Comparison of Antiplatelet and Antithrombotic Therapy for Secondary Prevention of Ischemic Stroke in Patients With Peripheral Artery Disease

– Population-Based Follow-up Study in Taiwan –

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Background: A limited number of studies have assessed the benefit and risk among the different antiplatelet and antithrombotic therapies in patient with stroke and peripheral artery disease (PAD). We compared the efficacy and safety of clopidogrel, cilostazol, warfarin, and aspirin.

Methods and Results: A retrospective cohort study analyzing the Taiwan National Health Insurance Research Dataset identified patients with stroke and PAD from 2002 to 2008. Patients were stratified according to their use of aspirin, clopidogrel, cilostazol, warfarin or combination therapy. A total of 1,686 patients were enrolled: aspirin (n=862), clopidogrel (n=92), warfarin (n=136), cilostazol only (n=515), and cilostazol-based combination therapy (n=81). Compared with aspirin, cilostazol could reduce the risk of ischemic stroke [hazard ratio (HR) 0.79, 95% confidence interval (CI) 0.63–0.98, P=0.0349] and no increase in hemorrhagic events (HR 0.98, 95% CI 0.74–1.32, P=0.9122). Clopidogrel decreased the risk of ischemic stroke (HR 0.47, 95% CI 0.29–0.78, P=0.0033) and hemorrhagic events (HR 0.64, 95% CI 0.31–0.96, P=0.034) more than aspirin. There was no statistical difference regarding the risk of stroke and hemorrhagic events among warfarin, cilostazol-based combination therapy and aspirin.

Conclusions: Cilostazol and clopidogrel were more effective in preventing recurrent ischemic stroke without increased hemorrhagic events than aspirin in patients with PAD. (*Circ J* 2013; **77**: 1046–1052)

Key Words: Aspirin; Cilostazol; Clopidogrel; Peripheral artery disease; Stroke

Cerebrovascular disease (CVD) can cause several physical and mental disabilities and results in a great economic burden on the Taiwanese healthcare system.^{1–3} In previous epidemiological studies, the major type of CVD has been cerebral infarction and 66% of the causes of acute cerebral infarction were large artery atherosclerosis, lacunae and cardiogenic embolism.^{4,5} Current treatments, including antiplatelet agents and anticoagulants, for prevention of stroke should be based on the underlying pathophysiology.

In the REACH (REduction of Atherothrombosis for Continued Health) registry, patients with more than 1 vascular bed affected by atherosclerotic disease, such as CVD plus CAD (coronary artery disease) and/or PAD (peripheral artery disease), had higher rates of cardiovascular and cerebrovascular events

than patients with CVD alone.^{6,7} In patient with ischemic stroke, a lower ankle-brachial index (ABI) was found to be associated with poor CVD outcome, more severe carotid artery stenosis, and a higher rate of cardiovascular events and death.^{8–10} Therefore, it is mandatory to prevent recurrent cerebrovascular events in patients with coexisting CVD and PAD.

Antiplatelet agents play an important role in preventing atherothrombotic events. Aspirin and clopidogrel are effective for protection of atherothrombotic disease in high-risk populations.^{11,12} Cilostazol is an antiplatelet agent that inhibits platelet aggregation via inhibition of cyclic AMP phosphodiesterase III and increase in cyclic AMP concentrations.¹³ It is indicated in PAD patients with intermittent claudication.¹⁴ In the recent Cilostazol Stroke Prevention Study (CSPS) and CSPS

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2 trials, it was more effective and safe than aspirin and placebo for the secondary prevention of non-cardioembolic ischemic stroke in Asian populations.^{15,16} Although anticoagulant therapy can reduce major cardiovascular events in patients with CAD, its benefit for intermittent claudication and risk reduction of vascular ischemic events in the PAD population is not established.^{14,17} Therefore, we investigated the efficacy and safety of aspirin, clopidogrel, cilostazol, warfarin, and cilostazol-based combination therapy for secondary prevention of ischemic stroke in patients with PAD.

