Effect of sarpogrelate and high-dose statin on the reduction of coronary spasm in vasospastic angina: A two by two factorial, pilot randomized study

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Abstract
Background: Vasospastic angina (VSA) is characterized by coronary spasm, which can be aggravated by vasoactive substances such as serotonin. Hypothesis Sarpogrelate, a selective serotonin receptor antagonist, and high-dose statin have some effects on the reduction of coronary spasm in patients with VSA.

Methods: We recruited 100 patients with angiographically confirmed VSA, and randomly assigned them into four groups: sarpogrelate with high-dose statin (Group A, n = 25), sarpogrelate with low-dose or no statin (Group B, n = 25), placebo with high-dose statin (Group C, n = 25), and placebo with low-dose or no statin (Group D, n = 25). The primary endpoint was the remission of coronary spasm on 1-year follow-up provocation test.

Results: The most common site of coronary spasm was left anterior descending artery (42%). Most patients (96%) took calcium channel blockers, and 46% were treated with vasodilators. Overall, 40% of patients reported no chest pain at 1 year, and 23% showed complete remission of coronary spasm on 1-year follow-up provocation test. No difference was observed in symptomatic and angiographically complete remission rate between the sarpogrelate and the placebo group. Although the apolipoprotein B level at the 1-year follow-up was significantly lower in the high-dose statin group, symptomatic and angiographic outcomes were not different according to statin intensity. Distal thrombolysis in myocardial infarction (TIMI) flow on initial

Abbreviations: CAG, coronary angiography; CCB, calcium channel blocker; CI, confidence interval; OR, odds ratio; TIMI, thrombolysis in myocardial infarction; VSA, vasospastic angina.

Drs. Kim and Choi contributed equally to this study.

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provocation test was independently associated with angiographically complete remission.

**Conclusions:** Sarpogrelate or high-dose statin did not significantly improve the angiographic remission rate in patients with VSA. Distal TIMI flow on initial provocation test could predict the complete remission of coronary spasm at follow-up.

**KEYWORDS**
coronary spasm, high-dose statin, remission, sarpogrelate, vasospastic angina

1 | INTRODUCTION

Vasospastic angina (VSA) is a clinical syndrome characterized by transient ST-segment elevation with recurrent episodes of angina at rest, due to spontaneous coronary artery spasm leading to myocardial ischemia. Ischemic episodes of VSA are aggravated by physical or psychological stress, exposure to the cold, or hyperventilation. Furthermore, several pharmacologic agents such as catecholamines, parasympathomimetic agents, anticholinesterase agents, beta-adrenergic blocking agents, ergonovine, serotonin, and histamine can induce coronary spasm. Serotonin (5-hydroxytryptamine or 5-HT) mediates vasoconstriction and platelet aggregation by 5-HT receptors on vascular smooth muscle cells and platelets. Sarpogrelate is a selective 5-HT antagonist, which inhibits vasoconstriction and platelet aggregation, and is theoretically beneficial in the treatment of VSA. However, there are no data on treating patients with VSA, even though sarpogrelate has been widely used as an antplatelet agent in peripheral artery disease.

Although the pathogenesis of VSA is not yet fully understood, vascular endothelial dysfunction, coronary microvascular dysfunction, and Ca-mediated vascular smooth muscle cell hyperplasia have been suggested to be the main contributors. Moreover, some investigators have proposed that coronary spasm is an early form of atherosclerosis, based on the results of several animal studies and intravascular imaging studies for assessment of spastic artery. However, there has been debate regarding the beneficial effects of statin, a well-known coronary artery plaque stabilizer, for patients with VSA.

To address this debate, we conducted a 2 × 2 factorial randomized controlled trial to evaluate the efficacy of sarpogrelate and high-dose statin for reduction of coronary spasm in patients with VSA.

