.03$ ).

**Conclusion**—VAACS patients showed worse clinical outcomes, driven mainly by recurrent MI. Therefore, intensive medical treatment might be required in VAACS patients. (*J Am Heart Assoc.* 2016;5:e004336 doi: 10.1161/JAHA.116.004336)

**Key Words:** acute coronary syndrome • myocardial infarction • variant angina • vasospasm

Coronary vasospastic angina (VA) is relatively common in East Asia.<sup>1</sup> Transient myocardial ischemia caused by epicardial coronary artery spasm is the main pathogenesis of VA<sup>2</sup>; however, initial manifestations are associated with a wide variety of clinical settings, including stable angina, acute coronary syndrome (ACS), life-threatening arrhythmia, and sudden cardiac death.<sup>3</sup> Although VA patients responding to calcium channel blockers have a good prognosis, their clinical risk varies.<sup>4</sup> The Japanese Coronary Spasm Association risk

score system analyzes VA severity based on clinical presentations including out-of-hospital cardiac arrest, angina at rest alone, and ST-segment elevation.<sup>4</sup> However, there are no data on the clinical manifestations of acute myocardial ischemia. Therefore, we distinguished VA patients presenting with ACS (VAACS) who demonstrated documented electrocardiographic changes (ST-segment elevation, ST-segment depression, or T-wave inversion in at least 2 contiguous leads), significant arrhythmia (ventricular tachycardia/fibrillation, sinus pause/arrest, junctional bradycardia, or second- or third-degree atrioventricular block), or elevation of cardiac biomarkers with at least 1 value above the 99th percentile upper-reference limit. The aim of the present study was to evaluate the clinical characteristics and long-term outcomes of VAACS patients without significant coronary artery stenosis.

## Methods

### Study Population

An intracoronary ergonovine provocation test was performed in 3595 patients from Samsung Medical Center between

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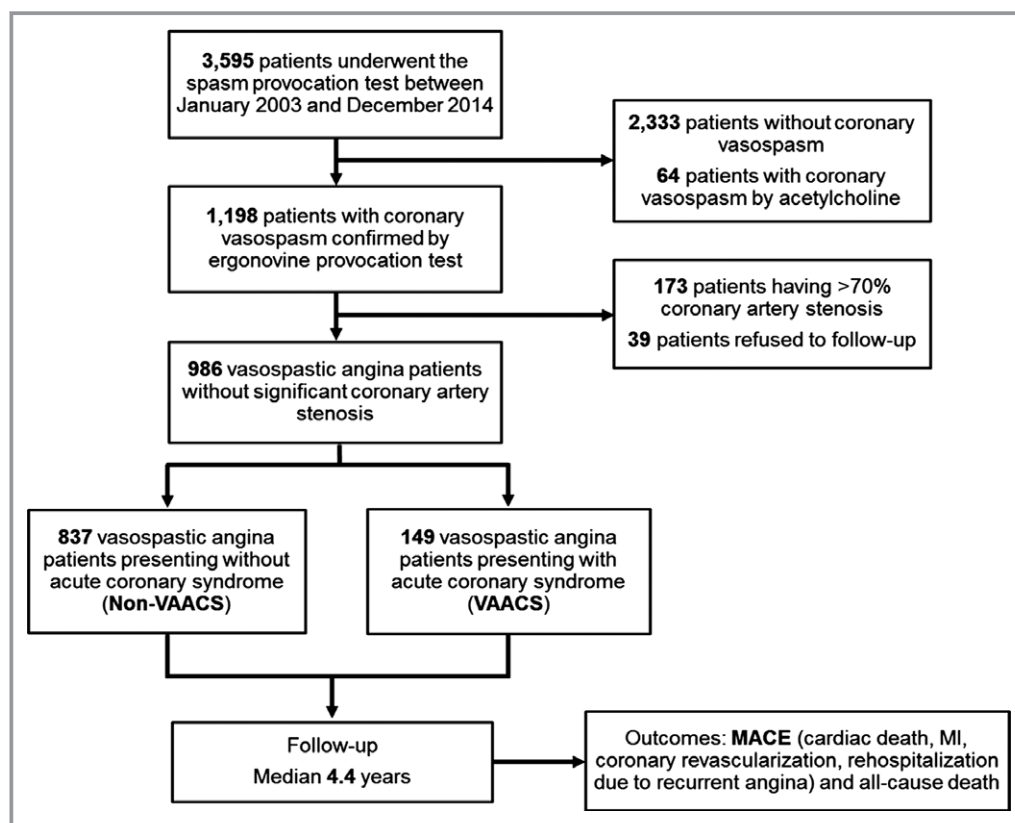
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January 2003 and December 2014. A total of 2333 patients showed the negative result of intracoronary ergonovine provocation test, and we enrolled 1198 patients with a positive intracoronary ergonovine provocation test (Figure 1). We excluded 173 patients with coronary artery stenosis greater than 70% and 39 patients who refused follow-up. Patients were divided into VAACS (n=149) and non-VAACS (n=837) groups. The Samsung Medical Center Institutional Review Board approved this study and waived the requirement for written informed consent for access to an institutional registry.

