

Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial



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Summary

Background The antiplatelet drug cilostazol is efficacious for prevention of stroke recurrence compared with placebo. We designed the second Cilostazol Stroke Prevention Study (CSPS 2) to establish non-inferiority of cilostazol versus aspirin for prevention of stroke, and to compare the efficacy and safety of cilostazol and aspirin in patients with non-cardioembolic ischaemic stroke.

Methods Patients aged 20–79 years who had had a cerebral infarction within the previous 26 weeks were enrolled at 278 sites in Japan and allocated to receive 100 mg cilostazol twice daily or 81 mg aspirin once daily for 1–5 years. Patients were allocated according to a computer-generated randomisation sequence by means of a dynamic balancing method using patient information obtained at registration. All patients, study personnel, investigators, and the sponsor were masked to treatment allocation. The primary endpoint was the first occurrence of stroke (cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage). The predefined margin of non-inferiority was an upper 95% CI limit for the hazard ratio of 1·33. Analyses were by full-analysis set. This trial is registered with ClinicalTrials.gov, number NCT00234065.

Findings Between December, 2003, and October, 2006, 2757 patients were enrolled and randomly allocated to receive cilostazol (n=1379) or aspirin (n=1378), of whom 1337 on cilostazol and 1335 on aspirin were included in analyses; mean follow-up was 29 months (SD 16). The primary endpoint occurred at yearly rates of 2·76% (n=82) in the cilostazol group and 3·71% (n=119) in the aspirin group (hazard ratio 0·743, 95% CI 0·564–0·981; p=0·0357). Haemorrhagic events (cerebral haemorrhage, subarachnoid haemorrhage, or haemorrhage requiring hospital admission) occurred in fewer patients on cilostazol (0·77%, n=23) than on aspirin (1·78%, n=57; 0·458, 0·296–0·711; p=0·0004), but headache, diarrhoea, palpitation, dizziness, and tachycardia were more frequent in the cilostazol group than in the aspirin group.

Interpretation Cilostazol seems to be non-inferior, and might be superior, to aspirin for prevention of stroke after an ischaemic stroke, and was associated with fewer haemorrhagic events. Therefore, cilostazol could be used for prevention of stroke in patients with non-cardioembolic stroke.

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Introduction

Platelets have a pivotal role in the pathogenesis of atherothrombosis, and findings of randomised trials and meta-analyses have shown the efficacy of antiplatelet therapies for secondary prevention after ischaemic stroke.¹ Comparisons of several antiplatelet regimens have shown statistically significantly different outcomes, though only marginal clinical benefit, in stroke prevention,^{2,3} and few regimens have proven significantly more effective than has aspirin alone. Dual antiplatelet therapy has been intensively studied, and in the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) and Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation, Management, and Avoidance (CHARISMA) trials combined aspirin and clopidogrel was not more effective for reduction of the risk of vascular events

than was either drug alone, but did result in more haemorrhagic events.^{4,5} Treatments targeting platelets alone have restricted clinical effectiveness, and attempts to augment antiplatelet effects seem to increase the risk of haemorrhage.⁶

Cilostazol is an antiplatelet drug that inhibits phosphodiesterase 3, increases cAMP concentrations and consequently inhibits platelet aggregation.⁷ Cilostazol also has vasodilatory activity, inhibits vascular smooth muscle proliferation, and protects the vascular wall and endothelium in vivo and in vitro.⁸ In several randomised trials, cilostazol significantly improved symptoms of intermittent claudication in patients with peripheral artery disease.⁹ The TASC II international guideline recommends cilostazol as the first-line drug for treatment of intermittent claudication.¹⁰ In the first Cilostazol Stroke Prevention Study (CSPS) in 1052 patients in

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Japan, compared with placebo cilostazol was significantly associated with lower incidence of recurrent cerebral infarction without increased occurrence of cerebral haemorrhage.¹¹ Cilostazol was also more effective than placebo for prevention of secondary cerebral infarction, particularly in patients with lacunar infarction and in high-risk patients with diabetes or hypertension.¹² On the basis of this evidence, cilostazol is used in Japan for secondary prevention of cerebral infarction and is listed in the Japanese guideline for the management of stroke.¹³ In a clinical trial in 720 Chinese patients with cerebral infarction, cilostazol lowered rates of both stroke and any haemorrhagic event compared with aspirin,¹⁴ although follow-up was quite short. We designed CSPS 2 to establish non-inferiority of cilostazol compared with aspirin, and to assess the safety and efficacy of cilostazol compared with aspirin for prevention of stroke in patients with non-cardioembolic cerebral infarction.

