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Benefit of Cilostazol in Patients with High Risk of Bleeding: Subanalysis of Cilostazol Stroke Prevention Study 2

Shinichiro Uchiyama[a] Yukito Shinohara[i] Yasuo Katayama[d]
Takenori Yamaguchi[k] Shunnosuke Handa[g] Kempei Matsuoka[f]
Yasuo Ohashi[e] Norio Tanahashi[j] Hiroko Yamamoto[n] Chokoh Genka[o]
Yasuhisa Kitagawa[h] Hideo Kusuoka[l] Katsuya Nishimaru[p] Motoo Tsushima[b]
Yukihiro Koretsune[l] Tohru Sawada[m] Chikuma Hamada[c] for the CSPS 2 group

[a]Department of Neurology, Tokyo Women's Medical University School of Medicine, [b]Department of Geriatric Medicine, School of Medicine, Keio University, [c]Tokyo University of Science, [d]Department of Neurology, Nippon Medical School Hospital, [e]Department of Biostatistics, School of Public Health, University of Tokyo, [f]Saiseikai Central Hospital, and [g]Department of Cardiovascular Medicine, Tokai University Tokyo Hospital, Tokyo, [h]Department of Neurology, Tokai University Hachioji Hospital, Hachioji, [i]Department of Neurology, Federation of National Public Service Personnel Mutual Aid Associations Tachikawa Hospital, Tachikawa, [j]Department of Neurology, Saitama Medical University International Medical Center, Hidaka, [k]National Cerebral and Cardiovascular Center, Suita, [l]Osaka National Hospital, Osaka, [m]Koshokai Aino Hospital, Ibaraki, [n]Namiki Hospital, Nagoya, [o]Department of Cardiovascular Medicine, IMS Group Yokohama Asahi Chuo General Hospital, Yokohama, and [p]Department of Neurology, Fukuoka University, Fukuoka, Japan

Key Words
Secondary prevention · Hemorrhagic stroke · Cilostazol · Aspirin · Lacunar stroke · Blood pressure

Abstract
Background: The Cilostazol Stroke Prevention Study 2 (CSPS 2) showed that cilostazol significantly reduced the risk of stroke by 25.7% relative to aspirin, with significantly fewer hemorrhagic events, in patients with prior ischemic stroke, excluding cardioembolic stroke. However, whether the benefit of cilostazol is sustained in patients with a high risk of bleeding has not been examined. ***Methods:*** We conducted a subanalysis of CSPS 2 to examine whether known risk factors for hemorrhagic stroke, such as stroke subtype and systolic blood pressure (SBP), influence the efficacy of the study drugs on hemorrhagic stroke. The relative risk reduction of hemorrhagic stroke was determined from the incidences calculated by the person-year method. The cumulative incidence rates of ischemic stroke and hemorrhagic stroke were estimated and plotted using the Kaplan-Meier method. Incidences of serious hemorrhage and hemorrhage requiring hospital admission were also evaluated in the two treatment groups. Hazard ratios (HR) and 95% confidence intervals (95% CI) calculated by the Cox proportion hazard model for

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E-Mail karger@karger.com
www.karger.com/ced

Shinichiro Uchiyama, MD, PhD, FAHA
Department of Neurology, Tokyo Women's Medical
University School of Medicine, 8-1 Kawada-cho, Shinjuku-ku
Tokyo 162-8666 (Japan)
E-Mail suchiyam@nij.twmu.ac.jp

