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The 24-Month Prognosis of Patients With Positive or Intermediate Results in the Intracoronary Ergonovine Provocation Test

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ABSTRACT

OBJECTIVES This study was an observational, multicenter registry to determine clinical characteristics and 24-month prognosis of patients who underwent intracoronary ergonovine provocation tests.

BACKGROUND The clinical characteristics and prognosis of patients who underwent the ergonovine provocation for vasospastic angina were not fully elucidated.

METHODS A total of 2,129 patients in the VA-KOREA (Vasospastic Angina in Korea) registry were classified into positive (n = 454), intermediate (n = 982), and negative (n = 693) groups by intracoronary ergonovine provocation tests. The 24-month incidences of cardiac death, new-onset arrhythmia, and acute coronary syndrome were determined (mean 26.7 ± 8.8 months).

RESULTS The number of smokers, frequency of angina before angiography, high-sensitivity C-reactive protein, and triglyceride were higher in the positive group than in other groups. The clinical characteristics of the intermediate and the negative groups were very similar. In the positive group, the incidences of diffuse, focal, and mixed spasm were 65.9%, 23.6%, and 10.6%. Coronary spasm was more frequently provoked on atherosclerotic segments. The 24-month incidences of cardiac death, arrhythmia, and acute coronary syndrome were low (0.9%, 1.6%, and 1.9%, respectively) in the positive group, and there was no cardiac death in the intermediate group (p = 0.02). In the positive group, frequent angina, current smoking, and multivessel spasm were independent predictors for adverse events.

CONCLUSIONS The 24-month prognosis of the positive group in the intracoronary ergonovine provocation test was relatively worse than that of the intermediate group. More intensive clinical attention should be paid to vasospastic angina patients with high-risk factors including frequent angina before angiography, current smoking, and multivessel spasm. (J Am Coll Cardiol Intv 2015;8:914–23) © 2015 by the American College of Cardiology Foundation.

Coronary spasm has been recognized as an important pathophysiology of myocardial ischemia in patients with or without coronary artery stenosis (1,2). Although vasospastic angina (VSA) has become less frequent, most likely due to the widespread use of calcium-channel blockers (CCBs), coronary spasm is still prevalent, and provocation tests for VSA are widely performed

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in Korea and Japan (1–4). Thus, VSA is regarded as one of the crucial functional coronary diseases, particularly in the East Asian countries (4,5).

In Japan, a number of studies have elucidated the pathogenesis, diagnosis, and characteristics of VSA (6,7). Moreover, the nationwide registry of the Japanese Coronary Spasm Association (JCSA) has established the clinical prognostic factors, such as out-of-hospital cardiac arrest and mixed-type spasm (8,9). Furthermore, the JCSA risk score was recently suggested for the comprehensive risk assessment and prognostic stratification of VSA patients (4).

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Many study groups in Korea have reported the clinical findings, prognostic factors, and possible new pharmacologic agents for Korean VSA patients with variable provocation methods (10–12). However, there have been few demographic reports so far from the large-scale analysis of Korean patients who underwent intracoronary ergonovine provocation tests. Moreover, most of the previous studies have not only included a small number of patients, but also applied different diagnostic methods and diverse criteria for the definition of VSA.

Consequently, we conducted a large-scale, multicenter registry for VSA patients who had been tested with the same provocation protocol using only intracoronary ergonovine. We also determined the clinical characteristics, prognosis, and associated risk factors in each of the groups of patients who were classified according to results of the ergonovine provocation.

METHODS

STUDY SUBJECTS. VA-KOREA (Vasospastic Angina in KOREA) is a prospective, observational, and web-based registry of clinical, angiographic, and prognostic data from patients who underwent intracoronary ergonovine provocation tests. Patients who had suspicious symptoms and underwent coronary angiography (CAG) with the ergonovine provocation test according to the clinician's decision were included. A total of 2,174 patients who underwent the ergonovine provocation test were consecutively entered into the registry from May 2010 to November 2013 in 11 cardiovascular centers and selected as the study subjects. All participated centers have performed high-volume CAG (>1,800 cases/year) and percutaneous coronary intervention (PCI) (>500 cases/year) and have used the same study protocol for the intracoronary ergonovine provocation test.

All of the registered patients had normal findings or minimal (<50% luminal diameter narrowing) atherosclerosis at the baseline CAG, whereas those with significant atherosclerosis (≥50% luminal diameter narrowing) were excluded. Patients with renal failure on continuous dialysis, known malignant or inflammatory diseases, and catheter-induced spasm at the baseline CAG were also excluded. All patients who showed positive results on their provocation tests or defined spontaneous spasm received medical treatments including CCBs and other vasodilators during the follow-up. Medications for nonpositive subjects were prescribed on the basis of the clinician's decision.

There was no industry involvement, and all patients gave their written informed consent. All of the surveys were approved by the institutional review board of each participating institution.