Methods

Patients

Patients were enrolled from 278 sites in Japan between December, 2003, and October, 2006, and were treated between December, 2003, and December, 2008. Inclusion criteria were a non-cardioembolic cerebral infarction (NINDS-III classification¹⁵) in the previous

26 weeks with evidence on a CT or MRI scan, clinical stability before randomisation, and age of 20–79 years. Patients were excluded if they had contraindications to one of the antiplatelet agents, including increased risk of haemorrhage, congestive heart failure, and peptic ulcer. Patients were also excluded if they had blood, hepatic, or renal disorders or cardiac diseases associated with cardioembolism, or had undergone or were scheduled to undergo percutaneous transluminal angioplasty or revascularisation for treatment of cerebral infarction. Patients who were taking thienopyridine derivatives or any other investigational drug were also excluded. Concomitant antiplatelet drugs, anti-coagulants, thrombolytic agents, non-steroidal anti-inflammatory drugs, and drugs that inhibit the effects of aspirin were not permitted. No restriction was imposed on diet or rehabilitation therapy. The evaluation committee validated the eligibility of every patient.

The study was done in accordance with ethical principles originating from the Declaration of Helsinki and in compliance with good clinical practice guidelines. The study was approved by the institutional review board of every participating institution. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned to receive 100 mg cilostazol twice daily or aspirin 81 mg once daily by use of a double-dummy method. Placebo tablets were identical in appearance to that of the drug that the patient was not assigned to. The randomisation table was generated with SAS (version 8.2) by the personnel responsible for drug allocation from the contract research organisation and random allocation was done with a dynamic balancing method with stratification by age, sex, and study institution to minimise differences in the distribution of baseline variables between the two groups. A randomisation number was pre-assigned to every drug pack. Patients were assigned a treatment number that was matched to a numbered drug pack by the personnel responsible for drug allocation from the contract research organisation at the registration centre. All patients, study personnel, investigators, and the sponsor were masked to treatment allocation throughout the study. The person responsible for drug allocation sealed the assignment list immediately after assignment, and kept it sealed until the designated point for unmasking.

Procedures

Patients were assessed at baseline, week 12, and every 24 weeks thereafter until the end of the trial. At each visit, haematological and biochemical laboratory analyses, blood pressure measurement, and electrocardiography (ECG) were done. All endpoint events were recorded by assessment of clinical records. Study treatment was continued for a minimum of 1 year and a maximum of 5 years.

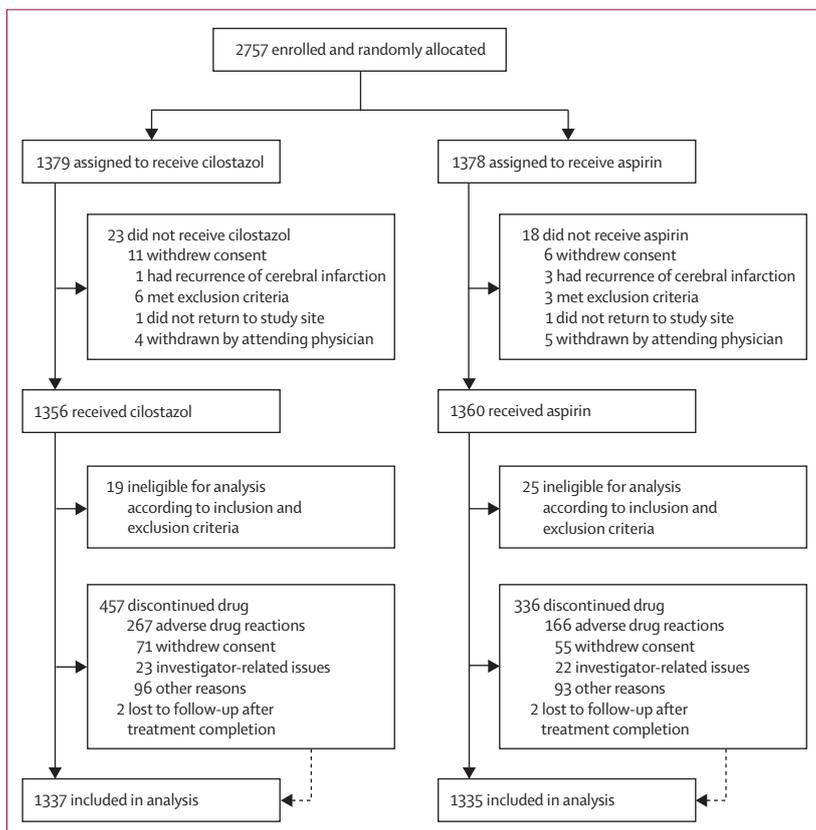


Figure 1: Trial profile

The evaluation committee, whose members were unaware of patients' treatment assignment, adjudicated all trial endpoints. The primary endpoint was the first occurrence of stroke (recurrence of cerebral infarction, or occurrence of cerebral haemorrhage or subarachnoid haemorrhage). Secondary endpoints were the first recurrence of cerebral infarction, ischaemic cerebrovascular events including cerebral infarction or transient ischaemic attack, death from any cause, and the composite of completed stroke (cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage), transient ischaemic attack, angina pectoris, myocardial infarction, heart failure, or haemorrhage requiring hospital admission (excluding cerebral haemorrhage and subarachnoid haemorrhage). We also did a subgroup analysis of the stroke subtypes included in the composite primary endpoint.

