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Impact of multi-vessel vasospastic angina on cardiovascular outcome

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HIGHLIGHTS

- Prevalence of multi-vessel vasospastic angina (VSA) is not low (39.0%) by strict definition.
- Baseline characteristics of multi-vessel and single vessel VSA groups were similar, but different from non-VSA group.
- Multi-vessel VSA group had worse clinical outcomes than the single vessel and non-VSA groups.
- Multi-vessel VSA itself is one of the independent predictors for MACE.

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ABSTRACT

Background and aims: Since clinical characteristics and prognosis of patients with multi-vessel vasospastic angina (VSA) are not clear, we investigated the nature and prognosis of multi-vessel VSA in Koreans.
Methods: Among 2960 patients enrolled in the VA-KOREA (Vasospastic Angina in Korea) registry, 104 definite multi-vessel VSA patients, 163 single vessel VSA patients and 737 non-VSA patients were identified using the intracoronary ergonovine provocation test.
Results: Multi-vessel VSA and single vessel VSA groups showed similar baseline characteristics and medical treatment on discharge, but different from the non-VSA group. The primary composite endpoint (cardiac death, acute coronary syndrome, and symptomatic new onset arrhythmia) over a 36-month follow-up period was significantly higher in the multi-vessel VSA group than in the single vessel VSA and non-VSA groups (8.7% *vs.* 1.8% and 1.1%, each log-rank $p < 0.05$, respectively). The rate of death and acute coronary syndrome of the multi-vessel VSA group was higher than in the single vessel VSA and non-VSA groups (5.8% *vs.* 1.2% and 0.9%, each log-rank $p < 0.05$, respectively). In addition, multi-vessel VSA was an independent predictor of the primary composite endpoint at 36 months (HR 8.5, 95% CI [2.6–27.2], $p < 0.0001$).
Conclusions: Patients with multi-vessel VSA had worse clinical outcomes than single vessel VSA and non-VSA groups, suggesting that the existence of multi-vessel VSA itself is highly prognostic.

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1. Introduction

Vasospastic angina (VSA) is an important factor in the pathophysiology of myocardial ischemia in patients with or without coronary artery stenosis [1,2]. VSA is more prevalent in Korea and Japan than in Western countries; therefore, provocation tests for VSA are widely performed in Korea and Japan [1–7]. The Vasospastic Angina in Korea (VA-KOREA) registry is a large-scale, prospective, web-based, multicenter registry designed to detect and evaluate the clinical characteristics and prognosis of VSA patients using a standardized ergonovine provocation protocol. We have previously reported the general characteristics and prognosis of VSA patients [4].

A challenge in assessing the prognosis of VSA patients is to determine whether the extent of vasospasm of the coronary arteries is associated with clinical prognosis. Patients with multi-vessel VSA reportedly have worse clinical outcomes than patients with single vessel VSA [4–11], although these findings are inconsistent [3,12]. Given that the detection of multi-vessel VSA and single vessel VSA requires simultaneous or sequential left and right coronary artery provocation test, the exact diagnosis can be cumbersome and difficult to implement leading to rare detection rates. Since previous many reports [3–12] do not precisely describe the definition and detection methods behind determining single- or multi-vessel VSA, the baseline characteristics and clinical outcome of multi-vessel VSA is yet to be clear. The VA-KOREA registry has a large sample size (n = 2960) and using a predefined systematic approach which allows studying large numbers of definite multi-vessel VSA, single vessel VSA and non-VSA patients. In this study, we investigate the nature and prognosis of multi-vessel VSA compared with single vessel VSA and non-VSA patients over a 36-month clinical follow up period.

2. Materials and methods

2.1. Study patients

VA-KOREA enrolled patients who had suspicious symptoms and underwent coronary angiography (CAG) with an ergonovine provocation test according to the decision of the responsible clinician [4]. All participating centers used the same study protocol for the intracoronary (IC) ergonovine provocation test. All potential study patients had normal findings or minimal (< 50% luminal diameter narrowing) atherosclerosis at the baseline CAG, whereas those with significant atherosclerosis (more than 50% luminal diameter narrowing) were excluded. Patients with end stage renal disease who require dialysis, known malignant or inflammatory diseases, and catheter-induced spasm at the baseline CAG were also excluded. All patients with positive results on their provocation tests received drug treatments including calcium channel blockers (CCBs) and other vasodilators as part of the ongoing treatment. The research protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of each participating institution, and all patients gave their written informed consent.

