ORIGINAL RESEARCH

Comparison Between Aspirin and Clopidogrel in Secondary Stroke Prevention Based on Real-World Data

Nai-Fang Chi, MD;* Chi-Pang Wen, MD, PhD;* Chung-Hsiang Liu, MD; Jie-Yuan Li, MD; Jiann-Shing Jeng, MD, PhD; Chih-Hung Chen, MD; Li-Ming Lien, MD, PhD; Ching-Huang Lin, MD; Yu Sun, MD; Wei-Lun Chang, MD; Chaur-Jong Hu, MD; Chung Y. Hsu, MD, PhD; on behalf of Taiwan Stroke Registry Investigators†

***Background*—**Clopidogrel was thought to be superior to aspirin for secondary prevention of vascular diseases in clinical trials. In this study we assessed the safety and efficacy of clopidogrel versus aspirin in real-world practice by using the Taiwan Stroke Registry.

***Methods and Results*—**Patients with ischemic stroke (2006–2016) on aspirin or clopidogrel for secondary stroke prevention were identified in the Taiwan Stroke Registry. Stroke recurrence and mortality rates in patients receiving aspirin (N=34 679) were compared with those receiving clopidogrel (N=7611) during a 12-month follow-up period. Propensity score matching and conditional Cox proportional hazards regression model were applied to control confounding factors with 6443 patients in each group. After propensity score matching, stroke recurrence rates were comparable between groups, with 223 patients in the aspirin (3.46%) and 244 in the clopidogrel group (3.79%) (hazard ratio=1.13, 95% confidence interval=0.89–1.43, *P*=0.311). However, the mortality rate was significantly higher in the clopidogrel group (362 patients, 5.62%) than in the aspirin group (302 patients, 4.69%) (hazard ratio=1.30, 95% confidence interval=1.07–1.58, *P*=0.008). Results were consistent before and after propensity score matching.

***Conclusions*—**Clopidogrel was as effective as aspirin for prevention of recurrent stroke in real-world practice. However, the mortality rate was significantly higher in the clopidogrel than in the aspirin group. **(*J Am Heart Assoc*. 2018;7:e009856. DOI: 10.1161/JAHA.118.009856)**

Key Words: aspirin • clopidogrel • prevention • stroke

Patients with ischemic stroke or transient ischemic attack carry a substantially higher risk of developing recurrent stroke and death than those without a previous stroke or transient ischemic attack.[1–6] Results of prospective clinical trials and subsequent systematic reviews have established well-accepted guidelines that antiplatelet agents are effective for secondary stroke prevention at both acute and chronic stages.[7–21] Aspirin is the most widely prescribed antiplatelet agent as the mainstay for secondary stroke prevention.[21,22] However, there have been several studies comparing the

From the Department of Neurology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan (N.-F.C., L.-M.L., C.-J.H.); Department of Neurology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan (N.-F.C., C.-J.H); Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan (N.-F.C.); Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan (C.-P.W.); Department of Neurology, China Medical University Hospital, Taichung, Taiwan (C.-H.L., C.Y.H.); Department of Neurology, E-Da Hospital, Kaohsiung, Taiwan (J.-Y.L.); School of Medicine, I-Shou University, Kaohsiung, Taiwan (J.-Y.L.); Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan (J.-S.J.); Department of Neurology, College of Medicine, National Cheng Kung University, Tainan, Taiwan (C.-H.C.); Stroke Center, National Cheng Kung University Hospital, Tainan, Taiwan (C.-H.C.); Department of Neurology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan (L.-M.L.); Department of Neurology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan (C.-H.L.); Department of Neurology, En Chu Kong Hospital, New Taipei City, Taiwan (Y.S.); Department of Neurology, Show-Chwan Memorial Hospital, Changhua, Taiwan (W.-L.C.); The PhD Program for Neural Regenerative Medicine, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan (C.-J.H.); Taipei Neuroscience Institute, Taipei Medical University, Taipei, Taiwan (C.-J.H); Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan (C.Y.H.).

Accompanying Appendix S1 and Tables S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009856

*Dr Chi and Dr Wen contributed equally to this work.

†A complete list of the Taiwan Stroke Registry Investigators is provided in Appendix S1.

Correspondence to: Chaur-Jong Hu, MD, Department of Neurology, Shuang Ho Hospital, Taipei Medical University, 291, Jhongheng Rd, Jhonghe District, New Taipei City, Taiwan. E-mail: chaurjongh@tmu.edu.tw

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Clinical Perspective

What Is New?

- In this 1-year retrospective study of real-world data comparing the safety and efficacy between aspirin and clopidogrel in the secondary prevention of ischemic stroke, stroke recurrence rates were comparable between aspirin and clopidogrel, but the mortality rate was higher in the clopidogrel group than in the aspirin group.

What Are the Clinical Implications?

- In patients with ischemic stroke, clopidogrel was not superior to aspirin for preventing either mortality or recurrent stroke according to real-world data, even though clinical trials have suggested that clopidogrel users have fewer major bleeding events than aspirin users.

efficacy and safety of aspirin with other antiplatelet agents.[7,8,23] Clopidogrel is another guideline-recommended antiplatelet agent[21,22] and has been shown to be superior to aspirin in preventing composite vascular events and reducing hemorrhagic complications in a randomized controlled trial, CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events).[7] However, whether clopidogrel is superior to aspirin in stroke prevention is unclear, and current guidelines do not recommend using clopidogrel instead of aspirin as the first-line antiplatelet agent for secondary stroke prevention. In addition, clopidogrel was proven to be as effective as aspirin plus dipyridamole in secondary stroke prevention with the advantage of fewer hemorrhagic complications in another randomized controlled trial, the PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial.[14] Although the 2 large clinical trials reported clopidogrel to have similar efficacy and lower hemorrhagic complication rates compared with aspirin in secondary stroke prevention, there has been no prior study comparing the safety and efficacy between these 2 major antiplatelet agents based on real-world practice outcomes. Thus, extrapolation from clinical trial results on aspirin versus clopidogrel in secondary stroke prevention to real-world practice outcomes remains to be established. It has been increasingly recognized that real-world practice outcomes or real-world evidence may not be consistent with results derived from randomized clinical trials.[24] Other studies have also raised concerns on extending clinical trial results of secondary stroke prevention to real-world practice.[25] Patients with older age and complex comorbidities are usually excluded from clinical trials, and up to 75% of the stroke patient population could be excluded based on preset exclusion criteria in clinical trials on stroke prevention.[26] Clopidogrel is more expensive than aspirin, and most cost effectiveness studies of clopidogrel monotherapy in the prevention of vascular events were based on the data of the CAPRIE trial.[27–30] The cost effectiveness of clopidogrel versus aspirin in real-world practice is unclear. The objective of the present study was to compare the safety and efficacy of clopidogrel with aspirin in secondary stroke prevention based on real-world practice outcome using the TSR (Taiwan Stroke Registry) with more than 130 000 stroke admissions. TSR data reflecting quality of care within its network hospitals have been reported earlier.[31]