All adverse events were recorded and those that occurred within 10 days of discontinuation or completion of treatment were included in the analyses. Only permanent discontinuations were recorded as discontinuations. The rate of haemorrhagic events (cerebral haemorrhage, subarachnoid haemorrhage, or haemorrhage requiring hospital admission) was analysed to assess drug safety. Follow-up to confirm the occurrence of fatal adverse events was done for 38 days after treatment completion or discontinuation.

Statistical analysis

The number of patients and length of the study period were set on the basis of the number of events needed to confirm the non-inferiority of cilostazol to aspirin. According to the results of a meta-analysis of antiplatelet therapy in patients with cerebral infarction,¹ aspirin did not reduce the risk of stroke by more than 40% compared with placebo, and the hazard ratio (HR) of aspirin to placebo based on exposure was estimated as about 0·6. In the first CSPS, cilostazol reduced the risk of recurrent cerebral infarction by 40% compared with placebo,¹¹ and on the basis of this result, the HR of cilostazol to placebo for stroke onset was also estimated to be about 0·6.

We calculated that if the upper 95% CI limit for the HR of cilostazol to aspirin was 1·33 (4/3) or lower, cilostazol would be non-inferior to aspirin. With the assumption that the margin of non-inferiority is an HR of cilostazol versus placebo of 1·33, the HR versus placebo would be 0·8 (0·6×1·33=0·798), so the results of the first CSPS could be reconfirmed. The statistical power was set at 80%. We used Freedman's method¹⁶ to calculate that a total of 385 events would be needed. On the assumption that the incidence of stroke would be 5% per year, an estimated 2600 patients would be needed in total to secure at least 385 events over a 4-year registration period and a 5-year study period.

After the end of follow-up, efficacy analyses were done on the full analysis set of patients, as predetermined in

the protocol. The full analysis set excluded patients who failed to satisfy inclusion criteria, violated exclusion criteria, did not take the study drugs, or had no follow-up of study-specified events after the start of the study drug. Patients who prematurely discontinued study treatment for any reason other than onset of the primary endpoint

	Cilostazol (n=1337)	Aspirin (n=1335)
Men	959 (72%)	957 (72%)
Age (years)	63·5 (9·2)	63·4 (9·0)
Body-mass index (kg/m ²)	24·0 (3·1)	23·9 (3·1)
Stroke subtype		
Atherothrombotic	435 (33%)	420 (31%)
Lacunar	869 (65%)	874 (65%)
Undetermined	33 (3%)	41 (3%)
Days after onset*		
≤28	414 (31%)	419 (31%)
29–56	354 (26%)	338 (25%)
57–112	343 (26%)	320 (24%)
>113	226 (17%)	258 (19%)
Stroke severity (modified Rankin scale)		
0	207 (15%)	186 (14%)
1	612 (46%)	613 (46%)
2	406 (30%)	432 (32%)
3	73 (5%)	69 (5%)
4	39 (3%)	35 (3%)
Drug use		
Cilostazol	304 (23%)	358 (27%)
Aspirin	794 (59%)	749 (56%)
Present smoker	385 (29%)	403 (30%)
Does not abstain from drinking alcohol	640 (48%)	624 (47%)
Complications		
Hypertension	976 (73%)	991 (74%)
Ischaemic heart disease	11 (1%)	18 (1%)
Diabetes mellitus	382 (29%)	393 (29%)
Dyslipidaemia	560 (42%)	599 (45%)

Data are number (%) or mean (SD). *Days from onset of cerebral infarction to start of treatment.

Table 1: Demographic and clinical characteristics at baseline

	Cilostazol (n=1337)	Aspirin (n=1335)	p value
Antihypertensive drugs	900 (67%)	999 (75%)	<0·0001
Angiotensin II receptor blockers	617 (46%)	723 (54%)	<0·0001
Calcium channel blockers	627 (47%)	753 (56%)	<0·0001
Angiotensin-converting-enzyme inhibitors	111 (8%)	121 (9%)	0·48
Lipid-lowering drugs	401 (30%)	452 (34%)	0·03
Statins	362 (27%)	402 (30%)	0·08
Antidiabetic drugs	271 (20%)	278 (21%)	0·72
Digestive drugs	863 (65%)	908 (68%)	0·06

Table 2: Concomitant drug treatments during the study

were handled as censored cases. We calculated the HRs (95% CIs) of cilostazol to aspirin for occurrence of the primary and secondary endpoints, including subgroup analysis by stroke subtypes, with the log-rank test. On the basis of the principle of a closed testing procedure, the log-rank test was used to verify the superiority of cilostazol to aspirin only if non-inferiority was verified. Because the independent data monitoring committee did a single unmasked interim analysis for safety only and two analyses for efficacy and safety according to the predetermined plan, the adjusted significance level for the superiority test of the primary endpoint was set at 0.0471 (two-tailed) according to the O'Brien-Fleming method.¹⁷ The cumulative incidence rates were estimated and plotted by use of Kaplan-Meier analysis. The occurrence rate per year was calculated in each group based on the log-transformed normal approximation. For the safety analysis, we used the χ^2 test to compare the cumulative incidences of adverse events in the two groups. All analyses were done with SAS (version 9.1).

