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# Long-Term Effectiveness of Cilostazol in Patients with Hemodialysis with Peripheral Artery Disease

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**Aim:** The aim of this study was to investigate the effects of continuous cilostazol use on emergency department (ED) visits, hospitalizations, and vascular outcomes in patients with hemodialysis (HD) with peripheral artery disease (PAD).

**Methods:** This retrospective cohort study recruited 558 adult patients, who had received chronic HD for at least 90 days between January 1, 2008 and December 31, 2012, from the National Health Insurance Research Database. Eligible patients were divided into two groups based on continuing or discontinuing cilostazol treatment. Outcome measures were ED visits, hospitalizations, mortality, and vascular outcomes such as percutaneous transluminal angioplasty, surgical bypass, lower leg amputation, ischemic stroke, hemorrhagic stroke, and cardiovascular events.

**Results:** Patients with continuous cilostazol use had significantly higher prevalence of stroke, cancer, vintage, and the use of angiotensin receptor blocker and $\beta$-blocker, but significantly lower incidence of ischemic stroke and cardiovascular events, as well as lower mortality, than those without continuous cilostazol use (all $p<.05$). Continuous cilostazol use was independently associated with lower risk of ED visits, hemorrhagic stroke, and cardiovascular events (adjusted hazard ratios: 0.79, 0.29, and 0.67; 95% confidence intervals: 0.62–0.98, 0.10–0.84, and 0.48–0.96, respectively; all $p<.05$). Continuous cilostazol use was significantly associated with higher ED visit-free and cardiovascular event-free rates (log-rank test; $p<.05$).

**Conclusion:** Continuous treatment of cilostazol in patients with HD with PAD significantly decreases the risk of ED visits, hemorrhagic stroke, and cardiovascular events and improves ED visit-free and cardiovascular event-free rates during long-term follow-up.

**Key words:** Cilostazol, Emergency department, Hemodialysis, Peripheral artery disease, Vascular outcome

## Introduction

Peripheral artery disease (PAD) refers to atherosclerosis-related partial or complete obstruction of the lower limb arteries, resulting in reduced blood flow and oxygen to the leg[1]. Critical limb ischemia (CLI), an advanced stage of PAD, is defined by the presence of ischemic rest pain, ulcers, or gangrene and is noted for its high amputation rate[2]. In addition to amputation, PAD is linked to increased cardiovascular disease, cerebrovascular disease, and mortality[3-5]. PAD is prevalent in patients with chronic kidney disease

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(CKD), especially those on dialysis or with end-stage renal disease (ESRD)[6]. Patients with CKD with PAD have a significantly higher risk of long-term mortality than patients with either disease alone[7].

Cilostazol, a selective phosphodiesterase 3 inhibitor, is regarded as a vasodilator that provides antiplatelet and antithrombotic effects and is shown to prevent platelet activation and aggregation, inhibit vascular smooth muscle proliferation, and improve endothelial cell function[8]. In patients with PAD with intermittent claudication, cilostazol increases maximal and pain-free walking distance[9, 10]. Cilostazol also prevents restenosis and re-occlusion and reduces the risk of major amputation after patients with PAD have received endovascular procedures[11-13]. The prevention of target lesion restenosis and re-occlusion by cilostazol can still be found in patients with hemodialysis (HD) with PAD after the endovascular procedure[14, 15]. In addition, cilostazol relieves the clinical symptoms of PAD in patients with HD via improving the lipid-related and endovascular inflammatory biochemical parameters[16].

Clinical trials have indicated that cilostazol is an effective and safe medication for the secondary prevention of ischemic stroke[17, 18]. Cilostazol has also remained to be effective in the prevention of stroke in patients with PAD[19]. Nevertheless, the influence of cilostazol on mortality and cardiovascular events in patients with PAD remains controversial. In a small retrospective study of patients with HD with asymptomatic PAD, low-dose cilostazol decreased cardiovascular events and all-cause mortality[20]. A previous study showed that cilostazol decreased major cardiovascular events, stroke, and mortality in patients with HD with PAD[21]. Meanwhile, data of cilostazol on clinical vascular outcomes in patients with chronic HD with prevalent PAD are minimal; to date, no studies have investigated the association between the treatment duration of cilostazol and clinical vascular outcomes in the HD population. Therefore, we designed a study to evaluate the effects of continuous cilostazol use versus the effects of discontinuous cilostazol use, analyzing data from patients with HD with prevalent PAD, including percutaneous transluminal angioplasty (PTA), surgical bypass, lower leg amputation, ischemic stroke, hemorrhagic stroke, cardiovascular events, and mortality. In addition, the current study investigated the emergency department (ED) visits and hospitalizations between the population with continuous cilostazol use and those with discontinuous cilostazol use.

## Aim

The present study aimed to investigate the impact of continuous cilostazol use on ED visits, hospitalizations, and clinical vascular outcomes in patients with HD with PAD.

## Methods

### Data Source

The National Health Insurance Research Database (NHIRD), which is managed by the Health and Welfare Data Science Center under the Ministry of Health and Welfare, Taiwan, contains claims data and detailed information on health services covered by the National Health Insurance (NHI) program. The NHI program was launched in Taiwan in 1985 and now covered more than 99% of the total population of Taiwan. The claims data include demographic data, ambulatory care, records of clinic visits, hospital admissions, dental services, operations, prescriptions, disease status, and dialysis history. Since the NHI system reimburses all dialysis-related expenditures, the claims data provide a comprehensive data source for information on patients with HD. For the present study, we obtained information on all chronic dialysis patients registered in the NHIRD, which classifies diseases according to the International Classification of Diseases, 9th and 10th Revisions, Clinical Modification (ICD-9-CM, ICD-10-CM).