2 | METHODS

2.1 | Study design and population

The present study was a 2 × 2 randomized prospective single-center trial. The study protocol was approved by the Institutional Review Board of Samsung Medical Center, and all patients provided written informed consent. From 2012 to 2016, 20- to 70-year-old patients with VSA were recruited. At the initial evaluation, coronary spasm was angiographically proven, which was defined as thrombolysis in myocardial infarction (TIMI) flow of less than 3 with chest pain or significant ST-T wave change by spontaneous coronary spasm or intracoronary ergonovine spasm provocation test. The main exclusion criteria were cardiac arrest due to coronary spasm, left main spasm, significant fixed coronary artery stenosis of more than 70%, severe left ventricular dysfunction (ejection fraction <30%), bleeding tendency, and significant liver and kidney disease. Patients with coagulation disorders, platelet count less than 50,000/μL, or prothrombin time more than 2.0 (international normalized ratio) were considered to indicate bleeding tendency. Significant liver disease was defined as aspartate aminotransferase or alanine aminotransferase of more than 100 U/mL, and renal failure was defined as serum creatinine of more than 2.0 mg/dL. Pregnant or breastfeeding patients were also excluded. Clinical Trial Registration Information: ClinicalTrials.gov, NCT01674686.

A total of 100 VSA patients were included. They were randomly assigned to a sarpogrelate or a placebo group at a one-to-one ratio. Each group was also randomly divided into a high-dose statin and a low-dose or no statin group. Randomization was done via a web-based system by computer-generated block randomization. The dose of sarpogrelate was 100 mg twice a day. The high-dose statin group was prescribed atorvastatin 80 mg once a day, while the low-dose or no statin group was prescribed simvastatin 20 mg once a day or no statin medication. Group A took sarpogrelate and high-dose statin, group B took sarpogrelate and low-dose or no statin, group C took placebo and high-dose statin, and group D took placebo and low-dose or no statin. Each group had 25 patients (Supporting Information, Figure S1). After randomization, to control symptoms, use of calcium channel blockers (CCBs) or nitrates was based on physician discretion.

2.2 | Study procedures and follow-up

Before the spasm provocation test, routine right and left coronary angiography (CAG) was performed. If any significant stenosis (angiographic luminal stenosis >70%) was observed, the spasm provocation test was canceled. After performing routine CAG, the intracoronary ergonovine spasm provocation test was started using the left coronary artery first. Two bolus doses of ergonovine maleate were injected into each coronary artery at an interval of 2 minutes: 10 μg followed by 20 μg for the left coronary artery and 10 μg followed by another 10 μg for the right. Before injection of the second dose, CAG
was performed and 12-lead ECG was taken. The test was stopped immediately after a positive result was obtained, and intracoronary nitroglycerin 200 to 600 mg was administered until the spasm had been relieved angiographically.

Vital signs, height, body weight, and blood tests including complete blood count, lipid profile, liver function test, blood urea nitrogen, creatinine, and C-reactive protein were checked at baseline, 1, 3, 6, and 12 months of follow-up. Echocardiography was performed at baseline. Prothrombin time level was checked at baseline, and creatine kinase level was checked at 1 and 12 months of follow-up. Apolipoprotein B, apolipoprotein A1, and lipoprotein (a) levels were checked at baseline and 12 months of follow-up.

2.3 Outcomes

Coronary arteries with luminal diameters of more than 2.5 mm were included for analysis of angiographic findings. The primary outcome was remission of coronary spasm at the 1-year follow-up CAG with spasm provocation test. Vasodilators or CCBs were held 48 hours before the spasm provocation test. Remission of coronary spasm was defined as improvement in distal TIMI flow grade in the spastic vessel compared to the baseline provocation test. Complete remission was defined as disappearance of coronary artery spasm at the 1-year follow-up provocation test. If one vessel showed improvement while the other vessel showed aggravation of coronary spasm, the angiographic result was considered to be “no interval change.” Secondary outcomes were changes of lipid profile, apolipoprotein B, apolipoprotein A1, and lipoprotein (a) levels over 1 year.

