ORIGINAL RESEARCH

Impact of Renin-Angiotensin System Inhibitors on Long-Term Clinical Outcomes of Patients With Coronary Artery Spasm

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***Background*—**Coronary artery spasm (CAS) is a well-known endothelial dysfunction, and a major cause of vasospastic angina (VSA). The renin–angiotensin system (RAS) is known to be closely associated with endothelial function. However, there are only a few studies that investigated the impact of RAS inhibitor on long-term clinical outcomes in VSA patients.

***Methods and Results*—**A total of 3349 patients with no significant coronary artery disease, diagnosed with CAS by acetylcholine provocation test were enrolled for this study. Significant CAS was defined as having ≥70% narrowing of the artery after incremental injections of 20, 50, and 100 μg of acetylcholine into the left coronary artery. Patients were divided into 2 groups according to whether the prescription included RAS inhibitor or not (RAS inhibitor group: n=666, non-RAS inhibitor group; n=2683). To adjust for any potential confounders that could cause bias, propensity score matching (PSM) analysis was performed using a logistic regression model. After PSM analysis, 2 matched groups (524 pairs, n=1048 patients, C-statistic=0.845) were generated and their baseline characteristics were balanced. During the 5-year clinical follow-up, the RAS inhibitor group showed a lower incidence of recurrent angina (8.7% versus 14.1%, *P*=0.027), total death (0.0% versus 1.3%, *P*=0.045), and total major adverse cardiovascular events (1.0% versus 4.1%, *P*=0.026) than the non-RAS inhibitor group.

***Conclusions*—**Chronic RAS inhibitor therapy was associated with lower incidence of cardiovascular events in VSA patients in the 5-year clinical follow-up. **(*J Am Heart Assoc*.2016;5:e003217 doi: 10.1161/JAHA.116.003217)**

Key Words: acetylcholine • angina • angiotensin converting enzyme inhibitor • angiotensin receptor blocker • coronary artery spasm • renin–angiotensin system • vasospasm

Coronary artery spasm (CAS) is a well-known endothelial dysfunction, and a major cause of vasospastic angina (VSA).[1] Obstructive CAS could lead to myocardial infarction (MI), acute coronary syndrome (ACS), and even sudden cardiac death.[2–4] Recently, the prevalence of CAS, as documented with the acetylcholine (Ach) provocation test, was reported at a rate of 33.4% to 57.6% in Western countries (consisted mostly of whites), 54.7% for South Korea, and 40% to 79% for Japan in Asian countries.[5–7]

Calcium channel blockers (CCBs) and nitrates are primary medications in the management of VSA as they are known to be effective in reducing cardiovascular complications.[8] Despite the availability of these treatment options, persistent angina remains a challenging problem.[5,9] In addition, chronic use of nitrates may lead to problems in tolerance, and even further raise cardiovascular risks.[10,11] Therefore, renin–angiotensin system (RAS) inhibitors such as the angiotensin-converting enzyme inhibitor and angiotensin receptor blocker may be effective in treating CAS patients since RAS is known to be closely associated with endothelial function, and RAS inhibitors are known to improve endothelial dysfunctions in patients with hypertension.[12,13] However, the long-term efficacy of RAS inhibitors on CAS patients is not thoroughly assessed. Thus, we sought to evaluate the impact of RAS inhibitors on long-term clinical outcomes of CAS patients.

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Methods

The design of this registry has been introduced before.[5] In brief, it is a single-center, prospective, all-comer registry designed to reflect "real world" practice since 2004. Data were collected by a trained study-coordinator with a standardized case report form. Standardized definitions of all patient-related variables and clinical diagnoses were used. The participants or their legal guardians were given a thorough literal and verbal explanation of the study procedures before granting a written consent to participate in the study. Institutional Review Board of Korea University Guro Hospital approved all of the consenting procedures. The authors of this article have certified that the information contained herein is true and correct as reflected in the records of the Institutional Review Board (#KUGH10045). Korea University Guro Hospital Institutional Review Board specifically approved this entire study.

Those enrolled in this study, a total of 10 177 patients with typical or atypical chest pain, underwent coronary angiography (CAG) at the Cardiovascular Center of Korea University Guro Hospital, Seoul, South Korea between November 2004 and May 2014. Among these, 6430 patients with typical or atypical chest pain without significant coronary artery disease (defined as having a stenosis diameter of less than 70% on the quantitative coronary angiography) underwent the intracoronary Ach provocation test. Patients were excluded if they had any of the following conditions: coronary artery bypass graft, prior percutaneous coronary intervention, prior cerebrovascular disease, advanced heart failure (New York Heart Association class III or IV), or serum creatinine ≥2 mg/dL, because these conditions could be major causes for adverse cardiovascular events and could bias the results. Of total, 3349 CAS patients were enrolled for this study and divided into 2 groups based on whether they have been on RAS inhibitor therapy or not: The RAS inhibitor group (n=666) and non-RAS inhibitor group (n=2683) (Figure 1).