2.2. CAG and provocation test for VSA

Vasodilator drugs such as CCBs and nitrates were discontinued at least 48 h prior to the CAG. After finishing baseline CAG on both coronary arteries, IC ergonovine was administered for the provocation test. For the left coronary artery (LCA) provocation test, incremental doses of 20 (E1), 40 (E2), and 60 μg (E3) were injected into the LCA. The right coronary artery (RCA) was also injected incremental doses of IC ergonovine [10 (E1), 20 (E2), and 40 μg (E3)] [4,6]. When tolerable to the patient, both the LCA and RCA provocation tests were sequentially performed. After the provocation test, IC nitrate (200 μg) was injected. All vascular responses to ergonovine in the provocation test and atherosclerosis on the baseline CAG were quantitatively analyzed for five coronary artery sites [left main and left anterior descending artery (LAD), diagonal branch, left circumflex artery (LCX), obtuse marginal branch, RCA] with diameter greater than 2.5 mm. Diameter change after IC ergonovine injection was compared with diameter after IC nitroglycerin injection in the site with the biggest diameter change. Angiographic data were analyzed online or offline by a dedicated quantitative coronary angiography program or manual assessment by investigators in each center. In addition, investigators at the core laboratory of Seoul St. Mary's Hospital, Seoul, South Korea, confirmed blindly the angiographic data offline by visual assessment, and classified patients into the study groups.

2.3. Definitions

The definition of a definite (positive) VSA was total or subtotal (> 90% luminal diameter narrowing) occlusion accompanied by ischemic symptoms and/or electrocardiographic (ECG) changes [1,4]. An ischemic ECG change was defined as an ST-segment elevation or depression > 0.1 mV or a negative U-wave in at least two related leads [4]. Intermediate result defined as patients with 50–90% luminal narrowing with or without ischemic symptoms and/or ECG changes were excluded from the current analysis. The definition of multi-vessel VSA in this study was established as total or subtotal (> 90% luminal diameter narrowing) occlusion of one coronary artery with coronary artery spasm (CAS) (more than 70% diameter stenosis) among other five coronary artery sites (Supplementary Figs. 1A and B). For example, when the ergonovine provocation test was only performed in the LCA, CAS of the LAD and diagonal or CAS of LCX and obtuse marginal artery, etc. were defined as multi-vessel VSA (Supplementary Fig. 1B). When the ergonovine provocation test only was done in the RCA, diagnosis of multi-vessel VSA, single-vessel VSA and non-VSA was not possible by definition. Such patients were excluded from current analysis.

Single vessel VSA was defined as total or subtotal occlusion of one coronary artery site without CAS in other coronary artery sites examined by both left and right ergonovine provocation test. Non-VSA was defined as both the LCA and RCA ergonovine provocation test with < 50% luminal narrowing without ischemic symptoms and ECG changes. The exclusion criteria of this analysis are shown in Supplementary data.

2.4. End-points

The primary endpoint was a composite of cardiac death, acute coronary syndrome (ACS), and symptomatic new-onset arrhythmia during the 36-month follow-up period. Cardiac death was defined as any death due to cardiac causes such as myocardial infarction, low-output heart failure, fatal arrhythmia, and death from unknown causes [4]. ACS was defined as recurrent or continuous chest pain lasting more than 20 min with ischemic ECG changes or elevation of cardiac markers including myocardial infarction. For patients who presented for the first time, clinically significant symptomatic arrhythmia, such as atrial or ventricular tachycardia/fibrillation, symptomatic premature beats, sick-sinus rhythm, or atrioventricular block were considered as symptomatic new-onset arrhythmia [4,13]. ECG was routinely checked during the regular or emergent visits, and 24-h Holter monitoring was performed in patients with suspicious symptoms. Emergency room (ER) revisits due to occurrence of primary endpoint or of any discomfort were reported. Each adverse event was analyzed as a secondary endpoint. All adverse events of interest were confirmed through source document review, including medical records as well as telephone interviews, and were adjudicated by the Local Events Committee of Seoul St. Mary's Hospital.

2.5. Statistical analysis

To compare the baseline clinical characteristics among the groups, we analyzed the data for enrolled patients. After testing data for normality, continuous variables were expressed as mean ± standard deviation (SD) or median (inter-quartile range) and the differences in the continuous variables were assessed with one-way analysis of variance or Kruskal-Wallis test. In the presence of significant differences among groups, the Bonferroni test was also performed for the post-hoc analysis. Categorical variables are presented as numbers and percentages. The chi-square test was used for the categorical variables to estimate the significance of differences among the groups.