### Study Design and Participants

We identified patients with chronic HD in the NHIRD who had received chronic HD therapy for at least 90 days between January 1, 2008 and December 31, 2012. Among the patients who met the criteria, we enrolled 3236 patients with chronic HD who were diagnosed with PAD after HD. We excluded 3 patients who were under 20 years old and 220 patients who had missing demographic data. Among these 3013 patients, 5 patients who shifted to peritoneal therapy, 3 patients who received a kidney transplant, and 5 patients who had died within 3 months were excluded. Of these 3000 adult patients with chronic HD with prevalent PAD, 558 patients who received oral cilostazol treatment were included. The baseline date in the study is the first date of PAD diagnosis. The continuation of cilostazol use was evaluated within 3 months after the baseline date, which we defined as the prescription period. The final study population was further stratified by the status of continuous use of cilostazol for more than 60 days, consisting of 187 patients with chronic HD with prevalent PAD who had continuous cilostazol

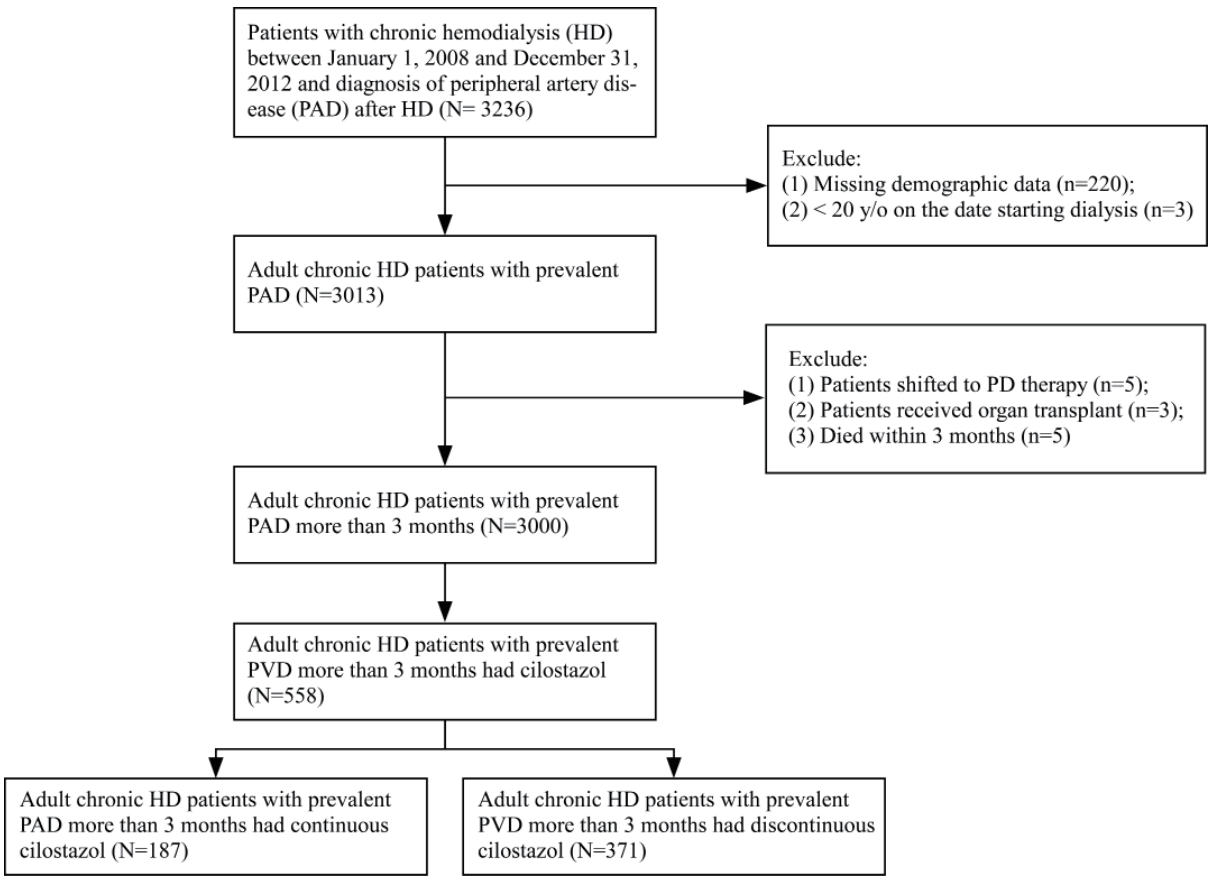


**Fig. 1.** Flowchart of patient selection for the study cohort

treatment and 371 patients with chronic HD with prevalent PAD who had discontinuous cilostazol treatment **(Fig. 1)**. Sixty days was used as the cut-off value because some studies have demonstrated that beneficial clinical effects, including secondary stroke prevention and vascular access maturation, appear after 60 days of cilostazol treatment[22, 23].

## Ethical Considerations

This study was performed in line with the principles of the Declaration of Helsinki. Because NHIRD data are deidentified and encrypted, this study was exempt from a full review. The study protocol was approved by the Institutional Review Board (IRB) of Shin Kong Wu Ho-Su Memorial Hospital (approval no 20210305R). Because all patient data from the NHIRD were deidentified, signed informed consent from included patients was waived by the IRB.

