Comparison of long-term efficacy and safety between cilostazol and clopidogrel in chronic ischemic stroke: a nationwide cohort study

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Abstract

Background: Previous clinical trials showed a significant difference in efficacy and safety among antiplatelets in acute ischemic stroke (IS). The present study wished to compare the efficacy and safety head-to-head between cilostazol and clopidogrel in chronic IS.

Methods: This open prospective cohort study recruited chronic IS patients with an index hospitalization between 2001 and 2013 from Taiwan National Health Insurance Research Database. In the 504,191 hospitalized patients, patients who had missing information and history of atrial fibrillation or rheumatic heart disease, received mechanical valve replacement or anticoagulants, expired during the index hospitalization, received follow-up ≤6 months, or had recurrent stroke within 6 months after index stroke were excluded.

Results: Among the 15,968 eligible patients, 502 patients who consistently received either cilostazol or clopidogrel from the 7th month after the index stroke were included for analysis after propensity score matching. The 3-year primary outcomes showed similar frequency of recurrent IS, all-cause mortality, and acute myocardial infarction (AMI), and similar frequency of intracerebral hemorrhage, gastrointestinal bleeding, and major bleeding between the cilostazol and clopidogrel groups. Subgroup analysis revealed that patients with a history of hypertension or gastrointestinal bleeding had a trend of having lower frequency of recurrent IS or major bleeding, respectively, in the cilostazol group.

Conclusion: The present real-world study demonstrated no significant difference in efficacy and safety between cilostazol and clopidogrel in chronic IS. However, cilostazol might be better than clopidogrel in patients with a history of hypertension or gastrointestinal bleeding.

Keywords: chronic stroke, cilostazol, clopidogrel, efficacy, ischemic stroke, safety

Introduction

Intensive triple antiplatelet therapy for recent ischemic stroke (IS) could not reduce the incidence and severity of recurrent stroke or transient ischemic attack (TIA). However, triple therapy was found to significantly increase the risk of major bleeding and was not suggested to be used in routine clinical practice for acute IS.[1] Dual antiplatelet therapy (DAPT) using aspirin and clopidogrel is reported to be a preferable choice to reduce recurrent IS, especially when given in acute IS.[2–4] DAPT was found to be effective only for short-term use,[2,5] and could cause increased risk of early major and gastrointestinal bleeding even in minor stroke.[2,3,6] Although the bleeding risks declined after the first month in trial cohorts,[7] DAPT is suggested to shift to antiplatelet monotherapy in chronic IS.

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Single antiplatelet agents have only modest efficacy in secondary prevention of IS, particularly in patients with multiple risk factors such as cervicocephalic arterial stenosis, diabetes, and hypertension. In patients with aspirin monotherapy, early treatment has been found to have a significant effect compared with placebo in Chinese and Caucasian populations.[8,9] Aspirin may have a higher risk of hemorrhagic complications in acute stroke compared with that in chronic stroke.[10] If patients on aspirin experience recurrent IS or TIA, switching to, or adding, another antiplatelet agent, especially in the first few days after the index event, was reported to be preventive against subsequent vascular events compared with maintaining aspirin alone.[11,12]

Clopidogrel was reported to have better efficacy than aspirin in reducing the combined risk of IS, myocardial infarction, or vascular death.[13] Also, clopidogrel is more effective and safer than aspirin in reducing adverse cardiovascular events in patients with atherosclerosis.[14] In the comparison between cilostazol and aspirin, both were reported to be effective in acute IS, and cilostazol prevented IS recurrence without increasing the incidence of serious bleeding.[15–18] The above-mentioned clinical trials compared antiplatelet monotherapy in acute IS (within 6 months of index stroke), and most of these trials showed better efficacy and/or safety of cilostazol and clopidogrel compared with aspirin. A recent review suggested antiplatelet therapies should differ in acute and chronic IS,[19] with more aggressive antiplatelet treatment in acute IS patients with high-risk stroke or TIA, whereas there is no solid evidence to support different antiplatelet strategies in acute and chronic IS in patients with low-risk noncardioembolic stroke.

Until now, no report has discussed comparison between cilostazol and clopidogrel in chronic IS. The present study wished to compare the long-term efficacy and safety between cilostazol and clopidogrel in chronic IS (from the 7th month after index stroke) head-to-head using a real-world database.

Materials and methods

Data source
In Taiwan, the National Health Insurance (NHI) program covers more than 99% of the entire population. The National Health Insurance Research Database (NHIRD) includes medical and cost data submitted to NHI. Clinical diagnoses are recorded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, and are monitored routinely by the NHI Bureau. The advantages of NHIRD for a nationwide cohort study include large sample size and low selection bias.