cilostazol versus aspirin were assessed, and a log-rank test was used for the comparison between treatments. ***Results:*** The incidence of hemorrhagic stroke was significantly lower in the cilostazol group than in the aspirin group among patients with prior lacunar stroke (0.36 vs. 1.20% in person-year, HR 0.35, 95% CI 0.18–0.70, p < 0.01), but not among those with prior atherothrombotic stroke (0.31 vs. 0.59% in person-year, HR 0.53, 95% CI 0.14–2.0, p = 0.34). The incidence of hemorrhagic stroke was significantly lower in the cilostazol group than in the aspirin group throughout all SBP categories (Poisson regression model including time-dependent covariates, p < 0.01) including SBP above 140 mm Hg (cilostazol 0.45% vs. aspirin 1.44% in person-year; Poisson regression model including time-dependent covariates, p = 0.02). Cilostazol, compared with aspirin, significantly reduced the incidence of cerebral hemorrhage (HR 0.36, 95% CI 0.19–0.70, p < 0.01), overall hemorrhage requiring hospital admission (HR 0.53, 95% CI 0.29–0.97, p = 0.04), and gastrointestinal (GI) bleeding requiring hospital admission (HR 0.44, 95% CI 0.21–0.90, p = 0.03). ***Conclusions:*** Hemorrhagic stroke was less frequent in the cilostazol group than in the aspirin group among patients with lacunar stroke as well as those with increased blood pressure levels. As for extracranial hemorrhage requiring hospitalization, GI bleeding was also less frequent in the cilostazol than in the aspirin group. Cilostazol is supposed to be a therapeutic option to replace aspirin for secondary stroke prevention, especially in these subgroups with high risks for hemorrhagic events.

Introduction

Survivors of ischemic stroke have an increased risk of recurrence of stroke. Platelets play an important role in the development of ischemic stroke, and antiplatelet therapy has been reported to be effective in many clinical trials for secondary prevention of stroke in high-risk patients [1]. However, aspirin is known to be associated with increased hemorrhagic risk, e.g. approximately a twofold increase in gastrointestinal (GI) bleeding [2, 3] or more prevalent intracranial hemorrhage [4, 5]. Recently, efforts have been made to identify antiplatelet agents which have stronger preventive effects on the occurrence of stroke without an increased hemorrhagic risk.

Cilostazol, a phosphodiesterase-3 inhibitor, reduced recurrent stroke, with no increase in cerebral hemorrhage in patients with ischemic stroke, including those with risk factors for hemorrhagic stroke such as lacunar stroke, hypertension or older age [6–9]. In a randomized, double-blind, controlled trial, the Cilostazol Stroke Prevention Study 2 (CSPS 2) conducted in Japanese patients with noncardioembolic ischemic stroke, cilostazol significantly reduced the risk of stroke by 25.7% relative to aspirin, with significantly fewer hemorrhagic events [10]. The results were supported by a meta-analysis of randomized controlled trials comparing cilostazol with aspirin [11]. However, whether the benefit of cilostazol is sustained in patients with a high risk of bleeding has not been examined.

In the present study, data from the CSPS 2 were reexamined, and a subanalysis was conducted to verify whether or not known risk factors for hemorrhagic stroke, such as stroke subtype and blood pressure level, influence the safety of cilostazol in comparison with aspirin. Risks of hemorrhagic events other than hemorrhagic stroke were also analyzed and compared between the two treatment groups.

Methods

Patients

All patients included for analyses in the CSPS 2 (Clinical Trials.gov, No. NCT00234065) were examined in the present study. The study design and results of CSPS 2 have been reported elsewhere [10]. In summary, 2,672 patients with a previous ischemic stroke, excluding cardioembolic stroke, whose onset of event was within 6 months prior to registration, were randomly assigned to treatment with either cilostazol (100 mg twice daily) or aspirin (81 mg once daily). The mean duration of follow-up was 29 months.

Procedures and Statistical Analysis

Incidences of ischemic stroke and hemorrhagic stroke during treatment with cilostazol or aspirin were calculated using the person-year method, according to prior stroke subtype (atherothrombotic or lacunar). Hemorrhagic stroke included cerebral hemorrhage and subarachnoid hemorrhage. Their relative risk reduction (RRR) was determined from the incidences calculated by the person-year method. The cumulative incidence rates of ischemic stroke and hemorrhagic stroke were estimated and plotted using the Kaplan-Meier method. Incidences of serious hemorrhages, including cerebral hemorrhage, subarachnoid hemorrhage and hemorrhage requiring hospital admission, were also evaluated in the two treatment groups. Hazard ratios (HR) and 95% confidence intervals (95% CI) calculated by the Cox proportion hazard model for cilostazol versus aspirin were assessed for hemorrhagic stroke by stroke subtypes and serious hemorrhage/hemorrhage requiring hospital admission, and a log-rank test was used for the comparison between treatments.

