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Authors

Seo, Woo-Keun
Kim, Jae-Young
Choi, Eun-Hyeok
et al.

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ORIGINAL RESEARCH

Association of Antiplatelet Therapy, Including Cilostazol, With Improved Survival in Patients With Moyamoya Disease in a Nationwide Study

Woo-Keun Seo, MD, PhD*; Jae-Young Kim, MSc*; Eun-Hyeok Choi, MD; Ye-Sel Kim, MD; Jong-Won Chung, MD, PhD; Jeffrey L. Saver, MD; Oh Young Bang, MD, PhD; Gyeong-Moon Kim, MD, PhD

BACKGROUND: Although antiplatelet agents are frequently prescribed in moyamoya disease in routine clinical practice, there are no large-scale epidemiologic trials or randomized trial evidence to support their use in patients with moyamoya disease.

METHODS AND RESULTS: Using the Korean National Health Insurance Service database, patients diagnosed with moyamoya disease between 2002 and 2016 were followed up for up to 14 years to assess, using time-dependent Cox regression in all patients and in a propensity score–matched cohort, the association of antiplatelet therapy and individual antiplatelet agents with survival. Among 25 978 patients with newly diagnosed moyamoya disease, mean age was 37.6±19.9 years, 61.6% were women, and total follow-up was 163 347 person-years. Among 9154 patients who were prescribed antiplatelet agents at least once during the follow-up period, the proportion prescribed cilostazol gradually increased from 5.5% in 2002 to 56.0% in 2016. Any antiplatelet use was associated with reduced risk of death (hazard ratio, 0.77; 95% CI, 0.70–0.84) in a multivariate model. Among individual antiplatelet agents, cilostazol was associated with greater reduction in mortality than the 5 other antiplatelet regimens. Subgroup analysis, according to the age group and history of ischemic stroke, and sensitivity analysis, using propensity score–matched analysis, revealed consistent results.

CONCLUSIONS: Antiplatelet therapy is associated with substantial improvement in survival in patients with moyamoya disease, and cilostazol is associated with greater survival benefit compared with other antiplatelet regimens. These results provisionally support the use of antiplatelet therapy in patients with moyamoya disease and the conduct of confirmatory randomized controlled trials.

Key Words: antiplatelet agent ■ cilostazol ■ moyamoya disease ■ stroke ■ survival

Moyamoya disease, an idiopathic intracranial arterial disease characterized by progressive stenosis of the distal internal carotid artery and additional basal cerebral arteries, with development of a hazy network of small collaterals, has limited treatment options to prevent stroke or inhibit the progression of disease. Presently, cerebral revascularization surgery is selectively performed in patients with ischemic symptoms and is considered the only recommended treatment, with moderate evidential support.[1] Current guidelines also recommend the administration of antiplatelet agents in patients with moyamoya disease to prevent ischemic events,[1] but recognize that supportive evidence is weak, resting on some observational

Correspondence to: Woo-Keun Seo, MD, PhD, Department of Neurology and Stroke Center, Samsung Medical Center, and Department of Digital Health, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, 81 Irwon-dong, Gangnam-gu, Seoul 135-710, South Korea. E-mail: mcastenosis@gmail.com

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†Dr Seo and J.-Y. Kim contributed equally to this work as co–first authors.

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CLINICAL PERSPECTIVE

What Is New?

- Use of antiplatelet agents in patients with moyamoya disease reduced the risk of death by 23% in this study of the Korean National Health Insurance Service database.
- Among the antiplatelet agents, cilostazol uniquely reduced mortality, irrespective of previous stroke history or age.

What Are the Clinical Implications?

- This study provides support for the guideline recommendation for the use of antiplatelet agents in moyamoya disease.
- For the selection of an antiplatelet agent, this study supports the use of cilostazol as the primary antiplatelet agent, irrespective of the previous stroke history and age group.

Nonstandard Abbreviations and Acronyms

NHIS	National Health Insurance Service

studies of modest size but not on large-scale observational evidence or randomized clinical trials.[2,3]

Cilostazol is a phosphodiesterase 3 inhibitor with antiplatelet, antithrombotic, and vasodilatory properties, whose efficacy and safety has been investigated in patients with ischemic stroke.[4–6] Phosphodiesterase inhibitors, compared with other antiplatelet agents, have 2 potentially advantageous properties for moyamoya disease: (1) less risk of intracranial bleeding[6] and (2) vasodilatory effects that could augment collateral flow. Accordingly, the potential usefulness of cilostazol in moyamoya disease has been suggested repeatedly.[7–9] However, there has been no large-scale study of the effect of cilostazol and other specific antiplatelet agents on clinical outcome in moyamoya disease. Therefore, we investigated the effect of antiplatelet agents, with an emphasis on cilostazol, on survival in patients with moyamoya disease using a nationwide health insurance database that covers nearly all Koreans.

METHODS

Study Design, Source of Data, and Ethical Review

This was a retrospective, population-based, longitudinal cohort study of the Korean National Health Insurance Service (NHIS). The Korean NHIS is a universal health insurance system run by the Korean government that is accessible to the entire population in South Korea and covers >97% (49 million) of the population.[10] The claims database contains healthcare use information from all health services, including principal diagnosis and comorbidities based on the *International Classification of Diseases, Tenth Revision* (*ICD-10*). The NHIS runs a copayment program for rare and intractable critical diseases, including moyamoya disease, only when their diagnosis is confirmed by a physician. Therefore, the data on rare and intractable diseases undergo additional quality checks to ensure they are reliable. The NHIS database provides individual-level data on medications at each time point and was therefore adequate for the purpose of this study.

The institutional review board of our institute approved the study protocol (SMC 2018-04-092). Because anonymized and open data were used in this study, the board waived the requirement for informed consent.

Following the NHIS's policy on providing data for personal information protection, all data have been analyzed inside the NHIS system and are not provided outside. Therefore, all data and materials cannot be provided to the other researchers or the third party.

Study Population

The inclusion criterion was a confirmed first-ever NHIS diagnosis of moyamoya disease rendered between 2002 and 2016.The diagnosis of moyamoya disease was considered confirmed when both the *ICD-10* code I67.5 and the rare and intractable disease code V128 were given for the subject at least once.

Outcomes

The primary outcome was survival, assessed via death dates recorded in the NHIS data set.

Additional Patient Features

We extracted data on patient demographics, vascular risk factors, and treatment details from the Korean NHIS database. Vascular risk factors included hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, history of ischemic or hemorrhagic stroke, and history of cancer based on *ICD-10* codes. For pharmacologic therapies, we collected data on the dates of prescription and the dosing regimen of drugs for antiplatelet agents and lipid-lowering therapy (statins) after the diagnosis of moyamoya disease. Individual antiplatelet agents were categorized as aspirin, clopidogrel, cilostazol, and others. The others category was composed of triflusal and ticlopidine. Aggrenox

(combined dipyridamole and aspirin) was not included in this study because it was not approved before 2016 in Korea. We calculated medication compliance at each visit as the ratio of the number of days between the last and current visit divided by the number of prescribed medication doses for between visits. If the days/daily doses ratio exceeded 1.3, then drug administration was considered discontinued/noncompliant. For patients with surgical revascularization, we collected data for the operative date and type of procedure (direct or indirect). Any statin use was considered as a covariate.

Statistical Analysis

The primary analysis was conducted in a whole moyamoya disease patient data set, and propensity score–matched data set was used for the sensitivity analysis.

