Original Article

Cardiovasc Prev Pharmacother 2022;4(1):26-33
eISSN 2671-700X
https://doi.org/10.36011/cpp.2022.4.e6

Cardiovascular Prevention and Pharmacotherapy

Safety and efficacy of low-dose aspirin in patients with coronary artery spasm: long-term clinical follow-up

Byoung Geol Choi[1], Kyung-Hee Kim[2], Seung-Woon Rha[1]

[1]*Department of Cardiology, Cardiovascular Center, Korea University Guro Hospital, Seoul, Korea*
[2]*Department of Cardiology, Cardiovascular Center, Incheon Sejong Hospital, Incheon, Korea*

Background: Aspirin is known to aggravate coronary artery spasm (CAS) regardless of the dose (100–325 mg/day). However, it is unclear whether low-dose aspirin (LDA; 100 mg) has deleterious impacts on the clinical course of CAS patients in the long-term. Thus, we investigated the impact of LDA on the long-term clinical outcomes of CAS patients.
Methods: A total of 5,697 consecutive patients without significant coronary artery disease who underwent an acetylcholine provocation test from November 2004 to May 2015 were enrolled. Of these patients, 3,072 CAS patients were enrolled in the study and divided into two groups based on whether they took LDA: the LDA group (n=338) and the non-LDA group (n=2,734). All CAS patients were prescribed anti-anginal medication as appropriate. To adjust for any potential confounders that could cause bias, a propensity score matching analysis was performed using a logistic regression model.
Results: After propensity score matching, two propensity-matched groups (524 pairs, 1,048 patients, C-statistic=0.827) were generated, and the baseline characteristics of the two groups were balanced. The two groups were showed no significant differences in any follow-up events, such as major adverse cardiac events and recurrent angina.
Conclusions: The main finding of the present study is that the use of LDA did not affect cardiovascular events up to 5 years in CAS patients. Therefore, the prescription of LDA in these patients should be individualized considering their clinical status.

Keywords: Coronary artery vasospasm; Aspirin; Acetylcholine

INTRODUCTION

Coronary artery spasm (CAS) is a well-known manifestation of endothelial dysfunction, and obstructive CAS in particular is a major cause of vasospastic angina and could also lead to ischemic heart disease and even sudden death [1–3]. CAS patients also have higher risks for comorbidities associated with cardiovascular disease, such as diabetes, dyslipidemia, and peripheral artery disease [3–9]. Low-dose aspirin (LDA; 100 mg/day) is a crucial drug for addressing various types of ischemic heart disease linked with atherosclerotic plaque, such as angina pectoris and acute coronary syndrome, in high-risk individuals. LDA treatment is also well-known for its ability to prevent cardiovascular events and

Received: January 7, 2022; **Revised:** January 13, 2022; **Accepted:** January 18, 2022
Correspondence to
Kyung-Hee Kim, MD, PhD
Department of Cardiology, Cardiovascular Center, Incheon Sejong Hospital, 20 Gyeyangmunhwa-ro, Gyeyang-gu, Incheon 21080, Korea.
E-mail: learnbyliving9@gmail.com

Seung-Woon Rha, MD, PhD
Department of Cardiology, Cardiovascular Center, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea.
E-mail: swrha617@yahoo.co.kr

strokes. Ironically, regardless of dose (100–325 mg/day), aspirin has been found to worsen CAS and has been occasionally contraindicated for usage in CAS patients [4,10]. Thus, the long-term clinical effects of LDA on CAS patients have not yet been well studied. In this study, we investigated the impact of LDA on the long-term clinical outcomes of CAS patients who received appropriate anti-anginal treatment.

METHODS

The design of this registry has been published before [4–8]. 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 using a standardized case report form. Standardized definitions of all patient-related variables and clinical diagnoses were used.

Ethical statement

The Institutional Review Board of Korea University Guro Hospital specifically approved this entire study and all the consent procedures (No. KUGH10045). The authors of this manuscript certify that the information contained herein is true and correct as reflected in the records of the Institutional Review Board.