## Main Outcomes

The primary outcomes were ED visits, hospitalizations, cardiovascular events, and mortality. The secondary outcomes were PTA, surgical bypass, lower leg amputation, ischemic stroke, and hemorrhagic stroke. We set the index date as 3 months after PAD diagnosis, and the index date was the starting point for outcome measures. We regarded the conditions of shift to PD or receiving transplantation as censored data for the analysis when health outcomes were evaluated.

The main outcomes in our study include PTA, surgical bypass, lower leg amputation, ischemic stroke, hemorrhagic stroke, cardiovascular events, and mortality. Most of these outcome events are events that urgently need appropriate clinical management. Previous studies have also shown that dialysis patients, especially patients with chronic HD, are more likely to use emergency services than other patients[24-26]. Furthermore, considering that patients with HD with PAD who need to come to the ED owing to clinical symptoms and signs are not necessarily hospitalized after emergent medical treatment, we selected ED visit as one of the main outcomes.

### Statistical Analysis

All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA). The demographic and clinical characteristics of the study cohort are presented as mean ± standard deviation for continuous variables and proportion (n, %) for categorical variables. Student's *t*-tests and chi-squared tests were used to compare continuous and categorical variables. Univariate Cox proportional hazard (PH) models were used to estimate the relative risk (crude hazard ratios [HRs]) of outcome events, including ED visits, hospitalizations, PTA, surgical bypass, lower leg amputation, ischemic stroke, hemorrhagic stroke, cardiovascular events, and all-cause mortality in patients with chronic HD with prevalent PAD receiving continuous cilostazol compared with those without continuous cilostazol during the follow-up period, followed by multivariate Cox analysis to estimate adjusted hazard ratios (aHRs). The survival and outcome event-free rates were calculated using the Kaplan–Meier method, and pairs of groups were compared using log-rank tests. We tested the PH assumption by generating time-dependent covariates through modeling interactions between the treatment and the function of survival time that we included in the model[27]. No PH assumptions were violated in our analyses.

In addition, propensity score-based models are applied to control the effects of potential confounders. For estimating the propensity scores for the continuous use of cilostazol, the variables used in the logistic regression models included patient age, gender, and comorbidities (i.e., history of hypertension [HTN], diabetes, hyperlipidemia, coronary artery disease [CAD], congestive heart failure [CHF], stroke, cancer, and amputation). We utilized a set of models across the stratified levels of probability for the continuous use of cilostazol based on the categorization of the propensity score distribution into quartiles[28] to estimate the average treatment effect (ATE). A two-sided $p$ value of $<0.05$ was considered as statistically significant.

## Results

### Baseline Characteristics of the Study Population

Table 1 shows the demographic and clinical characteristics of the study population. Among 558 adult patients with chronic HD with diagnosed PAD for more than 3 months, who received cilostazol treatment between 2008 and 2012, 187 patients were treated with cilostazol for more than 60 days without interruption (continuous cilostazol group), and 371 patients were treated with cilostazol but without continuous use for more than 60 days (discontinuous cilostazol group). The mean age of the total population was 70.07 ± 11.90 years, and the mean follow-up period was 4.60 ± 2.32 years. The prevalence of stroke was significantly lower ($p$=.002) and was higher for cancer ($p$=.003) in the continuous cilostazol group than in the discontinuous cilostazol group. Patients in the continuous cilostazol group also had higher angiotensin receptor blocker (ARB) ($p$=.004) and $\beta$-blocker use ($p$=.02) than those in the discontinuous cilostazol group. Dialysis vintage was higher in the continuous cilostazol group than in the discontinuous cilostazol group ($p$=.001). The distribution of the use of anti-platelet drugs during the observational period was shown in Supplementary Table 1.

### Incidence of Outcome Events between the Study Groups

Table 2 shows the incidence of ED visits, PTA, surgical bypass, lower leg amputation, ischemic and hemorrhagic stroke, cardiovascular events, and all-cause mortality between adult patients with chronic HD with PAD with or without continuous cilostazol use. Patients with discontinuous cilostazol use had a significantly higher incidence of ischemic stroke ($p$=.02), cardiovascular events ($p$=.003), and all-cause mortality ($p$=.02) than those receiving continuous cilostazol use during the follow-up period. Patients with discontinuous cilostazol use also had a higher incidence of lower leg amputation, surgical bypass, hemorrhagic stroke, cardiovascular death, and more ED visits than those with continuous cilostazol use during follow-up, but differences between groups were not significant. The distribution of reasons for hospitalization and emergency department visit was shown in Supplementary Table 2.

### Associations between Continuous Cilostazol Use and Clinical Vascular Outcomes

Table 3 shows the incidence of clinical outcome events and lists the crude HRs and aHRs in patients with chronic HD with PAD with continuous cilostazol use. Two multivariate-adjusted models are presented in Table 3. One model includes the significant covariates in bivariate testing (i.e., the history of stroke and cancer, the vintage of dialysis, and the use of ARBs and $\beta$-blockers). The other model includes all of the possible confounders for the adjustment (i.e., age; gender; the history of HTN, diabetes, hyperlipidemia, CAD, CHF, stroke, cancer, and amputation; the vintage of dialysis; the duration of HD; the type of vascular access; the use of anti-HTN drugs, angiotensin-converting-enzyme

