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Alex J. Ansara

Butler University, [aansara@butler.edu](mailto:aansara@butler.edu)

Dane L. Shiltz

Butler University, [dshiltz@butler.edu](mailto:dshiltz@butler.edu)

Jennifer B. Slavens

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# Use of Cilostazol for Secondary Stroke Prevention: An Old Dog with New Tricks?

Alexander J Ansara, Dane L Shiltz, Jennifer B Slavens

## Abstract

**OBJECTIVE:** To evaluate the safety and efficacy of cilostazol for secondary prevention of non-cardioembolic ischemic stroke.

**DATA SOURCES:** PubMed and MEDLINE searches were performed (January 1970-September 2011) using the key words cilostazol, antiplatelet, aspirin, acetylsalicylic acid, secondary stroke prevention, ischemic stroke, intracerebral hemorrhage, intracranial, cerebrovascular accident, and transient ischemic attack. Additionally, reference citations from publications identified were reviewed.

**STUDY SELECTION AND DATA EXTRACTION:** Articles published in English and relevant primary literature evaluating the efficacy and safety of cilostazol in the secondary prevention of atherosclerotic ischemic stroke were included.

**DATA SYNTHESIS:** Antiplatelet therapy plays a vital role in the multifaceted approach to secondary stroke prevention. Current American Heart Association/American Stroke Association clinical guidelines for secondary stroke prevention support the use of aspirin, clopidogrel, and combination aspirin/extended-release dipyridamole. The antiplatelet, antithrombotic, and vasodilatory effects of cilostazol make it a potential alternative agent for atherosclerotic stroke prevention. Recent literature has demonstrated superior efficacy of cilostazol 100 mg twice daily for secondary stroke prevention compared to placebo and aspirin. Three clinical trials were reviewed (1 placebo-controlled, 2 aspirin-controlled), all of which were conducted in Japan or China. Cilostazol reduced the primary outcome of recurrence of stroke, with significantly fewer major bleeding events when compared to aspirin.

**CONCLUSIONS:** Available literature suggests that cilostazol may be safer and more effective than aspirin in the secondary prevention of stroke in Asian patients. Further large-scale studies in more heterogeneous study populations are warranted to determine whether cilostazol is a viable therapeutic option for patients with a history of non-cardioembolic ischemic stroke.

Stroke is the third leading cause of death in the US, accounting for 1 of every 18 deaths in 2007.<sup>1</sup> While stroke death rates have fallen from 33.5% in 1996 to 16.7% in 2007, stroke remains a leading cause of disability, impaired functionality, and reduced quality of life.<sup>1</sup>

Atherosclerotic disease accounts for roughly 85% of the nearly 800,000 strokes that occur annually in the US.<sup>1</sup> Optimization of secondary stroke prevention requires a multifaceted approach that includes blood pressure control, cholesterol-lowering medications, smoking cessation, diet, and exercise, among others. Another mainstay of stroke prevention is antiplatelet therapy. Several antiplatelet agents, including aspirin, clopidogrel, ticlopidine, and aspirin/extended-release dipyridamole, are currently recommended by the American Heart Association (AHA) and American Stroke Association as suitable options for secondary stroke prevention.<sup>2</sup>

Aspirin is often prescribed as a first-line agent for secondary stroke prevention due to its lack of therapeutic monitoring, established efficacy in the treatment of acute ischemic stroke, and

significantly lower cost compared to all other antiplatelet agents. While the cost of aspirin is significantly the lowest among these antiplatelet agents, its use is associated with dosage-related gastrointestinal (GI) and intracranial hemorrhages (ICH).<sup>3</sup> Ticlopidine and clopidogrel use is associated with neutropenia, diarrhea, and skin rash, while up to 40% of patients taking aspirin/extended-release dipyridamole experience severe headaches.<sup>4-6</sup>

Recent clinical trial evidence suggests that cilostazol, a platelet inhibitor indicated for intermittent claudication, may be a safer and more effective alternative than aspirin for secondary stroke prevention in Asian patients. AHA guidelines do not yet provide recommendations on the role of cilostazol for secondary stroke prevention. This article details cilostazol's mechanism of action as an antiplatelet agent, provides a critique of secondary ischemic stroke prevention trials (all conducted in either Japan or China), and compares bleeding rates with cilostazol to those of other secondary stroke prevention treatment options.

## **Data Sources**

A literature search was performed (January 1970-September 2011) using PubMed and MEDLINE to identify relevant English-language review articles and clinical trials using the key words cilostazol, antiplatelet, aspirin, acetylsalicylic acid, secondary stroke prevention, ischemic stroke, intracerebral hemorrhage, intracranial, cerebrovascular accident, and transient ischemic attack. Reference citations of identified articles were used to identify additional literature for reference. Data from package inserts and unpublished clinical trials in progress (from [www.clinicaltrials.gov](http://www.clinicaltrials.gov)) were also reviewed. Article selection was focused on the pharmacology of antiplatelet agents, the pathophysiology of atherosclerotic stroke, clinical trials, and safety analyses.

