Stroke

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Dual Antiplatelet Therapy Using Cilostazol With Aspirin or Clopidogrel

Subanalysis of the CSPS.com Trial

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BACKGROUND AND PURPOSE: Although dual antiplatelet therapy (DAPT) with aspirin and clopidogrel reduces the recurrence of ischemic stroke while significantly increasing the bleeding events compared with monotherapy, the CSPS.com trial (Cilostazol Stroke Prevention Study combination) showed that DAPT using cilostazol was more effective without the bleeding risk. In the CSPS.com trial, aspirin or clopidogrel was used as the underlying antiplatelet drug. The effectiveness and safety of each combination were examined and clarified.

METHODS: In the CSPS.com trial, a multicenter, open-label, randomized controlled study, patients with high-risk, noncardioembolic ischemic stroke 8 to 180 days after onset treated with aspirin or clopidogrel alone at the discretion of the physician in charge were recruited. Patients were randomly assigned to receive either monotherapy or DAPT using cilostazol and followed for 0.5 to 3.5 years. The primary efficacy outcome was first recurrence of ischemic stroke. The safety outcome was severe or life-threatening bleeding. The analysis was based on the underlying antiplatelet agents.

RESULTS: A total of 763 patients taking aspirin and 1116 taking clopidogrel were included in the intention-to-treat analysis. Although the clopidogrel group had more risk factors than the aspirin group, the primary efficacy outcome and safety outcome did not differ significantly between the 2 groups. In the aspirin group, the primary efficacy outcome and safety outcome did not differ significantly between the DAPT group and the aspirin-monotherapy group. In the clopidogrel group, the primary end point occurred at a rate of 2.31 per 100 patient-years in the DAPT group and 5.19 per 100 patient-years in the clopidogrel-monotherapy group (hazard ratio, 0.447 [95% CI, 0.258–0.774]). Safety outcome did not differ significantly between groups (0.51 per 100 patient-years versus 0.71 per 100 patient-years, respectively; hazard ratio, 0.730 [95% CI, 0.206–2.588]).

CONCLUSIONS: The combination of cilostazol and clopidogrel significantly reduced the recurrence of ischemic stroke without increasing the bleeding risk in noncardioembolic, high-risk patients.

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Key Words: cilostazol ■ clopidogrel ■ dual anti-platelet therapy ■ high-risk ■ noncardioembolic ischemic stroke ■ secondary prevention

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Nonstandard Abbreviations and Acronyms

CAPRIE	Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events
CATHARSIS	Cilostazol-Aspirin Therapy Against Recurrent Stroke With Intracranial Artery Stenosis
CSPS2	Cilostazol Stroke Prevention Study 2
CSPS.com	Cilostazol Stroke Prevention Study combination
DAPT	dual antiplatelet therapy
HR	hazard ratio
TOSS	Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis

Antiplatelet therapy is the most basic treatment for the prevention of a secondary stroke in patients with noncardioembolic ischemic stroke. The combination of antiplatelets with different mechanisms is expected to prevent the recurrence of ischemic stroke events more effectively than monotherapy. The combination of aspirin and clopidogrel inhibits platelet function more than either of these agents alone, and several clinical trials and meta-analyses have shown that the aspirin and clopidogrel combination reduces the recurrence of ischemic stroke slightly, while significantly increasing the frequency of bleeding events, compared with aspirin or clopidogrel alone.[1–4] The relevant guidelines therefore recommend avoiding the use of dual antiplatelet therapies (eg, aspirin and clopidogrel) for preventing secondary stroke events in patients who are in the chronic phase of noncardioembolic ischemic stroke.[5]

Cilostazol selectively inhibits phosphodiesterase 3, and the results of the CSPS2 (Cilostazol Stroke Prevention Study 2) demonstrated that cilostazol treatment significantly reduces stroke recurrence with fewer bleeding events than aspirin.[6] In light of the lower rate of bleeding events in patients treated with cilostazol, the addition of cilostazol to a regimen with another antiplatelet therapy has been expected to decrease the recurrence of stroke without increasing the bleeding risk. The CSPS.com trial (Cilostazol Stroke Prevention Study combination) showed that, compared with aspirin or clopidogrel alone, combination treatment with cilostazol reduced the recurrence of ischemic stroke in patients in the chronic stage without increasing the bleeding risk.[7]

In the CSPS.com trial, aspirin or clopidogrel was used as the underlying antiplatelet drug. A small number of trials has demonstrated some effectiveness and