Methods

Data Source

Data from the National Health Insurance Research Dataset (NHIRD), published by the National Health Research Institute (NHI) in Taiwan, which provided a database of 1,000,000 random subjects, were analyzed. The NHI program has been operating in Taiwan since 1995, offering a comprehensive, unified, and universal health insurance program to all citizens who have established a registered domicile for at least 4 months in Taiwan. The coverage includes outpatient service, inpatient care, Chinese medicine, dental care, childbirth, physical therapy, preventive health care, home care, and rehabilitation for chronic mental illness. In 2000, 96.16% of the whole popula-

tion were covered and by the end of 2004 it had increased to 99%. The NHI medical claims database includes ambulatory care, hospital inpatient care, dental services, and prescription drugs. Therefore, the NHIRD is one of the largest and most complete nationwide population-based datasets in Taiwan and there were no statistically significant differences in age, sex, and average insured payroll-related amount between the sample group and all enrollees.

Study Sample

This study population consisted of all patients with more than 2 outpatient or inpatients claims with a diagnosis of PAD (ICD-9-CM: 250.7, 443, 443.81, 443.9, 444.2, 785.4) and prior stroke (ICD-9-CM: 430–438) between July 1, 2002, and December 31, 2008. The data of the first claim with a PAD diagnosis was considered the index date. Patients younger than 50 years and with any diagnosis of acute myocardial infarction (AMI; ICD-9-CM: 410) before the index date were excluded. Claims for antithrombotic or antiplatelet treatment were identified in the 120 days after each patient's index date.¹⁸ Antithrombotic or antiplatelet medication was classified as aspirin, clopidogrel, warfarin, cilostazol, or cilostazol-based combination therapy. The aspirin, clopidogrel, warfarin, and cilostazol groups were defined as use of a single medication for treatment during the follow-up. The cilostazol-based combination

Table 1. Characteristics of the Study Population

Variable, n (%)	Total cases (n=1,686)	Aspirin (n=862)	Clopidogrel (n=92)	Warfarin (n=136)	Cilostazol (n=515)	Combination (n=81)	P value
Sex							0.2777
Female	855 (50.7)	454 (52.7)	42 (45.7)	74 (54.4)	245 (47.6)	40 (49.4)	
Male	831 (49.3)	408 (47.3)	50 (54.3)	62 (45.6)	270 (52.4)	41 (50.6)	
Age		68.68±9.74	70.79±9.01	68.34±9.73	69.52±10.03	70.69±10.12	0.4014
CAD	445 (26.4)	247 (28.7)	40 (43.5)	36 (26.5)	102 (19.8)	20 (24.7)	<0.0001
CHF	104 (6.2)	39 (4.5)	13 (14.1)	19 (14.0)	25 (4.9)	8 (9.9)	<0.0001
Hypertension	1,027 (60.8)	558 (64.7)	66 (71.7)	68 (50.0)	294 (57.1)	41 (50.6)	0.0001
AF	45 (2.7)	9 (1.0)	4 (4.3)	20 (14.7)	8 (1.6)	4 (4.9)	<0.0001
Hyperlipidemia	406 (24.1)	220 (25.5)	34 (37.0)	21 (15.4)	113 (21.9)	18 (22.2)	0.0026
DM	826 (49.0)	414 (48.0)	55 (59.8)	41 (30.1)	272 (52.8)	44 (54.3)	<0.0001
COPD	112 (6.6)	65 (7.5)	4 (4.3)	5 (3.7)	33 (6.4)	5 (6.2)	0.4189
CKD	233 (13.8)	77 (8.9)	25 (27.2)	27 (19.9)	86 (16.7)	18 (22.2)	<0.0001
Prior GI event	218 (12.9)	87 (10.1)	29 (31.5)	16 (11.8)	68 (13.2)	18 (22.2)	<0.0001
PPI use	66 (3.9)	24 (2.8)	10 (10.9)	5 (3.7)	18 (3.5)	9 (11.1)	<0.0001

AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; GI, gastrointestinal; PPI, proton-pump inhibitor.

therapy group was defined as cilostazol combined with aspirin, clopidogrel, or warfarin in 1 prescription. Patients' sex, age, and treatment information were obtained, and comorbidities were extracted from all claims within the 180 days before the index data.

Study Outcomes

The outcome factors included ischemic stroke (ICD-9-CM: 433–435), hemorrhagic stroke (ICD-9-CM: 430–432), other stroke (436–438), all stroke (including ischemic, hemorrhagic, and other stroke), and hospitalization due to AMI (ICD-9-CM: 410), heart failure (ICD-9-CM: 428) and gastrointestinal (GI) events (including GI hemorrhage, gastric ulcer, duodenal ulcer, and peptic ulcer; ICD-9-CM: 578, 531, 532, 533).

