Efficacy and safety of clopidogrel and aspirin do not differ in patients with stable ischemic stroke

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Abstract

Background: The current study compared the efficacy and safety of clopidogrel vs aspirin in the secondary prevention of ischemic stroke (IS).

Methods: We included patients from the Taiwan National Health Insurance Research Database who were aged between 20 and 80 years, had their first ever IS, had no diagnosis of atrial fibrillation, and had not used an oral anticoagulant before the index IS between 2002 and 2010. We excluded patients who died or were admitted to a hospital due to acute myocardial infarction, recurrent IS, or major bleeding within 3 months of IS. Patients were then classified into clopidogrel as aspirin users. Propensity score matching was adopted to select clopidogrel and aspirin groups with similar baseline characteristics (n = 8457 vs 16,914, mean follow-up period of 2.1 years and 1.9 years, respectively). Conditional Cox proportional hazard regression was used to compare risks of all-cause death, cardiovascular death, recurrent stroke, acute myocardial infarction, and major bleeding in clopidogrel users and aspirin users.

Results: The risks of all-cause death, cardiovascular death, recurrent stroke, and acute myocardial infarction did not differ between clopidogrel and aspirin users. Subgroup analyses revealed that the results were consistent regardless of age, disease severity, or comorbidity.

Conclusion: According to real-world data, the efficacy and safety of clopidogrel and aspirin for secondary prevention of stable IS did not differ.

Keywords: Aspirin; Clopidogrel; Efficacy and safety; Ischemic stroke

1. INTRODUCTION

An antiplatelet agent is recommended for the prevention of noncardioembolic stroke.[1,2] Short-term dual antiplatelet therapy (DAPT) was more effective than single antiplatelet therapy (SAPT) in patients with minor ischemic stroke (IS) or those at a high risk of transient ischemic attack;[3,4] however, long-term DAPT was not found to be superior to SAPT in secondary stroke prevention.[5–7] Therefore, in most patients with noncardioembolic stroke, SAPT is administered at the chronic stage. Aspirin and clopidogrel are the most commonly prescribed antiplatelet agents. In a clinical trial of clopidogrel vs aspirin in patients at risk of ischemic events (CAPRIE), clopidogrel had superior efficacy in preventing composite vascular events (IS, myocardial infarction, and vascular death) and resulted in a lower rate of gastrointestinal bleeding compared with aspirin.[8] The CAPRIE trial was the only SAPT trial comparing aspirin with clopdiogrel in vascular disease prevention; however, it did not enroll the East Asian population, and it was not powered to compare the efficacy of aspirin and clopidogrel in secondary stroke prevention. In addition, exclusion criteria for the CAPRIE trial were relatively strict: patients of bedridden or demented status, patients who received carotid endarterectomy, patients with life expectancy of less than 3 years, and patients with uncontrolled hypertension were excluded. These medical conditions are commonly present in patients with IS. Because of the criteria, only 32% of real-world patients with IS would have been eligible for the CAPRIE trial.[9] In retrospective studies comparing efficacy and safety between aspirin and clopidogrel in secondary stroke prevention, results were inconsistent due to uncontrolled confounding factors.[10,11] Therefore, whether clopidogrel is superior to aspirin in real-world efficacy and safety remains unclear. The purpose of this study was to compare the efficacy and safety of aspirin and clopidogrel in secondary stroke prevention by using a nationwide health insurance database in Taiwan.