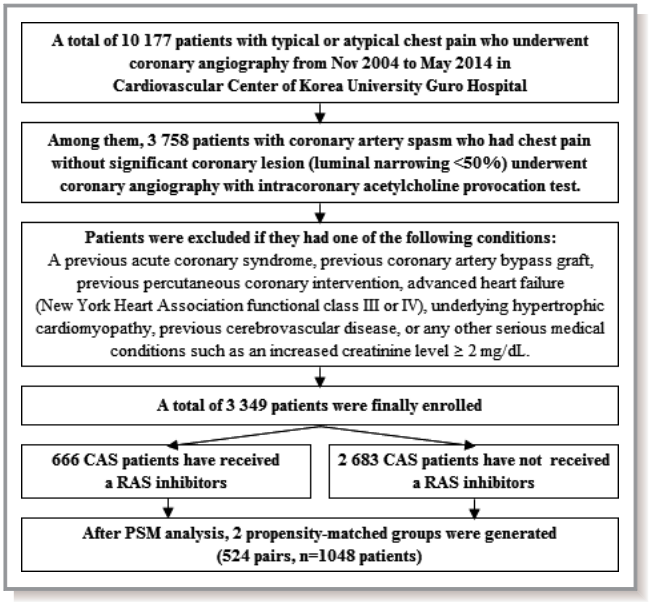

Figure 1. Flow chart. CAS, coronary artery spasm; PSM, propensity score matching; RAS, renin–angiotensin system.

Study Definition

Significant CAS was defined as greater than 70% of luminal narrowing of the artery during the Ach provocation test regardless of ischemic ECG changes or presence of chest pain. Deaths were regarded to be of cardiac cause unless a noncardiac death could be confirmed. Repeated CAG (mostly due to the recurrent angina)[5,9,14] was performed in patients who complained of recurrent angina despite adequate antianginal medication for at least 6 months since the onset of first CAS. In this case, the physician assumed that CAS may be progressed or there may be newly developing atherosclerotic coronary artery disease. Major adverse cardiovascular events (MACE) were defined as the composite of total death, recurrent MI, and revascularization including percutaneous coronary intervention and coronary artery bypass graft. Hypertension was diagnosed according to the history of hypertension and treatment with medications, diet, and/or exercises.

Ach Provocation Test

The design of the Ach provocation test has been introduced before.[5,14–17] An initial investigation for CAG included clinical history taking and noninvasive stress tests such as treadmill test, stress echocardiography, and radionuclide study. Then the CAG was performed to confirm the presence of significant coronary artery disease. However, CAG was immediately done without functional studies in case of typical resting ischemic chest pain to confirm VSA. Vasodilators or vasoconstrictors such as nitrates, CCBs, β-blockers, nicorandil, molsidomine, etc, were discontinued at least 72 hours before the CAG. CAS induction was tested by intracoronary injection of Ach immediately after a diagnostic angiography by either a transradial or transfemoral approach. Ach was injected by incremental doses of 20 (A1), 50 (A2), and 100 (A3) μg/min into the left coronary artery over a 1-minute period with 5-minute intervals up to the maximal tolerated dose under continuous monitoring by ECG and measuring blood pressure. Provocation of the right coronary artery was not done routinely due to safety issues, as the insertion of a temporary pacemaker is needed to prevent advanced atrioventricular block during Ach infusion. The angiography was repeated after each Ach dose until a significant focal or diffuse narrowing of greater than 70% was observed. If significant focal or diffuse vasoconstriction (>70%) of coronary arteries was induced at

any dose, Ach infusion was stopped. An intracoronary injection of 0.2 mg of nitroglycerine was administered after completing the Ach provocation test, followed by a CAG 2 minutes later. End-systolic images for each segment of the left coronary artery were chosen according to the corresponding points on the electrocardiographic trace (QRS onset or end of T wave) and analyzed using the proper quantitative coronary angiography system of the catheterization laboratory (FD-20; Phillips, Amsterdam, the Netherlands). The coronary artery diameters were measured by quantitative coronary angiography before and after the administration of Ach at the site that showed the greatest changes following drug administration. Reference vessel diameters were measured at the proximal and distal portions of each artery. The mean reference vessel diameter was used to assess diameter narrowing by quantitative coronary angiography. Myocardial bridge was defined as the characteristic phasic systolic compression of the coronary artery with a decrease of more than 30% in diameter on the angiogram after intracoronary nitroglycerin infusion, mostly in anterior–posterior cranial or right anterior oblique cranial projections. Multivessel spasm was defined as significant CAS of more than 2 major epicardial arteries. Diffuse CAS was defined as significant CAS with the site length of more than 30 mm. Spontaneous spasm was defined as focal or diffuse narrowing of greater than 30% in baseline CAG, compared to the reference vessel diameter after a nitroglycerin administration into the intracoronary route.

Statistical Analysis

For continuous variables, differences between the 2 groups were evaluated by unpaired *t*-test or Mann–Whitney rank test. Data were expressed as mean±SD. For discrete variables, differences were expressed as counts and percentages and analyzed with χ^2 or Fisher's exact test between the 2 groups. To adjust for any potential confounders, propensity score matching (PSM) analysis was performed using the logistic regression model. We tested all available variables that could be of potential relevance: age, sex, cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, current smokers, and current alcoholics), angiographic and clinical parameters (myocardial bridge, Ach dose [20, 50, and 100 μg/min], CAS site [left arterial descending, left circumflex], number of CAS vessels, CAS length, ECG change, chest pain, and atrioventricular block), and medical treatment (RAS inhibitors, CCBs, nitrate, trimetazidine, molsidomine, β-blockers, diuretics, aspirin, clopidogrel, cilostazol, warfarin, and statins). Matching was performed with the use of a 1:1 matching protocol without a replacement (nearest neighbor matching algorithm), with caliper width equal to 0.05 of the SD of the propensity score. Various clinical outcomes were estimated with the Kaplan–Meier method, and differences between the groups were compared with the log-rank test before and after PSM. Cox-proportional hazard models were used to assess the hazard ratio (HR) of the RAS inhibitor group compared with the non-RAS inhibitor group. For all analyses, a 2-sided $P<0.05$ was considered statistically significant. All data were processed with SPSS version 20.0 (SPSS-PC, Inc, Chicago, IL).

