

Impact of Statin Therapy on Clinical Outcome in Patients With Coronary Spasm

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Background—Statin therapy reduces the risk of cardiovascular events in patients with obstructive coronary artery disease. The aim of the present study was to determine the effects of statins on the prognosis of patients with coronary vasospastic angina (VSA) free of significant atherosclerotic stenosis.

Methods and Results—After exclusion of 475 from 1877 consecutive patients who underwent an acetylcholine-provocation test between January 1991 and December 2010, data of 640 VSA patients without significant organic stenosis of the remaining 1402 were analyzed retrospectively. Propensity score matching was performed to reduce the effect of treatment-selection bias and possible confounders. The primary endpoint was major adverse cardiac events (MACE), including cardiac death, nonfatal myocardial infarction, and unstable angina. Among the study population, dyslipidemia on admission was identified in 160 of 168 (95.2%) patients of the statin group compared with only 125 of 472 (26.5%) of the no-statin group. Of the 640 patients, 24 (3.8%) developed MACE. Multivariate Cox hazard regression analysis identified statin therapy as a significant negative predictor of MACE (hazard ratio, 0.11; 95% CI, 0.02–0.84; $P=0.033$). In the propensity-score matched cohorts ($n=128$ each), Kaplan–Meier survival curve showed a better 5-year MACE-free survival rate for patients of the statin group compared to the no-statin group (100% vs 91.7%, respectively; $P=0.002$).

Conclusions—Statin therapy correlated with a lower rate of cardiovascular events in VSA patients free of significant organic stenosis. Statins seems to improve the prognosis of VSA patients free of significant organic stenosis. (*J Am Heart Assoc.* 2016;5:e003426 doi: 10.1161/JAHA.116.003426)

Key Words: acetylcholine • angina • atherosclerosis • cardiovascular disease • coronary artery disease • statins • vasospasm

Coronary spasm is closely associated with endothelial dysfunction and plays a potential role in the progression of atherosclerosis.^{1–3} Whereas patients with coronary spasm have better prognosis for cardiovascular events than those with more-serious coronary artery disease (CAD), coronary atherosclerotic stenosis correlates with cardiovascular events in patients with coronary vasospastic angina (VSA).^{4–6}

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Statin reduce the risk of cardiovascular events in obstructive CAD^{7–11} and also ameliorate endothelial dysfunction.^{12–14} In a prospective, randomized study, we showed previously that the addition of fluvastatin at 30 mg/day to conventional medical therapy with calcium-channel blockers (CCBs) for 6 months significantly reduced acetylcholine (ACh)-provoked coronary spasm in VSA patients free of coronary organic stenosis.¹⁵ However, there is no evidence at present that statin therapy improves the prognosis of VSA patients. The purpose of this study was to assess the effects of statin therapy on clinical outcome of VSA patients free of coronary organic stenosis.

Methods

Study Population and ACh-Provocation Test

The present study was a retrospective observational study that enrolled 1877 consecutive Japanese patients who had typical or atypical angina-like chest pain and underwent ACh-provocation testing at our hospital between January 1991 and

December 2010. We excluded 117 patients for the following reasons: acute myocardial infarction (AMI; n=20), cardiomyopathy (n=75), Brugada syndrome (n=10), and other miscellaneous conditions (n=12). To investigate the prognosis of patients free of significant atherosclerotic stenosis, we also excluded 358 patients with significant atherosclerotic stenosis. Thus, 640 VSA patients from the remaining 1402 free of significant organic stenosis were included for analysis (Figure 1). We defined significant atherosclerotic stenosis (hereafter referred to as organic stenosis) as $\geq 75\%$ stenosis (51–75% narrowing of the luminal diameter) of the right, left anterior descending, or left circumflex coronary artery and the major branches, or $\geq 50\%$ stenosis (26–50% narrowing of the luminal diameter) of the left main trunk, as defined by the American Heart Association (AHA) classification (by visual estimation).¹⁶

The ACh-provocation test was conducted as described previously in the VSA Guideline by the Japanese Circulation Society.¹⁷ ACh-induced coronary spasm was defined as total or subtotal obstruction within the borders of a single isolated coronary segment, or severe diffuse vasoconstriction observed in more than 2 adjacent coronary segments of epicardial coronary arteries associated with transient myocardial ischemia, as evidenced by ischemic ST-segment changes on the electrocardiogram (ECG), as described previously.^{6,18}

The study protocol was approved by the Human Ethics Review Committee of Kumamoto University (Kumamoto,

Japan), and a signed consent form was obtained from each subject.

Data Collection

Baseline and clinical data were obtained from the medical records. We defined the risk factors for CAD as current smoking, hypertension, dyslipidemia, diabetes mellitus, and family history of ischemic heart disease (IHD), as described previously.^{6,18} Selection of medical treatments for VSA was left to the discretion of each attending physician. Statins represented atorvastatin, pitavastatin, rosuvastatin, pravastatin, simvastatin, or fluvastatin. The prescription for statins was not randomized because the study was retrospective and observational. Information on medical treatments was available at the beginning of the follow-up.