## Coronary Angiography and Provocation Test

We retrospectively analyzed an observational registry of patients with VA based on the Guidelines for Diagnosis and Treatment of Patients with VA.<sup>5</sup> An intracoronary ergonovine provocation test was performed according to the clinician's decision in patients who had suspicious symptoms and underwent coronary angiography. Baseline coronary angiography was performed for the right and left coronary arteries. Intracoronary ergonovine was infused for the provocation test. Incremental doses of 20, 40, and 80  $\mu\text{g}$  were injected into the left coronary artery. If coronary spasm was not

provoked in the left coronary artery, incremental doses of 10 and 20  $\mu\text{g}$  were injected into the right coronary artery. Once spasm was provoked, intracoronary nitroglycerin was infused. Vasoactive drugs were stopped at least 48 hours before coronary angiography. We classified the definite and intermediate VA according to ergonovine provocation test and defined these as a positive test. Total or subtotal (>90% luminal diameter narrowing) occlusion accompanied by chest pain or discomfort and/or ECG changes or spontaneous total or subtotal spasm on baseline coronary angiography resolved by intracoronary nitroglycerin was defined as a positive result. Additionally, we defined intermediate constriction as 50% to 90% luminal narrowing with or without ischemic symptoms and/or ECG changes were also defined as a positive result. A negative result was <50% luminal narrowing without chest pain or discomfort or ECG change. An ECG change during the provocation test was defined as an ST-segment elevation or depression in at least 2 contiguous leads. A multivessel spasm was defined as a positive spasm in more than 2 major ( $\geq 2.5$  mm) epicardial coronary arteries.<sup>6</sup> The types of spasm were classified as focal or diffuse. The focal type was defined as a discrete spasm localized in 1 coronary segment, whereas spasm observed continuously from the proximal to the distal segments was regarded as diffuse type.<sup>7,8</sup>



**Figure 1.** Study design and population. MACE indicates major adverse cardiac events; MI, myocardial infarction; VAACS, vasospastic angina patients presenting with acute coronary syndrome.

### Clinical Outcomes

The primary outcome was major adverse cardiac events (MACE), defined as a composite of cardiac death, myocardial infarction (MI), revascularization, and rehospitalization because of recurrent angina. All-cause death and individual

**Table 1.** Baseline Clinical Characteristic of VAACS and Non-VAACS Patients

Variable	Non-VAACS (n=837)	VAACS (n=149)	P Value
Age, y	56.8±9.2	54.5±9.7	0.01
Male	712 (85.1)	127 (85.2)	1.00
BMI, kg/m <sup>2</sup>	24.4±2.7	24.1±3.1	0.23
Typical morning angina	618 (73.8)	96 (64.4)	0.022
Medical history			
Diabetes mellitus	170 (20.3)	60 (40.3)	<0.001
Hypertension	315 (37.6)	68 (45.6)	0.07
Current smoking	229 (27.4)	50 (33.6)	0.14
Dyslipidemia	182 (21.7)	21 (14.1)	0.04
History of PCI	64 (7.6)	14 (9.4)	0.51
History of MI	14 (1.7)	18 (12.1)	<0.001
History of stroke	11 (1.3)	4 (2.7)	0.26
Laboratory findings			
Hemoglobin, g/dL	14.5±1.4	14.2±1.8	0.042
White blood cells, ×10 <sup>3</sup> /μL	6.9±1.9	8.5±3.7	<0.001
Glucose, mg/dL	114±34	134±53	<0.001
BUN, mg/dL	15.0±4.2	14.9±5.1	0.80
Creatinine, mg/dL	0.92±0.18	0.87±0.22	0.004
Total cholesterol, mg/dL	173±36	161±36	<0.001
Triglycerides, mg/dL	162±114	156±118	0.61
HDL, mg/dL	48±12	45±12	0.013
LDL, mg/dL	106±31	97±31	0.002
Hs-CRP, mg/dL	0.31±1.18	1.07±3.17	<0.001
LVEF, %	64.3±6.5	61.8±8.8	0.001
Medical treatments at discharge			
Aspirin	532 (63.8)	93 (62.4)	0.78
Statin	372 (44.6)	85 (57.0)	0.006
Calcium channel blocker	798 (95.7)	142 (95.3)	0.83
Nitrate	310 (37.2)	78 (52.3)	0.001
Nicorandil	270 (32.4)	59 (39.6)	0.09
ACEI or ARB	159 (19.1)	38 (25.5)	0.08

