RESEARCH ARTICLE OPEN ACCESS

Association of Timing for Starting Dual Antiplatelet Treatment With Cilostazol and Recurrent Stroke

A CSPS.com Trial Post Hoc Analysis

Kazunori Toyoda, MD, PhD, Katsuhiro Omae, PhD, Haruhiko Hoshino, MD, PhD, Shinichiro Uchiyama, MD, PhD, Kazumi Kimura, MD, PhD, Kaori Miwa, MD, PhD, Kazuo Minematsu, MD, PhD, Keiji Yamaguchi, MD, PhD, Yoshitaka Suda, MD, Shuta Toru, MD, PhD, Kazuo Kitagawa, MD, PhD, Masafumi Ihara, MD, PhD, Masatoshi Koga, MD, PhD, and Takenori Yamaguchi, MD, PhD, on behalf of the CSPS.com Trial Investigators

Correspondence
Dr. Toyoda
toyoda@ncvc.go.jp

Neurology® 2022;98:e983-e992. doi:10.1212/WNL.0000000000200064

Abstract

Background and Objectives

Long-term treatment with the combination of cilostazol with aspirin or clopidogrel showed a lower risk of stroke recurrence compared to aspirin or clopidogrel alone after high-risk non-cardioembolic ischemic stroke in a randomized trial. We aimed to determine whether the effect of the dual medication compared to monotherapy on risk of recurrent ischemic stroke differs according to timing of starting medication after stroke onset.

Methods

In a subanalysis of the randomized controlled trial, patients between 8 and 180 days after stroke onset were randomly assigned to receive aspirin or clopidogrel alone or a combination of cilostazol with aspirin or clopidogrel. They were divided into 3 groups according to the timing of starting trial treatment: between 8 and 14 days after stroke onset (8–14 days group), between 15 and 28 days after stroke onset (15–28 days group), and between 29 and 180 days after stroke onset (29–180 days group). The primary efficacy outcome was the first recurrence of ischemic stroke. Safety outcomes included severe or life-threatening bleeding.

Results

Of 1,879 patients, 498 belonged to the 8–14 days group, 467 to the 15–28 days group, and 914 to the 29–180 days group. There was a significant treatment-by-subgroup interaction for the recurrence of ischemic stroke between trial treatment and trichotomized groups. The recurrence of ischemic stroke was less common with dual therapy than with monotherapy in the 15–28 days group (annualized rate 1.5% vs 4.9%, respectively; adjusted hazard ratio 0.34 [95% CI 0.12–0.95]) and the 29–180 days group (1.9% vs 4.4%, respectively; 0.27 [0.12–0.63]) and similarly common in the 8–14 days group (4.5% for both; 1.02 [0.51–2.04]). Severe or life-threatening bleeding occurred similarly between patients on dual therapy and those on monotherapy in any of the trichotomized groups (crude hazard ratio 0.22 [95% CI 0.03–1.88] in the 8–14 days group, 1.07 [0.15–7.60] in the 15–28 days group, and 0.76 [0.24–2.39] in the 29–180 days group).

RELATED ARTICLE

Editorial
Advancing Secondary Stroke Prevention Strategies: Optimal Timing of Dual Antiplatelet Therapy With Cilostazol
Page 387

MORE ONLINE

Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

From the Departments of Cerebrovascular Medicine (K.T., K. Miwa, M.K., T.Y.), Data Science (K.O.), and Neurology (M.I.), National Cerebral and Cardiovascular Center, Suita; Department of Neurology (H.H.), Tokyo Saiseikai Central Hospital; Clinical Research Center for Medicine (S.U.), International University of Health and Welfare, Center for Brain and Cerebral Vessels, Sanno Medical Center; Department of Neurological Science (K.K.), Graduate School of Medicine, Nippon Medical School, Tokyo; Headquarters of the Iseikai Medical Corporation (K. Minematsu), Osaka; Department of Neurology (K.Y.), Ichinomiya Nishi Hospital; Department of Neurosurgery (Y.S.), Yuri Kumiai General Hospital, Yurihonjo; Department of Neurology (S.T.), Nitobe Memorial Nakano General Hospital; and Department of Neurology (K.K.), Tokyo Women's Medical University, Japan.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the AMED.

CSPS.com Trial Investigators are listed at links.lww.com/WNL/B766.

Glossary

AIC = Akaike information criterion; **ASA+CLO** = aspirin and clopidogrel; **cAMP** = cyclic adenosine monophosphate; **CLZ+ASA** = cilostazol and aspirin; **CLZ+CLO** = cilostazol and clopidogrel; **DAPT** = dual antiplatelet therapy; **HR** = hazard ratio; **IQR** = interquartile range; **MI** = myocardial infarction; **RCT** = randomized controlled trial.

Discussion

Long-term dual antiplatelet therapy using cilostazol starting 15–180 days after stroke onset, compared to therapy started 8–14 days after onset, was more effective for secondary stroke prevention than monotherapy without increasing hemorrhage risk.

Trial Registration Information

ClinicalTrials.gov NCT01995370; UMIN Clinical Trials Registry 000012180.

Classification of Evidence

This study provides Class II evidence that for patients with acute noncardioembolic stroke taking either aspirin or clopidogrel, the addition of cilostazol 15–180 days after stroke onset decreases the risk of recurrent ischemic stroke.

Although dual antiplatelet therapy (DAPT) using aspirin and clopidogrel (ASA+CLO) decreases the risk of recurrent stroke early after minor ischemic stroke or high-risk TIA compared to aspirin monotherapy,[1,2] its effect on risk reduction of stroke is attenuated after the first month, when it also starts to have a higher risk of major bleeding than monotherapy.[3-6] A meta-analysis showed that DAPT with ASA+CLO started mainly within the first 24 hours of stroke onset significantly reduced the risk of recurrent ischemic stroke within the initial 3 months, but significantly increased the risk of major bleeding more than a month after stroke onset.[7] Early initiation of DAPT, within 30 days of stroke, using ticagrelor and aspirin, compared to aspirin alone, was proven to decrease the risk of the composite of stroke or death, but this combination increased severe bleeding.[8] In addition, the effect at the second month or later has not been explored.