2.4 Statistical analysis

Continuous variables were compared using the Student’s t-test or Mann-Whitney test where applicable. Categorical data were assessed using the chi-square test or Fisher’s exact test, as appropriate. To identify independent predictors of complete remission, the odds ratio (OR) and 95% confidence interval (CI) were calculated using a multivariate logistic regression model that included sex, hypertension, diabetes mellitus, alcohol abstinence, sarpogrelate, high-dose statin, and follow-up in this study. Each group showed good compliance with both drugs (sarpogrelate vs placebo, and high-dose statin vs low-dose or no statin), and there was no statistically significant difference among the four groups (Figure S2). In the four-group comparison, the rate of remission (Group A 47.4%, Group B 58.3%, Group C 40.0%, and Group D 56.3%, \( P = .744 \)) and the rate of performing follow-up angiography at 1-year (Group A 30.6%, Group B 19.4%, Group C 24.2%, and Group D 25.8%, \( P = .236 \)) was not different.

Table 2 presents the primary and secondary outcomes according to the sarpogrelate administration. A total of 65 patients visited the
outpatient clinic 1 year after the index procedure, and 62 patients underwent CAG with spasm provocation test at the 1-year follow-up. Overall, 40% of patients reported no chest pain at the 1-year clinical follow-up. In 62 angiographically followed patients, no difference was observed in progression or improvement of fixed stenosis between the sarpogrelate and the placebo groups. In regard to coronary

| TABLE 1 | Baseline clinical and angiographic characteristics in the sarpogrelate vs the placebo groups |
|---------|------------------------------------------------------------------------------------------|
|          | Total (n = 100) | Sarpogrelate (n = 50) | Placebo (n = 50) | P-value |
| Age (y)  | 57.4 ± 7.8     | 57.6 ± 7.7            | 57.3 ± 7.9      | 0.850   |
| Male     | 92 (92)        | 48 (96)               | 44 (88)         | 0.269   |
| Systolic blood pressure (mm Hg) | 122.8 ± 17.2 | 121.1 ± 18.0          | 124.5 ± 16.4    | 0.335   |
| Diabetes mellitus | 10 (10.0) | 7 (14.0) | 3 (6.0) | 0.182   |
| Hypertension | 34 (34.0) | 14 (28.0) | 20 (40.0) | 0.205   |
| Dyslipidemia | 14 (14.0) | 6 (12.0) | 8 (16.0) | 0.564   |
| History of PCI | 4 (4.0) | 1 (2.0) | 3 (6.0) | 0.617   |
| Alcohol  | 78 (78.0)     | 41 (82.0)             | 37 (74.0)       | 0.334   |
| Current smoker | 39 (39.0) | 19 (38.0)            | 20 (40.0)       | 0.366   |

Laboratory tests

|                                      | Total (n = 100) | Sarpogrelate (n = 50) | Placebo (n = 50) | P-value |
|--------------------------------------|----------------|-----------------------|------------------|---------|
| Total cholesterol (mg/dL)            | 172.2 ± 42.1   | 171.3 ± 38.3          | 173.2 ± 46.0     | 0.819   |
| Triglyceride (mg/dL)                 | 124 (24-764)   | 130 (24-764)          | 115 (30-514)     | 0.391   |
| HDL (mg/dL)                          | 49 (24-145)    | 49 (24-101)           | 48 (29-145)      | 0.576   |
| LDL (mg/dL)                          | 103.2 ± 35.4   | 104.1 ± 34.5          | 102.4 ± 36.6     | 0.805   |
| Creatinine (mg/dL)                   | 0.91 ± 0.16    | 0.91 ± 0.17           | 0.91 ± 0.16      | 0.966   |
| CRP (mg/dL)                          | 0.06 (0.03-3.14)| 0.06 (0.03-3.14)     | 0.06 (0.03-1.50) | 0.582   |
| Apolipoprotein B (mg/dL)             | 78.3 ± 21.9    | 76.4 ± 19.0           | 80.0 ± 24.4      | 0.418   |
| Apolipoprotein A1 (mg/dL)            | 116.0 ± 27.9   | 118.1 ± 26.7          | 114.1 ± 29.1     | 0.489   |
| Lipoprotein(a) (mg/dL)               | 15.0 ± 13.1    | 11.7 (1.8-57.8)       | 10.8 (0.4-46.8)  | 0.760   |