Follow-up Data

Follow-up data were collected from the medical records, the patients, their families, or the attending physicians. The primary endpoint was defined as major adverse cardiac events (MACE), including cardiac death, hospitalization for AMI, and unstable angina. The secondary endpoint was all-cause mortality during the follow-up period that began from the date of the diagnosis of VSA to the date of the first event or until December 2012. We defined cardiac death as sudden death or death associated with AMI, and AMI as the presence of severe chest discomfort lasting >30 minutes associated with ST-segment changes and elevated cardiac enzyme levels. Unstable angina was defined as recurrence or worsening of chest discomfort or pain associated with ischemic ECG changes. Spasm-induced AMI and unstable angina were diagnosed by transient ischemic ECG changes during spontaneous nitrate-responsive angina episode, with at least one of the following: (1) absence of culprit lesion, spontaneous coronary spasm relieved by administration of intracoronary nitroglycerin, or ACh-provoked coronary spasm on coronary angiography or (2) absence of ischemic findings suggestive of significant atherosclerotic stenosis on stress testing (exercise ECG and/or myocardial scintigraphy).

Statistical Analysis

Data of normally distributed continuous variables are expressed as mean \pm SD, whereas those with skewed distribution are presented as median values (interquartile range; IQR), and categorical variables as frequencies and percentages. Group comparisons were analyzed by the unpaired *t* test or Mann–Whitney *U* test for continuous variables, the chi-square test or Fisher's exact test for categorical variables, and the log-rank test for MACE-free survival curves, as appropriate. Cox proportional hazards regression was used to

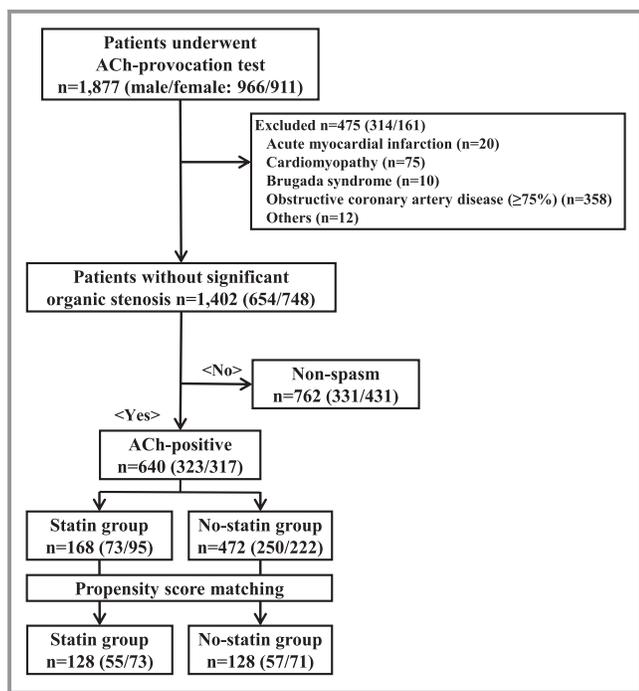


Figure 1. Flow chart of the patient recruitment process. The chart shows enrollment criteria and flow of patients. Ach indicates acetylcholine.

compute hazard ratios (HRs) and 95% CI as estimates for the endpoint. HRs were adjusted for clinical characteristics, angiographic findings, and medications according to univariate analysis for the endpoint. All variables with $P < 0.10$ on the univariate analysis were entered into the multivariate model using the step-wise backward selection method, and $P < 0.05$ was set for inclusion in the multivariate model. In addition, to reduce the effect of treatment selection bias and possible confounders, we performed adjustment for significant differences in the baseline characteristics of patients with propensity score matching. The predicted probability of use of statins was calculated by fitting a logistic regression model, using all clinically relevant variables such as age, sex, hypertension, current smoking, family history of IHD, total cholesterol, chest pain at rest only, and use of CCB, angiotensin II receptor blockers (ARB), nicorandil, and aspirin. One patient on statins was matched to 1 patient not treated with statins using nearest-neighbor matching within a caliper width of 0.01 without replacement. A 2-tailed $P < 0.05$ denoted the presence of a statistically significant difference. All statistical analyses were performed with The Statistical Package for Social Sciences software (version 23.0; IBM Corp, Armonk, NY).