A predictability of the incidence of hemorrhagic stroke was examined from systolic blood pressure (SBP) during the study period. This analysis was based on the individual SBP measurements at each time point and analyzed using the Poisson regression model (SBP levels by treatments were treated as time-dependent covariates [12]). A probability level <0.05 was considered to indicate significance.

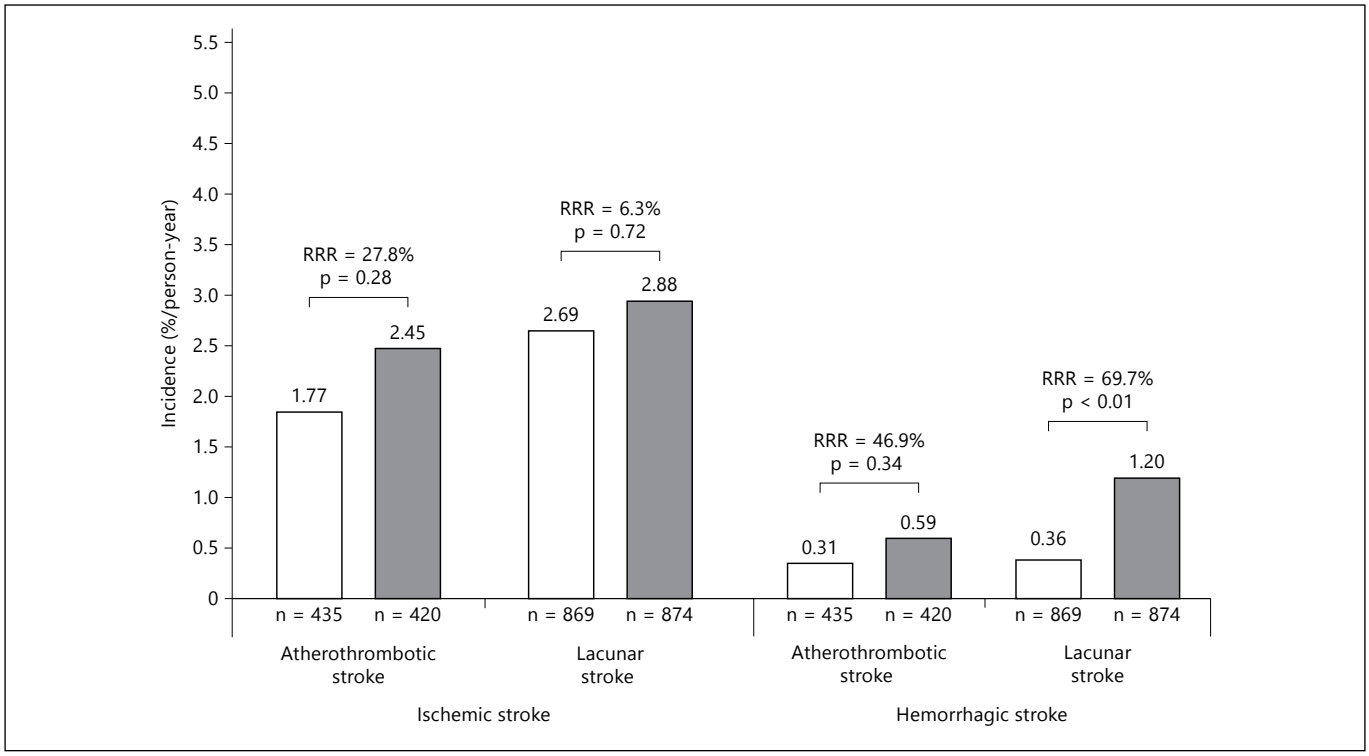

Fig. 1. Incidence of ischemic stroke and hemorrhagic stroke in patients with a prior history of atherothrombotic or lacunar stroke. White bars indicate cilostazol and dark bars aspirin.

