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ORIGINAL RESEARCH

Prognostic Impact of Chronic Vasodilator Therapy in Patients With Vasospastic Angina

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BACKGROUND: Chronic vasodilator therapy with long-acting nitrate is frequently used to treat vasospastic angina. However, the clinical benefits of this approach are controversial. We investigated the prognostic impact of vasodilator therapy in patients with vasospastic angina from the multicenter, prospective VA-KOREA (Vasospastic Angina in KOREA) registry.

METHODS AND RESULTS: We analyzed data from 1895 patients with positive intracoronary ergonovine provocation test results. The patients were divided into 4 groups: no vasodilator (n=359), nonnitrate vasodilator (n=1187), conventional nitrate (n=209), and a combination of conventional nitrate and other vasodilators (n=140). The primary end point was a composite of cardiac death, acute coronary syndrome, and new-onset arrhythmia at 2 years. Secondary end points were the individual components of the primary end point, all-cause death, and rehospitalization due to recurrent angina.

The groups did not differ in terms of the risk of the primary end point. However, the acute coronary syndrome risk was significantly higher in the conventional nitrate (hazard ratio [HR], 2.49; 95% CI, 1.01–6.14; *P*=0.047) and combination groups (HR, 3.34; 95% CI, 1.15–9.75, *P*=0.027) compared with the no-vasodilator group, as assessed using the inverse probability of treatment weights. Subgroup analyses revealed prominent adverse effects of nitrate in patients with an intermediate positive ergonovine provocation test result and in those with low Japanese Coronary Spasm Association scores.

CONCLUSIONS: Long-acting nitrate-based chronic vasodilator therapy was associated with an increased 2-year risk of acute coronary syndrome in patients with vasospastic angina, especially in low-risk patients.

Key Words: nitrates ■ outcomes ■ variant angina pectoris ■ vasodilator agents

Vasospastic angina (VSA) is distinct from classical atherosclerotic angina pectoris in terms of etiology, treatment, and prognosis.[1–3] VSA is caused by focal or diffuse spasms of an epicardial coronary artery.[4] Established pathogeneses include (1) vascular smooth muscle hyperreactivity,[5] (2) impairment of the autonomic nervous system,[6] and (3) microvascular dysfunction.[7] VSA generally has a favorable long-term prognosis because coronary artery vasospasm responds well to vasodilator therapy.[8] However, VSA can cause fatal ventricular arrhythmia and sudden cardiac death.[9–11] The mainstays of VSA treatment for the prevention of coronary vasospasm are calcium channel blockers (CCBs), with or without vasodilators.[12–14] However, some recent studies have raised

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CLINICAL PERSPECTIVE

What Is New?

- Chronic long-acting nitrate-containing regimen in vasospastic angina was associated with higher risk of acute coronary syndrome in the analysis of the prospective multicenter VA-KOREA (Vasospastic Angina in Korea) registry.
- Association between higher risk of acute coronary syndrome and chronic long-acting nitrate-containing regimen was observed only in a low-risk group with intermediate ergonovine provocation tes or low Japanese Coronary Spasm Association score.

What Are the Clinical Implications?

- Caution is required when prescribing chronic long-acting nitrate for patients with vasospastic angina, especially in low-risk groups with intermediate ergonovine provocation test or low Japanese Coronary Spasm Association score.

Nonstandard Abbreviations and Acronyms

CAG	coronary angiography
ERGT	ergonovine provocation test
VSA	vasospastic angina

questions regarding the clinical benefits of long-acting nitrates when used as vasodilators.[15,16] In a sample drawn from a Japanese multicenter registry, chronic nitrate therapy did not improve the long-term prognosis of patients with VSA when combined with CCBs. Furthermore, the application of multiple nitrates increased the risk of adverse cardiac events.[15] Data from a single-center Korean registry also indicated that chronic nitrate therapy has a harmful effect in patients with VSA.[16] However, nicorandil, which is a nonnitrate vasodilator, had a neutral effect on patients with VSA in the 2 aforementioned studies. As the clinical risks and benefits of chronic vasodilator therapy with long-acting nitrates have not been fully evaluated in patients with VSA, current guidelines recommend the use of long-acting nitrates.[13,14]

In this study, we investigated the prognostic impact of chronic vasodilator therapy in patients with VSA using data from the multicenter, prospective VA-KOREA (Vasospastic Angina in KOREA) registry.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Protocols

The VA-KOREA (Vasospastic Angina in Korea) is a prospective, observational, web-based registry of clinical, angiographic, and prognostic data from patients who underwent intracoronary ergonovine provocation tests (ERGT). The registry includes 2960 patients admitted to 11 major cardiovascular centers between January 2010 and July 2015. All participating institutions were high-volume centers for coronary angiography (CAG) (>1800 cases/year) and percutaneous coronary interventions (>500 cases/year) and performed intracoronary ERGT using the same protocol. The participating centers and investigators are summarized in Data S1. Patients with suspected VSA underwent CAG with an ERGT according to the discretion of the responsible physician. The exclusion criteria for the VA-KOREA were as follows: (1) patients with a severe fixed coronary artery stenosis at the baseline CAG (stenosis with a diameter reduction ≥50% at the left main coronary artery or ≥70% at a non-left main coronary artery according to quantitative coronary analysis) who underwent a percutaneous coronary intervention with or without coronary stenting, (2) those with end-stage renal disease who were undergoing continuous dialysis, (3) those with a known malignant or inflammatory disease, and (4) those with catheter-induced spasm at the baseline CAG. The ethics committees at each participating center approved the study protocol (institutional review board approval number: CNUH-2010-01-006), and all procedures followed the principles of the Declaration of Helsinki. All patients provided written informed consent before participation in the registry. The detailed study protocols have been published previously.[17]

Among the 2960 patients included in the VA-KOREA registry, we analyzed data from 1895 with a positive (definite or intermediate) ERGT result. We excluded patients with negative ERGTs (n=1003), those lost to follow-up (n=58), and those with insufficient data (n=4). The primary outcome was investigated according to vasodilator use, that is, vasodilator (n=1536) or no vasodilator (n=359), at the time of discharge. We also analyzed clinical outcomes according to various vasodilator usage patterns, that is, no vasodilator (n=359), nonnitrate vasodilator (n=1187), conventional nitrate (n=209), or a combination of vasodilators (n=140) including both conventional and nonnitrate vasodilator. Nonnitrate vasodilators included nicorandil, molsidomine, and trimetazidine. Patients in the combination

group received a conventional nitrate with at least 1 type of nonnitrate vasodilator.

CAG and Provocation Test for VSA

Vasoactive drugs such as CCBs and nitrates were discontinued for at least 48 hours before CAG. After baseline CAG, an intracoronary ERGT was performed to assess spasm provocation. Incremental doses of 10 (E1), 20 (E2), and 40 (E3) μg were injected into the right coronary artery, and doses of 20 (E1), 40 (E2), 60 (E3) μg were used for the left coronary artery.[17,18] If the patient could tolerate ERGTs, they were conducted for both the right and left coronary arteries. Once a spasm had been provoked and the provocation test was complete, intracoronary nitrate (200 μg) was injected. Fixed coronary stenosis with a diameter of ≥2.5 mm and the vascular response to ergonovine were quantitatively analyzed for 6 coronary artery sites (left main, left anterior descending, diagonal branch, left circumflex, obtuse marginal branch, and right coronary artery). The diameter after the intracoronary ergonovine injection was compared with that after the injection of intracoronary nitrate, in the site with the biggest change in diameter.

A definite positive ERGT result was defined as follows: (1) total or subtotal (>90% luminal diameter narrowing) occlusion with ischemic symptoms, with or without electrocardiographic changes; or (2) spontaneous total or subtotal spasm on baseline CAG. An intermediate positive ERGT result was defined as 50% to 90% luminal narrowing with or without ischemic symptoms and/or electrocardiographic changes. Staff at the core laboratory at Seoul St. Mary's Hospital, Seoul, South Korea analyzed the blinded angiographic data offline via quantitative coronary analysis.

Study Definitions and End Points

Pre-CAG angina was classified according to the established classification system. Specifically, grade I referred to near-daily attacks, grade II to ≥4 attacks/month, grade III to ≥1 but <4 attacks/month, and grade IV to <1 attack/month.[17] An ischemic electrocardiographic change was defined as an ST-segment–elevation or depression >0.1 mV or a negative U-wave in at least 2 related leads.[17] Fixed coronary artery stenosis was defined as fixed luminal narrowing by <50% at the left main coronary artery, and <70% at the non-left main coronary artery, as determined by quantitative coronary analysis. Myocardial bridging was defined as systolic narrowing of the coronary artery on CAG, and slow flow referred to a slow passage of contrast in the absence of an obstructive coronary artery lesion. Multivessel spasm was defined as a positive spasm in more than 2 major epicardial coronary arteries. Spasms were classified as focal, diffuse, or mixed. The focal type was defined as a discrete spasm localized in 1 coronary segment, whereas spasms that occurred continuously from the proximal to the distal segments were classified as diffuse. The mixed type referred to multivessel spasms in which at least 1 coronary artery had a focal spasm and the other(s) had a diffuse spasm. The Japanese Coronary Spasm Association (JCSA) risk score enables risk assessment and prognostic stratification of patients with VSA.[18] The JCSA risk score system has 3 risk strata: low (score=0–2), intermediate (3–5), and high (≥6) risk strata.