Results

Clinical Characteristics of VSA Patients of the Statin and No-statin Groups

ACh-provoked coronary spasm without significant atherosclerotic stenosis was observed in 640 of 1402 patients (Figure 1). Table 1 shows the clinical characteristics of the VSA patients of the statin group ($n=168$) and no-statin group ($n=472$). VSA patients of the statin group tended to be older, female, less likely to be smokers, and to have family history of IHD and chest pain at rest only and more likely to have hypertension, dyslipidemia, higher total cholesterol levels, higher low-density lipoprotein (LDL)-cholesterol levels, higher high-density lipoprotein (HDL)-cholesterol levels, lower C-reactive protein (CRP), and ARB, nicorandil, and aspirin use compared to those of the no-statin group. Dyslipidemia on admission was identified in 160 of 168 (95.2%) VSA patients of the statin group, but in only 125 of 472 (26.5%) VSA patients of the no-statin group. As shown in Table 1, LDL-cholesterol levels were significantly higher in VSA patients of the statin group than those of the other group (127.6 ± 41.6 vs 112.4 ± 29.9 mg/dL; $P < 0.001$). The remaining 8 of 168 (4.8%) patients were prescribed statins according to the VSA Guideline by the Japanese Circulation Society.¹⁷

After performing propensity score matching for the entire cohort, 128 matched pairs of patients were identified. For the logistic regression model to estimate propensity score, Hosmer-Lemeshow goodness of fit chi-square was 2.875

with a P value of 0.942 and the area under the curve of receiver operating characteristic curve was 0.776. There were no significant differences in clinically relevant variables between patients of the 2 treatment groups, except for incidence of dyslipidemia.

Types and Doses of Statins

Table 2 provides detailed information of statin therapy. Among 168 patients treated with statins, 26 (15.5%) were treated with atorvastatin, 17 (10.1%) with pitavastatin, 8 (4.8%) with rosuvastatin, 74 (44.0%) with pravastatin, 5 (3.0%) with simvastatin, and 38 (22.6%) with fluvastatin. In the matched-cohort, 17 (13.3%) patients were treated with atorvastatin, 13 (10.2%) with pitavastatin, 8 (6.3%) with rosuvastatin, 57 (44.5%) with pravastatin, 4 (3.1%) with simvastatin, and 29 (22.7%) with fluvastatin.

Clinical Outcomes and Factors Associated With MACE

The primary endpoints were identified in the number of patients indicated in Table 3 and Figure 2. During a median follow-up period of 60 months (IQR, 46–60), 24 (3.8%) patients of the entire cohort experienced the primary endpoints, including cardiac death in 3, acute myocardial infarction in 2, unstable angina in 18 of the VSA patients not on statins, and unstable angina in a single patient of the statin group. All-cause deaths were recorded in 19 patients of the entire cohort. Manifestations of cardiac events in VSA patients were identified in 15 of all 24 patients (62.5%) with MACE. Furthermore, 14 (58.3%) patients were diagnosed as spasm-induced MI or unstable angina, and the culprit lesion was identified on coronary angiography in 1 (4.2%) patient. In patients of the statin group, 1 was diagnosed with spasm-induced unstable angina. Manifestations of cardiac events in the remaining 9 patients could not be assessed because detailed information about events was not available. Kaplan–Meier survival curve indicated worse MACE-free 5-year survival rates in patients of the no-statin group compared to those of the statin group (94.3% vs 99.4%; $P=0.012$; Figure 2A).

Table 4 shows the results of univariate and multivariate Cox proportional hazards analyses for factors that correlated with MACE during follow-up. Multivariate Cox hazard regression analysis identified the use of statin as a significant negative correlate of MACE (HR, 0.11; 95% CI, 0.02–0.84; $P=0.033$) and ST-segment elevation during angina attack as a significant positive correlate of MACE (HR, 5.28; 95% CI, 2.19–12.7; $P < 0.001$).

Analysis of the matched cohort showed 2 cases with cardiac death and 7 with unstable angina among patients of