Methods

Taiwan Stroke Registry

Data for the present study were obtained from the TSR for the period from May 1, 2006 to February 29, 2016. The TSR program, which was launched in 2006, is a government-funded project with approval from Institutional Review Boards of 59 academic and community hospitals in Taiwan (Appendix S1). Informed consent from the participants in this study was waived. Registration of stroke patients who constitute the study population in the present study has been previously reported in detail.[31] TSR data have also been noted to be representative of the national stroke population in the National Health Insurance database.[31] The severity of stroke was assessed using the National Institutes of Health Stroke Scale,[30] and the outcome was determined using the modified Rankin Scale.[32,33] Each stroke patient was followed up by the case managers of each hospital through their medical record and/or telephone visit every 3 months for at least 12 months after discharge. Only the individuals for whom we confirmed survival status were included in this study. At each follow-up visit, data relevant to secondary stroke prevention, including data on stroke recurrence, other vascular event or death, were systematically collected. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Patients and Study Design

Patients continually receiving either aspirin or clopidogrel after the diagnosis of ischemic stroke but not transient ischemic attack were selected and analyzed. The observation period was 12 months. Inclusion and exclusion criteria are listed in Figure 1. The primary outcomes were stroke recurrence and death within 12 months after ischemic stroke under preventive measure using aspirin or clopidogrel. The exclusions were patients who received a combination of aspirin and clopidogrel (N=1443), received other medicine including aggrenox, ticlopidine, cilostazol, or warfarin (N=1995), died during hospitalization for acute ischemic stroke (N=101), with missing data for length of stay (N=9286), TOAST (Trial of Org 10172 in

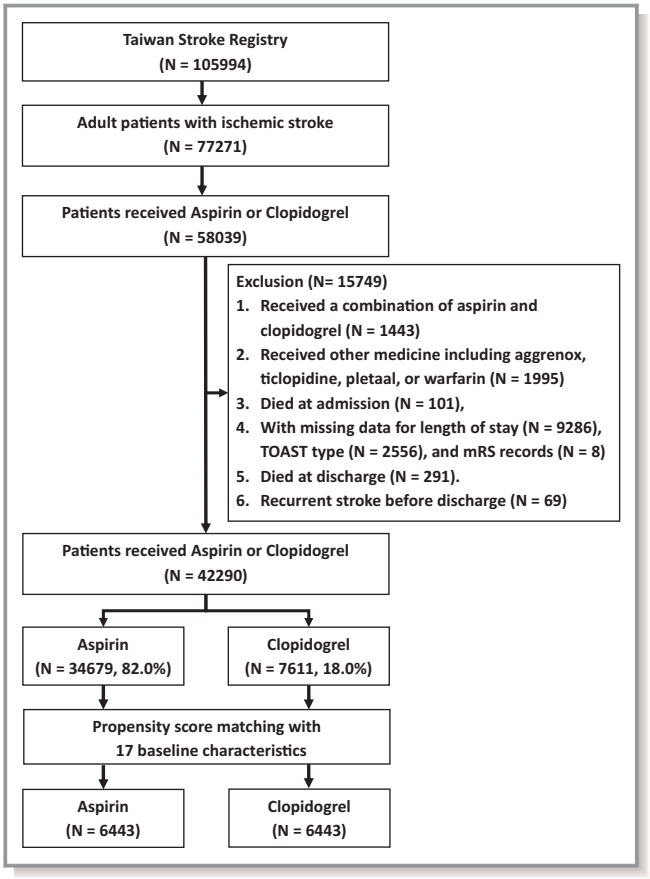

Figure 1. Flowchart of patient recruitment. TOAST indicates Trial of Org 10172 in Acute Stroke Treatment.

Acute Stroke Treatment) type (N=2556), modified Rankin Scale records (N=8), died at discharge (N=291), and with recurrent stroke before discharge (N=69) (Figure 1).

Statistical Analysis

To reduce baseline disparities anticipated in a retrospective study, propensity score matching (PSM) analysis was conducted to balance the distribution of variables between groups (Table 1).[34] The PSM applied logistic regression analysis with 17 variables, namely, age, body mass index, hospitalization length (in days), sex, stroke subtypes based on TOAST,[35] hypertension, diabetes mellitus, dyslipidemia, previous cerebrovascular event or transient ischemic attack, atrial fibrillation, ischemic heart disease including acute myocardial infarction, congestive heart failure, smoking, alcohol consumption, upper gastrointestinal bleeding, and National Institutes of Health Stroke Scale scores on admission and modified Rankin Scale upon discharge. We detected the collinearity of the variables using the Cox model before PSM. The result revealed that the correlations between the parameters were all lower than 0.01, and suggested that there was no collinearity of variables (Tables S1 and S2). Furthermore, patients in the aspirin group were matched with those in the clopidogrel group using the nearest logit of the propensity score.[36] The PSM ratio was 1:1. The distribution of confounders between patients with aspirin and clopidogrel was balanced between the group with PSM (propensity scores were 0.23 ± 0.14 and 0.23 ± 0.14, respectively, t test, P=0.973).

Baseline features of the matched patients were compared statistically between groups using independent t test and χ^2 test for means and percentages, respectively. The differences were considered significant when P values were <0.05. Kaplan–Meier analysis was used to estimate the survival curves for the stroke- and death-free probability.[37] The cumulative risk of recurrent stroke and death was calculated using the Cox proportional hazards regression model and expressed as hazard ratios (HRs).[38] Finally, the propensity score was used as a covariate to adjust the HR in the Cox models stratifying on matched pairs.[39] The precision of the HR estimates was described as 95% confidence intervals (95% CIs). The data were analyzed using the Statistical Analysis System (SAS System for Windows, Version 9.1, Cary, NC) and Statistical Package for the Social Sciences software (Version 18.0, SPSS Inc, Chicago, IL).

Results

Baseline Characteristics

In the TSR, 34 679 stroke patients on aspirin and 7611 stroke patients on clopidogrel were identified (Figure 1). Before the PSM, the baseline characteristics including confounding factors between groups were not comparable (Table 1). Compared with the aspirin group, the clopidogrel group had a higher proportion of upper gastrointestinal bleeding, certain stroke risk factors (except dyslipidemia, smoking, and alcohol use), and modified Rankin Scale in the range of 3 to 5 but a lower proportion of patients with small vessel disease, and National Institutes of Health Stroke Scale score <5 upon discharge (Table 1). To reduce biases caused by the uneven distribution of baseline features between groups, PSM was applied for further analysis.[34,40] No significant differences in baseline characteristics between groups were noted after PSM. The total number of patients in each study group was 6443.