As exposure to antiplatelet therapy could vary at the individual patient level during the study period, time-dependent Cox regression analysis was selected as the primary analytic method. Time-dependent variables include medication, vascular risk factors, and surgical revascularization. Patients were assessed for the occurrence of death and of stroke for up to 14 years, from the date of first moyamoya disease diagnosis forward. The effects of variables on outcome were visualized using the Simon-Makuch method.[11]

The propensity score was calculated using a multiple logistic regression model with covariates of age, sex, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, cancer, and cerebral revascularization surgeries, with any antiplatelet agent use as dependent variables. Propensity score matching was performed by 5 Greedy methods using 1:1 matching. The performance of the propensity matching was assessed by quantifying absolute standardized differences in patient characteristics using the Love plot. Evidence of heterogeneity of patient course was evaluated in antiplatelet therapy subgroups.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), and statistical significance was considered at 2-sided $P<0.05$.

RESULTS

Among 25 982 patients meeting study inclusion criteria, 4 were excluded for missing survival information, yielding a final study population of 25 978 individuals with newly diagnosed moyamoya disease (Figure 1). Among these patients, the mean age at time of diagnosis was 37.6±19.9 years (median, 40 years; interquartile range, 19–53 years); 61.6% were women, and mean follow-up was 6.3 years (total follow-up, 163 347 person-years). The number of patients annually with a

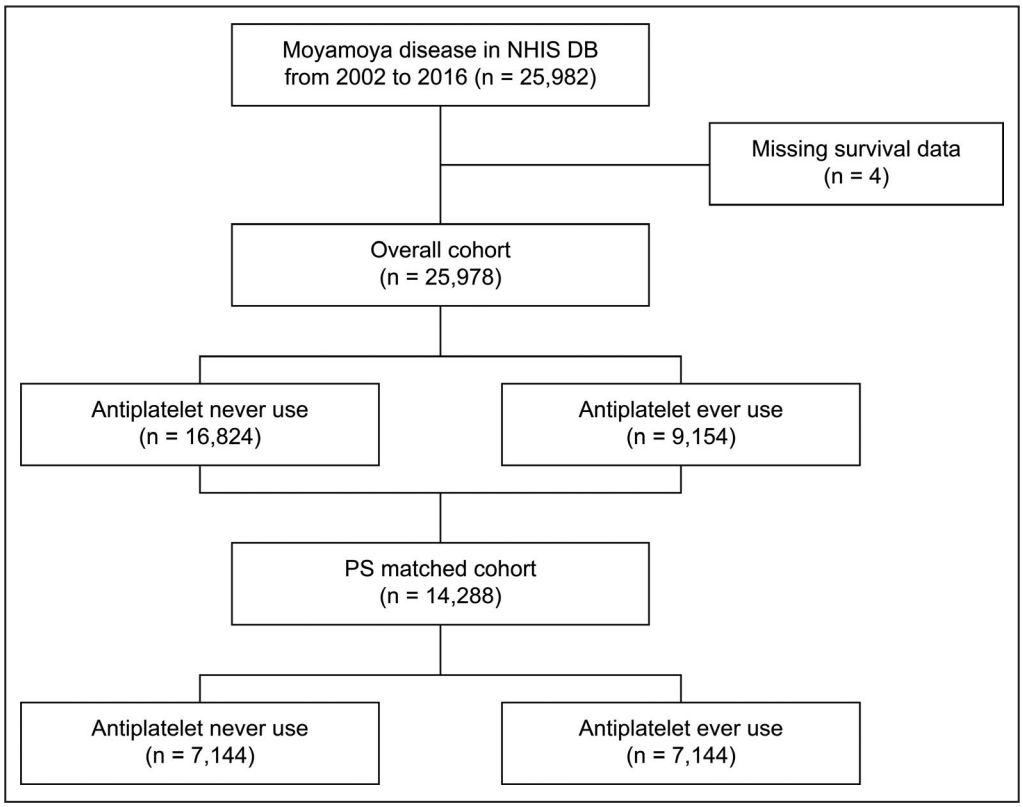

Figure 1. Flow of inclusion.
DB indicates database; NHIS, National Health Insurance Service; and PS, propensity score.

first-ever diagnosis of moyamoya disease increased gradually from 1760 patients in 2002 to 2391 patients in 2016. The overall mortality rate for the patients with moyamoya disease was 1.7 per 100 person-years, with a trend of decreasing from 2002 to 2016 (Figure S1). The slope for the decrement of mortality was stiff until 2010 but maintained after 2010. The mortality rate in patients with a history of ischemic stroke and hemorrhagic stroke at time of moyamoya disease diagnosis was 2.3 per 100 person-years and 4.3 per 100 person-years, respectively.

Characteristics of patients at the time of first-ever moyamoya disease diagnosis are shown in Table 1. Overall, 35.0% of patients had ischemic stroke, 20.4% of patients had hemorrhagic stroke, and 49.9% of patients had any stroke before or at the time of diagnosis of moyamoya disease. Hypertension was present in 40.6%, diabetes mellitus in 23.3%, dyslipidemia in 36.5%, and atrial fibrillation in 1.9%. Overall, 13.6% had been prescribed statins before or concurrent with the diagnosis of moyamoya disease. A total of 24.2% of patients had undergone surgery for direct or indirect revascularization.

Antiplatelet agents were prescribed to 9154 patients (35.2%) at least once after the diagnosis of moyamoya disease. Among the patients who received at least one antiplatelet agent, they received antiplatelet therapy during 19 251.5 patient-years (34.5%) of their observed course and no antiplatelet therapy during 36 583.6 patient-years (65.5%) of their observed course. Baseline characteristics according to each antiplatelet agent used are presented in Table S1. The pattern of antiplatelet use changed during the study period (Figure 2). In 2002, the most commonly prescribed antiplatelet agent was aspirin (55.2%), followed by clopidogrel (38.0%), others (8.1%), and cilostazol (5.5%). However, the proportion receiving cilostazol increased steadily and substantially throughout the study period. In contrast, the proportion receiving clopidogrel had no substantial change, and the proportion receiving aspirin decreased rapidly through 2004 and mildly further after that (Figure 2). As a result, by 2016, among

Table 1. Baseline Characteristics of Patients in Antiplatelet and No-Antiplatelet Groups

Characteristics	Overall Cohort		
	Did Not Use Antiplatelets (n=16 824)	Used Antiplatelets (n=9154)	*P* Value*
Age, n (%)			
<19 y	5869 (34.9)	735 (8.0)	<0.01
20–39 y	3667 (21.8)	2346 (25.6)	
40–59 y	5286 (31.4)	4551 (49.7)	
>60 y	2002 (11.9)	1522 (16.6)	
Female sex, n (%)	10 112 (60.1)	5897 (64.4)	<0.01
Hypertension, n (%)	5525 (32.8)	5021 (54.9)	<0.01
Diabetes mellitus, n (%)	3085 (18.3)	2968 (32.4)	<0.01
Hyperlipidemia, n (%)	4784 (28.4)	4700 (51.3)	<0.01
Ischemic heart disease, n (%)	2092 (12.4)	1854 (20.3)	<0.01
Cancer, n (%)	856 (5.1)	586 (6.4)	<0.01
Atrial fibrillation, n (%)	282 (1.7)	224 (2.4)	<0.01
Statin, n (%)†			
None	14 458 (85.9)	4315 (47.1)	<0.01
High potency	119 (1.2)	819 (9.0)	<0.01
Low potency	840 (5.0)	1752 (19.1)	<0.01
Stroke, n (%)			
None	8553 (50.8)	2082 (22.7)	<0.01
Hemorrhagic stroke	4008 (23.8)	1300 (14.2)	<0.01
Ischemic stroke	3913 (23.3)	5164 (56.4)	<0.01
Any stroke	6991 (41.6)	5968 (65.2)	<0.01
Cerebral revascularization surgery, n (%)‡			
None	13 476 (80.1)	6477 (70.8)	<0.01
Direct	613 (3.6)	1434 (15.7)	<0.01
Indirect‡	2825 (16.8)	1421 (15.5)	0.08

*P values for the difference between those who used antiplatelet agents and those who did not.
†High-potency statin was defined as atorvastatin, 40 to 80 mg, or rosuvastatin, 10 to 20 mg. The others were considered as low-potency statins.
‡Indirect cerebral revascularization surgery included encephaloduroarteriosynangiosis and encephalomyoarteriosynangiosis.