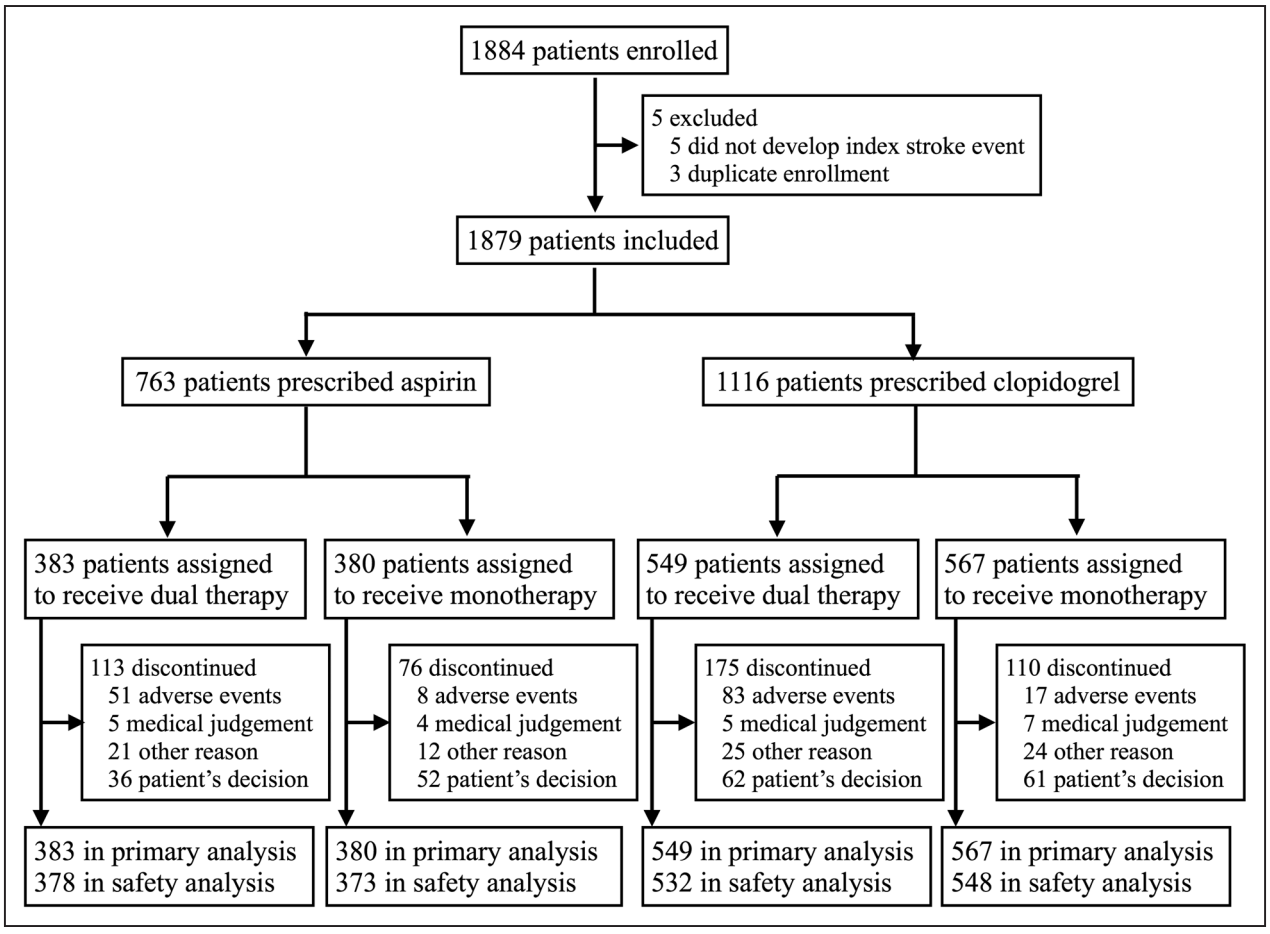

Figure 1. Study flow chart.

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safety for the combination of aspirin and cilostazol.[8,9] Since clopidogrel is reported to be more effective than aspirin,[10] the combination of clopidogrel and cilostazol has been expected to be useful for secondary stroke prevention, with greater effectiveness. However, the clinical utility of this combination therapy has not been reported, to the best of our knowledge. Thus, the effectiveness and safety of the combination of cilostazol and clopidogrel were analyzed in patients enrolled in the CSPS.com trial.

METHODS

Data Availability Statement

The deidentified individual participant data and the study protocol of the CSPS.com may be available upon request to Japan Cardiovascular Research Foundation. Researchers can request data disclosure until March 2022.

Design and Patients

Details regarding the CSPS.com trial rationale, design, and methods have been described elsewhere.[11] The protocol for the CSPS.com trial was approved by the ethics committee at each participating site, and all patients provided written, informed consent before randomization. In that multicenter, randomized, open-label, parallel-group trial, patients at 292 sites in Japan underwent assignment following randomization from December 2013 through March 2017. The steering committee extended the period of enrollment for 1 year to increase the number of anticipated patients. Any event related to the primary and secondary outcomes was reviewed by the event review committee, which was blinded to the patients' antiplatelet medications.

