Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischaemic stroke in Japan: a multicentre, open-label, randomised controlled trial

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Summary

Background Although dual antiplatelet therapy with aspirin and clopidogrel reduces early recurrence of ischaemic stroke, with long-term use this type of therapy is no longer effective and the risk of bleeding increases. Given that cilostazol prevents stroke recurrence without increasing the incidence of serious bleeding compared with aspirin, we aimed to establish whether dual antiplatelet therapy involving cilostazol is safe and appropriate for long-term use.

Methods In a multicentre, open-label, randomised controlled trial across 292 hospitals in Japan, patients with high-risk non-cardioembolic ischaemic stroke identified on MRI were randomly assigned to two groups in a 1:1 ratio to receive monotherapy with either oral aspirin (81 or 100 mg, once per day) or clopidogrel (50 or 75 mg, once per day) alone, or a combination of cilostazol (100 mg, twice per day) with aspirin or clopidogrel. Randomisation was done centrally (using block randomisation with a block size of six per each participating hospital) through a web-based registration system and was done by EPS Corporation. The patients were required to have at least 50% stenosis of a major intracranial or extracranial artery or two or more of the vascular risk factors. Trial medication was continued for half a year or longer, for a maximum of 3·5 years. The primary efficacy outcome was the rate of first recurrence of symptomatic ischaemic stroke. Safety outcomes were severe or life-threatening bleeding; any adverse events; serious adverse events; and any bleeding events. Efficacy analyses were done in the intention-to-treat population and safety analyses were done in the as-treated population. This trial was registered with ClinicalTrials.gov (number NCT01995370) and UMIN Clinical Trials Registry (number 000012180).

Findings Participants were recruited from Dec 13, 2013, to March 31, 2017. 932 patients assigned to the dual therapy group and 947 patients assigned to the monotherapy group were included in the intention-to-treat analysis. The trial was stopped after the enrolment of 1884 patients of an anticipated 4000 patients because of the delay in recruitment. Ischaemic stroke recurred in 29 (3%) of 932 patients (annualised rate 2·2%) on dual therapy including cilostazol and 64 (7%) of 947 patients (annualised rate 4·5%) on monotherapy during a median 1·4 years follow-up (hazard ratio [HR] 0·49, 95% CI 0·31–0·76, p=0·0010). Severe or life-threatening bleeding occurred in eight patients (annualised rate 0·6%) on dual therapy and 13 patients (annualised rate 0·9%) on monotherapy (HR 0·66, 95% CI 0·27–1·60, p=0·35). Occurrence of any type of adverse event was similar between the groups (255 [28%] of 910 patients in the dual therapy group *vs* 219 [24%] of 921 patients in the monotherapy group); as was occurrence of serious adverse events (87 [10%] *vs* 142 [15%]) and bleeding events (38 [4%] *vs* 33 [4%]). Gastrointestinal bleeding, which affected nine (<1%) of 910 patients in the monotherapy group and nine (<1%) of 921 patients in the dual therapy group, was the most common type of bleeding.

Interpretation The combination of cilostazol with aspirin or clopidogrel had a reduced incidence of ischaemic stroke recurrence and a similar risk of severe or life-threatening bleeding compared with treatment with aspirin or clopidogrel alone in patients at high risk for recurrent ischaemic stroke.

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Introduction

Patients with non-cardioembolic ischaemic stroke have a higher risk of recurrence when they have carotid stenosis,[1] intracranial arterial stenosis,[2] or multiple vascular risk factors than when they do not have these complications.[3,4] For such patients, comprehensive preventive therapy, including antiplatelet medication, has been proven beneficial. However, newer antiplatelet agents that are promising for patients with coronary artery disease and have been in commercial use for around 10 years, such as ticagrelor and prasugrel, did not show advantages over conventional antiplatelet agents for patients with stroke in randomised controlled trials (RCTs).[5,6]

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Research in context

Evidence before this study

We searched PubMed on Dec 31, 2018, for relevant articles in English published since Jan 1, 1999, using the search terms "antiplatelet therapy", "aspirin", "cilostazol", "clopidogrel", "stroke", "cerebral ischaemia", and "cerebral infarction". We also manually searched references from original articles and pertinent reviews. Searches were restricted to completed trials in humans with abstracts or full texts published.

In 2013, Lee and colleagues reported the results of a meta-analysis of data from seven randomised controlled trials of long-term dual-antiplatelet and single-antiplatelet therapy in patients with ischaemic stroke and transient ischaemic attack. The seven trials assessed the following antiplatelet regimens: aspirin plus clopidogrel versus aspirin monotherapy in the CHARISMA and SPS3 trials; aspirin plus dipyridamole, a phosphodiesterase inhibitor, versus aspirin monotherapy in the ESPRIT and JASAP trials; aspirin plus clopidogrel versus clopidogrel monotherapy in the MATCH trial; aspirin plus dipyridamole versus clopidogrel monotherapy in the PRoFESS trial; and aspirin plus ticlopidine versus ticlopidine monotherapy in the TOPALS trial. Recurrent stroke risk did not differ between patients receiving dual-antiplatelet therapy and those receiving monotherapy with any choice of antiplatelet agents. Risk for intracranial haemorrhage did not differ between patients receiving dual-antiplatelet therapy and those receiving aspirin monotherapy but it was greater in patients receiving dual-antiplatelet therapy than in those receiving clopidogrel monotherapy.

ESPS2 is another randomised controlled trial of long-term aspirin, dipyridamole, their combined use, and placebo in patients with ischaemic stroke and transient ischaemic attack. Risk reduction of recurrent stroke was greater with the combination therapy than with each monotherapy. Severe or fatal bleeding events were around twice as common in patients receiving aspirin monotherapy and those receiving dual therapy as those receiving dipyridamole monotherapy and those receiving placebo. A meta-analysis of data from randomised controlled trials of long-term aspirin plus dipyridamole versus aspirin alone in patients with ischaemic stroke and transient ischaemic attack, including the ESPS2, ESPRIT, JASAP, and other trials, showed greater reduction of the risk of recurrent ischaemic stroke with combination therapy 12 weeks after randomisation. The risk of bleeding of the combination was higher than clopidogrel monotherapy based on the results of the ESPS2 and PRoFESS trials.