CAG AND PROVOCATION TEST FOR VSA. VSA was diagnosed on the basis of the criteria in the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina of the Japanese Circulation Society (13). The baseline CAG was performed for the right coronary artery (RCA) and then the left coronary artery (LCA), respectively. Intracoronary infusion of ergonovine was used for the provocation test. Incremental doses of 20 (E1), 40 (E2), and 60 μg (E3) were injected into the LCA. If coronary spasm was not provoked on the LCA, incremental doses of 10 (E1), 20 (E2), and 40 μg (E3) were injected into the RCA (9). Once spasm was provoked, intracoronary nitrate was injected. The vasoactive drugs were discontinued at least 48 h before CAG.

The definition of a positive result was total or subtotal (>90% luminal diameter narrowing) occlusion accompanied by ischemic symptoms and/or electrocardiographic (ECG) changes (the positive group) (13). Patients who showed spontaneous total or subtotal coronary spasm on their baseline CAG resolved by nitrate were also included in the positive group. The definition of a negative result was <50% luminal narrowing without ischemic symptoms and ECG changes (the negative group). Additionally, we defined intermediate constriction as 50% to 90% luminal narrowing with or without ischemic symptoms and/or ECG changes (the intermediate group). All of the vascular responses to ergonovine in the provocation test and atherosclerosis on the baseline CAG were quantitatively analyzed for epicardial coronary artery diameters ≥2.5 mm by clinicians unaware of patient status at the core laboratory of Seoul St. Mary's Hospital, Seoul, South Korea.

ABBREVIATIONS AND ACRONYMS

CAG = coronary angiography
CCB = calcium-channel blocker
ECG = electrocardiography
JCSA = Japanese Coronary Spasm Association
LCA = left coronary artery
MI = myocardial infarction
RCA = right coronary artery
VSA = vasospastic angina

DEFINITIONS AND ENDPOINTS. An ischemic ECG change was defined as an ST-segment elevation or depression >0.1 mV or a negative U-wave in at least 2 related leads (2). A multivessel spasm was defined as a positive spasm in more than 2 major (≥2.5 mm) epicardial coronary arteries (2,12). The types of spasm were classified into focal, diffuse, and mixed types. The focal type was defined as a discrete spasm localized in 1 coronary segment, whereas the spasm observed continuously from the proximal to the distal segments was regarded as the diffuse type. The mixed type was defined as the multivessel spasm in which at least 1 coronary artery had focal spasm, and the other had diffuse spasm (9). Cardiac death was defined as any death due to a proximate cardiac cause such as myocardial infarction (MI), low-output failure, fatal arrhythmia, and death from unknown causes (2). MI was defined as "detection of a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile upper-reference limit and with at least one of the following: ischemia symptoms, new significant ST-T changes, or new left bundle branch block, development of pathological Q in the ECG, imaging evidence of new loss of viable myocardium or regional wall motion abnormality, identification of a thrombus by CAG" (14). Patients who presented with clinically-significant arrhythmia, including atrial or ventricular tachycardia/fibrillation, symptomatic premature beats, sick-sinus rhythm, and atrioventricular block, for the first time during the follow-up were considered to have the new-onset arrhythmia (15). The routine ECG was checked during the regular or emergent visits, and 24-h Holter monitoring was also performed in patients with suspicious symptoms. We also defined medication changes as adding drugs to the existing prescription or switching more than 1 drug due to repeated angina. The frequency of angina before angiography was presented according to the prior classification: grade I: near-daily attacks; II: ≥4 attacks/month; III: ≥1 but <4 attacks/month; and IV: <1 attack/month (16).

The primary endpoint was a composite of cardiac death, new-onset arrhythmia, and acute coronary syndrome. The 12- and 24-month incidences of each adverse event were also analyzed as the secondary endpoints. Additionally, the incidence of repeated angina leading to medication changes or rehospitalization, including emergency department visits, was estimated in this analysis. All adverse events of interest were confirmed through the source documents, including medical records as well as telephone interviews, and were also adjudicated by the Local Events Committee of Seoul St. Mary's Hospital.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD and compared with the analysis of variance. The Sheffe test was also performed for the post-hoc analysis. Categorical variables are presented as numbers and percents. The chi-square test or Fisher exact test was used for the categorical variables. The incidences of the endpoints in the positive and the intermediate groups were estimated at 12 and 24 months and are displayed with tables and Kaplan-Meier curves. The log-rank test was performed to compare the incidences of the endpoints between the 2 groups. To assess the center variance component, we performed the additional log-rank test by adding the center variable as the strata variable. Additionally, the Cox regression analysis was performed to identify the independent predictors of the adverse events in the positive group. The hazard ratio (HR) and the 95% confidence interval (CI) were also calculated. Values of $p < 0.05$ were considered statistically significant. The statistical analyses were performed using SPSS version 18.0 software (SPSS, Chicago, Illinois).