Study population

A total of 10,177 consecutive patients with typical or atypical chest pain were enrolled between November 2004 and May 2015 and underwent coronary angiography (CAG) at the Cardiovascular Center of Korea University Guro Hospital, Seoul, Republic of Korea. Among these, 6,430 patients with typical or atypical chest pain without significant coronary artery disease (defined as a stenosis diameter of less than 70% on quantitative coronary angiography) underwent an acetylcholine (ACH) provocation test. Ineligible patients were excluded, as presented in Fig. 1, if they had conditions that could be major causes of adverse cardiovascular events and could bias the results. In total, 3,072 CAS patients were enrolled in the study and divided into two groups based on whether they took LDA: the LDA group (n=338) and non-LDA group (n=2,734) (Fig. 1).

Study definition

Significant CAS was defined as having more than 70% of luminal narrowing of the artery during the ACH provocation test regardless of the presence of ischemic changes on electrocardiography (ECG) changes or chest pain. Deaths were regarded as being of cardiac causes unless a noncardiac death could be confirmed. Repeated CAG (mostly due to recurrent angina) was performed in patients who complained of recurrent angina despite having received adequate anti-anginal medication for at least 6 months since the onset of first CAG. In these cases, the physician assumed that CAS may have progressed or there may have been newly developing atherosclerotic coronary artery disease [5]. Major adverse cardiovascular events (MACE) were defined as the

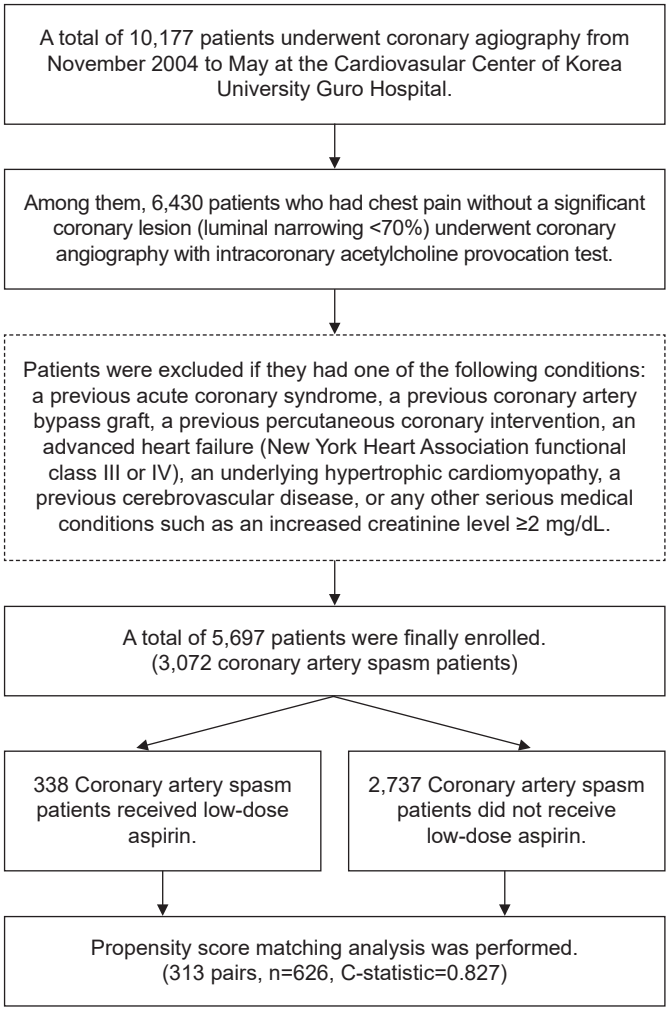

Fig. 1. Flowchart of the study population.

composite of total death, myocardial infarction (MI), and revascularization (including percutaneous coronary intervention [PCI] and coronary artery bypass graft [CABG]) [11]. Major adverse cardiovascular and cerebrovascular events (MACCE) 1 were defined as the composite of MACE and stroke events [11]. MACCE 2 were defined as the composite of MACCE 1 and recurrent angina.

ACH provocation test

The design of the ACH test has been described before [4–8]. In brief, CAS induction was tested by an intracoronary injection of ACH immediately after 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 maximum tolerated dose under continuous monitoring by ECG and measurements of blood pressure. Routine provocation tests of the right coronary artery were not done due to safety issues regarding the higher prevalence of advanced atrioventricular block, which needs a temporary pacemaker for maintaining an adequate ACH infusion rate and cost-effectiveness for the diagnosis and management of significant CAS. Angiography was repeated after each ACH dose until a significant focal or diffuse narrowing of more than 70% was observed. An intracoronary injection of 0.2 mg of nitroglycerine was administered after completing the ACH provocation test, followed by CAG 2 minutes later. If significant focal or diffuse vasoconstriction (>70%) of the coronary arteries was induced at any dose, the ACH infusion was stopped. End-systolic images for each segment of the left coronary artery were chosen according to the corresponding points on the ECG trace (QRS onset or end of T wave) and analyzed using the quantitative coronary arteriography system of the catheterization laboratory (FD-20; Phillips, Amsterdam, Netherlands).