In order to identify risk factors for hemorrhagic stroke, factorial analysis of the data using the Cox proportional hazard model was performed. Univariate analysis was first conducted, and variables identified significant ($p < 0.02$) in the univariate analysis were further assessed by multivariate analysis with the stepwise method using 2 independent variables at each step.

All analyses were performed using SAS version 9.2 software (SAS Institute).

Results

Incidence of Hemorrhagic Stroke by Stroke Subtypes

Figure 1 shows the incidence of ischemic and hemorrhagic strokes and RRR for cilostazol compared with aspirin, by baseline stroke subtype. The incidence of ischemic stroke was numerically lower for cilostazol compared with aspirin treatment, both in patients with atherothrombotic stroke (1.77 vs. 2.45% in person-year, RRR 27.8%) and lacunar stroke (2.69 vs. 2.88% in person-year, RRR 6.3%), although the differences were not statistically significant. A significant difference between the cilostazol and aspirin groups was observed for the incidence of hemorrhagic stroke in patients with lacunar stroke (0.36 vs. 1.20% in person-year, RRR 69.7%, $p < 0.01$), but not in those with atherothrombotic stroke. No interaction was observed between the ischemic stroke subtypes and the treatment effect for prevention of ischemic stroke ($p = 0.46$) or hemorrhagic stroke ($p = 0.58$).

Cumulative Incidence of Hemorrhagic Stroke

Figure 2 shows the cumulative incidence of hemorrhagic stroke in patients with atherothrombotic stroke or lacunar stroke. The HR for cilostazol compared with aspirin showed a significant reduction of hemorrhagic stroke in patients with lacunar stroke (HR 0.35, 95% CI 0.18–0.70, $p < 0.01$; fig. 2b), while the difference between the treatment groups was not significant in patients with atherothrombotic stroke (HR 0.53, 95% CI 0.14–2.0, $p = 0.34$; fig. 2a).

Incidence of Hemorrhagic Stroke by SBP Levels

A significantly lower incidence of hemorrhagic stroke was observed in the cilostazol group compared with the aspirin group throughout all SBP categories ($p < 0.01$) including SBP above 140 mm Hg (0.45 vs. 1.44% per per-