The incidences and rates of the end-points during 36-month follow-up between the groups were displayed with table and Kaplan-Meier curves. The log-rank test was performed to compare the incidences and rates of the endpoints among the groups. The hazard ratios (HRs) and 95% confidence intervals (CIs) of the endpoints between the groups were calculated. To identify risk factors for the primary composite endpoint during 36-month follow-up, well established cardiovascular risk factors and variables that had considerable significance between groups ($p < 0.3$) in the baseline characteristics were selected. Univariate and multivariate Cox proportional hazard analysis (backward likelihood ratio) was performed in all study patients including multi-vessel VSA, single vessel VSA and non VSA groups. The HRs and 95% CIs of each risk factor were calculated. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS (SPSS Inc. PASW Statistics for Windows, Version 19.0. Chicago: SPSS Inc.) and Medcalc for Windows, version 18.5 (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Patient enrollment and follow-up

Fig. 1 presents the study design as a flow chart. A total of 2960 patients were registered in the VA-KOREA. Under the definition and exclusion criteria of this study, 104 patients were identified as with multi-vessel VSA, 163 patients as with single vessel VSA, and 737 patients as with non-VSA. The incidence of multi-vessel VSA was 39.0% of enrolled VSA patients in this analysis.

3.2. Baseline characteristics of study population on admission

Table 1 shows baseline clinical and laboratory characteristics. The rate of male sex, current smoking and high alcohol consumption in multi-vessel VSA and single vessel VSA groups were significantly higher than the non-VSA group (each $p < 0.05$, respectively). Triglyceride and high density lipoprotein cholesterol levels differed significantly among groups (each $p < 0.05$, respectively). In the subgroup analysis, triglyceride and high density lipoprotein cholesterol levels were similar between multi-vessel VSA and single vessel VSA groups. The single vessel VSA group showed a significantly higher level of triglyceride than the non-VSA group ($p < 0.05$). In addition, there were no significant differences in other baseline characteristics between multi-vessel and single vessel VSA patients.

3.3. Medication on discharge after the provocation test

CCBs were the most frequently prescribed drugs for study patients. The prescription rate of CCBs was greater in the multi-vessel and single vessel VSA groups than in the non-VSA group (95.2%, 93.9% *vs*. 40.0%, $p < 0.0001$). However, there was no difference in prescription rate of CCBs between the multi-vessel and the single vessel VSA groups. Other medical treatments including nitrates, antiplatelet agents and statins showed similar trends with those of CCBs. The prescription rate of beta blockers was higher in the non-VSA group than in the multi-vessel and single vessel VSA groups (15.6% *vs*. 7.7% and 4.3%, $p < 0.0001$) (Supplementary Table 1).

3.4. Comparison of primary endpoint and revisit to the emergency room during a 36 month follow-up between groups

Over the three years of clinical follow-up, the incidence and rate of the primary composite endpoint in the multi-vessel VSA group was significantly higher than the single vessel VSA and non-VSA groups (8.7% *vs.* 1.8% and 1.1%, each log-rank $p < 0.05$, respectively, Table 2, HR [95% CIs] for single vessel VSA group, 4.8 [1.5–15.2], log-rank $p < 0.05$; HR for non-VSA group, 7.1 [1.8–28.6], log-rank $p < 0.0001$, Fig. 2A). Of interest, the incidence and rate of death and ACS during 36-month follow-up was higher in the multi-vessel VSA group than in the single vessel VSA and non-VSA groups (5.8% *vs.* 1.2% and 0.9%, each log-rank $p < 0.05$, respectively, Table 2, HR for single