Table 1. Clinical Characteristics in the VSA Patients With and Without Statins

	Entire Cohort			Matched Cohort		
	Statin Group (n=168)	No-Statins Group (n=472)	P Value	Statin Group (n=128)	No-Statins Group (n=128)	P Value
Age, y	65.2±9.9	62.8±10.8	0.009	64.6±9.9	64.8±9.7	0.838
Female sex	95 (56.5)	222 (47.0)	0.034	73 (57.0)	71 (55.5)	0.801
BMI, kg/m ²	24.2±3.6	23.6±3.7	0.081	24.2±3.8	23.8±4.3	0.473
Current smoking	63 (37.5)	250 (53.1)	0.001	50 (39.1)	51 (39.8)	0.898
Diabetes mellitus	33 (19.6)	73 (15.7)	0.236	26 (20.3)	21 (16.7)	0.454
Hypertension	86 (51.2)	160 (33.9)	<0.001	60 (46.9)	53 (41.4)	0.378
Dyslipidemia	160 (95.2)	125 (26.5)	<0.001	121 (94.5)	50 (39.1)	<0.001
Family history of IHD	11 (6.5)	90 (19.1)	<0.001	9 (7.0)	8 (6.3)	0.802
Total cholesterol, mg/dL	209.8±39.7	188.7±32.0	<0.001	201.2±33.5	203.9±29.6	0.491
LDL cholesterol, mg/dL	127.6±41.6	112.4±29.9	<0.001	119.5±34.7	126.9±28.7	0.066
HDL cholesterol, mg/dL	57.7±17.4	52.7±15.9	0.001	57.3±16.6	53.3±15.6	0.051
Triglyceride, mg/dL	111 (77–157)	102 (77–145)	0.306	106 (77–164)	103 (77–151)	0.853
CKD, eGFR <60 mL/min per 1.73 m ²	34 (21.5)	79 (19.5)	0.592	24 (19.5)	27 (23.1)	0.500
CRP, mg/dL	0.06 (0.03–0.14)	0.08 (0.05–0.23)	0.005	0.06 (0.03–0.14)	0.07 (0.05–0.23)	0.126
Clinical status of angina attack						
At rest only	104 (61.9)	332 (70.3)	0.044	79 (61.7)	83 (64.8)	0.604
Rest and effort	19 (11.3)	33 (7.0)	0.079	13 (10.2)	10 (7.8)	0.512
ST-segment change during angina attack						
ST-segment elevation	14 (8.3)	38 (8.1)	0.908	12 (9.4)	8 (6.3)	0.352
Angiographic characteristics						
Multivessel spasm	75 (44.6)	215 (45.6)	0.839	52 (40.6)	60 (46.9)	0.313
Diffuse spasm	73 (43.5)	227 (48.1)	0.301	59 (46.1)	68 (53.1)	0.261
ST-segment elevation in ACh test	59 (35.1)	158 (33.5)	0.699	42 (32.8)	35 (27.3)	0.340
Medications						
CCB	161 (95.8)	432 (91.5)	0.066	122 (95.3)	124 (96.9)	0.519
ACE inhibitor	21 (12.5)	43 (9.1)	0.212	17 (13.3)	17 (13.3)	1.000
ARB	30 (17.9)	25 (5.3)	<0.001	17 (13.3)	12 (9.4)	0.324
Nitrates	24 (14.3)	83 (17.6)	0.320	14 (10.9)	19 (14.8)	0.351
Nicorandil	15 (8.9)	22 (4.7)	0.043	9 (7.0)	9 (7.0)	1.000
β-blockers	10 (6.0)	24 (5.1)	0.671	8 (6.3)	6 (4.7)	0.582
Aspirin	50 (29.8)	87 (18.5)	0.002	37 (28.9)	35 (27.3)	0.781

Data are mean±SD, median (interquartile range), or n (%). ACE indicates angiotensin-converting enzyme; ACh, acetylcholine; ARB, angiotensin II receptor blockers; BMI, body mass index; CCB, calcium-channel blocker; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; VSA, vasospastic angina.

the no-statin group (Table 3). All-cause deaths were recorded in 7 patients in the matched cohort. Kaplan–Meier survival curve indicated significantly lower incidence of MACE in the statin group compared to the no-statin group (100% vs 91.7%; $P=0.002$; Figure 2B). Because of the limited number of events, it was considered that the data of the matched cohort could not be subjected to univariate and multivariate

Cox hazard regression analyses; any such analysis would overestimate MACE prognostic factors.

Discussion

Statin therapy is the standard treatment for obstructive CAD; however, it remains to be elucidated whether this therapy

Table 2. Details of Statin Therapy

	Entire Cohort (n=168)	Matched Cohort (n=128)
Atorvastatin	26 (15.5)	17 (13.3)
5 mg	4 (2.4)	4 (3.1)
10 mg	19 (11.3)	11 (8.6)
20 mg	3 (1.8)	2 (1.6)
Pitavastatin	17 (10.1)	13 (10.2)
1 mg	2 (1.2)	2 (1.6)
2 mg	15 (8.9)	11 (8.6)
Rosuvastatin	8 (4.8)	8 (6.3)
2.5 mg	7 (4.2)	7 (5.5)
5 mg	1 (0.6)	1 (0.8)
Pravastatin	74 (44.0)	57 (44.5)
5 mg	1 (0.6)	0 (0.0)
10 mg	62 (36.9)	47 (36.7)
20 mg	11 (6.5)	10 (7.8)
Simvastatin		
5 mg	5 (3.0)	4 (3.1)
Fluvastatin	38 (22.6)	29 (22.7)
10 mg	1 (0.6)	0 (0.0)
20 mg	4 (2.4)	3 (2.3)
30 mg	33 (19.6)	26 (20.3)

Data are n (%).