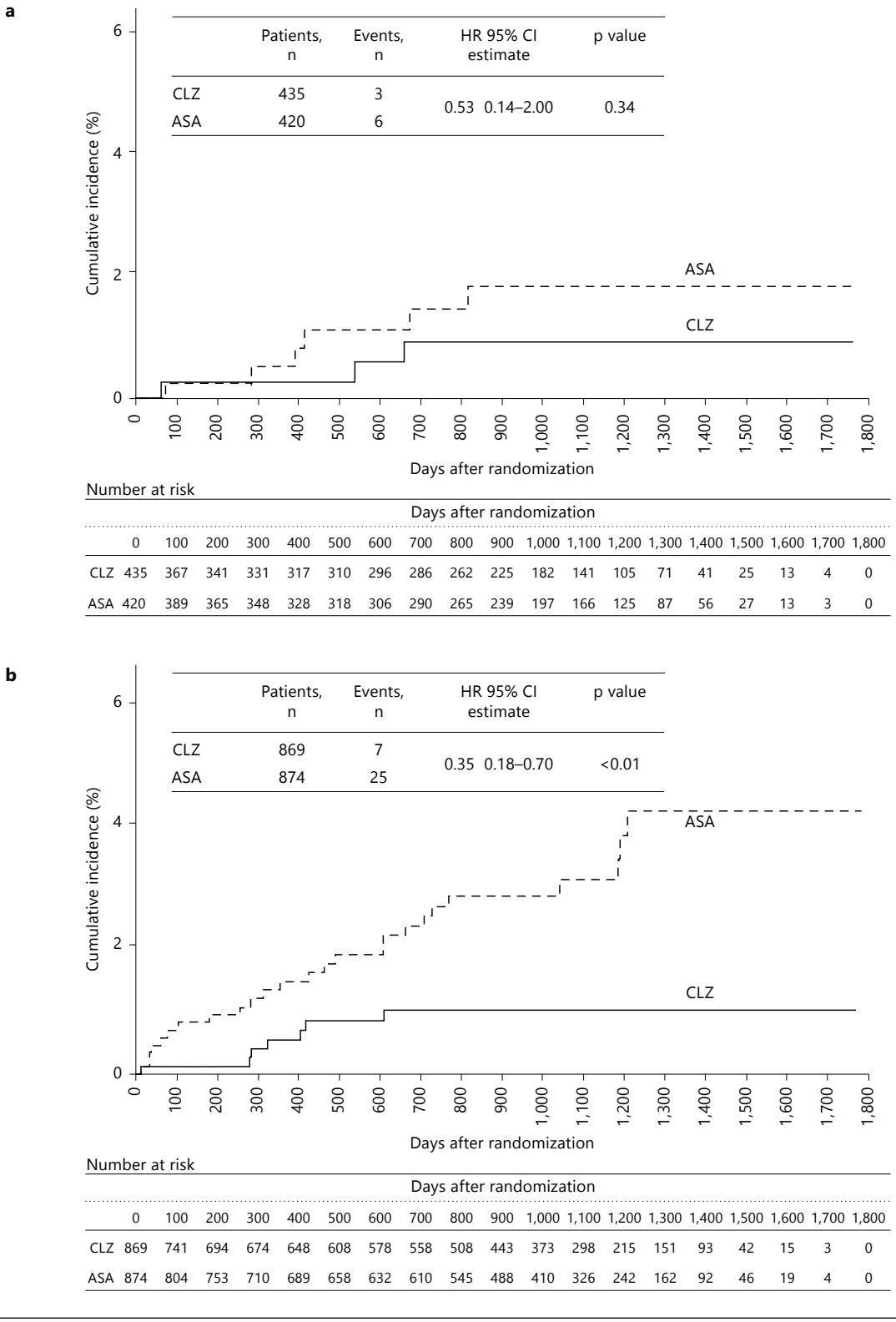

Fig. 2. Cumulative incidence of hemorrhagic stroke (cerebral hemorrhage or subarachnoid hemorrhage) in patients with a history of atherothrombotic stroke (**a**) or lacunar stroke (**b**). CLZ = Cilostazol; ASA = aspirin; p values assessed by the log-rank test.