Table 1. Baseline Characteristics

				Aspirin group			Clopidogrel group		
	Aspirin n=763	Clopidogrel n=1116	*P* value	Dual therapy n=383	Monotherapy n=380	*P* value	Dual therapy n=549	Monotherapy n=567	*P* value
Age, y	71 (65–76)	70 (65–76)	0.709	71 (64–76)	70 (65–76)	0.809	70 (65–76)	71 (65–76)	0.771
Female sex	240 (31.5)	319 (28.6)	0.182	125 (32.6)	115 (30.3)	0.484	170 (31.0)	149 (26.3)	0.085
Median blood pressure, mm Hg									
Systolic	138 (128–151)	136 (125–149)	0.015	137 (128–150)	140 (128–154)	0.080	136 (125–148)	137 (125–150)	0.702
Diastolic	78 (70–88)	78 (70–87)	0.983	78 (70–87)	79 (70–88)	0.417	78 (70–87)	79 (70–87)	0.659
Medical history									
Hypertension	656 (86.0)	914 (81.9)	0.180	333 (86.9)	323 (85.0)	0.520	448 (81.6)	466 (82.2)	0.867
Dyslipidemia	404 (52.9)	616 (55.2)	0.139	202 (52.7)	202 (53.2)	0.884	290 (52.8)	326 (57.5)	0.125
Diabetes	273 (35.8)	428 (38.4)	0.143	134 (35.0)	139 (36.6)	0.650	212 (38.6)	216 (38.1)	0.852
Chronic kidney disease	50 (6.6)	69 (6.2)	0.848	27 (7.0)	23 (6.1)	0.661	43 (7.8)	26 (4.6)	0.025
Peripheral arterial disease	20 (2.6)	29 (2.6)	1.000	9 (2.3)	11 (2.9)	0.658	18 (3.3)	11 (1.9)	0.189
History of ischemic stroke	89 (11.7)	183 (16.4)	0.002	40 (10.4)	49 (12.9)	0.311	85 (15.5)	98 (17.3)	0.466
History of ischemic heart disease	40 (5.2)	56 (5.0)	0.916	19 (5.0)	21 (5.5)	0.748	29 (5.3)	27 (4.8)	0.784
Current smoking	232 (30.4)	302 (27.1)	0.192	110 (28.7)	122 (32.1)	0.305	149 (27.1)	153 (27.0)	0.946
Two or more risk factors	702 (92.0)	996 (89.2)	0.047	355 (92.7)	347 (91.3)	0.507	488 (88.9)	508 (89.6)	0.772
Intracranial artery stenosis	198 (26.0)	349 (31.3)	0.003	97 (25.3)	101 (26.6)	0.802	178 (32.4)	171 (30.2)	0.467
Extracranial artery stenosis	82 (10.7)	171 (15.3)	0.001	39 (10.2)	43 (11.3)	0.557	77 (14.0)	94 (16.6)	0.177
modified Rankin Scale score at randomization of 0–1	426 (55.8)	597 (53.5)	0.565	217 (56.7)	209 (55.0)	0.768	299 (54.5)	298 (52.6)	0.580
Stroke subtype			<0.001			0.128			0.513
Lacunar	419 (54.9)	506 (45.3)		224 (58.5)	195 (51.3)		240 (43.7)	266 (46.9)	
Atherothrombotic	281 (36.8)	507 (45.4)		132 (34.5)	149 (39.2)		257 (46.8)	250 (44.1)	
Others	50 (6.6)	69 (6.2)		20 (5.2)	30 (7.9)		36 (6.6)	33 (5.8)	
Infarct location			0.147			0.828			0.675
Supratentorial	569 (74.6)	817 (73.2)		284 (74.2)	285 (75.0)		404 (73.6)	413 (72.8)	
Infratentorial	182 (23.9)	248 (22.2)		94 (24.5)	88 (23.2)		122 (22.2)	126 (22.2)	
Both	5 (0.7)	18 (1.6)		2 (0.5)	3 (0.8)		7 (1.3)	11 (1.9)	
Unreported	7 (0.9)	33 (3.0)		3 (0.8)	4 (1.1)		16 (2.9)	17 (3.0)	
Median time to randomization after index events, d	20 (11–46)	32 (15–75)	<0.001	18 (11–42)	21 (11–51.75)	0.390	33 (16.5–82)	30 (14–71)	0.134

Data are n (%) of overall patients, including those with missing data, or median (interquartile range).

The trial's eligible patients were subjects between 20 and 85 years old who had experienced a noncardioembolic ischemic stroke, as identified on magnetic resonance imaging, between 8 and 180 days before the start of the protocol treatment. These patients were administered either aspirin or clopidogrel alone as antiplatelet therapy after providing informed consent. The choice of whether to use aspirin or clopidogrel before randomization depended on the physician in charge. The patients were also required to meet one or more of the following 3 criteria indicating a high risk of stroke recurrence: (1) ≥50% stenosis of a major intracranial artery (to the level of A2, M2, or P2); (2) ≥50% stenosis of an extracranial artery (common carotid artery, internal carotid artery, vertebral artery, brachiocephalic artery, or subclavian artery); and (3) 2 or more of the following risk factors: age ≥65 years, diabetes, hypertension, peripheral arterial disease, chronic kidney disease, history of ischemic stroke other than the qualifying stroke for the trial, history of ischemic heart disease, and current smoking.[11]

In the CSPS.com trial, the patients were randomly assigned, in a 1:1 ratio using a block-randomization scheme, to receive either monotherapy with aspirin (81 or 100 mg) or clopidogrel (50 or 75 mg), administered once daily; or dual therapy using cilostazol (100 mg, twice daily; the recommended dose for stroke prevention in Japan) in combination with either aspirin (81 or 100 mg) or clopidogrel (50 or 75 mg), administered once daily. In Japan, clopidogrel at 50 mg is approved for older (eg, ≥75 years old) and low-weight patients (≤50 kg body weight). For the prevention of adverse drug reactions such as headache and tachycardia, treating physicians provided the option of initiating cilostazol treatment at 100 mg/day and increasing to 200 mg/day within 15 days. Changes in the choice of these 3 antiplatelet medications were not permitted after informed consent was obtained. The data of the CSPS.com trial were analyzed based on the underlying antiplatelet agents.