RESULTS

PATIENT ENROLLMENT AND FOLLOW-UP. A total of 2,174 patients were registered in VA-KOREA. Forty-five patients were excluded due to significant atherosclerosis on their baseline CAG (n = 33) and due to the other exclusion criteria (n = 12). Thus, a total of 2,129 patients (97.9%) were analyzed: 454 (21.3%) in the positive group, 982 (46.1%) in the intermediate group, and 693 (32.6%) in the negative group. The follow-up data for determining the 24-month prognosis were available in 432 patients (95.2%) in the positive group and 668 patients (68.0%) in the intermediate group. The mean follow-up duration was 26.7 ± 8.8 months.

BASELINE CLINICAL AND LABORATORY CHARACTERISTICS. The numbers of current smokers and males and the frequency of angina before CAG were higher in the positive group than in the 2 other groups. The baseline clinical characteristics of the intermediate group were very similar to those of the negative group (Table 1).

The positive group showed higher levels of baseline high-sensitivity C-reactive protein and triglyceride than the 2 other groups. Although the level of triglyceride in the intermediate group was higher than in the negative group, other laboratory findings were similar between the 2 groups (Table 2).

ANGIOGRAPHIC CHARACTERISTICS IN THE POSITIVE GROUP. The positive rate of the ergonovine provocation in our registry was 21.3%. The angiographic

TABLE 1 Baseline Clinical Characteristics

	Positive (n = 454)	Intermediate (n = 982)	Negative (n = 693)	p Value
Age, yrs	56.1 ± 10.5	55.2 ± 11.8	55.0 ± 12.8	0.44
Male	315 (69.4)	349 (35.5)	283 (40.9)	<0.001
Body mass index, kg/m^2	25.0 ± 3.3	25.6 ± 4.8	24.6 ± 3.5	0.21
Blood pressure, mm Hg				
Systolic	137.3 ± 18.6	132 ± 17.4	134.1 ± 18.8	0.09
Diastolic	78.0 ± 12.1	75.8 ± 13.4	76.4 ± 12.1	0.07
Frequency of angina before angiography				0.03
I/II	70 (15.4)/139 (30.6)	44 (4.5)/168 (17.1)	26 (3.8)/111 (16.0)	
III/IV	142 (31.3)/103 (22.7)	508 (51.7)/262 (26.7)	324 (46.8)/232 (33.5)	
Risk factors of coronary artery disease				
Hypertension	198 (43.6)	398 (40.5)	285 (41.1)	0.13
Diabetes	138 (30.4)	318 (32.4)	214 (30.9)	0.48
Current smoking	218 (48.0)	205 (20.9)	148 (21.4)	<0.001
Dyslipidemia	71 (15.6)	166 (16.9)	107 (15.5)	0.56
Family history of coronary artery disease	23 (5.1)	67 (6.8)	50 (7.3)	0.47

Values are mean ± SD or n (%).

characteristics in the positive group are presented in Table 3. Single-vessel spasm was seen in 326 patients (71.8%) and multivessel spasm in 128 (28.2%). Coronary spasm was most frequently provoked on the RCA (57.7%) in the patients with single-vessel spasm. In the patients with multivessel spasm, 61 (47.7%) had simultaneous spasm on their left anterior descending and left circumflex arteries. In single-vessel spasm, the prevalence rates of diffuse and focal spasm were 72.4% (n = 236) and 27.6% (n = 90). In multivessel spasm, the mixed type was observed in 48 (37.5%), the diffuse type in 63 (49.2%), and the focal type in 17 patients (13.3%). Coronary spasm was more frequently provoked on the segments with minimal atherosclerosis (365 segments, 57.6%) than on the segments without minimal stenosis (Table 3). The distributions of minimal atherosclerosis and coronary spasm are presented in Figure 1.

MEDICAL TREATMENTS. In the positive group, CCBs was prescribed in 428 patients (94.3%) and diltiazem was the most frequently prescribed (221 patients, 51.6%). In addition, long-acting vasodilators including nitrates, statins, and aspirin were used in 232 (51.1%), 178 (39.2%), and 172 patients (37.9%), respectively. However, the use of beta-blockers was limited to 11 patients (2.4%, 8 patients for heart failure and 3 for other conditions). Most patients in the positive group (n = 383, 84.4%) received combination-drug therapy, and CCBs plus nitrate was the most frequently prescribed (n = 145, 37.9%). In the intermediate group, medications were prescribed only for 223 patients (22.7%), and single therapy of nitrate was the most frequent (n = 142, 63.7%).

FOLLOW-UP AND CLINICAL OUTCOMES IN THE POSITIVE AND INTERMEDIATE GROUPS. Although continuous medical treatments were strongly recommended for the patients to whom medications were initially prescribed, 405 patients (93.8%) in the positive group and 108 patients (48.4%) in