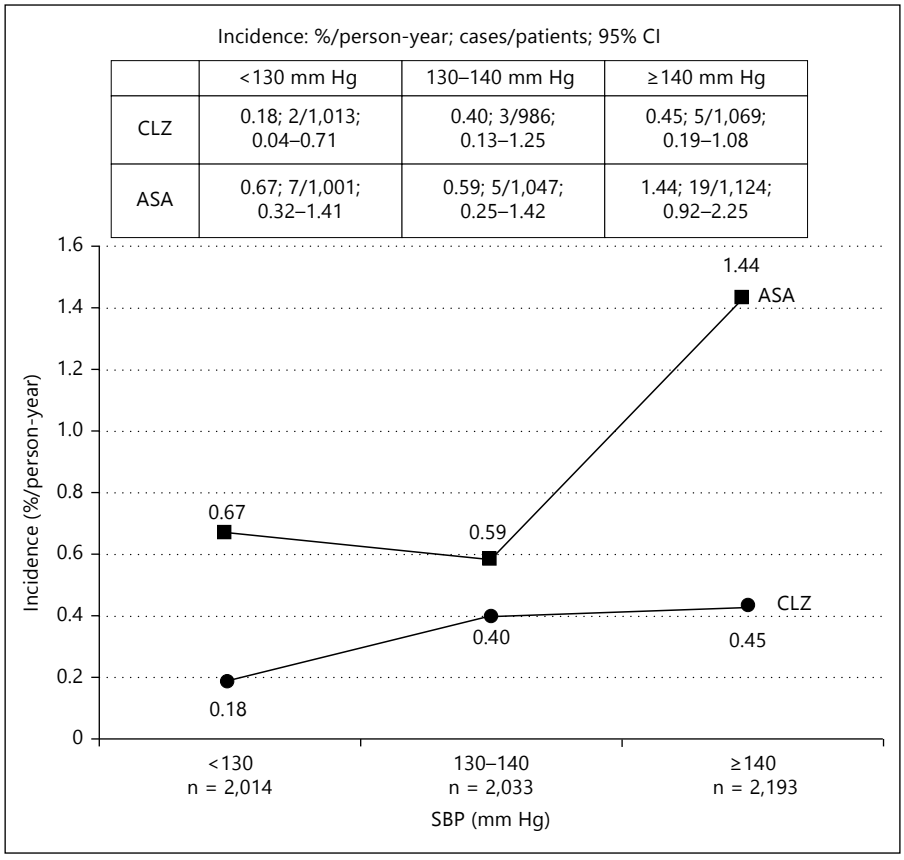

Fig. 3. Incidence of hemorrhagic stroke according to SBP. p = 0.61 for interaction; p < 0.01 for treatment. In this figure, 'patients' shows number of patients who showed the classified value at least once; ASA = Aspirin; CLZ = cilostazol.

son-year; p = 0.02; fig. 3). No interaction was observed between SBP levels and the treatment effect for prevention of hemorrhagic stroke (p = 0.61).

Risk Factors for Hemorrhagic Stroke

Univariate analysis found that age, body mass index, recurrent (versus first) stroke, modified Rankin Scale, stroke subtype, localization (e.g. cortex, subcortical white matter), vascular territory (e.g. vertebrobasilar artery, middle cerebral artery), SBP, diastolic blood pressure, triglyceride, concomitant use of angiotensin receptor blockers, Ca antagonists, lipid-lowering agents and statins were significant risk factors for hemorrhagic stroke. The multivariate analysis identified SBP as a significant factor.

Incidence of Serious Hemorrhagic Events

Incidences of intracranial hemorrhage and hemorrhage requiring hospital admission are shown in figure 4. Cilostazol, compared with aspirin, significantly reduced the incidence of cerebral hemorrhage (HR 0.36, 95% CI 0.19–0.70, p < 0.01), overall hemorrhage requiring hospital admission (HR 0.53, 95% CI 0.29–0.97, p = 0.04) and GI bleeding requiring hospital admission (HR 0.44, 95% CI 0.21–0.90, p = 0.03). No significant between-group differences were observed for incidence of subarachnoid hemorrhage, subdural hematoma, epistaxis or other hemorrhage requiring hospital admission.

Discussion

In the present study, the incidence of hemorrhagic stroke was similar in patients with prior atherothrombotic stroke (0.31% in person-year) and lacunar stroke (0.36% in person-year) among patients in the cilostazol group. On the other hand, in the aspirin group, the incidence of hemorrhagic stroke was twofold higher in patients with prior lacunar stroke than in those with prior atherothrombotic stroke (1.20 vs. 0.59% in person-year).

In a 10-year follow-up by the Hisayama study, patients with lacunar stroke had a higher incidence of hemorrhagic stroke than patients with atherothrombotic stroke [13]. Lacunar stroke was also reported to be associated with a