Patient enrollment and inclusion/exclusion criteria
This open prospective cohort study recruited patients with chronic IS (after the 7th month of index stroke) who were hospitalized due to acute IS between 1 January 2001 and 31 December 2013. The medical history of these enrolled patients was reviewed from 1997 to 2013. The reason for using NHIRD data before 2013 was that, after 2013, generic drugs for cilostazol and clopidogrel gradually came into use, which might cause bias in analysis. The primary diagnosis of acute IS in the NHIRD used ICD-9-CM codes (Supplemental Table S1). The diagnostic codes of acute IS have been validated in previous NHIRD studies.[20] Patients who had missing information and previous history of atrial fibrillation, rheumatic heart disease, mechanical valve replacement, or anticoagulant usage were excluded. Only those patients who received regular follow up in chronic IS were enrolled for analysis. Those who expired during the index hospitalization, whose follow up was less than 6 months due to any etiologies, or who had recurrent stroke or acute myocardial infarction (AMI) within 6 months after the index stroke were excluded. To compare long-term efficacy and safety between cilostazol and clopidogrel in chronic IS, patients who did not receive any antiplatelet treatment, or received antiplatelet treatment other than cilostazol or clopidogrel in chronic IS, were excluded.

Not all patients were directly contacted by researchers for these data in NHIRD, and all data were disconnected from the patients. Thus, informed consent from the study participants was not required[21]; the study was approved by the Ethics Institutional Review Board of our hospital (IRB No.: 201800708B1). Also, since there are strict safeguards implemented in NHIRD, the Taiwan government considers that, for research

purposes, there is no requirement for patients' informed consent (either in the form of an opt-in or an opt-out).[22]

Exposure to study drugs

We divided the eligible patients into two groups according to the antiplatelet drug prescribed in chronic IS: (1) cilostazol, and (2) clopidogrel. To ensure consistent use of the study drugs in each group, we excluded patients who took any cilostazol in the clopidogrel group, and those who took any clopidogrel in the cilostazol group for even 1 day during a 2-year exposure period. For assessment of adherent medication use, we determined the medication possession rate calculated by dividing the number of days of medication prescribed (numerator) by the number of days (denominator) in a time period of 6 months (183 days).[23,24] Patients were further excluded if their medication possession rates of the study drugs were less than 50% (<92 days) in chronic IS. We defined the index stroke as the first hospitalization due to acute IS between 1 January 2001 and 31 December 2013. The follow-up period was calculated from the admission day of the index stroke to the date of death, date of event occurrence, or until 31 December 2013, whichever occurred first.

Outcomes and covariate measurements

We defined a comorbidity of the enrolled population using the diagnosis code in at least two consecutive outpatient visits, or in one inpatient record in the years previous to the index hospitalization. Previous events (i.e., stroke) were detected using the hospitalization diagnosis prior to the index stroke and tracked backwards to 1997. In addition, we further verified the diagnoses of hemodialysis and cancer using the catastrophic illness certificates recorded in NHIRD. The Charlson comorbidity index (CCI) was used to measure the patient's global health condition. The majority of these comorbidities have previously been validated based on ICD-9-CM codes.[25,26] The stroke severity index was used to estimate the National Institutes of Health Stroke Scale (NIHSS) score to quantify the severity of IS, as validated in previous NHIRD studies.[27] We confirmed the use of other medications with Anatomical Therapeutic Chemical codes that fulfilled two outpatient prescriptions or one refill prescription in the pharmacy. The clinical functional outcomes were defined as admission due to recurrent acute IS, all-cause mortality, AMI, intracerebral hemorrhage (ICH), gastrointestinal bleeding, and major bleedings. These outcomes were detected using principal diagnosis at the index hospitalization. The definitions of all-cause mortality, AMI, gastrointestinal bleeding, and major bleeding were the same as those used in our previous NHIRD study.[28]

Statistical analysis

We used propensity score matching to balance the distribution of baseline characteristics and the use of non-study medications between the two study groups. The selected covariates in calculating propensity score included the variables listed in Table 1 and the index date. We adopted the greedy nearest neighbor matching algorithm, and set the caliper as $0.2\times$ the standard deviation (SD) of the logit of the propensity score. To minimize bias of treatment effect estimation, we used a 1:1 matching ratio.[29]

The baseline characteristics between the two groups were compared using two-sample *t* test for continuous variables and chi-square test for categorical variables. The risk of time to event between the two groups after propensity score matching was compared using a Cox proportional hazard model in which the study group was the independent variable and the matching pairs were stratified. We further analyzed whether the conclusions were consistent among different pre-specified subpopulations. Age, gender, stroke severity, use of calcium channel blockers or angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, and a history of gastrointestinal bleeding, coronary artery disease, peripheral artery disease, hypertension, and diabetes mellitus were the selected factors for subgroup analyses.

Because treatment of cardiovascular disease could have a direct impact on the stability of atherosclerotic plaque in the carotid arteries, we conducted a sensitivity analysis by excluding patients with cardiovascular disease. All data analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was set at $p < 0.05$, and no adjustment of multiple testing (multiplicity) was made in this study. The clinical significance of subgroup analyses was loosened to $p < 0.10$ because the

Table 1. Baseline characteristics before and after propensity score matching.