Antiplatelet Therapies on Recurrent Stroke

There were 1421 patients with recurrent stroke within 12 months of the previous stroke in the study population of 42 290 patients (Table 2); 1141 (3.29%) and 280 (3.68%) patients developed recurrent stroke during a 12-month follow-up period in the aspirin and clopidogrel groups, respectively, with no significant difference between groups (HR=1.12, 95%

Table 1. Baseline Characteristics Before and After PS Matching*

Characteristics	Before PS Matching			After PS Matching*		
	Aspirin (N=34 679)	Clopidogrel (N=7611)	*P* Value	Aspirin (N=6443)	Clopidogrel (N=6443)	*P* Value
Age (y), mean±SD	67.4±13.7	71.8±12.9	<0.001	71.8±16.3	71.4±13.2	0.140
BMI, mean±SD†	24.8±3.89	24.2±3.91	<0.001	24.1±3.73	24.2±3.92	0.210
Hospitalization length (d), median (interquartile range)	7 (7)	11 (16)	<0.001	9 (14)	10 (15)	0.340
Male, n (%)	21 159 (61.0)	4539 (59.6)	0.026	3878 (60.2)	3898 (60.5)	0.719
Obesity, n (%)‡	7974 (23.0)	1492 (19.6)	<0.001	1328 (20.6)	1448 (22.5)	0.010
TOAST subtype, n (%)						
LAA	9921 (28.6)	2580 (33.9)	<0.001	2204 (34.2)	2147 (33.3)	0.514
SVD	17 113 (49.4)	2960 (38.9)		2510 (39.0)	2593 (40.3)	
Cardioembolism	1816 (5.24)	731 (9.60)		635 (9.86)	598 (9.28)	
Specific cause	375 (1.08)	85 (1.12)		68 (1.06)	68 (1.06)	
Undetermined cause	5454 (15.7)	1255 (16.5)		1026 (15.9)	1037 (16.1)	
Risk factors, n (%)						
Hypertension	25 980 (74.9)	5966 (78.4)	<0.001	5100 (79.2)	5068 (78.6)	0.425
Diabetes mellitus	13 832 (39.9)	3202 (42.1)	<0.001	2724 (42.3)	2713 (42.1)	0.844
Dyslipidemia	17 100 (49.3)	3446 (45.3)	<0.001	2902 (45.0)	2956 (45.9)	0.339
Previous CVA/TIA	7607 (21.9)	2534 (33.3)	<0.001	2230 (34.6)	2106 (32.7)	0.021
Heart disease	7249 (20.9)	2598 (34.1)	<0.001	2129 (33.0)	2219 (34.4)	0.094
Atrial fibrillation	896 (2.58)	357 (4.69)	<0.001	279 (4.33)	277 (4.30)	0.931
Ischemic heart disease	3034 (8.75)	1274 (16.7)	<0.001	1155 (17.9)	1104 (17.1)	0.237
Congestive heart failure	411 (1.19)	181 (2.38)	<0.001	142 (2.20)	142 (2.20)	1.000
Acute MI	31 (0.09)	27 (0.35)	<0.001	16 (0.25)	22 (0.34)	0.330
Smoking	12 834 (37.0)	2531 (35.3)	<0.001	2148 (33.3)	2213 (34.4)	0.226
Alcohol use	4720 (13.6)	764 (10.0)	<0.001	600 (9.31)	657 (10.2)	0.091
UGI bleeding	141 (0.41)	442 (5.81)	<0.001	119 (1.85)	173 (2.69)	0.001
mRS scores at discharge, n (%)§						
0	2417 (6.97)	400 (5.24)	<0.001	343 (5.32)	372 (5.77)	0.022
1	8949 (25.8)	1164 (15.3)		1211 (18.8)	1087 (16.9)	
2	7273 (21.0)	1208 (15.9)		1127 (17.5)	1111 (17.2)	
3–5	16 040 (46.3)	4839 (63.6)		3762 (58.4)	3873 (60.1)	
NIHSS scores at discharge, n (%)‖						
<5	24 079 (69.4)	4058 (53.3)	<0.001	3733 (57.9)	3630 (56.3)	0.001
5–19	9522 (27.5)	2906 (38.2)		2309 (35.8)	2309 (35.8)	
≥20	1078 (3.11)	647 (8.50)		401 (6.22)	504 (7.82)	

BMI indicates body mass index; CVA, cerebrovascular attack; LAA, large artery atherosclerosis; MI, myocardial infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PS, propensity score; SVD, small vessel disease; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UGI, upper gastrointestinal.

*Before PS matching, the baseline characteristics of the 2 groups were significantly different ($P<0.05$) because of potential sampling bias (population ratio: aspirin/clopidogrel=5.05/1). After PS matching, there were no significant differences between the 2 groups for any variables.

†The BMI is the weight in kilograms divided by the square of the height in meters.

‡Obesity was defined as a BMI of 27 or more.

§Scores on the mRS ranged from 0 to 5, and higher scores indicated greater disability.

‖Higher scores on the NIHSS indicated greater stroke severity.

CI=0.98–1.27, $P=0.094$). In the propensity-score-matched pairs (N=6443, in each group), 223 patients (3.46%) in the aspirin group and 244 patients (3.79%) in the clopidogrel group developed recurrent stroke. The adjusted HR did not differ between the groups (HR=1.13; 95% CI=0.89–1.43, $P=0.311$, Table 2). During the 12-month follow-up period, the

Table 2. Primary Outcomes, Recurrent Stroke, and Death, Before and After PS Matching*

Outcome	Before PS Matching				After PS Matching			
	Aspirin (N=34 679)	Clopidogrel (N=7611)			Aspirin (N=6443)	Clopidogrel (N=6443)		
	N (%)		HR (95% CI)†	*P* Value	N (%)		HR (95% CI)‡	*P* Value
Recurrent stroke								
12 mo	1141 (3.29)	280 (3.68)	1.12 (0.98–1.27)	0.094	223 (3.46)	244 (3.79)	1.13 (0.89–1.43)	0.311
Death								
3 mo	385 (1.11)	183 (2.40)	2.11 (1.77–2.51)	<0.001	116 (1.80)	144 (2.23)	1.24 (0.94–1.63)	0.137
4–12 mo	582 (1.68)	266 (3.49)	2.16 (1.89–2.49)	<0.001	186 (2.89)	218 (3.38)	1.36 (1.04–1.78)	0.026
12 mo	967 (2.79)	449 (5.90)	2.14 (1.91–2.39)	<0.001	302 (4.69)	362 (5.62)	1.30 (1.07–1.58)	0.008

CI indicates confidence interval; HR, hazard ratio; PS, propensity score.
*Death significantly differed between the 2 groups (P<0.001) during 0–360 d and 91–360 d.
†Unadjusted HR.
‡Propensity score–adjusted HR.

stroke-free curves show no significant difference between groups (Figure 2A).