A combination of cilostazol, a phosphodiesterase-3 inhibitor, and aspirin did not increase bleeding compared with aspirin alone or aspirin plus clopidogrel in small trials in patients with stroke and intracranial arterial stenosis in the TOSS, TOSS-2, and CATHARSIS trials. In the CATHARSIS trial, the mean annual incidence of all vascular events, stroke, and ischaemic stroke tended to be lower in patients receiving dual therapy than in those receiving aspirin monotherapy.

To the best of our knowledge, no randomised controlled trial of dual therapy with cilostazol plus thienopyridines for stroke has been done.

Added value of this study

The results of our Cilostazol Stroke Prevention Study for Antiplatelet Combination indicate that recurrence of ischaemic stroke was less common with long-term dual therapy with the combination of cilostazol with aspirin or clopidogrel than with long-term monotherapy with aspirin or clopidogrel alone in patients who developed non-cardioembolic ischaemic stroke with major cephalocervical artery stenosis or multiple vascular risk factors. There was no evidence of a higher risk of severe or life-threatening bleeding with dual therapy than with monotherapy.

Implications of all the available evidence

The combination of cilostazol with aspirin or clopidogrel seems to be a pharmacotherapeutic approach that could be recommended in the chronic stage of high-risk, non-cardioembolic, ischaemic stroke.

Given that antiplatelet agents act through a range of mechanisms, including platelet inhibition of thromboxane A2 production, inhibition of cyclic adenosine 3',5'-monophosphate production, and inhibition of P2Y12 receptors, a combination of agents can produce more effective stroke prevention than single agents. The combination of dual antiplatelet therapy with aspirin and clopidogrel decreases the risk of early stroke recurrence in patients with minor ischaemic stroke or high-risk transient ischaemic attack compared with aspirin monotherapy.[7,8] Several weeks or months later, however, risk reduction of stroke with aspirin combined with clopidogrel was attenuated and dual therapy was harmful in such patients because of the higher risk of major bleeding than with monotherapy.[9–12]

Cilostazol, a phosphodiesterase 3 inhibitor, has antiplatelet and vasodilatory properties as well as antiinflammatory and antiproliferative effects,[13] and causes bleeding complications less frequently than other antiplatelet agents based in animal and human studies.[14,15] In RCTs, cilostazol decreased recurrent stroke in patients with non-cardioembolic ischaemic stroke, with a similar risk of serious bleeding compared with placebo and with half the risk of serious bleeding compared with aspirin.[16,17] In a meta-analysis involving patients with stroke and other atherothrombotic diseases, cilostazol was associated with significantly lower incidences of total vascular events and of cerebrovascular events than was placebo.[18] In another meta-analysis of secondary stroke prevention, cilostazol was associated with significantly less haemorrhagic

stroke, a reduced risk of the combined endpoint of stroke, myocardial infarction, and vascular death, and fewer bleeding events than aspirin.[19] Cilostazol monotherapy is recommended as first-line antiplatelet therapy for secondary prevention of non-cardioembolic ischaemic stroke in Japanese guidelines.[20]

A combination of aspirin and dipyridamole, another phosphodiesterase inhibitor, showed a greater reduction of the risk of recurrent ischaemic stroke than aspirin alone only in the chronic stage 12 weeks after random assignment to treatment in patients with ischaemic stroke and transient ischaemic attack.[21] However, dipyridamole increased major bleeding when added to aspirin.

By contrast, a combination of cilostazol and aspirin did not increase bleeding compared with aspirin alone or aspirin plus clopidogrel in small trials in stroke patients with intracranial arterial stenosis.[22–24] Triple medication with the addition of cilostazol did not increase bleeding compared with dual medication with aspirin and clopidogrel in a meta-analysis of patients with a drug-eluting coronary stent.[25] Thus, the addition of cilostazol might enhance the preventive effects of classic antiplatelet agents in patients with chronic stroke without increasing bleeding risk.

The Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com) was designed to test the hypothesis that a combination of cilostazol with aspirin or clopidogrel reduces recurrence of ischaemic stroke in the chronic stage without increasing the bleeding risk compared with aspirin or clopidogrel alone.