Statistical Analysis

The chi-square test was used to compare the distribution of sociodemographic characteristics between different treatments. Time-to-event analysis involved estimating the probability that an event would occur at different points in time. The follow-up time for survival started at the date of diagnosis and ended at the date of different categories developed or last observation up to December 31, 2008.

Two sets of hazard ratios (HRs) were computed for analysis factors by Cox regression analyses. The univariate HRs were estimated from separate Cox regressions with 1 analysis factor at a time. The multivariable-adjusted HRs were computed from Cox regression with additional variables of sex (men and women), age, CAD (ICD-9-CM: 411–414), congestive heart failure (CHF; ICD-9-CM: 428), hypertension (ICD-9-CM: 401–405), atrial fibrillation (AF; ICD-9-CM: 427.31), hyperlipidemia (ICD-9-CM: 272.0–272.4), diabetes mellitus (DM; ICD-9-CM: 250), chronic obstructive pulmonary disease (COPD; ICD-9-CM: 491, 492, 496), chronic kidney disease (CKD; ICD-9-CM: 250.4, 274.1, 283.11, 403, 404, 440.1, 442.1, 447.3, 572.4, 580–588, 642.1, 646.2) and PPI (proton-pump inhibitors). Significance was set at $P<0.05$. All the data processing and statistical analysis were performed with SAS 9.2 software (Cary, NC, USA).

Results

We identified 11,190 patients with PAD from January 2002 to December 2008. After excluding those patients who did not fit the inclusion criteria, a total of 1,686 patients (49.3% male) were included in the final analysis (Figure). Table 1 presents the baseline characteristics of the aspirin, clopidogrel, cilostazol, warfarin, and cilostazol-based combination therapy groups. There was a statistically significant difference regarding CAD, CHF, hypertension, AF, hyperlipidemia, diabetes, CKD, prior GI events and PPI use among the groups. There were more comorbidities, including CAD, CHF, hypertension, hyperlipidemia, DM, CKD and prior GI events, in the clopidogrel group.

Table 2 presents crude adjusted HRs and 95% confidence intervals (CIs) of hemorrhagic, ischemic, other stroke and all strokes among the 4 groups by conditional logistic regression. Compared with the aspirin group, the risks of other stroke (crude HR 0.70, 95% CI 0.57–0.87), and all stroke (crude HR 0.77, 95% CI 0.65–0.92) were significant lower in the cilostazol group. After adjustment for possible confounders (age, sex, CAD, CHF, hypertension, AF, hyperlipidemia, DM, COPD, CKD, prior GI events, PPI use, the risks of ischemic stroke (adjusted HR 0.79, 95% CI 0.63–0.98), other stroke (adjusted HR 0.66, 95% CI 0.53–0.82), and all stroke (adjusted HR 0.74, 95% CI 0.62–0.88) were significantly lower in the cilostazol group than in the aspirin group. In contrast, the risks of ischemic stroke (crude HR 1.79, 95% CI 1.31–2.45), other stroke (crude HR 1.58, 95% CI 1.15–2.16) and all stroke (crude HR 1.66, 95% CI 1.27–2.18) were significantly higher in the clopidogrel group than in the aspirin group. After adjustment for possible confounders, the risks of ischemic stroke (adjusted HR 1.47, 95% CI 1.07–2.04), and all stroke (adjusted HR 1.34, 95% CI 1.01–1.78) were still significantly higher in the clopidogrel group than in the aspirin group. There were no significant differences among the warfarin, cilostazol-based combination and aspirin groups for hemorrhagic, ischemic stroke, other stroke and all strokes.

With regard to safety, we analyzed AMI, GI events, and all hemorrhagic events (including hemorrhagic stroke and GI events) among the 4 groups (Table 3). There were no signifi-

Table 2. Risk of Hemorrhagic, Ischemic, Other Stroke and All Stroke in the 4 Treatment Groups