Antiplatelet Therapies on All-Cause Death

Before the PSM, a total of 1416 patients, 967 in the aspirin group and 449 in the clopidogrel group, died during the 12-month follow-up period (Table 2). The difference for HR of death was significant between groups in favor of aspirin (clopidogrel to aspirin HR=2.14, 95% CI=1.91–2.39, P<0.001). The difference between groups remains significant after adjustments based on PSM with the Cox proportional hazards regression model. The 12-month mortality in the clopidogrel group (5.62%) was 1.3-fold higher than that in the aspirin group

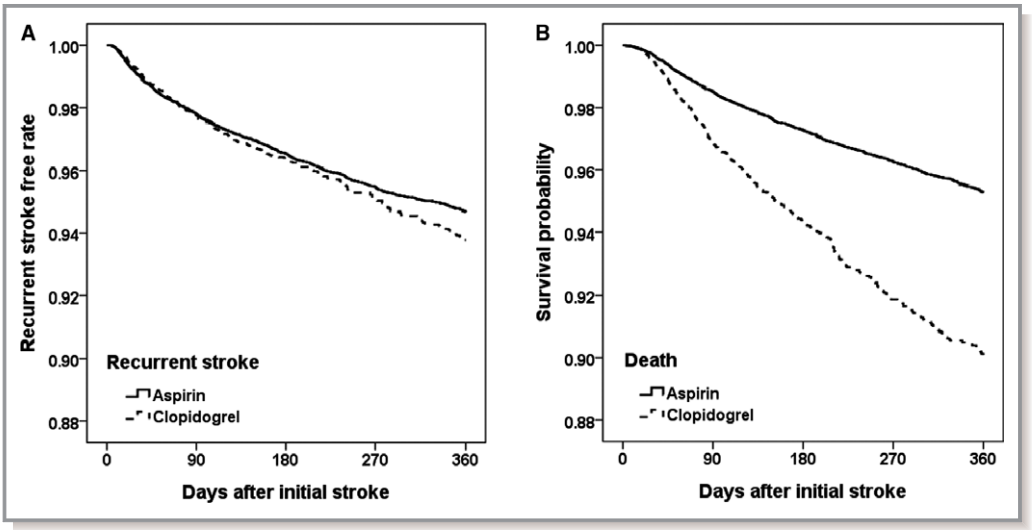

Figure 2. Survival probability in ischemic stroke patients receiving aspirin or clopidogrel: (A) recurrent stroke and (B) death after propensity score matching. Kaplan–Meier analysis was used to estimate the survival curves for the risk of recurrent stroke (A) during 12 months in the ischemic stroke patients in the aspirin group (—) and clopidogrel group (—). During the 12-month study period, 223 patients (3.46%) in the aspirin group and 244 patients (3.79%) in the clopidogrel group had recurrent stroke, respectively. The differences between the 2 study groups in recurrent stroke were not significant (HR=1.13, 95% CI=0.89–1.43, P=0.311). However, the survival curves showed a significant difference in the cumulative risk of death within 12 months after the prior stroke and the initiation of antiplatelet therapeutics (B). More ischemic stroke patients in the clopidogrel group (N=362, 5.62%) died during the 12-month follow-up period compared with those in the aspirin group (N=302, 4.69%). The propensity-adjusted cumulative risk of death in the aspirin group was significantly different from that in the clopidogrel group (HR=1.30, 95% CI=1.07–1.58, P=0.008). CI indicates confidence interval; HR, hazard ratio.

(4.69%) even after the data were adjusted by reducing potential biases associated with 17 common confounding factors (HR=1.30, 95% CI=1.07–1.58, *P*=0.008, Table 2 and Figure 2B). The mortality rates during the first 90 days were not different between groups, but significantly higher mortality in the clopidogrel group compared with the aspirin group was observed during the 4 to 12 months (adjusted clopidogrel to aspirin HR=1.36, *P*=0.026) (Table 2). The higher mortality rate in the clopidogrel group could not be ascribed to recurrent stroke rate, which is not different between groups.

Discussion

The data of patients with ischemic stroke included in the present study were collected from 59 hospitals in Taiwan. Stroke patients enrolled in TSR are representative of the population of all stroke patients in Taiwan and therefore reflect the stroke population receiving interventions for secondary stroke prevention in current practice in Taiwan.[37] The results from this retrospective study based on real-world practice outcomes show comparable risk of developing recurrent stroke within 12 months between groups. The adjusted recurrence rates were 3.46% and 3.79% (*P*=0.311) during the 12-month follow-up period in the aspirin and clopidogrel groups, respectively. The mortality rates during the first 90 days show no significant difference between groups, which agreed with the mortality rates observed in a short-term follow-up trial.[18] However, the adjusted 12-month mortality in the clopidogrel group (5.62%) was 1.3-fold higher than that in the aspirin group (4.69%) (HR=1.30, 95% CI=1.07–1.58, *P*=0.008).

The higher overall mortality in the clopidogrel group than in the aspirin group was unexpected, and was not observed in the CAPRIE trial. In the SPS3 trial (Secondary Prevention of Small Subcortical Strokes), an unexpected higher mortality was found in patients receiving clopidogrel plus aspirin compared with patients receiving aspirin alone, which was not attributed to fatal hemorrhage[41]; the mechanism was investigated but remained uncertain.[42] The average age of participants was similar between CAPRIE and SPS3 trials, but the proportions of vascular comorbidities such as hypertension and diabetes mellitus were higher in the SPS3 than in the CAPRIE trial. Therefore, clopidogrel may have an unknown detrimental effect on mortality only in lacunar stroke patients with complex comorbidities. In this study, the proportions of hypertension and diabetes mellitus before and after PSM were similar to those in the SPS3 trial; therefore, our results support that the higher overall mortality in the clopidogrel plus aspirin group of SPS3 trial may be attributed to complex comorbidities rather than by chance. It is known that diabetic patients have upregulation of the $P2Y_{12}$ pathway, which results in decreased therapeutic effect of clopidogrel and lower reduction in risk of overall mortality in patients with myocardial infarction.[43] Therefore, a potential contributing factor for the increased mortality of patients on clopidogrel is the reduced effectiveness of clopidogrel in diabetic patients, who comprised ≈40% of the study cohort.