2. METHODS

2.1. Data source and ethics statement

Patients were selected from the National Health Insurance Research Database (NHIRD), a population-based claims database, which covers most health care services to residents

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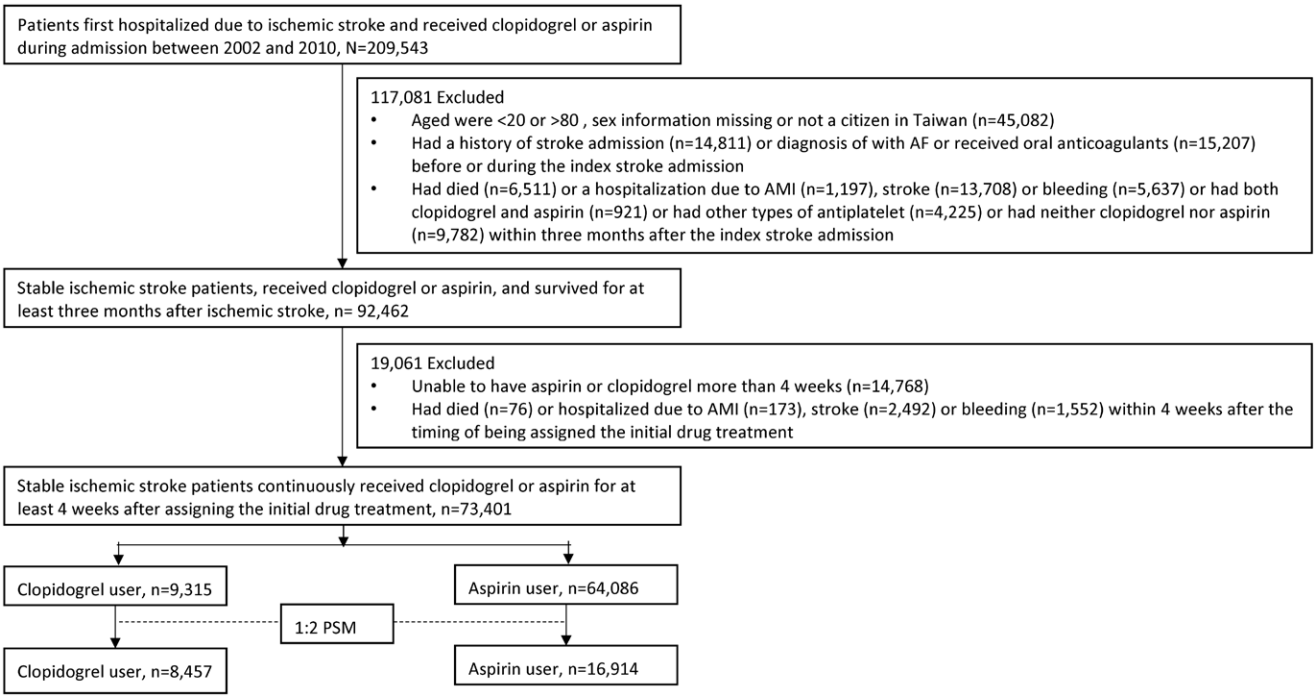

Fig. 1 Patient selection process. AF=atrial fibrillation; AMI=acute myocardial infarction; PSM=propensity score matching.

of Taiwan. By law, every resident must enroll in the National Health Insurance; the rate of coverage was 99% in 2015. The database we used is maintained by the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, Executive Yuan, Taiwan. In this retrospective cohort study, we extracted data from the NHIRD for the period 2000–2015. Death records were obtained from the National Death Registry, a population-based registry for cause of death. The two databases can be linked using unique encrypted identifiers regulated by the HWDC and the Personal Information Protection Act. The study was approved by the Taipei Medical University Joint Institutional Review Board (TMU-JIRB, approval no. N201807062).

2.2. Study cohort

Patients aged between 20 and 80 years who had the first IS and received SAPT of clopidogrel or aspirin at admission between 2002 and 2010 were identified using International Clinical of Diseases, Ninth Revision, Clinical Modification codes (ICD-9-CM: 433.xx, 434.xx, and 436.xx). The date of IS admission was treated as the index of IS. We excluded patients who had a diagnosis of atrial fibrillation or had received oral anticoagulants before and at the index date of IS.