	Aspirin (n=862)	Clopidogrel (n=92)	Warfarin (n=136)	Cilostazol (n=515)	Combination* (n=81)
Hemorrhagic stroke					
n (%)	36 (4.2)	6 (6.5)	6 (4.4)	13 (2.5)	5 (6.2)
Crude HR (95% CI)	1.00	1.7 (0.72–4.05)	1.00 (0.42–2.38)	0.85 (0.45–1.61)	2.22 (0.86–5.69)
Adjusted HR (95% CI)	1.00	1.69 (0.69–4.16)	1.07 (0.43–2.66)	0.84 (0.44–1.62)	2.34 (0.90–6.09)
P value	–	0.2541	0.8917	0.6086	0.08
Ischemic stroke					
n (%)	282 (32.7)	46 (50.0)	47 (34.6)	118 (22.9)	26 (32.1)
Crude HR (95% CI)	1.00	1.79 (1.31–2.45)	1.04 (0.76–1.42)	0.81 (0.66–1.01)	1.24 (0.83–1.85)
Adjusted HR (95% CI)	1.00	1.47 (1.07–2.04)	1.13 (0.82–1.56)	0.79 (0.63–0.98)	1.17 (0.78–1.77)
P value	–	0.0193	0.4532	0.0349	0.4422
Other stroke					
n (%)	310 (36.0)	45 (48.9)	52 (38.2)	119 (23.1)	23 (28.4)
Crude HR (95% CI)	1.00	1.58 (1.15–2.16)	1.05 (0.78–1.41)	0.70 (0.57–0.87)	0.95 (0.62–1.44)
Adjusted HR (95% CI)	1.00	1.38 (1.01–1.92)	1.10 (0.81–1.50)	0.66 (0.53–0.82)	0.88 (0.57–1.35)
P value	–	0.0513	0.5288	0.0002	0.5455
All stroke					
n (%)	419 (48.6)	60 (65.2)	63 (46.3)	182 (35.3)	34 (42.0)
Crude HR (95% CI)	1.00	1.66 (1.27–2.18)	0.93 (0.71–1.21)	0.77 (0.65–0.92)	1.02 (0.72–1.45)
Adjusted HR (95% CI)	1.00	1.34 (1.01–1.78)	1.01 (0.76–1.33)	0.74 (0.62–0.88)	0.96 (0.67–1.37)
P value	–	0.0413	0.9722	0.0008	0.8081

Some patients had 2 types of stroke and therefore the numbers for all stroke are less than the numbers of ischemic plus hemorrhagic plus other stroke.

*Cilostazol-based combination therapy. CI, confidence interval; HR, hazard ratio.

Table 3. Risk of AMI, GI Events and All Hemorrhagic Events in the 4 Treatment Groups

	Aspirin (n=862)	Clopidogrel (n=92)	Warfarin (n=136)	Cilostazol (n=515)	Combination* (n=81)
AMI					
n (%)	40 (4.6)	5 (5.4)	5 (3.7)	15 (2.9)	3 (3.7)
Crude HR (95% CI)	1.00	1.38 (0.54–3.50)	0.73 (0.29–1.85)	1.01 (0.55–1.85)	1.36 (0.42–4.44)
Adjusted HR (95% CI)	1.00	1.04 (0.39–2.79)	0.79 (0.31–2.06)	0.97 (0.53–1.8)	1.27 (0.38–4.17)
P value	–	0.9407	0.6361	0.9341	0.6987
GI events					
n (%)	126 (14.6)	29 (31.5)	29 (21.3)	60 (11.7)	12 (14.8)
Crude HR (95% CI)	1.00	2.7 (1.8–4.05)	1.42 (0.95–2.12)	1.15 (0.84–1.56)	1.50 (0.93–2.72)
Adjusted HR (95% CI)	1.00	1.78 (1.16–2.75)	1.32 (0.86–2.01)	1.03 (0.75–1.41)	1.20 (0.66–2.19)
P value	–	0.0085	0.2041	0.8587	0.5548
All hemorrhagic events					
n (%)	152 (17.6)	33 (35.9)	32 (23.5)	70 (13.6)	16 (19.8)
Crude HR (95% CI)	1.00	2.58 (1.77–3.76)	1.31 (0.89–1.92)	1.08 (0.81–1.43)	1.68 (1.01–2.82)
Adjusted HR (95% CI)	1.00	1.77 (1.18–2.65)	1.24 (0.83–1.85)	0.98 (0.74–1.32)	1.41 (0.83–2.38)
P value	–	0.0054	0.2919	0.9122	0.2032

*Cilostazol-based combination therapy. AMI, acute myocardial infarction. Other abbreviations as in Tables 1,2.

cant differences for AMI (adjusted HR 0.97, 95% CI 0.53–1.8), GI events (adjusted HR 1.03, 95% CI 0.75–1.41) and all hemorrhagic events (adjusted HR 0.98, 95% CI 0.74–1.32) between the cilostazol and aspirin groups. There was also no difference for AMI (adjusted HR 0.79, 95% CI 0.31–2.06), and GI events (adjusted HR 1.32, 95% CI 0.86–2.01) and all hemorrhagic events (adjusted HR 1.24, 95% CI 0.83–1.85) between the warfarin and aspirin groups. The risks of GI events (adjusted HR 1.78, 95% CI 1.16–2.75) and all hemorrhagic events (adjusted HR 1.77, 95% CI 1.18–2.65) were

significantly higher in the clopidogrel group than in the aspirin group. There was no statistical significance with regard to AMI (adjusted HR 1.27, 95% CI 0.38–4.17), GI events (adjusted HR 1.20, 95% CI 0.66–2.19) and all hemorrhagic events (adjusted HR 1.41, 95% CI 0.83–2.38) between the cilostazol-based combination therapy and aspirin groups.