TABLE 2 Baseline Laboratory Characteristics

	Positive (n = 454)	Intermediate (n = 982)	Negative (n = 693)	p Value	Post-Hoc 1: Positive 2: Intermediate 3: Negative
FBG, mg/dl	110.8 ± 36.2	114 ± 30.1	108.5 ± 36.8	0.64	
Cr, mg/dl	1.2 ± 0.8	1.3 ± 0.8	1.2 ± 0.4	0.38	
Troponin I, ng/ml	0.3 ± 1.2	0.4 ± 1.8	0.2 ± 1.3	0.29	
CK-MB, mg/dl	6.0 ± 18.4	7.1 ± 17.3	4.3 ± 11.9	0.22	
hsCRP, mg/l	1.1 ± 0.2	0.7 ± 0.6	0.6 ± 0.4	0.03	1>2,3
NT-proBNP, pg/ml	166.5 ± 300.1	146.0 ± 265.3	180.7 ± 847.5	0.42	
Lipid profile, mg/dl					
Total cholesterol	194.2 ± 36.1	208.8 ± 44.5	205.8 ± 36.3	0.29	
Triglyceride	151.8 ± 98.6	145.3 ± 116.6	129.3 ± 86.1	0.02	1>2>3
HDL cholesterol	45.5 ± 11.7	48.8 ± 13.7	48.3 ± 12.8	0.02	1<2,3
LDL cholesterol	111.6 ± 28.2	109.1 ± 31.7	107.0 ± 31.1	0.67	
Thyroid function*				0.55	
Normal	159 (61.9)	253 (60.7)	251 (64.2)		
Hyper-/hypo-	8 (3.1)/12 (4.7)	16 (3.8)/21 (5.0)	12 (3.1)/15 (3.8)		
Others	78 (30.4)	127 (30.5)	113 (28.9)		
Cardiac function					
LVEF, %	58.1 ± 6.6	58.3 ± 7.2	60.2 ± 6.5	0.79	
Mitral E/E′	10.5 ± 4.7	11.9 ± 5.9	11.3 ± 6.7	0.74	

Values are mean ± SD or n (%). *Thyroid function tests were performed in 257 patients in the positive group, 417 patients in the intermediate group, and 391 patients in the negative group.

CK-MB = creatine kinase-MB; Cr = creatinine; FBG = fasting blood glucose; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

TABLE 3 Results of Angiographic Provocation Test in the Positive Group (n = 454)

Single-vessel spasm	326 (71.8)
Left main	0 (0)
LAD	103 (31.6)
Diagonal	2 (0.6)
LCx	30 (9.2)
OM	3 (0.9)
RCA	188 (57.7)
Multivessel spasm	128 (28.2)
LAD + LCx	61 (47.7)
LAD + RCA	8 (6.3)
LAD + diagonal	22 (17.2)
LCx + OM	11 (8.6)
LAD + LCx + diagonal	10 (7.8)
LAD + LCx + OM	8 (6.3)
Others	8 (6.3)
Type of spasm	
Diffuse	299 (65.9)
Focal	107 (23.6)
Mixed	48 (10.6)
Ergonovine dose on spasm provocation	
E1/E2/E3	162 (35.7)/192 (42.3)/100 (22.0)
ST-segment change in provocation of spasm	
Elevation/depression	133 (29.3)/141 (31.1)
Elevation + depression/no change	96 (21.1)/84 (18.5)
Main symptom in provocation of spasm	
Chest pain/others/no symptom	305 (67.2)/91 (20.0)/58 (12.8)
Spontaneous spasm	76 (16.7)
Myocardial bridge on spastic segments	21 (4.6)
Association with minimal atherosclerosis*	
Spasm on atherosclerotic segment	365 (57.6)
Spasm on nonatherosclerotic segment	269 (42.4)

Values are n (%). *Total 634 segments of coronary spasm.
LAD = left anterior descending artery; LCx = left circumflex artery; OM = obtuse marginal artery; RCA = right coronary artery.

the intermediate group had taken ≥1 medication continuously at the end of the follow-up.

In the positive group, 127 patients (29.4%) had repeated angina leading to medication changes or rehospitalization, whereas only 47 patients (12.1%) experienced repeated angina in the intermediate group (Table 4). The prevalence rates of new-onset arrhythmia and acute coronary syndrome were very low in both groups (1.6% vs. 0.6%, p = 0.13; and 1.9% vs. 0.6%, p = 0.34, respectively). The rate of cardiac death during the follow-up was very low in the positive group (n = 4, 0.9%), whereas no cardiac death occurred in the intermediate group (p = 0.02) (Table 4). The detailed characteristics of the patients with cardiac death are presented in Table 5. The Kaplan-Meier curves for the primary endpoint and each adverse event are shown in Figures 2 and 3.

In the Cox regression analysis, the frequency of angina I/II before CAG (HR: 1.46 [95% CI: 0.87 to 2.04], p = 0.02), current smoking (HR: 3.62 [95% CI: 1.17 to 7.39], p = 0.001), and multivessel spasm (HR: 1.81 [95% CI: 1.21 to 3.78], p = 0.01) were revealed as the independent predictors of all adverse events in the positive group.