Study End Points

Primary end point was the incidence of total death, MI, de novo percutaneous coronary intervention, and MACE. Secondary end point was recurrent angina requiring repeat CAG. In this study, mean follow-up period was 1213±582 days (after PSM: 1217±589) and we followed up on the clinical data of all enrolled patients through face-to-face interviews at regular outpatient clinic, medical chart reviews, and telephone contacts.

Results

Baseline Clinical and Laboratory Characteristics

For this study, a total of 3349 CAS patients were enrolled, and among these 19.8% of patients fell into the RAS inhibitors group (Figure 1). Baseline clinical and laboratory characteristics are shown in Table 1. In the overall population, there was a considerable imbalance between the RAS inhibitor group and non-RAS inhibitor group in baseline clinical and angiographic characteristics such as sex, age, blood pressure, body mass index, left ventricular ejection fraction %, history of hypertension, diabetes mellitus, and dyslipidemia. After adjusting for baseline differences using PSM, the baseline clinical and laboratory characteristics of the 2 matched groups (524 pairs, n=1048 total) were balanced in all measured criteria (Table 1). Among these, 75.7% had a history of hypertension.

Ach Provocation Test Results

During the Ach provocation test, the incidence of CAS and angiographic and clinical characteristics was similar between the 2 groups after PSM analysis (Table 2). The use of RAS inhibitors did not have any impact on angiographic and clinical parameters during the Ach provocation test.

Medications for CAS

In the overall population, there was a considerable imbalance between the RAS inhibitor group and non-RAS inhibitor group, in medications such as calcium channel blockers, diltiazem, nitrate, trimetazidine, molsidomine, β-blockers, diuretics,

Table 1. Baseline Clinical Characteristics and Laboratory Findings

	Entire Patients			Matched Patients		
Variable, N (%)	RAS Inhibitor (N=666)	Non-RAS (N=2683)	*P* Value	RAS Inhibitor (N=524)	Non-RAS (N=524)	*P* Value
Sex (male)	379 (56.9)	1359 (50.6)	0.004	293 (55.9)	307 (58.5)	0.382
Age, y	59.4±10.6	55.9±11.6	<0.001	58.9±10.4	59.3±11.1	0.505
Blood pressure (BP)						
Systolic BP	140±21	132±19	<0.001	140±21	136±21	0.001
Diastolic BP	80±13	76±12	<0.001	81±12	78±12	<0.001
Body mass index	25.5±3.2	24.1±3.0	<0.001	25.5±3.2	24.8±3.0	<0.001
LVEF, %	58.1±5.4	59.2±3.3	<0.001	58.6±5.1	59.0±3.6	0.236
Risk factors						
Hypertension	533 (80.0)	956 (35.6)	<0.001	394 (75.1)	400 (76.3)	0.665
Diabetes mellitus	180 (27.0)	385 (14.3)	<0.001	125 (23.8)	120 (22.9)	0.715
New-onset diabetes mellitus	43 (6.4)	87 (3.2)	<0.001	24 (4.5)	32 (6.1)	0.272
Insulin	29 (4.3)	36 (1.3)	<0.001	18 (3.4)	16 (3.0)	0.727
Medication	112 (16.8)	242 (9.0)	<0.001	82 (15.6)	73 (13.9)	0.434
Dietary	11 (1.6)	33 (1.2)	0.392	11 (2.0)	7 (1.3)	0.342
Dyslipidemia	321 (48.1)	768 (28.6)	<0.001	228 (43.5)	245 (46.7)	0.291
Smokers	234 (35.1)	888 (33.0)	0.319	175 (33.3)	186 (35.4)	0.475
Current smokers	155 (23.2)	640 (23.8)	0.753	115 (21.9)	129 (24.6)	0.306
Alcohol drinkers	276 (41.4)	1021 (38.0)	0.108	211 (40.2)	218 (41.6)	0.660
Current drinkers	246 (36.9)	943 (35.1)	0.388	191 (36.4)	199 (37.9)	0.609
Laboratory findings						
Total cholesterol	175±39	180±37	0.012	177±38	178±43	0.671
HDL cholesterol	49±12	51±13	0.023	49±12	49±12	0.540
LDL cholesterol	110±34	113±33	0.067	112±34	111±38	0.666
Triglyceride	143±11	126±84	0.003	141±11	142±11	0.851
High-sensitivity CRP	3.1±9.2	2.7±10.7	0.588	2.7±7.5	3.3±11.9	0.506
Fasting blood glucose	107±26	101±21	<0.001	106±25	105±21	0.564
Hemoglobin A1c, %	6.3±1.0	5.9±0.7	<0.001	6.2±1.0	6.1±0.8	0.521
Insulin	10.8±12.0	10.0±6.7	0.430	9.7±6.0	11.5±7.6	0.101
Hemoglobin	13.6±1.5	13.5±1.5	0.305	13.7±1.5	13.6±1.6	0.548
Hematocrit	40.4±4.3	40.1±4.3	0.158	40.6±4.3	40.4±4.5	0.506
Creatinine	0.7±0.1	0.7±0.1	<0.001	0.7±0.1	0.7±0.1	0.589
Uric acid	5.2±1.4	4.8±1.4	<0.001	5.2±1.4	5.2±1.5	0.982

Data are presented as N (%) or mean±SD. CRP indicates C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; RAS, renin–angiotensin system.

aspirin, clopidogrel, cilostazol, warfarin, and statins. However, after a matched analysis, the medical treatments were balanced between the 2 groups (Table 3).