Values are mean±SD or n (%). ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BUN, blood nitrogen urea; HDL, high-density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; VAACS, vasospastic angina presenting with acute coronary syndrome.

outcomes of MACE were assessed for important secondary outcomes. All deaths were considered cardiac unless a definite noncardiac cause could be established. MI was defined as detection of increase and/or decrease of cardiac biomarkers with at least 1 value above the 99th percentile upper-reference limit and with at least 1 of the following: ischemia symptoms, new significant ST-T changes, new left bundle branch block, development of pathological Q waves, imaging evidence of new loss of viable myocardium or regional wall motion abnormality, or identification of a thrombus by coronary angiography.<sup>9</sup> Revascularization was defined as any revascularization of the epicardial coronary arteries by percutaneous coronary intervention or bypass graft surgery. Rehospitalization was defined as any hospitalization after index hospital discharge because of recurrent angina symptoms: typical chest pain, atypical chest pain, dyspnea, syncope or dizziness, palpitation, or aborted cardiac arrest.

**Table 2.** Angiographic Characteristics of VAACS and Non-VAACS Patients

Variable	Non-VAACS (n=837)	VAACS (n=149)	P Value
Spasm-positive vessel			
LM or LAD	310 (37.0)	78 (52.3)	0.001
LCx	168 (20.1)	21 (14.1)	0.09
RCA	417 (49.8)	63 (42.3)	0.09
Type of spasm			
Diffuse	251 (30.0)	35 (23.5)	0.12
Focal	586 (70.0)	114 (76.5)	
Spontaneous spasm	18 (2.2)	5 (3.4)	0.37
Myocardial bridging	15 (1.8)	3 (2.0)	0.75
ST-segment change			
No change	288 (34.4)	46 (30.9)	0.28
ST-segment elevation	452 (54.0)	92 (61.7)	
ST-segment depression	72 (8.6)	8 (5.4)	
T wave inversion	25 (3.0)	3 (2.0)	
TIMI flow			
TIMI 0 to 1	609 (72.8)	111 (74.5)	0.69
TIMI 2 to 3	228 (27.2)	38 (25.5)	
Fixed coronary stenosis on spasm-positive vessel			
0% to 30%	613 (73.2)	107 (71.8)	0.28
30% to 50%	166 (19.8)	29 (19.5)	
50% to 70%	58 (6.9)	13 (8.7)	

Values are n (%). LAD indicates left anterior descending; LCx, left circumflex; LM, left main; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction; VAACS, vasospastic angina presenting with acute coronary syndrome.

**Table 3.** Clinical Outcomes of VAACS and Non-VAACS Patients

Variable	Non-VAACS (n=837)	VAACS (n=149)	Unadjusted HR (95% CI)	P Value	Adjusted HR* (95% CI)	P Value
Major adverse cardiac events <sup>†</sup>	161 (19.2)	42 (28.2)	1.66 (1.18–2.33)	0.004	1.65 (1.14–2.37)	0.007
Cardiac death	9 (1.1)	4 (2.7)	2.62 (0.81–8.52)	0.11	1.68 (0.45–6.30)	0.45
Myocardial infarction	38 (4.5)	15 (10.1)	2.45 (1.35–4.46)	0.003	2.57 (1.35–4.87)	0.004
Revascularization	23 (2.7)	4 (2.7)	1.06 (0.37–3.07)	0.92	1.26 (0.42–3.83)	0.68
Rehospitalization because of recurrent angina	132 (15.8)	33 (22.1)	1.57 (1.07–2.30)	0.021	1.52 (1.01–2.29)	0.044
All-cause death	21 (2.5)	10 (6.7)	2.84 (1.34–6.02)	0.007	3.08 (1.33–7.14)	0.009

HR indicates hazard ratio; VAACS, vasospastic angina presenting with acute coronary syndrome.