DISCUSSION

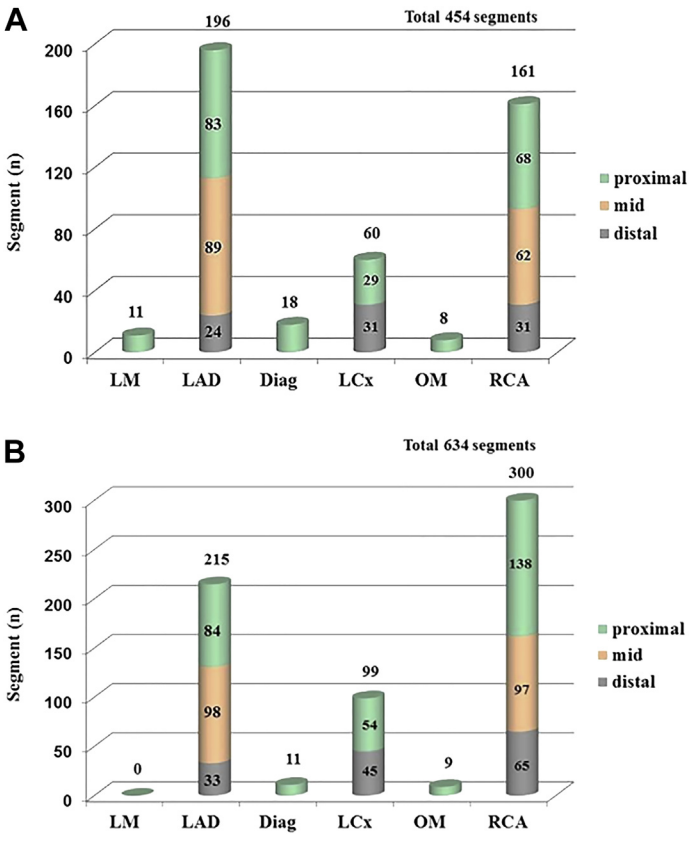
The incidence, clinical characteristics, medical treatment, 24-month clinical outcomes, and associated risk factors in the VSA patients diagnosed via intracoronary ergonovine provocation were reported from the VA-KOREA registry. To the best of our knowledge, this is the first large-scale, multicenter report on homogenous subjects who underwent only the intracoronary ergonovine provocation test. Additionally, the clinical characteristics and 24-month prognosis of the patients with intermediate constriction were novel and demonstrated helpful information for the clinical characteristics of the patients who underwent the ergonovine provocation test.

Although several diagnostic methods for VSA have been introduced, angiographic provocation with acetylcholine or ergonovine is most often used (7,9,10). Acetylcholine-induced coronary spasm may be the combined effects of endothelial dysfunction and vascular smooth muscle hyperconstriction (17,18). However, ergonovine-induced spasm may predominantly reflect endothelium-independent smooth muscle hyperconstriction, although its effect could be aggravated by endothelial dysfunction (19,20). Because of its long half-life, ergonovine-induced spasm is less likely to resolve spontaneously. Additionally, simultaneous spasm on the RCA and LCA may not be evaluated through the routine administration of ergonovine, because nitrate should be infused in the spasm-induced artery, and then spasm cannot be provoked in the other artery (9,17,21). With all of the faults of the ergonovine provocation test, however, it is still widely used in Korea and Japan (2,4,8,9). Recently, JCSA reported the safety of the ergonovine provocation test, compared with the acetylcholine provocation. Although both agents showed the acceptable level of safety, acetylcholine had a significantly higher incidence of test-related ventricular arrhythmia (9). In our registry, considering the clinicians' concerns over the potential risk of arrhythmia during the provocation and the unity of the mechanism of the provoked spasm in the subjects, we decided to use only ergonovine, not acetylcholine. Additionally, acetylcholine is not commercially available in Korea. Thus, this analysis had great merit for the homogenous subjects who underwent the VSA

provocation test using intracoronary ergonovine, not acetylcholine, under the same criteria for the positive result.

The degree of coronary constriction in response to ergonovine may vary, and a certain degree of nonspecific vasoconstriction could be shown in all individuals receiving ergonovine (20,22). Although total or subtotal occlusion was generally considered to be a positive response in the ergonovine provocation (2,4,8,9,13), some study groups have defined 75% or even 50% narrowing as a positive response (23). Thus, there has been no clear definition of the positive response to ergonovine, and it still remains unclear if hyper-responsiveness to ergonovine and VSA are essentially the same phenomena. Kashima et al. (24) suggested that patients with ergonovine-induced intermediate constriction might show a false negative response to ergonovine, so careful treatment should be continued (24). However, Sunagawa et al. (23) reported that the clinical characteristics of the patients who demonstrated intermediate constriction in the ergonovine provocation were similar to those of the patients with negative results rather than to those of the VSA patients (23). In our analysis, we also demonstrated that the clinical and laboratory findings in the intermediate group were similar to those in the negative group rather than the positive group. Moreover, the intermediate group had significantly lower rates of cardiac death and rehospitalization than the positive group despite the high rate of medication withdrawal. It has been well known that withdrawal of medication is the most important predictor for cardiac death in VSA patients (2). Our results could indicate the clinical differences between

FIGURE 1 Distribution of Minimal Atherosclerosis and Coronary Spasm



Minimal atherosclerosis was founded on 454 segments in the baseline angiography **(A)**, whereas coronary spasm was provoked on 634 segments **(B)**. LAD = left anterior descending; LCx = left circumflex; LM = left main; OM = obtuse marginal; RCA = right coronary artery.