The primary end point was a composite of cardiac death, acute coronary syndrome (ACS), and symptomatic new-onset arrhythmia during a 2-year clinical follow-up period. The secondary end points were cardiac death, ACS, symptomatic new-onset arrhythmia, all-cause mortality, and rehospitalization due to recurrent angina. We also investigated the rate of recurrent angina-induced changes in medication during the follow-up. All deaths were considered cardiac deaths unless there was a definite noncardiac cause. ACS was defined as recurrent or continuous chest pain lasting for more than 20 minutes with ischemic electrocardiographic changes or elevation of cardiac biomarkers, including myocardial infarction. For patients presenting with symptoms for the first time, clinically significant symptomatic arrhythmia, such as symptomatic premature beats, sick-sinus rhythm, atrial or ventricular tachycardia/fibrillation, or atrioventricular block was considered indicative of symptomatic new-onset arrhythmia. Twelve-lead electrocardiography was routinely conducted during regular or emergent visits, and 24-hour Holter monitoring was applied in patients with suspicious symptoms. Patients for whom drugs were added to their existing prescription, who switched to another drug because of recurrent angina, or who stopped all medications were regarded as having medication change. All adverse events were confirmed by consulting the medical records or conducting a telephone interview, and these events were assessed by the Local Events Committee of Seoul St. Mary's Hospital.

Statistical Analysis

Continuous variables, presented as means±SDs, were compared using an unpaired *t*-test, the Mann–Whitney rank-sum test, or 1-way analysis of variance. Discrete variables, expressed as counts with percentages, were compared using Pearson's chi-square test or Fisher's exact test. We used Kaplan-Meier curves and the log-rank test to compare the groups in terms of the end points.

We conducted 2 different analyses in the current study: (1) no vasodilator versus vasodilator at discharge, and (2) no vasodilator versus nonnitrate vasodilator versus

Table 1. Baseline Characteristics According to Vasodilator Use

	Unadjusted data (n=1895)				Matched data (n=686)			
	Vasodilator (n=1536)	No vasodilator (n=359)	*P* value	SMD	Vasodilator (n=343)	No vasodilator (n=343)	*P* value	SMD
Demographics								
Age, y	54.9 (11.3)	55.6 (11.5)	0.311	−0.061	55.6 (10.5)	55.7 (11.4)	0.881	−0.009
Male sex	972 (63.3)	199 (55.4)	0.006	0.161	191 (55.7)	192 (56.0)	0.939	−0.006
Medical history								
Ischemic heart disease	194 (12.6)	42 (11.7)	0.631	0.028	40 (11.7)	41 (12.0)	0.906	−0.009
Stable CAD	93 (6.1)	21 (5.8)	0.883	0.013	18 (5.2)	20 (5.8)	0.739	−0.026
History of percutaneous coronary intervention	37 (2.4)	3 (0.8)	0.062	0.128	6 (1.7)	3 (0.9)	0.314	0.071
Hypertension	584 (38.0)	136 (37.9)	0.961	0.002	122 (35.6)	130 (37.9)	0.526	−0.048
Diabetes	150 (9.8)	28 (7.8)	0.250	0.071	23 (6.7)	28 (8.2)	0.467	−0.057
Dyslipidemia	260 (16.9)	50 (13.9)	0.167	0.083	52 (15.2)	50 (14.6)	0.830	0.017
Atrial fibrillation or atrial flutter	12 (0.8)	6 (1.7)	0.118	−0.081	3 (0.9)	3 (0.9)	1.000	0
Cerebrovascular accident	24 (1.6)	8 (2.2)	0.378	−0.044	6 (1.7)	6 (1.7)	1.000	0
Thyroid disease	52 (3.4)	13 (3.6)	0.825	−0.011	13 (3.8)	10 (2.9)	0.525	0.050
Hyperthyroidism	23 (1.5)	2 (0.6)	0.160	0.088	5 (1.5)	2 (0.6)	0.254	0.088
Hypothyroidism	17 (1.1)	9 (2.5)	0.040	−0.105	6 (1.7)	6 (1.7)	1.000	0
Chronic airway disease	21 (1.4)	5 (1.4)	0.970	0	5 (1.5)	5 (1.5)	1.000	0
Familial history of CAD	94 (6.1)	15 (4.2)	0.155	0.086	21 (6.1)	15 (4.4)	0.304	0.076
Current or ex-smoking	650 (42.3)	136 (37.9)	0.125	0.090	126 (36.7)	131 (38.2)	0.693	−0.031
Past medication								
Aspirin	318 (20.7)	66 (18.4)	0.325	0.058	59 (17.2)	64 (18.7)	0.619	−0.039
Thienopyridine	55 (3.6)	15 (4.2)	0.589	−0.031	13 (3.8)	14 (4.1)	0.844	−0.015
Calcium-channel blocker	317 (20.6)	50 (13.9)	0.004	0.178	60 (17.5)	50 (14.6)	0.298	0.079
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	262 (17.1)	69 (19.2)	0.331	−0.055	53 (15.5)	64 (18.7)	0.264	−0.085
Beta blocker	109 (7.1)	36 (10.0)	0.060	−0.104	28 (8.2)	34 (9.9)	0.424	−0.059
Statin	242 (15.8)	49 (13.6)	0.319	0.062	48 (14.0)	48 (14.0)	1.000	0
Initial presentation								
Chest pain	1422 (92.6)	318 (88.6)	0.013	0.137	313 (91.3)	308 (89.8)	0.515	−0.051
Angina class >2	1032 (67.2)	252 (70.2)	0.272	−0.065	236 (68.8)	241 (70.3)	0.678	−0.033
Dyspnea	87 (5.7)	23 (6.4)	0.588	−0.029	16 (4.7)	21 (6.1)	0.398	−0.062
Syncope	20 (1.3)	4 (1.1)	0.774	0.018	6 (1.7)	4 (1.2)	0.524	0.042
Cardiac arrest	17 (1.1)	10 (2.8)	0.016	−0.123	7 (2.0)	6 (1.7)	0.779	0.022
Ventricular tachycardia or ventricular fibrillation	6 (0.4)	6 (1.7)	0.006	−0.128	4 (1.2)	2 (0.6)	0.412	0.064
ST-segment–elevation during chest pain	90 (5.9)	15 (4.2)	0.210	0.078	25 (7.3)	15 (4.4)	0.103	0.124
ST-segment depression during chest pain	13 (0.8)	4 (1.1)	0.628	−0.030	2 (0.6)	4 (1.2)	0.412	−0.064
T-wave inversion during chest pain	40 (2.6)	7 (1.9)	0.473	0.047	8 (2.3)	7 (2.0)	0.794	0.021

Values are expressed as mean (SD) or n (%). CAD indicates coronary artery disease; and SMD, standardized mean difference.

Table 2. Angiographic Characteristics and Medication at Discharge According to Vasodilator Use