\*Adjusted covariates included age, sex, diabetes mellitus, hypertension, current smoker, dyslipidemia, and history of myocardial infarction (MI).

<sup>†</sup>Defined as a composite of cardiac death, MI, revascularization, or rehospitalization because of recurrent angina during follow-up.

## Statistical Analysis

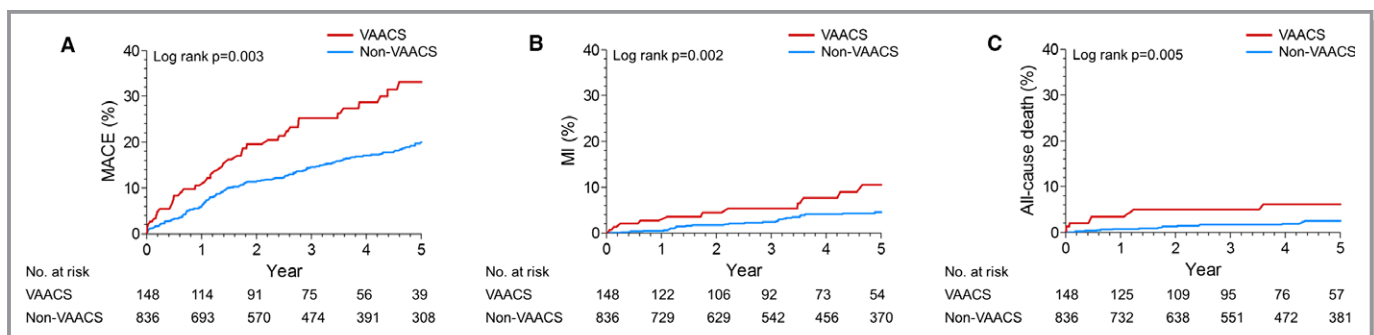
Categorical variables were expressed as percentage and were compared using  $\chi^2$  test or Fisher's exact test. Continuous variables were presented as mean $\pm$ SD and were compared using *t* test or Wilcoxon rank sum test. Survival curves were constructed using Kaplan–Meier estimates and were compared using the log-rank test. Differences in adjusted risk were evaluated using multivariable Cox regression analysis. Proportional hazard assumptions were confirmed by Schoenfeld's test, and no relevant violation was found. The clinically relevant variables included in the multivariable models were age, sex, diabetes mellitus, hypertension, current smoker, dyslipidemia, and history of MI. Multivariable logistic regression analysis was performed to determine the clinical and angiographic factors associated with VAACS and vasospastic angina presenting with myocardial infarction (VAMI), starting with a model of all clinically relevant factors at the same time: age, sex, body mass index, typical morning angina, diabetes mellitus, hypertension, current smoker, history of MI, white blood cell (WBC) count, total cholesterol, creatinine, high-sensitivity C-reactive protein (Hs-CRP), left ventricular

ejection fraction, and left main or left anterior descending coronary artery spasm during provocation test. All *P*-values are 2-tailed, and *P*<0.05 was considered to be statistically significant. SPSS 20.0 (IBM, Armonk, NY) was used for statistical analyses.

## Results

### Clinical, Laboratory, and Angiographic Characteristics

A total of 986 VA patients were analyzed. Among them, 149 patients (15.1%) presented with VAACS (Tables 1 and 2). Compared with non-VAACS patients, VAACS patients were younger, had a higher prevalence of diabetes mellitus, elevated WBC and Hs-CRP levels, and an increased history of MI; however, they had a lower left ventricular ejection fraction. VAACS patients were more frequently treated with statins (57.0%) and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (25.5%). In angiographic characteristics, left main or left anterior descending spasm during the provocation test frequently occurred in VAACS patients.