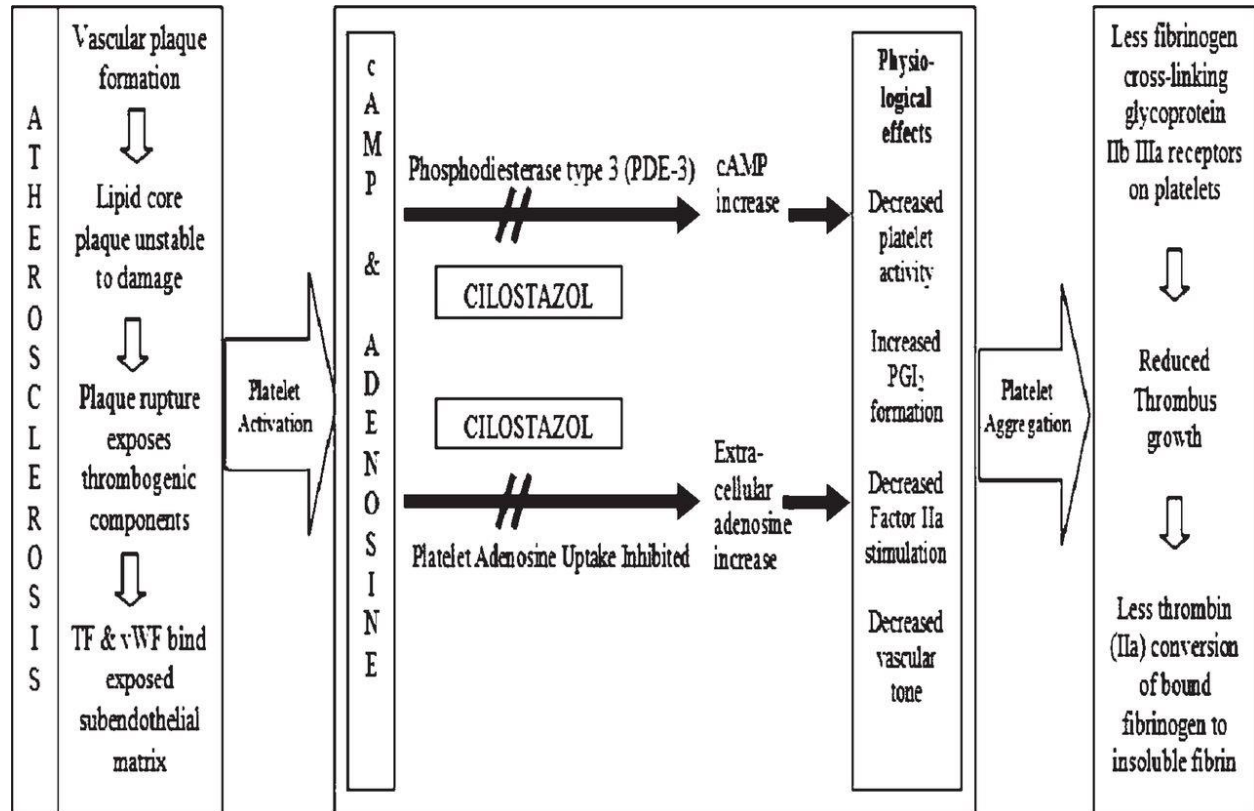
## **Mechanism of Action**

Atherosclerotic vascular plaques contain smooth muscle cells, macrophages, and collagen within a lipid core. Plaque erosion, fissure, and/or rupture due to shear stress expose the subendothelial matrix, collagen, and tissue factor found within the lipid core. Each of these serves as potent substrates for platelet-rich thrombus formation.<sup>7</sup>

Following rupture of unstable plaques, tissue factor and collagen-bound von Willebrand factor promote platelet adhesion and activation on the exposed subendothelial matrix surface. Activated platelets release adenosine diphosphate (ADP) and cyclooxygenase (COX)-produced thromboxane A<sub>2</sub>, mediators that promote vasoconstriction and additional platelet activation. Through the P2Y<sub>12</sub> receptor, ADP stimulates platelets to express glycoprotein IIb/IIIa receptors. Glycoprotein IIb/IIIa receptors cross-link platelets via fibrinogen that is further cleaved into fibrin by activated thrombin (factor IIa) to form a stable thrombus. This thrombus occludes blood flow through vessels, depriving tissues of necessary oxygen, and potentially contributing to cell and tissue death.<sup>7</sup>

Cilostazol's utility as a medication for ischemic stroke prevention extends from its Food and Drug Administration (FDA)-approved indication for the treatment of intermittent claudication in peripheral arterial disease because it exerts antiplatelet, antithrombotic, and vasodilatory effects.<sup>5</sup>