This trial is registered with ClinicalTrials.gov, number NCT00234065.

Role of the funding source

The funding source had a role in the study design, data collection, and data analysis, but not in data interpretation or writing of the report. Data were collected by the sponsor and entrusted to a contract research organisation (EPS) under a blinded condition. The contract research organisation did statistical analyses under the supervision of the trial statistician (CH) who was independent from the sponsor. Both the

corresponding author and CH had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit this paper for publication.

Results

2757 patients were enrolled and randomly assigned, of whom 41 did not receive any study drug, mostly because of withdrawal of informed consent (figure 1). A further 44 patients were judged to be ineligible according to exclusion criteria or violation of inclusion criteria that was missed at the enrolment stage, so 2672 patients were included in analyses. Of patients included in analyses, 34% in the cilostazol group and 25% in the aspirin group discontinued the study drug during the treatment period, and two patients (<1%) in each group were lost to follow-up after treatment completion. Reasons for discontinuation of the study treatment included adverse drug reactions, withdrawal of informed consent, and investigator-related issues.

Mean duration of follow-up was 29 months (SD 16, range 1–59 months). Demographic and clinical characteristics were well balanced between the treatment groups at baseline, including receipt of cilostazol or aspirin (table 1). A significantly higher proportion of patients in the aspirin group took concomitant antihypertensive drugs and lipid-lowering drugs during the treatment period than in the cilostazol group (table 2). The proportions of patients taking statins and, conversely, antidiabetic drugs were also higher in the aspirin group than the cilostazol group but the differences were not significant. The antidiabetic

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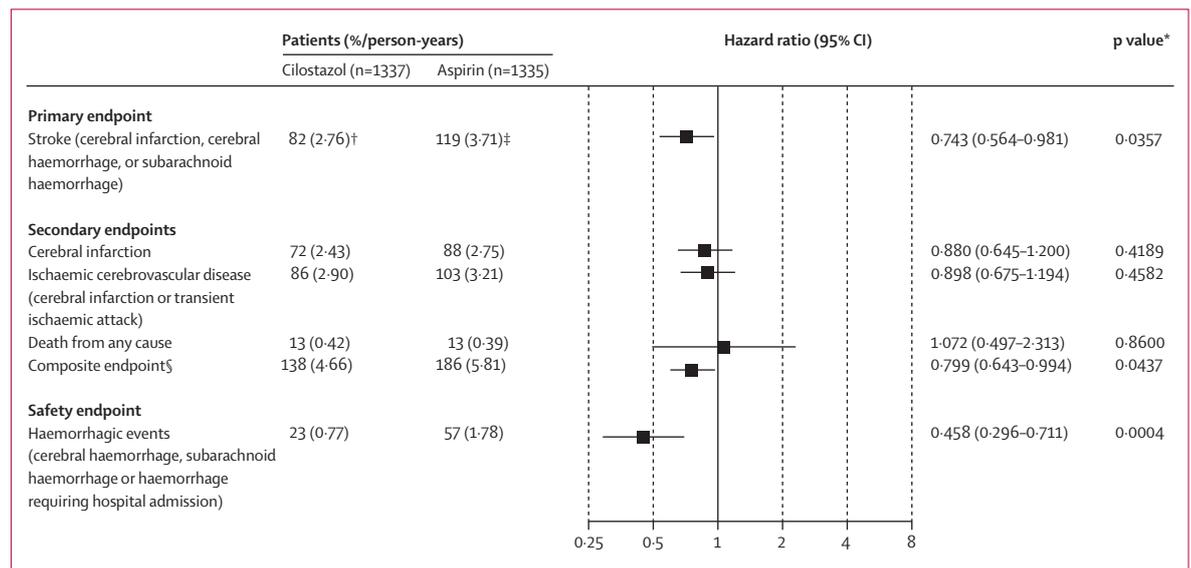


Figure 2: Incidences of primary and secondary endpoints

*Log-rank test. †72 patients had cerebral infarction, eight had cerebral haemorrhage, and two had subarachnoid haemorrhage. ‡88 patients had cerebral infarction, 27 had cerebral haemorrhage, and four had subarachnoid haemorrhage. §Composite of stroke (cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage), transient ischaemic attack, angina pectoris, myocardial infarction, heart failure, or any haemorrhage requiring hospital admission.

drug pioglitazone was used in 58 patients (4%) in the cilostazol group and 78 (6%) patients in the aspirin group.