The results derived from clinical trials and practice may be different because the inclusion and exclusion criteria of a clinical trial usually restrict enrollment of only a selective population of patients, which may not be representative of the whole patient population in real-world practice. Furthermore, most stroke clinical trials on preventive measures set an end point at 3 months after stroke onset. It should also be noted that patients in real-world practice are usually older with higher frequency of cormorbidities than those in randomized controlled trials.[26,44] Similar discrepancies have been noted in other diseases such as diabetes mellitus.[45,46] Therefore, the complication and mortality rates in real-world practice are usually higher than those in clinical trials. To understand the gap between clinical trials and real-world practice, real-world evidence has been increasingly recognized for its significance and impact. Real-world practice outcomes have been recognized by the US Food and Drug Administration in assessing the safety and efficacy of preventive and therapeutic drugs after valid clinical trials with postmarketing surveillance incorporating real-world practice outcomes. Healthcare payers including government agencies and insurance companies have also heightened their attention on real-world practice outcomes beyond the clinical trials. Analysis of registration database is one of the strategies for collecting real-world evidence. In the TSR, patients with carotid stenosis who were eligible for carotid endarterectomy accounted for 10.6% of ischemic stroke patients, and patients discharged in a severely handicapped status accounted for 11.2% of ischemic stroke survivors[31]; these patients could have a poorer outcome than those without these conditions, and they are commonly noted in the stroke patient population but excluded from clinical trials such as the CAPRIE trial according to the enrollment criteria. The patients excluded from clinical trials are more likely to develop certain side effects or complications that could confound the clinical trial results but would be under health care in real-world practice. For example, hormone replacement therapy showed benefits in postmenopausal patients with osteoporosis during clinical trials but was later found to increase the risk of coronary artery heart diseases, stroke, thromboembolic events, breast cancer, and cholecystitis after its wide application in the general population.[47,48] In addition to antiplatelet effects, which may reduce the death rate caused by vascular events, aspirin reduces metastasis and death in cancer.[49] Aspirin can also prevent free radical formation, lipid peroxidation, DNA damage, and oxidative tissue damage.[50] These antioxidant effects may contribute to the pharmacological benefits of

aspirin, including favorable effects in preventing further ischemic injury in the cardiovascular and cerebrovascular systems.[51] Aspirin also inhibits cyclooxygenase to exert anti-inflammatory and antipyretic actions. These additional effects of aspirin likely contribute in slowing the progression of cardiovascular and cerebrovascular diseases and, possibly, malignancy or other diseases that may affect lifespan. The TSR does not provide causes of death other than stroke, limiting the ability to elucidate the mechanism of action of aspirin in lowering mortality.

The effectiveness of clopidogrel is partially determined by genotypes of cytochrome CYP2C19 and interaction with proton pump inhibitors.[52,53] Both are involved in the formation of active metabolites of clopidogrel. CYP2C19*2 is associated with a weaker antiplatelet action of clopidogrel and results in a poorer cardiovascular outcome.[52] The allele frequencies of CYP2C19*2 in Taiwanese populations are not significantly different from those of whites.[54] In addition, proton pump inhibitors did not significantly affect rehospitalization rates in cardiovascular patients on clopidogrel therapy in Taiwan.[55] The exact cause of a higher mortality rate in the clopidogrel group remains to be explored.

Clopidogrel is usually restricted as the second-line drug, following aspirin, for secondary prevention of ischemic stroke by health insurance agencies, because the cost of clopidogrel is substantially higher than that of aspirin. Pharmacoeconomic analyses showed favorable cost-effectiveness of clopidogrel compared with aspirin,[27–30] but this finding was derived from clinical trial data in the CAPRIE trial, but not real-world evidence. Our results suggest that aspirin at a much lower cost than clopidogrel was as effective as clopidogrel in preventing recurrent stroke. Furthermore, stroke patients on clopidogrel had significantly higher mortality rates than those of patients on aspirin (HR=1.30; P=0.008). Based on these findings, we conclude that aspirin is not worse than clopidogrel in safety for secondary stroke prevention over a follow-up period of 12 months.

The present study has several limitations. First, biases might still exist in this retrospective study, although most measured confounders were balanced between the 2 groups through PSM. Unmeasured confounders (history of adverse events of using aspirin, or history of cancer) might trigger the prescription of clopidogrel and affect the outcome. Second, unmeasured confounders themselves might affect the results of this study, such as the causes of death other than stroke-related events. Further exploration of the differential mortality rates between groups in the TSR population and other patient populations in real-world practice is warranted.

In conclusion, the present study based on TSR shows real-world practice outcomes with aspirin and clopidogrel to be equally effective in secondary stroke prevention. However, a significantly higher mortality rate among stroke patients who were on clopidogrel than those on aspirin was noted in 12-month follow-up.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Appendix

List of Taiwan Stroke Registry Investigators:

China Medical University Hospital: Chung-Hsiang Liu (Principal Investigator), Chon-Haw Tsai, Wei-Shih Huang, Chung-Ta Lu, Tzung-Chang Tsai, Chun-Hung Tseng, Kang-Hsu Lin, Woei-Cherng Shyu, Yu-Wan Yang, Yen-Liang Liu, Der-Yang Cho, Chun-Chung Chen

National Taiwan University Hospital: Jiann-Shing Jeng (Principal Investigator), Sung-Chun Tang, Li-Kai Tsai, Shin-Joe Yeh, Chih-Hao Chen, Hsin-Hsi Tsai

E-Da Hospital: Jie-Yuan Li (Principle Investigator), Han-Jung Chen, Kan Lu, Shih-Pin Hsu, Hung-Chang Kuo, Jung-Chi Tsou, Yan-Tang Wang, Yi-Cheng Tai, Meng-Tsang Hsieh, Po-Chao Liliang, Cheng-Loong Liang, Hao-Kuang Wang, Yu-Tun Tsai, Kuo-Wei Wang, Jui-Sheng Chen, Po-Yuan Chen, Yi-Ching Wang

National Cheng Kung University Hospital: Chih-Hung Chen (Principal Investigator), Pi-Shan Sung, Han-Chieh Hsieh, Hui-Chen Su

Shin Kong WHS Memorial Hospital: Hou-Chang Chiu (Principal Investigator), Li-Ming Lien, Wei-Hung Chen, Chyi-Huey Bai, Tzu-Hsuan Huang, Chi-Ieong Lau,Ya-Ying Wu, Hsu-Ling Yeh, Anna Chang

Kaohsiung Veterans General Hospital: Ching-Huang Lin (Principal Investigator), Cheng-Chang Yen

Kaohsiung Medical University Chung-Ho Memorial Hospital: Ruey-Tay Lin (Principal Investigator), Chun-Hung Chen, Gim-Thean Khor, A-Ching Chao, Hsiu-Fen Lin, Poyin Huang

