**Cardiovascular Prevention
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Review Article

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Characteristics of Patients with Vasospastic Angina in Korea: Data from a Large Cohort (VA-KOREA)

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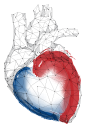[14]Department of Cardiovascular Medicine, Samsung Medical Center, Sungkyunkwan University, Seoul, Korea
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ABSTRACT

The Variant Angina Korea (VA-KOREA) registry is a nationwide prospective multicenter registry designed to reflect the real-world clinical data of Korean patients with vasospastic angina (VSA). A total of 2,960 patients with chest pain and presumed VSA who underwent coronary angiography (CAG) and an ergonovine provocation test were enrolled. The primary endpoint composite of death from any cause, acute coronary syndrome, and new-onset symptomatic arrhythmia during the 3-year follow-up was investigated for patient characteristics, laboratory findings, CAG findings, and medications. This article reviewed the current status of VSA in Korea and new findings from VA-KOREA registries to improve the treatment and prognosis of patients with VSA.

Keywords: Angina pectoris; Angina pectoris, variant; Coronary vasospasm

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INTRODUCTION

Although coronary artery vasospasm is now considered as one of the pathophysiologies of myocardial ischemia,[1] the description of "Prinzmetal's angina" is only half a page of the textbook of internal medicine.[2] The prevalence of coronary spasm in the United States is uncertain, probably because provocative testing is not routinely performed in this country. However, coronary spasm is more commonly reported in Japan[3] and Korea,[4] where provocative testing is used more frequently. There are many reports of vasospastic angina (VSA) in Japanese patients, and the Japanese guidelines for diagnosis and therapeutics of VSA[5] are the most widely accepted. Here, we provided data from a large Korean cohort, the Variant Angina Korea (VA-KOREA) registry (**Table 1**).

The VA-KOREA is a nationwide prospective multicenter registry designed to reflect real-world clinical data of Korean patients with VSA. A total of 2,960 patients with chest pain and presumed VSA, who underwent coronary angiography (CAG) and an ergonovine (EG) provocation test at 11 tertiary hospitals in Korea, were consecutively enrolled from May 2010 to June 2015. 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.[5] Positive results were defined as total or subtotal (>90% luminal diameter narrowing) occlusion accompanied by ischemic symptoms and/or electrocardiographic (ECG) changes (positive group). 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

Table 1. Publications of Variant Angina Korea data

Parameters	Results	Author	Journal and year
Patients characteristics			
Sex difference	Long-term clinical outcome was similar between sexes.	Kim et al.[6]	*Biology of Sex Differences*, 2020
Overweight/obesity	In patients with VSA, the overweight/obese group was associated with a favorable 1-year primary endpoint.	Lee et al.[7]	*Scientific Reports*, 2020
Smoking	Smoking was associated with higher rates of unfavorable clinical outcomes among patients with VSA taking antiplatelet agents.	Cho et al.[8]	*PLoS One*, 2021
Cystatin-C level	A high level of cystatin-C was independently associated with the prevalence of VSA and with a high-risk type of VSA.	Lee et al.[9]	*International Heart Journal*, 2015
Thyroid function	Hyperthyroidism is independently associated with the occurrence of VSA, especially in women, but did not affect the total death in patients with VSA.	Kim et al.[10]	*Journal of Clinical Medicine*, 2020
Potassium level	Hypokalemia at admission was associated with adverse clinical outcomes in VSA.	Seo et al.[11]	*Scientific Reports*, 2021
Angiographic findings			
Positive spasm test	The incidence of primary outcomes was low, and the 24-month prognosis of the positive group in the intracoronary ergonovine provocation test was relatively worse than that of the intermediate group.	Shin et al.[12]	*JACC, Cardiovascular Interventions*, 2015
Spasm type	Focal type of single vessel coronary artery spasm in patients with VSA is associated with poor clinical outcomes in 24 months.	Kim et al.[13]	*International Journal of Cardiology*, 2018
Multi-vessel spasm	Patients with multi-vessel VSA had worse clinical outcomes than those with single vessel VSA and non-VSA.	Han et al.[14]	*Atherosclerosis*, 2019
Coronary plaque characteristics and % stenosis	Spastic coronary artery had more plaque frequency, higher percentage of stenosis than non-spastic coronary in patients with VSA.	Jo et al.[15]	*Scientific Reports*, 2020
Treatment			
Calcium-channel blockers	The first and second generation CCB groups did not differ in terms of composite outcome occurrence.	Kim et al.[16]	*The Korean Journal of Internal Medicine*, 2021
Use of aspirin	Low-dose aspirin does not protect against future cardiovascular events in patients with VSA, even for patients who have concurrent minimal coronary artery stenosis.	Lee et al.[17]	*Cardiovascular Prevention and Pharmacotherapy*, 2019
Use of antiplatelet agents	Aspirin plus clopidogrel use in VSA patients is associated with a poor clinical outcome at 3 years, especially in ACS.	Cho et al.[18]	*Scientific Reports*, 2019
Use of statin	Statin therapy did not reduce adverse cardiovascular events in patients with VSA.	Seo et al.[19]	*Heart and Vessels*, 2020