**Table 1.** Demographic and clinical characteristics of adult chronic HD patients with prevalent PAD between continuous and discontinuous use of cilostazol

| Variables[§] | Total ($n$ = 558) | Continuous cilostazol ($n$ = 187) | Discontinuous cilostazol ($n$ = 371) | $p$ |
|---|---|---|---|---|
| Age (years)[§] | 70.1 ± 11.9 | 69.6 ± 11.9 | 70.3 ± 11.9 | 0.94 |
| Age ≥ 65 yrs (%) | 385 (69.0) | 127 (67.9) | 258 (69.5) | 0.69 |
| Gender | | | | 0.57 |
| Male (%) | 328 (58.8) | 113 (60.4) | 215 (58.0) | |
| Female (%) | 230 (41.2) | 74 (39.6) | 156 (42.1) | |
| Comorbidities (%) | | | | |
| Hypertension | 458 (82.1) | 159 (85.0) | 299 (80.6) | 0.20 |
| Diabetes mellitus | 432 (77.4) | 142 (75.9) | 290 (78.2) | 0.55 |
| Hyperlipidemia | 206 (36.9) | 76 (40.6) | 130 (35.0) | 0.20 |
| CAD | 217 (38.9) | 75 (40.1) | 142 (38.2) | 0.68 |
| CHF | 112 (20.1) | 30 (16.0) | 82 (22.1) | 0.09 |
| Stroke | 146 (26.2) | 34 (18.2) | 112 (30.2) | 0.002 |
| Cancer | 45 (8.1) | 24 (12.8) | 21 (5.7) | 0.003 |
| Amputation | 44 (7.9) | 11 (5.9) | 33 (8.9) | 0.22 |
| Dialysis vintage (year) | 1.6 ± 1.2 | 1.8 ± 1.3 | 1.5 ± 1.2 | 0.001 |
| HD duration[#] | 13.3 (0.4) | 13.3 (0.4) | 13.3 (0.4) | 0.78 |
| Vascular access | | | | 0.53 |
| Fistula | 422 (75.6) | 141 (75.4) | 281 (75.7) | |
| Graft | 126 (22.6) | 41 (21.9) | 85 (22.9) | |
| Else | 10 (1.8) | 5 (2.7) | 5 (1.4) | |
| Medication (%) | | | | |
| Anti-HTN drugs | 422 (75.6) | 141 (75.4) | 281 (75.7) | |
| ACE inhibitors | 113 (20.3) | 31 (16.6) | 82 (22.1) | 0.13 |
| ARB | 269 (48.2) | 106 (56.7) | 163 (43.9) | 0.004 |
| B-blockers | 251 (45.0) | 97 (51.9) | 154 (41.5) | 0.02 |
| Calcium antagonists | 334 (60.0) | 112 (59.9) | 222 (59.8) | 0.99 |
| Diuretics | 242 (43.4) | 76 (40.6) | 166 (44.7) | 0.36 |
| Statins | 221 (40.0) | 80 (42.8) | 141 (38.0) | 0.28 |
| OAD | 314 (56.3) | 105 (56.2) | 209 (56.3) | 0.97 |
| Insulin and analogues | 193 (35.0) | 65 (34.8) | 128 (34.5) | 0.95 |
| Aspirin | 266 (47.7) | 86 (46.0) | 180 (48.5) | 0.57 |
| Clopidogrel | 91 (16.3) | 28 (15.0) | 63 (17.0) | 0.54 |
| Warfarin | 91 (16.3) | 7 (3.74) | 19 (5.1) | 0.47 |
| CCPB | 51 (9.1) | 13 (7.0) | 38 (10.2) | 0.20 |

ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blockers; CAD, coronary artery disease; CHF, congestive heart failure; OAD, oral anti-diabetic drugs; CCPB, calcium-containing phosphate binder.
[§]Variables are expressed as mean ± standard deviation (SD) for continuous data or $n$ (%) for categorical data. Analyses are applied using Student's $t$-test for continuous data and Chi-square test for categorical data.
[#]Average frequency per month.

**Table 2.** Outcome events between chronic HD patients with prevalent PAD receiving continuous vs. discontinuous use of cilostazol

| Outcome events (%) | Total ($n$ = 558) | Continuous cilostazol ($n$ = 187) | Discontinuous cilostazol ($n$ = 371) | $p$ |
|---|---|---|---|---|
| Emergency department visit | 341 (61.1) | 112 (59.9) | 229 (61.7) | 0.68 |
| Hospitalization | 540 (96.8) | 180 (96.3) | 360 (97.0) | 0.62 |
| PTA | 170 (30.5) | 62 (33.2) | 108 (29.1) | 0.33 |
| Surgical bypass | 52 (9.3) | 13 (7.0) | 39 (10.5) | 0.17 |
| Lower leg amputation | 70 (12.5) | 18 (9.6) | 52 (14.0) | 0.14 |
| Ischemic stroke | 160 (28.7) | 42 (22.5) | 118 (31.8) | 0.02 |
| Hemorrhagic stroke | 33 (5.9) | 4 (2.1) | 29 (6.6) | 0.21 |
| Cardiovascular events | 177 (31.72) | 44 (23.53) | 133 (35.85) | 0.003 |
| All-cause mortality | 306 (54.8) | 90 (48.1) | 216 (58.2) | 0.02 |

PTA, percutaneous transluminal angioplasty.
Analyses are applied using Chi-square test.