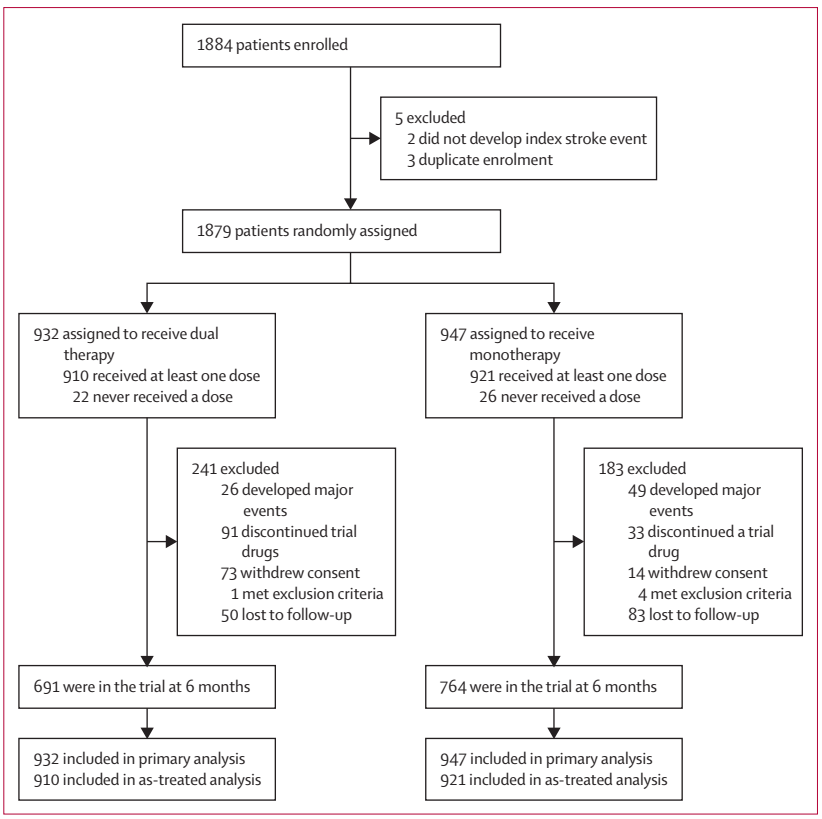

Figure 1: **Trial profile**
Major events include all vascular events, including stroke, myocardial infarction, other vascular events (eg, aortic dissection, aortic rupture, pulmonary embolism, heart failure, angina pectoris, or peripheral artery disease requiring hospitalisation, and revascularisation of the coronary artery, aorta, cephalocervical artery, and peripheral arteries), transient ischaemic attack, death from any cause, and severe or life-threatening bleeding as defined in the GUSTO classifications.

Methods

Study design and participants

In this multicentre, open-label, parallel-group RCT, patients were recruited at 292 hospitals across Japan (appendix). Details regarding the trial rationale, design, and methods have been described elsewhere.[26] The protocol was approved by the ethics committee at each participating site, and all patients gave written informed consent before being randomly assigned to treatment.

A Steering Committee was responsible for the design, interpretation, and supervision of the trial (appendix). The final trial protocol was prepared by the protocol committee (appendix). Any event related to the primary and secondary outcomes was reviewed by the Event Evaluation Committee who were masked to antiplatelet medications. Charges for trial drugs were covered by the health insurance of each patient. All investigators and coordinators who were provided access to the results were asked to sign a confidentiality agreement to ensure that the results were not disclosed to third parties before publication and presentation of the primary results.

Eligible patients were aged between 20 years and 85 years and had developed a non-cardioembolic ischaemic stroke identified on MRI between 8 days 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 one of the following three criteria indicating a high risk for stroke recurrence: at least 50% stenosis of a major intracranial artery (to the level of A2 [the postcommunicating segment of the anterior cerebral artery], M2 [the Sylvian segment of the middle cerebral artery], or P2 [the ambient segment of the posterior cerebral artery]); at least 50% stenosis of an extracranial artery (the common carotid artery, internal carotid artery, vertebral artery, brachiocephalic artery, or subclavian artery); and two or more risk factors derived from the Essen Stroke Risk Score and Fukuoka Stroke Risk Score,[3,4] including age 65 years or older, hypertension, diabetes mellitus, chronic kidney disease, peripheral arterial disease, history of ischaemic stroke other than the qualifying episode for this trial, history of ischaemic heart disease, and current smoking. Patients had to be able to visit the study centre throughout the observation period. Major exclusion criteria were high-risk sources of cardioembolism, use of anticoagulants, contraindication to MRI examination, and history of symptomatic non-traumatic intracranial haemorrhage, any other haemorrhagic disease, bleeding predisposition, or blood clotting disorders. Additional

See Online for appendix

	Dual therapy (n=932)	Monotherapy (n=947)
Age, years	69·6 ± 9·2	69·7 ± 9·2
Female sex	295 (32%)	264 (28%)
Male sex	637 (68%)	683 (72%)
Asian ethnicity*	932 (100%)	947 (100%)
Body-mass index	23·9 (3·6)	23·7 (3·4)
Median blood pressure, mm Hg		
Systolic	136 (126–149)	138 (126–151)
Diastolic	78 (70–87)	79 (70–88)
Medical history		
Hypertension	781 (84%)	789 (83%)
Dyslipidaemia	492 (53%)	528 (56%)
Diabetes	346 (37%)	355 (38%)
Chronic kidney disease	70 (8%)	49 (5%)
Peripheral arterial disease	27 (3%)	22 (2%)
History of ischaemic stroke†	125 (13%)	147 (16%)
History of ischaemic heart disease	48 (5%)	48 (5%)
Current smoking	259 (28%)	275 (29%)
Two or more risk factors	843 (90%)	845 (89%)
Intracranial artery stenosis	275 (30%)	272 (29%)
Extracranial artery stenosis	116 (12%)	137 (14%)
Modified Rankin Scale‡ score at randomisation of 0–1	843 (90%)	855 (90%)
Antiplatelet use at randomisation		
Aspirin	383 (41%)	380 (40%)
Clopidogrel§	549 (59%)	567 (60%)
Stroke subtype		
Lacunar	464 (50%)	461 (49%)
Atherothrombotic	389 (42%)	399 (42%)
Other or undetermined	79 (8%)	87 (9%)
Infarct location		
Supratentorial	688 (74%)	698 (74%)
Infratentorial	216 (23%)	214 (23%)
Both	9 (1%)	14 (1%)
Unreported	19 (2%)	21 (2%)
Median time to randomisation after index events, days	27 (13–63)	25 (13–64)

Data are n (%) of overall patients, including those with missing data, mean (SD), or median (IQR). 49 patients (23 in the dual therapy group and 26 in the monotherapy group) are missing data for body-mass index; 60 patients (28 in the dual therapy group and 32 in the monotherapy group) for blood pressure; 41 patients (20 in the dual therapy group and 21 in the monotherapy group) for medical history; 42 patients (20 in the dual therapy group and 22 in the monotherapy group) for current smoking; 155 patients (77 in the dual therapy group and 78 in the monotherapy group) for intracranial artery stenosis; 254 patients (116 in the dual therapy group and 138 in the monotherapy group) for extracranial artery stenosis; and 57 patients (26 in the dual therapy group and 31 in the monotherapy group) for modified Rankin Scale score at randomisation. *Self-reported; all are reported as Japanese. †Except the qualifying stroke for this trial. ‡The modified Rankin Scale measures the degree of disability in the daily activities of patients, ranging from 0 to 6, with higher scores indicating worse functional deficits than lower scores. §36 patients in the dual therapy group and 23 patients in the monotherapy group were taking clopidogrel 50 mg once per day; the other patients were taking clopidogrel 75 mg once per day.

