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Impact of statin therapy on long-term clinical outcomes of vasospastic angina without significant stenosis: A propensity-score matched analysis

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ABSTRACT

Background: Limited data are available on the efficacy of statin therapy for secondary prevention in patients with vasospastic angina (VSA). We investigated the association of statin therapy with long-term clinical outcomes in VSA patients without significant coronary artery disease.

Methods: From January 2003 to June 2014, we enrolled a total of 804 patients with VSA proven by an ergonovine provocation test without significant (≥70% diameter stenosis) coronary artery disease. We classified patients into a statin group (n = 330) and a no-statin group (n = 474) according to the use of statin. Primary outcome were major adverse cardiovascular events (MACE) defined as a composite of cardiovascular death, myocardial infarction, and any revascularization.

Results: Median follow-up duration was 4.5 years (interquartile range: 2.0 to 7.3 years). MACE occurred in 14 patients (4.2%) in the statin group, and 21 patients (4.4%) in the no-statin group. There were no differences between the two groups (p = 0.97). After 1:1 propensity-score matching (281 pairs), MACE (statin versus [vs.] no-statin; 3.2% vs. 4.3%, hazard ratio [HR]; 0.80, 95% confidence interval [CI]; 0.34–1.89, p = 0.60) and readmission due to chest pain (17.1% vs. 17.4%, HR; 1.08, 95% CI; 0.72–1.06, p = 0.72) were not statistically different between the two groups.

Conclusion: Our results suggest that statin therapy could not improve long-term clinical outcomes in VSA patients without significant coronary artery disease.

1. Introduction

Vasospastic angina (VSA) is caused by focal or generalized vasospasm of coronary arteries [1]. Previous studies have suggested the relationship between atherosclerosis and vasospasm [2,3], thus VSA is considered as one component of atherosclerotic disease [4]. Furthermore, endothelial dysfunction, smooth muscle hyper-reactivity, autonomic dysfunction, abnormal coronary microvascular function, vascular inflammation, and genetic & environmental background can also influence vasospasm [5–10]. However, the precise mechanism and dominant factors contributing to coronary vasospasm have not been fully established.

Statins have been used worldwide to reduce adverse events in various cardiovascular diseases and have been generally prescribed in patients with hyperlipidemia, and acute coronary syndrome [11–13]. It is known that statin stabilizes vascular plaques, improves endothelial dysfunction, and reduces vascular inflammation [14–17]. A recent study suggested that VSA with significant coronary stenosis may be a predictor of cardiac death and acute coronary syndrome [18]. However, there were limited data about the impact of statin therapy on long-term clinical outcomes in VSA patients without significant atherosclerosis. Therefore, we investigated the association between statin therapy and adverse cardiovascular events in patients with VSA confirmed by an ergonovine provocation test without significant coronary artery stenosis.

2. Methods

2.1. Study population

This is a prospective, single-center, observational study. A total of 1199 patients with newly diagnosed VSA who suffered from chest pain and underwent ergonovine provocation test from January 2003 to June 2014 at Samsung Medical Center were enrolled. Exclusion criteria were as follows; patients who were 1) already taking statin (n = 154), 2) treated with percutaneous coronary intervention (PCI) at the time of VSA diagnosis (n = 110), 3) underwent prior PCI or coronary artery bypass graft (CABG) or confirmed myocardial infarction

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(MI, n = 65), 4) absent follow-up or drug prescription records (n = 39), 5) accompanied with significant organic stenosis (n = 19), and 6) expired during initial presentation (n = 2).

A total of 804 subjects were divided into statin group (n = 330) and no-statin group (n = 474). High intensity statin therapy was defined as atorvastatin >40 mg or rosuvastatin >20 mg based on a previous study [13].

Baseline clinical, laboratory, and angiographic characteristics were collected from databases and medical records. This study received Institutional Review Board approval and informed consent was waived.

2.2. Provocation test

To diagnose VSA, the provocation test with ergonovine was proceeded as described in the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina from the Japanese Circulation Society in 2013 [19]. Baseline coronary angiography of the right and left coronary arteries was performed, and then intracoronary administration of ergonovine was preceded. Initially, 20 micrograms (E1) of ergonovine was injected into the left coronary artery. If coronary spasm was not provoked with the E1 dose, incremental doses of 10 micrograms (E1) and 20 micrograms (E2) were infused into the right coronary artery. Then 40 micrograms (E2) and 80 micrograms (E3) were injected into the left coronary artery. Coronary vasospasm was defined as total or >90% obstruction of the epicardial coronary arteries. Once coronary vasospasm was diagnosed, intracoronary nitrate with a dose sufficient to maximally dilate the coronary artery was injected. Vasoactive drugs and vasodilators were discontinued at least two days before coronary angiography.

2.3. Definitions and outcomes

Primary outcome was major adverse cardiac events (MACE), a composite of cardiac death, MI, and any revascularization. Secondary outcome was readmission due to chest pain. Any revascularization was defined as revascularization of either target or non-target vessels with PCI or CABG. A significant organic stenosis was defined as stenotic coronary lesion at least 70% of the diameter of a vessel with a reference diameter of >2.0 mm by visual estimation.