Chi Mei Medical Center: Huey-Juan Lin (Principal Investigator), Der-Shin Ke, Chia-Yu Chang, Poh-Shiow Yeh, Kao-Chang Lin, Tain-Junn Cheng, Chih-Ho Chou, Chun-Ming Yang, Hsiu-Chu Shen

Chung Shan Medical University Hospital: An-Chih Chen (Principal Investigator), Shih-Jei Tsai, Tsong-Ming Lu, Sheng-Ling Kung, Mei-Ju Lee, Hsi-Hsien Chou

Show Chwan Memorial Hospital: Wei-Lun Chang (Principal Investigator), Pai-Yi Chiu, Min-Hsien Hsu, Po-Chi Chan, Chau-Hsiung Pan, Hai-Ming Shoung, Yi-Chen Lo, Fu-Hwa Wang, Wei-Chieh Chang

Cheng Hsin General Hospital: Ta-Chang Lai (Principal Investigator), Jiu-Haw Yin, Chung-JenWang, Kai-ChenWang, Li-Mei Chen, Jong-Chyou Denq

En Chu Kong Hospital: Yu Sun (Principal Investigator), Chien-Jung Lu, Cheng-Huai Lin, Chieh-Cheng Huang, Chang-Hsiu Liu, Hoi-Fong Chan

Far Eastern Memorial Hospital: Siu-Pak Lee (Principal Investigator)

Kuang Tien General Hospital: Ming-Hui Sun (Principal Investigator),

Li-Ying Ke

Taichung Veterans General Hospital: Po-Lin Chen (Principal Investigator), Yu-Shan Lee

Ditmanson Medical Foundation Chiayi Christian Hospital: Sheng-Feng Sung (Principal Investigator), Cheung-Ter Ong, Chi-Shun Wu, Yung-Chu Hsu, Yu-Hsiang Su, Ling-Chien Hung

Tri-Service General Hospital: Jiunn-Tay Lee (Principal Investigator), Jiann-Chyun Lin, Yaw-Don Hsu, Jong-Chyou Denq, Giia-Sheun Peng, Chang-Hung Hsu, Chun-Chieh Lin, Che-Hung Yen, Chun-An Cheng, Yueh-Feng Sung, Yuan-Liang Chen, Ming-Tung Lien, Chung-Hsing Chou, Chia-Chen Liu, Fu-Chi Yang, Yi-ChungWu, An-Chen Tso, Yu- Hua Lai, Chun-I Chiang, Chia-Kuang Tsai, Meng-Ta Liu, Ying-Che Lin, Yu-Chuan Hsu

Cathay General Hospital: Tsuey-Ru Chiang (Principal Investigator), Pai-Hao Huang, Pin-Wen Liao, Mei-Ching Lee, Jen-Tse Chen, Sian-King Lie

Changhua Christian Hospital: Mu-Chien Sun (Principal Investigator), Pi-Ju Hsiao, Wei-Liang Chen, Ta-Cheng Chen, Chen-Shu Chang, Chien-Hsu Lai, Chieh-Sen Chuang, Yen-Yu Chen

Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan: Shinn-Kuang Lin, (Principal investigator), Yu-Chin Su, Jen-Lun Shiao, Fu-Yi Yang, Chih-Yang Liu, Han-Lin Chiang, Guei-Chiuan Chen, Po-Jen Hsu

Min Sheng General Hospital: Chun-Yuan Chang (Principal Investigator), I-sheng Lin,Chung-Hsien Chien,Yang-Chuang Chang

Lin Shin Hospital: Ping-Kun Chen (Principal Investigator), Pai-Yi Chiu

National Taiwan University Hospital Yunlin Branch: Yu-Jen Hsiao (Principal Investigator), Chen-Wen Fang

Landseed Hospital: Yu-Wei Chen (Principal Investigator), Kuo-Ying Lee, Yun-Yu Lin, Chen-Hua Li, Hui-Fen Tsai, Chuan-Fa Hsieh, Chih-Dong Yang, Shiumn-Jen Liaw, How-Chin Liao

Cheng Ching General Hospital: Shoou-Jeng Yeh (Principal Investigator), Ling-Li Wu, Liang-Po Hsieh, Yong-Hui Lee, Chung-Wen Chen

China Medical University Beigang Hospital: Chih-Shan Hsu(Principal Investigator),Ye-Jian-Jhih, Hao-Yu Zhuang, Yan-Hong Pan, Shin-An Shih

Taipei Medical University -Wan Fang Hospital: Chin-I Chen (Principal Investigator), Jia-Ying Sung, , Hsing-Yu Weng, Hao-Wen Teng, Jing-Er Lee, Chih-Shan Huang, Shu-Ping Chao

Taipei Medical University Hospital: Rey-Yue Yuan (Principal Investigator), , Jau- Jiuan Sheu, Jia-Ming Yu, Chun-Sum Ho, Ting-Chun Lin

Kuang Tien General Hospital Dajia Division: Shih-Chieh Yu(Principal

Investigator)

Changhua Christian Hospital Yunlin Branch: Jiunn-Rong Chen (Principal Investigator), Song-Yen Tsai

Chang Bing Show Chwan Memorial Hospital: Cheng-Yu Wei (Principal Investigator), Chao-Hsien Hung, Chia Fang Lee, Sheng-Kung Yang, Chih-Lin Chen, Wei Lin

Lotung Poh Ai Hospital: Hung-Pin Tseng (Principal Investigator), Chin-Hsiung Liu, Chun-Liang Lin, Hung-Chih Lin, Pi-Tzu Chen

Taipei Medical University - Shuang Ho Hospital: Chaur-Jong Hu (Principal Investigator) , Lung Chan, Nai-Fang Chi from Department of Neurology, Shuang-Ho Hospital, School of Medicine, College of Medicine, Taipei Medical University, New Taipei City

Taipei Veterans General Hospital & National Yang-Ming University School of Medicine: Chang-Ming Chern (Principal Investigator), Chun-Jen Lin, Shuu-Jiun Wang, Li-Chi Hsu, Wen-Jang Wong, I-Hui Lee, Der-Jen Yen, Ching-Piao Tsai, Shang-Yeong Kwan, Bing-Wen Soong, Shih-Pin Chen, Kwong-Kum Liao, Kung-Ping Lin, Chien Chen, Din-E Shan, Jong-Ling Fuh, Pei-Ning Wang, Yi-Chung Lee, Yu-Hsiang Yu, Hui-Chi Huang, Jui-Yao Tsai

Chi Mei Medical Center, Liouying: Ming-Hsiu Wu (Principle Investigator), Szu-Yi Chiang, Chiung-Yao Wang