improves the prognosis of VSA patients free of significant atherosclerotic coronary stenosis. The major finding of the present study was that statin therapy correlated with a lower rate of cardiovascular events in VSA patients free of significant stenosis. To the best of our knowledge, this is the first large-population study to investigate the prognostic

Table 3. Clinical Outcome of VSA Patients of the Statin and No-statin Groups

	Entire Cohort		Matched Cohort	
	Statin Group (n=168)	No-Statins Group (n=472)	Statin Group (n=128)	No-Statins Group (n=128)
MACE	1 (0.6)	23 (4.9)	0 (0)	9 (7.0)
Cardiac death	0 (0)	3 (0.6)	0 (0)	2 (1.6)
Nonfatal MI	0 (0)	2 (0.4)	0 (0)	0 (0)
Unstable angina	1 (0.6)	18 (3.8)	0 (0)	7 (5.5)

Data are n (%). MACE indicates major adverse cardiac events; MI, myocardial infarction; VSA, vasospastic angina.

effects and therapeutic implications of statin therapy in VSA patients free of significant coronary organic stenosis.

In the present study, the Kaplan–Meier survival curve indicated better 5-year MACE-free survival rates in VSA patients of the statin group, compared to those of the no-statin group (99.4% vs 94.3%, respectively) and matched cohort (100% vs 91.7%, respectively). Although previous studies showed better prognosis of VSA patients free of organic stenosis than those with organic stenosis,^{4–6} the results of this study would make better impact on the prognosis of VSA patients free of organic stenosis. Statin therapy has been established as a standard treatment for primary prevention. For example, 1 meta-analysis demonstrated the prognostic impact of statin therapy in patients at low risk of vascular disease.¹⁹ Recently, Chow et al.²⁰ reported that statin therapy was associated with significant reduction in mortality in individuals with nonobstructive CAD. Thus, the results demonstrated that statin therapy could improve the long-term clinical outcome, including cardiovascular events, even in patients with nonobstructive CAD, and the findings of the present study were consistently in agreement with these previous studies.

Statins reduce the risk of cardiovascular events by lowering LDL-cholesterol levels.^{10,21} Furthermore, previous studies showed that aggressive statin therapy provided better protection against coronary artery plaque formation and prevented cardiovascular events, compared with moderate treatment.^{7,8} In the present study, baseline LDL-cholesterol levels were significantly higher in patients of the statins group than those of the no-statin group (127.6 ± 41.6 vs 112.4 ± 29.9 mg/dL, respectively; $P < 0.001$), probably explaining the need for starting treatment with statin. Although LDL-cholesterol levels were not measured during follow-up, statin therapy seems to improve the prognosis of VSA patients by lowering LDL-cholesterol levels and preventing plaque formation. In addition, because our study included patients with mild-to-moderate organic coronary stenosis (25–50% stenosis), in addition to those with no coronary stenosis, such patients might have had a greater benefit from statin therapy against atherosclerosis progression.

Most patients of the present study received low-intensity statin therapy probably because Japanese are known to have higher responsiveness to statin treatment compared with Caucasian.²² The 2013 American College of Cardiology/AHA guidelines recommend the use of higher dose and aggressive statin therapy in high-risk patients with clinically confirmed atherosclerotic cardiovascular disease without titration to a specific LDL-C target for secondary prevention of cardiovascular diseases.²³ Based on the recommendation, higher dose of aggressive statin therapy might be needed in VSA patients. Prospective, randomized studies should be performed to investigate the relation between statin intensity (in terms of LDL-cholesterol target levels) and prognosis of VSA patients.