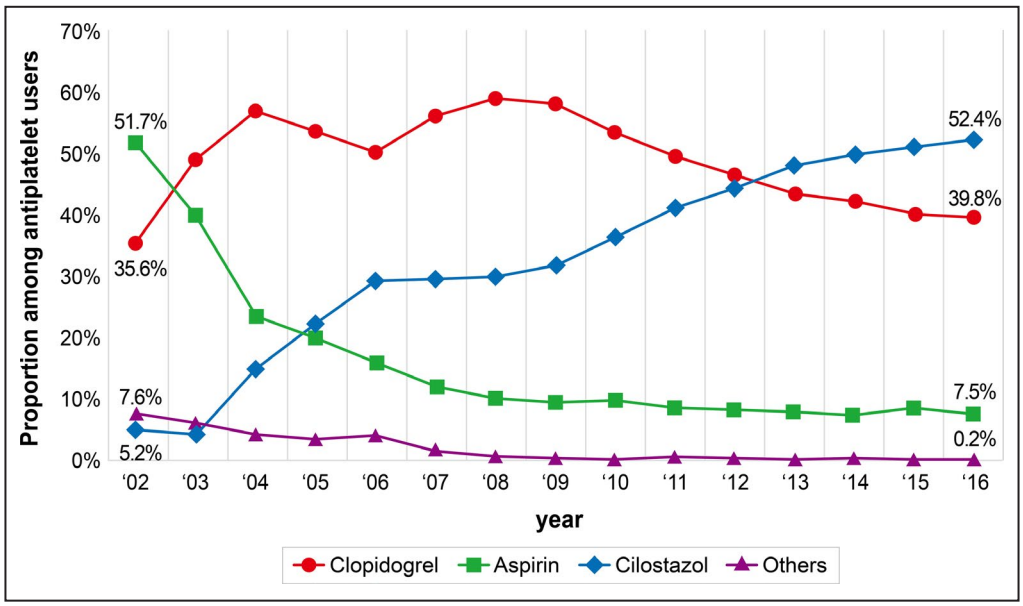

Figure 2. Trend of antiplatelet agent selection in moyamoya disease.
Proportions were calculated as the number of patients for each antiplatelet agent divided by the number of patients for any of 4 antiplatelet agents. Because ≥2 antiplatelet agents were used for some patients, the sum of each proportion of 4 antiplatelet agents can exceed 100%.

patients receiving antiplatelet agents, the proportions were as follows: cilostazol, 56.0%; clopidogrel, 42.6%; aspirin, 8.1%; and others, 0.2%. Overall, cilostazol was used in a total of 2761 patients, aspirin in 760 patients, clopidogrel in 3158 patients, other antiplatelet agents in 51 patients, and ≥2 antiplatelet agents in 2424 patients.

Patients receiving antiplatelet therapy were older and more likely to have hypertension, diabetes mellitus, and dyslipidemia than those not receiving antiplatelet therapy. A history of ischemic stroke was more frequent in patients with antiplatelet therapy (56.4%) than in those without it (23.3%), whereas a history of hemorrhagic stroke was more frequent in patients without antiplatelet treatment (23.8%) than in those with antiplatelet therapy (14.2%). The patients treated with antiplatelet therapy were also more likely to be treated with statins and direct revascularization surgery. Direct revascularization procedures were performed more frequently in patients with antiplatelet therapy than in those without it (15.7% versus 3.6%, respectively).

During the follow-up period, a total of 2711 patients died. The causes of death included stroke in 33.2%, malignancy in 6.5%, ischemic heart disease in 1.2%, and others in 59.1% (Table S2). The proportion of deaths related to stroke was higher in patients not taking antiplatelet therapy (37.4%). There was a consistent association between antiplatelet use and reduced mortality in both the univariate analysis (hazard ratio [HR], 0.54; 95% CI, 0.47–0.63) and the multivariate analysis (HR, 0.77; 95% CI, 0.70–0.84) in the covariate-adjusted models (Table 2 and Figure 3). When we divided the patients into 2 groups with diagnosis before and after 2007, there was no calendar time effect (Table S3). Statin use was associated with a decreased risk of death, but there was no dose-dependent difference in reduced mortality between high-intensity statins (HR, 0.68; 95% CI, 0.48–0.98) and low- to moderate-intensity statins (HR, 0.64; 95% CI, 0.53–0.76) in the multivariate model.

The association of individual antiplatelet agents with survival is presented in Table 3 and Figure 3. In the overall cohort analyses, cilostazol (HR, 0.57; 95% CI, 0.49–0.68), clopidogrel (HR, 0.78; 95% CI, 0.69–0.87), and ≥2 antiplatelet agents (HR, 0.78; 95% CI, 0.68–0.90) were significantly associated with reduced risk of death. The reduction associated with cilostazol was greater than that associated with each of the 5 other antiplatelet regimens (Table S4).

Mortality outcomes in patient subgroups of age <45 years, age ≥45 years, history of ischemic stroke, and history of hemorrhagic stroke are shown in Figure 4 and Table 3. Cilostazol was the only agent in agent-level analysis to be associated with reduced mortality in all 4 subgroups in multivariate model. In the age subgroups, among patients aged <45 years, cilostazol was associated with lower mortality (HR, 0.39; 95% CI, 0.27–0.56). Similarly, among patients aged ≥45 years, cilostazol was associated with lower mortality (HR, 0.71; 95% CI, 0.58–0.88). In patients aged <45 years, cilostazol was associated with a statistically superior reduction in mortality compared with all other antiplatelet regimens, whereas in patients aged ≥45 years,

Table 2. Patient Features Associated With the Mortality

Variable	Overall Cohort			
	Univariate		Multivariate	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y	1.06 (1.05–1.06)	<0.01	1.05 (1.05–1.05)	<0.01
Female sex	0.94 (0.88–1.01)	0.09		
Hypertension	2.64 (2.44–2.85)	<0.01	0.91 (0.83–0.99)	<0.04
Diabetes mellitus	2.43 (2.24–2.63)	<0.01	1.27 (1.17–1.40)	<0.01
Hyperlipidemia	1.56 (1.44–1.69)	<0.01	0.77 (0.70–0.84)	<0.01
Cancer	2.39 (2.10–2.72)	<0.01	1.33 (1.17–1.52)	<0.01
Atrial fibrillation	2.37 (1.93–2.90)	<0.01	1.37 (1.11–1.70)	<0.01
Ischemic heart disease	1.98 (1.81–2.17)	<0.01	0.99 (089–1.09)	0.79
Statin				
High potency	0.67 (0.47–0.96)	0.03	0.68 (0.48–0.98)	0.04
Low potency	0.74 (0.63–0.88)	<0.01	0.64 (0.53–0.76)	<0.01
Antiplatelet agent	0.54 (0.47–0.63)	<0.01	0.77 (0.70–0.84)	<0.01
Previous stroke				
Hemorrhagic stroke	4.04 (3.75–4.36)	<0.01	2.65 (2.44–2.87)	<0.01
Ischemic stroke	1.72 (1.59–1.85)	<0.01	1.32 (1.21–1.43)	<0.01
Surgery				
Direct	0.89 (0.75–1.06)	0.20		
Indirect	0.40 (0.35–0.46)	<0.01	0.91 (0.79–1.05)	0.21

Time-dependent Cox regression analyses were performed with age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and ischemic heart disease as time-fixed covariates, and all the other variables were considered as time-dependent variables. HR indicates hazard ratio; and PS, propensity score.

cilostazol showed superior or similar effect to the other antiplatelet agents (Table S4).