As a dose-dependent antiplatelet agent with a 3- to 6-hour onset, cilostazol blocks platelet adenosine uptake and adenosine-induced platelet activation to prevent platelet aggregation. Additional antiplatelet and antithrombotic actions involve platelet- and endothelial-derived phosphodiesterase type 3 (PDE-3) enzyme inhibition.<sup>8,9</sup> Intraplatelet cyclic adenosine monophosphate (cAMP) elevations due to PDE-3 inhibition prevent platelet aggregation and thrombus formation stimulated by thrombin, arachidonic acid, ADP, epinephrine, collagen, and sheer physical stress (Figure 1).<sup>7,9-11</sup> In vitro and in vivo data further demonstrate that cilostazol induces the expression of the endothelium-derived antiplatelet compound prostacyclin, while the COX inhibitor aspirin prevents prostacyclin formation, allowing for platelet aggregation.<sup>7,9</sup>



**Figure 1** Cilostazol mechanisms of action. Atherosclerotic plaque rupture permits binding of TF and vWF to exposed collagen and subendothelial matrix to initiate the platelet activation process. Following platelet activation, platelet adenosine concentrations increase through reuptake while cAMP concentrations decrease through the PDE-3 enzyme metabolism. In combination with thrombin, epinephrine, ADP and other mediators, these actions serve to promote platelet aggregation and thrombus formation.<sup>7</sup> Cilostazol inhibits PDE-3 to maintain cAMP levels while preventing platelet adenosine uptake. These principal actions prevent platelet aggregation, augment production of the antiplatelet prostacyclin, decrease response to platelet stimuli such as thrombin, epinephrine, and ADP, and also vasodilate major blood vessels that perfuse organs including the brain, heart, and extremities.<sup>9-11</sup> ADP = adenosine diphosphate; cAMP = cyclic adenosine monophosphate; PDE-3 = phosphodiesterase type 3; PGI<sub>2</sub> = prostacyclin; TF = tissue factor; vWF = von Willebrand factor.

Compared to cilostazol, aspirin/extended-release dipyridamole also prevents platelet adenosine uptake, but also inhibits cyclic guanosine monophosphate to prevent platelet activation. The aspirin component inhibits the COX enzyme to prevent thromboxane A<sub>2</sub> production, platelet aggregation, and vasoconstriction.<sup>6</sup> Clopidogrel is another FDA-approved antiplatelet agent used for secondary stroke prevention. Clopidogrel is activated via the CYP2C19 enzyme to selectively and irreversibly inhibit the binding of ADP to its platelet P2Y<sub>12</sub> receptor and the subsequent

ADP-mediated activation of the glycoprotein IIb/IIIa complex, thereby inhibiting platelet aggregation.<sup>5</sup>

Cilostazol reduces vascular tone, promoting more vasodilation in vertebral and femoral arteries than renal arteries.<sup>10</sup> Cilostazol also increases human carotid, cerebral, coronary, and dermal blood flow.<sup>9,10</sup> Additional effects on vasculature include inhibition of human smooth muscle proliferation due to growth factors including insulin, insulin-like growth factor, serum growth factor, and platelet-derived growth factor. Emerging evidence suggests that, by inhibiting the PDE-3 enzyme found within human smooth muscle cells, cilostazol inhibits smooth muscle cell proliferation and thus may prevent and possibly even reverse intracranial atherosclerotic lesions, improving cerebral blood flow.<sup>12,13</sup> Additionally, cilostazol increases vascular endothelial growth factor, which serves to repair damaged vascular epithelium.<sup>9,10</sup> These combined antiplatelet, antithrombotic, and vascular properties all favorably contribute to cilostazol's utility for stroke prevention.

### **Clinical Trials**

Three clinical trials encompass the body of evidence supporting the use of cilostazol as an alternative agent for secondary stroke prevention in Asian patients. These clinical trials include the placebo-controlled CSPS (Cilostazol Stroke Prevention Study) and 2 aspirin-controlled trials: the CASISP (Cilostazol as an Alternative to Aspirin After Ischaemic Stroke) trial and the CSPS-2 (Cilostazol for Prevention of Secondary Stroke) trial. Comparisons and findings of these trials are summarized in Table 1.<sup>11,14,15</sup>

The impetus for conducting these trials was a relative lack of representation of Asian patients in stroke prevention studies, as most large-scale trials had been conducted in North American and Western European countries. Compared to other ethnic categories, the prevalence of 2 or more risk factors (diabetes, smoking, high blood pressure or cholesterol, obesity, physical inactivity) for stroke is lowest among Asian Americans (25.9%)<sup>16</sup>; therefore, the age-adjusted prevalence of stroke among Asian Americans 18 years of age and over remains relatively low, at 1.3%.<sup>17</sup> However, the age-adjusted incidence of ICH for individuals 55 years and older in the Chinese population is higher than that seen in individuals in Western populations.<sup>18,19</sup> While the primary goal of antiplatelet therapy is to prevent ischemic events, minimizing the risk of ICH remains an essential focus of stroke prevention therapy.