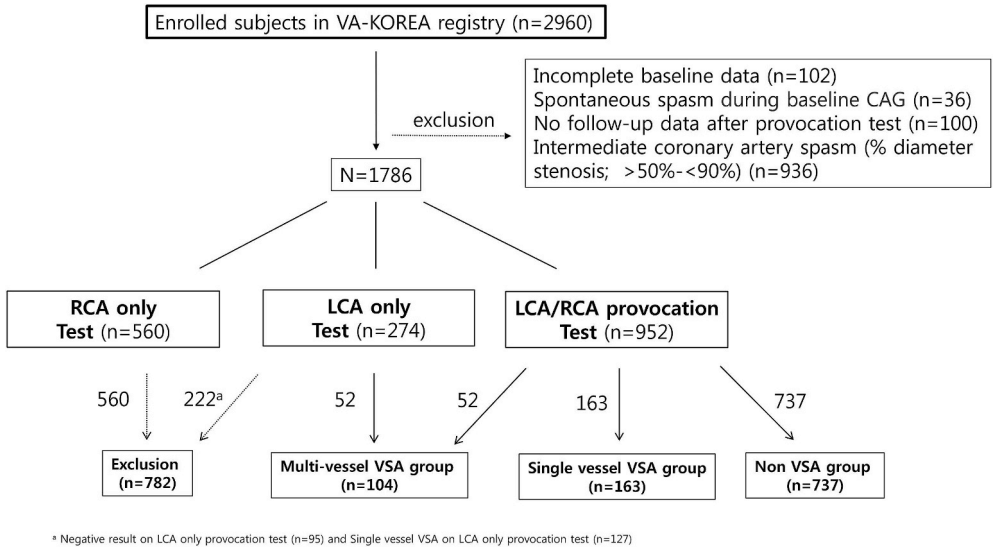

Fig. 1. Study flow chart.
[a] Negative result on LCA only provocation test (n = 95) and single vessel VSA on LCA only provocation test (n = 127). VA-KOREA, The Vasospastic Angina in Korea; RCA, right coronary artery; LCA, left coronary artery; VSA, vasospastic angina.

Table 1
Baseline characteristics of study patients.

	Multi vessel VSA (n = 104)	Single vessel VSA (n = 163)	Non-VSA (n = 737)	*p* value
Age, years	57.3 ± 9.7	56.6 ± 11.9	54.9 ± 12.9	0.09
Male	73 (70.2)[a]	113 (69.3)[c]	281 (38.0)	< **0.0001**
Body mass index, kg/m^2	24.9 ± 3.0	24.9 ± 2.9	24.7 ± 3.4	0.78
High Alcohol consumption	30 (28.8)[a]	42 (25.8)[c]	104 (13.7)	< **0.0001**
Hypertension	45 (50.1)	60 (38.7)	263	0.17
Diabetes	15 (14.4)	24 (14.7)	131 (17.8)	0.28
Current smoking	34 (32.7)[a]	42 (25.8)[c]	98 (13.3)	< **0.0001**
History of dyslipidemia	15 (14.4)	24 (14.7)	131 (17.8)	0.28
Creatinine, mg/dL	0.86 ± 0.36	0.80 ± 0.25	0.77 ± 0.59	0.24
Troponin I, ng/mL	0.35 ± 0.93	0.27 ± 1.61	0.27 ± 1.94	0.97
CK-MB, ng/mL	3.74 ± 6.34	6.91 ± 29.40	3.73 ± 7.01	0.07
hsCRP, ml/L	0.09 (0.04–0.30)	0.14 (0.05–0.30)	0.10 (0.03–0.30)	0.71
Total cholesterol, mg/dL	166.4 ± 35.5	174.2 ± 38.7	175.9 ± 36.5	0.07
Triglyceride, mg/dL	114.0 (79.0–160.0)	115.5 (77.8–198.3)[c]	100.0 (72.0–152.0)	**0.003**
HDL cholesterol, mg/dL	45.7 ± 11.9	45.5 ± 12.0	48.0 ± 12.5	**0.046**
LDL cholesterol, mg/dL	100.9 ± 30.6	101.0 ± 31.0	105.3 ± 31.1	0.19
LVEF, %	63.3 ± 7.7	64.0 ± 7.0	64.6 ± 6.1	0.14

Values are mean ± SD or n (%) or median (25–75 percentile).
VSA, vasospastic angina; CK-MB, creatine kinase-MB; hsCRP, high sensitivity C reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction.
[a] *p* value for multi-vessel VSA group *vs*. non-VSA group < 0.05.
[b] *p* value for multi-vessel VSA group *vs*. single vessel VSA group < 0.05.
[c] *p* value for single vessel VSA group *vs*. non-VSA group < 0.05.

Table 2
Cumulative events during 36 month follow up.