Statistical analysis

For continuous variables, differences between the two groups were evaluated by the unpaired t-test or Mann-Whitney rank test. Data were expressed as mean±standard deviation. For discrete variables, differences between the two groups were expressed as counts and percentages and analyzed with the chi-square or Fisher exact test. To adjust for any potential confounders, propensity score matching (PSM) was performed using a logistic regression model. We tested all available variables that could be of potential relevance: age, sex, cardiovascular risk factors (hypertension, diabetes, dyslipidemia, current smokers, and current alcohol drinkers), 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 changes, chest pain, and atrioventricular block), and medical treatment (renin-angiotensin system inhibitors, calcium channel blockers, diltiazem, nitrate, trimetazidine, molsidomine, beta-blockers, diuretics, aspirin, and statins). The propensity score was estimated using the C-statistic in the logistic regression model, and the propensity score for the two groups was 0.827. Matching was performed using a 1:1 matching protocol without replacements (nearest neighbor matching algorithm), with a caliper width equal to 0.05 of the standard deviation of the logit 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. A proportional-hazard model was used to assess the hazard ratio of the LDA group compared with the non-LDA group in the PSM population. For all analyses, a two-sided $P<0.05$ was considered to indicate statistical significance. All data were processed with IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA).

Medications

After diagnosis, CAS patients were prescribed anti-anginal medication such as nitrate, calcium channel blockers (including diltiazem), and/or nicorandil for at least 6 months depending on the physician's discretion.

Study endpoints

The primary endpoint was the cumulative incidence of major clinical endpoints such as various composite events of total death, MI, PCI, CABG, stroke, and repeat CAG. The secondary endpoint was recurrent angina. In this study, the mean follow-up period was 1,216±597 days (after PSM, 1,318±561 days), and we could follow up the clinical data of all enrolled patients through face-to-face interviews at regular outpatient clinic visits, medical chart reviews, and

telephone contacts.

RESULTS

Baseline clinical and angiographic characteristics

In this study, a total of 3,072 CAS patients were enrolled, among whom 11.0% received LDA (Fig. 1). The patients' baseline clinical characteristics are shown in Table 1, and their angiographic characteristics are presented in Table 2. In the overall population, there was a considerable imbalance between the LDA group and non-LDA group in baseline clinical characteristics such as sex, age, body mass index, left ventricular ejection fraction, and history of hypertension, diabetes, and dyslipidemia. However, there were no significant differences between both groups in angiographic characteristics. After a matched analysis, the baseline clinical and angiographic characteristics of the two PSM groups (313 pairs, n=626 total) were balanced in all measured criteria (Tables 1, 2).

Medication treatment for CAS

In the overall population, there was a considerable imbalance between the LDA and non-LDA groups in the use of medications such as calcium channel blockers, beta-blockers, diuretics, renin-angiotensin-aldosterone system inhibitors (e.g., angiotensin receptor blockers or angiotensin-converting enzyme inhibitors), and statins. However, in the matched analysis, the medical treatments were balanced between the two groups (Table 3).

Clinical outcomes

In the 5-year clinical follow-up of the entire population, in comparison with the non-LDA group, the LDA group showed significantly higher rates of MACCE1, MACCE2, and recurrent angina. However, after PSM analysis to adjust for baseline confounders, the two groups were undifferentiated regarding all follow-up events (Fig. 2). Multiple Cox-regression analysis after PSM showed that LDA use did not affect any follow-up events (Table 4).