Table 1: **Baseline characteristics of patients**

information regarding the inclusion and exclusion criteria is provided in the protocol (appendix).[26]

Randomisation and masking

Patients were randomly assigned to two groups in a 1:1 ratio to receive one of the following treatments: monotherapy with aspirin (81 mg or 100 mg) or clopidogrel (50 mg or 75 mg) once per day; or dual therapy with Pletaal (Otsuka Pharmaceutical, Tokyo, Japan), a brand of cilostazol (100 mg, twice per day, the recommended dose for stroke prevention in Japan), together with either aspirin (81 mg or 100 mg) or clopidogrel (50 mg or 75 mg), once per day. Randomisation was done centrally through a web-based registration system administered by the EPS Corporation. A permuted block-randomisation scheme was used with a block size of six for each participating hospital. Placebo agents were not used because of the limited amount of funding.

Procedures

Choice of the antiplatelet agent at randomisation, either aspirin or clopidogrel administered orally, was established by the decision of each physician in charge. Clopidogrel 50 mg once per day is officially approved in Japan for patients who are older (eg, aged ≥75 years) or those with low weight (≤50 kg), although 75 mg once per day is mainly used in clinical practice for patients who are older or those with low weight. Trial medication was continued for 6 months 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 once per day and increased to 100 mg twice per day within 15 days. Changes in these three antiplatelet medications were not permitted after informed consent was obtained. Patients who stopped taking the trial drugs for longer than 4 weeks were withdrawn from the trial. Follow-up intervals were at 1 month, 3 months, 6 months, and every 6 months thereafter, with modified Rankin Scale, blood pressure, compliance to the study drug, and adverse events being assessed at each visit.

Outcomes

The primary efficacy outcome was the first recurrence of symptomatic ischaemic stroke. The secondary efficacy outcomes were as follows: any stroke (ischaemic or haemorrhagic); haemorrhagic stroke (intracerebral or subarachnoid haemorrhage, symptomatic); ischaemic stroke or transient ischaemic attack; death from any cause; a composite of stroke, myocardial infarction, and vascular death; and all vascular events, including stroke, myocardial infarction, and other vascular events (eg, aortic dissection; aortic rupture; pulmonary embolism; heart failure, angina pectoris, or peripheral artery disease requiring hospital admission; revascularisation of a coronary artery, aorta, cephalocervical artery, and peripheral arteries).

Safety outcomes were as follows: severe or life-threatening bleeding as defined in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries classification, which includes symptomatic intracranial haemorrhage (haemorrhagic stroke and subdural or epidural haemorrhage) and bleeding resulting in substantial haemodynamic compromise requiring treatment;[27] symptomatic intracranial haemorrhage; any adverse events; serious adverse events; and any bleeding events.

Investigators at each participating site were aware of the study allocation used. The efficacy and safety outcomes were always evaluated by the Independent Data Monitoring Committee and the Event Evaluation Committee, in which all members were masked to treatment allocation. Investigators at each participating site needed to submit additional clinical data upon request from the committees.

Statistical analysis

Details are provided in the statistical analysis plan, which is available with the protocol (appendix). Briefly, the plan was to enrol 4000 patients and follow them for a maximum of 3·5 years, to detect a 30% relative rate reduction in the dual therapy group with 80% power, on the basis of an estimated rate of occurrence of the primary outcome of 4% per year in the monotherapy group.

Efficacy analyses were done in the intention-to-treat population, focused only upon time to first event. Safety analyses were done 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 hazard ratios (HRs) and 95% CIs for the dual therapy group compared with the monotherapy group. Patients who did not develop events were treated as censored at the last observational date. The assumption of proportional hazards was confirmed when performing each analysis. The treatment groups are shown by Kaplan-Meier plots and compared using the log-rank test. A CI for the number needed to treat was obtained by taking reciprocals of the values defining the CI for the hazard ratio. Subgroup analyses were done following stratification by age, sex, body-mass index, medical history, current smoking status, stenosis of intracranial arteries, stenosis of extracranial arteries, modified Rankin Scale score at randomisation, antiplatelet agents (aspirin or clopidogrel), and subtype of ischaemic stroke. All these components were prespecified in the protocol. Tests for interaction between the treatment groups and subgroups were done using the Cox proportional hazards model. A secondary as-treated (per-protocol) analysis of the primary outcome that included patients who had received at least one dose of a trial regimen, with data censored 1 day after permanent discontinuation of trial medication, was also performed. As a post-hoc analysis, we calculated mean values of change in systolic blood pressure from the baseline value and analysed the difference between groups using a Wilcoxon rank sum test.

	Number of patients in the dual therapy group (n=91)	Number of patients in the monotherapy group (n=33)
Adverse event	66 (73%)	12 (36%)
Palpitations or tachycardia	28* (31%)	0
Headache	9* (10%)	0
Skin adverse event	8 (9%)	3 (9%)
Minor bleeding	7 (8%)	2 (6%)
Cancer	7 (8%)	2 (6%)
Gastrointestinal adverse event	4 (4%)	3 (9%)
Other adverse event	7 (8%)	2 (6%)
Medical judgment to stop, add, or change antithrombotics	11 (12%)	14 (42%)
Initiation of prohibited concomitant medications	3 (3%)	9 (27%)
Development of non-severe ischaemia	4 (4%)	1 (3%)
Interruption of medication before or after surgical procedure	1 (1%)	3 (9%)
Other reason	3 (3%)	1 (3%)
Other physician-determined reason	14 (15%)	5 (15%)
Change to generic cilostazol products	9 (10%)	0
By mistake	4 (4%)	4 (12%)
Other reason	1 (1%)	1 (3%)
Discontinuation by patient's decision	0	2 (6%)

*Four patients with simultaneous palpitations and headache were listed twice in this table.