Similarly, in subgroup with the history of ischemic stroke, only cilostazol (HR, 0.71; 95% CI, 0.56–0.91) was associated with lower mortality and was superior to reduce mortality compared with other antiplatelet regimens (Table S4). In subgroup with the history of hemorrhagic stroke, every antiplatelet agent reduced mortality (Table 3).

In an analysis assessing 13 additional subgroups for features potentially modifying mortality reduction associated with antiplatelet agents, 8 subgroups showed homogeneity of effect (Figure 5). In the 5 subgroups with heterogeneity, magnified association of antiplatelet with mortality reduction was observed in those aged >45 years, women, those with history of diabetes mellitus or ischemic stroke, and patients without indirect revascularization surgery.

Sensitivity analysis using propensity score matching data set included 7144 pairs of patients with or without antiplatelet use. Across the matched patient groups, baseline covariates were generally well balanced, with age, statin use, previous stroke, and revascularization surgery differing between antiplatelet and no antiplatelet groups (Table S5). Among the antiplatelet patients, there was ≤2.5 of absolute standardized difference for all variables. The effect of antiplatelet agent on mortality was similar to the effects in overall cohort. Mortality rates were 1.52% per year on antiplatelet therapy and 2.33% per year on no antiplatelet therapy (HR, 0.60; 95% CI, 0.50–0.71; Table S6). Among the antiplatelet regimens, cilostazol (HR, 0.66; 95% CI, 0.55–0.79) and clopidogrel (HR, 0.82; 95% CI, 0.72–0.94) were significantly associated with reduced risk of death (Table S7).

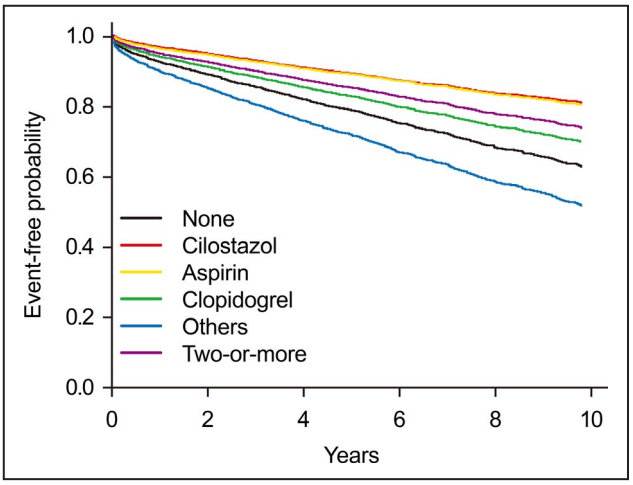

Figure 3. Simon and Makuch plot for survival, according to each antiplatelet agent use in moyamoya disease, in propensity score–matched patients.

Table 3. Association of Antiplatelet Use With Mortality in Patients With Moyamoya Disease

Variable	All Patient Cohort (n=25 978)			
	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Overall cohort (n=25 978)				
No antiplatelet	1		1	
Aspirin	0.77 (0.61–0.97)	0.03	0.87 (0.69–1.10)	0.23
Cilostazol	0.64 (0.54–0.75)	<0.01	0.57 (0.49–0.68)	<0.01
Clopidogrel	1.08 (0.97–1.21)	0.15	0.78 (0.69–0.87)	<0.01
Others	1.80 (1.06–3.05)	0.03	1.20 (0.71–2.03)	0.50
≥2	0.89 (0.77–1.01)	0.08	0.78 (0.68–0.90)	<0.01
Aged <45 y (n=14 944)				
No antiplatelet	1		1	
Aspirin	0.90 (0.61–1.33)	0.60	1.07 (0.72–1.58)	0.74
Cilostazol	0.58 (0.40–0.82)	<0.01	0.39 (0.27–0.56)	<0.01
Clopidogrel	1.27 (1.00–1.61)	0.052	0.81 (0.63–1.04)	0.10
Others	1.95 (0.63–6.06)	0.25	1.42 (0.46–4.44)	0.54
≥2	1.05 (0.80–1.37)	0.75	0.67 (0.050–0.88)	<0.01
Aged ≥45 y (n=11 034)				
No antiplatelet	1		1	
Aspirin	0.75 (0.56–1.00)	0.049	0.80 (0.58–1.11)	0.18
Cilostazol	0.45 (0.37–0.54)	<0.01	0.71 (0.58–0.88)	<0.01
Clopidogrel	0.62 (0.54–0.70)	<0.01	0.87 (0.75–1.01)	0.06
Others	1.06 (0.58–1.91)	0.86	1.20 (0.64–2.24)	0.57
≥2	0.54 (0.46–0.63)	<0.01	0.93 (0.77–1.12)	0.44
Prior ischemic stroke cohort (n=9077)†				
No antiplatelet	1		1	
Aspirin	0.59 (0.43–0.82)	<0.01	1.01 (0.68–1.50)	0.96
Cilostazol	0.49 (0.39–0.61)	<0.01	0.71 (0.56–0.91)	<0.01
Clopidogrel	0.75 (0.65–0.87)	<0.01	0.87 (0.74–1.03)	0.11
Others	1.67 (0.92–3.03)	0.09	1.45 (0.75–2.82)	0.27
≥2	0.62 (0.53–0.73)	<0.01	0.90 (0.74–1.09)	0.27
Prior hemorrhagic stroke cohort (n=5308)†				
No antiplatelet	1		1	
Aspirin	0.46 (0.30–0.70)	<0.01	0.49 (0.32–0.75)	<0.01
Cilostazol	0.37 (0.28–0.50)	<0.01	0.40 (0.30–0.53)	<0.01
Clopidogrel	0.60 (0.48–0.74)	<0.01	0.57 (0.46–0.71)	<0.01
Others	0.88 (0.33–2.36)	0.80	0.88 (0.33–2.35)	0.80
≥2	0.41 (0.30–0.56)	<0.01	0.43 (0.31–0.60)	<0.01

Time-dependent Cox regression analyses were performed. HR indicates hazard ratio.

*Age, sex, hypertension, diabetes mellitus, hyperlipidemia, cancer, atrial fibrillation, statin, previous stroke, and cerebral revascularization surgery were included as covariates.

†For these subgroups, the index date for survival analyses was determined as the date of moyamoya disease diagnosis if the patient had a previous stroke. If the patient had no stroke before the diagnosis of moyamoya disease, the date of stroke diagnosis was set as the index date for survival analysis.

DISCUSSION

In this analysis of a large, nationwide, population-based cohort, use of antiplatelet agents was associated with substantially reduced risk of death in patients with moyamoya disease. In the primary, propensity score–matched analysis, mortality rates were two thirds lower in patients receiving antiplatelet therapy, with the lower mortality observed as steadily increasing from the time of therapy start up to 10 years later. Among individual antiplatelet agents, cilostazol uniquely was associated with reduced mortality, irrespective of a history of stroke or age groups at the time of moyamoya disease diagnosis.