<b>Table 1. Secondary Stroke Prevention Trials Utilizing Cilostazol</b>							
<b>Study</b>	<b>Patient s (N)</b>	<b>Patient Characteristics</b>	<b>Treatment Arms</b>	<b>Treatment Duration</b>	<b>Primary Endpoint</b>	<b>Results</b>	<b>p Value</b>
CSPS (2000) <b>14</b>	1052	65% male; median age 65 y; 65% MCA stroke; 75% small infarction ( $\leq 1.5$ cm); 61% HTN; 51% <60 days since CVA	Cilostazol 100 mg bid vs placebo	1.7 Years	Cerebral infarction	Event rate per year: cilostazol 3.37% vs placebo 5.78% (RRR = 41.7%)	0.015 (95% CI 9.2% to 62.5%)
CASISP (2008) <b>15</b>	719	69% male; median age 60 y; 82% modified Rankin scale score $\leq 2$ ; 79% HTN; 62% on aspirin at baseline; 18% daily history of DM	Cilostazol 100 mg bid vs aspirin 100 mg	1 year	Any stroke: Ischemic stroke, cerebral hemorrhage, subarachnoid hemorrhage	Composite endpoint: cilostazol 3.62% vs aspirin 6.41% (540- day estimated recurrence rates)	0.62 (95% CI 0.3 to 1.26)
CSPS-2 (2010) <b>11</b>	2672	72% male; mean age 63 y; 92% Rankin scale score $\leq 2$ ; 82% <2 months post-stroke; 73% HTN; 42% hyperlipidemia; 58% on aspirin at baseline; 25% on cilostazol at baseline	Cilostazol 100 mg bid vs aspirin 81 mg daily	2.4 years	Any stroke: cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage	Composite endpoint: cilostazol 2.76%/y vs aspirin 3.71%/y Ischemic stroke: cilostazol 2.43%/y vs aspirin 2.75%/y	Composite endpoint: p = 0.0357 (95% CI 0.564 to 0.981) Ischemic stroke: p = 0.419 (95% CI 0.65 to 1.2)
CASISP = Cilostazol as an Alternative to Aspirin After Ischaemic Stroke; CSPS = Cilostazol Stroke Prevention Study; CSPS-2 = Cilostazol for Prevention of Secondary Stroke; CVA = cerebrovascular accident; DM = diabetes mellitus; HTN = hypertension; MCA = middle cerebral artery; RRR = relative risk reduction.							

## CILOSTAZOL STROKE PREVENTION STUDY

The CSPS was an intention-to-treat study conducted in Japan at 183 clinical institutions from April 1992 to March 1996. Patients (N = 1052; 65% male) less than 80 years old with a prior cerebral infarction were randomized in a double-blinded manner to receive cilostazol 100 mg orally twice daily (n = 526) or placebo (n = 526) starting 1-6 months after infarction.<sup>14</sup> Patients with ICH, cardiogenic emboli, hemostatic disorders, need for non-study antiplatelet agents, severe cerebral deficit, dementia, or a wide variety of cardiac valve or chamber-associated complications were excluded, as were any pregnant or nursing women. The primary endpoint was the recurrence of cerebral infarction. Secondary endpoints included all-cause mortality, ICH, transient ischemic attack (TIA), and multiple composite endpoints including the composite of cerebral infarction, ICH, or TIA. Safety and adverse effects were also assessed on 4 occasions, including 2 interim analyses that also included assessments of efficacy.

Mean time from the primary cerebrovascular accident until treatment initiation was 83 days in both treatment arms and mean duration of follow-up was 1.7 years. While the 83-day mean time to treatment initiation with cilostazol appears inappropriate for a secondary stroke prevention study, many patients were already receiving secondary stroke prevention with various other

anticoagulant and antiplatelet agents. However, the authors do not identify the medications, doses, or percentages of patients utilizing these medications prior to study initiation. Baseline characteristics of age (65 years), blood pressure, infarction size, and past medical histories were comparable in both groups. Additionally, the involved arteries of the primary cerebrovascular infarction were comparable in both groups: middle cerebral arteries (64.7% and 66.3%) and vertebrobasilar arteries (19.5% and 21.3%) accounted for the majority of the infarctions in the cilostazol and placebo groups, respectively. It is noteworthy that approximately 75% of all primary cerebral infarctions were lacunar infarcts,<sup>14</sup> a form of small artery occlusive stroke associated with the lowest rates of early recurrence and best rates of survival and motor deficit improvements among the various types of strokes.<sup>20</sup>