The primary endpoint occurred at a higher yearly rate in the aspirin group than in the cilostazol group, and cilostazol reduced the risk of stroke by 25.7% compared with aspirin (figure 2, figure 3A). Because the upper 95% CI limit was lower than the prespecified non-inferiority margin of 1.33, cilostazol seems to be non-inferior to aspirin for the prevention of stroke; because the *p* value for the primary analysis (*p*=0.0357) was lower than the adjusted significance level for superiority testing (*p*=0.0471), cilostazol also seems to be superior to aspirin. In the analysis of stroke subtypes, cilostazol was associated with a relative risk reduction of 32.0% for atherothrombotic stroke and 24.8% for lacunar stroke versus aspirin, although the differences between the drugs were not significant (figure 4). Although all analyses were done on the full analysis set, intention-to-treat analysis of the primary endpoint in 1379 patients on cilostazol and 1378 on aspirin confirmed the findings of our study (HR 0.749, 95% CI 0.568–0.988; *p*=0.0404).

In the secondary endpoint analysis, the composite endpoint occurred in significantly fewer patients in the cilostazol group than in the aspirin group (figure 2, figure 3B). Cilostazol reduced the risk of these events by 20.1% compared with aspirin. For occurrences of all other secondary endpoints, differences between treatment groups were not significant (figure 2).

Haemorrhagic events occurred in significantly fewer patients in the cilostazol group than in the aspirin group (figure 2, figure 3C), and cilostazol reduced the risk of these events by 54.2%. Haemorrhagic events were recorded more frequently in the aspirin group than in the cilostazol group for both the composite of symptomatic cerebral haemorrhage, intraventricular haemorrhage, thalamus haemorrhage, putamen haemorrhage, and cerebellar haemorrhage (27 vs 8, *p*=0.0027) and gastrointestinal haemorrhage that required hospital admission (21 vs 8, *p*=0.0257). Overall, haemorrhagic adverse events occurred in 161 patients (12%) in the cilostazol group and 240 (18%) patients in the aspirin group. Other haemorrhagic adverse events that were most frequently reported were nasal haemorrhage, conjunctival haemorrhage, and subcutaneous haemorrhage (webappendix pp 1–2).

However, several adverse events other than haemorrhage were significantly more common in cilostazol recipients than in aspirin recipients (in descending order of occurrence in the cilostazol group): headache, diarrhoea, palpitations, dizziness, and tachycardia (table 3). Investigator-designated increase in blood pressure and constipation occurred in a higher proportion of patients in the aspirin group than in the cilostazol group (table 3). 267 patients (20%) in the cilostazol group and 166 (12%) in the aspirin group discontinued treatment owing to adverse drug reactions.