TABLE 4 12- and 24-Month Cumulative Outcomes in the Positive and Intermediate Groups

	12 months		24 months			
	Positive (n = 432)	Intermediate (n = 668)	Positive (n = 432)	Intermediate (n = 668)	p Value (Log-Rank)	Adjusted p Value* (Log-Rank)
Primary endpoint†	14 (3.2)	6 (0.9)	17 (3.9)	8 (1.2)	0.04	0.02
Arrhythmia	5 (1.2)	2 (0.3)	7 (1.6)	4 (0.6)	0.13	0.49
VT/VF	0 (0)	0 (0.0)	1 (0.2)	0 (0.0)		
Atrial fibrillation	0 (0)	1 (0.1)	1 (0.2)	1 (0.1)		
AV block	3 (0.7)	0 (0.0)	3 (0.7)	1 (0.1)		
Others	2 (0.5)	1 (0.1)	2 (0.5)	2 (0.3)		
Acute coronary syndrome	7 (1.6)	4 (0.6)	8 (1.9)	4 (0.6)	0.34	0.10
STEMI	0 (0)	0 (0.0)	0 (0)	0 (0.0)		
NSTEMI/unstable angina	7 (1.6)	4 (0.6)	8 (1.9)	4 (0.6)		
Cardiac death	3 (0.7)	0 (0.0)	4 (0.9)	0 (0.0)	0.02	0.03
Medication change	51 (11.8)	7 (3.1)‡	68 (15.7)	17 (7.6)‡	0.06	0.08
Rehospitalization/ED visit	44 (10.2)	24 (3.6)	59 (13.7)	30 (4.5)	0.04	0.01

Values are n (%). *Adjusted by the center variance component. †The primary endpoint was a composite of cardiac death, new-onset arrhythmia, and acute coronary syndrome. ‡The rate of medication change was estimated in 223 patients of the intermediate group who had the initial medications prescribed.

AV = atrioventricular; ED = emergency department; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE 5 Detailed Characteristics of the VSA Patients With Cardiac Deaths

	Sex/Age (yrs)	Current Smoking	DM/HTN	LVEF (%)	Type of Spasm	MS	Involved Vessel	Beta-Blocker	Medication	D-1*	D-2†	JCSA Score
1	Male/59	Yes	No/no	58	Diffuse	No	LAD	No	Continuous	11		4
2	Male/65	Yes	No/yes	46	Mixed	Yes	LAD + LCx	Yes	Discontinue	6	7	8
3	Male/67	Yes	Yes/no	66	Mixed	Yes	LAD + RCA	No	Discontinue	4	6	6
4	Female/61	Yes	Yes/no	43	Diffuse	No	RCA	Yes	Discontinue	3	6	6

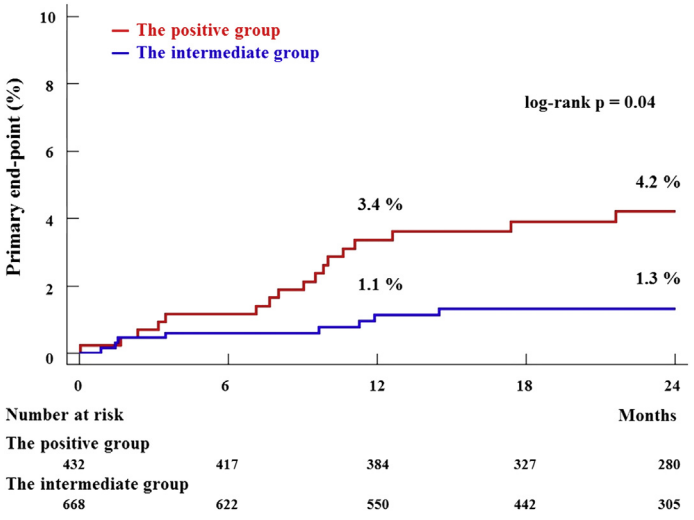
*D-1 is defined as the duration of medical treatments (months). †D-2 is defined as the duration from discontinuation of medication to cardiac deaths (months).
DM = diabetes mellitus; HTN = hypertension; LVEF = left ventricular ejection fraction; MS = multivessel spasm; VSA = vasospastic angina.

intermediate vasoconstriction and true VSA, and also emphasize the need for strict positive criteria in the ergonovine provocation test. However, there may be several confounding factors in the rate of rehospitalization due to repeated angina. Although the frequency and severity of angina in the intermediate group could be less severe than those in the positive group, the effect of the differences in the medical treatments could also have played an important role in the different rate of rehospitalization. Additionally, repeated angina is a subjective symptom rather than an objective sign influenced by different personal traits such as the pain threshold. Therefore, the definite clinical meanings of the intermediate constriction could still be open to debate (23,24). Further larger-scale studies on the clinical features of intermediate constriction should be conducted.