	Multi-vessel VSA (n = 104)	Single vessel VSA (n = 163)	Non-VSA (n = 737)	*Log-rank p* value
Primary endpoints	9 (8.7) [ab]	3 (1.8)	8 (1.1)	< 0.0001
Death	2 (1.9)[a]	0 (0)	1 (0.1)	0.06
ACS	4 (3.8)[a]	2 (1.2)	7 (0.9)	0.17
Symptomatic new onset arrhythmia	3 (2.9)[a]	1 (0.6)	1 (0.1)	**0.02**
VT, VF	0	0	0	
Atrial fibrillation	2	0	1	
Symptomatic AV block	1	1	0	
Death/ACS	6 (5.8) [ab]	2 (1.2)	7 (0.9)	**0.02**
Revisit to ER	16 (15.4)[a]	18 (11.0)[c]	37 (5.0)	< **0.001**

Values are expressed as number (%).
VSA, vasospastic angina; ACS, acute coronary syndrome; VT, ventricular tachycardia; VF, ventricular fibrillation; AV, atrioventricular; ER, emergency room.
[a] *p* value for multi-vessel VSA group *vs*. non-VSA group < 0.05.
[b] *p* value for multi-vessel VSA group *vs*. single vessel VSA group < 0.05.
[c] *p* value for single vessel VSA group *vs*. non-VSA group < 0.05.

vessel VSA group, 4.7 [1.1–19.5], log-rank $p < 0.05$; HR for non-VSA group, 5.4 [1.1–26.5], log-rank $p < 0.001$, Fig. 2).

The incidence and rate of revisit to ER in the multi-vessel VSA was higher than in non-VSA group (15.4% *vs*. 5.0%, log-rank $p < 0.05$, Table 2, HR for non-VSA group 2.83 [1.3–6.3], log-rank $p < 0.001$, Fig. 2C) but similar with single vessel VSA group (*vs*. 11.0%, log-rank p = NS, Table 2, HR for single vessel VSA group 1.4 [0.7–2.8], log-rank p = NS, Fig. 2C).

3.5. Vasodilator treatment in patients with primary endpoint

All three patients with primary endpoint events among the single vessel VSA group received both CCBs and nitrates. Among the patients who had a primary endpoint in the multi-vessel VSA group, one patient did not receive CCBs and another patient did not receive any nitrates (Supplementary Table 2).

3.6. Predictors for primary endpoint during the 36-month clinical follow-up

In the multivariate Cox proportional hazards analysis (backward likelihood ratio) including all study patients, multi-vessel VSA was one of the independent predictors of the primary endpoint (HR 8.5, 95% CI [2.6–27.2], $p < 0.0001$, Table 3). In addition, hypertension and a history of dyslipidemia were independent predictors for the primary endpoint (Table 3). However, single vessel VSA was not an independent predictor of the primary endpoint in this model (HR 2.9, 95% CI [0.6–14.9], p = NS). The Omnibus test of model coefficients for this model was significant ($p < 0.05$).

4. Discussion

Our study provides important information regarding the nature and prognosis of multi-vessel VSA in Koreans. First, the prevalence of multi-vessel VSA is not low (39.0%). Second, the baseline clinical characteristics of the multi-vessel and single vessel VSA groups were similar but significantly different from the non-VSA group. Third, the multi-