	Unadjusted data (n=1895)				Matched data (n=686)			
	Vasodilator (n=1536)	No vasodilator (n=359)	*P* value	SMD	Vasodilator (n=343)	No vasodilator (n=343)	*P* value	SMD
Fixed stenosis	535 (34.8)	136 (37.9)	0.276	−0.064	119 (34.7)	129 (37.6)	0.427	−0.060
Left main	17 (1.1)	3 (0.8)	0.651	0.031	4 (1.2)	1 (0.3)	0.178	0.104
LAD or diagonal	368 (24.0)	100 (27.9)	0.123	−0.089	91 (26.5)	96 (28.0)	0.668	−0.034
LCX or OM	157 (10.2)	37 (10.3)	0.962	−0.003	29 (8.5)	36 (10.5)	0.361	−0.068
RCA	272 (17.7)	61 (17.0)	0.748	0.018	55 (16.0)	58 (16.9)	0.757	−0.024
Significant stenosis*	59 (3.8)	20 (5.6)	0.140	−0.085	18 (5.2)	15 (4.4)	0.592	0.037
LAD or diagonal	36 (2.3)	13 (3.6)	0.170	−0.077	12 (3.5)	11 (3.2)	0.832	0.017
LCX or OM	13 (0.8)	2 (0.6)	0.578	0.024	2 (0.6)	2 (0.6)	1.000	0
RCA	16 (1.0)	7 (1.9)	0.157	−0.075	5 (1.5)	4 (1.2)	0.737	0.026
Other finding								
Myocardial bridge	110 (7.2)	13 (3.6)	0.014	0.160	20 (5.8)	13 (3.8)	0.212	0.094
Slow flow	86 (5.6)	12 (3.3)	0.082	0.112	7 (2.0)	12 (3.5)	0.245	−0.092
Spasm provocation test								
Spasm positive arteries								
Left main	17 (1.1)	1 (0.3)	0.145	0.096	4 (1.2)	1 (0.3)	0.178	0.104
LAD or diagonal	759 (49.4)	178 (49.6)	0.954	−0.004	182 (53.1)	166 (48.4)	0.222	0.094
LCX or OM	346 (22.5)	101 (28.1)	0.024	−0.129	78 (22.7)	93 (27.1)	0.186	−0.102
RCA	773 (50.3)	192 (53.5)	0.281	−0.064	167 (48.7)	179 (52.2)	0.359	−0.070
Multivessel spasm	362 (23.6)	103 (28.7)	0.042	−0.116	86 (25.1)	92 (26.8)	0.601	−0.039
Spontaneous spasm	227 (14.8)	49 (13.6)	0.585	0.034	55 (16.0)	48 (14.0)	0.454	0.056
Diffuse spasm	951 (61.9)	234 (65.2)	0.250	−0.069	207 (60.3)	219 (63.8)	0.345	−0.072
Focal spasm	596 (38.8)	134 (37.3)	0.605	0.031	140 (40.8)	127 (37.0)	0.309	0.078
Mixed spasm	129 (8.4)	41 (11.4)	0.071	−0.101	36 (10.5)	35 (10.2)	0.900	0.010
Spasm on fixed stenosis	340 (22.1)	77 (21.4)	0.777	0.017	76 (22.2)	72 (21.0)	0.710	0.029
Chest pain during spasm	934 (60.8)	207 (57.7)	0.273	0.063	200 (58.3)	199 (58.0)	0.938	0.006
Result of provocation test			0.448	0.043			0.388	0.066
Definite positive	598 (38.9)	132 (36.8)			137 (39.9)	126 (36.7)		
Intermediate positive	938 (61.1)	227 (63.2)			206 (60.1)	217 (63.3)		
ECG change								
ST-segment–elevation	128 (8.3)	29 (8.1)	0.874	0.007	30 (8.7)	28 (8.2)	0.784	0.018
ST-segment depression	65 (4.2)	16 (4.5)	0.849	−0.015	13 (3.8)	14 (4.1)	0.844	−0.015
T-wave inversion	77 (5.0)	15 (4.2)	0.508	0.038	18 (5.2)	15 (4.4)	0.592	0.037
Medication at discharge								
Calcium-channel blocker	1404 (91.4)	301 (83.8)	<0.001	0.232	297 (86.6)	293 (85.4)	0.660	0.035
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	271 (17.6)	68 (18.9)	0.563	−0.034	51 (14.9)	64 (18.7)	0.184	−0.102
Antiplatelet	715 (46.5)	166 (46.2)	0.916	0.006	153 (44.6)	156 (45.5)	0.818	−0.018
Statin	755 (49.2)	161 (44.8)	0.142	0.088	150 (43.7)	155 (45.2)	0.701	−0.030
Beta blocker	100 (6.5)	21 (5.8)	0.645	−0.029	21 (6.1)	19 (5.5)	0.745	0.026
Alpha blocker	17 (1.1)	5 (1.4)	0.649	−0.027	4 (1.2)	5 (1.5)	0.737	−0.026

Values are expressed as mean (SD) or n (%). LAD indicates left anterior descending artery; LCX, left circumflex artery; OM, obtuse marginal; RCA, right coronary artery; and SMD, standardized mean difference.

*There was no significantly fixed coronary artery stenosis in left main.

conventional nitrate versus a combination of conventional nitrate and at least 1 type of nonnitrate vasodilator. As differences in baseline characteristics could significantly affect outcomes, sensitivity analyses were performed to adjust for confounding factors. First, a multivariate Cox regression model was used to obtain cutoffs for each of these measures, including covariates with a *P* value<0.1 in the univariate analysis and a center as a categorical variable. The proportional hazards assumption was evaluated using the log-minus-log plot and Schoenfeld residual test. All Cox regression models for the clinical end points satisfied the proportional hazards assumption. Second, we performed propensity score matching to compare the no-vasodilator and vasodilator groups. A 1:1 matching process without replacements was performed using a greedy algorithm with a caliper width of 0.2; 343 patients in the vasodilator group were matched with 343 controls in the no-vasodilator group. The standardized mean difference after propensity score matching was within 0.1 for nearly all matched covariates, demonstrating well-balanced groups (Tables 1 and 2). Third, the inverse of the propensity score was used to compare the 4 groups (no-vasodilator versus nonnitrate vasodilator versus conventional nitrate versus combination). To assess the inverse probability of treatment weighting, we calculated the absolute standardized mean differences in the covariates used to generate the propensity score. We applied 4 treatment conditions using the multinomial propensity score[19] (Figure S1). All the variables in Tables 1 and 2 were used for propensity score matching and inverse probability of treatment weighting. The Toolkit for Weighting and Analysis of Nonequivalent Groups (https://www.rand.org/statistics/twang/stata-tutorial.html) was used to calculate the multinomial propensity score.

Hazard ratios (HRs) and 95% CIs were calculated during the Cox regression analysis. We used a multivariate Cox proportional hazard model to identify independent predictors of primary end points and ACS. All analyses were 2 tailed, and *P*<0.05 was taken to indicate statistical significance. All analyses were performed using Stata/MP 16.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Characteristics and Clinical Outcomes According to Vasodilator Use

The median follow-up duration was 756 days (25thpercentile:333 and 75th percentile 1103 days). Patient baseline clinical characteristics, angiographic profiles, and discharge medication are given in Tables 1 and 2, respectively. The vasodilator group had a higher proportion of male patients. Otherwise, there were no significant group differences in age or medical history except for a higher prevalence of hypothyroidism in the no-vasodilator group (1.1 versus 2.5%, *P*=0.040). The rate of previous ischemic heart disease (12.6 versus 11.7%, *P*=0.631) and history of smoking (42.3% versus 37.9%, *P*=0.125) was not statistically different between the vasodilator and novasodilator groups. Regarding previous medications, CCBs had been prescribed more frequently in the vasodilator group compared with the no-vasodilator group (20.6 versus 13.9%, *P*=0.004). At initial presentation, the patients in the no-vasodilator group were more likely to present with cardiac arrest (1.1 versus 2.8%, *P*=0.016) and ventricular arrhythmia (0.4 versus 1.7%, *P*=0.006). The frequency of angina and rate of electrocardiographic changes during chest pain did not differ significantly between the groups. The rate of fixed coronary stenosis and significantly fixed coronary stenosis was comparable between the 2 groups for all epicardial coronary arteries. At the baseline CAG, myocardial bridging was more frequent in the vasodilator group (7.2 versus 3.6%, *P*=0.014). In the spasm provocation test, multivessel spasm (23.6 versus 28.7%, *P*=0.042) and spasm of the left circumflex artery or obtuse marginal branch (22.5 versus 28.1%, *P*=0.024) were more frequently provoked in the no-vasodilator group. There were no statistically significant group differences in the rate of spontaneous spasm, diffuse spasm, focal spasm, chest pain during spasm, definite positive ERGT result, or electrocardiographic change during provocation. Regarding medications at discharge, CCBs were more frequently prescribed in the vasodilator group (91.4 versus 83.8%, *P*<0.001). After propensity score matching, the difference between the 2 unmatched groups disappeared. Clinical outcomes at the 2-year follow-up are described in Table 3 and Figure 1. The primary end point incidence was not significantly different between the groups (propensity score matched HR: 0.92; 95% CI: 0.48 to 1.77; *P*=0.806). Secondary end points also occurred at a similar rate between the groups. The rate of medication change during the follow-up period was not significantly different in both groups (63.1 versus 60.8%). There was no patient who terminated all medications during follow-up.