**Figure 2.** Kaplan–Meier curves for clinical outcomes including (A) MACE, (B) MI, and (C) all-cause death in non-VAACS and VAACS patients. MACE indicates major adverse cardiac events; MI, myocardial infarction; VAACS, vasospastic angina patients presenting with acute coronary syndrome.

**Table 4.** Baseline Clinical Characteristics of VAMI and Non-VAMI Patients

Variable	Non-VAMI (n=905)	VAMI (n=81)	P Value
Age, y	56.6±9.3	54.4±10.0	0.06
Male	768 (84.9)	71 (87.7)	0.63
BMI, kg/m <sup>2</sup>	24.4±2.2	24.3±3.0	0.69
Typical morning angina	664 (73.4)	50 (61.7)	0.028
Medical history			
Diabetes mellitus	194 (21.4)	36 (44.4)	<0.001
Hypertension	343 (37.9)	40 (49.4)	0.044
Current smoking	247 (27.3)	32 (39.5)	0.028
Dyslipidemia	191 (21.1)	12 (14.8)	0.20
History of PCI	71 (7.8)	7 (8.6)	0.83
History of MI	18 (2.0)	14 (17.3)	<0.001
History of CVA	12 (1.3)	3 (3.7)	0.12
Laboratory findings			
Hemoglobin, g/dL	14.5±1.5	14.4±1.7	0.66
White blood cells, ×10 <sup>3</sup> /μL	7.0±2.1	8.8±3.6	<0.001
Glucose, mg/dL	116±36	133±54	0.007
BUN, mg/dL	15.0±4.3	14.9±4.7	0.89
Creatinine, mg/dL	0.91±0.19	0.88±0.24	0.19
Total cholesterol, mg/dL	172±36	166±35	0.15
Triglycerides, mg/dL	160±114	166±118	0.69
HDL, mg/dL	47±12	46±12	0.40
LDL, mg/dL	105±31	98±29	0.06
Hs-CRP, mg/dL	0.37±1.38	1.16±3.61	<0.001
LVEF, %	64.1±6.8	61.6±8.7	0.006
Medical treatments at discharge			
Aspirin	573 (63.5)	52 (64.2)	1.00
Statin	406 (45.0)	51 (63.0)	0.002
Calcium channel blocker	863 (95.7)	77 (95.1)	0.78
Nitrate	354 (39.2)	34 (42.0)	0.64
Nicorandil	289 (32.0)	40 (49.4)	0.002
ACEI or ARB	175 (19.4)	22 (27.2)	0.11

Values are mean±SD or n (%). ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BUN, blood urea nitrogen; CVA, cerebrovascular accident; HDL, high-density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; VAMI, vasospastic angina presenting with myocardial infarction.

### Clinical Outcomes

During the follow-up period (median 4.4 years), 42 patients (28.2%) in the VAACS group and 161 patients (19.2%) in the non-VAACS group had MACE. Recurrent MI occurred in 15 (10.1%) VAACS patients and in 38 (4.5%) non-VAACS patients

**Table 5.** Angiographic Characteristics in VAMI and Non-VAMI Patients

Variable	Non-VAMI (n=905)	VAMI (n=81)	P Value
Spasm-positive vessel			
LM or LAD	345 (38.1)	43 (53.1)	0.009
LCx	178 (19.7)	11 (13.6)	0.24
RCA	446 (49.3)	34 (42.0)	0.25
Type of spasm			
Diffuse	265 (29.3)	21 (25.9)	
Focal	640 (70.7)	60 (74.1)	
Spontaneous spasm	21 (2.3)	2 (2.5)	0.71
Myocardial bridging	17 (1.9)	1 (1.2)	1.00
ST-segment change			
No change	310 (34.3)	24 (29.6)	
ST-segment elevation	492 (54.4)	52 (64.2)	
ST-segment depression	76 (8.4)	4 (4.9)	
T wave inversion	27 (3.0)	1 (1.2)	
TIMI flow grade			
TIMI flow grade 0 to 1	663 (73.3)	57 (70.4)	
TIMI flow grade 2 to 3	242 (26.7)	24 (29.6)	
Fixed coronary stenosis on spasm-positive vessel			
0% to 30%	661 (73.1)	59 (72.9)	
30% to 50%	178 (19.7)	17 (21.0)	
50% to 70%	66 (7.3)	5 (6.2)	