An alternative DAPT, cilostazol, a phosphodiesterase 3 inhibitor, coupled with aspirin (CLZ+ASA) or clopidogrel (CLZ+CLO) reduced the risk of recurrent ischemic stroke and had a similar risk of severe or life-threatening bleeding compared to aspirin or clopidogrel alone in patients at high risk for recurrent ischemic stroke in long-term use of a median 1.4 years in the Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com), a randomized controlled trial (RCT).[9-11] If DAPT using cilostazol is effective when started within 1 month after stroke onset, we may be able to obtain a promising therapeutic strategy by switching the aspirin or clopidogrel to cilostazol and continuing DAPT from shortly after stroke onset for years.

We examined the hypothesis that starting DAPT using cilostazol within the initial several weeks was more effective and as safe as monotherapy using aspirin or clopidogrel by analyzing the data from the CSPS.com dataset. The primary research question was to determine the optimal time for starting long-term medication with the combination of cilostazol with aspirin or clopidogrel after onset of high-risk noncardioembolic ischemic stroke.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

CSPS.com was registered at ClinicalTrials.gov (NCT01995370) and the University Hospital Medical Information Network clinical trial registry in Japan (UMIN 000012180) and approved by the ethics committee at each participating site. All patients gave written informed consent before randomization. This study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Patients

CSPS.com was a multicenter, randomized, open-label, parallel-group trial, involving participants from 292 sites across Japan registered from December 2013 through March 2017. The trial protocol, statistical analysis plan, and design and main results of CSPS.com were described previously.[9,12]

Eligible patients were between 20 and 85 years of age and had a noncardioembolic ischemic stroke identified on MRI between 8 and 180 days before the start of the protocol treatment and were taking either aspirin or clopidogrel alone as antiplatelet therapy when providing informed consent. The patients were required to meet at least 1 of the following 3 criteria indicating a high risk for stroke recurrence: (1) ≥50% stenosis of a major intracranial artery; (2) ≥50% stenosis of an extracranial artery; and (3) 2 or more of the following risk factors: age ≥65 years, hypertension, diabetes mellitus, chronic kidney disease, peripheral arterial disease, history of ischemic stroke other than the qualifying one for this trial, history of ischemic heart disease, and current smoking. Additional information regarding the inclusion and exclusion

criteria is provided elsewhere.[9,12] For example, patients with emboligenic heart disease were excluded from the study.

In this substudy, the patients were trichotomized according to the time of initiation of the trial medication: between 8 and 14 days (the 8–14 days group), between 15 and 28 days (the 15–28 days group), and between 29 and 180 days (the 29–180 days group) after stroke onset. Fourteen and 28 days are meaningful time points to estimate when DAPT using cilostazol could replace DAPT using ASA+CLO, which is effective within the initial 3 to 4 weeks.[1-6]

Patients were randomly assigned in a 1:1 ratio to receive either monotherapy with aspirin (81 or 100 mg) or clopidogrel (50 or 75 mg) once daily or dual therapy with Pletal, a brand-name product of cilostazol (100 mg, twice daily, the recommended dose for stroke prevention in Japan) and either aspirin (81 or 100 mg) or clopidogrel (50 or 75 mg), once daily. Trial medication was continued for half a year or longer, for a maximum of 3.5 years. To prevent adverse drug reactions such as headache and tachycardia, cilostazol treatment could be started at 100 mg/d and increased to 200 mg/d within 15 days. Changes in these 3 antiplatelet medications were not permitted after informed consent was obtained.

Outcomes

The primary efficacy outcome was the first recurrence of ischemic stroke. The secondary efficacy outcomes were (1) any stroke (ischemic or hemorrhagic); (2) a composite of stroke, myocardial infarction (MI), and vascular death; (3) all vascular events, including stroke, MI, and other vascular events (e.g., aortic dissection; aortic rupture; pulmonary embolism; heart failure, angina pectoris, or peripheral artery disease requiring hospitalization; revascularization of a coronary artery, aorta, cephalocervical artery, or peripheral arteries); and (4) death from any cause.

Safety outcomes were (1) severe or life-threatening bleeding as defined in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) classification,[13] which includes symptomatic intracranial hemorrhage (hemorrhagic stroke, subdural or epidural hemorrhage) and bleeding resulting in substantial hemodynamic compromise requiring treatment; and (2) symptomatic intracranial hemorrhage. In addition, as early side effects specific to cilostazol, a composite of occurrence of headache, palpitations, and tachycardia was assessed.[14-16]

Statistical Analysis

Efficacy and safety analyses were performed on the intention-to-treat population. A Cox proportional hazards model with a forward-backward stepwise selection algorithm based on Akaike information criterion (AIC) was applied to calculate adjusted hazard ratios (HRs) and 95% CIs for the dual therapy relative to the monotherapy. Multivariate analysis was not performed when the number of events was small. Moreover, the interaction between the treatment groups and the time of initiation of the trial medication was evaluated using the Cox proportional hazards model, as well as the exploratory evaluation of the optimal time to initiation of trial treatment.

The risk of ischemic stroke with dual therapy compared to monotherapy according to the time of initiation of the trial medication is plotted in the following manner: the point estimates and 95% CIs of crude HRs of ischemic stroke in the subgroup were calculated for each day for starting medication (day X), where the subgroup was defined as patients starting medication between X and 180 days after stroke onset.

A value of $p < 0.1$ was considered significant for assessment of the treatment by cohort interaction. In the other comparisons, a value of $p < 0.05$ based on a 2-sided test was considered significant. Statistical analysis was performed using R (version 4.0.2, Microsoft).