Clinical Outcomes

Figure 2 showed the incidence of individual and composite cumulative clinical outcomes. There was no difference between the RAS inhibitor group and non-RAS inhibitor group during the 5-year follow-up. However, after a matched analysis, major clinical end points such as the incidence of recurrent angina, total death, and MACE (composed of total death, myocardial infarction, and percutaneous coronary intervention) were significantly lower in the RAS inhibitor group compared with the non-RAS inhibitor group.

Table 2. Angiographic and Clinical Characteristics During Acetylcholine Provocation Test

	Entire Patients			Matched Patients		
Variable, N (%)	RAS Inhibitor (N=666)	Non-RAS (N=2683)	*P* Value	RAS Inhibitor (N=524)	Non-RAS (N=524)	*P* Value
Quantitative coronary angiography (QCA)						
MND, mm (during Ach Test)	0.7±0.3	0.7±0.3	0.802	0.7±0.3	0.6±0.3	0.217
MND, % (during Ach Test)	70.4±12.5	70.4±12.9	0.939	70.3±12.4	71.4±13.2	0.154
RD, mm (after NTG injection)	2.3±0.5	2.3±0.7	0.985	2.3±0.5	2.3±0.5	0.070
Ach dose						
A1 (20 μg)	35 (5.2)	150 (5.5)	0.747	27 (5.1)	37 (7.0)	0.200
A2 (50 μg)	249 (37.5)	944 (35.1)	0.265	191 (36.5)	187 (35.6)	0.779
A3 (100 μg)	380 (57.2)	1589 (59.2)	0.349	305 (58.3)	300 (57.2)	0.727
Spasm site						
Left anterior descending	617 (92.6)	2528 (94.2)	0.127	487 (92.9)	495 (94.4)	0.309
Left circumflex	268 (40.2)	1011 (37.6)	0.224	204 (38.9)	194 (37.0)	0.524
Spasm position						
Proximal to distal	256 (38.4)	1115 (41.5)	0.143	202 (38.5)	215 (41.0)	0.412
Mid to distal	299 (44.8)	1007 (37.5)	<0.001	231 (44.0)	216 (41.2)	0.349
Proximal only	33 (4.9)	210 (7.8)	0.011	29 (5.5)	27 (5.1)	0.784
Mid only	64 (9.6)	306 (11.4)	0.186	53 (10.1)	58 (11.0)	0.616
Distal only	14 (2.1)	45 (1.6)	0.456	9 (1.7)	8 (1.5)	0.807
Diffuse spasm	584 (87.6)	2298 (85.6)	0.174	458 (87.4)	463 (88.3)	0.636
Multivessel spasm	223 (33.4)	885 (32.9)	0.807	169 (32.2)	170 (32.4)	0.947
ECG change	42 (6.3)	169 (6.2)	0.994	36 (6.8)	32 (6.1)	0.616
ST-segment elevation	18 (2.7)	52 (1.9)	0.217	15 (2.8)	9 (1.7)	0.215
ST-segment depression	12 (1.8)	63 (2.3)	0.394	10 (1.9)	14 (2.6)	0.409
T-inversion	5 (0.7)	32 (1.1)	0.329	5 (0.9)	3 (0.5)	0.478
Atrial fibrillation	7 (1.0)	22 (0.8)	0.565	6 (1.1)	6 (1.1)	1.000
AV block	163 (24.4)	718 (26.7)	0.230	135 (25.7)	125 (23.8)	0.474
Chest pain	427 (64.1)	1740 (64.8)	0.721	344 (65.6)	335 (63.9)	0.561

Data are presented as N (%) or mean±SD. Ach indicates acetylcholine; AV, atrioventricular; MND, minimum narrowing diameter; NTG, nitroglycerin; RAS, renin–angiotensin system; RD, reference diameter.

Subgroup Analysis

To determine whether there is any difference in outcome among various subgroups during the 5-year follow-up, we calculated a propensity-score adjusted HR for total MACE and recurrent angina. Compared with the non-RAS inhibitor group, the RAS inhibitor group showed a significantly reduced risk for total MACE (HR: 0.406, 95% CI: 0.175–0.942) and recurrent angina (HR: 0.678, 95% CI: 0.465–0.988). Moreover, RAS inhibitor was associated with improved outcomes. Compared with the non-RAS inhibitor group, the RAS inhibitor group was associated with a significantly lower incidence of total MACE in subgroups: elderly (≥60), female, uncontrolled blood pressure, uncontrolled hypertension, diabetes mellitus, dyslipidemia, and co-medical treatment with CCBs (Figure 3). In addition, the RAS inhibitor group was associated with a significantly lower incidence of recurrent angina than the non-RAS inhibitor group in subgroups: elderly (≥60), female, uncontrolled blood pressure BP, multivessel spasm, and co-medical treatment with nitrates, diuretics, and nonaspirin medication (Figure 3).