Treatment with cilostazol was associated with reductions in the recurrence of cerebral infarction, as 30 and 57 strokes occurred in the cilostazol and placebo groups, respectively (event rates 3.37%/year vs 5.78%/year;  $p = 0.015$ ).<sup>14</sup> This correlated to a relative risk reduction (RRR) of 41.7% and a number needed to treat (NNT) of 42 patients. The greatest risk reduction (43.4% with cilostazol vs placebo;  $p = 0.0373$ ) occurred in patients with initial lacunar infarcts, a finding that suggests that cilostazol may have a specific effect against small-vessel cerebrovascular disease.<sup>21</sup> Treatment with cilostazol was also associated with favorable effects on the composite endpoint of cerebral infarction, ICH, or TIA (event rates 4.17%/year vs 7.06%/year; RRR 40.9%;  $p = 0.009$ ) as well as rates of all-cause mortality during the trial period (RRR 43.8%;  $p = 0.042$ ).<sup>14</sup>

ICH developed in 4 patients receiving cilostazol and 7 patients receiving placebo. While no ischemic or hemorrhagic strokes were fatal in the cilostazol group, there were 3 ischemic and 1 hemorrhagic fatal strokes among the 534 patients in the placebo group. Patients receiving cilostazol reported significantly higher rates of mild headaches (12.8% vs 3.2%), palpitations (5.3% vs 0.4%), and elevated heart rates (19.0% vs 7.9%), most of which were often self-limited. A higher percentage of patients in the cilostazol group experienced reductions in serum triglycerides (6.6% cilostazol vs 2.9% placebo;  $p = 0.0097$ ) and elevations in high-density lipoprotein levels (14.3% cilostazol vs 5.2% placebo;  $p = 0.00$ ), although specific data on the use of lipid-lowering agents in study participants were not provided. The investigators also did not define, nor quantify, what entailed a reduction in triglyceride levels or an increase in high-density lipoprotein levels.<sup>14</sup> The reductions in stroke associated with cilostazol are more likely attributed to the antiplatelet and vasodilatory effects that result from cAMP-phosphodiesterase inhibition and not the antilipidemic effects observed in this trial.<sup>22,23</sup> These vasodilatory effects also explain the significantly higher rates of headaches reported in subjects receiving cilostazol.<sup>14</sup>

The ethicality of this placebo-controlled stroke trial can be questioned given that the AHA/American Stroke Association secondary stroke guidelines suggest antiplatelet drugs with a level I class A evidence recommendation in this study population.<sup>2</sup> The findings demonstrate that cilostazol reduces the recurrence of cerebrovascular infarctions compared to placebo.<sup>14</sup> The beneficial effects of cilostazol were apparent early, continued throughout the study, and were comparable in men and women, without increased rates of cerebral hemorrhage. Based on the CSPS data, the pilot CASISP study and larger CSPS-2 study were designed to assess the efficacy and safety of cilostazol as a direct comparator to aspirin in the setting of secondary stroke prevention.

## CILOSTAZOL AS AN ALTERNATIVE TO ASPIRIN AFTER ISCHEMIC STROKE

Following the published results of the CSPS, data were still lacking on cilostazol versus an active comparator. In 2008, Huang and colleagues published CASISP, an intent-to-treat trial designed to assess the safety and efficacy of cilostazol versus aspirin for secondary stroke prevention.<sup>15</sup> CASISP was a randomized, double-blind, multicenter, pilot trial that enrolled 719 Chinese patients (69% male) who had experienced an image-diagnosed ischemic stroke. Patients were randomized to receive cilostazol 100 mg orally twice daily (n = 360) or aspirin 100 mg orally once daily (n = 359) starting 1-6 months after infarction. Patients were followed for 12-18 months and evaluated on the primary outcome of recurrence of stroke as defined by any of the following: ischemic stroke, cerebral hemorrhage, or subarachnoid hemorrhage. Patients with a history of subarachnoid hemorrhage, ICH, cardioembolic cerebral infarct, contraindication to antiplatelet therapy, use of antiplatelet therapy other than cilostazol during the study period, severe disability, uncontrolled severe comorbidities, or modified Rankin scale score of 4 or greater were not eligible for inclusion in this study. A score of 4 or greater on the modified Rankin scale (which assigns a number between 0 and 6 to assess a patient's level of independence after stroke) represents moderate-to-severe disability, including patients unable to walk without assistance or bedridden patients requiring constant nursing care. A score of 6 is assigned for death.<sup>24,25</sup> Specific uncontrolled severe comorbidities and disabilities qualifying patients for exclusion were not stated.<sup>15</sup> Patients with hypertension and dyslipidemia at baseline were given antihypertensives and/or statins. No statement of specific agents utilized, number of patients affected in each treatment group, or criteria to define hypertension or dyslipidemia were disclosed.