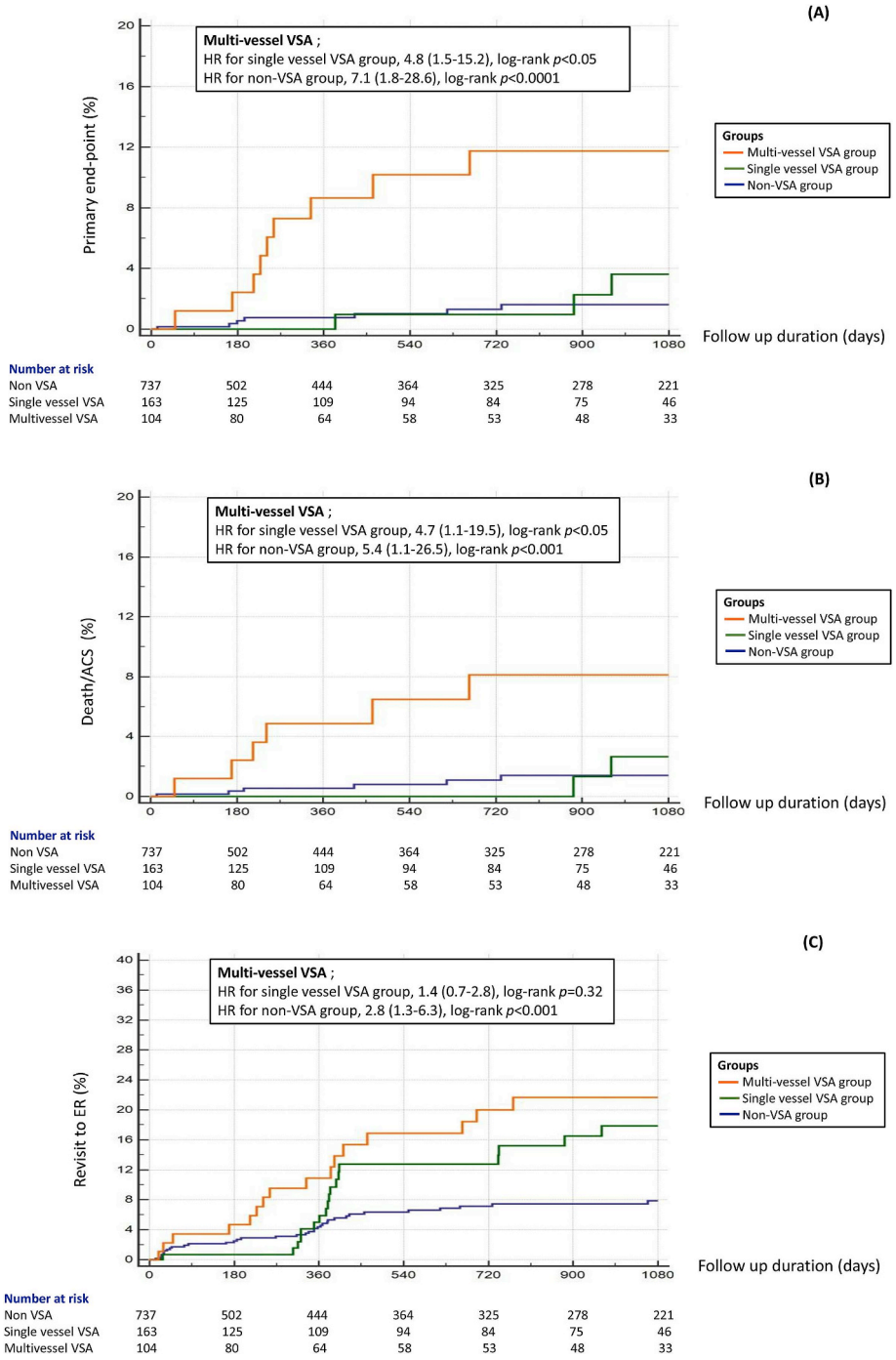

Fig. 2. Kaplan-Meier curve for the endpoints over 36-month clinical follow up.
(A) For the primary endpoint, (B) for the death and acute coronary syndrome, and (C) for the revisit to emergency room due to occurrence of primary endpoint or other discomforts. VSA, vasospastic angina; HR, hazard ratio; ACS, acute coronary syndrome; ER, emergency room.

vessel VSA group had worse clinical outcomes than the single vessel VSA and non-VSA groups. During the clinical follow-up of over three years, the incidence and rate of the primary composite endpoint and hard primary endpoint (death and ACS) in multi-vessel VSA group was significantly higher than the single vessel VSA and non-VSA groups. In addition, multi-vessel VSA was one of the independent predictors of the primary endpoint in the multi variate Cox proportional hazards analysis, even recommended medical treatments. Therefore, the presence of multi-vessel VSA itself is highly prognostic of poor future cardiovascular outcomes. Further investigation of the effective treatment for the multi-vessel VSA is warranted.

Coronary spasm is important in the pathogenesis not only for VSA but for ischemic heart diseases in general, including effort angina, unstable angina, acute myocardial infarction, and sudden cardiac death [14]. The coronary artery spasm provocation test is recommended in European Society of Cardiology as a Class IIa, level of evidence B [2] and in the Japanese Circulation Society as a Class I indication [1] in patients with suspected VSA without a diagnosis by non-invasive evaluations. Among the provocation test drugs, ergonovine-induced coronary hyper-constriction may be mediated by the activation of serotonergic receptors with a subsequent increase in calcium influx into the vascular smooth muscle cells [15]. The sensitivity and specificity of the ergonovine provocation test were reported to be 77–100% and 98–99%, respectively [16,17].