**Table 3.** Cox proportional hazards analysis of associations between continuous cilostazol use in chronic HD patients with prevalent PAD and vascular outcome events

| Event outcome | Crude | Adjusted | |
|---|---|---|---|
| | HR (95% CI) | Model 1[§] HR (95% CI) | Model 2[§§] HR (95% CI) |
| Emergency department visits | | | |
| Continuous cilostazol use | 0.74 (0.59-0.93) | 0.75 (0.60-0.95) | 0.79 (0.62-0.98) |
| Hospitalization | | | |
| Continuous cilostazol use | 0.69 (0.42-1.14) | 0.68 (0.40-1.14) | 0.66 (0.39-1.12) |
| PTA | | | |
| Continuous cilostazol use | 0.87 (0.63-1.19) | 1.00 (0.72-1.37) | 1.07 (0.78-1.48) |
| Surgical bypass | | | |
| Continuous cilostazol use | 0.51 (0.27-0.96) | 0.56 (0.30-1.07) | 0.61 (0.32-1.15) |
| Lower leg amputation | | | |
| Continuous cilostazol use | 0.53 (0.31-0.90) | 0.64 (0.37-1.10) | 0.69 (0.39-1.20) |
| Ischemic stroke | | | |
| Continuous cilostazol use | 0.50 (0.35-0.72) | 0.58 (0.40-0.82) | 0.77 (0.54-1.11) |
| Hemorrhagic stroke | | | |
| Continuous cilostazol use | 0.21 (0.08-0.61) | 0.24 (0.08-0.69) | 0.29 (0.10-0.84) |
| Cardiovascular events | | | |
| Continuous cilostazol use | 0.24 (0.08-0.67) | 0.53 (0.38-0.75) | 0.67 (0.48-0.96) |
| All-cause mortality | | | |
| Continuous cilostazol use | 0.88 (0.69-1.13) | 0.87 (0.67-1.12) | 0.99 (0.77-1.27) |

PTA, percutaneous transluminal angioplasty
[§]Adjusted for the history of stroke and cancer; the vintage of dialysis; and the use of ARB and β-blockers.
[§§]Adjusted for age; gender; the history of hypertension, diabetes, hyperlipidemia, CAD, CHF, stroke, cancer, and amputation; the vintage of dialysis; the duration of HD; the type of vascular access; and the use of anti-HTN drugs, ACE inhibitors, ARB, β-blockers, calcium antagonists, diuretics, statins, OAD, insulin and analogues, aspirin, clopidogrel, warfarin, and CCPB.

inhibitors, ARBs, β-blockers, calcium antagonists, diuretics, statins, oral antidiabetic drugs, insulin and analogs, aspirin, clopidogrel, warfarin, and calcium-containing phosphate binder). The HRs for ED visits, hospitalizations, PTA, surgical bypass, lower leg amputation, ischemic stroke, hemorrhagic stroke, cardiovascular events, and all-cause mortality were 0.74, 0.69, 0.87, 0.51, 0.53, 0.50, 0.21, 0.24, and 0.88 (95% confidence intervals [CIs]: 0.59–0.93, 0.42–1.14, 0.63–1.19, 0.27–0.96, 0.31–0.90, 0.35–0.72, 0.08–0.61, 0.08–0.67, and 0.69–1.13, respectively) in those with continuous cilostazol use. After adjusting for the significant variables listed in **Table 1**, continuous cilostazol use remained a significant protective factor for ED visits, hospitalizations, PTA, surgical bypass, lower leg amputation, ischemic stroke, hemorrhagic stroke, cardiovascular events, and all-cause mortality (aHRs: 0.79, 0.66, 1.07, 0.61, 0.69, 0.77, 0.29, 0.67, and 0.99; 95% CIs: 0.62–0.98, 0.39–1.12, 0.78–1.48, 0.32–1.15, 0.39–1.20, 0.54–1.11, 0.10–0.84, 0.48–0.96, and 0.77–1.27, respectively). **Table 4** shows the ATEs estimated by using propensity score quartile-stratified Cox PH models and related informations were provided in **Supplementary Table 3**.

**Fig. 2** depicts the Kaplan–Meier curves for (A) emergency department visit (B) hospitalization (C) PTA (D) surgical bypass (E) amputation of lower leg extremities (F) ischemic stroke (G) hemorrhagic stroke (H) cardiovascular events and (I) survival curve in chronic HD patients with prevalent PAD between continuous and discontinuous use of cilostazol over the 10-year follow-up period. ED visit-, ischemic stroke-, hemorrhagic stroke-, and cardiovascular event-free rates were higher in patients with chronic HD with PAD who had continuous use of cilostazol (11.47%, 68.42%, 97.09%, and 66.99%, respectively) than in those with discontinuous use of cilostazol (3.32%, 51.33%, 85.68%, and 44.74%, respectively) (**Fig. 2A, F, G, and H**; log-rank test, $p < .05$).

## Discussion

In summary, results of the present study demonstrated that the incidence of clinical vascular

**Table 4.** Propensity score quartile-stratified Cox proportional hazard models of associations between continuous cilostazol use in chronic HD patients with prevalent PAD and vascular outcome events

| Event outcome | Average treatment effect |
|---|---|
| Emergency department visits | |
| Continuous cilostazol use | 0.83 |
| Hospitalization | |
| Continuous cilostazol use | 0.70 |
| PTA | |
| Continuous cilostazol use | 1.18 |
| Surgical bypass | |
| Continuous cilostazol use | 0.56 |
| Lower leg amputation | |
| Continuous cilostazol use | 0.78 |
| Ischemic stroke | |
| Continuous cilostazol use | 0.61 |
| Hemorrhagic stroke | |
| Continuous cilostazol use | 0.40 |
| Cardiovascular events | |
| Continuous cilostazol use | 0.58 |
| All-cause mortality | |
| Continuous cilostazol use | 0.95 |

PTA, percutaneous transluminal angioplasty

events and mortality is significantly lower in patients with HD with PAD who received continuous cilostazol treatment. Continuous treatment with cilostazol, relative to discontinuous cilostazol use, significantly decreased the risk of ED visits, hemorrhagic stroke, and cardiovascular events in patients with chronic HD with PAD. Patients with continuous treatment of cilostazol also had a better ED visit-free rate, ischemic stroke-free rate, hemorrhagic-free rate, and cardiovascular event-free rate during long-term follow-up.