Characteristics, n (%)	Before matching			After matching		
	Cilostazol (n = 632)	Clopidogrel (n = 15,336)	p value	Cilostazol (n = 502)	Clopidogrel (n = 502)	p value
Age (years, mean ± SD)	71.6 ± 11.9	69.7 ± 11.8	<0.001	71.9 ± 11.3	71.5 ± 10.5	0.556
Age group			<0.001			0.465
<40 years	8 (1.3)	178 (1.2)		4 (0.8)	3 (0.6)	
40–75 years	342 (54.1)	9628 (62.8)		272 (54.2)	291 (58.0)	
>75 years	282 (44.6)	5530 (36.1)		226 (45.0)	208 (41.4)	
Gender			<0.001			1.000
Male	337 (53.3)	9254 (60.3)		267 (53.2)	267 (53.2)	
Female	295 (46.7)	6082 (39.7)		235 (46.8)	235 (46.8)	
Previous event						
Previous ischemic stroke	64 (10.1)	1605 (10.5)	0.785	46 (9.2)	56 (11.2)	0.296
Previous hemorrhage stroke	6 (0.9)	147 (1.0)	0.982	3 (0.6)	1 (0.2)	0.316
Previous myocardial infarction	22 (3.5)	641 (4.2)	0.388	17 (3.4)	20 (4.0)	0.615
Previous epilepsy	22 (3.5)	472 (3.1)	0.566	15 (3.0)	17 (3.4)	0.719
Previous dementia	26 (4.1)	450 (2.9)	0.087	19 (3.8)	19 (3.8)	1.000
Old major bleeding	53 (8.4)	970 (6.3)	0.038	27 (5.4)	27 (5.4)	1.000
Old gastrointestinal bleeding	175 (27.7)	3866 (25.2)	0.160	120 (23.9)	120 (23.9)	1.000
Comorbidity						
Coronary artery disease	160 (25.3)	3612 (23.6)	0.306	122 (24.3)	123 (24.5)	0.941
Chronic kidney disease	68 (10.8)	965 (6.3)	<0.001	38 (7.6)	29 (5.8)	0.255
Dialysis	33 (5.2)	330 (2.2)	<0.001	8 (1.6)	8 (1.6)	1.000
Chronic obstructive pulmonary disease	61 (9.7)	1477 (9.6)	0.986	47 (9.4)	49 (9.8)	0.830
Peripheral arterial disease	160 (25.3)	459 (3.0)	<0.001	58 (11.6)	58 (11.6)	1.000
Hypertension	392 (62.0)	9054 (59.0)	0.134	310 (61.8)	315 (62.7)	0.745
Diabetes mellitus	291 (46.0)	4826 (31.5)	<0.001	216 (43.0)	216 (43.0)	1.000
Heart failure	54 (8.5)	745 (4.9)	<0.001	36 (7.2)	33 (6.6)	0.708
Dyslipidemia	132 (20.9)	2732 (17.8)	0.049	97 (19.3)	108 (21.5)	0.389

(Continue)

Table 1. (Continue)

Characteristics, *n* (%)	Before matching			After matching		
	Cilostazol (*n* = 632)	Clopidogrel (*n* = 15,336)	*p* value	Cilostazol (*n* = 502)	Clopidogrel (*n* = 502)	*p* value
Malignancy	36 (5.7)	830 (5.4)	0.757	28 (5.6)	30 (6.0)	0.787
Liver cirrhosis	14 (2.2)	289 (1.9)	0.550	11 (2.2)	15 (3.0)	0.427
Lipid lowering agent						
Statin	178 (28.2)	5041 (32.9)	0.013	144 (28.7)	159 (31.7)	0.302
DM medication						
Insulin	91 (14.4)	1053 (6.9)	<0.001	58 (11.6)	46 (9.2)	0.214
Metformin	165 (26.1)	3452 (22.5)	0.034	126 (25.1)	138 (27.5)	0.390
TZD	61 (9.7)	663 (4.3)	<0.001	38 (7.6)	29 (5.8)	0.255
Sulfonylurea	158 (25.0)	3532 (23.0)	0.250	124 (24.7)	141 (28.1)	0.224
Anti-HTN drug						
Beta-blocker	189 (29.9)	4074 (26.6)	0.063	138 (27.5)	131 (26.1)	0.618
Alpha-blocker	35 (5.5)	1020 (6.7)	0.270	32 (6.4)	40 (8.0)	0.328
CCB	242 (38.3)	6684 (43.6)	0.009	198 (39.4)	205 (40.8)	0.652
ARB	251 (39.7)	6438 (42.0)	0.258	194 (38.6)	209 (41.6)	0.334
ACEI	112 (17.7)	2633 (17.2)	0.718	92 (18.3)	91 (18.1)	0.935
Diuretics	105 (16.6)	1946 (12.7)	0.004	81 (16.1)	69 (13.7)	0.288
Others	9 (1.4)	269 (1.8)	0.534	6 (1.2)	8 (1.6)	0.590
Estimated NIHSS	6.2 ± 4.5	7.2 ± 5.4	<0.001	6.4 ± 4.7	6.7 ± 4.8	0.303
Estimated NIHSS group			<0.001			0.553
≤5	443 (70.1)	9618 (62.7)		346 (68.9)	333 (66.3)	
6–13	130 (20.6)	3397 (22.2)		105 (20.9)	108 (21.5)	
>13	59 (9.3)	2321 (15.1)		51 (10.2)	61 (12.2)	
CCI score	3.2 ± 1.9	2.9 ± 1.8	<0.001	3.0 ± 1.8	3.1 ± 1.9	0.784
Hospital level			<0.001			1.000
Medical center	101 (16.0)	6634 (43.3)		84 (16.7)	84 (16.7)	
Region hospital	321 (50.8)	6912 (45.1)		279 (55.6)	279 (55.6)	
District hospital	210 (33.2)	1790 (11.7)		139 (27.7)	139 (27.7)	