Clinical Outcomes According to Various Vasodilator Use

The characteristics and frequencies of clinical outcomes at the 2-year follow-up are compared among the 4 groups in Table S1 and Table 4, respectively. In the comparison of baseline characteristics between subgroups, the combination group had higher rate of previous ischemic heart disease (18.6%, *P*=0.049) with higher rate of stable coronary artery disease (11.4%, *P*=0.028) compared other groups. The rate of smoking (ex or current) was significantly higher in the conventional nitrate group (52.6%, *P*=0.005). As described in Table 2, CCB was less frequently prescribed in the no

Table 3. Comparison of 2-Year Clinical Outcomes According to Vasodilator Use

	Vasodilator (n=1536)	No vasodilator (n=359)	Unadjusted		Multivariable-adjusted		Propensity-score matched	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Primary end point*	71 (4.6)	18 (5.0)	0.86 (0.51–1.44)	0.569	0.88 (0.51–1.50)	0.628	0.92 (0.48–1.77)	0.806
Cardiac death	2 (0.1)	2 (0.6)	0.22 (0.03–1.57)	0.131	0.22 (0.03–1.58)	0.131	0.93 (0.13–6.60)	0.941
Acute coronary syndrome†	50 (3.3)	8 (2.2)	1.36 (0.65–2.87)	0.417	1.30 (0.59–2.84)	0.512	1.38 (0.57–3.38)	0.478
Non–ST-segment–elevation myocardial infarction	4 (0.3)	0						
Unstable angina	46 (3.0)	8 (2.2)						
Arrhythmia	22 (1.4)	9 (2.5)	0.53 (0.25–1.15)	0.110	0.62 (0.28–1.38)	0.242	0.51 (0.17–1.51)	0.224
Atrial fibrillation	7 (0.5)	3 (0.8)						
Atrioventricular block	3 (0.2)	4 (1.1)						
Ventricular tachycardia or ventricular fibrillation	7 (0.5)	0						
Cardiac arrest	2 (0.1)	1 (0.3)						
All-cause death	7 (0.5)	6 (1.7)	0.25 (0.83–0.73)	0.012	0.21 (0.07–0.65)	0.007	0.44 (0.11–1.77)	0.250
Rehospitalization	242 (15.8)	53 (14.8)	0.99 (0.74–1.33)	0.942	1.08 (0.80–1.46)	0.634	1.00 (0.68–1.48)	0.994
Medication change‡	969 (63.1)	203 (60.8)						

Values are expressed as n (%). HR indicates hazard ratio.

*The primary end point was defined as a composite of cardiac death, acute coronary syndrome, or new-onset arrhythmia.

†There was no ST-segment–elevation myocardial infarction in all groups.

‡Data for medication change was available in 1535 (99.9%) with vasodilator group and 334 (93.0%) with no vasodilator group. There was no patient who terminated all medications during follow-up.

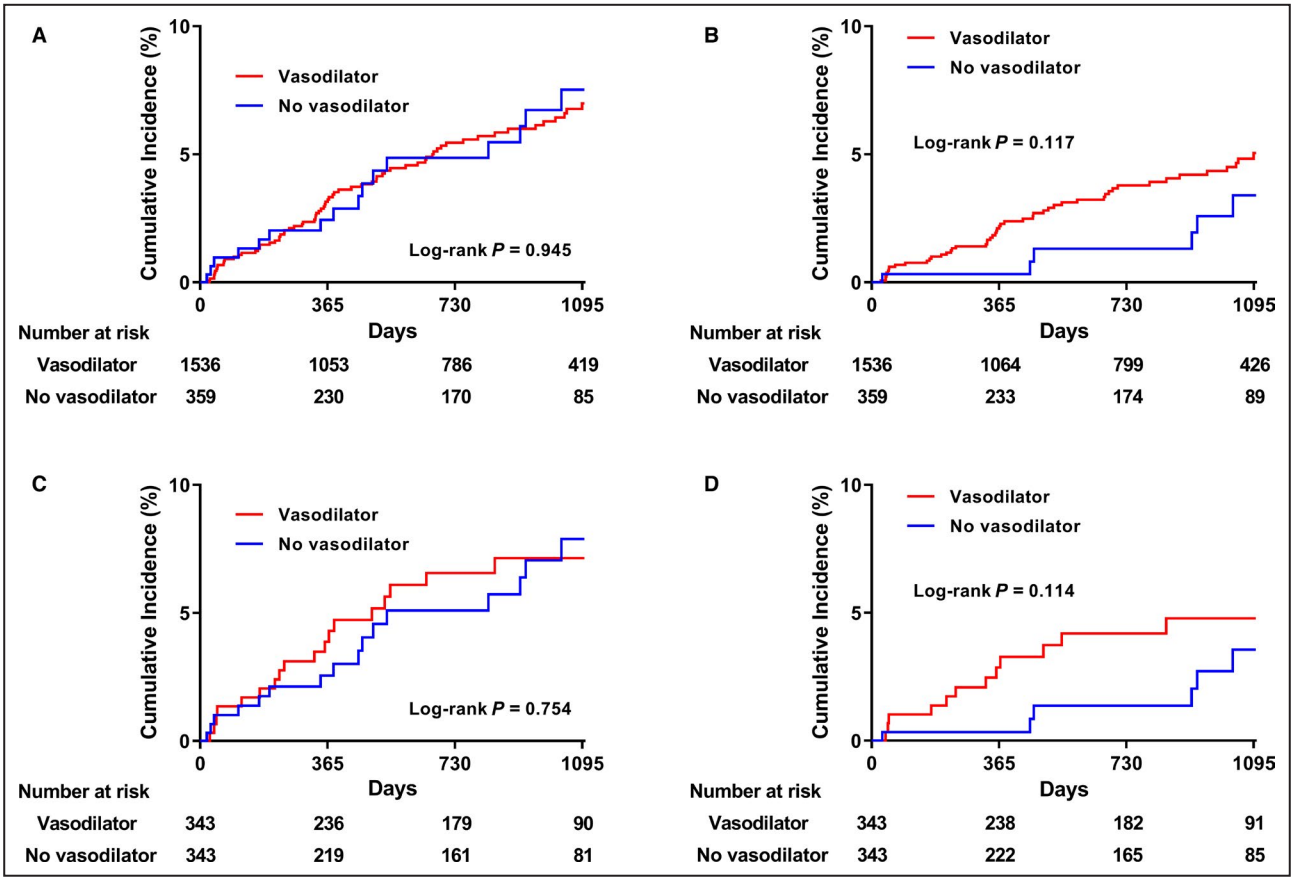

Figure 1. Cumulative incidence of primary end point and acute coronary syndrome between vasodilator group and no vasodilator group.
Composite outcome of cardiac death, acute coronary syndrome, and new-onset arrhythmia before (**A**) and after (**C**) propensity score matching; acute coronary syndrome before (**B**) and after (**D**) propensity score matching.

-asodilator group compared with all vasodilator subgroups. As shown in Table 4, the crude incidence rates of the primary end point (5.0 versus 3.7 versus 7.2 versus 8.6%, *P*=0.017) and ACS (2.2 versus 2.1 versus 6.2 versus 8.6%, *P*<0.001) were significantly higher in the conventional nitrate and combination groups, and the all-cause mortality rate was lower in the nonnitrate vasodilator group. There were no significant differences in other secondary outcomes according to different vasodilator usage. The risk of the primary end point was similar among the 4 groups; however, the risk of ACS was significantly higher in the conventional nitrate group (HR, 2.49; 95% CI, 1.01 to 6.14; *P*=0.047) and combination group (HR, 3.34; 95% CI, 1.15 to 9.75, *P*=0.027) compared with the no-vasodilator group after inverse probability of treatment weighting adjustment (Table 5 and Figure 2). Furthermore, the risk of all-cause death was lower in the nonnitrate vasodilator group (HR, 0.11; 95% CI, 0.03 to 0.46, *P*=0.002). We investigated the detailed characteristics of the patients with death (Table 4). The most deaths were noncardiac death (69.2%), and about 70% of patients were diagnosed as VSA by definite positive ERGT. Information about patients who died during the whole follow-up period is summarized in Table S2.

Subgroup Analyses

We performed subgroup analyses according to the intensity of the positive ERGT results and risk stratification. The higher risk of ACS associated with conventional nitrate usage or combination was observed in an intermediate positive ERGT (multivariable-adjusted HR, 7.28; 95% CI, 1.48–35.77; *P*=0.015 for the conventional nitrate group; and HR, 8.16; 95% CI, 1.65–40.30; *P*=0.010 for the combination group) and those with a low JCSA risk score (multivariable-adjusted HR, 5.71; 95% CI, 1.15–28.34; *P*=0.033 for the conventional nitrate group; and 1HR, 0.79; 95% CI, 2.24–51.95; *P*=0.003 for the combination group). This association was maintained in inverse probability of treatment weighting adjusted analysis. There was no significant difference in the risk of ACS according to vasodilator usage patterns in the subgroup of a definite positive

Table 4. Clinical Outcomes at 2 Years According to Various Usage Pattern of Vasodilator

	Overall (n=1895)	No vasodilator (n=359)	Vasodilator			*P* value*
			Nonnitrate vasodilator (n=1187)	Conventional nitrate (n=209)	Combination (n=140)	
Primary end point†	89 (4.7)	18 (5.0)	44 (3.7)	15 (7.2)	12 (8.6)	0.017
Cardiac death	4 (0.2)	2 (0.6)	2 (0.2)	0	0	0.410
Acute coronary syndrome‡	58 (3.1)	8 (2.2)	25 (2.1)	13 (6.2)	12 (8.6)	<0.001
Non–ST-segment–elevation myocardial infarction	4 (0.2)	0	1 (0.1)	1 (0.5)	2 (1.4)	0.007
Unstable angina	54 (2.8)	8 (2.2)	24 (2.0)	12 (5.7)	10 (7.1)	<0.001
Arrhythmia	31 (1.6)	9 (2.5)	20 (1.7)	2 (1.0)	0	0.200
Atrial fibrillation	10 (0.5)	3 (0.8)	7 (0.6)	0	0	0.460
Atrioventricular block	7 (0.4)	4 (1.1)	2 (0.2)	1 (0.5)	0	0.063
ventricular tachycardia or ventricular fibrillation	7 (0.4)	0	6 (0.5)	1 (0.5)	0	0.473
Cardiac arrest	3 (0.2)	1 (0.3)	2 (0.2)	0	0	0.828
All-cause death	13 (0.7)	6 (1.7)	5 (0.4)	0	2 (1.4)	0.030
Rehospitalization	295 (15.6)	53 (14.8)	187 (15.8)	29 (13.9)	26 (18.6)	0.654
Medication change§	1172 (62.7)	203 (60.8)	747 (62.9)	132 (63.2)	90 (64.7)	0.844

Values are expressed as n (%).
*The *P* values are derived from the chi-square test for group comparison.
†The primary end point was a composite of cardiac death, acute coronary syndrome, and new-onset arrhythmia.
‡There was no ST-segment–elevation myocardial infarction in all groups.
§Data for medication change were available in 334 (93.0%) with no vasodilator group, 1187 (100%) with nonnitrate vasodilator group, 209 (100%) with conventional nitrate group, and 139 (99.3%) with combination group.