DISCUSSION

The use of LDA has recently increased to prevent secondary heart attacks and strokes in high-risk patients [12–14]. A large amount of aspirin aggravates CAS, but it is not well-known whether the use of LDA in CAS patients has an adverse impact on severe CAS and long-term clinical out-

Table 1. Baseline clinical characteristics and laboratory findings

Variable	All patients			Matched patients		
	LDA (n=338)	Non-LDA (n=2,734)	P-value	LDA (n=313)	Non-LDA (n=313)	P-value
Male sex	197 (58.2)	1,345 (49.1)	0.002	178 (56.8)	166 (53.0)	0.335
Age (yr)	61.1±10.0	55.3±11.5	<0.001	60.8±10.1	61.7±9.89	0.315
Body mass index (kg/m^2)	24.8±3.1	24.3±3.1	0.008	24.7±3.1	24.6±3.0	0.752
LVEF (%)	58.1±6.1	59.2±2.9	0.008	58.2±5.9	59.1±3.3	0.087
History of risk factors						
Hypertension	193 (57.1)	1,109 (40.5)	<0.001	179 (57.1)	188 (60.0)	0.465
Diabetes	102 (30.1)	380 (13.8)	<0.001	85 (27.1)	85 (27.1)	NS
New-onset diabetes	16 (4.7)	104 (3.8)	0.405	15 (4.7)	10 (3.1)	0.307
Insulin	19 (5.6)	28 (1.0)	<0.001	10 (3.1)	13 (4.1)	0.524
Medication	72 (21.3)	222 (8.1)	<0.001	59 (18.8)	63 (20.1)	0.687
Dietary	6 (1.7)	34 (1.2)	0.416	6 (1.9)	5 (1.5)	0.761
Dyslipidemia	140 (41.4)	777 (28.4)	<0.001	127 (40.5)	139 (44.4)	0.332
History of smoking	122 (36.0)	852 (31.1)	0.066	112 (35.7)	104 (33.2)	0.501
Current smokers	78 (23.0)	616 (22.5)	0.821	74 (23.6)	70 (22.3)	0.704
History of alcohol drinking	123 (36.3)	1,053 (38.5)	0.448	113 (36.1)	112 (35.7)	0.934
Current alcohol drinkers	107 (31.6)	979 (35.8)	0.132	100 (31.9)	101 (32.2)	0.932

Values are presented as number (%) or mean±standard deviation.
LDA, low-dose aspirin; LVEF, left ventricular ejection fraction; NS, not significant.

Table 2. Angiographic and clinical outcomes of acetylcholine provocation tests

Variable	All patients			Matched patients		
	LDA (n=338)	Non-LDA (n=2,734)	P-value	LDA (n=313)	Non-LDA (n=313)	P-value
Quantitative coronary angiography						
MND (mm, during ACH test)	0.69±0.36	0.70±0.35	0.491	0.69±0.37	0.71±0.37	0.491
MND (%, during ACH test)	71.1±13.2	70.3±12.7	0.333	71.3±13.4	70.4±13.3	0.447
RD (mm, after NTG injection)	2.39±0.55	2.41±0.72	0.751	2.40±0.55	2.37±0.58	0.569
Acetylcholine dose						
A1 (20 μg)	15 (4.4)	135 (4.9)	0.684	13 (4.1)	22 (7.0)	0.115
A2 (50 μg)	125 (36.9)	933 (34.1)	0.304	116 (37.0)	110 (35.2)	0.639
A3 (100 μg)	198 (58.5)	1,663 (60.8)	0.411	184 (58.7)	180 (57.6)	0.782
Spasm site						
Left main	0	7 (0.2)	0.352	0	1 (0.3)	0.317
Left anterior descending	318 (94.0)	2,562 (93.7)	0.789	295 (94.2)	296 (94.5)	0.862
Left circumflex	137 (40.5)	1,023 (37.4)	0.265	126 (40.2)	125 (39.9)	0.935
Location						
Proximal	150 (44.3)	1,344 (49.1)	0.097	142 (45.3)	138 (44.0)	0.748
Mid	314 (92.8)	2,470 (90.3)	0.128	290 (92.6)	289 (92.3)	0.879
Distal	275 (81.3)	2,215 (81.0)	0.879	255 (81.4)	257 (82.1)	0.836
Diffuse spasm	290 (85.7)	2,343 (85.6)	0.960	269 (85.9)	269 (85.9)	NS
Multivessel spasm	118 (34.9)	889 (32.5)	0.376	109 (34.8)	112 (35.7)	0.802
ECG change	25 (7.3)	171 (6.2)	0.418	23 (7.3)	19 (6.0)	0.523
ST-segment elevation	10 (2.9)	59 (2.1)	0.349	8 (2.5)	6 (1.9)	0.589
ST-segment depression	10 (2.9)	57 (2.0)	0.300	10 (3.1)	8 (2.5)	0.632
T-inversion	2 (0.5)	33 (1.2)	0.315	2 (0.6)	4 (1.2)	0.412
Atrial fibrillation	3 (0.8)	22 (0.8)	0.873	3 (0.9)	1 (0.3)	0.316
AV block	90 (26.6)	700 (25.6)	0.685	82 (26.1)	77 (24.6)	0.646
Cough	84 (24.8)	648 (23.7)	0.640	76 (24.2)	70 (22.3)	0.571
Pacing	6 (1.7)	52 (1.9)	0.872	6 (1.9)	7 (2.2)	0.779
Chest pain	211 (62.4)	1,803 (65.9)	0.199	198 (63.2)	189 (60.3)	0.459