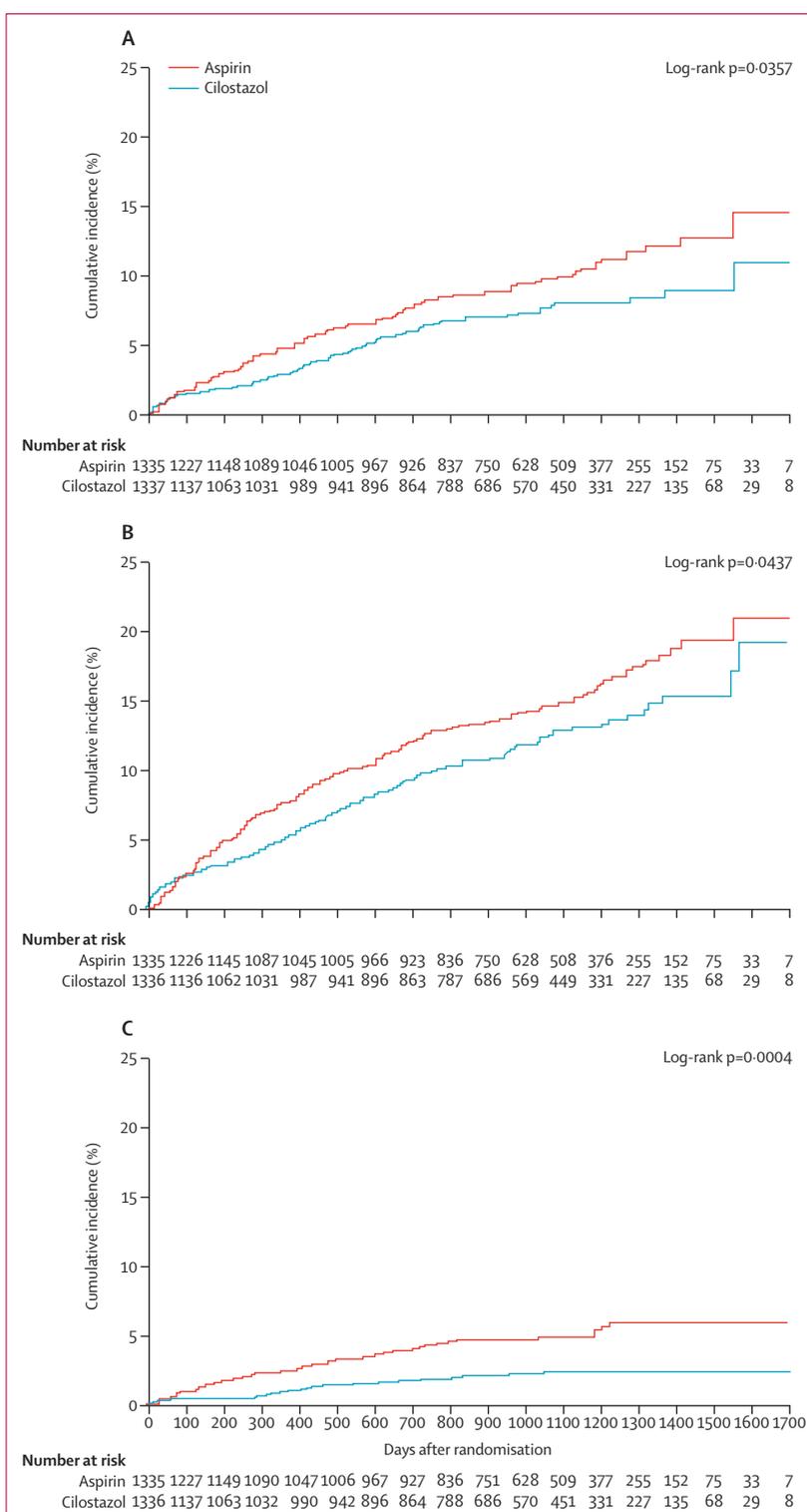


Figure 3: Cumulative incidences of primary and secondary endpoints

(A) Primary endpoint: cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage. (B) Secondary composite endpoint: stroke (cerebral infarction, cerebral haemorrhage, or subarachnoid haemorrhage), transient ischaemic attack, angina pectoris, myocardial infarction, heart failure, or any haemorrhage requiring hospital admission. (C) Safety endpoint of haemorrhagic events: cerebral haemorrhage, subarachnoid haemorrhage, or haemorrhage requiring hospital admission.

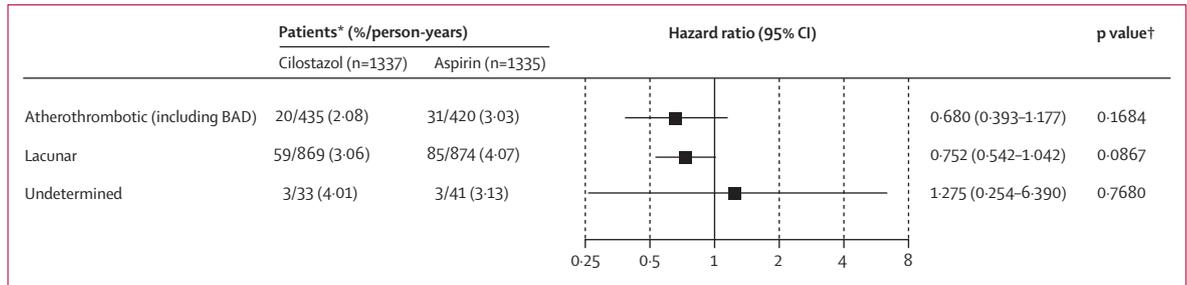


Figure 4: Incidence of stroke by ischaemic stroke subtype

*n of total N of patients with the stroke subtype at baseline. †Log-rank test. BAD=branch atheromatous disease.

	Cilostazol (n=1337)	Aspirin (n=1335)	p value*
Headache			
Events	313 (23%)†	217 (16%)	<0.0001
Discontinuations	64 (5%)	6 (<1%)	..
Diarrhoea			
Events	164 (12%)	85 (6%)	<0.0001
Discontinuations	4 (<1%)	1 (<1%)	..
Palpitations			
Events	156 (12%)	71 (5%)	<0.0001
Discontinuations	39 (3%)	2 (<1%)	..
Dizziness			
Events	129 (10%)‡	97 (7%)§	0.0268
Discontinuations	3 (<1%)	2 (<1%)	..
Tachycardia			
Events	89 (7%)	21 (2%)	<0.0001
Discontinuations	14 (1%)	0	..
Investigator-designated increase in blood pressure			
Events	120 (9%)	185 (14%)	<0.0001
Discontinuations	3 (<1%)	1 (<1%)	..
Constipation			
Events	110 (8%)	155 (12%)	0.0034
Discontinuations	0	0	..

*χ² test. †One event was a serious adverse event. ‡Seven events were serious adverse events. §Six events were serious adverse events.

Table 3: Adverse events other than haemorrhage

37 patients (3%) in each treatment group had serious cardiac adverse events (43 events in the cilostazol group and 41 in the aspirin group), including angina pectoris (10 and 11), myocardial infarction (14 and 11), heart failure (8 and 7), arrhythmias (8 and 5), and others (3 and 7), with no significant differences in occurrence between the groups. Cardiac events resulted in death in four patients (<1%) in the cilostazol group and two patients (<1%) in the aspirin group.