Medication

|                                      | Total (n = 100) | Sarpogrelate (n = 50) | Placebo (n = 50) | P-value |
|--------------------------------------|----------------|-----------------------|------------------|---------|
| Calcium channel blocker, n (%)       | 96 (96.0)      | 46 (92.0)             | 50 (100.0)       | 0.117   |
| Vasodilators                         | 46 (46.0)      | 25 (50.0)             | 21 (42.0)        | 0.422   |

Coronary angiography

|                                      | Total (n = 100) | Sarpogrelate (n = 50) | Placebo (n = 50) | P-value |
|--------------------------------------|----------------|-----------------------|------------------|---------|
| No fixed stenosis                    | 47 (47.0)      | 25 (50.0)             | 22 (44.0)        | 0.548   |
| LAD                                  | 36 (36.0)      | 18 (36.0)             | 18 (36.0)        | 1.000   |
| LAD %DS                              | 30 (20-60)     | 30 (20-60)            | 30 (20-50)       | 0.990   |
| LCX                                  | 19 (19.0)      | 9 (18.0)              | 10 (20.0)        | 0.799   |
| LCX %DS                              | 30 (20–60)     | 30 (20–60)            | 40 (30-60)       | 0.586   |
| RCA                                  | 12 (12.0)      | 4 (8.0)               | 8 (16.0)         | 0.218   |
| RCA %DS                              | 30 (20–60)     | 35 (20-60)            | 30 (20-40)       | 0.246   |
| Spasm location                       |                |                       |                  | 0.246   |
| Multivessel                          | 2 (2.0)        | 0 (0)                 | 2 (4.0)          |         |
| LAD                                  | 42 (42.0)      | 25 (50.0)             | 17 (34.0)        |         |
| LCX                                  | 21 (21.0)      | 10 (20.0)             | 11 (22.0)        |         |
| RCA                                  | 35 (35.0)      | 15 (30.0)             | 20 (40.0)        |         |
| Spontaneous spasm                    | 3 (3.0)        | 1 (2.0)               | 2 (4.0)          | 1.000   |
| Distal TIMI flow                     |                |                       |                  | 0.840   |
| TIMI 0                               | 57 (57.0)      | 28 (56.0)             | 29 (58.0)        |         |
| TIMI ≥1                              | 43 (43.0)      | 22 (44.0)             | 21 (42.0)        |         |

Abbreviations: CRP, C-reactive protein; HDL, high-density lipoprotein; LAD, left anterior descending artery; LCX, left circumflex artery; LDL, low-density lipoprotein; %DS, percent diameter stenosis; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction. Data are presented as mean ± SD, median (range), or n (%).

*Fixed stenosis was observed in 53 patients and 67 vessels were involved.
vasospasm, 55% (n = 34) showed improved distal TIMI flow in the spastic vessel compared with the baseline spasm provocation test, and 23% (n = 14) showed complete remission of coronary vasospasm, despite stopping of CCBs or vasodilators 48 hours before the follow-up provocation test. However, the proportion of total remission (sarpogrelate vs placebo, 51.6% vs 58.1%, P = .610) and complete remission (25.8% vs 19.4%, P = .544) did not differ between the two groups. Similarly, there were no significant differences in the secondary outcomes, including the values of lipid profiles, apolipoprotein B, apolipoprotein A1, or lipoprotein (a) at the 1-year follow-up between the sarpogrelate and placebo groups.