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TZD, thiazolidinedione.
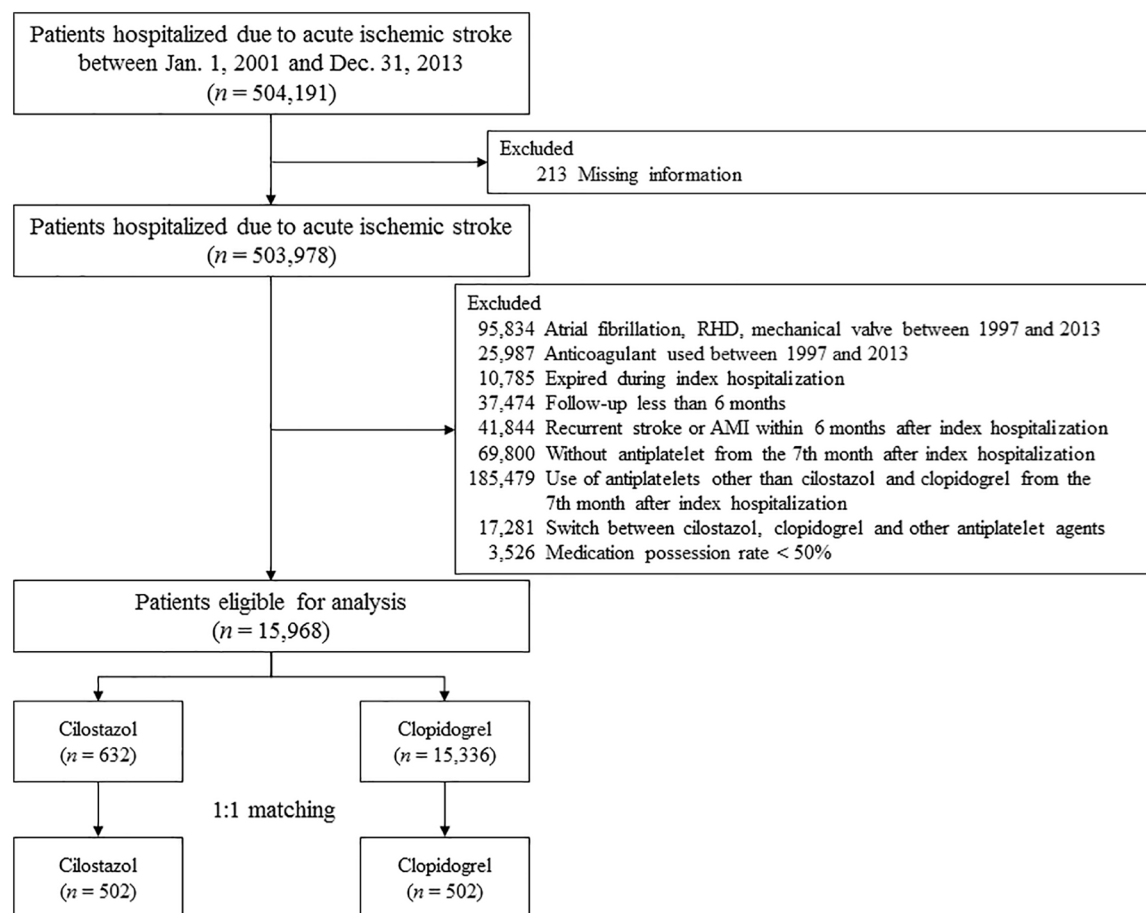
Figure 1. Flow chart of the enrollment of study patients.
Patients hospitalized due to acute IS are enrolled after relevant exclusions and then further divided into two groups according to the prescribed cilostazol and clopidogrel therapy.
AMI, acute myocardial infarction; IS, ischemic stroke; RHD, rheumatic heart disease.

interaction test was known to be more conservative and less powerful.[29,30]

Results

Study patients

Between 1 January 2001 and 31 December 2013, among 504,191 hospitalized patients due to acute IS, 503,978 patients (99.96%) without missing information were included. Based on the inclusion/exclusion criteria, 15,968 patients (3.17%) were eligible for analysis. There were 502 patients in each group after propensity score matching (Figure 1). Aspirin was the most common treatment regimen (97.9%) in the 185,479 patients, with the use of antiplatelets other than cilostazol and clopidogrel from the 7th month after index hospitalization (Figure 1).

Baseline characteristics

Before propensity score matching, there were 632 patients in the cilostazol group and 15,336 patients in the clopidogrel group. The age at stroke was older in the cilostazol group (cilostazol *versus* clopidogrel; 71.6 ± 11.9 *versus* 69.7 ± 11.8, $p < 0.001$). The cilostazol group had more female patients and higher frequency of chronic kidney disease, peripheral artery disease, diabetes mellitus, heart failure, and dyslipidemia than the clopidogrel group ($p < 0.05$). The excluded patients had less stroke severity, with estimated NIHSS score 5.6 ± 3.7 compared with 6.2 ± 4.5 in Cilostazol group and 7.2 ± 5.4 in Clopidogrel group ($p < 0.001$, Table 1 and Supplemental Table S2). After propensity score matching, the frequency of baseline characteristics, comorbidities, previous events, stroke severity, and medications including anti-diabetic agents, lipid lowering agents, and anti-hypertensive

Table 2. Primary outcomes during follow up.