Discussion

The main findings of this study are as follows: (1) Chronic RAS inhibitor therapy, as compared with non-RAS inhibitor therapy, was associated with lower incidence of cardiovascular events in VSA patients. (2) In terms of total MACE, RAS inhibitor was

Table 3. Medication Treatments for Coronary Artery Spasm

	Entire Patients			Matched Patients		
Variable, N (%)	RAS Inhibitor (N=666)	No-RAS (N=2683)	*P* Value	RAS Inhibitor (N=524)	No-RAS (N=524)	*P* Value
RAS inhibitors						
ARBs	550 (82.5)	0 (0.0)	<0.001	428 (81.6)	0 (0.0)	<0.001
ACE inhibitors	138 (20.7)	0 (0.0)	<0.001	116 (22.1)	0 (0.0)	<0.001
CCBs	543 (81.5)	2290 (85.3)	0.015	439 (83.7)	435 (83.0)	0.740
Diltiazem	511 (76.7)	2230 (83.1)	<0.001	415 (79.1)	416 (79.3)	0.939
Nitrate	487 (73.1)	1707 (63.6)	<0.001	372 (70.9)	377 (71.9)	0.732
Trimetazidine	375 (56.3)	1409 (52.5)	0.079	295 (56.2)	295 (56.2)	1.000
Molsidomine	52 (7.8)	196 (7.3)	0.658	37 (7.0)	41 (7.8)	0.638
β-blockers	125 (18.7)	182 (6.7)	<0.001	78 (14.8)	71 (13.5)	0.536
Diuretics	187 (28.0)	114 (4.2)	<0.001	93 (17.7)	77 (14.6)	0.180
Aspirin	252 (37.8)	292 (10.8)	<0.001	161 (30.7)	156 (29.7)	0.737
Statins	411 (61.7)	964 (35.9)	<0.001	299 (57.0)	318 (60.6)	0.233

Data are presented as N (%). ACE inhibitors indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; RAS, renin–angiotensin system.

effective in subgroups with relatively high-risk profiles such as elderly (≥60), female, uncontrolled blood pressure, uncontrolled hypertension, diabetes mellitus, dyslipidemia, and co-medical treatment with CCBs. (3) Also, in terms of recurrent angina requiring a follow-up CAG, RAS inhibitor was effective in subgroups with the following characteristic profiles: elderly (≥60), female, uncontrolled blood pressure, multivessel spasm, and co-medical treatment with nitrates, diuretics, and nonaspirin user.

As aforementioned, endothelial dysfunction is the well-known main mechanism of CAS.[1] The other mechanism of CAS is hyperreactivity of vascular smooth muscle cells.[18] The action of angiotensin II on smooth muscle cells produces contraction and also proliferation.[13] Therefore, RAS inhibitors such as angiotensin-converting enzyme inhibitor and angiotensin receptor blocker may be helpful to CAS patients since RAS is known to be closely associated with endothelial function, and RAS inhibitors are known to improve endothelial dysfunction in patients with hypertension.[12,13] However, the long-term effects of RAS inhibitors are not studied thoroughly enough for use in CAS patients yet. Thus, we sought to evaluate the impact of RAS inhibitors on long-term clinical outcomes in CAS patients as documented with the Ach provocation test.

Possible Mechanisms by Which RAS Inhibitors Render Favorable Effects on VSA Patients

Vascular endothelial cells express angiotensin-converting enzyme, which mediates a conversion of angiotensin I to angiotensin II. Then, angiotensin II decomposes peptides of kinin series such as bradykinin or kallidin, which has a vasodilating effect. In the vasculature, angiotensin II causes elevation of blood pressure, vasoconstriction, proliferation or migration of smooth muscle cells, inhibition of the activation of NO via increasing reactive oxygen species, etc.[13,19] Angiotensin receptor blocker may improve endothelial function by inhibiting the action of angiotensin II by blocking angiotensin II type I receptors at the endothelium. Also, angiotensin-converting enzyme inhibitors may improve endothelial function by interfering with the conversion of angiotensin I to angiotensin II.

Administration of these medications has been considered a mere symptomatic treatment thus far. However, the result of the present study shows that RAS inhibitor has preventive effects on total MACE and recurrent angina in VSA patients. Also, our study results provide clinical evidence that RAS inhibitor may be effective due to an association between RAS and endothelial function. Although CCBs could reduce major cardiovascular complications in VSA patients, persistent angina still remains a challenging problem.[5,9] Also, several studies reported that chronic nitrate therapy does not improve long-term prognosis of VSA patients when combined with CCBs.[10,11] It may lead to problems in tolerance, and even raise cardiovascular risks. Seo et al reported that despite combination therapy with CCBs and nitrates, which improved chest pain, the spasmodic nature of coronary arteries still remained.[20] In this situation, RAS blocker may provide an additional role in controlling significant CAS for improving longer-term clinical outcomes.