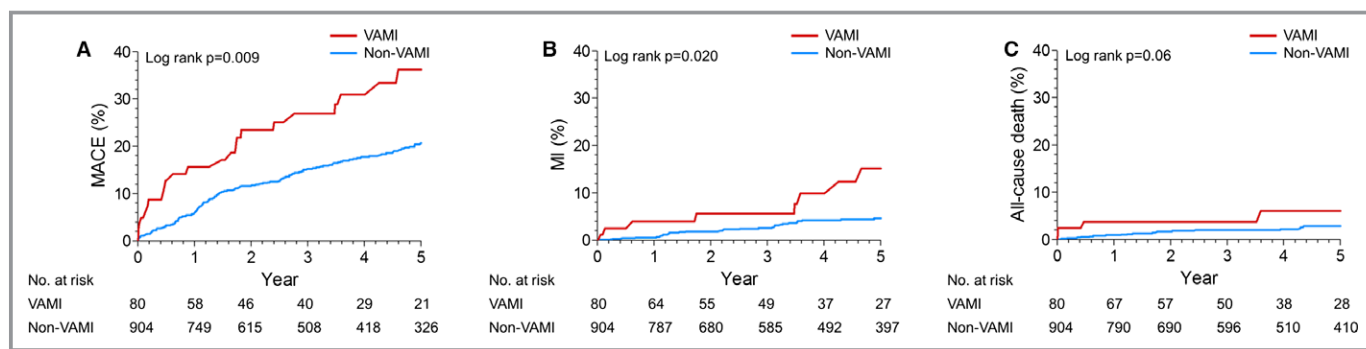
Values are n (%). LAD indicates left anterior descending; LCx, left circumflex; LM, left main; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction; VAMI, vasospastic angina presenting with myocardial infarction.

(Table 3). The Kaplan–Meier curves for MACE, recurrent MI, and all-cause death in VAACS and non-VAACS patients are shown in Figure 2. In multivariable Cox regression analyses, VAACS patients had significantly increased risk of MACE (hazard ratio [HR], 1.65; 95% CI, 1.14–2.37; *P*=0.007), recurrent MI (HR, 2.57; 95% CI, 1.35–4.87; *P*=0.004), and all-cause death (HR, 3.08; 95% CI, 1.33–7.14; *P*=0.009) compared with non-VAACS patients (Table 3).

### VA Patients Presenting With MI Caused by Coronary Vasospasm

The present study included 81 VA patients (8.2%) presenting with MI (VAMI). VAMI patients had higher prevalence of diabetes mellitus, hypertension, current smoking, and history of MI, as well as high WBC and Hs-CRP levels, but lower left ventricular ejection fraction (Tables 4 and 5). Left main or left anterior descending spasm during the provocation test





**Figure 3.** Kaplan–Meier curves for clinical outcomes including (A) MACE, (B) MI, and (C) all-cause death in non-VAMI and VAMI patients. MACE indicates major adverse cardiac events; MI, myocardial infarction; VAMI, vasospastic angina presenting with myocardial infarction.

frequently occurred in VAMI patients. The Kaplan–Meier curves for MACE, recurrent MI, and all-cause death in VAMI patients are shown in Figure 3. In multivariable Cox regression analyses, VAMI patients had significantly increased risk of MACE (HR, 1.75; 95% CI, 1.11–2.76;  $P=0.016$ ) and recurrent MI (HR, 2.43; 95% CI, 1.09–5.40;  $P=0.03$ ; Table 6).

### Multivariable Models for Determining Factors Associated With VAACS and VAMI

Diabetes mellitus, history of MI, and higher WBC (more than  $10.0 \times 10^3/\mu\text{L}$ ) and Hs-CRP (more than 0.3 mg/dL) levels were factors significantly associated with VAACS and VAMI (Table 7).

### Discussion

We found that the prognosis of patients presenting with ACS was worse than that of other VA patients without significant coronary artery stenosis. The main findings of this study are as follows: (1) VAACS patients were associated with increased risk of MACE, recurrent MI, rehospitalization because of recurrent angina, and all-cause death; (2) VAMI patients more frequently suffered from MACE and recurrent MI than non-

VAMI patients; (3) diabetes mellitus, history of MI, and higher WBC (more than  $10.0 \times 10^3/\mu\text{L}$ ) and Hs-CRP (more than 0.3 mg/dL) levels were independently associated with VAACS and VAMI.