Outcomes

The primary efficacy outcome was the first recurrence of ischemic stroke. The secondary efficacy outcomes were (1) any stroke (ischemic or hemorrhagic); (2) hemorrhagic stroke (intracerebral or subarachnoid hemorrhage); (3) ischemic stroke or transient ischemic attack; (4) death from any cause; (5) a composite of stroke, myocardial infarction, and vascular death; and (6) all vascular events, including stroke, myocardial infarction, and other vascular events.

The safety outcomes were severe or life-threatening bleeding as defined in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries classification, which includes intracranial hemorrhage and bleeding resulting in substantial hemodynamic compromise requiring treatment.

Statistical Analysis

Efficacy analyses were conducted in the intention-to-treat population, focused only on time to first event. Safety analyses were conducted with patients who had received at least one dose of a trial regimen. The treatment groups were compared using the log-rank test. Cox proportional hazard models were used to calculate the hazard ratios (HRs) and 95% CIs for the comparison of the dual therapy group with the monotherapy group. Annual recurrence rates were estimated using the person-year method. Subgroup analyses were performed following stratification by age, sex, type of ischemic stroke (atherothrombotic or lacunar), stenosis of extracranial arteries, stenosis of intracranial arteries, modified Rankin Scale score, medical history and complications, current smoking status, obesity, and time to randomization. Tests for interactions between the treatment arms and subgroups were performed using the Cox proportional hazards model. Two-sided $P<0.05$ were considered significant. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Aspirin Group Versus Clopidogrel Group

At randomization and before enrollment in the study, clopidogrel was being taken by 1116 (59%) of the 1879 patients, and aspirin was being taken by the remaining 763 (41%) patients (Figure 1). Some of the background clinical features of the aspirin and clopidogrel groups differed. The clopidogrel group had a significantly higher prevalence of a history of ischemic stroke compared with the aspirin group (183 [16.4%] patients versus 89 [11.7%] patients, respectively; $P=0.0021$), intracranial artery stenosis (349 [31.3%] versus 198 [26.0%] patients, $P=0.0028$), extracranial artery stenosis (171 [15.3%] versus 82 [10.7%] patients, $P=0.0014$), and atherothrombotic stroke subtype (507 [45.4%] patients versus 281 [36.8%] patients, $P<0.0001$). The systolic blood pressure was significantly lower in the clopidogrel group (median 136 versus 138 mm Hg, $P=0.0148$). The median time to randomization was significantly longer in the patients treated with clopidogrel than in those treated with aspirin (32 [15–75] days versus 20 [11–46] days, respectively; $P<0.0001$; Table 1).

Despite the slightly higher prevalence of risk factors among the patients in the clopidogrel group, the clopidogrel group and the aspirin group did not differ significantly in the primary ischemic stroke recurrence outcome (62 patients [3.82 per 100 patient-years] versus 31 patients [2.82 per 100 patient-years], respectively; HR, 0.729 [95% CI, 0.474–1.122]), in any of the secondary efficacy outcomes, or in the safety outcome (10 patients [0.62 per 100 patient-years] versus 11 patients [1.00 per 100 patient-years], respectively; HR, 1.618 [95% CI, 0.687–3.812]) (Table 2). The rate of discontinuing follow-up for reasons other than the development of a major event did not differ significantly between the clopidogrel and aspirin groups (285 patients [25.5%] versus 189 patients [24.8%], respectively; $P=0.625$; Table 3).

Efficacy and Safety Outcomes in the Aspirin Group

The clinical background characteristics did not differ significantly between the dual therapy patients who received the added cilostazol and the aspirin-monotherapy patients

Table 2. Efficacy and Safety Outcomes

	Aspirin		Clopidogrel			Aspirin group	
						Dual therapy	
	No. of patients	Annual event rate	No. of patients	Annual event rate	HR (95% CI)	No. of patients	Annual event rate
Primary efficacy outcomes	n=763		n=1116			n=383	
Ischemic stroke	31	2.82	62	3.82	0.729 (0.474–1.122)	11	2.04
Secondary efficacy outcomes							
Any stroke	38	3.46	67	4.12	0.828 (0.556–1.233)	13	2.42
Hemorrhagic stroke	7	0.64	5	0.31	2.070 (0.657–6.523)	2	0.37
Ischemic stroke or TIA	35	3.18	66	4.06	0.774 (0.514–1.167)	13	2.42
Death from any cause	5	0.45	8	0.49	0.940 (0.307–2.874)	1	0.19
Composite stroke+MI +vascular death	43	3.91	73	4.49	0.861 (0.590–1.255)	14	2.60
All vascular events	52	4.73	85	5.23	0.894 (0.633–1.263)	19	3.53
Safety outcomes	n=751		n=1080			n=378	
Severe or life-threatening bleeding	11	1.00	10	0.62	1.618 (0.687–3.812)	4	0.74
Intracranial hemorrhage	11	1.00	10	0.62	1.618 (0.687–3.812)	4	0.74
Hemorrhagic adverse event	30	2.73	41	2.52	1.072 (0.670–1.718)	15	2.79

(*Continued*)

(Table 1). The primary end point of ischemic stroke occurred in 11 (2.04 per 100 patient-years) of the 383 patients during follow-up in the dual therapy group and in 20 (3.56 per 100 patient-years) of the 380 patients in the monotherapy group (HR, 0.569 [95% CI, 0.273–1.189]) (Table 2, Figure 2A). None of the secondary efficacy outcomes was significantly different (Table 2). The rate of the safety outcome of severe or life-threatening hemorrhage did not differ significantly between these 2 groups (4 patients [0.74 per 100 patient-years] versus 7 patients [1.25 per 100 patient-years], respectively; HR, 0.595 [95% CI, 0.174–2.034]) (Table 2, Figure 2B). The rate of discontinuation for reasons other than the development of a major event was significantly higher in the dual therapy patients compared with the aspirin-monotherapy patients (113 patients [29.5%] versus 76 patients [20.0%], respectively; P=0.001). Palpitations or tachycardia and headache were common reasons for discontinuation in the dual therapy group (Table 3).