Table 2: **Reasons for discontinuation of trial drugs**

Missing data were not imputed, as baseline data were available for all intention-to-treat patients. Data with a missing value for included variables in the Cox regression model were excluded from the analysis. The statistical analysis committee prepared and finalised the statistical analysis plan. The Independent Data Monitoring Committee monitored the trial. Statistical analysis was delegated to a contract research organisation (EPS Corporation, Tokyo, Japan). All statistical analyses were done using SAS software version 9.4. The CSPS.com trial is registered with ClinicalTrials.gov (number NCT01995370) and UMIN Clinical Trials Registry (number 000012180).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants were recruited from Dec 13, 2013, to March 31, 2017 (initially planned to March 31, 2016); the steering committee extended the period of enrolment for 1 year to increase the number of anticipated patients. However, the number of enrolled patients (1884 patients) did not reach half the estimated number needed to reach a power of 80% (figure 1). The steering committee judged that the complete enrolment of 4000 patients was

	Dual therapy		Monotherapy		HR (95% CI)	p value
	Number of patients	Annual event rate	Number of patients	Annual event rate		
Primary efficacy outcome	n=932		n=947			
Ischaemic stroke*	29 (3%)	2·2	64 (7%)	4·5	0·49 (0·31–0·76)	0·0010
Secondary efficacy outcomes	n=932		n=947			
Any stroke	34 (4%)	2·6	71 (7%)	5·0	0·51 (0·34–0·77)	0·0012
Haemorrhagic stroke*	5 (1%)	0·4	7 (1%)	0·5	0·77 (0·24–2·42)	0·65
Ischaemic stroke or transient ischaemic attack	32 (3%)	2·4	69 (7%)	4·9	0·50 (0·33–0·76)	0·00091
Death from any cause	6 (1%)	0·5	7 (1%)	0·5	0·92 (0·31–2·73)	0·88
Composite of stroke, myocardial infarction, and vascular death	38 (4%)	2·9	78 (8%)	5·5	0·52 (0·35–0·77)	0·00079
All vascular events	47 (5%)	3·6	90 (10%)	6·4	0·56 (0·39–0·80)	0·0011
Safety outcomes	n=910		n=921			
Severe or life-threatening bleeding	8 (1%)	0·6	13 (1%)	0·9	0·66 (0·27–1·60)	0·35
Intracranial haemorrhage	8 (1%)	0·6	13 (1%)	0·9	0·66 (0·27–1·60)	0·35
Haemorrhagic adverse events	38 (4%)	2·9	33 (4%)	2·4	1·23 (0·77–1·96)	0·38

Annual event rate indicates the number of events per 100 person-years. HR=hazard ratio. *Two patients who developed ischaemic stroke (one in each of the two treatment groups) and two patients who developed haemorrhagic stroke (one in each of the two treatment groups) had fatal outcomes.

Table 3: **Efficacy and safety outcomes**

unlikely by the further extension within the limit of funding, and therefore finally decided to stop enrolment on March 31, 2017. Final observations were done on March 31, 2018. No interim analysis was done given that enrolment did not reach 2000 patients. Of the 1884 patients who consented to participate in the study between Dec 13, 2013, and March 31, 2017, 1879 (>99%) were randomly assigned to treatment; two patients (<1%) did not develop ischaemic stroke as an index event and three patients (<1%) were registered twice. Thus, 932 patients assigned to the dual therapy group and 947 patients assigned to the monotherapy group were included in the intention-to-treat analysis. Regarding conditions indicating a high risk of stroke recurrence, 547 (29%) of 1879 patients had at least 50% stenosis of a major intracranial artery, 253 (13%) of 1879 patients had at least 50% stenosis of an extracranial artery, and 1698 (90%) of 1879 patients had two or more risk factors (table 1). At randomisation and before enrolment into the study, clopidogrel was being taken by 1116 (59%) of 1879 patients; 59 (5%) of these 1116 patients were taking clopidogrel 50 mg once per day, and the remaining 1057 (95%) were taking clopidogrel 75 mg once per day (table 1; appendix). Characteristics at baseline are shown in table 1. The median time from the qualifying stroke to randomisation was 26 days (IQR 13–62).

The median duration of follow-up was 1·4 years overall (IQR 0·6–2·2), resulting in 2724·1 patient-years of follow-up. The median duration of follow-up in the dual therapy group was 1·4 years (IQR 0·8–2·2), resulting in 1316·4 patient-years of follow-up, and the median duration of follow-up in the monotherapy group was 1·4 years (IQR 0·5–2·2), resulting in 1408·1 patient-years of follow-up. Discontinuation of follow-up within 6 months for reasons other than development of major events occurred in 215 (23%) of 932 patients in the dual therapy group and 134 (14%) of 947 patients in the monotherapy group (figure 1). These 349 patients were older (mean 70·5 years, SD 8·9, *vs* 69·4 years, SD 9·2), and less commonly had dyslipidaemia (43% *vs* 57%) and two or more risk factors (82% *vs* 92%) than the remaining 1530 patients. Of these, 91 patients in the dual therapy group and 33 patients in the monotherapy group discontinued trial drugs. Reasons for the discontinuation of trial drugs are shown in table 2. Palpitations or tachycardia (24 patients), headache (five patients), and both palpitations or tachycardia and headache (four patients) were common reasons for the discontinuation of trial drugs, events that were only recorded in the dual therapy group (33 [4%] of 932).

Systolic blood pressure (SBP) is shown in the appendix. The dual therapy group had SBP levels that were 2–4 mm Hg lower than the monotherapy group throughout the follow-up period (p=0·29).