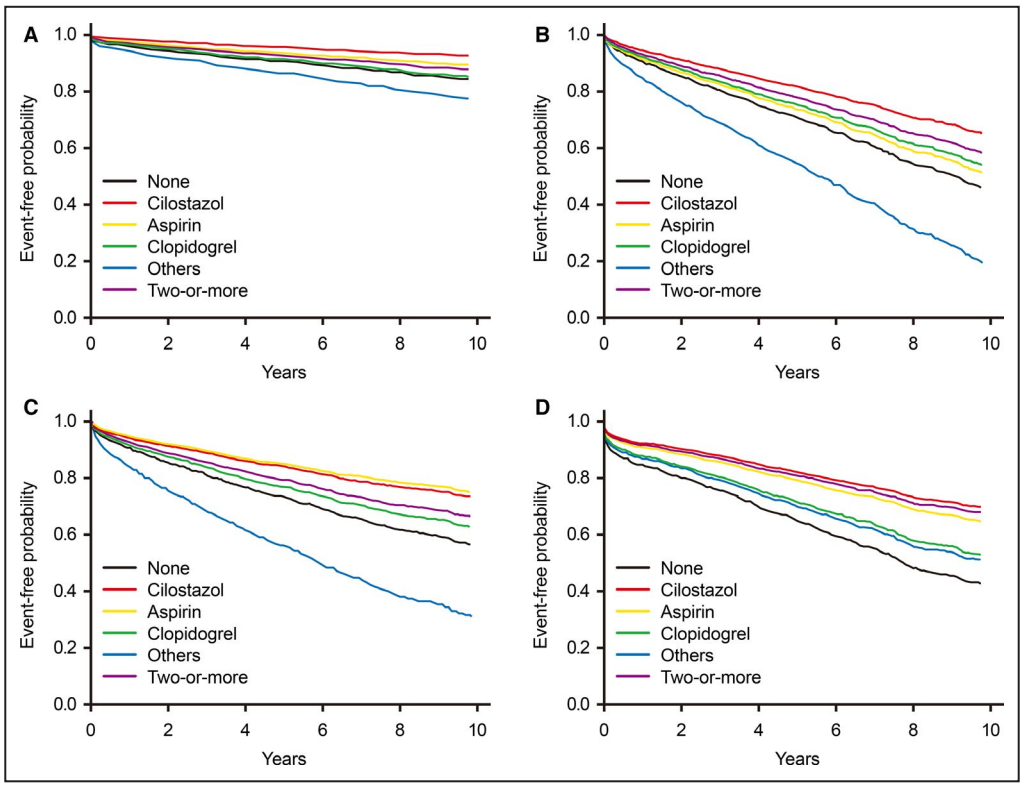

Figure 4. Simon and Makuch plots showing the association of each antiplatelet agent with survival in propensity score–matched patients in 4 subgroups.
A, Aged <45 years. **B**, Aged ≥45 years. **C**, Prior ischemic stroke. **D**, Prior hemorrhagic stroke.

The findings of the current study are consistent with pathophysiologic understanding of moyamoya disease and contrast with findings of a prior long-term investigation. Moyamoya disease is characterized by hyperplasia of the smooth muscle cells and thickening of the intima, resulting in decreased cerebral perfusion.[12,13] Although decreased cerebral perfusion in moyamoya disease frequently causes ischemic symptoms,[1] intraluminal thrombosis is another important pathological feature of moyamoya disease.[12] The formed intraluminal thrombus can occlude the cerebral artery in situ or can embolize, causing distal artery obstruction.[7,14] These findings suggest that antiplatelet agents could reduce ischemic stroke incidence in patients with moyamoya disease. An observation study showed that the prehospital antiplatelet agent use was associated with functional status at admission.[2] However, there has been only one prior prospective cohort study investigating the long-term effect of antiplatelet agents for the prevention of ischemic events in patients with moyamoya disease. In that cohort study, among 728 patients with moyamoya disease with a history of transient ischemic attack or ischemic stroke, the effect of antiplatelet agents was assessed on recurrent stroke, and antiplatelet treatment was associated with reduced recurrent hemorrhagic stroke but not reduced recurrent ischemic events.[3] However, these results should be interpreted cautiously because that study omitted an adjustment for baseline comorbidity, did not consider medication changes during the course of follow-up, did not include cilostazol as an antiplatelet agent, and had a sample size more than an order of magnitude smaller than the current investigation.

We revealed that the group with antiplatelet use had the lower proportion of stroke-related death than the group without antiplatelet use, consistent with pathophysiologic expectations. In addition, the prior study did not assess the association of antiplatelet therapy with survival, so the current investigation is the first to indicate that antiplatelet therapy is associated with reduced long-term mortality in moyamoya disease.

The current study additionally supports differential efficacy and safety of cilostazol as an antiplatelet agent in patients with moyamoya disease. Cilostazol use was associated with greater reductions in mortality than all 5 other antiplatelet regimens in both overall cohort and subgroups. Mechanistically, phosphodiesterase inhibitors, like cilostazol, possess 2 additional features not shared by other antiplatelet agent classes that are potentially of particular benefit in moyamoya disease:

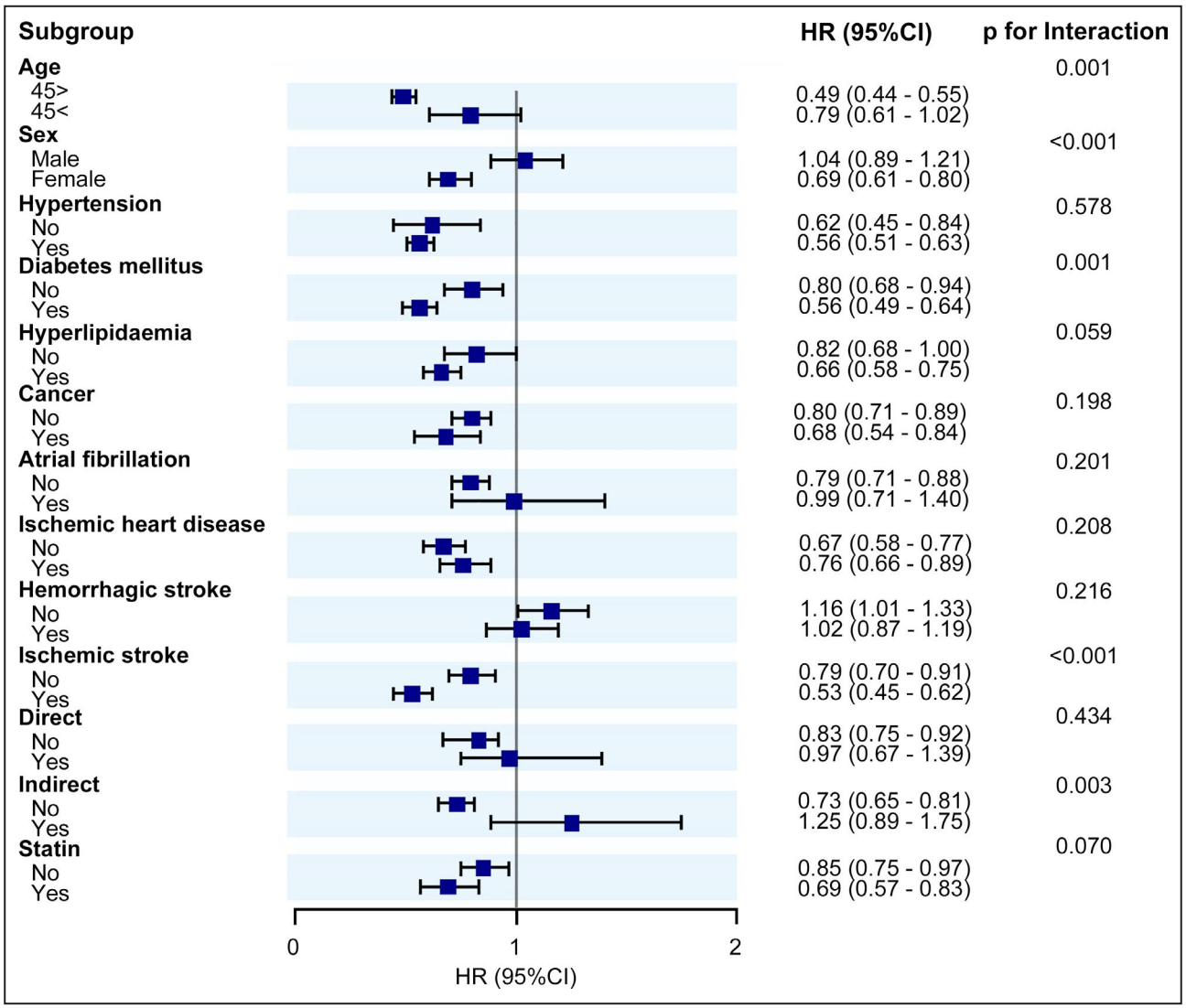

Figure 5. Assessment for heterogeneity in the association between cilostazol use and mortality reduction across patient subgroups.
HR indicates hazard ratio.