Buddhist Dalin Tzu Chi General Hospital: Ming-Chin Hsu (Principal Investigator)

St. MARTIN DE PORRES HOSPITAL: Chien-Chung Chen (Principal Investigator), Po-Yen Yeh, Yu-Tai Tsai, Ko-Yi Wang

Tainan Sin-Lau Hospital: Tsang-Shan Chen (Principal Investigator), Cheng-Yang Hsieh, Wei-Fen Chen

Cardinal Tien Hospital: Ping-Keung Yip (Principal Investigator), Vinchi Wang, Kaw-ChenWang, Chung-Fen Tsai, Chao-Ching Chen, Chih-Hao Chen, Yi-Chien Liu, Shao-Yuan Chen, Zi-Hao Zhao, Zhi-Peng Wei

Yumin Medical Corporation Yumin Hospital: Shey-Lin Wu(Principal Investigator)

Kaohsiung Municipal Hsiao-kang Hospital: Ching-Kuan Liu (Principal Investigator)

Wei Gong Memorial Hospital: Ryh-Huei Lin (Principal Investigator), Ching-Hua Chu

Taipei City Hospital Ren Ai Branch: Sui-Hing Yan (Principal Investigator), Yi-Chun Lin, Pei-Yun Chen, Sheng-Huang Hsiao

National Taiwan University Hospital Hsin-Chu Branch: Bak-Sau Yip (Principal Investigator), Pei-Chun Tsai, Ping-Chen Chou, Tsam-Ming Kuo, Yi-Chen Lee, Yi-Pin Chiu, Kun-Chang Tsai

Taichung Hospital Department of Health : Yi-Sheng Liao (Principal Investigator)
Tainan Municipal An-Nan Hospital-China Medical University: Ming-Jun Tsai (Principal Investigator), Hsin-Yi Kao

Table S1. The correlation matrices of the variables for one-year mortality by Cox model.

						TOAST Subtype													
	Aspirin / Clopidogrel	Age	BMI	Hospitalization length	Male	SVD	Cardioembolism	Specific etiology	Undetermined etiology	Hypertension	Diabetes mellitus	Dyslipidemia	Previous CVA/TIA	Atrial fibrillation	Ischemic heart disease	Congestive heart failure	Acute MI	Smoking	Alcohol use	UGI bleeding	NIHSS scores at discharge
Aspirin / Clopidogrel	--	<0.0001	<0.0001	<0.0001	0.0001	-0.0003	0.0002	<0.0001	-0.006	0.00001	<0.0001	-0.0001	<0.0001	-0.0004	0.0001	0.0009	0.002	-0.0001	-0.0004	0.0003	<0.0001
Age	<0.0001	--	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
BMI	<0.0001	<0.0001	--	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	-0.0002	<0.0001	<0.0001	<0.0001	<0.0001
Hospitalization length	<0.0001	<0.0001	<0.0001	--	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.00001	<0.0001	<0.0001	<0.0001	<0.0001
Male	0.0001	<0.0001	<0.0001	<0.0001	--	0.0003	0.0003	-0.001	-0.0003	0.0009	0.0004	0.0005	-0.0002	0.0003	-0.0003	0.0004	-0.003	-0.004	-0.0009	-0.0009	<0.0001
TOAST Subtype																					
SVD	-0.0003	<0.0001	<0.0001	<0.0001	0.0003	--	--	--	--	0.0003	0.0003	0.00001	-0.0001	-0.002	-0.0005	<0.0001	-0.002	<0.0001	<0.0001	0.0009	<0.0001
Cardioembolism	0.0002	<0.0001	<0.0001	<0.0001	0.0003	--	--	--	--	0.0001	0.0003	0.0002	-0.0003	-0.002	-0.0008	-0.0004	-0.0002	0.00001	<0.0001	0.00002	<0.0001
Specific etiology	<0.0001	<0.0001	<0.0001	<0.0001	-0.001	--	--	--	--	-0.002	-0.0005	-0.0006	<0.0001	0.0003	-0.0007	0.00008	-0.002	0.00005	0.001	0.003	<0.0001
Undetermined etiology	-0.0006	<0.0001	<0.0001	<0.0001	-0.003	--	--	--	--	-0.0007	-0.0007	-0.0003	-0.0004	0.007	0.0008	-0.001	0.004	-0.0005	0.0004	0.00002	<0.0001
Hypertension	0.0001	<0.0001	<0.0001	<0.0001	0.0009	0.0003	0.0001	-0.001	<0.0001	--	-0.001	-0.0006	-0.0009	<0.0001	-0.0005	<0.0001	-0.0002	-0.0002	-0.0002	-0.001	<0.0001
Diabetes mellitus	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0003	0.0003	-0.0005	-0.0007	-0.001	--	-0.0008	-0.0007	-0.00003	-0.0005	-0.00004	-0.002	<0.0001	<0.0001	0.0004	<0.0001
Dyslipidemia	-0.001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	0.00002	-0.0006	-0.0003	-0.0006	-0.00008	--	-0.0001	<0.0001	-0.0002	<0.0001	0.0005	-0.0006	<0.0001	<0.0001	<0.0001
Previous CVA/TIA	0.0006	<0.0001	<0.0001	<0.0001	-0.002	-0.0001	-0.0003	<0.0001	-0.0004	-0.0009	-0.007	-0.0001	--	-0.0005	-0.0008	<0.0001	0.001	<0.0001	0.0003	0.0007	<0.0001

Atrial fibrillation	-0.004	<0.0001	<0.0001	<0.0001	0.0003	-0.002	-0.002	0.0003	0.007	-0.00001	-0.003	<0.0001	-0.0005	--	0.0006	-0.008	0.0003	-0.0002	<0.0001	-0.005	<0.0001
Ischemic heart disease	0.001	<0.0001	<0.0001	<0.0001	-0.003	-0.005	-0.0008	-0.007	0.0008	-0.0005	-0.0005	-0.0002	<0.0001	0.0006	--	-0.002	-0.003	-0.0003	0.0004	0.002	<0.0001
Congestive heart failure	0.0009	<0.0001	<0.0001	<0.0001	0.0004	-0.0001	-0.0004	0.00009	-0.001	<0.0001	-0.0004	<0.0001	<0.0001	-0.008	-0.002	--	-0.003	<0.0001	<0.0001	-0.003	<0.0001
Acute MI	0.002	<0.0001	-0.002	0.0001	-0.003	-0.002	-0.002	-0.002	0.004	-0.0002	-0.002	0.00005	0.0001	0.0003	-0.003	-0.003	--	0.0009	0.0002	0.0003	<0.0001
Smoking	-0.001	<0.0001	<0.0001	<0.0001	-0.004	<0.0001	0.0001	0.0005	-0.0005	-0.0002	<0.0001	-0.0006	-0.0001	-0.0002	-0.0003	<0.0001	<0.0001	--	-0.004	-0.0004	<0.0001
Alcohol use	-0.004	<0.0001	<0.0001	<0.0001	-0.009	0.0001	<0.0001	0.001	0.0004	-0.0002	<0.0001	<0.0001	0.00003	0.00004	0.0004	<0.0001	0.0002	-0.004	--	0.0005	<0.0001
UGI bleeding	0.003	<0.0001	<0.0001	<0.0001	-0.0009	0.0009	0.0002	0.003	0.0002	0.001	0.0004	<0.0001	0.00007	-0.005	0.001	-0.003	0.0003	-0.0004	0.0005	--	<0.0001
NIHSS scores at discharge	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	--

Table S2. The correlation matrices of the variables for one-year stroke recurrence by Cox model.