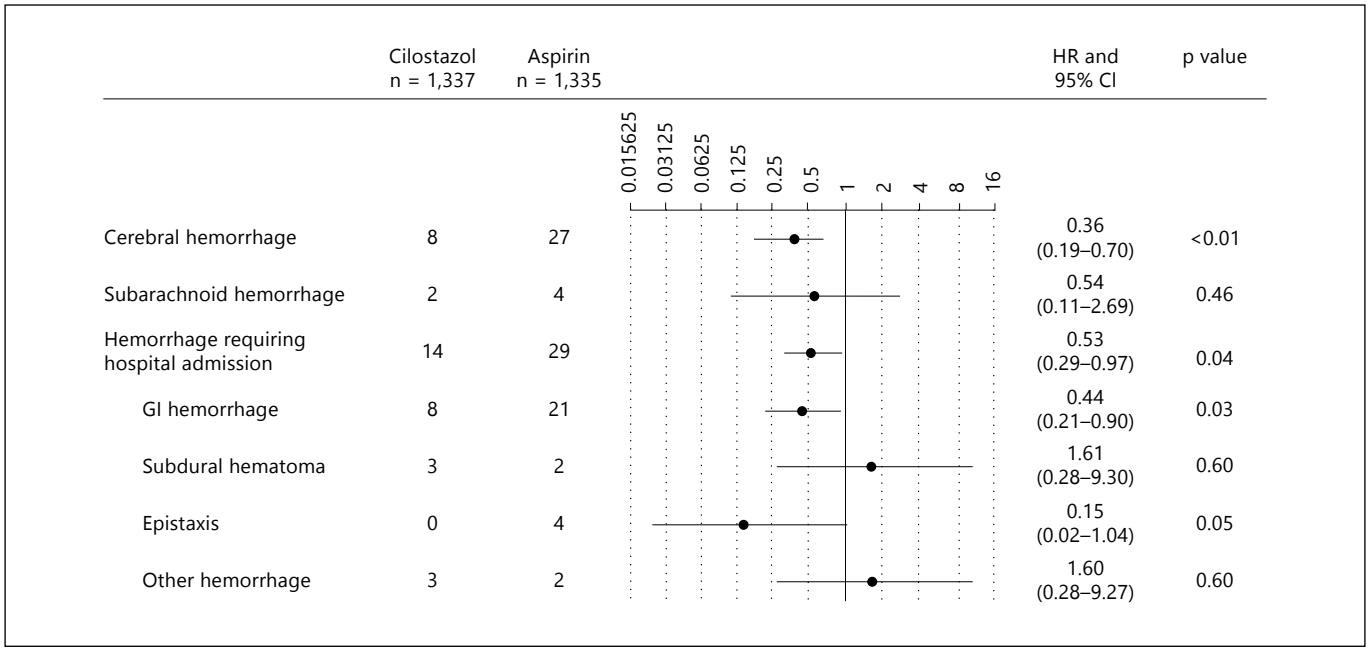

Fig. 4. Incidence of serious hemorrhage and hemorrhage requiring hospital admission. p values assessed by the log-rank test.

significant increase in asymptomatic hemorrhagic transformation of infarction, defined by follow-up CT [14], suggesting a close relationship between lacunar stroke and intracerebral hemorrhage.

The multivariate analysis to identify risk factors for hemorrhagic stroke identified SBP as a significant factor. Though stroke subtype was not included, we conducted the present subanalysis including stroke subtype based on the above-mentioned findings.

Endothelial dysfunction rather than chronic platelet activation is reported to play a central role in the pathophysiology of lacunar stroke [15], and also, acute ischemic stroke is considered associated with endothelial dysfunction of the peripheral vascular beds [16], suggesting that treatment which can improve endothelial dysfunction might be necessary for the prevention of lacunar stroke and hemorrhagic stroke. Aspirin therapy is known to be associated with increased hemorrhagic risk, and dual antiplatelet therapy with clopidogrel and aspirin was reported to add no benefit, but increased the bleeding risk in patients with lacunar stroke for long-time treatment [17, 18]. As far as we are aware, this is the first report to demonstrate a higher risk of hemorrhagic stroke in patients with lacunar stroke than in those with atherothrombotic stroke among patients on aspirin. However, the number of atherothrombotic stroke patients was half of that of lacunar stroke, suggesting that the lack of findings of significant differences between the study drugs in the atherothrombotic group may be attributable to the smaller sample size compared to the lacunar stroke group.