The primary efficacy outcome of ischaemic stroke occurred in 29 (3%) of 932 patients (2·2 events per 100 person-years) during follow-up in the dual therapy group and in 64 (7%) of 947 patients (4·5 events per 100 person-years) in the monotherapy group (HR 0·49; 95% CI 0·31–0·76; p=0·0010; table 3 and figure 2A). The numbers needed to prevent ischaemic stroke were 43 (95% CI 27–103). The secondary efficacy outcome of any stroke was lower in the dual therapy group (34 [4%] of 932 patients than in the monotherapy group (71 [7%] of 947 patients; table 3). Haemorrhagic stroke occurred in five (1%) of 932 patients in the dual therapy group and in seven (1%) of 947 patients in the monotherapy group

(table 3). A composite of stroke, myocardial infarction, and vascular death occurred in 38 (4%) of 932 patients in the dual therapy group and in 78 (8%) of 947 patients in the monotherapy group (table 3 and figure 2B). Other secondary outcomes are reported in table 3. We observed no significant treatment-by-subgroup interactions among the prespecified subgroups (appendix).

In the as-treated (per-protocol) analysis, ischaemic stroke occurred in 28 (3%) of 910 patients (annualised rate 2·1%) in the dual therapy group and in 62 (7%) of 921 patients (annualised rate 4·4%) in the monotherapy group (HR 0·49, 95% CI 0·31–0·76, p=0·0010; appendix).

Severe or life-threatening bleeding occurred in eight (1%) of 910 patients (annualised rate 0·6%) during follow-up in the dual therapy group and in 13 (1%) of 921 patients (0·9 events per 100-person years) in the monotherapy group (table 3 and figure 2C). All of these 21 events were intracranial haemorrhage events.

Any type of adverse event occurred in 255 (28%) of 910 patients during follow-up in the dual therapy group and in 219 (24%) of 921 patients in the monotherapy group. Non-serious adverse events were also recorded, although these events occurred only in the dual therapy group; 26 patients developed headache, 33 developed palpitations, and 26 developed tachycardia (table 4 and appendix). Serious adverse events occurred in 87 (10%) of 910 patients in the dual therapy group and in 142 (15%) of 921 patients in the monotherapy group (p=0·00017; appendix). Bleeding events occurred in 38 (4%) of 910 patients in the dual therapy group and in 33 (4%) of 921 patients in the monotherapy group (p=0·55; appendix). Gastrointestinal bleeding, which affected nine (<1%) of 910 patients in the monotherapy group and nine (<1%) of 921 patients in the dual therapy group, was the most common type of bleeding.

Discussion

In this multicentre RCT of secondary stroke prevention in patients with high-risk non-cardioembolic ischaemic stroke, the recurrence of ischaemic stroke was less common with long-term dual therapy with cilostazol plus aspirin or clopidogrel than with long-term monotherapy with aspirin or clopidogrel alone. We found no evidence of a higher risk of severe or life-threatening bleeding with dual antiplatelet therapy than with monotherapy.

Addition of cilostazol to single antiplatelet therapy almost halved the incidence rates of recurrent ischaemic stroke, any stroke, ischaemic stroke or transient ischaemic attack, a composite of stroke, myocardial infarction, and vascular death, and all vascular events. Given that the rate reduction was strong compared with our estimate (30%),[26] positive effects of dual therapy on efficacy outcomes were shown despite the smaller-than-planned sample size. The majority of the enrolled patients (59%) were taking clopidogrel, and the addition of cilostazol to clopidogrel reduced the rate of recurrent ischaemic stroke by 55% in this cohort. Such a beneficial effect for patients receiving