ACS = acute coronary syndrome; CCB = calcium-channel blocker; VSA = vasospastic angina.
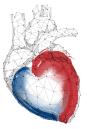
negative result was <50% luminal narrowing without ischemic symptoms and ECG changes (negative group). Additionally, intermediate constriction was defined as 50–90% luminal narrowing with or without ischemic symptoms and/or ECG changes (intermediate group). The primary endpoint was the composite of death from any cause, acute coronary syndrome (ACS), and new-onset symptomatic arrhythmia during the 3-year follow-up.

Herein, we review and summarize the published data from the VA Korea registry to understand patient characteristics and current therapeutic management for VSA patients in Korea.

PATIENTS CHARACTERISTICS

Among 2,960 patients, 1,892 were judged to have positive (definite, 680) and intermediate (1,212) results in their provocation tests. The patients were younger (mean age, 55.1±11.3 years) than the Japanese cohort (average age, 65.2 years),[5] and 62.1% were male, similar to the high male ratio of Japanese[3] or Western country reports.[20] Male patients were younger and were more frequently smokers and alcohol drinkers than female patients.[6] There was no sex difference in the occurrence of composite events (log-rank p=0.649). Interestingly, obesity (body mass index [BMI] ≥25 kg/m^2) was associated with better prognosis in female patients with VA (hazard ratio [HR], 0.22; 95% confidence interval [CI], 0.07–0.68; p=0.008). To evaluate the effect of overweight/obesity on the clinical outcomes of patients with VSA, patients with BMI data were divided into two groups using the Asian cut-off value.[7] The overweight/obese (BMI ≥23 kg/m^2, n=378) group had a lower rate of the primary endpoint (2.4% vs. 7.9%, p=0.004) and ACS (0.8% vs. 4.3%, p=0.007) than the normal weight group at the 1-year follow-up; however, there were no significant differences in cardiac death and new-onset arrhythmia. Overweight/obesity (HR, 0.258; 95% CI, 0.106–0.629; p=0.003), and dyslipidemia (HR, 3.732; 95% CI, 1.471–9.469; p=0.006) were independent predictors of the primary endpoint in patients with VSA. These findings are largely consistent with past reports of the phenomenon of "obesity paradox" in the coronary artery disease setting.[21] Among laboratory data, hypokalemia[11] and high levels of cystacin-C[9] at admission were suggested as markers of poor outcomes in patients with VSA. To detect mild renal dysfunction, it can be helpful to evaluate cystatin C levels in patients with VSA.

ANGIOGRAPHIC FINDINGS

From an early report comparing the 24-month prognosis between the positive and intermediate groups in the intracoronary EG provocation test, the positive group showed worse outcomes than the intermediate group.[12] Coronary spasm develops in sclerotic lesions of varying severity.[22][23] Coronary spasm was more frequently provoked on atherosclerotic segments. Concomitant significant (≥50%) organic coronary stenosis was associated with worse clinical outcomes in both male (HR, 1.97; 95% CI, 1.01–3.85; p=0.047) and female (HR, 3.26; 95% CI, 1.07–9.89; p=0.037) patients.[6] To evaluate coronary plaque distribution, frequency, and cut-off value of percent stenosis for developing vasospasm, the overall frequency of plaque, percentage of diameter stenosis (defined as ≥1% luminal narrowing) and the mean of each segmental stenosis were compared among three groups: VSA patients with index coronary spasm positive, those with index arterial spasm negative/other arterial spasm positive, and non-VSA patients.[15] The spastic coronary artery had a higher plaque frequency and higher percentage of stenosis than the non-spastic coronary artery in patients
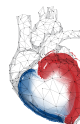
with VA. Coronary stenosis ≥35% in the left anterior descending artery (LAD), ≥35% in the left circumflex artery, or ≥40% in the right coronary artery were independent predictors of developing spasm (odds ratio [OR], 2.019; 95% CI, 1.315–3.100; p=0.001).