Data Availability

Deidentified individual participant data of CSPS.com may be available upon request to Japan Cardiovascular Research Foundation if the request is intended to contribute to the improvement of people's health and welfare.

Results

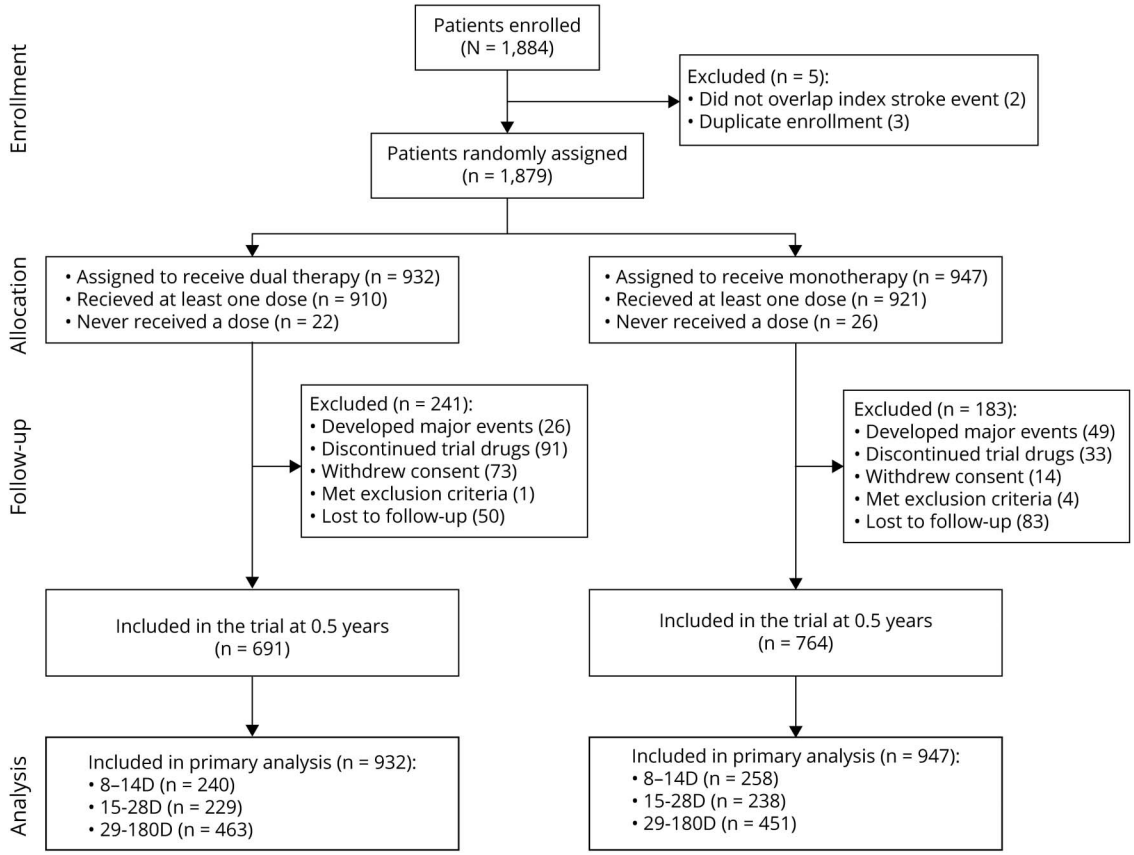
Of the 1,879 randomized patients, 932 were assigned to dual therapy and 947 to monotherapy. Of these, 498 (26.5% [240 assigned to dual therapy and 258 to monotherapy]) started trial medication between 8 and 14 days, 467 (24.9% [229 and 238, respectively]) between 15 and 28 days, and the remaining 914 (48.6% [463 and 451, respectively]) between 29 and 180 days after stroke onset (Figure 1). Their baseline characteristics are shown in Table 1.

There was a significant treatment by subgroup interaction for the primary efficacy outcome of ischemic stroke between assigned treatment and trichotomized groups ($p = 0.07$ for the 15–28 days group, $p = 0.022$ for the 29–180 days group, and $p = 0.012$ for the combined group of the above two [15–180 days group] compared with the 8–14 days group).

Patients Starting Trial Medication Between 8 and 14 Days After Stroke Onset

The median duration of follow-up was 1.3 years overall (interquartile range [IQR] 0.5–2.1 years), resulting in 713.8 person-years of follow-up. Ischemic stroke occurred in 15 patients (annualized rate 4.5%) during follow-up in the dual therapy group and 17 (4.5%) in the monotherapy group (crude HR 1.02 [95% CI 0.51–2.04]) (Table 2 and Figure 2A); assigned treatment was not chosen after stepwise selection by AIC. There were no significant differences in any secondary efficacy outcomes between the 2 groups. Severe or life-threatening bleeding occurred in 1 (0.4%) and 5 (1.7%), respectively (crude HR 0.22 [95% CI 0.03–1.88]; Table 3). All 6 events were intracranial hemorrhages.

Figure 1 Trial Profile



Patients Starting Trial Medication Between 15 and 28 Days After Stroke Onset

The median duration of follow-up was 1.3 years overall (IQR 0.6–2.1 years), resulting in 658.1 patient-years of follow-up. Ischemic stroke occurred in 5 patients (annualized rate 1.5%) on dual therapy and 16 (4.9%) on monotherapy (adjusted HR 0.34 [95% CI 0.12–0.95]) (Table 2 and Figure 2B). All vascular events occurred less commonly in patients on dual therapy than on monotherapy. Severe or life-threatening bleeding occurred in 2 (0.9%) and 2 (1.0%), respectively (crude HR 0.95 [95% CI 0.13–6.74]; Table 3). All 4 events were intracranial hemorrhages.