Outcome	Event (%)		Cilostazol *versus* Clopidogrel	
	Cilostazol (*n* = 502)	Clopidogrel (*n* = 502)	HR (95% CI)	*p* value
1-year F/U				
ICH	3 (0.6)	2 (0.4)	1.29 (0.20, 8.39)	0.789
GI bleeding	27 (5.4)	37 (7.4)	0.71 (0.42, 1.18)	0.187
Major bleeding	20 (4.0)	27 (5.4)	0.73 (0.40, 1.33)	0.304
Recurrent AIS	22 (4.4)	26 (5.2)	0.72 (0.40, 1.30)	0.271
AMI	3 (0.6)	3 (0.6)	1.46 (0.26, 8.09)	0.666
All-cause mortality	20 (4.0)	21 (4.2)	1.11 (0.58, 2.09)	0.760
2-year F/U				
ICH	5 (1.0)	8 (1.6)	0.73 (0.22, 2.41)	0.609
GI bleeding	46 (9.2)	55 (11.0)	0.84 (0.56, 1.26)	0.390
Major bleeding	39 (7.8)	49 (9.8)	0.85 (0.55, 1.33)	0.484
Recurrent AIS	47 (9.4)	51 (10.2)	0.96 (0.63, 1.46)	0.850
AMI	3 (0.6)	5 (1.0)	0.63 (0.14, 2.84)	0.545
All-cause mortality	49 (9.8)	51 (10.2)	1.13 (0.74, 1.70)	0.576
3-year F/U				
ICH	9 (1.8)	11 (2.2)	0.97 (0.38, 2.48)	0.943
GI bleeding	62 (12.4)	73 (14.5)	0.85 (0.60, 1.21)	0.362
Major bleeding	51 (10.2)	65 (12.9)	0.83 (0.56, 1.21)	0.328
Recurrent AIS	57 (11.4)	66 (13.1)	0.89 (0.61, 1.29)	0.525
AMI	6 (1.2)	8 (1.6)	0.97 (0.32, 3.00)	0.963
All-cause mortality	71 (14.1)	75 (14.9)	1.10 (0.78, 1.55)	0.585

AIS, acute ischemic stroke; AMI, acute myocardial infarction; CI, confidence interval; F/U, follow up; GI, gastrointestinal; HR, hazard ratio; ICH, intracerebral hemorrhage.

drugs was comparable between the two study groups ($p > 0.05$, Table 1).

The dose of cilostazol was 121.2 ± 53.6 mg/day, with ≤100 mg/day in 302 (47.8%) patients and >100 mg/day in 330 (52.2%) patients before propensity score matching, and 119.0 ± 51.2 mg/day with ≤100 mg/day in 241 (48.0%) patients and >100 mg/day in 261 (52.0%) patients after propensity score matching ($p > 0.05$). The dose of clopidogrel was 75 mg/day before and after propensity score matching.

Primary outcomes

The primary outcomes in a follow-up period of 3 years were compared between the two study groups after propensity score matching (Table 2). Compared with the clopidogrel group, the cilostazol group had similar efficacy in the occurrence of recurrent acute IS [cilostazol *versus* clopidogrel: 11.4% *versus* 13.1%; hazard ratio (HR), 0.89; 95% confidence interval (CI), 0.61–1.29; Figure 2A], all-cause mortality (14.1% *versus* 14.9%; HR, 1.10; 95% CI, 0.78–1.55; Figure 2B), and AMI (1.2% *versus* 1.6%;
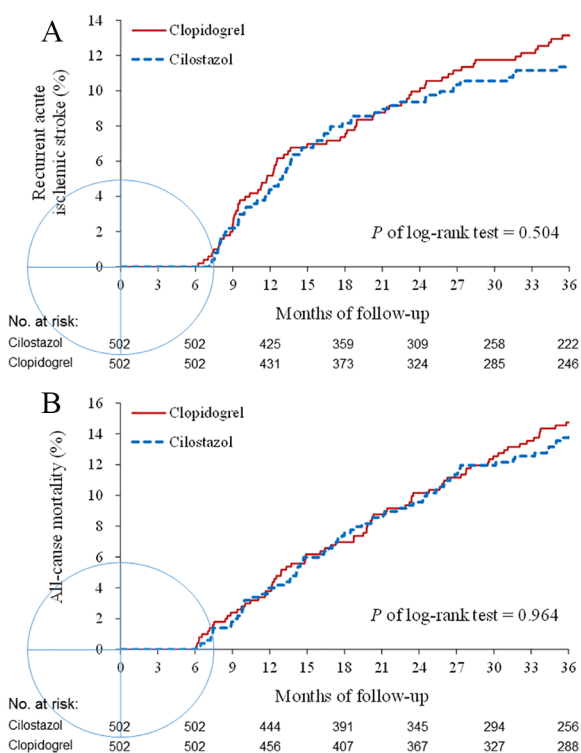
Figure 2. Comparisons of efficacy in the cumulative occurrence of recurrent acute IS (A) and all-cause mortality (B) between cilostazol and clopidogrel groups.
The curves show a similar trend of recurrent acute IS and all-cause mortality between the two groups.
IS, ischemic stroke.