Baseline characteristics were similar between the 2 groups. Systolic blood pressure was significantly higher in the aspirin group at baseline (p = 0.03). These patients were treated with antihypertensives, with resolution of hypertension after 1 month of therapy. No statements of the medications utilized, number of patients treated for hypertension, or goal blood pressure were made. Sixty-two percent of the patients in both groups were taking aspirin prior to enrollment. One percent or less of the patients in each group was on cilostazol prior to enrollment. A majority (82%) of the patients in both groups had a modified Rankin scale score of 2 or less.<sup>15</sup>

The primary endpoint was reached by 12 patients (3.33%) in the cilostazol group and 20 patients (5.57%) in the aspirin group, resulting in an RRR of 38.1% (95% CI 0.3 to 1.26%; p = 0.18). Ischemic strokes occurred in 26 patients: 11 with cilostazol (3.1%) and 15 with aspirin (4.2%), but this finding also did not reach statistical significance. As a component of the primary endpoint, hemorrhagic strokes accounted for 8% of the cilostazol-related strokes (1/12) and 25% of the aspirin-related strokes (RR 7.14; p = 0.038). New microbleeds and asymptomatic hematomas were reported less commonly in the cilostazol group than in the aspirin group; however, no statement of significance was disclosed. Other adverse effects reported more frequently in the cilostazol group were headache, dizziness, palpitations, and tachycardia. Extracranial bleeding was reported more frequently in the aspirin group (4% cilostazol vs 9% aspirin). Fecal occult bleeding, hematuria, GI bleeding, and rhinorrhagia were common types of extracranial bleeding.<sup>15</sup>



Results of this study support a trend toward improved efficacy of cilostazol over aspirin and improved safety, shown by the statistically significant reduction in bleeding events in the cilostazol group.<sup>15</sup> The finding that hemorrhagic stroke occurred less frequently with cilostazol is salient considering the higher incidence of cerebral hemorrhage in patients of Asian ethnicity relative to other ethnic groups.<sup>26,27</sup> Nevertheless, based on the hypothesis-generating results of the CASISP trial, further analysis in a large Phase 3 trial was warranted to evaluate the trend toward improved efficacy of cilostazol over aspirin for secondary stroke prevention.

## CILOSTAZOL STROKE PREVENTION STUDY 2

The CSPS-2 trial was designed to establish noninferiority of cilostazol when compared to aspirin.<sup>11</sup> Similar to the CSPS trial, the CSPS-2 trial was conducted exclusively in Japan at 278 sites between December 2003 and December 2008. Patients (N = 2672; 72% male) between the ages of 20 and 79 years with a prior cerebral infarction within the past 6.5 months, with no evidence of cardiogenic emboli, were randomized in double-blinded fashion to receive cilostazol 100 mg orally twice daily (n = 1337) or aspirin 81 mg orally once daily (n = 1335) for 1-5 years. Patients were excluded if they had contraindications to cilostazol or aspirin, congestive heart failure, peptic ulcer disease, renal failure, liver disease, cardiac diseases associated with cardioemboli, or planned revascularization procedures. Prior to study entry, 83% of patients were receiving either cilostazol (25%) or aspirin (58%), although concurrent use of thienopyridines or other drugs affecting platelet function or hemostasis was prohibited. The primary endpoint was the first recurrence of stroke (cerebral infarction, cerebral hemorrhage, or subarachnoid hemorrhage). Secondary endpoints included death from any cause, ICH, cardiovascular events, and hemorrhage requiring hospital admission.

Baseline characteristics of the 2 groups were comparable overall, with the exception of significantly higher percentages of patients in the aspirin arm receiving lipid-lowering (30% vs 27%; p = 0.03) and antihypertensive medications (75% vs 67%; p < 0.0001). Blood pressures, however, were similarly controlled in both groups throughout the study period. A large proportion of patients (92%) had modified Rankin scores of 0-2, while 46% of patients had a score of 1. Similar proportions of patients had prior subtypes of lacunar infarcts (65% in both groups) and atherothrombotic strokes (cilostazol 33% vs aspirin 31%).<sup>11</sup>

Data from the Antithrombotic Trialists' Collaboration meta-analysis of antiplatelet therapy in patients with cerebral infarction and the CSPS trial results suggested hazard ratios of 0.6 for aspirin and cilostazol when compared to placebo.<sup>28</sup> As a result, a predefined hazard ratio of 1.33 for the noninferiority of cilostazol was set prior to initiation of the CSPS-2 trial.<sup>11</sup> The adjusted significance level for superiority testing was set at 0.0471.

After a mean duration of treatment of 2.4 years, treatment with cilostazol was associated with significant reductions in the primary endpoint of stroke, as there were 82 strokes in the cilostazol group and 119 strokes in the aspirin group (event rates 2.76%/year vs 3.71%/year, respectively; RRR 25.7%; p = 0.0357). The p value was lower than the adjusted level of significance for testing of superiority (p = 0.0471); therefore, a conclusion that cilostazol may be superior to aspirin 81 mg daily for the secondary prevention of any stroke is plausible. The secondary endpoint of cerebral infarction, however, demonstrated similar efficacy between cilostazol and

aspirin, as event rates were 2.43% and 2.75% per person-year, respectively ( $p = 0.419$ ). Consequently, the comparative efficacies of cilostazol and aspirin for the secondary prevention of ischemic stroke are similar. No differences were observed in the incidences of death or cardiovascular events.<sup>11</sup>