Values are presented as mean±standard deviation or number (%).
LDA, low-dose aspirin; MND, minimum narrowing diameter; ACH, acetylcholine; RD, reference diameter; NTG, nitroglycerin; NS, not significant; ECG, electrocardiography; AV, atrioventricular.

Table 3. Medication treatments for coronary artery spasm

Variable	All patients			Matched patients		
	LDA (n=338)	Non-LDA (n=2,734)	P-value	LDA (n=313)	Non-LDA (n=313)	P-value
CCB	274 (81.0)	2,365 (86.5)	0.007	257 (82.1)	263 (84.0)	0.523
Diltiazem	253 (74.8)	2,313 (84.6)	<0.001	239 (76.3)	252 (80.5)	0.206
Nitrate	229 (67.7)	1,772 (64.8)	0.285	210 (67.0)	207 (66.1)	0.799
Trimetazidine	179 (52.9)	1,462 (53.4)	0.858	167 (53.3)	172 (54.9)	0.688
Nicorandil	20 (5.9)	204 (7.4)	0.303	19 (6.0)	23 (7.3)	0.523
Molsidomine	117 (34.6)	838 (30.6)	0.137	104 (33.2)	108 (34.5)	0.736
Beta-blockers	52 (15.3)	161 (5.8)	<0.001	45 (14.3)	46 (14.6)	0.910
Diuretics	70 (20.7)	187 (6.8)	<0.001	59 (18.8)	74 (23.6)	0.143
RAS inhibitors						
ARB	108 (31.9)	338 (12.3)	<0.001	93 (29.7)	95 (30.3)	0.862
ACE inhibitor	37 (10.9)	63 (2.3)	<0.001	31 (9.9)	28 (8.9)	0.682
Statins	223 (65.9)	920 (33.6)	<0.001	200 (63.8)	211 (67.4)	0.355

Values are presented as number (%).
LDA, low-dose aspirin; CCB, calcium channel blockers; RAS, renin-angiotensin system; ARB, angiotensin receptor blockers; ACE inhibitors, angiotensin-converting enzyme inhibitors.