Although there has been a report of favorable outcomes of multivessel spasm in patients with VSA,[24] patients with multivessel VSA reportedly have worse clinical outcomes than patients with single-vessel VSA.[12)25] If the definition of multi-vessel VSA is total or subtotal (>90% luminal diameter narrowing) occlusion of one coronary artery with coronary artery spasm (more than 70% diameter stenosis) among the other 5 coronary artery sites (left main and LAD, diagonal branch, left circumflex artery, obtuse marginal branch, right coronary artery), the primary composite endpoint over a 36-month follow-up period was significantly higher in the multivessel VSA group than in the single vessel VSA and non-VSA groups (8.7% vs.1.8% and 1.1%, respectively; log-rank p<0.05).[14] 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).For single-vessel VSA, focal-type spasms have worse outcomes than diffuse types. In particular, unstable angina in ACS components play a major role in this effect (HR, 2.365; 95% CI, 1.100–5.087; p=0.028).[13]

TREATMENT

In contrast to β-receptor blockers for effort angina, calcium-channel blockers (CCBs) are considered the main treatment for controlling angina symptoms and improving outcomes in patients with VSA.[26] From the VA-KOREA data, over 90% of patients were prescribed CCBs. Diltiazem was the most widely used drug (79.0%), followed by amlodipine (11.1%), nifedipine (5.8%), and benidipine (4.1%).[16] Although there was no statistical difference in terms of composite outcome according to the generation of CCBs (diltiazem and nifedipine vs. amlodipine and benidipine), the incidence of ACS was significantly lower in the second generation CCBs group with a person-month incidence rate of 1.66 vs. 0.35 (HR, 0.22; 95% CI, 0.05–0.89; p=0.034). Interestingly, the use of benidipine showed a significantly better control of angina symptoms, than diltiazem for 3 years (OR, 0.17; 95% CI, 0.09–0.32; p<0.0001 at 3rd year). Benidipine is the least prescribed medication for VSA; however, there is a chance to improve control of angina symptoms with this newer generation drug.[27)28]

Nitrates are another important medication for VSA. However, VA-KOREA data showed that the use of nitrates was a significant risk factor for the primary outcome in patients with VSA (HR, 1.99; 95% CI, 1.23–3.20; p=0.005). Although nitrates are frequently used to treat angina symptoms, several studies have demonstrated a neutral or worse prognosis in patients with VSA after treatment with nitrates.[29)30]

The 2 controversial medications for VSA are antiplatelet drugs and statins. Because coronary vasospasm usually occurs with atherosclerosis, antiplatelet agents and/or statins are frequently prescribed to patients with VSA. However, long-term clinical outcomes from the use of these drugs have rarely been investigated. From the VA-KOREA data, there was no significant difference in the composite outcome between the aspirin and control groups (3.1% vs. 4.1%; HR, 1.18; 95% CI, 0.61–2.26; p=0.623).[17] For dual antiplatelet therapy, the primary composite outcome was significantly more common in the dual antiplatelet (aspirin plus clopidogrel) group at 10.8% (14/130) than in the non-antiplatelet group at 4.4% (44/1011), (HR, 2.41; 95% CI, 1.32–4.40; p=0.004). Aspirin alone appears to be safe because
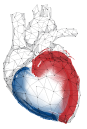
of similar primary and individual event rates compared to the non-antiplatelet agent group (HR, 0.96; 95% CI, 0.59–1.55; p=0.872).[18] Smoking was especially harmful to patients with VSA using antiplatelet agents, with the highest incidence rate in the primary composite outcome.[8] The incidence rate was 3.49 per 1,000 person-month (95% CI, 2.30–5.30, log-rank test for primary outcome p=0.017) and HR of smoking and using antiplatelet agents was 1.66 (95% CI, 0.98–2.81). After exclusion of patients with absolute indication for statins (patients with a history of percutaneous coronary intervention, transient ischemic attack, and 50% stenosis on CAG), the primary outcome between patients with or without statins was compared. Although some reports have demonstrated improved endothelial function with statins in patients with VSA,[31][32] statin therapy did not show benefits for cardiovascular outcome in the VA-KOREA data.[19] The primary outcome occurred in 32 patients (4.3%) in the statin group and 28 patients (3.1%) in the non-statin group. In the Kaplan-Meier analysis before and after propensity score matching, there was no significant difference in the cumulative incidence of primary outcomes between the groups. However, further studies are needed to confirm this result, as the 3-year outcome may have been an insufficient endpoint to evaluate statin effects, considering the relatively low adverse event rate of VSA.

CONCLUSION

From a nationwide prospective multicenter registry of The VA-KOREA, we investigated the demographic, angiographic, and therapeutic characteristics of Korean patients with VSA. The patients were younger than the Japanese cohort, and 62.1% were male. There were no sex differences in the occurrence of adverse outcomes. Multi-vessel VSA was an independent predictor of the primary composite endpoint at 36 months, and the spastic coronary artery had more plaque frequency and higher percentage of stenosis than the non-spastic coronary arteries. CCB is prescribed for over 90% of patients with VSA, and the new-generation CCB, benidipine, showed favorable outcomes. Nitrate use was associated with worse outcomes. Aspirin alone appears safe in VSA patients; however, dual antiplatelet therapy could be harmful in patients with VSA. From the VA-KOREA data, we could not find the benefits of statins in patients with VSA. Although the major limitation of these investigations came from the nature of the observational study design, it was meaningful to look into many aspects of Korean VSA patients' characteristics.

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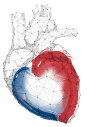
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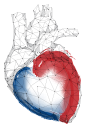
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