Early recurrence of IS or mortality (within 3 months of IS, referred to hereafter as acute stage) was largely determined by etiologies,[12] comorbitidies,[13] and complications.[14–16] In observational studies, these factors confound the efficacy and safety analysis of antiplatelet drugs and may with difficulty be controlled for by using complex study design or statistical methods. Therefore, we excluded patients who died or were admitted to a hospital due to acute myocardial infarction (AMI), recurrent IS, or major bleeding in the acute stage. Briefly, patients in our study were survivors of the first IS who had neither a new vascular event nor major bleeding within 3 months of IS (stable first IS).

Because interchanges between aspirin and clopidogrel were common in these patients in the acute stage, we applied strict criteria to include only patients who continuously received aspirin or clopidogrel for at least 4 weeks in the stable stage in the final analysis to reduce the effect of antiplatelet changes on vascular events. Therefore, an aspirin user was defined as a patient who continuously used aspirin for more than 4 weeks in the stable stage. If a patient died or had AMI, IS, or major bleeding before completing the first 4 weeks of clopidogrel or aspirin use, they were excluded. The observational period of vascular events started after 4-week SAPT, and SAPT had to have been started within 3 months after stroke. Fig. 1 depicts the process of patient selection in more detail. Detailed information on the ICD-9-CM for disease diagnostic coding and Anatomical Therapeutic Chemical codes for medications is provided in Supplementary Table. A total of 9315 clopidogrel users and 64,086 aspirin users were identified.

2.3. Previous or coexisting diseases or medications

Baseline characteristics were derived according to patients' inpatient, outpatient, and pharmacy claims. The observation period was 11 months before and 1 month after the index of IS. We adopted the proxy of the National Institute of Health Stroke Scale (NIHSS) score developed by Sung et al. based on administrative databases to adjust the severity of IS admission.[17] The Charlson comorbidity index (CCI), an indicator of comorbidity, was also applied. Previous and coexisting diseases included hypertension, diabetes mellitus, dyslipidemia, and AMI. To increase the validity of a disease diagnosis, patients were identified as having a specific disease if they had a hospital admission or visited a clinic at least twice with the same diagnosis during the observation period. Major bleeding was defined as having a hospital admission due to a bleeding event.

2.4. Propensity score matching

The baseline characteristics of the initial defined clopidogrel users (n = 9315) and aspirin users (n = 64,086) differed. Thus, a propensity score was used to select a clopidogrel user matching two aspirin users. Logistic regression was used to calculate the propensity scores of using aspirin or clopidogrel based on age,

sex, NIHSS score, CCI score, previous coexisting disease, use of PPIs, and years since IS diagnosis.

2.5. Outcomes

The outcomes of interest were recurrent IS, AMI, composite vascular events (recurrent IS + AMI), cardiovascular disease (CVD) death, all-cause death, and major bleeding within a 5-year follow-up period. CVD death was defined as death due to ischemic or hemorrhagic stroke or AMI. For recurrent IS, AMI, and major bleeding, we used discharge claims to identify occurrence.

2.6. Statistical analysis

Both clopidogrel and aspirin users were followed from the date when the drug was assigned until a 5-year observational period. The observational period ended when the patient had recurrent IS, AMI, or major bleeding. For patients who did not have an outcome event, the observational period ended at the date of the last database entry or when they (1) died before the occurrence of recurrent IS, AMI, or major bleeding, (2) switched the initially assigned antiplatelet or received any other type of antiplatelet, or (3) stopped receiving the initially assigned antiplatelet. Standardized mean differences (SMDs) among all covariates were used to evaluate differences between matched pairs. An imbalance was defined as an absolute value of >0.1. Cox proportional hazard regression analysis was used to compare the risk of outcomes of interest between clopidogrel and aspirin users, conditional to matched pairs. All analyses were performed using SAS/STAT 9.4 software (SAS Institute Inc., Cary, NC, USA) and STATA 14 software (Stata Corp LP, College Station, TX, USA).