ERGT and an intermediate or high JCSA risk score (Table 6 and Figure 3).

Independent Predictors of Primary End Point and ACS

The multivariate Cox proportional hazard model identified independent predictors of the primary and secondary outcomes (Table S3). Atrial fibrillation or flutter at initial electrocardiography and fixed coronary artery stenosis were independent predictors of both the primary end point and ACS. Dyslipidemia predicted the incidence of ACS only during the 2-year follow-up and did not predict the primary end point.

DISCUSSION

In the present study, we compared clinical outcomes during a 2-year period according to the use of various types of vasodilators in patients with ERGT-confirmed VSA drawn from a nationwide, multicenter, prospective registry. Our main findings were (1) the use of a vasodilator at discharge was not associated with the clinical outcomes of interest, including recurrent angina-induced rehospitalization and the rate of medication change; and (2) conventional nitrate, or a combination of conventional nitrate with at least one kind of nonnitrate vasodilator, was associated with an increased risk of ACS compared with no vasodilator use at discharge. There were no significant differences in the incidence rates of the study end points between patients who did not use a vasodilator and those who used a nonnitrate vasodilator. However, subgroup analyses according to the intensity of spasm and JCSA risk score revealed that the adverse effects of long-acting nitrate were prominent in patients with intermediate positive ERGT results and a low JCSA risk score but not in those with a definite positive ERGT result and intermediate-to-high JCSA risk score.

Current Evidence for Chronic Vasodilator Therapy in VSA

CCBs administered with or without long-acting nitrates are mainstays of treatment for VSA[20] that have been found to effectively reduce angina symptoms and provide favorable clinical outcomes.[12–14] Nitrates can dilate veins, arteries, and coronary arteries by relaxing vascular smooth muscle, and their anti-ischemic effect is mainly due to a decrease in myocardial oxygen demand

Table 5. Comparison of 2-Year Clinical Outcomes According to Various Usage Pattern of Vasodilator

	Unadjusted		Multivariable-adjusted		IPTW-adjusted*	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Primary end point†						
No vasodilator (reference)	1		1		1	
Nonnitrate vasodilator	0.70 (0.40–1.20)	0.193	0.74 (0.42–1.31)	0.301	0.73 (0.39–1.33)	0.301
Conventional nitrate	1.29 (0.65–2.56)	0.468	1.25 (0.61–2.56)	0.539	1.25 (0.62–2.54)	0.537
Combination	1.59 (0.76–3.29)	0.217	1.48 (0.69–3.18)	0.320	1.44 (0.57–3.62)	0.436
Cardiac death						
No vasodilator (reference)	1		1		1	
Nonnitrate vasodilator	0.29 (0.04–2.07)	0.217	0.28 (0.04–2.04)	0.210	0.30 (0.01–7.07)	0.453
Conventional nitrate‡						
Combination‡						
Acute coronary syndrome						
No vasodilator (reference)	1		1		1	
Nonnitrate vasodilator	0.88 (0.40–1.95)	0.754	1.05 (0.46–2.38)	0.912	0.92 (0.39–2.13)	0.841
Conventional nitrate	2.56 (1.06–6.18)	0.037	2.86 (1.15–7.15)	0.025	2.49 (1.01–6.14)	0.047
Combination	3.64 (1.49–8.92)	0.005	4.04 (1.58–10.30)	0.003	3.34 (1.15–9.75)	0.027
Arrhythmia						
No vasodilator (reference)	1		1		1	
Nonnitrate vasodilator	0.64 (029–1.40)	0.265	0.74 (0.33–1.66)	0.461	0.72 (0.23–2.23)	0.571
Conventional nitrate	0.33 (0.71–1.52)	0.154	0.37 (0.08–1.79)	0.217	0.30 (0.06–1.58)	0.156
Combination‡						
All-cause death						
No vasodilator (reference)	1		1		1	
Nonnitrate vasodilator	0.23 (0.07–0.75)	0.015	0.20 (0.06–0.68)	0.010	0.11 (0.03–0.46)	0.002
Conventional nitrate‡						
Combination	0.78 (0.16–3.87)	0.761	0.58 (0.11–3.04)	0.516	2.18 (0.39–12.29)	0.378
Rehospitalization						
No vasodilator (reference)	1		1		1	
Non-nitrate vasodilator	0.99 (0.74–1.35)	0.985	1.08 (0.79–1.47)	0.636	1.02 (0.72–1.46)	0.909
Conventional nitrate	0.82 (0.52–1.29)	0.387	0.93 (0.59–1.48)	0.769	0.81 (0.51–1.29)	0.368
Combination	1.20 (0.75–1.91)	0.454	1.29 (0.80–2.08)	0.299	1.14 (0.63–2.07)	0.661

Values are expressed as n (%). HR indicates hazard ratio; and IPTW, inverse probability of treatment weighting.
*IPTW was derived from multinomial propensity score.
†The primary end point was defined as a composite of cardiac death, acute coronary syndrome, or new-onset arrhythmia.
‡No event.

as a result of systemic vasodilation.[21] However, nitrate has some adverse effects, such as headache, and many patients discontinue nitrate because of such effects.[22] Furthermore, recent studies have raised questions about the clinical benefit of long-acting nitrate as a vasodilator in patients with VSA.[15,16] Retrospective data from 1429 patients with VSA indicated that chronic nitrate therapy did not reduce the rate of cardiac death, nonfatal myocardial infarction, hospitalization due to unstable angina, heart failure, or appropriate implantable cardioverter defibrillator shocks compared with nonnitrate therapy, after propensity-score matching.[15] This study also showed that the combination of long-acting nitrate and nicorandil was associated with a 2-fold increase in the incidence of the composite end point. In another observational study including data from 1154 patients with VSA and positive ERGT results, nitrate use increased the risk of a composite of cardiac death, myocardial infarction, revascularization, and rehospitalization due to recurrent angina.[16] The researchers described putative mechanisms underlying the neutral or deleterious effects of long-acting nitrates, namely a rebound phenomenon in which angina abruptly increases during nitrate withdrawal and nitrate-free periods.[23] Increased vasoconstriction during nitrate-free periods, along with decreased vasodilatory effects of nitric oxide, was proposed as a mechanism.[24]

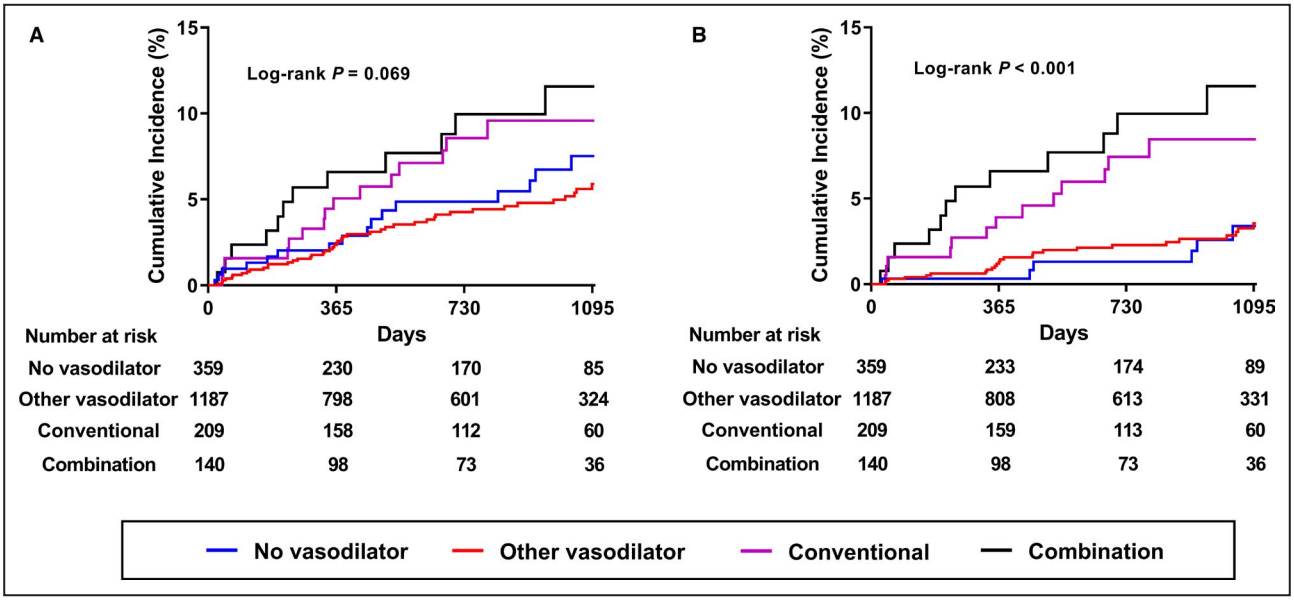

Figure 2. Cumulative incidence of primary end point and acute coronary syndrome among 4 groups.
A, Composite outcome of cardiac death, acute coronary syndrome, and new-onset arrhythmia; (**B**) acute coronary syndrome.