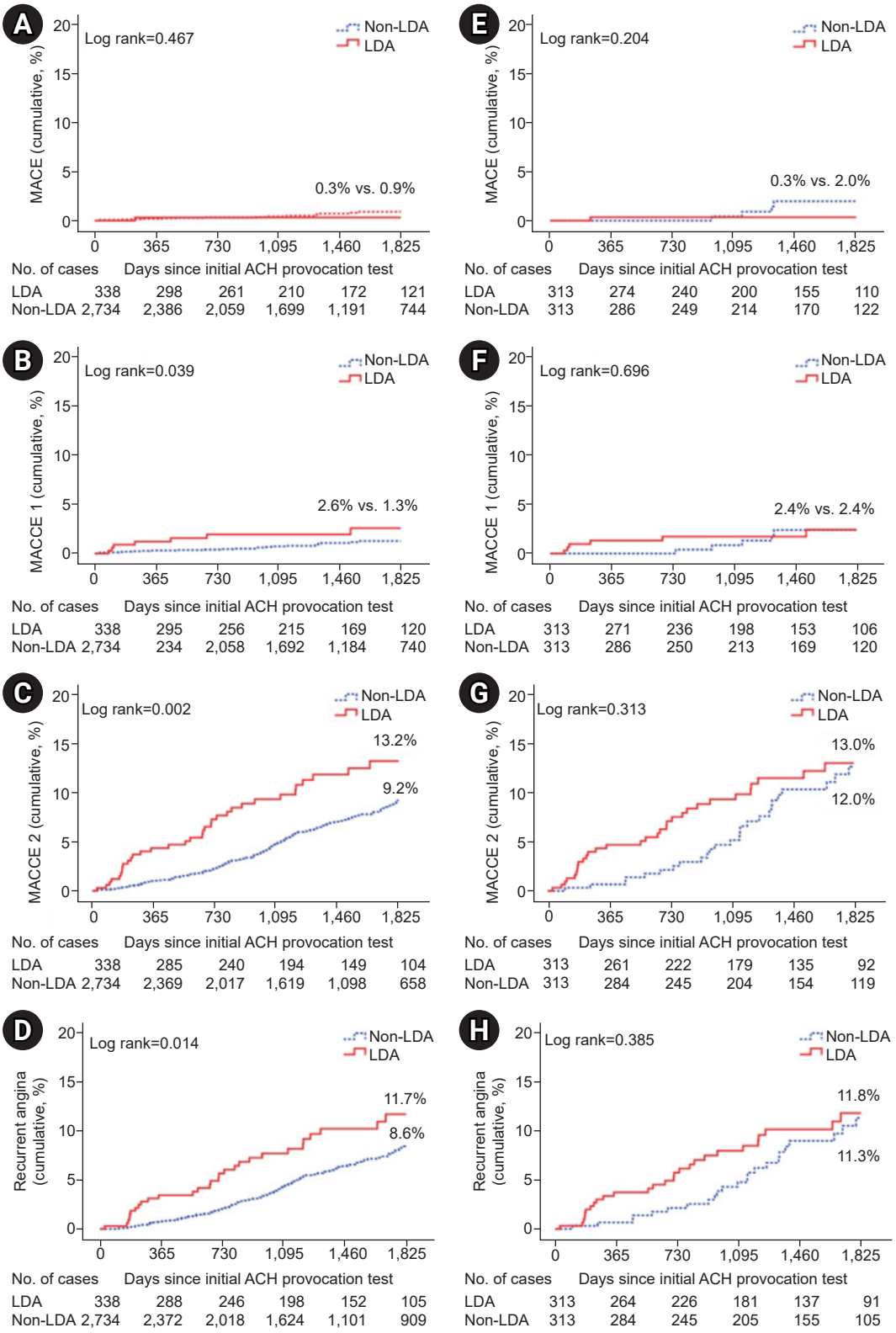

Fig. 2. Kaplan-Meier survival curves: cumulative incidence of various cardiovascular events. Entire patients (A) major adverse cardiac events (MACE), (B) major adverse cardiovascular and cerebrovascular events (MACCE) 1, (C) MACCE 2, (D) recurrent angina. Matched patients (E) MACE, (F) MACCE 1, (G) MACCE 2, (H) recurrent angina. ACH, acetylcholine; LDA, low-dose aspirin.

Table 4. Hazard ratios of low-dose aspirin treatment on various endpoints

Variable	Hazard ratio (95% confidence interval)	P-value
Recurrent angina	1.319 (0.750–2.320)	0.336
MACE	0.294 (0.032–2.696)	0.280
MACCE 1	1.404 (0.423–4.659)	0.579
MACCE 2	1.332 (0.786–2.257)	0.286

MACE, major adverse cardiac events; MACCE, major adverse cardiovascular and cerebrovascular events.

comes. In a previous study, we evaluated all-comer patients who underwent an ACH provocation test. The patients taking LDA had more risk factors, including old age, diabetes mellitus, hypertension, and hyperlipidemia, and in the ACH provocation test, the patients taking LDA had higher incidence rates of ACH-induced CAS, severe and multivessel spasm, frequent ischemic symptoms, and a vulnerable response to lower doses of ACH [4]. However, in the present study, we analyzed only patients with CAS identified by an ACH provocation test. The prevalence of risk factors for atherosclerosis, including old age, diabetes mellitus, hypertension, and hyperlipidemia were higher in patients taking LDA. However, we performed PSM analysis to make the patients well balanced in their baseline clinical and angiographic characteristics. As a result, the proportion of patients with multivessel and diffuse spasm accompanying CAS was not significantly different between the two groups of CAS patients, and the use of LDA did not affect cardiovascular events up to 5 years in CAS patients. Therefore, we interpret these results as suggesting that in patients who are diagnosed with CAS by an ACH provocation test, there is no need for hesitation or discontinuation of LDA use.