3. RESULTS

The patient selection process is displayed in Figure 1. The baseline characteristics are described in Table 1. Before propensity score matching (PSM), clopidogrel users were more likely to be older, have higher NIHSS and CCI scores, have a history of major bleeding, and have received more PPIs compared with aspirin users. After 1:2 PSM, 8457 clopidogrel users and 16,914 aspirin users with similar baseline characteristics were enrolled for the final analysis. The mean follow-up period was 2.1 and 1.9 years for clopidogrel and aspirin users, respectively.

The comparisons of outcomes between clopidogrel and aspirin users are presented in Table 2. The incidence rates of recurrent IS, AMI, composite vascular events, CVD death, all-cause death, major bleeding, and gastrointestinal bleeding with PPI use were not significantly different between clopidogrel and aspirin users. The adjusted risks of all outcomes for aspirin users were not significantly different from those for clopidogrel users (hazard ratios were not significant). The Kaplan–Meier curves of all outcomes are provided in Supplementary Figures S1–S6.

Given the base characteristics of the study cohort before PSM, clopidogrel was likely favored over aspirin in the SAPT of older patients with higher stroke severity and more comorbidities. Therefore, we conducted subgroup analyses to investigate whether clopidogrel was superior to aspirin (Table 1). The results of subgroup analyses comparing recurrent IS and CVD death between clopidogrel users and aspirin users are presented in Fig. 2. In the subgroups of age ≥ 70 years, NIHSS score ≥ 5, CCI score ≥ 3, history of AMI, hypertension, diabetes mellitus, dyslipidemia, or major bleeding, the risk of recurrent IS or CVD

Table 1

Baseline characteristics of patients with stable ischemic stroke who received clopidogrel or aspirin prior to and after PSM

	Before PSM					After PSM				
	Clopidogrel users		Aspirin Users			Clopidogrel users		Aspirin users		
	n	(%)	n	(%)	SMD	n	(%)	n	(%)	SMD
Sample size, n	9315		64,086			8457		16,914		
Male	5734	(61.6)	38,974	(60.8)	0.015	5169	(61.1)	10,338	(61.1)	<0.001
Age, y [mean, SD]	[65.4, 9.8]		[63.6, 10.6]			[65.5, 9.6]		[65.5, 9.6]		
<40	114	(1.2)	1366	(2.1)	0.071	85	(1.0)	167	(1.0)	0.002
40–64	3637	(39.0)	29,401	(45.9)	0.139	3316	(39.2)	6630	(39.2)	<0.001
65–74	3750	(40.3)	22,626	(35.3)	0.102	3423	(40.5)	6846	(40.5)	<0.001
≥75	1814	(19.5)	10,693	(16.7)	0.073	1633	(19.3)	3271	(19.3)	0.001
NIHSS [mean, SD]	[6.2, 4.0]		[5.2, 2.8]			[5.9, 3.7]		[5.9, 3.6]		
0–4	6647	(71.4)	53,621	(83.7)	0.298	6304	(74.5)	12,608	(74.5)	<0.001
5–9	1366	(14.7)	6541	(10.2)	0.135	1187	(14.0)	2374	(14.0)	<0.001
≥10	1302	(14.0)	3924	(6.1)	0.263	966	(11.4)	1932	(11.4)	<0.001
CCI, [mean, SD]	[2.9, 1.8]		[2.5, 1.6]			[2.7, 1.7]		[2.6, 1.7]		
0–2	4724	(50.7)	37,665	(58.8)	0.162	4553	(53.8)	9099	(53.8)	0.001
3–5	3749	(40.2)	23,032	(35.9)	0.089	3348	(39.6)	6696	(39.6)	<0.001
≥6	842	(9.0)	3389	(5.3)	0.146	556	(6.6)	1119	(6.6)	0.002
Previous or coexisting diseases, yes										
Hypertension	7137	(76.6)	49,274	(76.9)	0.006	6500	(76.9)	13,196	(78.0)	0.028
Diabetes mellitus	3977	(42.7)	26,732	(41.7)	0.02	3531	(41.8)	7075	(41.8)	0.002
Dyslipidemia	3612	(38.8)	24,760	(38.6)	0.003	3297	(39.0)	6462	(38.2)	0.016
Myocardial infarction	214	(2.3)	701	(1.1)	0.093	163	(1.9)	233	(1.4)	0.043
Major bleeding	586	(6.3)	1894	(3.0)	0.159	266	(3.1)	525	(3.1)	0.002
Proton pump inhibitors	344	(3.7)	421	(0.7)	0.209	38	(0.4)	76	(0.4)	<0.001
Year of ischemic stroke diagnosis										
2002–2004	3473	(37.3)	19,166	(29.9)	0.157	3235	(38.3)	6470	(38.3)	<0.001
2005–2007	2677	(28.7)	22,444	(35.0)	0.135	2401	(28.4)	4802	(28.4)	<0.001
2008–2010	3165	(34.0)	22,476	(35.1)	0.023	2821	(33.4)	5642	(33.4)	<0.001
Follow-up period, y [mean, SD]	[2.1, 1.9]		[2.8, 2.0]			[2.1, 1.9]		[1.9, 1.8]		