Efficacy and Safety Outcomes in the Clopidogrel Group

Regarding the patients' clinical background characteristics, the prevalence of chronic kidney disease was significantly higher in the cilostazol and clopidogrel dual therapy group than in the clopidogrel-monotherapy group (43 [7.8%] patients versus 26 [4.6%] patients, respectively; P=0.0253) (Table 1). The primary end point of ischemic stroke occurred in 18 (2.31 per 100 patient-years) of the 549 patients during follow-up in the dual therapy group and in 44 (5.19 per 100 patient-years) of the 567 patients in the monotherapy group (HR, 0.447 [95% CI, 0.258–0.774]) (Table 2, Figure 3A). Any stroke, ischemic stroke or transient ischemic attack, composite vascular events and all vascular events were also significantly lower in the dual therapy group (Table 2). The rate of the safety outcome of severe or life-threatening hemorrhage did not differ significantly between the 2 groups (4 patients [0.51 per 100 patient-years] versus 6 patients [0.71 per 100 patient-years], respectively; HR, 0.730 [95% CI, 0.206–2.588]) (Table 2, Figure 3B). The rate of discontinuation for reasons other than the development of a major event was significantly higher in the dual therapy patients than in the clopidogrel-monotherapy patients (175 [31.9%] patients versus 110 [19.4%] patients, respectively; P<0.001). As for the aspirin group, palpitations or tachycardia and headache were common reasons for discontinuation in the dual therapy group. Minor bleeding and skin adverse events were common in the clopidogrel group, especially in the patients treated with cilostazol (dual therapy; Table 3).

The results of the subgroup analysis demonstrated that the dual therapy was more effective than the monotherapy in male patients (9/379 [2.37%] patients versus 36/418 [8.61%] patients, respectively; HR, 0.285 [95% CI, 0.137–0.593]; Figure in the Data Supplement).

In the whole group analysis, there was no significant interaction of subgroup (aspirin or clopidogrel)-by-treatment (cilostazol or not), which was tested using the multivariate Cox proportional hazards model with the main effect of subgroup and treatment; the adjusted HR was 0.79 [95% CI, 0.31–1.97] for the efficacy analysis and 1.23 [95% CI, 0.21–7.17] for the safety analysis.

DISCUSSION

To the best of our knowledge, this is the first study to show that the combination of clopidogrel and cilostazol reduces

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Table 2. Continued

Aspirin group			Clopidogrel group				
Monotherapy			Dual therapy		Monotherapy		
No. of patients	Annual event rate	HR (95% CI)	No. of patients	Annual event rate	No. of patients	Annual event rate	HR (95% CI)
n=380			n=549		n=567		
20	3.56	0.569 (0.273–1.189)	18	2.31	44	5.19	0.447 (0.258–0.774)
25	4.45	0.538 (0.275–1.051)	21	2.70	46	5.43	0.499 (0.298–0.836)
5	0.89	0.411 (0.080–2.118)	3	0.39	2	0.24	1.632 (0.273–9.777)
22	3.92	0.611 (0.308–1.213)	19	2.44	47	5.55	0.443 (0.260–0.755)
4	0.71	0.253 (0.028–2.267)	5	0.64	3	0.35	1.841 (0.440–7.703)
29	5.17	0.494 (0.261–0.935)	24	3.08	49	5.78	0.536 (0.329–0.874)
33	5.88	0.590 (0.335–1.037)	28	3.60	57	6.73	0.539 (0.343–0.847)
n=373			n=532		n=548		
7	1.25	0.595 (0.174–2.034)	4	0.51	6	0.71	0.730 (0.206–2.588)
7	1.25	0.595 (0.174–2.034)	4	0.51	6	0.71	0.730 (0.206–2.588)
15	2.67	1.047 (0.512–2.142)	23	2.96	18	2.12	1.372 (0.739–2.545)

Annual event rate indicates the number of events per 100 person-years. HR indicates hazard ratio; MI, myocardial infarction; and TIA, transient ischemic attack.

the rate of secondary ischemic stroke without increasing the bleeding risk. There have been several previous reports on the combined use of aspirin and cilostazol. These trials of the combination of aspirin and cilostazol described a tendency toward more effective reductions of the recurrent ischemic stroke rate and the progression of intracranial artery stenosis compared with those seen with aspirin alone. The TOSS (Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis) demonstrated that the progression of intracranial artery stenosis was significantly lower in the cilostazol and aspirin group than in the aspirin group (6.7% versus 28.8%, respectively; *P*=0.008) in follow-up of only 6 months.[8] The CATHARSIS trial (Cilostazol-Aspirin Therapy Against Recurrent