(1) vasodilating effects, improving collateral flow and averting hemodynamic stroke; and (2) less hemorrhagic stroke tendency. Cilostazol has a vasodilation effect by modulating the endothelial activity and relaxing the vascular smooth muscle cells.[15] These effects of cilostazol improve cerebral perfusion in animal models and clinical study,[9,16] and can be an advantage over the other antiplatelet agents. In a prospective cohort of 71 nonsurgical patients with moyamoya disease, cilostazol improved cerebral blood flow in comparison with clopidogrel,[9] and this cilostazol-induced change in the cerebral perfusion enhanced cognitive function in patients with moyamoya disease.[8]

Cilostazol is now widely used in patients with ischemic stroke in countries where cilostazol has been approved for stroke prevention based on the validated efficacy and safety in patients with non–moyamoya disease causes of stroke.[4,6,17] Accordingly, cilostazol has become the principal antiplatelet agent in patients with moyamoya disease. A survey of stroke physicians in Japan found cilostazol is the second most commonly used antiplatelet agent (behind aspirin) in patients with moyamoya disease.[18] We found an even higher use rate in Korea, with cilostazol deployment increasing during the stud period to become the most frequent antiplatelet agent, accounting for more than half of all antiplatelet prescriptions. The evidence in this study that cilostazol use is associated with substantial reductions in mortality, and differentially, compared with other agents, provides support for the increased use of cilostazol in moyamoya disease.

Considering the currently suggested concept of the pathogenesis of moyamoya disease being related to complex genetic, inflammatory, and environmental

factors,[13] the benefit of cilostazol on the vascular outcome in moyamoya disease might be caused by a "beyond antiplatelet effect," so-called pleiotropic effect. The positive association of statin therapy with survival or the positive interaction of cilostazol use with revascularization surgery in this study could be understood in a similar context. Statins are another potential candidate for medical treatment in moyamoya disease because of their pleiotropic effect. Revascularization surgery relies on neovascularization of the cortical surface via angiogenic mechanisms from pedicle-based grafts.[19] But, the enhanced collateral channel by surgical revascularization could reduce the favorable effect of cilostazol on outcome.

There are several limitations in this study. First, although the data set comprehensively captured nearly all patients in the nation, the observational design meant that patient allocation to antiplatelet therapy occurred at the discretion of the treating physician rather than by randomization, creating the possibility of confounding by indication when interpreting the drug effect. This limitation was addressed by the use of propensity score–matching and time-dependent survival analyses. However, residual or unmeasured confounding could still be present.

Second, there is a concern for the diagnostic accuracy both as recorded in a national health insurance database and as clinically rendered in a condition sometimes difficult to diagnose, like moyamoya disease. But this concern is mitigated by the special administrative and clinical attention arising from the regulation that patients with moyamoya disease be registered in the "Rare and Intractable Disease" category in the Korean NHIS in addition to the labeling of *ICD-10* code. Therefore, moyamoya disease cases must be reviewed and approved for the diagnosis by the attending expert physician. In addition, overall study findings were similar in the subgroup of patients aged <45 years, among whom other causes of stroke are much less frequent and the diagnosis of moyamoya disease is therefore likely to have enhanced accuracy.

Third, incident new ischemic and hemorrhagic stroke during the study observation period could not be reliably identified, as administrative coding in the NHIS database has limitation to differentiate incident stroke from the history of stroke. Future investigations may potentially be able to address this limitation by linkage analysis between the national administrative database and more detailed hospital-based clinical registries.

Finally, cautious approach must be taken to apply the results of this study to non-Asian patients with moyamoya disease.

In conclusion, in patients with moyamoya disease, antiplatelet therapy was associated with reduced mortality. Among individual antiplatelet agents, cilostazol was more strongly than other agents associated with reduced mortality overall, and in younger patients, older patients, and patients with prior ischemic stroke at the time of moyamoya disease diagnosis. Accordingly, antiplatelet therapy generally, and cilostazol particularly, shows observational evidence of potential benefit as medical treatment for patients with moyamoya disease; these findings merit validation by testing in formal randomized clinical trials.

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Affiliations

From the Department of Neurology and Stroke Center, Samsung Medical Center, Seoul, Korea (W.S., J.K., E.C., Y.K., J.C., O.Y.B., G.K.); Department of Digital Health, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul, Korea (W.S., J.K., J.L.S.); and Department of Neurology, University of California, Los Angeles, CA (J.L.S.).

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Supplementary Material

Tables S1–S7
Figure S1

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Supplemental Material

Table S1. Baseline patient characteristics among patients receiving different individual antiplatelet agents.

	Cilostazol (n=2761)	Aspirin (n=760)	Clopidogrel (n=3158)	Others (n=51)	None (n=16824)	Two drugs (n=2424)	P
Age, n (%)							
< 19 years	140 (5.1)	356 (46.8)	119 (3.8)	5 (9.8)	5,869 (34.9)	115 (4.7)	<0.001
20–39 years	853 (30.9)	114 (15.0)	726 (23.0)	16 (31.4)	3,667 (21.8)	637 (26.3)	
40–59 years	1,344 (48.7)	214 (28.2)	1,631 (51.6)	16 (31.4)	5,286 (31.4)	1,346 (55.5)	
> 60 years	424 (15.4)	76 (10.0)	682 (21.6)	14 (27.5)	2,002 (11.9)	326 (13.4)	
Female sex, n (%)	1,858 (67.3)	473 (62.2)	1,949 (61.7)	26 (51.0)	10,112 (60.1)	1,591 (65.6)	<0.001
Hypertension, n (%)	1,435 (52.0)	241 (31.7)	1,936 (61.3)	27 (52.9)	5,525 (32.8)	1,382 (57.0)	<0.001
Diabetes mellitus, n (%)	898 (32.5)	133 (17.5)	1,083 (34.3)	9 (17.6)	3,085 (18.3)	845 (34.9)	<0.001
Hyperlipidaemia, n (%)	1,539 (55.7)	193 (25.4)	1,698 (53.8)	15 (29.4)	4,784 (28.4)	1,255 (51.8)	<0.001
CAD, n (%)	523 (18.9)	84 (11.1)	738 (23.4)	6 (11.8)	2,092 (12.4)	503 (20.8)	<0.001
Cancer, n (%)	201 (7.3)	25 (3.3)	223 (7.1)	2 (3.9)	856 (5.1)	135 (5.6)	<0.001
Atrial fibrillation, n (%)	57 (2.1)	12 (1.6)	92 (2.9)	0 (0)	282 (1.7)	63 (2.6)	<0.001
Statin, n (%)†							
None	2,334 (84.5)	705 (92.8)	2,588 (82.0)	48 (94.1)	16,322 (97.0)	1,814 (74.8)	<0.001
High-potency	201 (7.3)	27 (3.6)	300 (9.5)	0 (0)	199 (1.2)	291 (12.0)	<0.001
Low-potency	515 (18.7)	73 (9.6)	601 (19.0)	5 (9.8)	840 (5)	558 (23.0)	<0.001
Stroke, n (%)							
None	567 (20.5)	186 (24.5)	729 (23.1)	15 (29.4)	4,762 (28.3)	545 (22.5)	<0.001
Hemorrhagic stroke	399 (14.5)	122 (16.1)	437 (13.8)	11 (21.6)	3,893 (23.1)	259 (10.7)	<0.001
Ischemic stroke	1,167 (42.3)	284 (37.4)	1,826 (57.8)	25 (49.0)	3,526 (21.0)	1,471 (60.7)	<0.001
Any stroke	1,464 (53)	379 (49.9)	2,091 (66.2)	32 (62.7)	6,590 (39.2)	1,622 (66.9)	<0.001
Surgery, n (%)							
None	2,127 (77.0)	399 (52.5)	2,396 (75.9)	37 (72.5)	13,476 (80.1)	1,518 (62.6)	<0.001
Direct	354 (12.8)	104 (13.7)	421 (13.3)	8 (15.7)	613 (3.6)	547 (22.6)	<0.001
Indirect‡	321 (11.6)	274 (36.1)	389 (12.3)	6 (11.8)	2,825 (16.8)	431 (17.8)	<0.001

CAD, coronary artery disease

* P-values for the difference of distribution among those who used each antiplatelet agent and those who did not.