Patients Starting Trial Medication Between 29 and 180 Days After Stroke Onset

The median duration of follow-up was 1.4 years overall (IQR 0.5–2.2 years), resulting in 1,352.2 patient-years of follow-up. Ischemic stroke occurred in 9 patients (annualized rate 1.9%) on dual therapy and 31 (4.4%) on monotherapy (adjusted HR 0.27 [95% CI 0.12–0.63]) (Table 2 and Figure 2C). The incidence of ischemic stroke between patients on dual therapy and those on monotherapy was also different in the combined 29–180 days plus 15–28 days groups (15–180 days group, adjusted HR 0.34 [95% CI 0.18–0.65]) (Figure 2D). Any secondary efficacy outcomes other than death occurred less commonly in the 29–180 days patients on dual therapy than on monotherapy. Proportionality of the hazards in the multivariable models was not balanced regarding any stroke (p = 0.044; p values for the other outcomes are described in the footnote of Table 2). Severe or life-threatening bleeding occurred in 5 (1.1%) and 7 (1.6%), respectively (crude HR 0.78 [95% CI 0.25–2.45]; Table 3). All 12 events were intracranial hemorrhages.

Figure 3 demonstrates that the adjusted HR and 95% CI for the risk of ischemic stroke in the dual therapy group compared to the monotherapy group tended to be lowest when the trial medication was started 17 days after stroke onset. A composite of headache, palpitations, and tachycardia was seen in 22 patients (9.1%) assigned to dual therapy in the 8–14 days group, 10 (4.4%) in the 15–28 days group, and 45 (9.7%) in the 29–180 days group (p = 0.047).

This study provides Class II evidence that for patients with acute noncardioembolic stroke taking either aspirin or clopidogrel, the addition of cilostazol 15–180 days after stroke onset decreases the risk of recurrent ischemic stroke.

Discussion

CSPS.com shows the efficacy and safety of long-term DAPT for secondary prevention in high-risk, noncardioembolic

Table 1 Baseline Characteristics

	8–14 days (n = 498)	15–28 days (n = 467)	29–180 days (n = 914)
Age, y	69.1 ± 9.6	69.8 ± 9.1	69.8 ± 9.0
Female sex	136 (27.3)	142 (30.4)	281 (30.7)
Asian race[a]	498 (100.0)	467 (100.0)	914 (100.0)
Body mass index, kg/m^2*	24.1 ± 3.7	23.9 ± 3.3	23.6 ± 3.5
Median blood pressure, mm Hg			
Systolic	138 (127–152)	137 (126–150)	136 (125–149)
Diastolic	80 (70–88)	78 (70–88)	78 (70–87)
Medical history			
Hypertension*	436 (88.6)	399 (86.4)	735 (83.1)
Dyslipidemia	277 (56.4)	253 (54.8)	490 (55.4)
Diabetes mellitus	182 (37.0)	186 (40.3)	333 (37.7)
Chronic kidney disease	31 (6.3)	26 (5.6)	62 (7.0)
Peripheral arterial disease	14 (2.9)	10 (2.2)	25 (2.8)
History of ischemic stroke*,[b]	91 (18.5)	68 (14.7)	113 (12.8)
History of ischemic heart disease	25 (5.1)	26 (5.6)	45 (5.1)
Current smoking***	172 (35.0)	147 (31.8)	215 (24.3)
Intracranial artery stenosis***	116 (24.5)	139 (32.0)	292 (35.8)
Extracranial artery stenosis	65 (14.9)	67 (15.9)	121 (15.8)
Antiplatelets at randomization***			
Aspirin	263 (52.8)	198 (42.4)	302 (33.0)
Clopidogrel	235 (47.2)	269 (57.6)	612 (67.0)
Stroke subtype**			
Lacunar	278 (56.5)	227 (49.1)	420 (47.5)
Atherothrombotic	187 (38.0)	195 (42.2)	406 (45.9)
Other	27 (5.5)	40 (8.7)	59 (6.7)
Infarct location**			
Supratentorial	362 (73.6)	355 (76.8)	669 (75.6)
Infratentorial	122 (24.8)	106 (22.9)	202 (22.8)
Both	8 (1.6)	1 (0.2)	14 (1.6)
Time to initiation of trial treatment after index events, d***	11 (9–12)	20 (17–23.5)	65.5 (42–107)

Data are number (%), mean ± SD, or median (interquartile range).
[a] Self-reported. All are reported as Japanese.
[b] Except the qualifying one for this trial.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ among the groups.

ischemic stroke by using CLZ+ASA or CLZ+CLO. In this subanalysis of the trial, DAPT with this regimen was more effective and similarly safe in patients who started trial medication 15 days or later after stroke onset compared to aspirin or clopidogrel monotherapy, but not in those starting medication between 8 and 14 days after stroke onset.

Cilostazol inhibits phosphodiesterase activity and suppresses cyclic adenosine monophosphate (cAMP) degradation, increases intracellular cAMP concentrations, activates the cAMP-dependent protein kinase A, and inhibits platelet aggregation.[14-16] The same mechanism causes a vasodilatory effect on smooth muscle cells. In addition, cilostazol has pleiotropic effects, such as