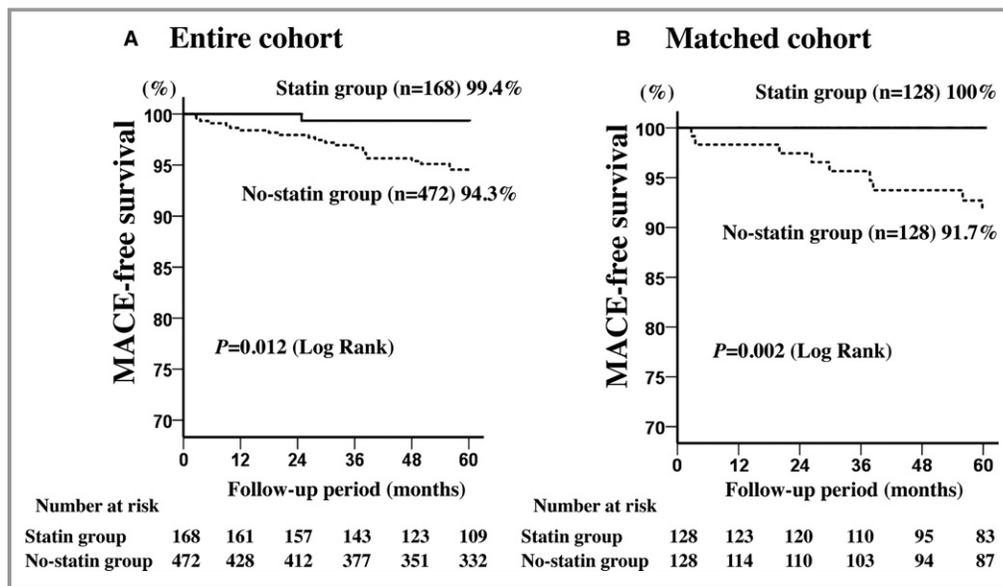


Figure 2. MACE-free survival rate for patients with coronary spasm. Kaplan–Meier curves for MACE-free survival for vasospastic angina patients of (A) the entire statins and no-statins groups and (B) the matched cohort. MACE indicates major adverse cardiac events.

Although the present study identified the manifestations of cardiac events, more than half of the patients had spasm-induced unstable angina. Therefore, it seems that statins do not only reduce the risk of cardiovascular events in VSA patients through the prevention of coronary artery plaque progression, but also by direct suppression of coronary spasm. What are the mechanisms of statin-induced suppression of coronary spasm? Yasue et al.¹⁵ demonstrated that fluvastatin specifically suppressed vasoconstrictor response in the spasm segment, probably through its pleiotropic effects of amelioration of endothelial dysfunction, suppression of inflammation, and inhibition of the Rho A/Rho-kinase pathway. Their conclusion was based on the observation of decreased endothelial nitric oxide bioactivity and increased levels of inflammation markers in patients with coronary spasm.^{1,24,25} Interestingly, previous studies from our laboratories have also demonstrated that statins significantly increased endothelial nitric oxide synthase mRNA level, mRNA stability, and endothelial nitric oxide activity. Considered together, the above studies strongly suggest that statins seem to improve endothelial dysfunction and suppress coronary spasm.²⁶ Furthermore, it is also reported that statins therapy results in significant falls in serum levels of CRP, a marker of inflammation.¹⁵ Ridker et al.²⁷ also demonstrated that statin therapy lowered levels of LDL-C and CRP, suggesting that the low levels of LDL-C and CRP after statin therapy are associated with low incidence of cardiovascular events. In the present study, CRP levels were significantly lower in VSA patients treated with statins than

those without (0.06 [0.03–0.14] vs 0.08 [0.05–0.23], respectively; $P=0.005$). However, because LDL-C and CRP were measured only at the beginning of the follow-up, comparison of data obtained during and at end of follow-up are needed to confirm the anti-inflammatory effect of statins. Vascular smooth muscle cell hyper-responsiveness is one of the mechanisms of coronary artery spasm.²⁸ This suggests that activation of the Rho A/Rho-kinase pathway could be involved in the pathogenesis of coronary spasm. In fact, previous studies reported that statin therapy suppresses coronary spasm through inhibition of the Rho A/Rho-kinase pathway.^{29,30}

The present study has several limitations. First, this study was an observational, single-center, retrospective study. The cause-effect relationship between medical treatment and pathological condition could not be assessed fully because the selection of medical treatments for VSA was left to the discretion of the attending physicians. However, the use of the propensity score matching reduced the effect of treatment-selection bias and possible confounders. Nevertheless, other confounding factors that were not investigated in the present study could have affected the risk for cardiovascular events, and thus overestimation of the effects of statin therapy on coronary spasm attributed to the limited number of events cannot be ruled out. A randomized, prospective study should be conducted to confirm that statin therapy suppresses coronary spasm. Second, the low absolute number of events in the present study limits the precision of the estimate of prognostic factors. For this reason, the

Table 4. Results of Univariate and Multivariate Cox Proportional Hazards Analyses of Data of the Entire Cohort for Factors Associated With MACE

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P Value	HR	95% CI	P Value
Old age (age ≥ 75 years)	0.53	0.13 to 2.26	0.390			
Female sex	0.79	0.36 to 1.77	0.570			
BMI ≥ 25 kg/m ²	0.58	0.22 to 1.57	0.283			
Current smoking	1.66	0.74 to 3.74	0.220			
Diabetes mellitus	0.22	0.03 to 1.62	0.137			
Hypertension	0.92	0.40 to 2.10	0.845			
Dyslipidemia	0.48	0.20 to 1.16	0.104			
Family history of IHD	0.46	0.11 to 1.96	0.293			
CKD, eGFR <60 mL/min per 1.73 m ²	0.91	0.31 to 2.71	0.870			
ST-segment elevation during angina attack	5.05	2.10 to 12.19	<0.001	5.28	2.19 to 12.7	<0.001
Chest pain at rest only	1.71	0.64 to 4.57	0.288			
Multivessel spasm	1.66	0.74 to 3.73	0.222			
Diffuse spasm	0.53	0.23 to 1.23	0.139			
CCB	0.60	0.18 to 2.03	0.414			
ACE inhibitor	1.80	0.62 to 5.26	0.284			
ARB	0.04	0.00 to 22.53	0.325			
Nitrates	2.65	1.13 to 6.19	0.024		Not selected*	
Nicorandil	0.77	0.10 to 5.67	0.793			
β -blockers	0.85	0.12 to 6.32	0.876			
Statins	0.12	0.02 to 0.87	0.036	0.11	0.02 to 0.84	0.033
Aspirin	1.25	0.50 to 3.14	0.640			

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; BMI, body mass index; CCB, calcium-channel blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IHD, ischemic heart disease; MACE, major adverse cardiac events.