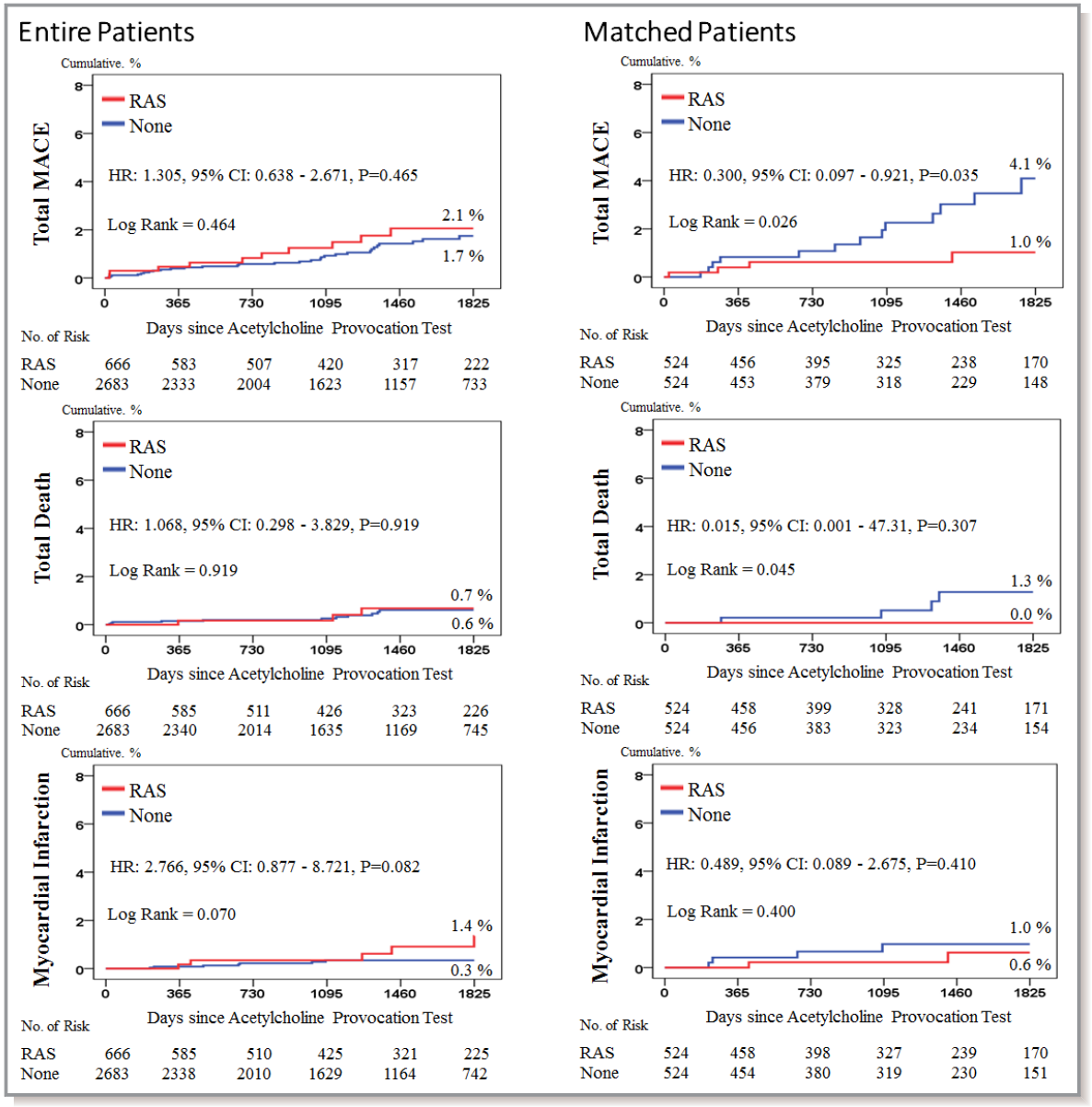

Figure 2. Cumulative survival curve of the various end points before and after propensity score matching. Figure shows the cumulative incidences of mortality, myocardial infarction, de novo percutaneous coronary intervention (PCI), recurrent angina, and the composite of death, myocardial infarction, or de novo PCI (MACE). The renin–angiotensin system (RAS) inhibitor group (indicated by red) received RAS inhibitors such as angiotensin receptor blockers (ARB) and angiotensin converting enzyme (ACE) inhibitors. The "none" group (indicated by blue) received no RAS inhibitors. HR indicates hazard ratio; MACE, major adverse cardiac events.

Clinical Outcomes in the Entire Population, Matched Population, and Subgroup

A total of 3349 CAS patients were enrolled in this study. Among these, 44.4% of patients received hypertensive medications, 19.8% received RAS inhibitors, and 84.5% received CCBs (the majority of which were diltiazem). Although the RAS inhibitor group exhibited worse clinical baseline characteristics than the non-RAS inhibitor group, there was no difference in clinical outcomes such as total MACE and recurrent angina during the 5-year follow-up. However, when analyzed with PSM analysis after balancing the baseline characteristics, the RAS inhibitor group showed a lower incidence of recurrent angina (8.7% versus 14.1%, *P*=0.027), total death (0.0% versus 1.3%, *P*=0.045), and total MACE (1.0% versus 4.1%, *P*=0.026) than the non-RAS inhibitor group (Figure 2). Interestingly, RAS inhibitor significantly reduced the risk of total MACE when combined with CCBs, as it did for the risk of recurrent angina when combined with nitrates (Figure 3).