HR, 0.97; 95% CI, 0.32–3.00). The cilostazol group also had similar safety in the occurrence of ICH (cilostazol *versus* clopidogrel: 1.8% *versus* 2.2%; HR, 0.97; 95% CI, 0.38–2.48; Figure 3A), gastrointestinal bleeding (12.4% *versus* 14.5%; HR, 0.85; 95% CI, 0.60–1.21; Figure 3B), and major bleeding (10.2% *versus* 12.9%; HR, 0.83; 95% CI, 0.56–1.21; Figure 3C). After excluding patients with cardiovascular disease, the results showed that the two groups did not differ in the risks of outcomes (Supplemental Tables S3 and S4).

Subgroup analysis
Compared with the clopidogrel group, patients with a hypertension history had a trend of lower risk of recurrent acute IS in the cilostazol group (*p* for interaction, 0.067; Supplemental Figure S1A). Patients with a history of gastrointestinal bleeding also had a trend of lower risk of major bleeding in the cilostazol group (*p* for interaction, 0.094; Supplemental Figure S1B). However, this

trend was not found in the subgroup analysis for gastrointestinal bleeding and all-cause mortality (Supplemental Figure S2A and B).

Discussion
The present study showed that there was no significant difference in efficacy and safety between cilostazol and clopidogrel groups in chronic IS. These results suggest that, after the acute phase of IS, long-term use of cilostazol and clopidogrel could be of similar efficacy and safety for secondary stroke prevention. However, there was a trend of lower frequency of recurrent acute IS or major bleeding in patients with a history of hypertension or gastrointestinal bleeding, respectively, in the cilostazol group. This subgroup analysis may suggest that, in chronic IS, cilostazol has the potential to act better than clopidogrel in some situations. We have summarized all the clinical studies of antiplatelets (Supplemental Table S5) to help the reader better understand that our present study is unique.
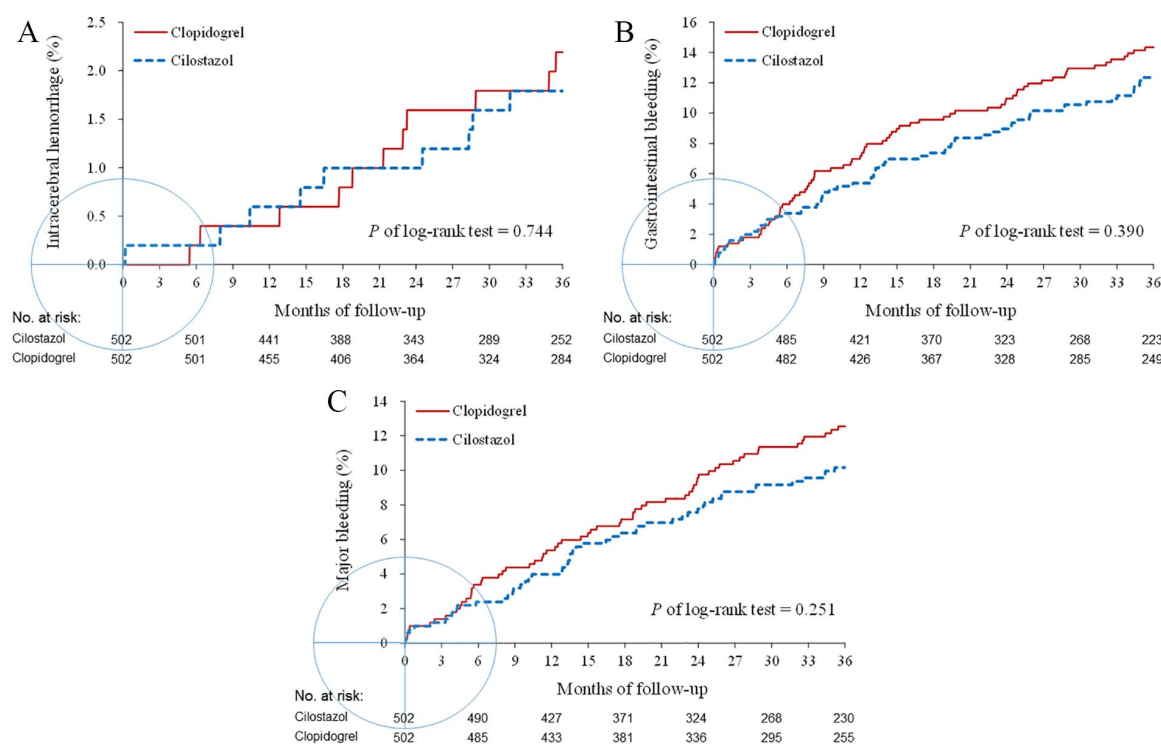
Figure 3. Comparisons of safety in the cumulative occurrence of intracerebral hemorrhage (A), gastrointestinal bleeding (B), and major bleeding (C) between cilostazol and clopidogrel groups. The curves show a similar trend of intracerebral hemorrhage, gastrointestinal bleeding, and major bleeding between the two groups.