Follow-up period was measured from the date of start to the end of the study period or date of all-cause death.

CCI=Charlson comorbidity index; NIHSS=National Institute of Health Stroke Scale; PSM=propensity score matching; SMD=standardized mean difference; an imbalance was defined as absolute value of >0.1.

Table 2

Incidence (per 1000 PY) and adjusted HR of death, recurrent stroke, myocardial infarction, and major bleeding in stable ischemic stroke patients receiving clopidogrel or aspirin

Outcomes/user group	PY	No. of events	Incidence (95% CI)	Adjusted* HR (95% CI)
Recurrent ischemic stroke				
Clopidogrel	16,819	500	29.7 (27.2–32.5)	1.00 (Ref.)
Aspirin	30,418	875	28.8 (26.9–30.7)	0.94 (0.85–1.05)
Acute myocardial infarction				
Clopidogrel	17,473	71	4.06 (3.22–5.13)	1.00 (Ref.)
Aspirin	31,504	110	3.49 (2.90–4.21)	0.87 (0.64–1.17)
Recurrent stroke & myocardial infarction				
Clopidogrel	16,791	560	33.4 (30.7–36.2)	1.00 (Ref.)
Aspirin	30,394	966	31.8 (29.8–33.9)	0.93 (0.84–1.04)
CVD death				
Clopidogrel	17,506	130	7.43 (6.25–8.82)	1.00 (Ref.)
Aspirin	31,533	238	7.55 (6.65–8.57)	1.00 (0.81–1.24)
All-cause death				
Clopidogrel	17,506	784	44.8 (41.8–48.0)	1.00 (Ref.)
Aspirin	31,533	1403	44.5 (42.2–46.9)	1.00 (0.91–1.09)
Major bleeding				
Clopidogrel	15,575	1187	76.2 (72.0–80.7)	1.00 (Ref.)
Aspirin	28,924	2087	72.2 (69.1–75.3)	0.94 (0.87–1.01)

*Adjusted all covariates listed in Table 1.

CI=confidence interval; CVD=cardiovascular disease; HR=hazard ratio; Ref=reference group.

death was not significantly different between clopidogrel users and aspirin users.

4. DISCUSSION

In this study, we determined that clopidogrel is not superior to aspirin in the prevention of secondary IS, AMI, composite vascular events, death, or major bleeding complications. Subgroup analyses revealed that the results were consistent regardless of age, disease severity, or comorbidity.

The advantage of the current study is the use of a nationwide population database, which includes the data of numerous patients and thus reflects real-world practice. The size of the current study (clopidogrel vs aspirin, n = 8457 vs 16,914) was larger than that of the CAPRIE trial (n = 9599 vs 9586 in all participants, and n = 3223 vs. 3198 in the stroke subgroup) and was larger than that in the Danish nationwide registry (n = 3885 vs 3043) and Taiwan Stroke Registry (n = 6443 vs 6443) studies.[10,11] In addition, the mean follow-up period of the present study (2.1 and 1.9 years for clopidogrel and aspirin users, respectively) was comparable to that of the CAPRIE trial (1.9 years) and was longer than that of the Danish nationwide registry (335 days) and Taiwan Stroke Registry (12 months) studies.[10,11] Therefore, the results of the current study are robust.