There have been a few reports for the prognosis of patients who demonstrated the negative result in the ergonovine provocation. Although they showed lower incidences of recurrent angina, MI, and cardiac death compared with those with ergonovine-induced VSA in previous Japanese and European retrospective studies (24,25), the negative groups in their studies might include the intermediate group in our analysis. Thus, the clinical outcomes of the true negative group in the ergonovine provocation are still unclear. The protocol of the VA-KOREA recommended regular follow-up in the negative group to address this issue, although medications were not prescribed. However, the follow-up rate was too low to analyze the 24-month prognosis. In our analysis, the 1-month follow-up rate was 66.2% (n = 459), but the 12- and 24-month follow-up rates were only 15.4% (n = 107) and 3.2% (n = 22), respectively, which was most likely due to the lack of symptoms. Only 1 patient in the negative group showed defined new-onset arrhythmia (atrial fibrillation) at 9 months of follow-up. However, it could not indicate the precise clinical prognosis of the negative group due to the low follow-up rate, and consequently, we could not present the 24-month prognosis in the negative group.

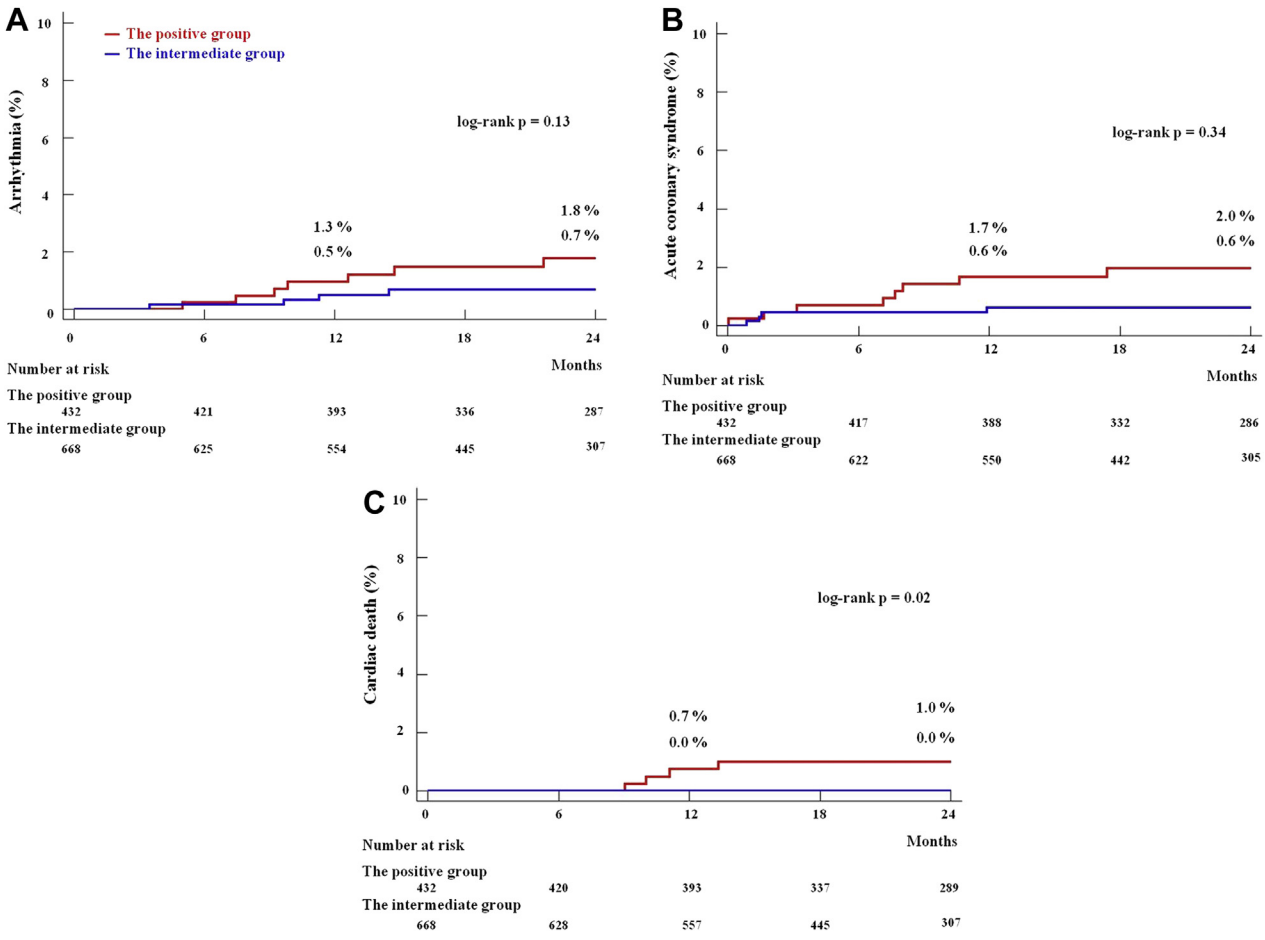
We demonstrated that the high frequency of angina before CAG, current smoking, and multivessel spasm were independent predictors of worse outcomes in VSA patients, consistent with the results of previous studies (2,3,6,12). In Japan, JCSA recently suggested a prognostic scoring system for VSA that consists of 7 predictors for adverse cardiovascular events (4). Because the VA-KOREA had already been designed before the score was introduced, we did not include several values of the scoring system. Specifically, we excluded the patients with significant organic stenosis on their baseline CAG. It has been noted that VSA patients without significant stenosis have an excellent long-term prognosis (12). Nevertheless, in our analysis, 75% of the patients who experienced cardiac death had been assigned to the high-risk group of the JCSA system, which could imply the possibility of effectively applying this score to Korean VSA patients in a further analysis. Meanwhile, the JCSA score did not include discontinuation