Table 3. Reasons for the Discontinuation of Trial Drugs

	Aspirin n=763	Clopidogrel n=1116	Aspirin group		Clopidogrel group	
			Dual therapy n=383	Monotherapy n=380	Dual therapy n=549	Monotherapy n=567
Total	189 (24.8)	285 (25.5)	113 (29.5)	76 (20.0)	175 (31.9)	110 (19.4)
Adverse event						
Palpitation or tachycardia	22 (11.6)	22 (7.7)	22 (19.5)	0 (0.0)	22 (12.6)	0 (0.0)
Headache	10 (5.3)	10 (3.5)	10 (8.8)	0 (0.0)	10 (5.7)	0 (0.0)
Minor bleeding	4 (2.1)	15 (5.3)	3 (2.7)	1 (1.3)	14 (8.0)	1 (0.9)
Cancer	5 (2.6)	13 (4.6)	3 (2.7)	2 (2.6)	9 (5.1)	4 (3.6)
Skin adverse event	2 (1.1)	13 (4.6)	1 (0.9)	1 (1.3)	9 (5.1)	4 (3.6)
Gastrointestinal adverse event	1 (0.5)	8 (2.8)	1 (0.9)	0 (0.0)	6 (3.4)	2 (1.8)
Renal disease	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	3 (1.7)	0 (0.0)
Other adverse event	15 (7.9)	17 (6.0)	11 (9.7)	4 (5.3)	10 (5.7)	7 (6.4)
Medical judgment to stop, add, or change antithrombotics						
Atrial fibrillation	5 (2.6)	8 (2.8)	3 (2.7)	2 (2.6)	5 (2.9)	3 (2.7)
Deep venous thrombosis	1 (0.5)	3 (1.1)	0 (0.0)	1 (1.3)	0 (0.0)	3 (2.7)
Interruption of medication before or after surgical procedure	2 (1.1)	1 (0.4)	2 (1.8)	0 (0.0)	0 (0.0)	1 (0.9)
Peripheral arterial disease	1 (0.5)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Change to generic products	5 (2.6)	14 (4.9)	5 (4.4)	0 (0.0)	12 (6.9)	2 (1.8)
Other physician-determined reason	28 (14.8)	35 (12.3)	16 (14.2)	12(15.8)	13 (7.4)	22 (20.0)
Discontinuation by patient's decision	88 (46.6)	123 (43.2)	36 (31.9)	52 (68.4)	62 (35.4)	61 (55.5)

Data are n (%) of overall patients.

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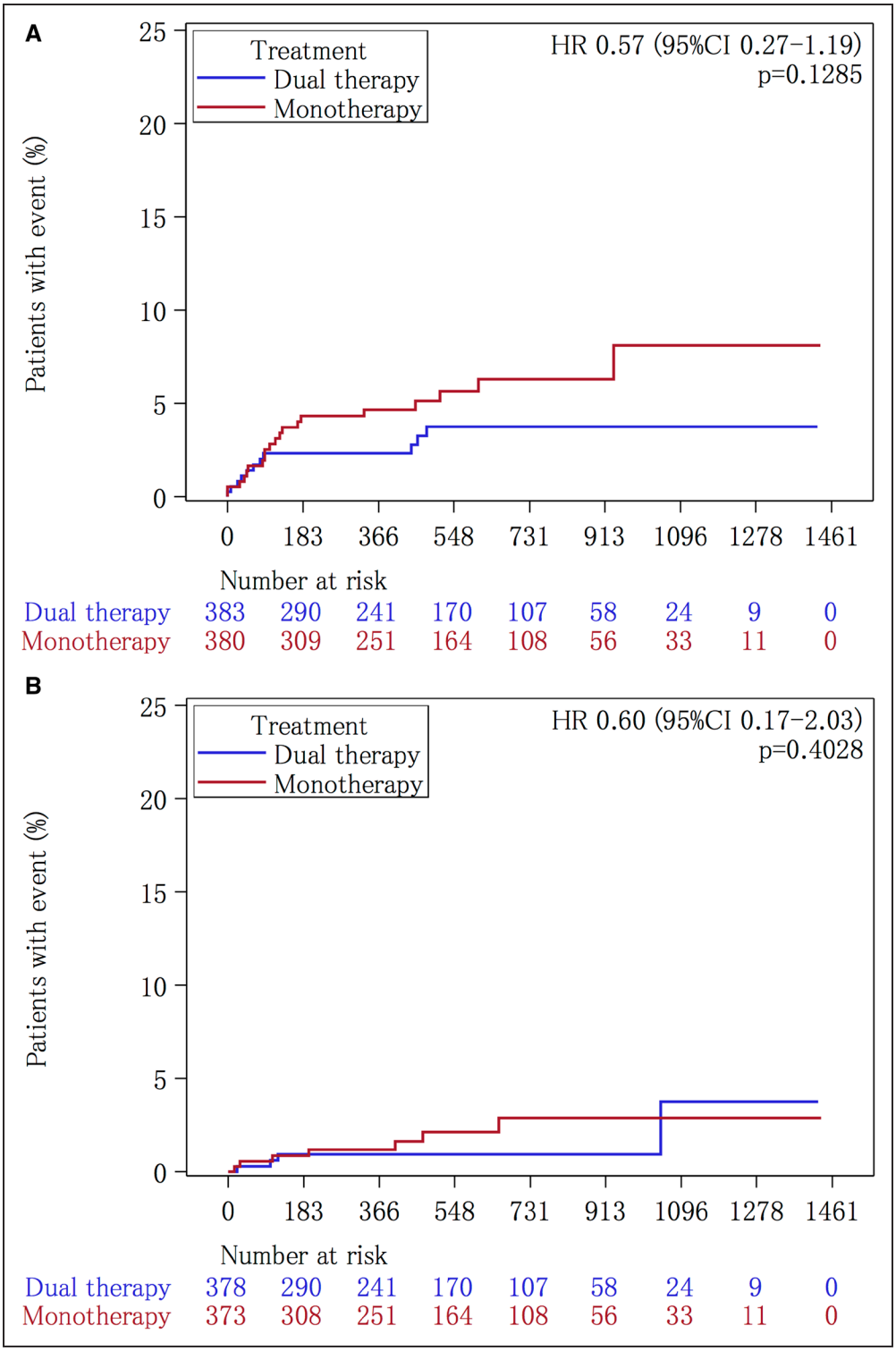