As observed in the CASISP study, the risk of hemorrhagic events was notably lower in the cilostazol group, as hemorrhagic events occurred in 57 aspirin-treated patients and only 23 cilostazol-treated patients (RRR 54.2%;  $p = 0.0004$ ). The composite of symptomatic cerebral, thalamic, intraventricular, cerebellar, or putamen hemorrhages occurred less frequently with cilostazol than aspirin (8 vs 27;  $p = 0.0027$ ), as did the rate of hospitalization secondary to GI bleeding (21 vs 8;  $p = 0.026$ ). As seen in the CSPS trial, patients receiving cilostazol in the CSPS-2 trial reported significantly higher rates of mild headaches (23% vs 16%;  $p < 0.0001$ ), palpitations (12% vs 5%;  $p < 0.0001$ ), and tachycardia (7% vs 2%;  $p < 0.0001$ ). Overall, a higher percentage of patients in the cilostazol group discontinued treatment (20% vs 12%) due to adverse effects.<sup>11</sup>

While cilostazol resulted in a 41.7% RRR compared to placebo in CSPS and a 38.1% RRR compared to aspirin in the CASISP study, decisive conclusions regarding the comparative efficacy between cilostazol and aspirin could not be made. In the CSPS-2 trial, the treatment effects of aspirin and cilostazol in the 83% of patients taking these medications prior to study initiation cannot be ascertained. Early initiation of antiplatelet therapy for secondary prevention is essential, but the CSPS-2 study is confounded by the late start date of the study drugs, as only 31% of patients in each treatment arm were initiated on their study drugs within 28 days from the onset of cerebral infarction.<sup>11</sup> Stroke recurrence rates are estimated to be highest (8.6% of patients) within the first 6 months of the first incident.<sup>29</sup> More recent data suggest recurrence rates up to 18% at 3 months after a TIA or stroke.<sup>30</sup> It is therefore difficult to accurately quantify the impact of cilostazol on secondary stroke prevention given these study limitations.

The results of CSPS-2, however, support the findings of the CASISP study and demonstrate that cilostazol significantly lowers the risks of stroke and cerebral hemorrhage when compared to low doses (81-100 mg daily) of aspirin.<sup>11</sup> The reduction in the composite stroke endpoint is likely driven by significant reductions in hemorrhagic stroke and the comparative efficacies of aspirin and cilostazol specific to ischemic stroke are similar.

## CILOSTAZOL BLEEDING EVENTS

Trials that evaluate bleeding risk with antithrombotic therapies vary in their definition and classification of hemorrhagic events. These descriptions depend on the assessment method used when either a universal definition was not available or not utilized at the time of data collection. In addition, the description of a bleeding event and its severity are sometimes inadequately defined, leaving the bleeding risk and severity of a given antithrombotic agent somewhat open to reader interpretation. Consequently, it proves difficult to accurately stratify and compare severities of bleeding events between studies that evaluate safety. A literature-based effort to classify the terminology for hemorrhagic events is provided below.

Any bleeding includes major and minor hemorrhagic events, but intracranial bleeding cases may be omitted depending on the trial.<sup>14,31,32</sup> The definition of major bleeding can vary, but it typically includes bleeding with persistent sequelae that contributes to significant disability, intraocular bleeding leading to significant vision loss, transfusion of 3 or more units of packed red blood cells, or need for hospitalization. A major hemorrhagic event may be life-threatening or non-life-threatening.<sup>11,31,33,34</sup> Minor bleeding does not meet major bleeding criteria and may include epistaxis or other bleeding that does not require transfusion, cause disability, or require hospitalization.<sup>31,34</sup> Life-threatening bleeding generally refers to a fatal bleeding event, a decrease in hemoglobin of 5 g/dL or more, significant hypotension requiring inotropic support, symptomatic intracranial hemorrhage, need for emergent surgical intervention, or need for transfusion of 4 units or more of packed red blood cells.<sup>33,34</sup>

Despite these inherent limitations that complicate comparisons, the bleeding incidences reported in various stroke trials that included placebo, cilostazol, aspirin, dipyridamole, and/or clopidogrel are reported with p values and confidence intervals, when available, in Table 2.<sup>31-37</sup>

**Table 2.** Major, Minor, and Fatal or Life-Threatening Bleeding in Secondary Stroke Prevention Trials

Drug	Studies	Major Bleeding Incidence (%)	Minor Bleeding Incidence (%)	Fatal or Life-Threatening Bleeding Incidence (%)
Cilostazol	Shinohara (2010), <sup>11</sup> Gotoh (2000), <sup>14</sup> Huang (2008) <sup>15</sup>	0.28 <sup>a</sup>	Not defined	None reported
Dipyridamole	Diener (1996) <sup>31</sup>	0.4	Not defined	0.4
Clopidogrel	Diener (2004), <sup>33</sup> Sacco (2008), <sup>34</sup> CAPRIE steering committee (1996) <sup>32</sup>	1-3.6	1	1
Aspirin (30-325 mg/day)	CAPRIE steering committee (1996), <sup>32</sup> ESPRIT study group (2006), <sup>35</sup> CAST collaborative group (1997), <sup>36</sup> IST collaborative group (1997) <sup>37</sup>	1.95-3.9	12.2	0.8-1.2
Aspirin + clopidogrel	Diener (2004) <sup>33</sup>	2	3	3
Aspirin + dipyridamole	Diener (1996), <sup>31</sup> Sacco (2008), <sup>34</sup> ESPRIT study group (2006) <sup>35</sup>	2.6-4.1	12.5	1.6