† High-potency statin was defined as atorvastatin 40–80 mg or rosuvastatin 10–20 mg. The others were considered as low-potency statins.

‡ Indirect cerebral revascularisation surgery included encephaloduroarteriosynangiosis (EDAS) and encephalomyoarteriosynangiosis (EMAS).

Table S2. Causes of death according to the class of antiplatelet agents.

Category of cause of death*	None (n=1,852)	Aspirin (n=75)	Cilostazol (n=161)	Clopidogrel (n=370)	Two-or-more (n=239)	Total (n = 2,711)
Stroke	693 (37.4)	16 (21.3)	37 (23.0)	101 (27.3)	49 (20.5)	900 (33.2)
IHD	13 (0.7)	2 (2.7)	4 (2.5)	7 (1.9)	6 (2.5)	32 (1.1)
Cancer	116 (6.3)	5 (6.7)	18 (11.2)	27 (7.3)	12 (5.0)	178 (6.6)
Others	1030 (55.6)	52 (69.3)	102 (63.3)	235 (63.5)	172 (72.0)	1601 (59.1)

IHD, Ischemic heart disease

*Category of cause of death was defined the principle diagnosis based-on ICD-10 code at the time of the diagnosis of death (stroke I60-I65; ischemic heart disease I20 – I25; cancer C.00 – C.99).

Table S3. The effect of antiplatelet agent on mortality according to the date of diagnosis.

	Before 2007y	After 2007y	
	HR (95%CI)	HR (95%CI)	p for interaction
Antiplatelet	0.88 (0.75 – 1.03)	0.78 (0.68 – 0.90)	0.270.
None	1	1	0.248
Aspirin	1.00 (0.65 - 1.54)	0.81 (0.47 - 1.40)	
Cilostazol	0.77 (0.55 - 1.07)	0.48 (0.37 - 0.62)	
Clopidogrel	0.88 (0.71 - 1.10)	0.96 (0.80 - 1.15)	
Others	0.94 (0.66 - 1.33)	1.10 (0.70 - 1.74)	
Two or more	0.99 (0.62 - 1.61)	0.77 (0.50 - 1.19)	

Year <= 2007, Year > 2007

Table S4. The relative risk for death of each antiplatelet agent compared to cilostazol use.

	Overall cohort (n = 25,978)		PS matched cohort (n = 14,288)	
	HR (95% CI)	p	HR (95% CI)	p
	All patients (n = 25,978)		All patients (n =14,288)	
Cilostazol	1		1	
Aspirin	1.52 (1.15 – 2.00)	<0.01	1.39 (1.03 - 1.89)	0.03
Clopidogrel	1.36 (1.13 - 1.63)	<0.01	1.24 (1.01 - 1.52)	0.04
Others	2.09 (1.21 - 3.62)	0.01	2.09 (1.16 - 3.79)	0.01
Two or more	1.36 (1.11 - 1.66)	<0.01	1.29 (1.03 - 1.62)	0.03
None	1.75 (1.48 - 2.06)	<0.01	1.51 (1.26 - 1.81)	<0.01
	Age < 45 years (n =14,944)		Age < 45 years (n =6,410)	
Cilostazol	1		1	
Aspirin	2.75 (1.64 - 4.60)	<0.01	2.88 (1.68 - 4.95)	<0.01
Clopidogrel	2.08 (1.38 - 3.15)	<0.01	1.82 (1.16 - 2.87)	0.01
Others	3.66 (1.12 – 12.00)	0.03	3.78 (1.14 - 12.53)	0.03
Two or more	1.71 (1.11 - 2.64)	0.02	1.59 (0.98 - 2.58)	0.06
None	2.57 (1.79 - 3.68)	<0.01	2.04 (1.37 - 3.02)	<0.01
	Age => 45 years (n=11,034)		Age => 45 years (n =7,374)	
Cilostazol	1		1	
Aspirin	1.13 (0.78 - 1.64)	0.53	1.30 (0.93 - 1.82)	0.12
Clopidogrel	1.22 (0.97 - 1.54)	0.09	1.22 (0.99 - 1.50)	0.07
Others	1.68 (0.88 - 3.24)	0.12	1.65 (0.89 - 3.06)	0.11
Two or more	1.31 (1.01 - 1.69)	0.04	1.26 (1.01 - 1.58)	0.04
None	1.41 (1.14 - 1.73)	<0.01	1.63 (1.36 - 1.96)	<0.01
	Prior ischemic stroke cohort (n=9,077)‡		Prior ischemic stroke cohort (n=6,934)‡	
Cilostazol	1		1	
Aspirin	1.66 (1.13 - 2.42)	0.01	1.44 (0.93 - 2.25)	0.11
Clopidogrel	1.28 (1.01 - 1.62)	0.04	1.24 (0.95 - 1.61)	0.12
Others	2.35 (1.25 - 4.42)	0.01	2.07 (1.03 - 4.18)	0.04
Two or more	1.28 (0.99 - 1.65)	0.06	1.26 (0.95 - 1.67)	0.12
None	1.62 (1.30 - 2.01)	<0.01	1.43 (1.12 - 1.82)	<0.01
	Prior hemorrhagic stroke cohort (n=5,308)‡		Prior hemorrhagic stroke cohort (n =2,376)‡	
Cilostazol	1		1	
Aspirin	1.23 (0.74 - 2.05)	0.43	1.22 (0.73 - 2.05)	0.45
Clopidogrel	1.44 (1.00 - 2.06)	0.05	1.40 (0.97 - 2.03)	0.08
Others	2.22 (0.80 - 6.17)	0.13	1.78 (0.55 - 5.77)	0.34
Two or more	1.09 (0.71 - 1.67)	0.70	1.01 (0.64 - 1.59)	0.96
None	2.52 (1.88 - 3.39)	<0.01	1.93 (1.40 - 2.67)	<0.01

Table S5. Baseline characteristics of patients in antiplatelet and no-antiplatelet groups in PS-matched cohort.