In cases with intracranial artery stenosis, cilostazol is reported to prevent the progression of symptomatic intracranial artery stenosis, either alone or in combination with aspirin, and to have better effect than aspirin.[31–33] Also, acute medication with cilostazol was found to be beneficial for the outcome of cerebral infarction due to small vessel disease,[34] and cilostazol could decrease cerebral arterial pulsatility in small vessel disease patients with mild white matter hyperintensity.[35] However, cilostazol plus aspirin had no significant difference compared with clopidogrel plus aspirin with respect to the reduced progression of artery stenosis, new ischemic lesions, and major hemorrhagic complications.[36]

One network meta-analysis study of antiplatelet agents showed that cilostazol had better estimates for overall stroke and hemorrhagic stroke than aspirin.[15–18,37] Another network meta-analysis showed cilostazol significantly reduced IS recurrence in comparison with aspirin or dipyridamole, and also significantly reduced intracerebral hemorrhage compared with aspirin, clopidogrel,

terutroban, ticlopidine, aspirin plus clopidogrel, and aspirin plus dipyridamole.[38] A meta-analysis including 24 randomized trials with over 85,000 patients found long-term monotherapy could be a better choice than long-term dual therapy, and cilostazol demonstrated the best risk–benefit profile for long-term secondary prevention after stroke or TIA.[38] In patients with prior non-cardioembolic IS or TIA, cilostazol had significantly better effectiveness than aspirin and clopidogrel alone in the long-term prevention of serious vascular events, and a significantly lower bleeding risk than low-dose aspirin and aspirin plus dipyridamole.[39] Wang *et al.* also revealed in their network meta-analysis, that cilostazol could improve overall stroke and hemorrhagic stroke in IS or TIA patients compared with other therapies in Asian patients, but with low statistical significance.[37] In a meta-analysis using the Cochrane Stroke Group Trials Registry, cilostazol showed a significantly lower risk of composite outcome of vascular events and hemorrhagic stroke and minor adverse effects compared with aspirin.[40] The use of cilostazol plus aspirin also did not

cause significant increase in bleeding events compared with aspirin monotherapy.[4] It is suggested that DAPT involving cilostazol may therefore be safer than conventional DAPT.[4]

However, some reports did not reveal special benefit when using cilostazol. Kwok *et al.* evaluated the efficacy of different antiplatelets in the secondary prevention after lacunar stroke using 17 trials and concluded that cilostazol showed no consistent reduction in stroke recurrence compared with aspirin.[41] Malloy *et al.* compared different combinations of antiplatelets in the secondary prevention against stroke and found that, although cilostazol had fewer hemorrhagic events compared with aspirin plus dipyridamole or aspirin plus clopidogrel, there was no difference between these combinations in terms of stroke prevention.[42] The latest 2014 American Stroke Association (ASA) Guidelines on secondary stroke prevention also suggested that although some randomized trials in Asian patients showed cilostazol was non-inferior to aspirin in reducing stroke and bleeding events,[43] whether this effect is translatable to other ethnics was uncertain since cilostazol was not studied in non-Asian populations.

In the CHANCE subanalysis, it was found that, when compared with aspirin alone, the use of clopidogrel plus aspirin could reduce the risk of recurrent stroke only in those patients who were noncarriers of CYP2C19 loss-of-function allele and had normal glycated albumin levels.[44,45] This finding suggests that clopidogrel may have limited effect for secondary stroke prevention in Chinese patients due to the high frequency of patients (58.8%) being carriers of CYP2C19 loss-of-function alleles.[44] A Korean study also showed clopidogrel plus aspirin was not superior to aspirin alone in the prevention of new ischemic lesion and clinical vascular events in patients with acute IS caused by large artery atherosclerosis.[46]

In the Sweden cohort study of clopidogrel responsiveness with respect to the presence of microvascular and macrovascular pathology, clopidogrel was nonresponsive in patients with cerebral small vessel disease but not with carotid atherosclerosis.[47] Among Caucasian patients with recent lacunar strokes, the addition of clopidogrel to aspirin did not significantly reduce the risk of recurrent stroke compared with aspirin alone.[48] However, in symptomatic intracranial artery stenosis, the combination therapy of clopidogrel and aspirin was found to be more effective than aspirin alone in reducing microembolic signals and recurrent stroke.[49,50] Since the frequency of intracranial artery stenosis and cerebral infarction due to small vessel disease is reported more commonly in Asian IS patients, it is possible cilostazol could be competitive to clopidogrel in secondary stroke prevention in Asian patients.