Table 2 Efficacy Outcomes

Outcome	Dual therapy		Monotherapy		Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	p^b
	N (%)	Annual event rate[a]	N (%)	Annual event rate[a]			
8–14 days	(n = 240)		(n = 258)				
Ischemic stroke	15 (6.3)	4.5	17 (6.6)	4.5	1.02 (0.51–2.04)	—	—
Any stroke	16 (6.7)	4.8	19 (7.4)	5.0	0.97 (0.50–1.88)	—	—
Composite of stroke, myocardial infarction, and vascular death	18 (7.5)	5.4	20 (7.8)	5.3	1.03 (0.54–1.95)	—	—
All vascular events	20 (8.3)	6.0	23 (8.9)	6.1	0.99 (0.54–1.80)	—	—
Death from any cause	2 (0.8)	0.6	1 (0.4)	0.3	2.24 (0.20–24.8)	—	—
15–28 days	(n = 229)		(n = 238)				
Ischemic stroke	5 (2.2)	1.5	16 (6.7)	4.9	0.31 (0.11–0.85)	0.34 (0.12–0.95)	0.040
Any stroke	6 (2.6)	1.8	17 (7.1)	5.2	0.35 (0.14–0.90)	0.39 (0.15–1.01)	0.053
Composite events	7 (3.1)	2.1	19 (8.0)	5.8	0.37 (0.15–0.87)	0.41 (0.17–1.01)	0.053
All vascular events	9 (3.9)	2.7	22 (0.2)	6.7	0.41 (0.19–0.89)	0.38 (0.16–0.87)	0.022
Death from any cause	0	0.0	2 (0.8)	0.6	—	—	—
29–180 days	(n = 463)		(n = 451)				
Ischemic stroke	9 (1.9)	1.9	31 (6.9)	4.4	0.31 (0.15–0.65)	0.27 (0.12–0.63)	0.002
Any stroke	12 (2.6)	2.6	35 (7.8)	5.0	0.37 (0.19–0.70)	0.34 (0.16–0.70)	0.003
Composite events	13 (2.8)	2.8	39 (8.6)	5.6	0.36 (0.19–0.67)	0.35 (0.18–0.70)	0.003
All vascular events	18 (3.9)	3.9	45 (10.0)	6.4	0.42 (0.25–0.73)	0.42 (0.23–0.76)	0.004
Death from any cause	4 (0.9)	0.9	4 (0.9)	0.6	1.05 (0.26–4.20)	—	—
15–180 days (15–28 days + 29–180 days)	(n = 692)		(n = 689)				
Ischemic stroke	14 (2.0)	1.4	47 (6.8)	4.6	0.31 (0.17–0.57)	0.34 (0.18–0.65)	0.001

Adjusted analyses are performed using variables chosen after stepwise selection by Akaike information criterion (AIC) from all the variables in Table 1 except for Asian race and time to initiation of trial treatment. Regarding ischemic stroke of the 15–28 days group, assigned treatment, age, diabetes mellitus, current smoking, and antiplatelets at randomization are chosen. Regarding ischemic stroke of the 29–180 days group, assigned treatment, age, median blood pressure, history of ischemic stroke, current smoking, and extracranial artery stenosis are chosen. Regarding ischemic stroke of the 15–180 days group, assigned treatment, age, diastolic blood pressure, diabetes mellitus, history of ischemic stroke, current smoking, and antiplatelets at randomization are chosen. Assigned treatment was not chosen after stepwise selection by AIC in all the events of the 8–14 days group. Adjusted analyses are not performed for death due to the small numbers of patients who died. *p* Values for treatment-by-subgroup interaction between assigned treatment and trichotomized groups (15–28 days/29–180 days compared with the 8–14 days group) are 0.07/0.002 for ischemic stroke, 0.1/0.04 for any stroke, 0.07/0.02 for composite events, and 0.09/0.04 for all vascular events. The value of 15–180 days compared with 8–14 days for ischemic stroke is 0.012. *p* Values for proportionality of the hazards in the multivariable models in the 15–28 days group are 0.145 for ischemic stroke, 0.436 for any stroke, 0.446 for composite events, and 0.095 for all vascular events. *p* Values for proportionality of the hazards in the 29–180 days group are 0.265 for ischemic stroke, 0.044 for any stroke, 0.225 for composite events, and 0.067 for all vascular events. *p* Value for proportionality of the hazards in the 15–180 days group for ischemic stroke is 0.09.

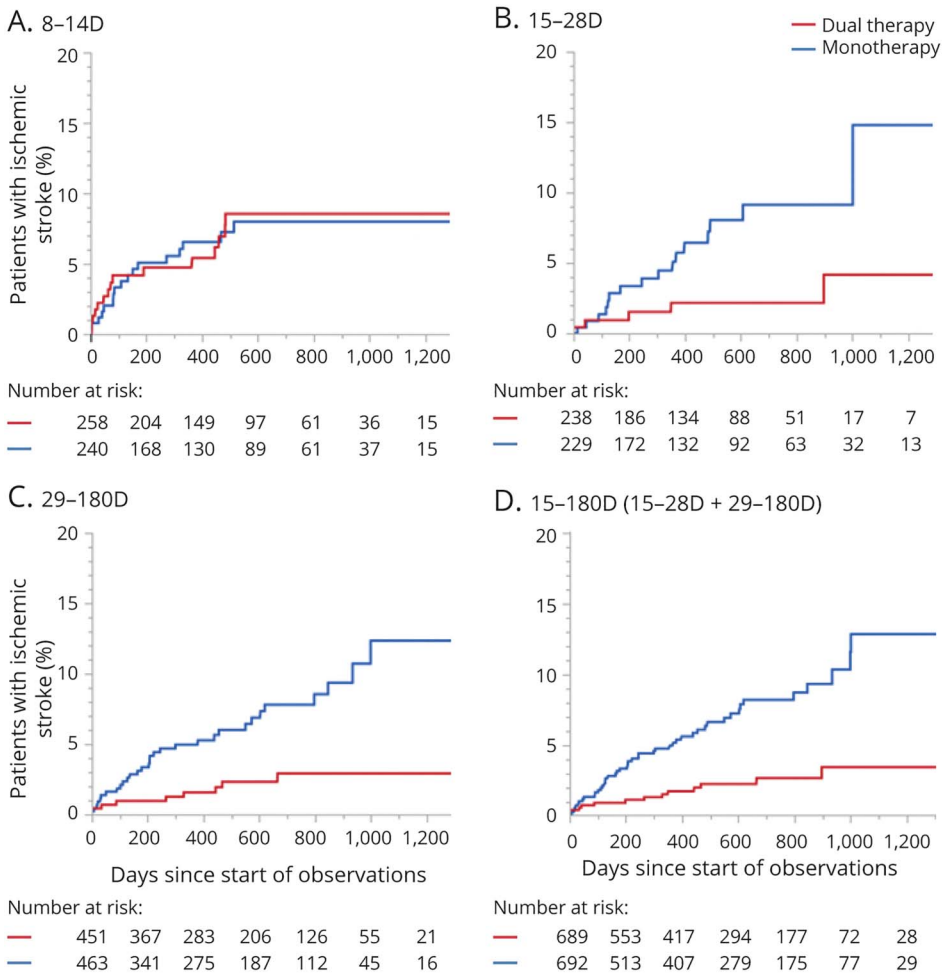
[a] Annual event rate indicates the number of events per 100 person-years.