Outcomes according to statin therapy are presented in Table 3. More patients showed improvement of fixed stenosis in the high dose statin group than in the low-dose or no statin group without statistical significance (4 vs 1, P = .366). The alcohol abstinence rate was not different between the two groups. Neither the symptomatic remission nor the angiographically complete remission rates were different between the high-dose statin and the low-dose or no statin groups. Triglyceride, apolipoprotein A1, and lipoprotein (a) levels were not different according to statin therapy. On the other hand, the total cholesterol, low-density lipoprotein (LDL), and apolipoprotein B levels were significantly lower in the high-dose statin group than in the low-dose or no statin group (Figure 1).

### 3.4 Independent predictors of angiographically complete remission at the 1-year follow-up visit

According to the baseline characteristics of coronary vasospasm, patients were divided into three groups; spontaneous spasm (n = 3), Distal TIMI 0 flow (n = 56), and TIMI 1 or 2 flow (n = 41). Patients who showed transient luminal narrowing with distal TIMI 1 or 2 flow showed higher rate of complete remission of coronary vasospasm at 1-year compared to others (spontaneous spasm vs distal TIMI 0 vs distal TIMI 1 or 2, 0% vs 15.8% vs 38.1%, P = .095) (Table S2). Independent predictors of complete remission were evaluated using a multivariate logistic regression model (Table 4). Sarpogrelate, high-dose statin, and alcohol abstinence were not associated with angiographically complete remission of VSA. Only distal TIMI 0 flow at initial provocation test was independently associated with lower rates of complete remission on 1-year follow-up provocation test (OR 0.23, 95% CI 0.06-0.93, P < .039).

### 4 DISCUSSION

This prospective randomized trial evaluated the efficacy and safety of sarpogrelate and high-dose statin for patients with VSA in addition to standard treatment including CCB and/or vasodilators. The principal
findings of the current study are as follows. First, sarpogrelate did not appear to affect complete remission of coronary vasospasm in VSA. Second, high-dose statin was attributed to improvement in the lipid profile, but it could not modify the symptomatic and angiographic outcomes in VSA. Finally, distal TIMI 0 flow at the initial provocation test appeared to adversely affect complete remission of coronary spasm on 1-year follow-up.

VSA is caused by coronary vasospasm. However, the mechanisms of coronary vasospasm are poorly understood.22 Endothelial dysfunction and hyper-reactivity of vascular smooth muscle cells have been proposed to be the main mechanisms of coronary spasm.1,23 CCB and nitrates had been evaluated for decreasing angina symptoms in VSA based on these mechanisms,24-26 and are recommended in current guidelines to manage VSA.27,28 However, some patients have recurrent angina symptoms even while taking sufficient medication including CCB and nitrates. Furthermore, one study also suggested that angina symptoms could occur more frequently during the CCB withdrawal period.24

In regard to these limitations, several medications that were perceived to be relevant to coronary spasm were evaluated for managing VSA. Serotonin (5-hydroxytryptamine, 5-HT) is one of the most important vasoconstrictor triggers with a possible role in coronary spasm. It mediates vasoconstriction by 5-HT2A receptors on vascular smooth muscle cells, and also promotes platelet aggregation.10 However, the role of serotonin in VSA is controversial.29-31 Sarpogrelate hydrochloride, a selective 5-HT2A antagonist, suppresses platelet aggregation and inhibits thrombus formation and vascular smooth muscle cell proliferation, and is widely used to improve vascular function in peripheral arterial disease.10 It has been also reported to inhibit serotonin-induced coronary vasospasm in an animal study32 and to improve exercise capacity by increasing collateral flow in effort angina.33 On the basis of the known clinical efficacy of sarpogrelate, we hypothesized this medication might have a benefit on VSA. However, no significant effect on VSA was observed with sarpogrelate in the present study.