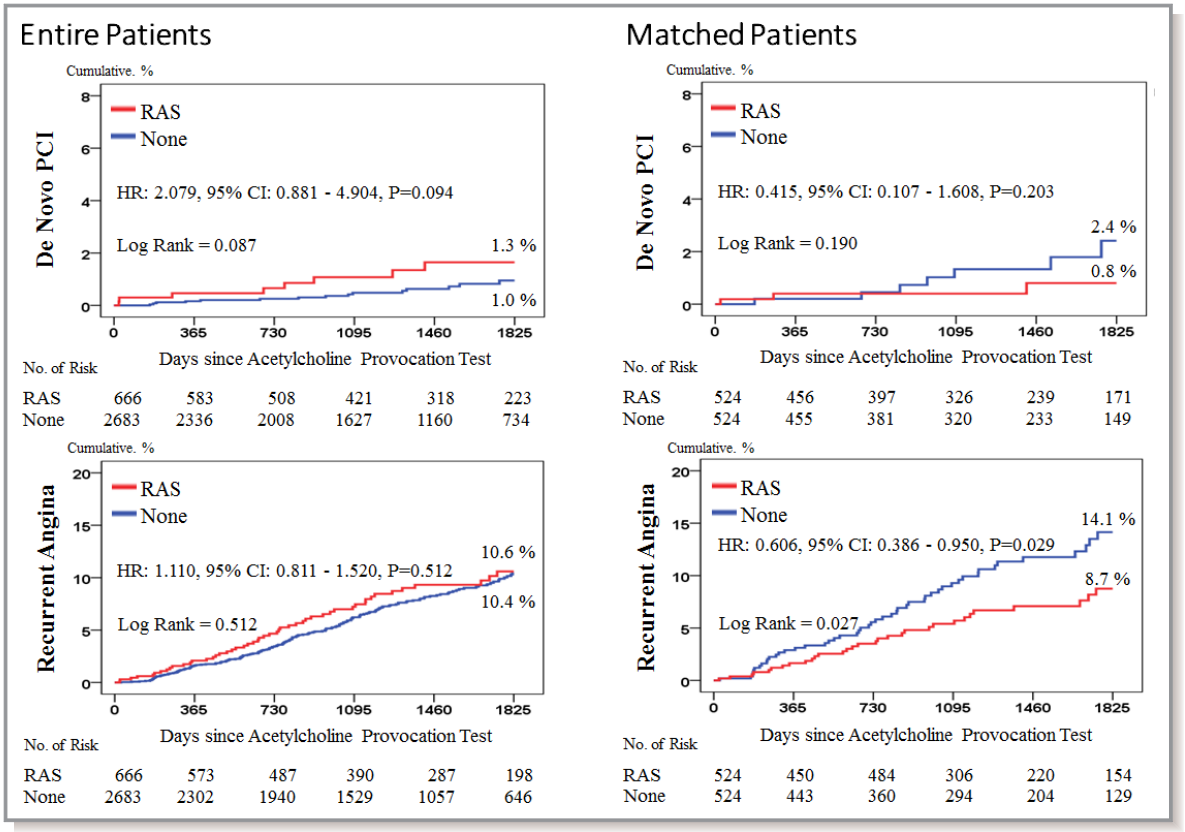

Figure 2. Continued.

Hypertension, diabetes mellitus, and dyslipidemia are well-known cardiovascular risk factors, and in CAS patients with such risk factors, RAS inhibitor may help to prevent cardiovascular events from occurring. In the present study, after PSM analysis (n=1048 total), among these patients, 75.7% had a history of hypertension. During the 5-year clinical follow-up, the use of RAS inhibitors significantly reduced the incidence of recurrent angina and total MACE in subgroups exhibiting uncontrolled blood pressure and uncontrolled hypertension. In a previous study by Chen et al, hypertension and uncontrolled blood pressure were negatively associated with CAS.[15] This effect may have been influenced by using RAS inhibitors for hypertension treatment. RAS inhibitors are known to potentially improve both endothelial function and insulin resistance and prevent a new onset of diabetes mellitus, as several studies have reported that RAS inhibitors improved endothelial function in patients with hypertension and type I diabetes mellitus.[12,19,21,22] Similarly, the present study showed that RAS inhibitors significantly reduced the incidence of total MACE during the long-term clinical follow-up of diabetic patients. In the series, RAS inhibitors significantly reduced the incidence of total MACE in dyslipidemia. Nickenig et al reported that hypercholesterolemic rabbits display enhanced vascular expression of angiotensin II type I receptors, which mediate an increased activity of angiotensin II.[23] RAS inhibitor may potentially have a beneficial effect on CAS patients with dyslipidemia.[20] In the present study, RAS inhibitors significantly reduced the incidence of recurrent angina and total MACE in female and elderly patients (≥60). Recently, Kawana et al reported that there is a sex-specific difference in characteristics and outcomes of VSA patients.[24] They showed that the prevalence of CAS was higher in men than women despite showing no difference in MACE during the 5-year follow-up, which suggests the importance of sex-specific management in VSA patients.