*This variable was not selected by the step-wise backward selection entry method.

relation between the dose of statins and prognosis could not be analyzed. Third, the information about medical treatment and compliance was not sufficient. Because we obtained such information only at the beginning of the follow-up, we could not assess the relationship between changes in medications during the follow-up period and the clinical outcome, thus limiting the value of analysis of prognosis and the main conclusion of the study. Similarly, because we obtained the data of LDL-cholesterol and CRP levels only at the beginning of follow-up, we could not establish the exact mechanism of statin therapy, suggesting that lowering LDL-cholesterol or CRP levels plays at least some role in lowering incidence of coronary spasm. Thus, a prospective study is needed to confirm the roles of LDL-cholesterol and CRP levels in the observed effects of statin therapy. Fourth, it is possible that statin therapy was not tolerated by at least some of the patients of the no-statin group. This is especially possible

because we did not check for side effects. Withdrawal of statin therapy might have an impact on the conclusion made regarding the effectiveness of statin therapy.

Conclusions

The present study demonstrated the impact of statin therapy on clinical outcome in VSA patients free of coronary atherosclerotic stenosis. The results indicated that statin therapy correlated with a lower rate of cardiovascular events in VSA patients free of significant organic stenosis. Based on these findings, we conclude that statin therapy not only prevents the progression of coronary atherosclerotic plaque formation, but also seems to suppress coronary spasm through improvement of endothelial function and, consequently, reduces the likelihood of cardiovascular events in patients with coronary spasm.

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Disclosures

None.