It has been documented that coronary artery spasm is an important etiology of ACS in patients without obstructive coronary artery disease.<sup>10</sup> ACS patients with coronary spasm and nonobstructive coronary artery disease have a favorable prognosis for survival and coronary events.<sup>11,12</sup> In the Coronary Artery Spasm in Patients with Acute Coronary Syndrome study, nonobstructive ACS patients with documented coronary spasm showed no cardiac death or nonfatal MI during a 3-year follow-up.<sup>11</sup> In a Japanese population, cardiovascular events occurred in 15 (4.7%) patients with coronary artery spasm, including 1 (0.3%) patient with cardiovascular death and 4 (1.3%) patients with MI during a mean follow-up duration of 20 months.<sup>12</sup> Although nonobstructive ACS patients with documented coronary spasm have an excellent prognosis for survival and coronary events compared with patients with obstructive ACS, there are no long-term follow-up data. Furthermore, a recent study proposed that acute presentations including out-of-hospital cardiac arrest, angina at rest alone, and ST-segment elevation were significant predictors of adverse outcomes in VA

**Table 6.** Clinical Outcomes of VAMI and Non-VAMI Patients

Variable	Non-VAMI (n=905)	VAMI (n=81)	Unadjusted HR (95% CI)	P Value	Adjusted HR* (95% CI)	P Value
Major adverse cardiac events <sup>†</sup>	179 (19.8)	24 (29.6)	1.75 (1.15–2.69)	0.010	1.75 (1.11–2.76)	0.016
Cardiac death	10 (1.1)	3 (3.7)	3.66 (1.01–13.31)	0.049	2.26 (0.51–9.98)	0.28
Myocardial infarction	45 (5.0)	8 (9.9)	2.39 (1.12–5.08)	0.024	2.43 (1.09–5.40)	0.030
Revascularization	25 (2.8)	2 (2.5)	1.04 (0.25–4.42)	0.95	1.32 (0.30–5.88)	0.71
Rehospitalization due to recurrent angina	147 (16.2)	18 (22.2)	1.58 (0.97–2.58)	0.07	1.54 (0.92–2.59)	0.10
All-cause death	26 (2.9)	5 (6.2)	2.41 (0.92–6.27)	0.07	2.06 (0.71–6.05)	0.19

Values are n (%). HR indicates hazard ratio; VAMI, vasospastic angina presenting with myocardial infarction.

\*Adjusted covariates included age, sex, diabetes mellitus, hypertension, current smoker, dyslipidemia, and history of myocardial infarction.

<sup>†</sup>Defined as a composite of cardiac death, myocardial infarction, revascularization, or rehospitalization due to recurrent angina during follow-up.

**Table 7.** Multivariable Models for Determining Factors Associated With VAACS or VAMI

Variable	VAACS		VAMI	
	OR (95% CI)*	P Value	OR (95% CI)*	P Value
Age >60 y	0.64 (0.37–1.11)	0.11	0.37 (0.18–0.75)	0.006
Sex	0.88 (0.40–1.93)	0.75	1.15 (0.47–2.82)	0.76
BMI >25 kg/m <sup>2</sup>	0.70 (0.40–1.20)	0.20	0.61 (0.32–1.19)	0.15
Typical morning angina	1.02 (0.59–1.74)	0.96	0.76 (0.41–1.44)	0.40
Diabetes mellitus	2.48 (1.47–4.20)	0.001	2.53 (1.35–4.75)	0.004
Hypertension	1.38 (0.82–2.32)	0.23	1.59 (0.85–2.98)	0.15
Current smoker	1.30 (0.75–2.25)	0.35	1.53 (0.80–2.93)	0.20
History of MI	9.61 (3.08–30.04)	<0.001	13.37 (4.39–40.79)	<0.001
WBC >10.0×10 <sup>3</sup> /μL	4.27 (1.88–9.70)	0.001	2.59 (1.06–6.29)	0.036
Total cholesterol >240 mg/dL	0.52 (0.13–2.03)	0.35	0.62 (0.13–3.08)	0.56
Creatinine >1.30 mg/dL	1.27 (0.25–6.56)	0.77	1.56 (0.27–9.15)	0.62
Hs-CRP >0.3 mg/dL	2.36 (1.29–4.32)	0.005	2.10 (1.04–4.24)	0.038
LVEF >55%	0.40 (0.18–0.87)	0.021	0.61 (0.25–1.50)	0.28
LM or LAD spasm	1.89 (1.13–3.13)	0.015	1.39 (0.76–2.56)	0.29

BMI indicates body mass index; Hs-CRP, high-sensitivity C-reactive protein; LAD, left anterior descending; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OR, odds ratio; VAACS, vasospastic angina presenting with acute coronary syndrome; VAMI, vasospastic angina presenting with myocardial infarction; WBC, white blood cells.