[b] For adjusted hazard ratio.

vasoprotection, neuroprotection, antiproliferation, anti-inflammation, lipid-lowering, and protection against ischemia-reperfusion injury.[16] These long-lasting effects seem to be beneficial for long-term stroke prevention. Cilostazol was recommended as the first-line antiplatelet agent for secondary stroke prevention in Japan[17] and several Asian countries and was weakly recommended for stroke or TIA attributable to moderate to severe intracranial artery stenosis in the United States.[18]

Cilostazol has potential strengths for use during acute stroke, including a rapid onset of action and a low risk of bleeding.[14-16] Some RCTs showed similar or somewhat better efficacy and safety after early initiation of cilostazol alone or CLZ+ASA within 48 hours after stroke onset than aspirin alone.[19,20] However, in a relatively large RCT involving 1,201 participants, initiation of CLZ+ASA within 48 hours of stroke onset did not show a decrease in the rate of a composite of neurologic deterioration, symptomatic stroke recurrence, and TIA within 14 days, and showed an insignificant tendency ($p = 0.086$) for an increased rate of modified Rankin Scale score of 0–1 at 3 months and a similar incidence of hemorrhagic stroke relative to aspirin

Figure 2 Kaplan-Meier Analysis for Time to the First Event of the Primary Efficacy Outcome, Defined as Ischemic Stroke



(A) 8–14 days group. (B) 15–28 days group. (C) 29–180 days group. (D) 15–180 days group.

monotherapy.[21] In a systematic review and meta-analysis involving these RCTs, initiation of cilostazol within 2 weeks of stroke onset did not show a better outcome at 1–4 months than the control treatment.[14] Thus, CLZ+ASA would not be an optimal alternative choice to ASA+CLO during an acute stroke. Accordingly, it seemed to be important to clarify whether DAPT including cilostazol is effective for patients at 3–4 weeks after onset, the time when ASA+CLO starts to lose its advantage.[1,7]

In the present study, CLZ+ASA or CLZ+CLO significantly decreased the risk of ischemic stroke compared to monotherapy in both the 15–28 days and 29–180 days groups. The event curves of ischemic stroke during dual therapy and during monotherapy separated gradually from 3 to 4 months after randomization in the 15–28 days group. A similar separation of the event curves was observed in other RCTs that compared cilostazol monotherapy or CLZ+ASA with aspirin monotherapy.[22,23] In the meta-analysis, cilostazol reduced recurrent ischemic stroke more when given more than 6 months than when given short term.[14] The delayed preventive effect against stroke suggests the contribution of the above-mentioned long-lasting pleiotropic mechanisms unique to cilostazol.[14-16] A potential antidementia effect of cilostazol might maintain quality of life and indirectly prevent stroke.[14,24] The mechanisms would be commonly shared by phosphodiesterase inhibitors, as adding dipyridamole, a phosphodiesterase 5 inhibitor, to aspirin reduced the risk of recurrent stroke only after 12 weeks in a meta-analysis.[25] A particularly desirable time for starting DAPT using cilostazol between 15 and 180 days after stroke onset would be around 17 days based on the data shown in Figure 3.

In contrast, CLZ+ASA or CLZ+CLO did not decrease the risk of ischemic stroke relative to monotherapy in the 8–14 days group. This would be partly due to milder antiplatelet effects presumed by the lower risk of bleeding than aspirin or clopidogrel, which is a critical defect in the acute to subacute stage when the patient is at high risk for recurrent thromboembolism.[15,26] The event curves in this group were almost identical between dual therapy and monotherapy not only during the subacute stage, but also during the long-term chronic stage. A reason why dual therapy did not show superiority during the chronic stage would be the difference in the baseline characteristics of the patients between the 8–14

Table 3 Safety Outcomes

Outcome	Dual therapy N (%)	Dual therapy Annual event rate[a]	Monotherapy N (%)	Monotherapy Annual event rate[a]	Crude hazard ratio (95% CI)	*p* Value
8–14 days	(n = 240)		(n = 258)			
Severe or life-threatening bleeding	1 (0.4)	0.3	5 (1.7)	1.3	0.22 (0.03–1.88)	0.17
Intracranial hemorrhage	1 (0.4)	0.3	5 (1.7)	1.3	0.22 (0.03–1.88)	0.17
15–28 days	(n = 229)		(n = 238)			
Severe or life-threatening bleeding	2 (0.9)	0.6	2 (1.0)	0.6	1.07 (0.15–7.60)	0.95
Intracranial hemorrhage	2 (0.9)	0.6	2 (1.0)	0.6	1.07 (0.15–7.60)	0.95
29–180 days	(n = 463)		(n = 451)			
Severe or life-threatening bleeding	5 (1.1)	0.8	7 (1.6)	1.0	0.76 (0.24–2.39)	0.98
Intracranial hemorrhage	5 (1.1)	0.8	7 (1.6)	1.0	0.76 (0.24–2.39)	0.98

[a] Annual event rate indicates the number of events per 100 person-years.