Because of more comorbidities in the clopidogrel group, we used the modified Charlson Comorbidity Index score matching analysis of the aspirin and clopidogrel groups (Table 4). The risks of ischemic stroke (adjusted HR 0.47, 95% CI 0.29–

Table 4. Risk of Hemorrhagic, Ischemic, Other Stroke, All Stroke AMI, GI Events and All Hemorrhagic Events Between Aspirin and Clopidogrel in the Modified Charlson Comorbidity Index Score Matching Model

	Aspirin (n=91)	Clopidogrel (n=92)
Hemorrhagic stroke		
Adjusted HR (95% CI)	1.00	0.85 (0.25–2.92)
P value	–	0.8001
Ischemic stroke		
Adjusted HR (95% CI)	1.00	0.47 (0.29–0.78)
P value	–	0.0033
Other stroke		
Adjusted HR (95% CI)	1.00	0.71 (0.44–1.10)
P value	–	0.1235
All stroke		
Adjusted HR (95% CI)	1.00	0.73 (0.42–0.94)
P value	–	0.0252
AMI		
Adjusted HR (95% CI)	1.00	0.41 (0.08–2.14)
P value	–	0.2874
GI events		
Adjusted HR (95% CI)	1.00	0.61 (0.27–0.93)
P value	–	0.0295
All hemorrhagic events		
Adjusted HR (95% CI)	1.00	0.64 (0.31–0.96)
P value	–	0.034

Abbreviations as in Tables 1–3.

0.78), all stroke (adjusted HR 0.73, 95% CI 0.42–0.94), GI events (adjusted HR 0.61, 95% CI 0.27–0.93) and all hemorrhagic events (adjusted HR 0.64, 95% CI 0.31–0.96) were significantly lower in the clopidogrel group than in the aspirin group in this model.

Discussion

There are 3 major findings from this study. First, cilostazol significantly reduced the risk of ischemic stroke with similar safety to aspirin. Second, clopidogrel also significantly reduced the risk of ischemic stroke and was safer than aspirin. Third, there was no statistical significance for any stroke, AMI, GI and hemorrhagic events for warfarin or cilostazol-based combination therapy compared with aspirin.

Cilostazol has been shown in some clinical trials to be effective and safe for the secondary prevention of ischemic stroke, especially in Asian populations. In the CSPS (cilostazol vs. aspirin for secondary ischemic stroke prevention) trial in Japan, cilostazol was significantly associated with a 41.7% relative risk reduction in recurrent cerebral infarction without an increase in adverse drug reactions.¹⁶ However, cilostazol was only as effective as aspirin in the prevention of secondary ischemic stroke for Chinese patients in the CASISP (Cilostazol vs. Aspirin for Secondary Ischemic Stroke Prevention) and Korean patients in the CAIST (Cilostazol in Acute Ischemic Stroke Treatment) trials. It significantly reduced the rate of recurrent stroke and had lower hemorrhagic events compared with aspirin in the CSPS 2 trial in Japan.^{15,19,20} Our results similarly showed that cilostazol significantly reduced (21%) the risk of ischemic stroke, with similar safety to aspirin for Taiwanese patients with PAD and CVD. We consider that the

reduced risk of recurrent stroke with cilostazol may be attributed to not only its antiplatelet effect, but also pleiotropic effects. The pleiotropic effects include inhibiting smooth muscle proliferation and inflammation, inhibiting superoxide formation and oxidative cell death, vasodilating effect by increased production of nitric oxide, and increasing cerebral blood flow and reducing infarct volume as reported from an animal model.^{21–27} These pleiotropic effects with cilostazol are thought to contribute to its prevention of secondary vascular events. Our study also demonstrated that cilostazol was still efficacious and safe for secondary prevention of stroke in Asian patients with PAD.