In this study, there were several limitations. First, the present study was analyzed retrospectively, and PSM analysis was performed to minimize the confounding factors that might influence the results otherwise. Also, the registry was designed with an all-comer prospective registry from 2004. However, we could not adjust for all the limiting factors not shown through medical records or collected through telephone contact. Second, the rate of (+) Ach provocation test was relatively higher due to relatively less strict diagnostic criteria, (which uses 70% narrowing cut-off value) as compared with other criteria such as subtotal or total occlusion by Ach provocation, particularly with A1 and A2 dose and visual assessment at the time of Ach provocation test for patient's safety. Third, only

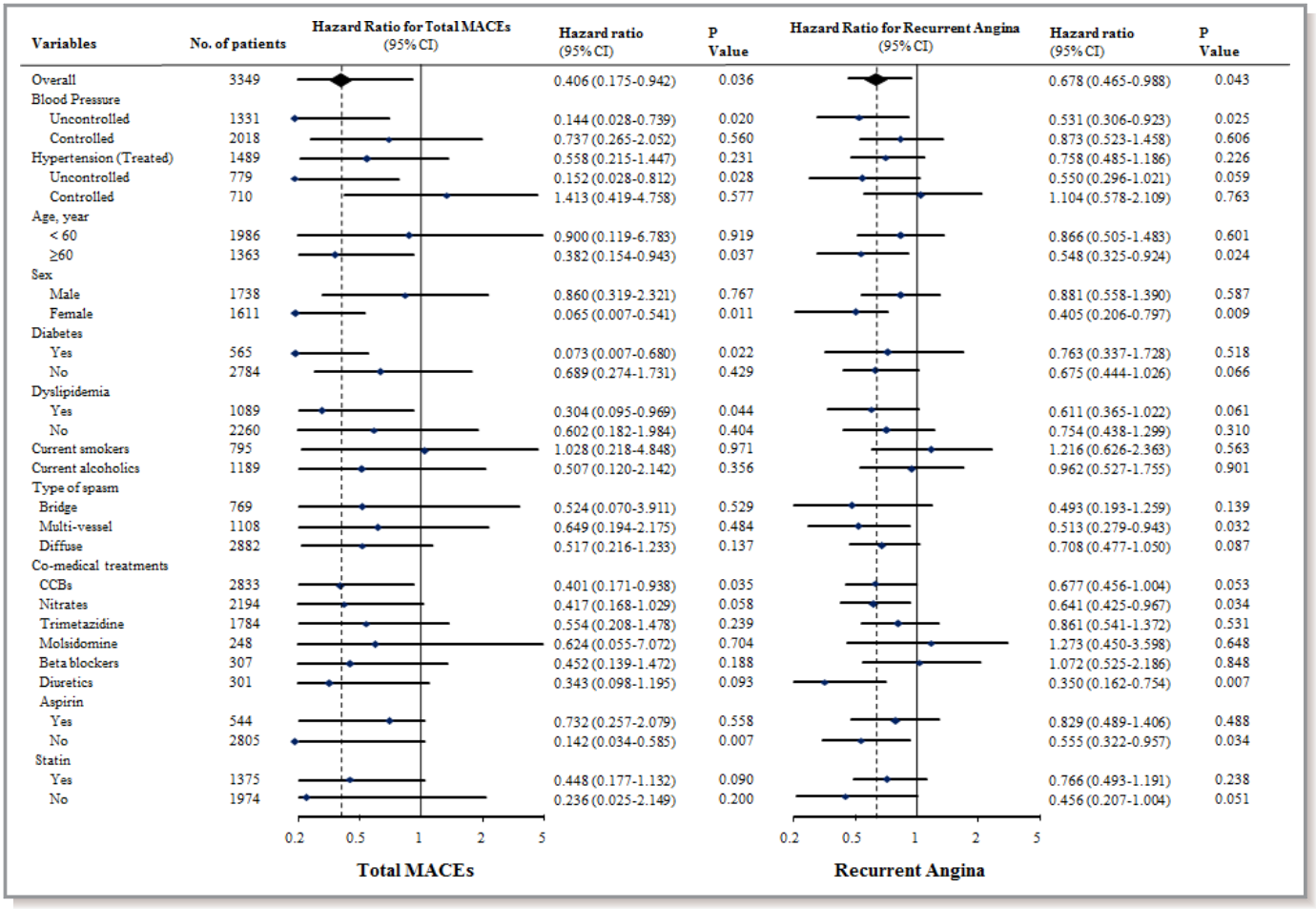

Figure 3. Comparative propensity-score adjusted hazard ratios of total MACE and recurrent angina for subgroups. Figure shows the risk of total MACE and recurrent angina in various subgroups. The RAS inhibitor group was compared with the non-RAS inhibitor group. Hazard ratio of the entire population was adjusted by a propensity score. Data are presented as hazard ratios and 95% CIs. CCBs indicates calcium channel blockers; MACE, major adverse cardiac events; RAS, renin–angiotensin system.

medication information attained through diagnosis was used. Although medication history is very important for a more detailed analysis, each patient's drug dosage, duration of prescription, and change of drugs were too complex to analyze. However, all patients received anti-anginal medications until free of angina symptoms and clinical remission. All the VSA patients were strongly recommended to maintain lower doses of anti-anginal medications for safety. Also, patients received different disease-modifying medications for hypertension, dyslipidemia, diabetes mellitus, and other risk factors according to their needs. Fourth, RAS inhibitor-type medications were prescribed at the discretion of individual clinicians for controlling either risk factors or CAS. Therefore, there might be a potential bias, although we did use PSM to adjust for any possible bias during medication selection.

In conclusion, the use of RAS inhibitor on CAS patients was associated with improved long-term clinical outcomes and reduced incidences of cardiovascular events in the 5-year follow-up. These findings suggest that the RAS inhibitor may play an important role in the long-term clinical treatment of CAS.

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Disclosures

None.

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