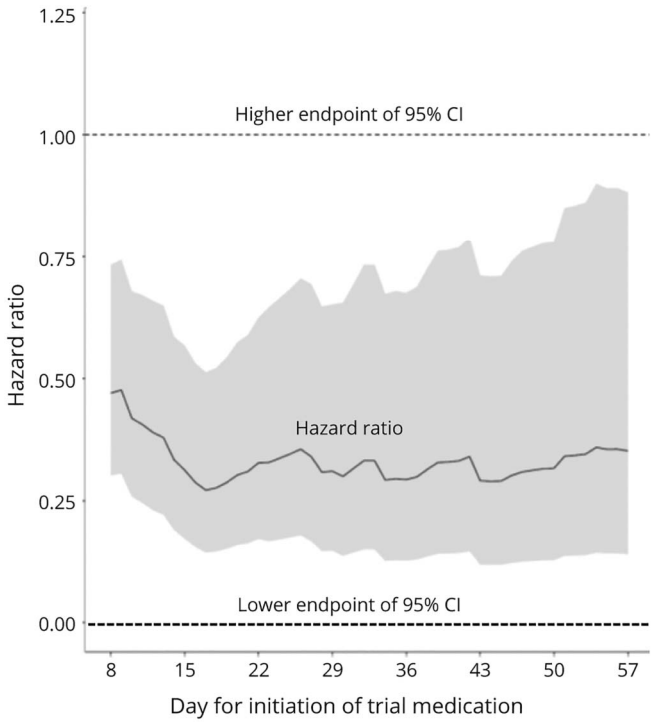
days group and the others; intracranial artery stenosis and clopidogrel usage at randomization, both regarded to be suitable conditions for dual therapy in CSPS.com and other studies,[9-11,27] were less common in the 8–14 days group.

Secondary efficacy outcomes except for any death were less common or marginally less common during dual therapy than monotherapy in both the 15–28 days and 29–180 days groups. Bleeding events were similarly common between dual therapy and monotherapy in any of the 3 groups divided by timing. A low risk of bleeding is a strength of cilostazol that enables safe long-term DAPT including cilostazol. The composite of headache, palpitations, and tachycardia was similarly common between the 8–14 days and 29–180 days groups and somewhat less common in the 15–28 days group. At least these events should be prevented regardless of the timing. The optional choice of cilostazol 100 mg once per day (half a regular dose) as an initial dose for 15 days adopted in CSPS.com seemed to decrease such early side effects.[8]

The limitations of CSPS.com were described elsewhere, including the smaller number of enrolled patients than planned, relatively low occurrence of the primary efficacy endpoint, uncertainty of the generalizability of the findings to non-Japanese populations, and relatively frequent discontinuation of trial medication due to headache and palpitations, known early side effects of cilostazol.[9] Because this was a subanalysis that divided the overall participants into 3 groups, efficacy endpoints and, in particular, safety endpoints in each group were even fewer, which might cause statistical bias. In addition, there were differences in the baseline characteristics of the patients among the 3 groups divided by timing, because timing was not randomized. This made the interpretation of intergroup differences in efficacy outcomes complicated. Finally, the present findings might not be generalizable to women given that only three-tenths enrolled were women.

Long-term DAPT using cilostazol was more effective for secondary prevention of noncardioembolic stroke than monotherapy in high-risk patients who started the medication 15 days or later after stroke onset without increasing hemorrhage risk. The finding suggests the feasibility of a seamless

Figure 3 Risk of Ischemic Stroke During Dual Therapy Compared to Monotherapy According to Time of Initiation of the Trial Medication



Adjusted hazard ratio and 95% CI for the patients who started trial medication on the day shown on the X axis or later.

DAPT strategy after stroke, switching from ASA+CLO in the acute to subacute stage to CLZ+ASA or CLZ+CLO at 15 days or later. Clinical studies to prove this strategy are needed.

Study Funding

Supported by grants from the Japan Agency for Medical Research and Development (AMED: 21lk0201094h0003 and 21lk0201109h0002). CSPS.com was conducted under a trial contract between the consignee, Japan Cardiovascular Research Foundation, and the consignor, Otsuka Pharmaceutical Co., Ltd. The Japan Cardiovascular Research Foundation received funding for trial implementation and management from Otsuka. Otsuka did not directly contribute to trial design, data management, or statistical analysis of CSPS.com and did not contribute to any issues in this substudy.

Disclosure

S. Uchiyama and K. Minematsu report honoraria from Otsuka Pharmaceutical Co., Ltd. The other authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* July 27, 2021. Accepted in final form December 27, 2021.

Appendix 1 Authors

Name	Location	Contribution
Kazunori Toyoda, MD, PhD	National Cerebral and Cardiovascular Center, Suita, Japan	Study concept or design, drafting/revision of the manuscript, financial support
Katsuhiro Omae, PhD	National Cerebral and Cardiovascular Center, Suita, Japan	Statistical analysis
Haruhiko Hoshino, MD, PhD	Tokyo Saiseikai Central Hospital, Japan	Major role in revision of the manuscript, major role in the acquisition of data
Shinichiro Uchiyama, MD, PhD	International University of Health and Welfare and Sanno Medical Center, Tokyo, Japan	Central role in the conduct of CSPS.com, major role in revision of the manuscript
Kazumi Kimura, MD, PhD	Graduate School of Medicine, Nippon Medical School, Tokyo, Japan	Major role in revision of the manuscript, major role in the acquisition of data
Kaori Miwa, MD, PhD	National Cerebral and Cardiovascular Center, Suita, Japan	Supportive role in statistical analysis and writing the manuscript
Kazuo Minematsu, MD, PhD	Headquarters of the Iseikai Medical Corporation, Osaka, Japan	Major role in revision of the manuscript
Keiji Yamaguchi, MD, PhD	Ichinomiya Nishi Hospital, Ichinomiya, Japan	Major role in the acquisition of data
Yoshitaka Suda, MD	Yuri Kumiai General Hospital, Yurihonjo, Japan	Major role in the acquisition of data
Shuta Toru, MD, PhD	Nitobe Memorial Nakano General Hospital, Tokyo, Japan	Major role in the acquisition of data
Kazuo Kitagawa, MD, PhD	Tokyo Women's Medical University, Tokyo, Japan	Major role in the acquisition of data
Masafumi Ihara, MD, PhD	National Cerebral and Cardiovascular Center, Suita, Japan	Major role in the acquisition of data
Masatoshi Koga, MD, PhD	National Cerebral and Cardiovascular Center, Suita, Japan	Major role in the acquisition of data
Takenori Yamaguchi, MD, PhD	National Cerebral and Cardiovascular Center, Suita, Japan	Supervision of CSPS.com trial as the principal investigator

Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B766.