<sup>a</sup>A cilostazol meta-analysis demonstrated that the serious bleeding incidence in peripheral arterial disease populations ranges from 0.4% to 2.8%.<sup>38</sup>

Data from these trials demonstrate lower rates of major bleeding, including intracerebral hemorrhages, associated with cilostazol use when compared to other AHA-approved antiplatelet agents for secondary stroke prevention. A meta-analysis of cilostazol trials demonstrated that the serious bleeding incidence in peripheral arterial disease populations ranges from 0.4% to 2.8%.<sup>38</sup>

## Discussion

Collective data from the CSPS, CASISP, and CSPS-2 trials suggest that cilostazol may be more effective than aspirin in the secondary prevention of stroke and is associated with lower rates of

hemorrhagic stroke in the Asian population.<sup>11,14,15</sup> While the primary endpoint in CASISP did not reach statistical significance, this may be a direct result of small sample size and short follow-up period. On the basis of this collective evidence, Japanese guidelines for the management of stroke recommend cilostazol as a treatment alternative for secondary prevention of cerebral infarction.<sup>39</sup>

The use of aspirin as a first-line agent for the secondary prevention of ischemic stroke is supported by the AHA and American Stroke Association.<sup>2</sup> The low NNT of 42 patients for secondary stroke prevention with cilostazol in the CSPS trial is comparable to the NNT of 35 patients when low-dose aspirin (50 mg daily) was compared to placebo for secondary stroke prevention in the European Stroke Prevention Study 2 (ESPS-2), a study in which aspirin alone resulted in a 21% RRR compared to placebo.<sup>31</sup> While cilostazol resulted in a 42% RRR compared to placebo in CSPS,<sup>14</sup> direct comparisons between the efficacy of cilostazol and aspirin in the CSPS and ESPS-2 trials are not statistically valid due to differences in patient demographics, as CSPS was conducted exclusively in Asian patients while ESPS-2 participants were primarily white. Additionally, the large differences in the percentages of patients with ischemic heart disease and diabetes in these 2 trials make it difficult to directly compare the efficacy of cilostazol and aspirin across trials.

Calculations from the Antiplatelet and Antithrombotic Trialists' Collaboration data demonstrate that aspirin and thienopyridines are associated with an NNT of 26-28 patients to prevent one stroke in a 2.5- to 3-year treatment period.<sup>28,40</sup> The NNT for cilostazol from a subgroup analysis of hypertensive or diabetic patients in the CSPS study was 18.7 patients per 3-year treatment period.<sup>41</sup>

Despite these promising data, uncertainty regarding cilostazol's utility as a first-line agent for secondary stroke prevention remains. The AHA/American Stroke Association have identified racial disparities in stroke care of Asian American patients and recommend more research in this population.<sup>42</sup> Further prospective, randomized trials are warranted in a more diverse patient population to determine if the benefits of cilostazol on stroke reduction are universal or specific to the Chinese and Japanese patient populations. Treatment with cilostazol is significantly more expensive than treatment with over-the-counter aspirin. Additionally, while the risk of major bleeding is lower with cilostazol in the Asian study population, a high rate of discontinuation (20%) due to adverse effects was associated with cilostazol use in the CSPS-2 trial. Although cilostazol has been proven to reduce incidence of hemorrhagic strokes, it has not yet been proven to be more effective than aspirin in the secondary prevention of strokes that are ischemic in nature.

While cilostazol's antiplatelet effects occur within 3-6 hours of initiation,<sup>8</sup> prospective clinical data supporting its use in the treatment of acute (<48 hours) ischemic stroke are limited to one small study that demonstrated noninferiority and similar rates of bleeding with cilostazol 200 mg daily when compared to aspirin 300 mg.<sup>43</sup> Treatment with cilostazol should therefore be reserved as an option for secondary prevention in Asian patients who have already received treatment with an appropriate alternative antiplatelet agent. Based on available data, the optimal time to initiate treatment with cilostazol after ischemic stroke remains undefined and warrants further investigation.

## Summary

Cilostazol use for the secondary prevention of stroke may be optimal for Asian patients at high risk of hemorrhagic events or intolerant to aspirin. However, further large-scale trials with more heterogeneous study populations are warranted before treatment with cilostazol can be universally recommended as a first-line pharmacologic agent for secondary stroke prevention.

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