Previous studies evaluating the morphological characteristics in the spastic vessel using intravascular ultrasound or optical coherence tomography have demonstrated that coronary vasospasm occurs at the site with greater plaque accumulation.15,34 As several studies have suggested that 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors (statins) could improve endothelial dysfunction and vascular inflammation,35,36 the role of statin therapy in VSA has come to the fore. Yasue et al reported that addition of fluvastatin to a CCB reduced coronary vasospasm at a 6-month follow-up provocation test.37 In addition, a study from Korea Acute Myocardial Infarction Registry suggested that statin therapy could reduce the 1-year incidence of myocardial

| 1-year follow-upa | High-dose statin (n = 36) | Low-dose or no statin (n = 29) | P-value |
|-------------------|---------------------------|-------------------------------|---------|
| Symptom-free      | 21 (58.3)                 | 18 (62.1)                     | 0.760   |
| Alcohol abstinence| 13 (38.2)                 | 10 (35.7)                     | 0.838   |
| Follow-up CAGb (N = 62) | N = 34                 | N = 28                        |         |
| Coronary stenosis |                           |                               |         |
| No change         | 27 (79.4)                 | 24 (85.7)                     | 0.740   |
| Improvement       | 4 (11.8)                  | 1 (3.6)                       | 0.366   |
| Progression       | 3 (8.8)                   | 3 (10.7)                      | 1.000   |
| PCI               | 2 (5.9)                   | 0 (0)                         | 0.497   |
| Coronary vasospasm|                           |                               |         |
| No change         | 16 (47.1)                 | 12 (42.9)                     | 0.741   |
| Remission         | 18 (52.9)                 | 16 (57.1)                     | 0.741   |
| Complete remission| 6 (17.6)                  | 8 (28.6)                      | 0.306   |
| Progression       | 0 (0)                     | 0 (0)                         |         |
| Total cholesterol (mg/dL) | 128.2 ± 24.2          | 169.4 ± 32.9                  | <0.001  |
| Triglyceride (mg/dL) | 99.5 ± 43.6             | 119.0 ± 57.6                  | 0.141   |
| HDL (mg/dL)       | 54.0 ± 10.9               | 55.7 ± 16.3                   | 0.638   |
| LDL (mg/dL)       | 63.2 ± 20.7               | 101.2 ± 29.0                  | <0.001  |
| Apolipoprotein B (mg/dL) | 57.5 ± 17.6          | 80.5 ± 17.5                   | <0.001  |
| Apolipoprotein A1 (mg/dL) | 132.3 ± 21.5        | 131.3 ± 33.4                  | 0.895   |
| Lipoprotein (a) (mg/dL) | 15.5 (1.3-79.4)        | 9.9 (1.9-44.2)                | 0.185   |

Abbreviations: CAG, coronary angiography; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention.

Data are presented as mean ± SD, median (range), or n (%).
a65 patients visited the outpatient clinic for 1-year follow-up.
b62 patients underwent CAG for 1-year follow-up.
infarction in patients with coronary spasm-induced AMI. On the other hand, recent large-scale studies showed that statin therapy could not reduce the adverse cardiac events in VSA patients. Our data suggest that statin therapy does not modify the VSA-related symptomatic and angiographic outcomes of VSA patients even though lipid profiles improved over the follow-up period.

Pathophysiology of VSA is complex. Other than aforementioned mechanisms, inflammation of coronary adventitia and perivascular adipose tissue had been proposed to be associated with coronary vasospasm. In this regard, anti-inflammatory therapies might have a role in VSA as shown in myocardial infarction with reducing recurrent cardiovascular event. Serotonin-induced coronary vasospasm is only one of

**FIGURE 1** Trends of lipid profile. Curves denote trends of lipid profile in each group over 12 months of follow-up. Group A, sarpogrelate with high-dose statin group; Group B, sarpogrelate with low-dose or no statin group; Group C, placebo with high-dose statin group; Group D, placebo with low-dose or no statin group. Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Sarpogrelate and high-dose statin did not appear to affect the symptomatic or angiographic outcomes of VSA. With proper medical therapies such as CCB, 23% of followed patients with VSA showed complete remission of coronary spasm at the 1-year follow-up. If coronary spasm was severe enough to show distal TIMI 0 flow at the initial spasm test, the chance of complete remission of coronary spasm was lower at the 1-year follow-up.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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