When examining the different phases of stroke, Shi *et al.* found in their meta-analysis,[51] cilostazol had no effect on major outcomes in acute stroke, but showed a significantly reduced risk of stroke recurrences and hemorrhagic stroke compared with placebo or aspirin in chronic stroke. In the acute phase of stroke, increased intracranial pressure and blood pressure can be the precipitating factors to induce bleeding from stress ulcer under the use of antiplatelets.[52] In the review reports of adverse event submitted to the United States Food and Drug Administration, both aspirin and clopidogrel were associated with hemorrhage, but the association was more noteworthy for clopidogrel. As for gastrointestinal bleeding complications, the statistical metrics suggested a stronger association for aspirin than clopidogrel.[52] In the population-based retrospective cohort study using Taiwan NHIRD, the clopidogrel alone group and the clopidogrel plus PPI group were found to have lower risk of gastrointestinal events than the aspirin plus PPI group.[53] In the comparison of quantitative bleeding time and platelet aggregation test among aspirin, clopidogrel, and cilostazol, cilostazol was found to be as effective as aspirin or clopidogrel in inhibiting platelet aggregation. Aspirin and clopidogrel could cause prolonged bleeding time, but cilostazol did not alter any bleeding time parameters.[54] These data suggest that cilostazol has similar efficacy in inhibiting platelet aggregation without prolonging the bleeding time and changing the bleeding pattern. Animal studies showed that clopidogrel could increase gastric bleeding and ulcerogenic responses induced by aspirin, whereas cilostazol suppressed these responses.[55] It is suggested cilostazol may be used safely in combination with aspirin without increasing the risk of gastric bleeding.[55] The present study demonstrated that both cilostazol and clopidogrel had similar bleeding risk, including ICH, gastrointestinal bleeding, and major bleeding in chronic IS. In clinical practice, it is likely that both cilostazol and clopidogrel can be used to replace

aspirin when there is aspirin-induced bleeding in either acute or chronic IS.

The present study had some limitations. First, ICD-9-CM might be coded inaccurately. However, a previous validation study had proved high accuracy of NHIRD in recording IS diagnoses, suggesting that NHIRD appears to be a valid resource for population research in IS.[20] Second, NHIRD does not record stroke severity (NIHSS) and clinical functional outcome (Barthel index and mRS). To adjust for this limitation, we used the stroke severity index as a valid proxy for NIHSS, since NHIRD-based stroke severity index has been validated to be an effective adjustment for stroke severity in stroke outcome studies.[27,56] Also, we used admission due to comorbidities, including recurrent acute IS, all-cause mortality, AMI, ICH, gastrointestinal bleeding, and major bleeding as clinical outcome. Third, drug switching, combinations, and adherence are important confounders. The present study managed to control for adherence to cilostazol and clopidogrel, and only those patients who consistently used the study drugs were included. Fourth, it is difficult to know from NHIRD why cilostazol or clopidogrel was used for secondary stroke prevention instead of aspirin since Taiwan Stroke Society guidelines suggest aspirin should be used as the first-line medication (http://www.stroke.org.tw/guideline/guideline_index.asp). However, as seen in Table 1, 50.8% in cilostazol group and 47.2% in clopidogrel group had previous events of stroke, AMI, or bleeding, which suggested that cilostazol or clopidogrel might be used to replace aspirin due to aspirin failure or aspirin-related side effects. Also, there were high comorbidity rates of coronary artery disease, chronic kidney disease, peripheral artery disease, and heart failure in both groups, which may encourage doctors to use high-potency antiplatelets for the prevention of vascular events. Fifth, NHIRD does not contain adequate data for the definite classification of stroke subtypes. Also, s previous study has reported that the use of modifier codes was not effective in helping improve the accuracy of ICD-9-CM coding for the identification of patients with acute IS and the classification of stroke subtype.[57] So, we did not attempt stroke subtyping in our manuscript. Sixth, for stroke prevention, cilostazol is advised to be taken at a dose of 200 mg/day. However, in the present study, about 48% patients took cilostazol ≤100 mg/day, which could be due to the side effects of headache and tachycardia that discourage patients from taking the full dose. It is possible that cilostazol may be more effective than clopidogrel if the full dose is taken. Future study is needed to clarify this issue by comparing patients with full dose cilostazol with those with clopidogrel in a larger patient population. Lastly, most clinical trials focus on comparing the efficacy and safety of antiplatelets in acute IS, and the efficacy and safety for cilostazol were studied mainly in Asian patients in our and other studies. Generalizability to non-Asian patients awaits further investigation, and larger controlled clinical trials, which should also include non-Asian stroke patients, are needed for further confirmation.

Conclusion

The present study is the first real-world study with strict inclusion/exclusion criteria to compare long-term efficacy and safety between cilostazol and clopidogrel in chronic IS in Asian stroke patients. Although previous clinical trials have demonstrated significant differences in efficacy and safety among antiplatelets in acute IS, the present study revealed no significant difference in efficacy and safety between cilostazol and clopidogrel in chronic IS. It is possible that, in the chronic phase of IS, besides antiplatelet treatment, other regimens such as risk factor control for hypertension, diabetes, dyslipidemia, and smoking, and lifestyle modification, etc., could be also important in the secondary prevention of IS.

Author contributions

THL participated in generating original ideas, in study design and analysis of data, in drafting of the manuscript critically for important intellectual content and in final approval of the manuscript submitted. Other co-authors participated in (1) conception and design or analysis and interpretation of data, or both: YSL and CHL; (2) drafting of the manuscript or revising it critically for important intellectual content: YSL, CCC, CWL, JDL, TIP, and CHL; (3) data acquirement and statistics performing: YSL and CHL and (4) final approval of the manuscript submitted: THL, YSL, CCC, CWL, JDL, TIP, and CHL.

Conflict of interest statement

TH Lee is the consultant of "Clopidogrel study in stroke" advisory board conducted by SANOFI-AVENTIS GROUP.

The other authors have no conflict of interest to disclosure.

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Supplemental material
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