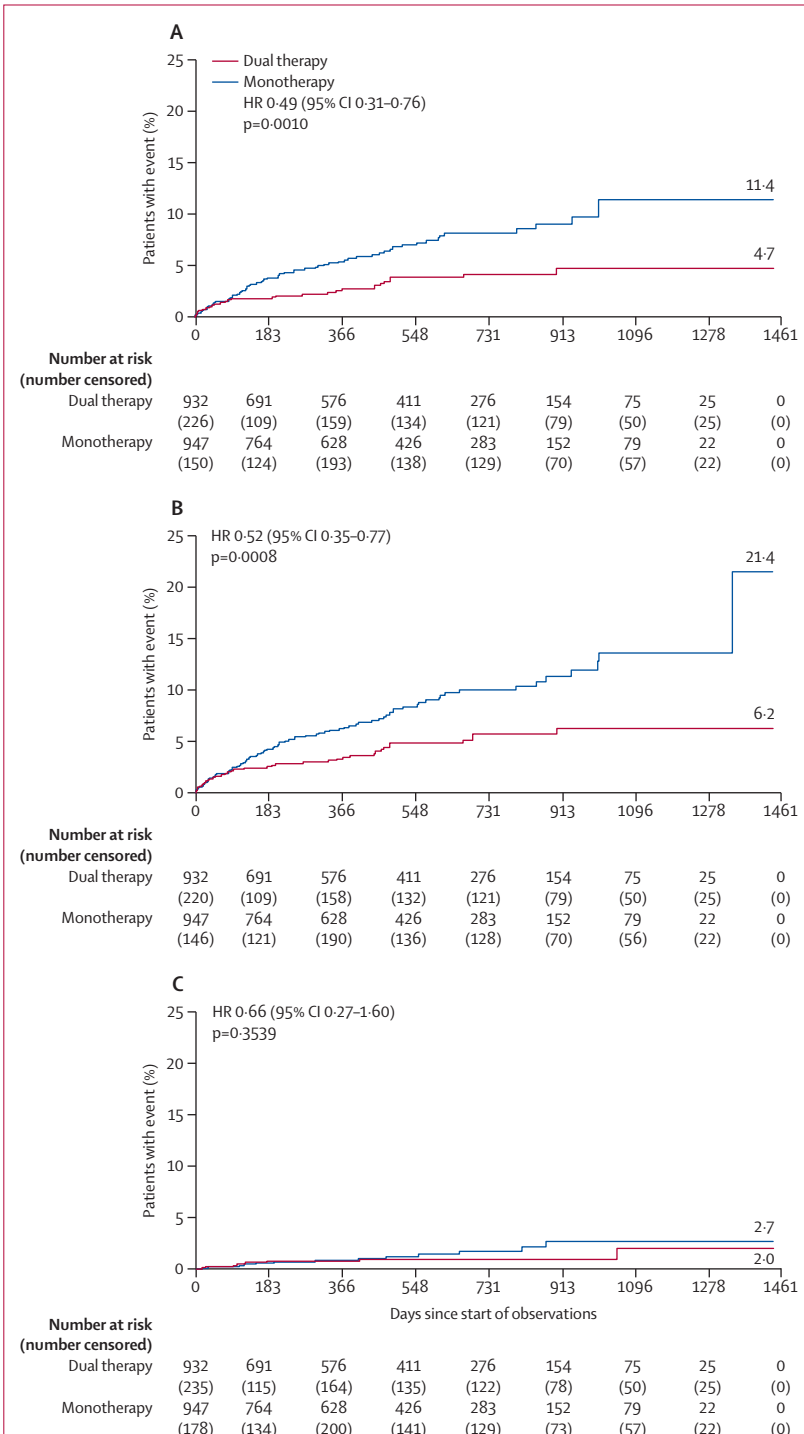

Figure 2: **Kaplan-Meier analysis of outcomes**

The Kaplan-Meier curves for the time to the first event of the primary efficacy outcome, defined as ischaemic stroke (A), that of the secondary efficacy outcome of a composite of stroke, myocardial infarction, and vascular death (B), and that of the safety outcome of severe or life-threatening bleeding (C) are shown. Data are from the intention-to-treat analysis. HR=hazard ratio.

	Number of patients in dual therapy group (n=910)			Number of patients in monotherapy group (n=921)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Total	138 (15%)	83 (9%)	34 (4%)	86 (9%)	103 (11%)	30 (3%)
Nervous system disorders	41 (5%)	36 (4%)	6 (1%)	39 (4%)	42 (5%)	10 (1%)
Cerebral infarction	15 (2%)	18 (2%)	3 (<1%)	28 (3%)	30 (3%)	5 (1%)
Headache	16 (2%)	9 (1%)	1 (<1%)	0	0	0
Transient ischaemic attack	1 (<1%)	2 (<1%)	0	3 (<1%)	3 (<1%)	0
Cardiac disorders	56 (6%)	12 (1%)	10 (1%)	5 (1%)	6 (1%)	6 (1%)
Palpitations	27 (3%)	4 (<1%)	2 (<1%)	0	0	0
Tachycardia	22 (2%)	4 (<1%)	0	0	0	0
Gastrointestinal disorders	21 (2%)	6 (1%)	0	8 (1%)	12 (1%)	1 (<1%)
Diarrhoea	10 (1%)	2 (<1%)	0	0	0	0
Infections and infestations	7 (1%)	4 (<1%)	5 (1%)	7 (1%)	9 (1%)	4 (<1%)
Injury, poisoning, and procedural complications	4 (<1%)	3 (<1%)	6 (1%)	7 (1%)	9 (1%)	1 (<1%)
Benign, malignant, and unspecified neoplasms (including cysts and polyps)	1 (<1%)	10 (1%)	5 (1%)	3 (<1%)	5 (1%)	4 (<1%)
Skin and subcutaneous tissue disorders	13 (1%)	2 (<1%)	0	7 (1%)	5 (1%)	0

Only adverse events with greater than 1% incidence are presented. Severity of adverse events are classified into three levels: mild, causing discomfort but no interference with daily activities; moderate, causing discomfort that is sufficient to restrict or affect daily activities; and severe, cannot perform work or daily activities.

Table 4: **Adverse events according to severity**

clopidogrel seemed to provide more substantial rate reduction in patients overall.

The efficacy outcomes for ischaemic events were generally identical between monotherapy and dual therapy during the initial 100 days, and they showed intergroup differences thereafter. The comparably favourable effect of monotherapy in the early days partly coincides with pooled data from randomised trials showing that the absolute risk of recurrent ischaemic stroke decreased gradually, with no reduction after 12 weeks with aspirin alone compared with the control.[21] As a pleiotropic effect, other than its antiplatelet effect, cilostazol combined with aspirin prevented stenosis progression after ischaemic stroke with intracranial arterial atherosclerosis and reduced restenosis after coronary stenting compared with aspirin alone,[22,28] although the change in arterial stenosis during the follow-up period was not assessed in this trial. Cilostazol has been reported to reduce the intima-media thickness and decrease lipid and necrotic components in the carotid plaque.[29] The divergence of the efficacy event curves during the long-term chronic stage after stroke also appeared in the European and Australasian Stroke Prevention in Reversible Ischaemia Trial,[30] an RCT that compared the combination of dipyridamole plus aspirin with aspirin monotherapy for the secondary prevention of stroke of presumed arterial origin. A meta-analysis including this trial showed that adding dipyridamole to aspirin reduced the risk of recurrent ischaemic stroke only after 12 weeks.[21] Additionally, the combination of dipyridamole plus aspirin for patients with stroke showed a somewhat lower risk of recurrent stroke than clopidogrel monotherapy after around 3 years of treatment in the Prevention Regimen for Effectively Avoiding Second Strokes trial.[31] These findings suggest that phosphodiesterase inhibitors, including cilostazol and dipyridamole, prevented stroke via long-lasting mechanisms, such as vasoprotection and anti-atherogenic activity.