References

- Kugiyama K, Yasue H, Okumura K, Ogawa H, Fujimoto K, Nakao K, Yoshimura M, Motoyama T, Inobe Y, Kawano H. Nitric oxide activity is deficient in spasm arteries of patients with coronary spastic angina. *Circulation*. 1996;94:266–271.
- Kuga T, Tagawa H, Tomoike H, Mitsuoka W, Egashira S, Ohara Y, Takeshita A, Nakamura M. Role of coronary artery spasm in progression of organic coronary stenosis and acute myocardial infarction in a swine model. Importance of mode of onset and duration of coronary artery spasm. *Circulation*. 1993;87:573–582.
- Suzuki H, Kawai S, Aizawa T, Kato K, Sunayama S, Okada R, Yamaguchi H. Histological evaluation of coronary plaque in patients with variant angina: relationship between vasospasm and neointimal hyperplasia in primary coronary lesions. *J Am Coll Cardiol*. 1999;33:198–205.
- Takagi Y, Yasuda S, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Sato T, Ogawa S, Kubo N, Momomura S, Ogawa H, Shimokawa H. Clinical characteristics and long-term prognosis of vasospastic angina patients who survived out-of-hospital cardiac arrest: multicenter registry study of the Japanese Coronary Spasm Association. *Circ Arrhythm Electrophysiol*. 2011;4:295–302.
- Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation*. 2000;101:1899–1906.
- Ishii M, Kaikita K, Sato K, Tanaka T, Sugamura K, Sakamoto K, Izumiya Y, Yamamoto E, Tsujita K, Yamamoto M, Kojima S, Soejima H, Hokimoto S, Matsui K, Ogawa H. Acetylcholine-provoked coronary spasm at site of significant organic stenosis predicts poor prognosis in patients with coronary vasospastic angina. *J Am Coll Cardiol*. 2015;66:1105–1115.
- Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291:1071–1080.
- Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504.
- Ishii M, Hokimoto S, Akasaka T, Fujimoto K, Miyao Y, Kaikita K, Oshima S, Nakao K, Shimomura H, Tsunoda R, Hirose T, Kajiwara I, Matsumura T, Nakamura N, Yamamoto N, Koide S, Oka H, Morikami Y, Sakaino N, Matsui K, Ogawa H. Differential effects of strong and regular statins on the clinical outcome of patients with chronic kidney disease following coronary stent implantation—the Kumamoto Intervention Conference Study (KICS) Registry. *Circ J*. 2015;79:1115–1124.
- Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
- Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, Komura N, Sakamoto K, Oka H, Nakao K, Nakamura S, Ishihara M, Matsui K, Sakaino N, Nakamura N, Yamamoto N, Koide S, Matsumura T, Fujimoto K, Tsunoda R, Morikami Y, Matsuyama K, Oshima S, Kaikita K, Hokimoto S, Ogawa H. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention. The Multicenter Randomized Controlled PRECISE-IVUS Trial. *J Am Coll Cardiol*. 2015;66:495–507.
- Liao JK, Laufs U. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol*. 2005;45:89–118.
- Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol*. 2005;46:1425–1433.
- Schonbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? *Circulation*. 2004;109:1118–1126.
- Yasue H, Mizuno Y, Harada E, Itoh T, Nakagawa H, Nakayama M, Ogawa H, Tayama S, Honda T, Hokimoto S, Ohshima S, Hokamura Y, Kugiyama K, Horie M, Yoshimura M, Harada M, Uemura S, Saito Y. Effects of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, fluvastatin, on coronary spasm after withdrawal of calcium-channel blockers. *J Am Coll Cardiol*. 2008;51:1742–1748.
- Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*. 1975;51:5–40.
- Ogawa H, Akasaka T, Hattori R, Inoue T, Kawashima S, Kawasuji M, Kimura K, Miwa K, Mizuno K, Mohri M, Murohara T, Node K, Okumura K, Shimokawa H, Sueda S, Takeyama Y, Tanabe Y, Tsuchihashi K, Yamagishi M, Yasuda S, Yoshimura M, Abe S, Ibuki C, Ishibashi K, Kaikita K, Kawano H, Kawashiri MA, Kojima S, Kosuge M, Nakayama M, Noguchi T, Ogawa T, Soejima H, Suzuki H, Takahashi J, Haze K, Hirayama A, Miyazaki S, Tomoike H, Yokoyama M. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary Spastic Angina) (JCS 2013). *Circ J*. 2014;78:2779–2801.
- Sato K, Kaikita K, Nakayama N, Horio E, Yoshimura H, Ono T, Ohba K, Tsujita K, Kojima S, Tayama S, Hokimoto S, Matsui K, Sugiyama S, Yamabe H, Ogawa H. Coronary vasomotor response to intracoronary acetylcholine injection, clinical features, and long-term prognosis in 873 consecutive patients with coronary spasm: analysis of a single-center study over 20 years. *J Am Heart Assoc*. 2013;2:e000227 doi: 10.1161/JAHA.113.000227.
- Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380:581–590.
- Chow BJ, Small G, Yam Y, Chen L, McPherson R, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng VY, Chinnaiyan K, Cury R, Delago A, Dunning A, Feuchtneger G, Hadamitzky M, Hausleiter J, Karlsberg RP, Kaufmann PA, Kim YJ, Leipsic J, LaBounty T, Lin F, Maffei E, Raff GL, Shaw LJ, Villines TC, Min JK. Prognostic and therapeutic implications of statin and aspirin therapy in individuals with nonobstructive coronary artery disease: results from the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: an International Multicenter Registry) Registry. *Arterioscler Thromb Vasc Biol*. 2015;35:981–989.
- Sipahi I, Nicholls SJ, Tuzcu EM, Nissen SE. Coronary atherosclerosis can regress with very intensive statin therapy. *Cleve Clin J Med*. 2006;73:937–944.
- Yang J, Li LJ, Wang K, He YC, Sheng YC, Xu L, Huang XH, Guo F, Zheng QS. Race differences: modeling the pharmacodynamics of rosuvastatin in Western and Asian hypercholesterolemia patients. *Acta Pharmacol Sin*. 2011;32:116–125.
- Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2889–2934.
- Itoh T, Mizuno Y, Harada E, Yoshimura M, Ogawa H, Yasue H. Coronary spasm is associated with chronic low-grade inflammation. *Circ J*. 2007;71:1074–1078.
- Yasue H, Kugiyama K. Coronary spasm: clinical features and pathogenesis. *Intern Med*. 1997;36:760–765.
- Abe K, Nakayama M, Yoshimura M, Nakamura S, Ito T, Yamamoto M, Sakamoto T, Miyamoto Y, Yoshimasa Y, Saito Y, Nakao K, Yasue H, Ogawa H. Increase in the transcriptional activity of the endothelial nitric oxide synthase gene with fluvastatin: a relation with the -787T>C polymorphism. *Pharmacogenet Genomics*. 2005;15:329–336.
- Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med*. 2005;352:20–28.
- Shimokawa H, Takeshita A. Rho-kinase is an important therapeutic target in cardiovascular medicine. *Arterioscler Thromb Vasc Biol*. 2005;25:1767–1775.
- Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arterioscler Thromb Vasc Biol*. 2001;21:1712–1719.
- Rikitake Y, Liao JK. Rho GTPases, statins, and nitric oxide. *Circ Res*. 2005;97:1232–1235.