Table 3
Predictors for primary endpoint during 36-month clinical follow up.

	Univariate analysis				Multivariate analysis			
	HR	95% CI		*p* value	HR	95% CI		*p* value
Age, years	1.0	1.0	1.1	**0.02**				
Male	0.6	0.2	1.5	0.24				
High alcohol consumption[a]	0.8	0.2	2.8	0.75				
Hypertension	1.6	0.7	3.9	0.27	3.3	1.1	9.9	**0.03**
Diabetes	1.5	0.4	5.2	0.51				
Current smoking [b]	0.3	0.0	2.0	0.19				
History of dyslipidemia [c]	2.6	1.0	6.6	**0.04**	5.1	1.8	14.8	**0.003**
Creatinine, mg/dL	0.2	0.0	2.3	0.20				
CK-MB, ng/mL	1.0	1.0	1.0	0.68				
hsCRP, ml/L	0.8	0.3	2.1	0.61				
LVEF, %	1.0	0.9	1.0	0.53				
Single vessel VSA [d]	1.5	0.4	5.6	0.55	2.9	0.6	14.9	0.21
Multi-vessel VSA [d]	7.1	2.7	18.4	< **0.0001**	8.5	2.6	27.2	< **0.0001**

Bold characters mean *P* values are statistically significant, ≤ 0.05.
HR, hazard ratio; CI, confidence interval; BP, blood pressure; CK-MB, creatine kinase-MB; hsCRP, high sensitivity C reactive protein; LVEF, left ventricular ejection fraction; VSA, vasospastic angina.
[a] High alcohol consumption was defined as more than 2 times alcohol drinking in a week.
[b] The status of current smoking is assessed at the time of intracoronary ergonovine provocation test.
[c] Definition of history of dyslipidemia: previous diagnosis of dyslipidemia base on past medical history by attending physicians or drug treatment for dyslipidemia on index admission.
[d] HRs are calculated by comparison with the non-VSA group.

In the current study, the prevalence of multi-vessel VSA was 39.0%, similar to the previously reported Japanese prevalence of multi-vessel VSA (Japanese 24–32%) [1]. Although rate of revisit to the ER in the current study was similar between multi-vessel VSA and single vessel VSA groups, the rates of primary endpoint and death/ACS were significantly higher in multi-vessel VSA group than in single vessel VSA and non-VSA groups. Therefore, our study demonstrates that the multi-vessel VSA led to poor clinical outcomes compared to the single vessel and non-VSA groups. In addition, multi-vessel VSA was one of the independent predictors of the primary endpoint over a 36-month follow-up with adjustment for covariates and confounders.

Few studies [3,12] report that cardiovascular event rates are similar between multi-vessel spasm and other types of spasm in VSA patients. Park et al. [3] has shown that the prognosis of diffuse multi-vessel spasm had similar rate of chest pain free survival with very rare hard clinical events compared to other types of spasm on recommended medical treatments. These data were consistent with our findings in terms of similar rates of chest pain free survivor between diffuse multi-vessel spasm and other types of spasm, although differences in hard clinical events were observed in the current analysis. Because our current study enrolled larger numbers of patients and followed up a longer period, the rate of hard clinical endpoints may have been significantly different between the multi-vessel VSA and single vessel VSA groups. In addition, similar with the current study, many previous studies reported poor clinical outcomes in multi-vessel spasm [4–11]. Multi-vessel VSA documented by ST segment elevation in both the anterior and inferior leads during chest pain showed low survival rate compared to the single vessel VSA (85% *vs*. 96–97%, $p < 0.01$) and was an independent predictor for survivor among 245 patients [8]. In another study with 202 VSA patients, the only variable significantly associated with major cardiac events was the detection of ST-segment elevation in both anterior and inferior ECG leads (odds ratio 3.24; 95% CI 1.43–7.36, $p = 0.005$) during angina [9]. Previous small studies [10,11] also showed the higher incidence of cardiovascular events in multi-vessel VSA and good prognosis in patients with single vessel VSA. These results are consistent with our current results.