In the CAPRIE trial, clopidogrel was found to be superior to aspirin with fewer composite vascular events and less gastrointestinal bleeding.[8] These advantages were not present in the current study. The differing results between the current study and the CAPRIE trial may be explained by participants' characteristics. The prevalence of hypertension and diabetes in the current study (77% and 42%, respectively) was higher than that in the CAPRIE trial (65% and 25% in the stroke subgroup, respectively), a reflection that clinical trials intend to exclude patients with more comorbidities. Therefore, clopidogrel may be superior to aspirin only in patients with fewer comorbidities. However, the subgroup analysis in the current study identified no difference between patients with CCI ≥ 3 and those with CCI < 3; thus, clopidogrel and aspirin were similarly effective in patients with few or multiple comorbidities.

The current study estimated vascular events after more than 3 months of IS, whereas the CAPRIE trial estimated vascular events after more than 1 week of IS. Therefore, clopidogrel may be more effective than aspirin at acute to subacute but not chronic stage of IS. However, in trials of aspirin vs control in the secondary prevention of stroke, aspirin was found to be superior to control predominantly within 6 weeks of IS, and the difference in efficacy between aspirin and control diminished with time.[18] In trials of DAPT (clopidogrel plus aspirin) vs SAPT (aspirin alone), DAPT was found to be superior to SAPT