Figure 2. Kaplan-Meier analysis of outcomes in the aspirin group.
The Kaplan-Meier curves for time to the first event of the primary efficacy outcome, defined as ischemic stroke (**A**), and to the safety outcome of severe or life-threatening bleeding (**B**), are shown. HR indicates hazard ratio.

Stroke With Intracranial Artery Stenosis) showed that progression of intracranial stenosis was observed in 9.6% of the cilostazol and aspirin dual therapy group and in 5.6% of the aspirin-monotherapy group, with no significant intergroup difference (*P*=0.53). CATHARSIS also demonstrated that the mean annual recurrence ratio of ischemic stroke was 2.5% in the cilostazol and aspirin dual therapy group and 4.5% in the aspirin-monotherapy group (adjusted HR, 0.47 [95% CI, 0.13–1.73]).[9] The number of cases included in the CATHARSIS trial was

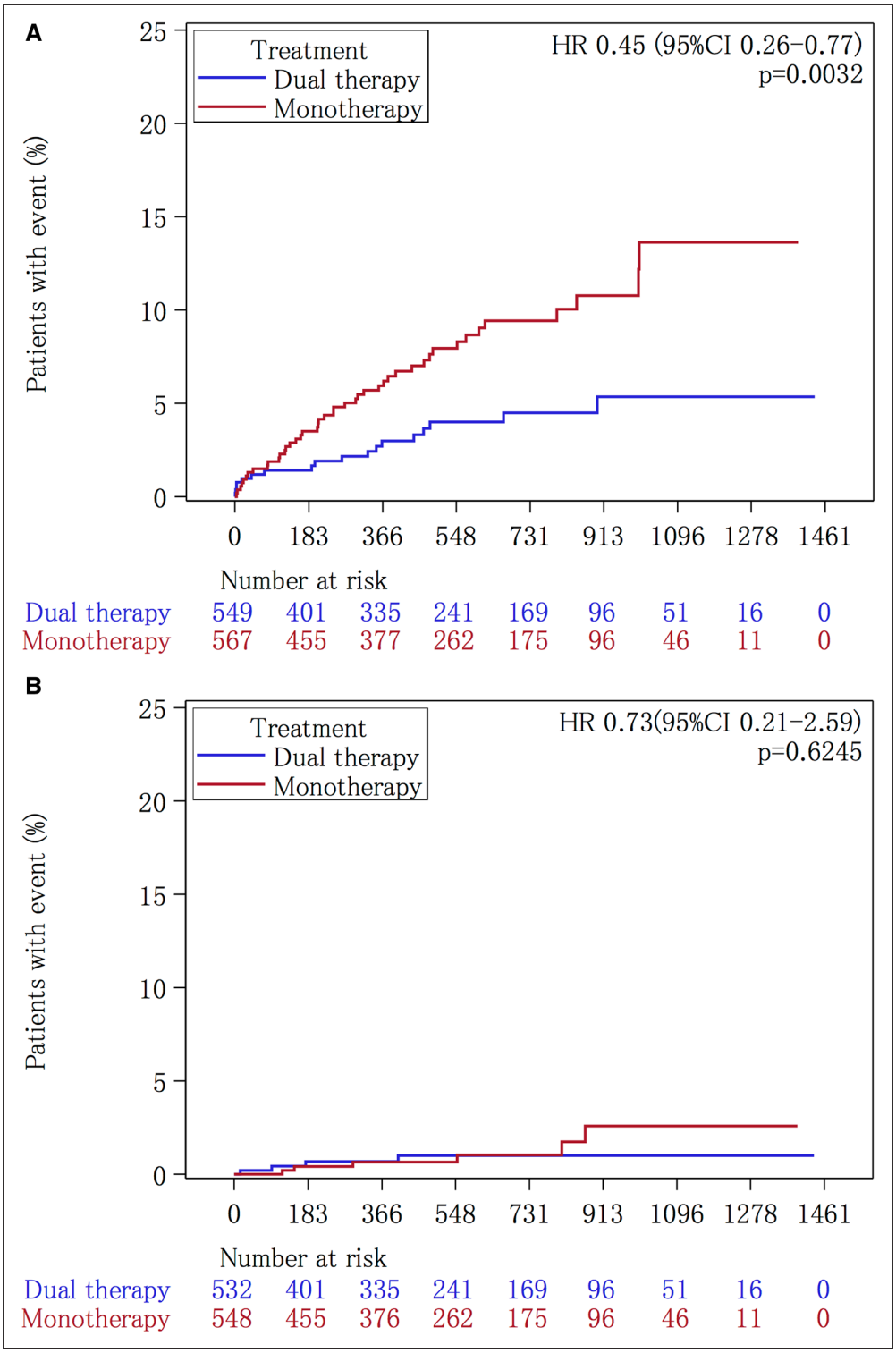

Figure 3. Kaplan-Meier analysis of outcomes in the clopidogrel group.
The Kaplan-Meier curves for the time to the first event of the primary efficacy outcome, defined as ischemic stroke (**A**), and to the safety outcome of severe or life-threatening bleeding (**B**), are shown. HR indicates hazard ratio.