\*Multivariable logistic models including all clinically relevant variables at the same time.

patients.<sup>4</sup> However, there were no comparative data of VA patients presenting with or without ACS.

In our study, VAACS patients with documented myocardial ischemia had increased risk of MACE, driven mainly by recurrent MI compared with non-VAACS patients. These findings could possibly be explained by the fact that urgent presentation with documented myocardial ischemia reflects severe stenosis or occlusion of the coronary artery by vasospasm. In these patients, disturbances of the coronary microcirculation result in decreased coronary reserve or microvascular spasm that causes repetitive angina during exercise or at rest.<sup>11</sup> In addition, the increased risks of MACE and recurrent MI were consistently observed in VAMI patients. It is likely that prolonged coronary spasm mimicking true MI caused repetitive myocardial damage and inflammation. In our study, VAACS and VAMI patients had higher levels of inflammatory markers such as WBC and Hs-CRP. A previous study has also reported that laboratory findings including significant elevation of Hs-CRP and fibrinogen levels were similar to those seen in patients with acute MI with significant stenosis.<sup>13</sup> Furthermore, we hypothesized that suboptimal use of medications that improve the prognosis of ACS and MI such as statins or renal angiotensin system blockades might lead to adverse outcomes in VAACS and VAMI patients. In the present study, statins were prescribed in approximately half of VAACS patients, and renal angiotensin system blockades were prescribed in one quarter of VAACS patients. A recent

study showed that statin therapy in patients with coronary spasm-induced AMI with nonobstructive coronary artery disease was associated with improved clinical outcomes.<sup>14</sup> Previous studies have also demonstrated that the incidence of cardiac death and nonfatal MI was significantly increased in VA patients in whom medications were reduced or discontinued.<sup>15–17</sup> Accordingly, appropriate pharmacological treatment should be considered for VAACS and VAMI patients without obstructive coronary artery disease.

In the present study, clinical factors associated with VAACS and VAMI were diabetes mellitus, history of MI, and higher level of inflammatory markers. Diabetes mellitus is a chronic inflammatory condition, and our and previous data suggest that inflammation might be associated with severe coronary vasospasm.<sup>3</sup> Most importantly, our data showed that prior MI in VA patients is a strong associated factor of VAACS and VAMI, and that VAACS and VAMI patients have increased rates of recurrent MI. Therefore, VA patients with diabetes mellitus and prior MI are a high-risk group, and more intensive management and follow-up should be required.

This study had several limitations inherent to a retrospective analysis of observational data. First, some of the baseline and angiographic characteristics were unfavorable in the VAACS group compared with the non-VAACS group, which may have contributed to the differences in adverse outcomes between the 2 groups. Accordingly, it is difficult to assert that the presence of coronary spasm is the direct cause of worse

outcomes. However, adjusted Cox regression analysis showed that VAACS patients were at increased risk of adverse outcomes after adjustment for pre-existing cardiovascular risk factors. Therefore, severe coronary vasospasm causing electrocardiographic changes, significant arrhythmias, or elevation of cardiac biomarkers might be closely associated with worse clinical outcomes. However, we could not elucidate the pathogenesis of severe presentation and higher probability of future MI in VAACS patients in this study. Second, the cause–effect relationship between treatment and patient outcomes could not be established. We are conducting a study on the long-term follow-up results of a prospective VA-KOREA (Vasospastic Angina in Korea) registry to further analyze this relationship.

## Conclusion

VAACS patients had worse clinical outcomes, driven mainly by recurrent MI, compared with non-VAACS patients. These findings were observed consistently in VAMI patients. Therefore, more intensive clinical attention and medical treatment are required in VAACS and VAMI patients without obstructive coronary artery disease.

## Disclosures

None.

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