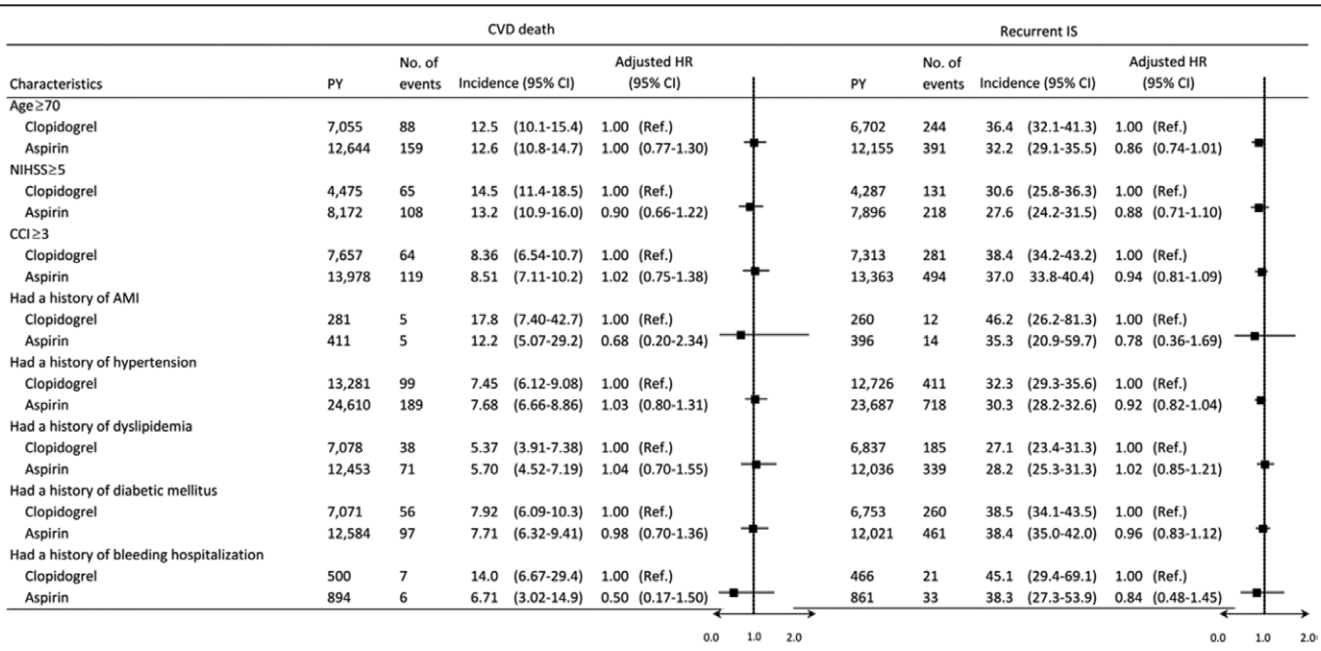

Fig. 2 Subgroup analysis of the incidence rate (per 1000 patient-year) and adjusted hazard ratios of cardiovascular disease death and recurrent ischemic stroke in clopidogrel users compared with aspirin users. CVD=cardiovascular disease; HR=hazard ratio; IS=ischemic stroke; PY=patient-year.

predominantly within 3 weeks of IS.[3,19] Therefore, the efficacy of antiplatelet therapy in the prevention of IS diminishes with time, which may explain the lack of a difference in efficacy between clopidogrel and aspirin after 3 months of IS, as in the current study. However, in a trial of ticagrelor vs aspirin for secondary prevention of cardiovascular diseases, ticagrelor was not identified to be significantly superior to aspirin within 3 months of IS.[20] It is possible that the efficacies of SAPTs currently available do not differ in the prevention of IS regardless of the disease stage.

More than 90% of the CAPRIE trial participants were Caucasians, whereas the current study enrolled only East Asians. The incidence rate of clopidogrel resistance caused by CYP2C19 loss-of-function alleles is approximately 50% in East Asians and 26% in Caucasians.[21,22] In a trial of DAPT with clopidogrel plus aspirin in Chinese patients with minor stroke or transient ischemic attack, DAPT was determined to be superior to aspirin alone in reducing recurrent stroke only in patients without CYP2C19 loss-of-function alleles.[23] Therefore, clopidogrel may be more effective in the prevention of CVDs than aspirin in Caucasians but not in East Asians. In addition, in the current study, clopidogrel users had a higher chance of using PPIs than did aspirin users, reflecting that the reason for choosing clopidogrel was the presence of a peptic ulcer or gastrointestinal bleeding. Certain PPIs, such as omeprazole and esomeprazole, reduce the activity of CYP2C19, and the active metabolite level of clopidogrel in blood[24] and may negatively affect the efficacy of clopidogrel in East Asians carrying CYP2C19 loss-of-function alleles. Nevertheless, in the current study, the number of PPI users was low (0.4%) in either group after PSM; thus, the problem of PPI-related clopidogrel activity inhibition was alleviated.

The current study has several limitations. First, the reason for choosing clopidogrel or aspirin was not recorded in the database. In real-world practice, the reason for choosing a medicine is usually according to the clinical characteristics of the patient, which usually results in an imbalance of baseline characteristics between groups using different medicines. In addition, many variables affecting the risk of vascular events such as tobacco smoking and exercise habits as well as the stroke type were also not recorded in the database. Therefore, potential selection bias could not be excluded, although we matched most known risk factors for vascular disease and mortality in the PSM. Second, because we investigated only vascular events after 3 months of IS, the results may not apply in vascular events within 3 months of IS. Additional studies are encouraged to investigate the drug effect on patients in the acute stage because the majority of vascular events would be in the acute stage. Third, we enrolled only patients in Taiwan; thus, the results may not generalize to other ethnic groups, especially Caucasians. Fourth, coding errors may exist in a claim-based study and may affect the accuracy of conclusions.

In conclusion, the efficacy and safety of clopidogrel and aspirin for secondary prevention of stable IS do not differ according to real-world data. In view of health resource allocation, aspirin should be preferred to clopidogrel for patients with stable IS. The prescription of clopidogrel instead of aspirin for stable IS should be based on a justification other than efficacy or safety.