No randomized controlled trials have examined this issue, and few studies have reported on the adverse effects of long-acting nitrate use in patients with VSA. Therefore, current guidelines still recommend the use of long-acting nitrates as a second-line treatment for the treatment of VSA.[12–14] To address this, the current study investigated the prognostic impact of chronic vasodilator therapy, including long-acting nitrates, in patients with VSA drawn from a multicenter, prospective registry.

Impact of Chronic Vasodilator in Patients With VSA

In the current study, we found no significant differences in clinical outcomes according to vasodilator use at discharge. This result is consistent with the 2 aforementioned observational studies.[15,16] We further analyzed the data according to various vasodilator usage patterns.

The analysis revealed adverse effects of conventional nitrate, including in combination with other treatments, compared with nonnitrate vasodilator use. Surprisingly, 77.3% of the patients who used vasodilators were prescribed a nonnitrate vasodilator instead of a conventional nitrate at discharge. Prior studies reported that nicorandil had a neutral effect on clinical outcomes.[15,16] In the current study, the nonnitrate vasodilators included nicorandil, molsidomine, and trimetazidine. The mechanisms by which these medications vasodilate are different from those of nitrate. Nicorandil can vasodilate via the cGMP signaling pathway, in which K^+ channels open and induce an increase in nitric oxide.[25] Nicorandil is not associated with tolerance or rebound angina.[26] The nonnitrate vasodilator molsidomine also produces nitric oxide by mechanisms other than nitrate.[27] Therefore, we hypothesized that the adverse effects of nitrate in the current study were a result of nitrate tolerance or rebound angina.

Subgroup Analyses

To ascertain whether patients with more severe vasospasms received conventional nitrate alone or in combination with other treatments in the current study, we performed subgroup analyses according to the intensity of spasm provocation and JCSA risk score. Contrary to our hypothesis, adverse effects of nitrate were prominent in patients with intermediate positive ERGT results or a low JCSA risk score but not in high-risk patients. In a previous report using data from the VA-KOREA registry, patients with an intermediate positive ERGT result had more favorable clinical outcomes, in terms of lower cardiac mortality, compared with those with a definite positive ERGT result.[17] Patients with a low JCSA risk score also had a lower incidence of major adverse cardiac events compared with those with intermediate or high JCSA risk scores.[18] Although the exact explanation for different clinical outcomes according to risk stratification after vasodilator use is unclear, we think that patients with low risk or intermediate vasospasm have different endothelium-dependent responsiveness of vascular smooth muscle cell, which is an important pathogenesis of VSA. As far as we know, there have been no basic or clinical

Table 6. Risks for ACS According to Various Subgroups

	No. (%)	Unadjusted		Multivariable-adjusted		IPTW adjusted*	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Definite positive ERGT†	730 (38.5)						
No vasodilator (reference)	132 (7.0)	1		1		1	
Nonnitrate vasodilator	459 (24.2)	0.51 (0.19–1.37)	0.505	0.41 (0.14–1.22)	0.109	0.33 (0.11–1.01)	0.052
Conventional nitrate	81 (4.3)	1.33 (0.41–4.37)	0.637	0.99 (0.28–3.49)	0.989	1.10 (0.30–3.97)	0.888
Combination	58 (3.1)	2.09 (0.64–6.86)	0.224	1.25 (0.35–4.46)	0.733	1.61 (0.44–5.87)	0.472
Intermediate positive ERGT†	1165 (61.5)						
No vasodilator (reference)	227 (12.0)	1		1		1	
Nonnitrate vasodilator	728 (38.4)	1.97 (0.45–8.67)	0.370	2.00 (0.45–8.94)	0.363	2.13 (0.47–9.59)	0.327
Conventional nitrate	128 (6.8)	6.15 (1.31–28.95)	0.022	7.28 (1.48–35.77)	0.015	6.89 (1.38–34.45)	0.019
Combination	82 (4.3)	8.30 (1.72–39.96)	0.008	8.16 (1.65–40.30)	0.010	7.52 (1.45–38.86)	0.016
Intermediate or high JCSA risk score‡	569 (30.0)						
No vasodilator (reference)	122 (6.4)	1		1		1	
Nonnitrate vasodilator	328 (17.3)	0.65 (0.24–1.76)	0.396	0.62 (0.22–1.72)	0.355	0.59 (0.21–1.67)	0.324
Conventional nitrate	76 (4.0)	1.36 (0.44–4.22)	0.594	1.11 (0.34–3.63)	0.858	1.17 (0.34–3.65)	0.857
Combination	43 (2.3)	1.17 (0.29–4.67)	0.827	0.91 (0.22–0.3.82)	0.893	1.01 (0.23–4.47)	0.985
Low JCSA risk score‡	1326 (70.0)						
No vasodilator (reference)	237 (12.5)	1		1		1	
Nonnitrate vasodilator	859 (45.3)	1.77 (0.40–7.80)	0.449	1.56 (0.35–6.93)	0.562	1.59 (0.35–7.13)	0.546
Conventional nitrate	133 (7.0)	6.00 (1.24–28.99)	0.026	5.71 (1.15–28.34)	0.033	5.64 (1.13–28.07)	0.035
Combination	97 (5.1)	11.29 (2.43–52.41)	0.002	10.79 (2.24–51.95)	0.003	10.73 (2.23–51.67)	0.003

Values are expressed as n (%). ACS indicates acute coronary syndrome; ERGT, ergonovine provocation test; HR, hazard ratio; IPTW, inverse probability of treatment weighting; and JCSA, Japanese Coronary Spasm Association.

*Adjusted by IPTW and variables included in multivariable-adjusted model.

†Adjusted by center identifier, ischemic heart disease, dyslipidemia, atrial fibrillation or flutter, current or ex-smoking, ST-T changes during chest pain, and significant coronary stenosis.

‡Adjusted by center identifier, ischemic heart disease, dyslipidemia, and atrial fibrillation or flutter.

studies evaluating this issue, and a large-scale randomized trial is needed to confirm this.

Study Limitations

This study had several limitations. First, we used observational registry data. Therefore, selection bias was inevitable. However, we performed various sensitivity analyses to adjust for measured or unmeasured confounders for various clinical characteristics. Second, data on the dosage and type of vasodilator were not available in the registry. In a prior study, the type of nitrate was found to affect clinical outcomes.[15] In terms of maintenance of medication during follow-up, the registry provided only the rate of medication change, which included an addition, switch to different class of medication, or termination of all medications without detailed information about drug type or dosage. Third, there were no data regarding percutaneous coronary interventions during follow-up. The rate of fixed coronary artery stenosis at baseline CAG was not low (up to 4.1%), and this was an independent predictor of ACS occurrence.