Patients with HD visit the ED more frequently than the general population because they tend to be frail and elderly and have multiple comorbidities[29, 30]. Frequent ED visits influence the quality of dialysis patient care, the burden of ED service, medical resources, and medical costs. However, knowledge regarding ED visits of patients with HD with PAD is insufficient. Patients with HD with PAD are believed to have more frequent ED visits because PAD serves as an important marker for advanced systemic atherosclerosis, which increases the risk for CAD, cerebrovascular disease, vascular dysfunction, morbidity, and mortality[3-5]. In the present study, reduced HRs indicated that continuous use of cilostazol decreased ED visits during long-term follow-up in the HD with PAD population. The percentage of patients who visited the ED did not differ significantly between the two groups. However, the HR revealed that continuous cilostazol use significantly reduced ED visits by 21%. Considering that the Cox PH model not only analyzed whether an event occurred but also took the time-to-event into consideration, one of the possible reasons for this reduction is that cilostazol may delay the onset of emergency clinical symptoms in patients.

In contrast, the effect of continuous cilostazol use was not significant with respect to hospitalization in our study. A previous study[31] showed that the majority of ED patients triaged as urgent accounted for nearly 70% of ED patients, and that more than 20% of urgent patients after primary management in the ED still need admission. Therefore, the events with the urgent need for appropriate clinical management, such as difficulty walking accompanied by discomfort, weakness, cramping, other symptoms in the hips or lower extremities, and patients with HD with PAD who possibly visit the ED with symptoms and signs, were not necessarily hospitalized. But even so, considering that the ED visit is a vaguer outcome than hospitalization, the reason that continuous cilostazol use reduces the risk of ED visit but not hospitalization still needs further exploration.

Revascularization is an essential therapy for patients with CLI to improve limb perfusion distal to the area of arterial stenosis or occlusion and to