2.4. Statistical analysis

Continuous variables were compared using the *t*-test or Wilcoxon rank-sum test where applicable. Categorical data were assessed using the chi-square test or Fisher's exact test, as appropriate. Survival curves were constructed using Kaplan–Meier estimates and compared with the log-rank test. The Cox proportional hazard model was used to compare the risks of adverse cardiac events between the statin group and no-statin group.

Propensity scores were estimated using multiple logistic-regression analysis. A full non-parsimonious model was developed that included age, sex, hypertension, diabetes mellitus, current smoking, body mass index, creatinine, high and low density cholesterol, triglyceride, high-sensitivity C-reactive protein, aspirin, calcium channel blocker, nitrate, nicorandil, angiotensin converting enzyme inhibitor, and angiotensin receptor blocker (Table 1), and severity of organic coronary stenosis categorized into four groups (none, 0–30%, 30–50%, 50–70%) (Table 2). The discrimination and calibration abilities of the propensity-score model were assessed by means of the c-statistic and the Hosmer–Lemeshow statistic. Cox regression analysis using pairs matched by a greedy algorithm and the nearest available pair-matching method among patients with an individual propensity score was also performed to evaluate the reduction in outcome risk. The covariate balance achieved by matching was assessed by calculating the absolute standardized differences in covariates between the two groups. An absolute standardized difference < 10% for the measured covariate suggests appropriate balance between the groups. Continuous variables were compared with a paired *t*-test or the Wilcoxon signed-rank test, as appropriate, and categorical variables were compared with the McNemar's or Bowker's test of symmetry as appropriate. The reduction in risk of an adverse outcome was compared by use of a stratified Cox regression model. Cumulative incidence rates of individual clinical outcomes and composite outcomes were estimated by the Kaplan–Meier method and compared by the paired Prentice–Wilcoxon test.

Table 1
Clinical characteristics and laboratory findings.

	All population				Propensity score-matched population			
	No-statin (n = 474)	Statin (n = 330)	p value	SMD	No-statin (n = 281)	Statin (n = 281)	p value	SMD
Age, years	56.0 ± 9.2	55.8 ± 9.2	0.75	−2.3	55.7 ± 9.2	55.8 ± 9.2	0.86	1.5
Men	404 (85.2)	280 (84.8)	0.92	1.1	241 (85.8)	238 (84.7)	0.72	3.0
Diabetes mellitus	92 (19.4)	88 (26.7)	0.016	16.4	73 (26.0)	71 (25.4)	0.85	−1.6
Hypertension	147 (31.0)	139 (42.1)	0.001	22.5	111 (39.5)	110 (39.1)	0.93	−0.7
Current smoker	128 (27.0)	106 (32.1)	0.13	10.9	82 (29.2)	89 (31.7)	0.52	5.3
BMI, kg/m^2	24.2 ± 2.7	24.9 ± 2.8	0.17	9.8	24.5 ± 2.6	24.4 ± 2.7	0.82	−1.9
LVEF, %	64.1 ± 6.2	63.6 ± 7.6	0.42	−8.3	63.9 ± 6.2	64.0 ± 6.8	0.79	−1.3
Laboratory, mg/dL								
Creatinine	0.91 ± 0.17	0.91 ± 0.20	0.86	1.2	0.91 ± 0.16	0.91 ± 0.21	0.36	−2.8
Total cholesterol	171.6 ± 30.3	181.9 ± 39.5	<0.001	26.3	176.4 ± 30.2	177.2 ± 37.6	0.79	3.1
HDL-C	47.0 ± 12.8	47.3 ± 11.3	0.72	3.0	48.0 ± 12.9	47.3 ± 10.9	0.51	−5.3
LDL-C	105.1 ± 26.1	113.9 ± 34.0	<0.001	26.4	108.6 ± 26.6	109.3 ± 32.3	0.76	4.2
TG	158.5 ± 116.7	168.2 ± 39.5	0.27	8.4	166.0 ± 125.0	164.4 ± 118.9	0.88	−0.6
hsCRP, mg/L	0.41 ± 1.49	0.49 ± 2.11	0.64	3.8	0.44 ± 1.66	0.37 ± 1.57	0.67	−1.8
Discharge medications								
Aspirin	270 (57.0)	220 (66.7)	0.007	20.6	179 (63.7)	180 (64.1)	0.93	0.8
Calcium channel blocker	449 (94.7)	323 (97.9)	0.027	21.8	274 (97.5)	274 (97.5)	0.99	0.0
Nitrate	203 (42.8)	123 (37.3)	0.125	−11.5	105 (37.4)	108 (38.4)	0.79	2.2
Nicorandil	122 (25.7)	139 (42.1)	<0.001	33.1	97 (34.5)	102 (36.3)	0.66	3.6
ACEi or ARB	66 (13.9)	65 (19.7)	0.033	14.5	49 (17.4)	50 (17.8)	0.91	0.9

Values are expressed as mean ± SD or n (%). N/A = not available.
Abbreviation: ACEi — angiotensin converting enzyme inhibitor, ARB — angiotensin receptor blocker, BMI — body mass index, HDL-C — high density lipoprotein cholesterol, hsCRP — high sensitivity C-reactive protein, LDL-C — low density lipoprotein cholesterol, LVEF — left ventricular ejection fraction, SMD — standard mean difference, TG — triglyceride.