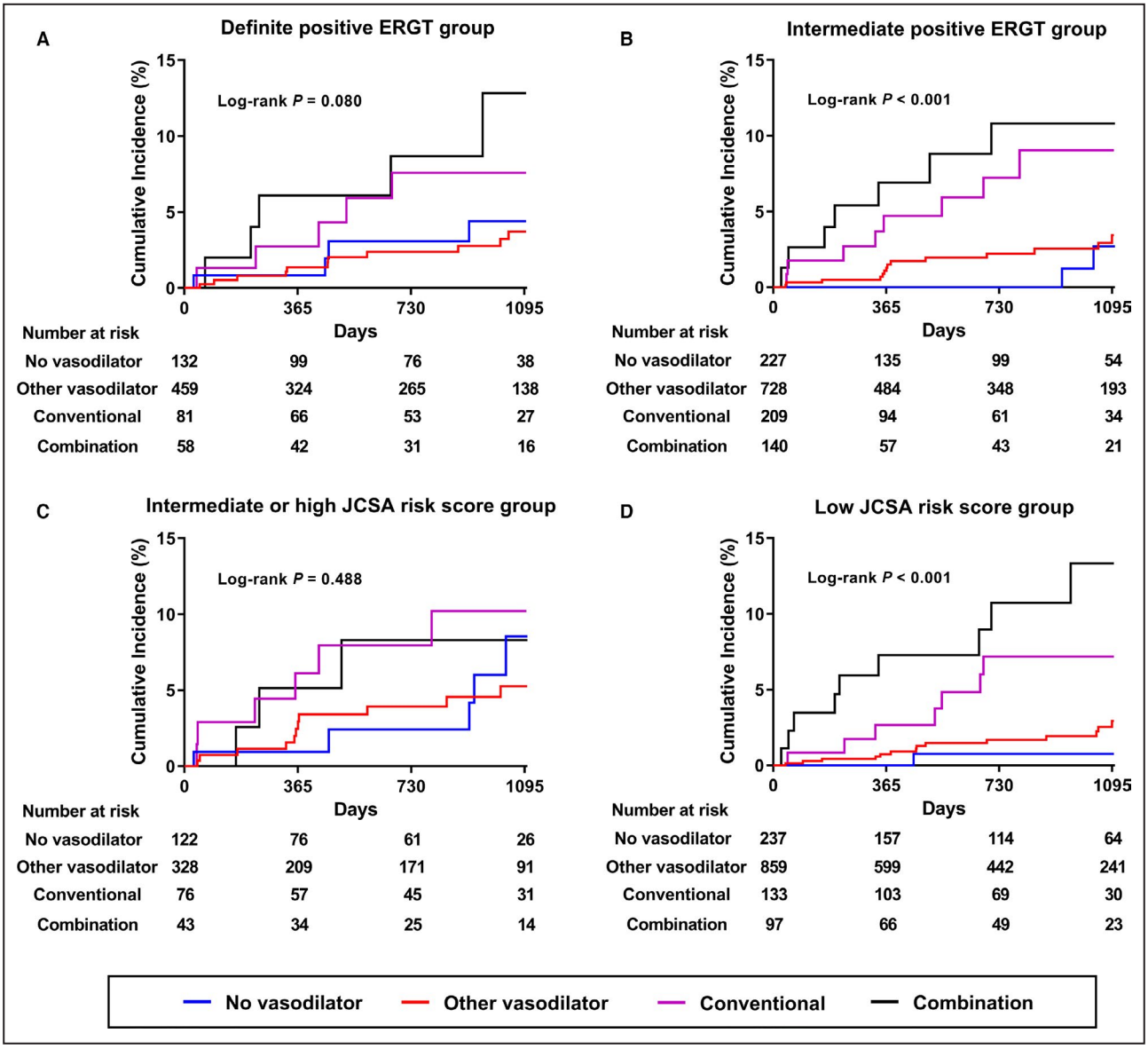

Figure 3. Cumulative incidence of acute coronary syndrome in various subgroups.
A, Definite positive ERGT group; (**B**) intermediate positive ERGT group; (**C**) intermediate or high JCSA risk score group; (**D**) low JCSA risk score group. ERGT indicates ergonovine provocation test; and JCSA, Japanese Coronary Spasm Association.

However, the revascularization rate according to nitrate usage did not differ from previous findings.[16]

CONCLUSIONS

Routine prescription of vasodilators did not affect clinical outcomes in patients with ERGT-confirmed VSA in a nationwide, multicenter, prospective registry. However, long-acting nitrate-based chronic vasodilator therapy was associated with an increased 2-year risk of ACS in patients with VSA, especially in low-risk patients. However, as this study used a retrospective design, additional large-scale randomized trials are required for validation.

ARTICLE INFORMATION

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Disclosure

None.

Supplemental Material

Data S1
Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Data S1. METHODS

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Table S1 **Baseline and Angiographic Characteristics According to Various Vasodilator**

	No vasodilator (n = 359)	Vasodilator			p Value†
		Non-nitrate vasodilator* (n = 1,187)	Conventional nitrate (n = 209)	Combination (n = 140)	
Demographics					
Age, years	55.6 (11.5)	55.4 (11.2)	52.9 (11.3)	53.8 (11.9)	0.012
Male	199 (55.4)	753 (63.4)	138 (66.0)	81 (57.9)	0.018
Medical history					
Ischemic heart disease	42 (11.7)	150 (12.6)	18 (8.6)	26 (18.6)	0.049
Stable CAD	21 (5.8)	69 (5.8)	8 (3.8)	16 (11.4)	0.028
History of PCI	3 (0.8)	28 (2.4)	3 (1.4)	6 (4.3)	0.077
Hypertension	136 (37.9)	448 (37.7)	86 (41.1)	50 (35.7)	0.747
Diabetes mellitus	28 (7.8)	117 (9.9)	20 (9.6)	13 (9.3)	0.710
Dyslipidemia	50 (13.9)	188 (15.8)	40 (19.1)	32 (22.9)	0.063
AF or AFL	6 (1.7)	10 (0.8)	1 (0.5)	1 (0.7)	0.439
Cerebrovascular accident	8 (2.2)	18 (1.5)	3 (1.4)	3 (2.1)	0.778
Thyroid disease	13 (3.6)	45 (3.8)	1 (0.5)	6 (4.3)	0.097
Hyperthyroidism	2 (0.6)	21 (1.8)	0	2 (1.4)	0.100
Hypothyroidism	9 (2.5)	14 (1.2)	0	3 (2.1)	0.064

Chronic airway disease	5 (1.4)	17 (1.4)	3 (1.4)	1 (0.7)	0.922
Familial history of CAD	15 (4.2)	76 (6.4)	15 (7.2)	3 (2.1)	0.082
Current or ex-smoking	136 (37.9)	484 (40.8)	110 (52.6)	56 (40.0)	0.005
Past medication					
Aspirin	66 (18.4)	257 (21.7)	34 (16.3)	27 (19.3)	0.226
Thienopyridine	15 (4.2)	34 (2.9)	13 (6.2)	8 (5.7)	0.048
Calcium-channel blocker	50 (13.9)	248 (20.9)	31 (14.8)	38 (27.1)	0.001
ACE inhibitor or ARB	69 (19.2)	213 (17.9)	30 (14.4)	19 (13.6)	0.280
Beta-blocker	36 (10.0)	92 (7.8)	9 (4.3)	8 (5.7)	0.074
Statin	49 (13.6)	200 (16.8)	25 (12.0)	17 (12.1)	0.121
Initial presentation					
Chest pain	318 (88.6)	1,095 (92.2)	196 (93.8)	131 (93.6)	0.073
Angina class >2	252 (70.2)	752 (63.4)	176 (84.2)	104 (74.3)	<0.001
Dyspnea	23 (6.4)	77 (6.5)	5 (2.4)	5 (3.6)	0.073
Syncope	7 (1.9)	12 (1.0)	4 (1.9)	1 (0.7)	0.391
Cardiac arrest	10 (2.8)	7 (0.6)	5 (2.4)	5 (3.6)	0.001
VT or VF	6 (1.7)	4 (0.3)	1 (0.5)	1 (0.7)	0.048
STE during chest pain	15 (4.2)	58 (4.9)	19 (9.1)	13 (9.3)	0.012
STD during chest pain	4 (1.1)	6 (0.5)	4 (1.9)	3 (2.1)	0.068
TWI during chest pain	7 (1.9)	22 (1.9)	12 (5.7)	6 (4.3)	0.004

Fixed stenosis	136 (37.9)	409 (34.5)	76 (36.4)	50 (35.7)	0.678
Left main	3 (0.8)	12 (1.0)	3 (1.4)	2 (1.4)	0.882
LAD or diagonal	100 (27.9)	280 (23.6)	50 (23.9)	38 (27.1)	0.358
LCX or OM	37 (10.3)	119 (10.0)	23 (11.0)	15 (10.7)	0.973
RCA	61 (17.0)	209 (17.6)	43 (20.6)	20 (14.3)	0.488
Significant stenosis‡	20 (5.6)	47 (4.0)	7 (3.3)	5 (3.6)	0.499
LAD or diagonal	13 (3.6)	28 (2.4)	4 (1.9)	4 (2.9)	0.535
LCX or OM	2 (0.6)	10 (0.8)	2 (1.0)	1 (0.7)	0.946
RCA	7 (1.9)	14 (1.2)	2 (1.0)	0	0.325
Other finding					
Myocardial bridge	13 (3.6)	82 (6.9)	20 (9.6)	8 (5.7)	0.035
Slow flow	12 (3.3)	67 (5.6)	10 (4.8)	9 (6.4)	0.320
Spasm provocation test					
Spasm positive arteries					
Left main	1 (0.3)	9 (0.8)	0	8 (5.7)	<0.001
LAD or diagonal	178 (49.6)	573 (48.3)	106 (50.7)	80 (57.1)	0.250
LCX or OM	101 (28.1)	273 (23.0)	38 (18.2)	35 (25.0)	0.048
RCA	192 (53.5)	593 (50.0)	116 (55.5)	64 (45.7)	0.199
Multivessel spasm	103 (28.7)	280 (23.6)	44 (21.1)	38 (27.1)	0.121
Spontaneous spasm	49 (13.6)	175 (14.7)	24 (11.5)	28 (20.0)	0.158