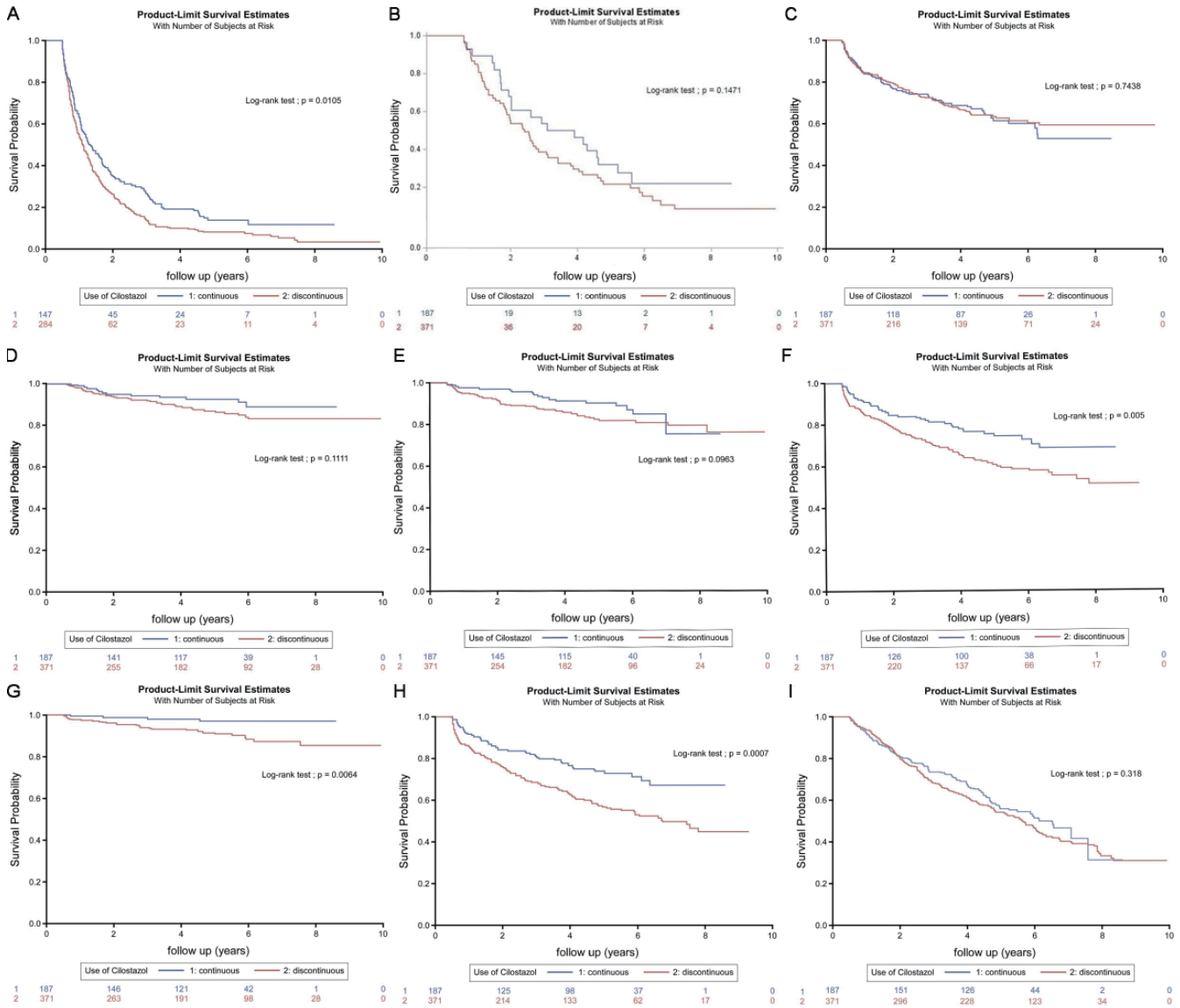


**Fig. 2.** Kaplan–Meier curves for (A) emergency department visit, (B) hospitalization, (C) PTA, (D) surgical bypass, (E) amputation of lower leg extremities, (F) ischemic stroke, (G) hemorrhagic stroke, (H) cardiovascular events, and (I) survival curve in patients with chronic HD with prevalent PAD between continuous and discontinuous use of cilostazol over the 10-year follow-up period

alleviate symptoms and salvage the affected limb[32]. Historically, an open surgical bypass was considered standard therapy for CLI, but additional evidence indicated that endovascular revascularization is an effective and safe therapy for CLI[33, 34]. In a previous study of patients with chronic HD with CLI, no significant differences were found in clinical outcomes, such as overall survival, major amputation, and major adverse limb events, between surgical bypass and endovascular therapy[35]. Despite this, endovascular therapy may be a better option for patients with HD than surgical bypass because perioperative complications are less frequent with endovascular therapy than with surgical revascularization. In fact, endovascular therapy has been regarded as first-line therapy for patients with chronic HD with CLI, and surgical bypass was performed in patients with vessels unsuitable for endovascular therapy[36]. In the present study, continuous cilostazol use significantly decreased the incidence of surgical bypass but not the incidence of PTA only before adjustment of all variables. Given that continuous cilostazol use could possibly help decelerate the progression of CLI and reduce or eliminate the need for surgical bypass, it should be

investigated in further studies.

Cilostazol had a beneficial effect on ulcer wound healing[37] and prevention of lower leg amputation among patients with PAD after lower extremity revascularization, even in those with ESRD or the dialysis population[12, 13, 38]. The effect of cilostazol in patients with HD with PAD who have not undergone revascularization remains unclear. In the present study, continuous cilostazol use significantly decreased the incidence of lower leg amputation among patients with HD with PAD only before the adjustment of all variables. Further studies are needed to provide data supporting that continuous cilostazol use decreases the progression of CLI and improves wound ulcer healing in the population of patients with HD and PAD.

Among all mono- or dual antiplatelet regimens, cilostazol has been demonstrated to have the best long-term secondary protection after transient ischemic attack (TIA) and ischemic stroke[39, 40]. In addition, cilostazol improves overall stroke and hemorrhagic stroke and reduces the incidence of fatal stroke in patients with previous TIA[41]. The optimal time to prevent recurrent stroke or hemorrhagic events is during the chronic phase of a stroke[42]. As such, these previous studies support the neuroprotective effects of cilostazol against ischemic or hemorrhagic injury. The neuroprotective potential of cilostazol may be dependent on its anti-inflammatory and antiapoptotic effects and endothelial and blood–brain barrier protection[43, 44]. As for patients with HD with PAD, cilostazol also improves stroke events after endovascular therapy[21]. In the present study, continuous cilostazol use reduced the incidence of hemorrhagic stroke in patients with chronic HD with PAD significantly more than that in those with discontinuous cilostazol use.

The precise role of cilostazol in preventing cardiovascular events is controversial. According to a previous study, the usage of cilostazol may be associated with an increased risk of hospitalization due to heart failure[45]. However, adjunctive cilostazol based dual antiplatelet medication is associated with a lower risk of major adverse cardiovascular events (MACE), target lesions or vessel revascularization, cardiovascular mortality, and all-cause mortality after stent placement[46-49]. Cilostazol administration has also been shown to prevent MACE after endovascular therapy in patients with HD with PAD[21]. Results of the present study revealed that continuous cilostazol treatment significantly reduced cardiovascular events in the HD with PAD population.

Although a meta-analysis found that cilostazol use is associated with improved primary patency and lower risk of major amputation and target lesion revascularization in patients with PAD after peripheral endovascular interventions, the mortality associated with cilostazol use in the general population as part of antiplatelet regimens remains unclear[13]. In the current study, the continuous use of cilostazol did not result in the better survival outcomes in patients with chronic HD with prevalent PAD than those without continuous use of cilostazol. However, patients with continuous use of cilostazol had fewer cardiovascular and cerebrovascular events than those without.

The present study has a few limitations, including that the NHIRD lacks detailed information on certain factors that may affect vascular outcomes, such as smoking, ankle-brachial index, laboratory data, severity and location of PAD, and reasons for discontinuing cilostazol. Although the baseline differences between patients with continuous and discontinuous use of cilostazol were adjusted appropriately, the existence of residual biases that may have affected individual and collective outcomes cannot be ruled out. In addition, because NHIRD is an administrative healthcare database that was used instead of actual patient data, the number of days covered by the prescriptions were assumed to be consistent with the actual number of days of drug use. Furthermore, due to the lack of information regarding out-of-pocket healthcare services, whether a given patient was continuously receiving medication may be misclassified. Finally, all results of this population-based study were from Taiwan and are not generalizable to other populations, ethnic backgrounds, or geographic locations. Hence, future large-scale population studied conducted in other geographic areas is warranted to confirm the findings of this study.