						TOAST Subtype														
	Aspirin / Clopidogrel	Age	BMI	Hospitalization length	Male	SVD	Cardioembolism	Specific etiology	Undetermined etiology	Hypertension	Diabetes mellitus	Dyslipidemia	Previous CVA/TIA	Atrial fibrillation	Ischemic heart disease	Congestive heart failure	Acute MI	Smoking	Alcohol use	UGI bleeding	NIHSS scores at discharge
Aspirin / Clopidogrel	--	<0.0001	<0.0001	<0.0001	<0.0001	-0.0001	<0.0001	-0.0001	-0.0003	<0.0001	<0.0001	<0.0001	0.0004	<0.0001	0.0006	0.0001	0.0008	<0.0001	-0.0002	0.003	<0.0001
Age	<0.0001	--	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
BMI	<0.0001	<0.0001	--	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Hospitalization length	<0.0001	<0.0001	<0.0001	--	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Male	<0.0001	<0.0001	<0.0001	<0.0001	--	0.0001	<0.0001	-0.0003	-0.0002	0.0004	0.0002	0.0003	-0.0002	<0.0001	-0.0003	<0.0001	-0.0008	-0.002	-0.0005	-0.0002	<0.0001
TOAST Subtype																					
SVD	-0.0001	<0.0001	<0.0001	<0.0001	0.0001	--	--	--	--	0.0002	0.0002	<0.0001	-0.0001	-0.0002	-0.0002	-0.0003	-0.003	<0.0001	0.0001	0.0001	<0.0001
Cardioembolism	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	--	--	--	--	0.0001	<0.0001	<0.0001	<0.0001	-0.002	-0.0004	-0.0003	-0.002	<0.0001	<0.0001	<0.0001	<0.0001
Specific etiology	-0.0001	<0.0001	<0.0001	<0.0001	-0.0003	--	--	--	--	-0.0006	-0.0006	-0.0002	-0.0001	-0.0005	-0.0004	-0.0006	-0.003	0.0001	<0.0001	0.002	<0.0001
Undetermined etiology	-0.0003	<0.0001	<0.0001	<0.0001	-0.0002	--	--	--	--	-0.0001	-0.0003	-0.0002	<0.0001	0.01	0.0005	-0.0009	0.0004	-0.0002	0.0002	-0.0009	<0.0001
Hypertension	<0.0001	<0.0001	<0.0001	<0.0001	0.0004	0.0002	0.0001	-0.0007	<0.0001	--	-0.0006	-0.0004	-0.0006	-0.0002	-0.0003	-0.0001	0.0006	-0.0001	-0.0001	-0.0004	<0.0001
Diabetes mellitus	<0.0001	<0.0001	<0.0001	<0.0001	0.0002	0.0002	<0.0001	-0.0006	-0.0003	-0..0006	--	-0.004	-0.0003	<0.0001	-0.0003	-0.0003	-0.0003	<0.0001	<0.0001	<0.0001	<0.0001
Dyslipidemia	<0.0001	<0.0001	<0.0001	<0.0001	0.0003	<0.0001	<0.0001	-0.0002	-0.0002	-0.0006	-0.0004	--	<0.0001	<0.0001	-0.0001	<0.0001	<0.0001	-0.003	<0.0001	<0.0001	<0.0001
Previous CVA/TIA	0.0004	<0.0001	<0.0001	<0.0001	-0.0002	-0.0001	<0.0001	-0.0001	<0.0001	-0.0006	-0.0003	<0.0001	--	<0.0001	<0.0001	<0.0001	0.0003	<0.0001	0.00001	0.00002	<0.0001

Atrial fibrillation	0.0008	<0.0001	<0.0001	<0.0001	-0.0008	-0.002	-0.002	-0.0005	0.01	-0.0002	<0.0001	<0.0001	<0.0001	--	0.0005	-0.08	0.004	<0.0001	0.0002	-0.003	<0.0001
Ischemic heart disease	0.0006	<0.0001	<0.0001	<0.0001	-0.0003	-0.0002	-0.0004	-0.0004	0.0005	-0.0003	-0.0003	-0.0001	<0.0001	0.0005	--	-0.002	-0.003	-0.0001	0.0002	<0.0001	<0.0001
Congestive heart failure	0.00001	<0.0001	<0.0001	<0.0001	<0.0001	-0.0003	-0.0003	-0.0006	-0.0009	-0.0001	-0.0003	<0.0001	<0.0001	-0.008	-0.002	--	-0.001	<0.0001	<0.0001	-0.003	<0.0001
Acute MI	0.0008	<0.0001	<0.0001	<0.0001	-0.0007	-0.003	-0.002	-0.003	0.004	0.0006	-0.0003	<0.0001	0.0003	0.004	-0.003	-0.001	--	-0.0004	<0.0001	<0.0001	<0.0001
Smoking	<0.0001	<0.0001	<0.0001	<0.0001	-0.002	<0.0001	<0.0001	0.0001	-0.0002	-0.0001	<0.0001	-0.0003	<0.0001	<0.0001	-0.0001	<0.0001	-0.0004	--	-0.001	-0.0001	<0.0001
Alcohol use	-0.0002	<0.0001	<0.0001	<0.0001	-0.0005	0.0001	0.0001	<0.0001	0.0002	-0.0001	<0.0001	<0.0001	0.0001	0.0002	0.0002	<0.0001	0.0004	-0.001	--	-0.0003	<0.0001
UGI bleeding	0.0003	<0.0001	<0.0001	<0.0001	-0.0002	0.0001	<0.0001	0.002	-0.0009	-0.0004	<0.0001	<0.0001	0.0002	-0.003	0.0005	-0.003	0.00007	-0.0001	<0.0001	--	<0.0001
NIHSS scores at discharge	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	--