too small to allow conclusions about the clinical outcome differences, but treatment with the combination of cilostazol and aspirin might be expected to reduce the risk of recurrent ischemic stroke. A clinical trial in the acute phase, the ADS study (Acute Aspirin Plus Cilostazol Dual Therapy for Noncardiogenic Stroke Patients Within 48 Hours of Symptom Onset) showed that the combination of cilostazol and aspirin, while safe, did not reduce the rate of short-term neurological worsening after 14 days in noncardioembolic stroke patients.[12] In the present

analysis of a subset of the CSPS.com data, the combination of cilostazol and aspirin did not result in significant differences in the clinical outcome compared with aspirin alone in the chronic phase. This lack of significance may reflect the fact that the sample size was small and the analysis was underpowered, or that the incidence rate of vascular events was lower in the aspirin group.

In the analysis described here, patients in the clopidogrel group had a higher prevalence of risk factors than those in the aspirin group. Based on the results of a randomized, blinded trial of CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events), which showed that clopidogrel was safe and more effective than aspirin in atherothrombotic stroke patients,[10] treating physicians currently tend to select clopidogrel for their higher-risk patients, such as those with large-artery stenosis and a previous history of stroke before the trial. Thus, in the present study, a higher rate of primary events occurred in the clopidogrel group compared with the aspirin group. Notably, in these higher-risk patients (especially those with an atherothrombotic infarction), adding cilostazol to a clopidogrel regimen significantly reduced the rate of recurrent ischemic stroke compared with clopidogrel alone. Another reason explaining the usefulness of the combination of cilostazol and clopidogrel may be the higher prevalence of poor metabolizers with a polymorphism of *CYP2C19* in Asian patients, including Japanese patients.[13] Poor metabolizers might not achieve full clinical antiplatelet inhibition with clopidogrel alone. A meta-analysis demonstrated that, in patients with acute ischemic stroke or transient ischemic attack treated with clopidogrel, carriers of *CYP2C19* loss-of-function alleles are at greater risk of both stroke and composite vascular events with similar bleeding rates compared with noncarriers.[14] However, another meta-analysis that included patients with mostly coronary artery disease demonstrated that there was no significant association between the patient genotype and cardiovascular events.[15] Compared with the trials conducted with patients in the acute phase, the clinical trials in Japanese stroke patients showed that the poor metabolizers were not at greater risk of cerebrovascular events.[16] The addition of cilostazol is expected to further promote the antiplatelet effect of clopidogrel. The combination of aspirin and cilostazol, which have different mechanisms of action, may result in an additive increase in antiplatelet activity. On the other hand, the antiplatelet effect pathway of clopidogrel includes the elevation of intracellular cyclic adenosine monophosphate,[17,18] which indicates that cilostazol is able to enhance clopidogrel's effect synergistically and to enhance other pleotropic effects such as those related to vasodilatory properties.[19] Other reported predictors of clopidogrel resistance are the concomitant use of other drugs or the presence of vascular risk factors, in particular smoking and diabetes.[20] However, no other significant characteristic clinical features were identified in the subanalysis presented here.

Limitations

Some limitations of the present analysis need to be acknowledged. First, this result was a subanalysis of the CSPS.com data. The CSPS.com trial was designed to assess the effectiveness and safety of adding cilostazol to an aspirin or clopidogrel regimen, and the trial could not include the case numbers expected in the protocol. The power was not sufficient to permit a direct comparison of the 2 dual-therapy groups, that is, the utility of separating the dual-therapy patients into distinct clopidogrel and aspirin groups. Thus, some outcomes could not achieve statistical significance, especially in the aspirin group. A larger clinical trial might be able to assess the precise clinical effectiveness of the combination of cilostazol and aspirin.

Second, the patients in the present analyses were all of Japanese heritage. Most of the large clinical trials of cilostazol have been conducted with East Asian patients. It is not yet clear whether the results of these trials (including the CSPS.com trial) can be generalized to other populations.

Conclusions

In a subanalysis of the CSPS.com data, the present study demonstrated that, compared with clopidogrel alone, the combination of cilostazol and clopidogrel reduced the recurrence of ischemic stroke in patients at the chronic stage without increasing the bleeding risk. To the best of our knowledge, the combination of cilostazol and clopidogrel has not been well studied. Since the present findings were obtained in a study population consisting solely of Japanese patients, further clinical trials will be needed to investigate the efficacy and safety of combined treatment with cilostazol and clopidogrel in other high-risk, noncardioembolic ischemic stroke populations.

ARTICLE INFORMATION

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Supplemental Materials

Online Figure

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