Compared with previous reports, the strength of our study is that the analysis was limited to data from patients who were confidently diagnosed with VSA (luminal narrowing > 90%) and true multi-vessel VSA, single vessel VSA and non-VSA group by strict angiographic definition. The well-defined criteria of multi-vessel and single-vessel VSA in this study exclude intermediate results, incomplete studies. Although detection of multi-vessel VSA with ECG can be still helpful, it can be applied to limited numbers of patients because contemporary practice undergo directly CAG in most patients with suspected symptoms. To our knowledge, this is the first data analysis investigating the nature and prognosis of well-defined multi-vessel VSA compared to single vessel VSA and non-VSA patients using standardized ergonovine provocation test.

The possible pathophysiologic mechanisms for the poor clinical outcome of multi-vessel VSA are suggested below. Patients with multi-vessel VSA have a more severe, extensive and prolonged myocardial ischemia who are more likely to have lethal arrhythmias and sudden death than those with single vessel VSA [10,11,18,19]. In addition, the fibrinolytic function is more impaired and the incidence of refractory angina during hospitalization is higher in patients with multi-vessel VSA than in single vessel VSA or control group [10].

Although less attention is being paid to VSA in current clinical practice, multi-vessel VSA is not rare [1,3,6] and leads to poor clinical outcomes despite medical treatment. The total number of hard primary endpoint (death and ACS) in multi-vessel VSA was relatively low. This may have been caused by the medical treatment during the follow up periods and the exclusion of patients with significant coronary artery stenosis. Nevertheless, our data show that multi-vessel VSA itself is highly prognostic of poor outcomes.

Although our study could not answer whether good compliance of medical treatment and intensive medical treatments such as full dosage of drug treatments, combination treatments in multi-vessel VSA patients could improve the clinical outcomes, large scaled-prospective researches for the effectiveness of good compliance of medical treatment, intensive medical treatment and new therapeutic agents will be required in the future. As our study did not delineate the differences of underlying pathophysiology between multi-vessel VSA and single vessel VSA groups, further investigations on the pathogenesis behind multi-vessel VSA including genetic analysis and other characteristics should be pursued.

4.1. Study limitations

There are several limitations to our study. First, it was a non-

randomized observational study and the results are prone to be influenced by inherent limitations of the enrolled patients, especially in the non-VSA group which had shorter follow-up periods and where some patients were lost during follow-up. Second, the low number of the endpoint for multivariate analysis and a possibility of underlying unmeasured confounders may have influenced the results. Third, status of smoking and alcohol consumption during follow-up periods may have been related with the occurrence of primary endpoint in VSA patients. Regarding this important question, we need further investigation in the near future. Forth, patients with significant atherosclerosis (> 50% luminal diameter narrowing) were excluded from the registry. Thus, our results cannot be generalized to VSA patients with significant coronary artery disease. Fifth, the mean follow-up duration was relatively short. Investigations on longer clinical follow-up for VSA patients will be necessary. Sixth, we performed only the ergonovine provocation test, which predominantly reflects endothelium-independent smooth muscle hyper-constriction, although its effect could be aggravated by endothelial dysfunction [20]. Therefore, our results cannot be generalized to VSA patients induced by acetylcholine provocation test. Seventh, we were not able to address the effects of adherence to medical treatment and intensive medical treatments in patients with multivessel spasm. Eighth, as the current study only enrolled Koreans, our data may only be applied to far east Asians.

4.2. Conclusions

In conclusion, patients with multi-vessel VSA had worse clinical outcomes than the single vessel VSA and non-VSA groups, suggesting that the existence of multi-vessel VSA itself is highly prognostic.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

- Study concept and design: Seung Hwan Han and Sang Hong Baek designed this analysis.
- Acquisition of data: Seung Hwan Han, Kwan Yong Lee, Sung Ho Her, Youngkeun Ahn, Keun-Ho Park, Dong-Soo Kim, Tae-Hyun Yang, Dong-Ju Choi, MD, Jung-Won Suh, Hyuck Moon Kwon, Byoung Kwon Lee, Hyeon-Cheol Gwon, Seung-Woon Rha, Sang-Ho Jo, Sang Hong Baek performed ergonovine provocation test and contributed to acquisition of data.
- Analysis and interpretation of data: Seung Hwan Han, Kwan Young Lee, Kwang-Pil Ko contributed to statistical analysis and interpretation of data.
- Drafting of the manuscript: Seung Hwan Han, Kwan Young Lee, Jung-Won Suh, Sang-Ho Jo, Kwang-Pil Ko, Sang Hong Baek contributed to drafting of the manuscript.
- Critical revision: All authors contributed to critical revision of manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2018.12.018.

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