Although use of antihypertensive drugs was significantly more common in the aspirin group than in the cilostazol group, mean blood pressure during treatment was fairly well controlled in both groups. Descriptive statistics for blood pressure (webappendix pp 3–4), transition of blood pressure (webappendix p 5),

and analysis of values for blood pressure with a mixed-effect model (webappendix p 6) showed significant differences in systolic blood pressure and no significant differences in diastolic blood pressure between the treatment groups, but we recorded no interaction between treatment group and measurement timepoints for systolic or diastolic blood pressure. Because increase in blood pressure was recorded more frequently in the aspirin group than in the cilostazol group, two further post-hoc analyses were done to investigate the association of blood pressure and the safety endpoint: the first adjusted treatment effect for time-varying blood pressure by use of Cox regression model with systolic blood pressure measurements as time-dependent covariates (webappendix p 7); and the second adjusted treatment effect for investigator-designated increase in blood pressure elevation (webappendix p 8).

Discussion

In CSPS 2, the incidence of stroke, the primary endpoint, was extremely low in both the cilostazol and aspirin groups, in accordance with the known benefits of antiplatelet therapy and risk factor management for prevention of stroke. Nevertheless, cilostazol significantly lowered the risk of stroke compared with aspirin, and seemed to be non-inferior and superior to aspirin for prevention of stroke in patients with cerebral infarction, with significantly fewer haemorrhagic events (panel). Cilostazol also seemed to be superior to aspirin for prevention of a cluster of secondary endpoints, including stroke, transient ischaemic attack, angina pectoris, myocardial infarction, heart failure, and haemorrhage requiring hospital admission.

The effectiveness of aspirin or thienopyridine derivatives for prevention of secondary vascular events has been validated in patients with ischaemic stroke.¹ However, according to calculations from Antiplatelet Trialists' Collaboration¹⁸ and Antithrombotic Trialists' Collaboration data,¹ the number needed to treat (NNT) for these antiplatelet drugs is about 26–28 in a 2.4–3-year treatment period, which is not satisfactory. The NNT for cilostazol was about 18.7 per 3 years,¹² which is a little better than for conventional antiplatelet drugs, although the patients might have had different subtypes of

ischaemic stroke. Therefore, CSPS 2 was designed for direct comparison of cilostazol and aspirin.

Our findings are consistent with those of CASISP,¹⁴ a pilot study done before CSPS 2, in which cilostazol seemed to be superior to aspirin with a relative risk reduction of 38.1% ($p=0.185$), but the sample size was too small (720 patients) and the trial period was too short (740 person-years) to establish a significant difference. In the CAPRIE study in patients with cerebral infarction, myocardial infarction, or peripheral artery disease, clopidogrel was significantly superior to aspirin in terms of the incidence of ischaemic events, but the risk reduction was only 8.7% ($p=0.043$).² Moreover, in a subgroup analysis of patients with ischaemic stroke, the risk reduction by clopidogrel for vascular events was about 7% compared with aspirin, and this difference was not significant. In the TASS study of patients with a history of transient ischaemic attack or mild cerebral infarction,^{3,19} ticlopidine treatment led to significantly lower occurrence of non-fatal stroke and death (primary endpoint) than did aspirin, but the risk reduction was only 12%. Although ticlopidine resulted in a 21% reduction in the risk of fatal and non-fatal stroke (a secondary endpoint) compared with aspirin, a greater risk reduction was recorded with cilostazol versus aspirin in CSPS 2.

In studies comparing combined clopidogrel and aspirin with clopidogrel alone (MATCH trial⁴) and aspirin alone (CHARISMA trial³), clopidogrel plus aspirin did not show an evident suppressive effect on vascular events, and conversely resulted in an increase in haemorrhagic events. The results of these large-scale trials indicated that treatments targeting platelets alone to prevent stroke or other vascular events have restricted clinical efficacy and inevitably increase the risk of haemorrhage. Rudolf Virchow pointed out the importance of endothelial cell functions of the vessel wall as another treatment target for the prevention of thrombus formation.²⁰ Caplan and colleagues²¹ supported Virchow's idea that three components (blood constituents, vessel wall, and blood flow) should be considered together as a treatment target to prevent thrombus formation. Treatment with a combination of dipyridamole and aspirin has been reported to be more effective than aspirin alone.²² In PROFESS,²³ however, combined dipyridamole and aspirin was not more efficacious than clopidogrel alone for prevention of recurrent cerebral infarction, so the benefit of dipyridamole as an adjunct to antiplatelet monotherapy has not been proven.

We believe that the reduced risk of stroke with cilostazol in CSPS 2 can be ascribed not only to the antiplatelet effect, but also to effects on other factors associated with thrombus formation. These effects include improvement of endothelial function and dilation of blood vessels by increased production of nitric oxide, an endogenous vasodilating factor, and

Panel: Research in context

Systematic review

Trials of antiplatelet drugs, including cilostazol and aspirin, were identified by searches of Medline (January, 1950, to January, 2010) and PubMed (January, 1950, to January, 2010). We also hand-searched relevant journals, reference lists of included papers, and guidelines. For discussion of efficacy and safety of antiplatelet therapies, we restricted searches to human studies and included the results of only large-scale clinical trials or meta-analyses of more than 1000 patients, apart from the preliminary study CASISP.