References

1. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med.* 2013;369(1):11-19.
2. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med.* 2018;379(3):215-225.
3. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet.* 2004;364:331-337.
4. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med.* 2006;354(16):1706-1717.
5. The SPS 3 Investigators. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med.* 2012;367:817-825.
6. Lee M, Saver JL, Hong KS, Rao NM, Wu YL, Ovbiagele B. Risk-benefit profile of long-term dual- versus single-antiplatelet therapy among patients with ischemic stroke: a systematic review and meta-analysis. *Ann Intern Med.* 2013;159(7):463-470.
7. Rahman H, Khan SU, Nasir F, Hammad T, Meyer MA, Kaluski E. Optimal duration of aspirin plus clopidogrel after ischemic stroke or transient ischemic attack. *Stroke.* 2019;50(4):947-953.
8. Johnston SC, Amarenco P, Denison H, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med.* 2020;383(3):207-217.
9. Toyoda K, Uchiyama S, Yamaguchi T, et al. Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischaemic stroke in Japan: a multicentre, open-label, randomised controlled trial. *Lancet Neurol.* 2019;18(6):539-548.
10. Hoshino H, Toyoda K, Omae K, et al. Dual antiplatelet therapy using cilostazol with aspirin or clopidogrel: subanalysis of the CSPS.com trial. *Stroke.* 2021;52(11):3430-3439.
11. Uchiyama S, Toyoda K, Omae K, et al. Dual antiplatelet therapy using cilostazol in stroke patients with intracranial arterial stenosis. *J Am Heart Assoc.* 2021;10(20):e022575.
12. Toyoda K, Uchiyama S, Hoshino H, et al. Protocol for Cilostazol Stroke Prevention Study for antiplatelet combination (CSPS.com): a randomized, open-label, parallel-group trial. *Int J Stroke.* 2015;10(2):253-258.
13. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med.* 1993;329:673-682.
14. McHutchison C, Blair GW, Appleton JP, et al. Cilostazol for secondary prevention of stroke and cognitive decline: systematic review and meta-analysis. *Stroke*. 2020;51(8):2374-2385.
15. de Havenon A, Sheth K, Madsen T, et al. Cilostazol for secondary stroke prevention: history, evidence, limitations, and possibilities. *Stroke.* 2021;52:e635-e645.
16. Kherallah RY, Khawaja M, Olson M, et al. Cilostazol: a review of basic mechanisms and clinical uses. *Cardiovasc Drugs Ther.* Epub 2021 Apr 16.
17. Toyoda K, Inoue M, Koga M. Small but steady steps in stroke medicine in Japan. *J Am Heart Assoc.* 2019;8(16):e013306.
18. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke.* 2014;45 :2160-2236.
19. Lee YS, Bae HJ, Kang DW, et al. Cilostazol in Acute Ischemic Stroke Treatment (CAIST trial): a randomized double-blind non-inferiority trial. *Cerebrovasc Dis.* 2011;32(1):65-71.

20. Nakamura T, Tsuruta S, Uchiyama S. Cilostazol combined with aspirin prevents early neurological deterioration in patients with acute ischemic stroke: a pilot study. *J Neurol Sci.* 2012;313(1-2):22-26.
21. Aoki J, Iguchi Y, Urabe T, et al. Acute aspirin plus cilostazol dual therapy for non-cardioembolic stroke patients within 48 hours of symptom onset. *J Am Heart Assoc.* 2019;8(15):e012652.
22. Shinohara Y, Katayama Y, Uchiyama S, et al. Cilostazol for Prevention of Secondary Stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol*. 2010;9(10):959-968.
23. Uchiyama S, Sakai N, Toi S, et al. Final results of Cilostazol-Aspirin Therapy Against Recurrent Stroke With Intracranial Artery Stenosis (CATHARSIS). *Cerebrovasc Dis Extra* 2015;5:1-13.
24. Saito S, Kojima S, Oishi N, et al. A multicenter, randomized, placebo-controlled trial for cilostazol in patients with mild cognitive impairment: the COMCID study protocol. *Alzheimers Dement.* 2016;2:250-257.
25. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet.* 2016;388(10042):365-375.
26. Wilhite DB, Comerota AJ, Schmieder FA, Throm RC, Gaughan JP, Rao AK. Managing PAD with multiple platelet inhibitors: the effect of combination therapy on bleeding time. *J Vasc Surg.* 2003;38(4):710-713.
27. Kwon SU, Cho YJ, Koo JS, et al. Cilostazol prevents the progression of symptomatic intracranial arterial stenosis: the Multicenter Double-Blind Placebo-Controlled Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis. *Stroke.* 2005;36(4):782-786.

Association of Timing for Starting Dual Antiplatelet Treatment With Cilostazol and Recurrent Stroke: A CSPS.com Trial Post Hoc Analysis

Kazunori Toyoda, Katsuhiro Omae, Haruhiko Hoshino, et al.

Neurology 2022;98;e983-e992 Published Online before print January 24, 2022
DOI 10.1212/WNL.0000000000200064