Diffuse spasm	234 (65.2)	755 (63.6)	120 (57.4)	76 (54.3)	0.045
Focal spasm	134 (37.3)	427 (36.0)	102 (48.8)	67 (47.9)	<0.001
Mixed spasm	41 (11.4)	111 (9.4)	13 (6.2)	5 (3.6)	0.021
Spasm on fixed stenosis	77 (21.4)	248 (20.9)	56 (26.8)	36 (25.7)	0.184
Chest pain during spasm	207 (57.7)	692 (58.3)	149 (71.3)	93 (66.4)	0.001
Result of provocation test					0.806
Definite positive	132 (36.8)	459 (38.7)	81 (38.8)	58 (41.4)	
Intermediate positive	227 (63.2)	728 (61.3)	128 (61.2)	82 (58.6)	
ECG change					
STE	29 (8.1)	99 (8.3)	15 (7.2)	14 (10.0)	0.824
STD	16 (4.5)	48 (4.0)	11 (5.3)	6 (4.3)	0.877
TWI	15 (4.2)	55 (4.6)	11 (5.3)	11 (7.9)	0.349
Medication at discharge					
Calcium-channel blocker	301 (83.8)	1,088 (91.7)	191 (91.4)	125 (89.3)	<0.001
ACE inhibitor or ARB	68 (18.9)	218 (18.4)	32 (15.3)	21 (15.0)	0.533
Antiplatelet	166 (46.2)	558 (47.0)	96 (45.9)	61 (43.6)	0.886
Statin	161 (44.8)	592 (49.9)	97 (46.4)	66 (47.1)	0.353
Beta-blocker	21 (5.8)	86 (7.2)	6 (2.9)	8 (5.7)	0.109
Alpha blocker	5 (1.4)	15 (1.3)	0	2 (1.4)	0.420

Values are expressed as mean (SD) or n (%). *Non-nitrate vasodilator includes nicorandil, molsidomine and trimetazidine. †The p Values are derived from the chi-square test for categorical variables, when appropriate, and from one-way analysis of variance F-test or Kruskal-Wallis test for continuous variables for between-group comparison. ‡There was no significantly fixed coronary artery stenosis in left main.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin II receptor blocker; CAD = coronary artery disease; ECG = electrocardiography; LAD = left anterior descending artery; LCX = left circumflex artery; LVEF = left ventricular ejection fraction; OM = obtuse marginal; PCI = percutaneous coronary intervention; RCA = right coronary artery; SMD = standardized mean difference; STD = ST-segment depression; STE = ST-segment elevation; TWI = T-wave inversion; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table S2 Detailed Characteristics of the VSA Patients With All-Cause Deaths

	Sex	Age (yrs)	JCSA score	DL	AF or AFL	Smoking	Significant fixed stenosis	ERGT positive type	Spasm type	MS	Involved vessel	Medication Change	Time to death (days)
1	Female	77	5	Yes	No	Yes	No	Definite	Mixed	Yes	LAD, LCX	Yes	242
2	Female	72	3	No	No	Yes	No	Definite	Diffuse	No	RCA	No	259
3	Male	65	6	No	No	Yes	No	Definite	Diffuse	No	LAD	Yes	570
4	Male	46	8	No	No	Yes	No	Definite	Diffuse	No	RCA	No	572
5*	Male	61	4	Yes	No	Yes	No	Definite	Diffuse	Yes	LAD/RCA	No	169
6	Female	60	9	No	No	No	No	Intermediate	Diffuse	Yes	LAD/RCA	No	439
7*	Male	45	2	No	No	Yes	No	Definite	Mixed	No	RCA	No	19
8	Male	55	2	No	No	Yes	No	Definite	Diffuse	No	LAD	No	418
9*	Male	56	2	No	No	Yes	No	Definite	Focal	No	RCA	Yes	119
10*	Male	60	2	No	No	No	No	Definite	Focal	No	RCA	Yes	529
11	Female	60	0	No	No	No	No	Intermediate	Diffuse	No	LAD	Yes	173
12	Female	68	2	No	No	No	No	Intermediate	Diffuse	Yes	LAD, LCX	No	858
13	Female	62	2	Yes	No	Yes	No	Intermediate	Diffuse	No	LCX	No	1,280

*Cardiac death.

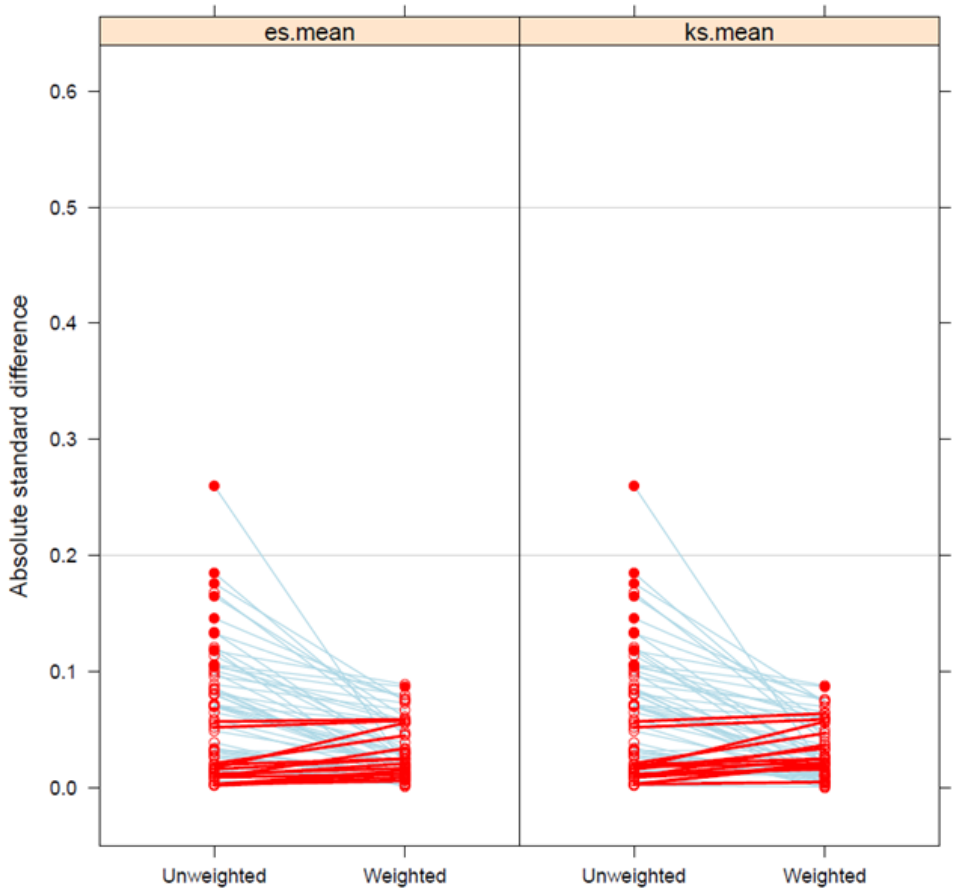
AF = atrial fibrillation; AFL = atrial flutter; DL = dyslipidemia; JCSA = Japanese Coronary Spasm Association; LVEF = left ventricular ejection fraction; MS = multivessel spasm.

Table S3 Independent Predictors for Primary Endpoint or Acute Coronary Syndrome			
	Hazard Ratio	**95% Confidence Interval**	**p Value***
Primary endpoint*			
Non-nitrate vasodilator (no vasodilator group as a reference)	0.74	0.42-1.31	0.301
Conventional nitrate (no vasodilator group as a reference)	1.25	0.61-2.56	0.539
Combination (no vasodilator group as a reference)	1.48	0.69-3.18	0.320
Atrial fibrillation or flutter	3.22	1.13-9.19	0.029
Significantly fixed coronary artery stenosis†	2.58	1.33-4.99	0.005
ACS			
Non-nitrate vasodilator (no vasodilator group as a reference)	0.92	0.40-2.11	0.842
Conventional nitrate (no vasodilator group as a reference)	2.31	0.91-5.86	0.077
Combination (no vasodilator group as a reference)	3.18	1.22-8.28	0.018
Dyslipidemia	1.89	1.05-3.38	0.033
Atrial fibrillation or flutter	4.91	1.45-16.70	0.011
Significantly fixed coronary artery stenosis	3.04	1.33-6.98	0.009

*The primary endpoint was a composite of cardiac death, acute coronary syndrome, and new-onset arrhythmia. †The definition was more than 50% diameter stenosis in left main and more than 70% stenosis in non-left main coronary artery.

ACS= acute coronary syndrome.

Figure S1 Absoulte Standardized Difference for Multinominal Propensity Score



Standardized effect size plot for estimating the propensity scores. ES = effect size; KS = Kolmogorov-Smirnov.