Interpretation

Treatments targeting platelets alone to prevent stroke or other vascular events seem to have restricted clinical efficacy and increase the risk of haemorrhage. However, the results of this study provide evidence that cilostazol reduces the occurrence of stroke, especially haemorrhagic stroke, compared with aspirin, which might be attributable to the antiplatelet effect and other actions such as improvement of endothelial function. This study adds to the evidence supporting the recommendation of the antiplatelet cilostazol as an option for the prevention of stroke in patients with ischaemic stroke, particularly those with increased risk of haemorrhage.

reduction of intracellular calcium ion concentrations.²⁴ Cilostazol also inhibits smooth muscle proliferation²⁵ and inflammation^{26,27}—the processes underlying atherosclerosis—in various vascular beds, including the intracranial,²⁸ carotid,²⁹ coronary,³⁰ and peripheral arteries.³¹ These actions are thought to contribute to the prevention of secondary vascular events with this drug. In our study, we also assessed the cardiac safety of cilostazol in relation to the increase in heart rate. We did not record increases in myocardial infarction, angina pectoris, heart failure, or serious arrhythmias associated with increased heart rate, at least in this group of patients with non-cardioembolic stroke and without congestive heart failure. Some adverse events other than haemorrhage occurred more frequently in the cilostazol group than in the aspirin group, but none was serious, and all symptoms resolved after discontinuation or dose tapering of cilostazol. Incremental increases in dose from 50 mg cilostazol might avoid these events in some patients. The higher rate of haemorrhagic events in our study than in studies done in white patients might be attributable to the high proportion of patients with lacunar stroke in our study. This high rate of haemorrhagic events is consistent with results from the S-ACCESS study³² in a Japanese population and the CHARISMA subanalysis,³³ which showed that bleeding tendency was higher in Asian than in white patients. Findings of the post-hoc analyses of the association of blood pressure with the safety

endpoint showed that blood pressure was not related to haemorrhagic side-effects.

The results of CSPS 2 suggest that cilostazol can be recommended as an option for the prevention of stroke in Asian patients with non-cardioembolic stroke who can tolerate long-term treatment with this drug. However, cilostazol also seems to be effective for patients of different ethnic origin who have peripheral artery disease—for example, in a study in the USA, cilostazol reduced cerebrovascular events versus placebo.³⁴ Because significantly fewer haemorrhagic events were recorded in the cilostazol group than in the aspirin group, cilostazol might be particularly useful in patients with increased risk of haemorrhage.

Contributors

YS, YKa, SU, TY, and TS contributed to the study concept and design, and supervised the study. All authors contributed to acquisition of data. YS, YKa, SU, TY, YO, NT, HY, SH, KM, TS, and CH did data analysis and interpretation. YS and CH drafted the report, and all other authors critically revised the report for important intellectual content. CH did the statistical analysis, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest

YS has provided consultancy for Schering-Plough and Pfizer Japan; received grants from the Japan Ministry of Health, Labour and Welfare; and received lecture fees from Sanofi-Aventis, Mitsubishi Tanabe Pharma, Otsuka Pharmaceutical, Bayer HealthCare, Kyorin Pharmaceutical, and Daichi-Sankyo. SU's institution has

received grants from Otsuka Pharmaceutical, Sanofi-Aventis, Boehringer Ingelheim, Daiichi-Sankyo, Bayer HealthCare, and Schering-Plough. TY has provided consultancy for Otsuka Pharmaceutical and Mitsubishi Tanabe Pharma; received honoraria from Otsuka Pharmaceutical, Sanofi-Aventis, Bayer HealthCare, and Mitsubishi Tanabe Pharma; payment for manuscript preparation from Sanofi-Aventis; payment for development of educational presentations from Otsuka Pharmaceutical, Sanofi-Aventis, and Bayer HealthCare; and travel or accommodation expenses from Otsuka Pharmaceutical. YO's institution, University of Tokyo, has received grants from Otsuka Pharmaceutical; and Statcom, for which YO is a chairman, has received consultancy fees for this study from Otsuka Pharmaceutical. NT has received payment for development of educational presentations from Mitsubishi Tanabe Pharma, Pfizer Japan, Sanofi-Aventis, and Otsuka Pharmaceutical. HY has served as a board member for J-STARS, which was done by the Japan Ministry of Health, Labour and Welfare; and received honoraria and payment for development of educational presentations from Novartis Pharma and Sanofi-Aventis; and her institution has received grants from Ono Pharmaceutical. YKI has provided consultancy for Daiichi-Sankyo and Kowa Shinyaku; and received payment for development of educational presentations from Eisai, Pfizer Japan, Novartis Pharma, and Astellas Pharma. KN has received honoraria from Mitsubishi Tanabe Pharma. YKO has received honoraria from Eisai, Daiichi-Sankyo, Bristol-Myers Squibb, Bayer HealthCare, and Boehringer Ingelheim; and payment for development of educational presentations from Bayer HealthCare. YKA, SH, KM, CG, HK, MT, TS, and CH declare that they have no conflicts of interest.

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