The mild reduction of systolic blood pressure during follow-up on dual therapy might be protective against stroke recurrence. Vasodilation, suppression of angiotensin 2-induced hypertensive endothelial dysfunction, and other effects of cilostazol might influence blood pressure.[32]

The incidence of severe or life-threatening bleeding as a core safety outcome was almost the same over 1 year between the two groups, although their low incidences might weaken statistical power. This finding is compatible with previous reports on mono, dual, or triple antiplatelet therapy involving cilostazol, showing that cilostazol did not increase bleeding compared to pharmacotherapy without cilostazol.[18,19,22–25] Thus, dual medication involving cilostazol is effective and safe during the chronic stage of non-cardioembolic ischaemic stroke or transient ischaemic attack; during this stage, guidelines do not recommend taking the combination of aspirin and clopidogrel.

A strength of this trial is that MRI with angiography was routinely done to identify infarct distribution and for intracranial vascular imaging. The widespread presence of MRI devices in Japan enabled us to set its performance as an indispensable inclusion criterion without missing many patients. The second strength was the combination of a thienopyridine with cilostazol compared with thienopyridine monotherapy in an RCT in a large population for the first time, to our knowledge. Care should be taken in interpreting this comparison because this was a prespecified subgroup analysis without significant treatment-by-subgroup interactions.

The limitations of this trial include that the number of enrolled patients was only 47% of the planned number. Use of health insurance to cover the costs of trial drugs instead of free-of-charge provision from a manufacturer, in addition to prohibiting the use of generic cilostazol products that were much cheaper than the brand-name drug, was a possible reason for the delay in recruiting patients, which might weaken statistical power for the prespecified subgroups. This cost issue could also be the main reason for the high numbers of consent withdrawals in the dual therapy group.

Another limitation was that patients developing the primary efficacy outcomes were few (93 patients), given that the trial was stopped before reaching half of the planned sample size, although the annual event rate (5%) was similar to the estimated event rate (4%). The few primary efficacy events could reduce statistical accuracy. Additionally, the trial treatment was not masked. Thus, the trial investigators were aware of the study drug allocation.

Generalisability of the present findings to other countries is uncertain because the ethnicity was limited to Japanese people within this trial, although differences in the pharmacokinetics of cilostazol among ethnicities have not been suggested.

Furthermore, discontinuation of trial medication within 6 months occurred in the dual therapy group three times as frequently as in the monotherapy group. Occurrence of headache and palpitations, which are known early side-effects of cilostazol,[13] was partly the cause of the difference. Discontinuation of cilostazol because of headache, palpitations, or tachycardia (3·5%) was less than half as common in patients assigned to receive cilostazol in the CSPS2 trial.[17] Optional choice of cilostazol 100 mg once per day during the initial 15 days in the present trial seemed to decrease early side-effects.

In conclusion, for secondary prevention in patients with stroke at high-risk for stroke recurrence, long-term treatment with a combination of cilostazol with aspirin or clopidogrel had a lower rate of ischaemic stroke and other efficacy endpoints, including stroke or vascular events, and a similar risk of severe or life-threatening bleeding than long-term treatment with aspirin or clopidogrel alone. Addition of cilostazol to aspirin or clopidogrel seems to be a pharmacotherapeutic regimen that could be recommended in the chronic stage of high-risk non-cardioembolic ischaemic stroke for patients who can tolerate the early side-effects of cilostazol, such as palpitations and headache.

Contributors

All authors, except JDE, were involved in the design and execution of the Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com) trial. KaT wrote the first draft of the manuscript and provided tables, figures, and references. SU had a central role in revising the first draft of the manuscript. TY supervised the trial. All other authors edited the manuscript and approved the final draft.

Declaration of interests

The CSPS.com trial was conducted under a trial contract between the consignee, Japan Cardiovascular Research Foundation, and the consignor, Otsuka Pharmaceutical. The Japan Cardiovascular Research Foundation received funding for trial implementation and management from Otsuka Pharmaceutical. Participating members, including the authors and each committee member, received scientific consultancy fees for trial design and management, depending on their roles. KaT reports personal fees from Otsuka Pharmaceutical and Bayer Yakuhin outside the submitted work. SU reports grants and personal fees from Bayer, Boehringer Ingelheim, Daiichi Sankyo, Sanofi, Otsuka, Takeda, AstraZeneca, Dainippon Sumitomo, Mitsubishi Tanabe, Shionogi, Astellas Amgen, Bristol-Myers Squibb, and the Japan Cardiovascular Foundation outside the submitted work. JDE reports grants from the US National Institutes of Health (National Institutes of Health and National Institute of Neurological Disorders and Stroke) and personal fees from Boehringer Ingelheim outside the submitted work. KK reports personal fees from Bayer Yakuhin outside the submitted work. HH reports personal fees from Otsuka Pharmacertical outside the submitted work and speaker's fees from Nippon Boehringer Ingelheim, Bayer Yakuhin, Bristol-Meyers Squibb, Daichi Sankyo, Pfizer Japan, and Sanofi KK. NK reports personal fees from Otsuka Pharmaceutical outside the submitted work and personal fees (honoraria for lecture presentations) from Bayer Yakuhin and Daiichi Sankyo. YO reports personal fees (honoraria for lecture presentations) from Otsuka, Daiichi Sankyo, Pfizer, Bristol Myers-Squibb, Bayer, and Boehringer Ingelheim, outside the submitted work. KM reports personal fees from Otsuka Pharmaceutical outside the submitted work, and personal fees (honoraria for seminar presentations) and other fees (advisory board) from Bayer Yakuhin. All other authors declare no competing interests.

Data sharing

Deidentified individual participant data and the study protocol are available upon request to koubo@jcvrf.jp, only if the request is intended to contribute to the improvement of people's health and welfare. Researchers can request data disclosure between 18 months and 36 months following the publication of the Article. Only the researchers who requested disclosure are entitled to use the data and only in a way consistent with the principle of safeguarding study participants' privacy and the provisions of informed consent.

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