FIGURE 2 Kaplan-Meier Curve for the Primary Endpoint



The primary endpoint was a composite of cardiac death, new-onset arrhythmia, and acute coronary syndrome.

FIGURE 3 Kaplan-Meier Curves for Each Adverse Event



The 24-month event-free survival rates for new-onset arrhythmia **(A)**, acute coronary syndrome **(B)**, and cardiac death **(C)** were 98.2%, 98.0%, and 99.0%, respectively, in the positive group. There was no cardiac death in the intermediate group.

of medications as a predictive factor, and it was not revealed as an independent factor of adverse events in our analysis, although 75% of the patients who experienced cardiac death had discontinued medications. However, the JCSA score was derived from the subjects for whom appropriate medications including CCBs (93.0%) were continuously prescribed. Similarly, most of the VSA patients (93.8%) in our registry had also continuously taken ≥1 medication. Thus, in further studies, the JCSA score should be applied on the premise that patients with VSA should receive adequate medical treatment.

To generalize our results in other settings without a clinical interest in VSA, there are many factors to consider. However, our results were from the analysis in patients who underwent the angiographic ergonovine provocation test under the clearly-defined protocol in the cardiovascular centers that had the proactive clinical interest for VSA. Our results could suggest the values of the clinical interest and the proactive angiographic investigation for VSA under the well-defined homogenous protocol. In our registry, the positive rate of the ergonovine provocation test was 21.3%, similar to those of the previous reports using the ergonovine provocation (12,20). The incidence of VSA seems to be decreasing globally, probably due to the use of CCBs and fewer smokers (2,17). Thus, interest in organic stenosis and coronary intervention is growing among cardiologists and less attention is being paid to VSA. Additionally, recent technological advances have driven the increasing use of noninvasive diagnostic methods for coronary artery diseases. Therefore, under these circumstances, fewer cardiologists may pay attention to

VSA (17). However, VSA is still prevalent (2–5) and may be refractory to conventional medications (6,11,17). Thus, it could be important for clinicians not only to have greater interest in VSA, but also to conduct a larger-scale analysis of the clinical and pathologic characteristics of VSA.

STUDY LIMITATIONS. First, this was an observational registry study, which has inherent limitations. Second, we could not clearly explain the precise causes of the low follow-up rate and the relatively high rate of medication withdrawal in the intermediate group. However, given the lower rate of rehospitalization due to repeated angina in the intermediate group compared with the positive group, the severity of angina might be an explanation for those rates. Additionally, a definite treatment plan for the intermediate constriction could not be suggested. Third, the mean follow-up duration was only about 2 years. Considering the few adverse events, a longer follow-up period could be helpful in estimating the clinical outcomes of VSA. Finally, we could not address several novel issues in VSA, including the tissue characterization, the effect of risk factor modification, and specific ECG changes. Moreover, although the association between VSA and the progression of atherosclerosis leading to PCI has been regarded as a controversial issue, we could not present the data to address this association. Thus, we are planning to conduct new analyses to address these important issues. Despite these limitations, this analysis could provide helpful information for understanding the clinical features of patients who underwent the ergonovine provocation test.

CONCLUSIONS

The 24-month clinical outcomes of the positive group in the intracoronary ergonovine provocation test were relatively worse than those of the intermediate group according to the results from the VA-KOREA registry. More proactive and intensive clinical attention should be paid to VSA patients with high risk factors including frequent angina before angiography, current smoking, and multivessel spasm.

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PERSPECTIVES

WHAT IS KNOWN? We determined the 24-month clinical prognosis of Korean patients with positive or intermediate results in intracoronary ergonovine provocation tests for VSA.

WHAT IS NEW? The clinical characteristics and the incidences of cardiac death, new-onset arrhythmia, acute coronary syndrome, and repeated angina were estimated. Patients with intermediate coronary constriction demonstrated better 24-month clinical outcomes than those with VSA, which suggests that the homogenous strict positive criteria in the ergonovine provocation test should be established to distinguish true VSA from hyper-responsiveness to ergonovine. In addition, more intensive clinical attention should be paid to VSA patients with high risk factors including frequent angina before angiography, current smoking, and multivessel spasm.

WHAT IS NEXT? The prospective, international, multicenter registry and a prospective, randomized controlled clinical study would be helpful in providing the right answers to the many unsolved questions about VSA in real evidence-based medicine.

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