In this study, there were several limitations. First, the present study analyzed patients' data retrospectively and PSM analysis was performed to minimize the confounding factors, which might have influenced the results otherwise. Furthermore, although the registry was designed as an all-comer prospective registry from 2004, we could not adjust for all the limiting factors not contained in medical records or collected through telephone interviews. Second, only medication information from after the diagnosis was used. Although medication history is very important for a further detailed analysis, each patient's drug dosage, duration of prescription, and changes of drugs were too complex to analyze. However, all patients received anti-anginal treatment medication until they were free of angina symptoms and showed clinical remission. Moreover, all patients received disease-modifying medications for hypertension, dyslipidemia, diabetes, or other conditions depending on the physician's discretion during the follow-up period.

In conclusion, the use of LDA did not affect cardiovascular events for up to 5 years in CAS patients. Therefore, the prescription of LDA in these patients should be individualized with a careful consideration of patients' clinical status.

ARTICLE INFORMATION

Ethical statement

The Institutional Review Board of Korea University Guro Hospital specifically approved this entire study and all the consent procedures (No. KUGH10045). The authors of this manuscript certify that the information contained herein is true and correct as reflected in the records of the Institutional Review Board.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

None.

Author contributions

Conceptualization: BGC, KHK; Data curation: BGC, KHK; Formal analysis: BGC, KHK; Investigation: BGC, KHK; Methodology: SWR; Project administration: SWR; Supervision: SWR; Validation: SWR; Visualization: SWR; Writing–original draft: BGC; Writing–review & editing: KHK, SWR. All authors read and approved the final manuscript.

ORCID

Byoung Geol Choi, https://orcid.org/0000-0002-6090-869X
Kyung-Hee Kim, https://orcid.org/0000-0003-0708-8685
Seung-Woon Rha, https://orcid.org/0000-0001-9456-9852

REFERENCES

1. Picard F, Sayah N, Spagnoli V, Adjedj J, Varenne O. Vasospastic angina: a literature review of current evidence. Arch Cardiovasc Dis 2019;112:44–55.
2. Stern S, Bayes de Luna A. Coronary artery spasm: a 2009 update.

Circulation 2009;119:2531–4.
3. Yasue H, Nakagawa H, Itoh T, Harada E, Mizuno Y. Coronary artery spasm: clinical features, diagnosis, pathogenesis, and treatment. J Cardiol 2008;51:2–17.
4. Park JY, Rha SW, Poddar KL, Ramasamy S, Chen KY, Li YJ, et al. Impact of low-dose aspirin on coronary artery spasm as assessed by intracoronary acetylcholine provocation test in Korean patients. J Cardiol 2012;60:187–91.
5. Choi BG, Park SH, Rha SW, Park JY, Choi SY, Park Y, et al. Five-year clinical outcomes in patients with significant coronary artery spasm: a propensity score-matched analysis. Int J Cardiol 2015;184:533–9.
6. Chen KY, Rha SW, Li YJ, Poddar KL, Jin Z, Minami Y, et al. Peripheral arterial disease is associated with coronary artery spasm as assessed by an intracoronary acetylcholine provocation test. Clin Exp Pharmacol Physiol 2009;36:e78–82.
7. Chen KY, Rha SW, Li YJ, Poddar KL, Jin Z, Minami Y, et al. Impact of hypertension on coronary artery spasm as assessed with intracoronary acetylcholine provocation test. J Hum Hypertens 2010;24:77–85.
8. Li YJ, Hyun MH, Rha SW, Chen KY, Jin Z, Dang Q, et al. Diabetes mellitus is not a risk factor for coronary artery spasm as assessed by an intracoronary acetylcholine provocation test: angiographic and clinical characteristics of 986 patients. J Invasive Cardiol 2014;26:234–9.
9. Mishra PK. Variations in presentation and various options in management of variant angina. Eur J Cardiothorac Surg 2006;29:748–59.
10. Miwa K, Kambara H, Kawai C. Effect of aspirin in large doses on attacks of variant angina. Am Heart J 1983;105:351–5.
11. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
12. Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005;353:2373–83.
13. Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. Arch Intern Med 2002;162:2197–202.
14. Berger JS, Brown DL, Becker RC. Low-dose aspirin in patients with stable cardiovascular disease: a meta-analysis. Am J Med 2008;121:43–9.