## Conclusions

This population-based retrospective cohort study revealed that continuous cilostazol use reduces the risk of unfavorable clinical outcomes in patients with HD with PAD, including ED visits, hemorrhagic stroke, and cardiovascular events. Therefore, we propose that patients with chronic HD with PAD receiving cilostazol should not have their treatment interrupted unless a contraindication to cilostazol usage is present.

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## Conflicts of Interest

The authors declare no competing financial interests.

## Author Contributions

Conception and design: C-KW and Y-YC
Analysis and interpretation: C-KW and Y-YC
Data collection: C-KW, Y-BY, and Y-YC
Writing the article: C-KW
Assistance in writing the article: C-HL, NY, and Y-YC
Critical revision of the article: C-KW, C-HL, and Y-YC
Final approval of the article: C-KW, C-HL, NY, Z-KK, Y-BY, and Y-YC
Statistical analysis: Z-KK, Y-YC
Overall responsibility: Y-YC

## Data Sharing Statement

The data that support the findings of this study are available from the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare (MOHW) (http://www.mohw.gov.tw/cht/DOS/) for the researchers in Taiwan. Data are available at http://dep.mohw.gov.tw/DOS/np-2497-113.html (Chinese only currently) with the permission of HWDC, Department of Statistics, MOHW.

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**Supplementary Table 1.** Distribution of the use of anti-platelet drugs during the observational period

| Variables[§] | Total ($n$ = 558) | Continuous cilostazol ($n$ = 187) | Discontinuous cilostazol ($n$ = 371) | $p$ |
|---|---|---|---|---|
| Aspirin use | | | | |
| In the first year after enrollment | 225 (40.3) | 72 (38.5) | 153 (41.2) | 0.53 |
| In the second year after enrollment | 180 (32.3) | 59 (31.6) | 121 (32.6) | 0.80 |
| Clopidogrel use | | | | |
| In the first year after enrollment | 115 (20.60) | 72 (19.4) | 43 (23.0) | 0.32 |
| In the second year after enrollment | 96 (17.2) | 64 (17.3) | 32 (17.1) | 0.97 |

[§]Variables are expressed as $n$ (%) for categorical data. Analyses are applied using Chi-square test for categorical data.

**Supplementary Table 2.** Distribution of reasons for hospitalization and emergency department visit between chronic HD patients with prevalent PAD receiving continuous vs. discontinuous use of cilostazol

| Reasons (%) | Total ($n$ = 558) | Continuous cilostazol ($n$ = 187) | Discontinuous cilostazol ($n$ = 371) | $p$ |
|---|---|---|---|---|
| For emergency department visit | | | | |
| Cardiovascular event | 87 (15.6) | 30 (16.0) | 57 (15.4) | 0.83 |
| Cerebrovascular event | 37 (6.6) | 10 (5.4) | 27 (7.3) | 0.39 |
| Peripheral vascular event | 45 (8.1) | 12 (6.4) | 33 (8.9) | 0.31 |
| For hospitalization | | | | |
| Cardiovascular event | 152 (27.2) | 52 (27.8) | 100 (27.0) | 0.83 |
| Cerebrovascular event | 61 (10.9) | 16 (8.6) | 45 (12.1) | 0.20 |
| Peripheral vascular event | 102 (18.3) | 34 (18.2) | 68 (18.3) | 0.97 |

**Supplementary Table 3.** Propensity score quartile-stratified Cox proportional hazard models of associations between continuous cilostazol use in chronic HD patients with prevalent PAD and vascular outcome events

| Event outcome | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
|---|---|---|---|---|
| | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| Emergency department visits | | | | |
| Continuous cilostazol use | 1.01 (0.57-1.78) | 0.87 (0.56-1.36) | 0.70 (0.45-1.08) | 0.73 (0.48-1.14) |
| Hospitalization | | | | |
| Continuous cilostazol use | 0.81 (0.23-2.88) | 0.73 (0.23-2.35) | 0.58 (0.22-1.53) | 0.68 (0.28-1.62) |
| PTA | | | | |
| Continuous cilostazol use | 0.98 (0.48-2.02) | 0.55 (0.27-1.10) | 1.95 (1.05-3.63) | 1.24 (0.67-2.27) |
| Surgical bypass | | | | |
| Continuous cilostazol use | 0.35 (0.05-2.68) | 0.47 (0.13-1.70) | 0.54 (0.15-1.97) | 0.86 (0.29-2.56) |
| Lower leg amputation | | | | |
| Continuous cilostazol use | 1.12 (0.41-3.00) | 0.44 (0.14-1.32) | 0.99 (0.34-2.90) | 0.57 (0.17-1.94) |
| Ischemic stroke | | | | |
| Continuous cilostazol use | 0.75 (0.39-1.44) | 0.68 (0.35-1.31) | 0.28 (0.10-0.79) | 0.72 (0.39-1.32) |
| Hemorrhagic stroke | | | | |
| Continuous cilostazol use | 0.47 (0.06-3.69) | 0.16 (0.02-1.29) | 0.80 (0.15-4.10) | 0.15 (0.02-1.15) |
| Cardiovascular events | | | | |
| Continuous cilostazol use | 0.75 (0.40-1.40) | 0.57 (0.30-1.08) | 0.31 (0.12-0.81) | 0.67 (0.37-1.20) |
| All-cause mortality | | | | |
| Continuous cilostazol use | 1.03 (0.58-1.82) | 0.72 (0.44-1.18) | 1.16 (0.71-1.87) | 0.88 (0.53-1.46) |

PTA, percutaneous transluminal angioplasty.