A relationship between the incidence of hemorrhagic stroke and blood pressure level has been reported in several studies. For example, Toyoda et al. [19] reported a relationship between increased blood pressure level and incidence of hemorrhagic stroke during antithrombotic treatment. The SPS 3 study also demonstrated that the incidence of stroke was reduced in the lower target SBP group (<130 mm Hg, mean 127 mm Hg) compared with the higher target SBP group (130–149 mm Hg, mean 138 mm Hg) in patients with lacunar stroke, and the difference was significant when limited to the reduction of hemorrhagic stroke, suggesting that the use of an SBP target less than 130 mm Hg might be beneficial for the reduction of hemorrhagic stroke in patients with lacunar stroke [20]. The present study demonstrated that the risk of hemorrhagic stroke was lower in patients on cilostazol than in those on aspirin in all the SBP categories including patients with SBP level over 140 mm Hg, demonstrating usefulness of cilostazol in patients with a high risk of bleeding such as lacunar stroke or high SBP.

Cilostazol exerts an antiplatelet action by inhibiting phosphodiesterase-3 and increasing cyclic adenosine monophosphate levels in platelets. It can also increase blood flow by vasodilation mediated through improvement of vascular endothelial cell function with increased nitric oxide production and barrier function, reducing the expression of adhesion molecules or preventing vascular smooth muscle cell proliferation [21–23]. In addition, cilostazol inhibits the expression of matrix metalloproteinase-9, which is one of the proteases associated with fragility of small vessels [24], and inhibits degeneration of small penetrating arteries in the brains of hypertensive rats [25]. Based on the findings, it could be speculated that endothelial dysfunction induced by high blood pressure was partly reversed by cilostazol.

It has been reported that the incidence of GI bleeding was significantly increased even with low-dose aspirin [2], and the odds ratio for GI bleeding with aspirin was 8.2 in a Japanese case-control study [26]. In the present study, the incidence of GI bleeding was significantly higher in the aspirin group than in the cilostazol group. Unlike aspirin, cilostazol does not induce damage to the gastric mucosa, which might explain the difference in the incidence of GI bleeding between the two study drugs. The limitation of the present study was that CSPS 2 was conducted in a Japanese population, and confirmatory studies in other ethnic groups are required. Additionally, this analysis may have been underpowered to demonstrate significant treatment differences for some factors.

Conclusion

Cilostazol was associated with fewer hemorrhagic strokes in patients with a high risk of hemorrhagic stroke, such as those with lacunar stroke and high SBP levels, and was also associated with less GI bleeding than aspirin.

Cilostazol is supposed to be a therapeutic option to replace aspirin for secondary stroke prevention, especially in these high-risk subgroups for hemorrhagic events. Further comprehensive analyses on larger numbers of patients, including other ethnic subpopulations, are required to obtain conclusive results.

Disclosure Statement

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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 statistical analyses were entrusted to a contract research organization (EPS). The contract research organization did statistical analyses under the supervision of the trial statistician (C.H.), who was independent from the sponsor. Both the corresponding author and C.H. had full access to all the data in the study, and the corresponding author had the final responsibility for the decision to submit this paper for publication.

Shinichiro Uchiyama's institution has received grants and honoraria for lecture from Otsuka Pharmaceutical, Sanofi-Aventis, Boehringer Ingelheim, Daiichi-Sankyo and Bayer Health Care.

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Norio Tanahashi has received payment for the development of educational presentations from Mitsubishi Tanabe Pharma, Pfizer Japan, Sanofi-Aventis and Otsuka Pharmaceutical.

Hiroko Yamamoto 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 the development of educational presentations from Novartis Pharma and Sanofi-Aventis; her institution has received grants from Ono Pharmaceutical.

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Yasuo Katayama, Shunnosuke Handa, Kempei Matsuoka, Chokoh Genka, Hideo Kusuoka, Motoo Tsushima, Tohru Sawada and Chikuma Hamada declare that they have no conflicts of interest.

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