The effectiveness of aspirin or clopidogrel for prevention of secondary vascular events has been well established in high-risk patients.¹¹ In the CAPRIE trial, clopidogrel was significantly superior to aspirin, with 8.7% risk reduction of major ischemic vascular events and death in all study patients and 23.8% risk reduction in the subgroup of PAD patients.¹² Similarly, our results showed that clopidogrel significantly reduced by 27% the risk of all recurrent stroke with more safety than aspirin for Taiwanese patients with PAD. However, the combination of aspirin and clopidogrel was not more effective in preventing major vascular events but rather had more risk of life-threatening bleeding than aspirin alone in the CHARISMA trial²⁸ or clopidogrel alone in the MATCH trial.²⁹ In the post hoc analysis of the patients with symptomatic or asymptomatic PAD in the CHARISMA trial, clopidogrel plus aspirin provided some benefit over aspirin alone in reducing the rate of MI (2.3% vs. 3.7%, $P=0.028$) and hospitalization for ischemic events (16.5% vs. 20.1%, $P=0.011$).³⁰ There are no large clinical trials investigating the efficacy of secondary prevention of major vascular events by comparing cilostazol-based combination therapy with aspirin or clopidogrel alone. One small pilot study with 76 patients, comparing cilostazol plus aspirin with aspirin alone, showed that the combination therapy had less neurological deterioration within 14 days in patient with acute ischemic stroke in Japan.³¹ In our study, cilostazol-based combination therapy seemed not to provide additional benefit to the prevention of recurrent stroke, but instead a trend to increased hemorrhagic events, especially hemorrhagic stroke. Because of the small number of cases in the combination group, a future large clinical trial may be needed to evaluate the efficacy and safety of cilostazol-based combination treatment in patients with PAD and CVD.

Vitamin K antagonists, such as warfarin, have for more than 50 years been the most effective antithrombotic therapy for the prevention of ischemic stroke in patients with AF.³² Recently, several novel oral anticoagulants, such as direct thrombin or factor Xa inhibitors, demonstrated efficacy and safety and were well tolerated in patients with nonvalvular AF in Asian populations.^{33–36} In our study, patients with AF were significantly in the warfarin group than in the other treatment groups. We suspect warfarin might be prescribed for the prevention of cardiac embolization in patients with PAD and AF. The European Society of Cardiology guidelines recommend the use of the new 'CHA₂DS₂-VASC' score to evaluate the risk for stroke in patients with AF.³⁷ In Taiwan, a nationwide cohort study showed the odds ratio of ischemic stroke was 1.814 for patient with PAD and nonvalvular AF.³⁸ Even though the mean level of the international normalized ratio was 1.9 in Chinese patients under long-term warfarin treatment, the incidence of bleeding events remains of concern.³⁹ In our study, warfarin did not reduce the risk of recurrent stroke and AMI, and there seemed to be more hemorrhagic events in CVD patients with PAD in that treatment group.

Study Limitations

First, the NHI provide the population base database which may have possible disease misclassification and influence diagnostic codes for increasing payment to hospitals and affect the medication of administration. For example, if patients had either specific or non-specific symptoms, physicians might arrange some image or laboratory examination and wrote some disease codes. Maybe, some patients did not have any “really” diseases. Thus, simply diagnostic codes did not confirm what diseases patients did have. It was a reliable method that we identified PAD with CVD subjects by not only the diagnostic code but also related medication.⁴⁰ Second, we did not know the real data for ABI, carotid intima-media thickness, NIH Stroke Scale (NIHSS), and modified Rankin Scale (mRS).^{8–10} These factors may affect the severity of stroke and major vascular outcomes. Third, because of the lack of echocardiographic assessment, we could hardly distinguish cardioembolic from non-cardioembolic stroke. Fourth, despite the population-based database, this study did not have any randomization, which may have introduced some selection bias in this study. The safety and efficacy of cilostazol in ischemic stroke patients with peripheral arterial disease study (SPAD, Clinical trial.gov, NCT01188824), a randomized, double-blind, ongoing trial in Taiwan, may provide additional information of cilostazol’s benefit on the stroke prevention.

Conclusions

Similar to previous landmark trials such as CSPS, CSPS 2, CASISP and CAPRIE, we found that cilostazol and clopidogrel are more efficacious and safer than aspirin for the secondary prevention of stroke in CVD patients with PAD. However, warfarin provided no additional benefit than aspirin alone in our study population. Further randomized controlled trials are necessary to confirm our findings.

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