.	PS-matched cohort		
	Did not use antiplatelets (n =7144)	Used antiplatelets (n =7144)	p*
Age, n (%)			
< 19 years	821 (11.5)	696 (9.7)	<0.01
20–39 years	1548 (21.7)	1899 (26.6)	
40–59 years	3269 (45.8)	3440 (48.2)	
> 60 years	1506 (21.1)	1109 (15.5)	
Female sex, n (%)	4719 (66.1)	4624 (64.7)	0.10
Hypertension, n (%)	3766 (52.7)	3713 (52.0)	0.38
Diabetes mellitus, n (%)	2168 (30.0)	2182 (30.5)	0.80
Hyperlipidaemia, n (%)	3431 (48.0)	3349 (46.9)	0.17
Ischemic heart disease, n (%)	1421 (19.9)	1431 (20.0)	0.83
Cancer, n (%)	497 (7.0)	472 (6.6)	0.41
Atrial fibrillation, n (%)	198 (2.8)	172 (2.4)	0.17
Statin, n (%)†			
None	5539 (77.5)	3622 (50.7)	<0.01
High-potency	163 (2.3)	568 (8.0)	<0.01
Low-potency	610 (8.5)	1217 (17.0)	<0.01
Stroke, n (%)			
None	1969 (27.6)	1988 (27.8)	0.72
Hemorrhagic	1725 (24.1)	1176 (16.5)	<0.01
Ischemic stroke	3386 (47.4)	3543 (49.6)	<0.01
Any stroke	4350 (60.9)	4303 (60.2)	0.42
Cerebral revascularization surgery, n (%)‡			
None	5660 (50.5)	5545 (49.5)	0.02
Direct	560 (7.8)	574 (8.0)	0.67
Indirect‡	1012 (14.2)	1092 (15.3)	0.06

* P-values for the difference between those who used antiplatelet agents and those who did not.
† High-potency statin was defined as atorvastatin 40–80 mg or rosuvastatin 10–20 mg. The others were considered as low-potency statins.
‡ Indirect cerebral revascularisation surgery included encephaloduroarteriosynangiosis (EDAS) and encephalomyoarteriosynangiosis (EMAS).

Table S6. Patient features associated with the mortality in the overall and PS-matched cohorts.

	PS matched cohort			
	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, yr	1.06 (1.06 – 1.06)	<0.01	1.05 (1.05 – 1.06)	<0.01
Female sex	0.82 (0.74 – 0.91)	<0.01	0.79 (0.72 – 0.88)	<0.01
Hypertension	2.44 (2.20 – 2.71)	<0.01	1.04 (0.92 – 1.17)	0.54
Diabetes mellitus	2.20 (2.20 – 2.71)	<0.01	1.26 (1.13 – 1.41)	<0.01
Hyperlipidaemia	1.47 (1.33 – 1.63)	<0.01	0.81 (0.72 -0.91)	<0.01
Cancer	2.26 (1.93 – 2.64)	<0.01	1.35 (1.14 – 1.60)	<0.01
Atrial fibrillation	2.30 (1.82 – 2.91)	<0.01	1.38 (1.08 – 1.75)	0.01
Ischemic heart disease	1.82 (1.63 – 2.03)	<0.01	0.98 (0.87 – 1.10)	0.70
Statin				
High-potency	0.56 (0.36 – 0.87)	<0.01	0.61 (0.39 – 0.95)	0.03
Low-potency	0.72 (0.59 – 0.87)	<0.01	0.71 (0.58 – 0.86)	<0.01
Antiplatelet agent	0.51 (0.43 – 0.60)	<0.01	0.60 (0.50 – 0.71)	<0.01
Previous stroke				
Hemorrhagic stroke	2.66 (2.41 – 2.93)	<0.01	2.14 (1.94 – 2.37)	<0.01
Ischemic stroke	1.71 (1.55 – 1.88)	<0.01	1.42 (1.28 – 1.58)	<0.01
Surgery				
Direct	0.66 (0.52 – 0.85)	<0.01	0.97 (0.75 – 1.25)	0.81
Indirect	0.43 (0.36 – 0.51)	<0.01	1.03 (0.85 – 1.24)	0.79

Time-dependent Cox regression analyses were performed with age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and ischemic heart disease as time-fixed covariate and all the other variables were considered as time-dependent variables.

* Propensity score matching was performed for subjects who used and those who did not use any antiplatelet agent. The logistic regression model for propensity score calculating included age, sex, hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, atrial fibrillation, cancer, and surgeries.

Table S7. Association of antiplatelet use with mortality in patients with moyamoya disease.

	PS matched cohort (n=14288)			
	Univariable analysis		Multivariable analysis*	
	HR (95% CI)	p	HR (95% CI)	P
	PS matched cohort (n =14288)			
No antiplatelet	1		1	
Aspirin	0.51 (0.39 – 0.65)	<0.01	0.92 (0.71 – 1.20)	0.54
Cilostazol	0.50 (0.41 – 0.59)	<0.01	0.66 (0.55 – 0.79)	<0.01
Clopidogrel	0.80 (0.70 – 0.91)	<0.01	0.82 (0.72 – 0.94)	<0.01
Others	1.34 (0.76 – 2.36)	0.32	1.38 (0.78 – 2.45)	0.26
Two or more	0.68 (0.58 – 0.80)	<0.01	0.86 (0.73 – 1.01)	0.058
	PS matched cohort with age < 45 years (n =6410)			
No antiplatelet	1		1	
Aspirin	0.68 (0.45 – 1.02)	0.059	1.42 (0.93 – 2.15)	0.11
Cilostazol	0.46 (0.31 – 0.69)	<0.01	0.49 (0.33 – 0.73)	<0.01
Clopidogrel	0.92 (0.69 – 1.23)	0.58	0.90 (0.67 – 1.20)	0.46
Others	1.44 (0.46 – 4.51)	0.53	1.86 (0.59 – 5.85)	0.29
Two or more	0.78 (0.56 – 1.09)	0.15	0.78 (0.56 – 1.10)	0.15
	PS matched cohort with age => 45 years (n =7374)			
No antiplatelet	1		1	
Aspirin	0.89 (0.64 – 1.23)	0.48	0.80 (0.60 – 1.06)	0.13
Cilostazol	0.62 (0.50 – 0.76)	<0.01	0.61 (0.51 – 0.74)	<0.01
Clopidogrel	0.84 (0.72 – 0.97)	0.02	0.75 (0.65 – 0.85)	<0.01
Others	1.63 (0.87 – 3.04)	0.13	1.01 (0.56 – 1.83)	0.97
Two or more	0.75 (0.62 – 0.90)	<0.01	0.77 (0.66 – 0.91)	<0.01
	Prior ischemic stroke cohort after PS matching (n=6934)‡			
No antiplatelet	1		1	
Aspirin	0.54 (0.67 – 0.79)	<0.01	1.01 (0.68 – 1.49)	0.97
Cilostazol	0.58 (0.46 – 0.74)	<0.01	0.70 (0.55 – 0.89)	<0.01
Clopidogrel	0.85 (0.72 – 0.10)	0.042	0.86 (0.73 – 1.02)	0.08
Others	1.72 (0.89 – 3.33)	0.11	1.45 (0.75 – 2.82)	0.27
Two or more	0.75 (0.62 – 0.90)	<0.01	0.88 (0.73 – 1.07)	0.19
	Prior hemorrhagic stroke cohort after PS matching (n =2376)‡			
No antiplatelet	1		1	

Aspirin	0.57 (0.37 – 0.88)	0.01	0.63 (0.41 – 0.98)	0.04
Cilostazol	0.49 (0.35 – 0.67)	<0.01	0.52 (0.37 – 0.71)	<0.01
Clopidogrel	0.79 (0.62 – 1.01)	0.06	0.72 (0.57 – 0.93)	0.01
Others	0.83 (0.27 – 2.60)	0.75	0.92 (0.29 – 2.89)	0.89
Two or more	0.52 (0.36 – 0.74)	<0.01	0.52 (0.37 – 0.75)	<0.01

Time dependent Cox regression analyses were performed.

* Age, sex, hypertension, diabetes mellitus, hyperlipidaemia, cancer, atrial fibrillation, statin, previous stroke, and cerebral revascularisation surgery were included as covariates.

† Propensity score matching was performed for any antiplatelet use. The logistic regression model for propensity score calculating included age, sex, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, cancer, and surgical revascularisation.

‡ For these subgroups, the index date for survival analyses was determined as the date of moyamoya disease diagnosis if the patient had a previous stroke. If the patient had no stroke before the diagnosis of moyamoya disease, the date of stroke diagnosis was set as the index date for survival analysis.

Figure S1. Trends of moyamoya disease diagnosis and mortality rate among moyamoya patients.