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REFERENCES

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al.; American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018;**49**:e46–e110.
2. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al.; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:2160–236.
3. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al.; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;**369**:11–9.
4. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, et al. Clopidogrel and aspirin in acute ischemic stroke and high-eisk TIA. *N Engl J Med* 2018;**379**:215–25.
5. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al.; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;**354**:1706–17.
6. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al.; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004;**364**:331–7.
7. SPS3 Investigators, Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, et al. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med* 2012;**367**:817–25.
8. Committee CS. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;**348**:1329–39.
9. Maasland L, van Oostenbrugge RJ, Franke CF, Scholte Op Reimer WJ, Koudstaal PJ, Dippel DW; Netherlands Stroke Survey Investigators. Patients enrolled in large randomized clinical trials of antiplatelet treatment for prevention after transient ischemic attack or ischemic stroke are not representative of patients in clinical practice: the Netherlands Stroke Survey. *Stroke* 2009;**40**:2662–8.
10. Christiansen CB, Pallisgaard J, Gerds TA, Olesen JB, Jørgensen ME, Numé AK, et al. Comparison of antiplatelet regimens in secondary stroke prevention: a nationwide cohort study. *BMC Neurol* 2015;**15**:225.
11. Chi NF, Wen CP, Liu CH, Li JY, Jeng JS, Chen CH, et al.; Taiwan Stroke Registry Investigators. Comparison Between Aspirin and Clopidogrel in Secondary Stroke Prevention Based on Real-World Data. *J Am Heart Assoc* 2018;**7**:e009856.
12. Ay H, Gungor L, Arsava EM, Rosand J, Vangel M, Benner T, et al. A score to predict early risk of recurrence after ischemic stroke. *Neurology* 2010;**74**:128–35.
13. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007;**369**:283–92.
14. Langhorne P, Stott DJ, Robertson L, MacDonald J, Jones L, McAlpine C, et al. Medical complications after stroke: a multicenter study. *Stroke* 2000;**31**:1223–9.
15. Katzan IL, Cebul RD, Husak SH, Dawson NV, Baker DW. The effect of pneumonia on mortality among patients hospitalized for acute stroke. *Neurology* 2003;**60**:620–5.
16. Ogata T, Kamouchi M, Matsuo R, Hata J, Kuroda J, Ago T, et al.; Fukuoka Stroke Registry. Gastrointestinal bleeding in acute ischemic stroke: recent trends from the fukuoka stroke registry. *Cerebrovasc Dis Extra* 2014;**4**:156–64.
17. Sung SF, Hsieh CY, Kao Yang YH, Lin HJ, Chen CH, Chen YW, et al. Developing a stroke severity index based on administrative data was feasible using data mining techniques. *J Clin Epidemiol* 2015;**68**:1292–300.
18. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet* 2016;**388**:365–75.
19. Johnston SC, Elm JJ, Easton JD, Farrant M, Barsan WG, Kim AS, et al.; POINT and Neurological Emergencies Treatment Trials Network

Investigators. Time Course for Benefit and Risk of Clopidogrel and Aspirin After Acute Transient Ischemic Attack and Minor Ischemic Stroke. *Circulation* 2019;**140**:658–64.
20. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, et al.; SOCRATES Steering Committee and Investigators. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N Engl J Med* 2016;**375**:35–43.
21. Lee YC, Liao YC, Chang FC, Huang HC, Tsai JY, Chung CP. Investigating CYP2C19 loss-of-function allele statuses and their association with stroke of different etiologies in a Taiwanese population. *J Chin Med Assoc* 2019;**82**:469–72.
22. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* 2010;**304**:1821–30.
23. Wang Y, Zhao X, Lin J, Li H, Johnston SC, Lin Y, et al.; CHANCE investigators. Association Between CYP2C19 Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack. *JAMA* 2016;**316**:70–8.
24. Chua D, Bolt J, Lo A, Lo A. Clopidogrel and proton pump inhibitors: a new drug interaction? *Can J Hosp Pharm* 2010;**63**:47–50.