Cilostazol for the Prevention of Recurrent Stroke: Results from CSPS II

Cilostazol (CLZ) is significantly more effective than aspirin in preventing recurrent stroke and is associated with fewer hemorrhagic events. Yukito Shinohara, MD, Federation of National Public Service Personnel Mutual Aid Associations Tachikawa Hospital, Tokyo, Japan, presented findings from the Cilostazol Stroke Prevention Study II (CSPS II).

CSPS II was a multicenter, double-blind, parallel-group, randomized, prospective comparative study that included 2757 patients with CT- or MRI-proven noncardioembolic stroke from 278 Japanese institutes. Efficacy and safety analyses were based on 2672 patients, of whom 1337 were in the CLZ group and 1335 were in the aspirin group. Patients were randomized to receive either CLZ 100 mg twice daily (n=1337) or aspirin 81 mg once daily (n=1335). There was no significant difference in baseline characteristics between the two groups. Treatment duration was 1 to 5 years.

The aim of this study was to establish noninferiority (defined as upper limit of 95% CI for HR ≤1.33) of CLZ compared with aspirin for the prevention of stroke recurrence in patients with noncardioembolic cerebral infarction. The primary endpoint was the occurrence of symptomatic stroke, including recurrence of cerebral infarction, or occurrence of intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH) during the treatment period. Secondary endpoints were the recurrence of symptomatic cerebral infarction, the occurrence of ischemic cerebrovascular events, including cerebral infarction or transient ischemic attack (TIA); death from any cause; and the composite of stroke, TIA, angina pectoris, myocardial infraction (MI), heart failure, or hemorrhage that required hospitalization during the treatment period. Safety endpoints were bleeding events, including ICH, SAH, or hemorrhage that required hospitalization.

The primary endpoint of stroke occurred more frequently in patients who were treated with aspirin (n=119) than with CLZ (n=82) (HR, 0.743; 95% CI, 0.564 to 0.981; p=0.0357). This demonstrated a 25.7% relative risk reduction in stroke occurrence in patients who were treated with CLZ. There was also a 20.1% relative risk reduction in the composite secondary endpoint of stroke, TIA, angina pectoris, MI, heart failure, or hemorrhage that required hospitalization in patients who were treated with CLZ versus aspirin (p=0.0437). Results for the remaining secondary endpoints—cerebral infarction, transient ischemic attack (TIA), or death from any cause—were similar for both groups (Table 1).

Table 1. Incidence of Primary and Secondary Endpoints.

	CLZ (n=1337)	ASA (n=1335)	HR (95% CI)	Log-rank test p value
	No. of Patients (%/person-year)			
Efficacy endpoint				
Primary endpoint Stroke (Cerebral infarction, ICH, SAH)	82 (2.75)	119 (3.71)	0.743 (0.564-0.981)	0.0357
Secondary endpoint				
Cerebral infarction	72 (2.43)	88 (2.75)	0.880 (0.645-1.200)	0.4189
Ischemic cerebrovascular disorder (Cerebral infarction, TIA)	86 (2.90)	103 (3.21)	0.898 (0.675-1.194)	0.4582
Death from any cause	13 (0.42)	13 (0.39)	1.072 (0.497-2.313)	0.8600
Secondary endpoint cluster	138 (4.66)	186 (5.81)	0.799 (0.643-0.994)	0.0437
Safety endpoint				
Bleeding events (ICH, SAH, bleeding requiring hospitalization)	23 (0.77)	57 (1.78)	0.458 (0.296-0.711)	0.0004

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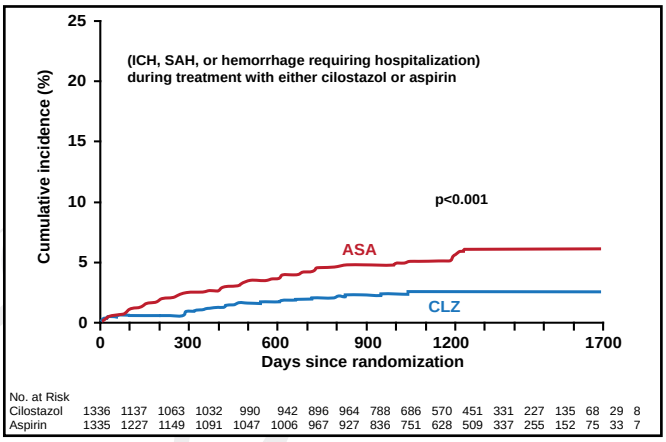
Safety results also demonstrated favorable outcomes with the use of CLZ versus aspirin. Hemorrhagic events occurred less frequently in patients who were treated with CLZ than in those who were treated with aspirin (p<0.001; Figure 1). Adverse drug reactions that resulted in treatment discontinuation occurred in 19.8% of patients in the CLZ group versus 12.2% in the aspirin group. The most common adverse events other than bleeding were headache, diarrhea, palpitations, dizziness, and tachycardia in the CLZ group and hypertension and constipation in the aspirin group.

Figure 1. Safety Endpoint: Hemorrhagic Events.



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This study demonstrated noninferiority of CLZ compared with aspirin in preventing stroke recurrence. In fact, CLZ was significantly more effective and was associated with a lower incidence of bleeding compared with aspirin. Based on these results, Dr. Shinohara concluded that CLZ is a possible treatment option for the prevention of stroke recurrence in patients with noncardioembolic stroke who can tolerate long-term administration of CLZ. Subgroup and cost-effectiveness analyses of this study are ongoing.

How Does Dabigatran Compare with Warfarin for Secondary Stroke Prevention? Subgroup Analysis of the RE-LY Study

A subgroup analysis of the Randomized Evaluation of Long-term anticoagulant therapy (RE-LY; NCT00262600) trial revealed that dabigatran 110 mg or 150 mg twice daily is as effective as warfarin for stroke prevention in patients who have had a prior stroke or transient ischemic attack (TIA). Dabigatran is also associated with a lower incidence of any hemorrhage, including hemorrhagic stroke, compared with warfarin.

The RE-LY study was a large, international, multicenter, randomized trial that included 18,113 patients with nonvalvular atrial fibrillation (AF) who were at moderate to high risk of stroke or systemic embolism and had at least one additional risk factor. Patients were randomized to receive dabigatran 110 mg twice daily (1195 had prior stroke and 4819 had no prior stroke), dabigatran 150 mg twice daily (1233 had prior stroke and 4843 had no prior stroke), or warfarin (INR 2.0-3.0; 1195 had prior stroke and 4827 had no prior stroke). The mean observation time was 2 years, and those with renal insufficiency (CrCl <30 ml/min) were excluded from study participation. Events were independently and blindly adjudicated following a PROBE design (prospective randomized open with blinded endpoint evaluation). The primary outcome was stroke or systemic embolism.

The subgroup analysis includes the secondary stroke prevention part of the RE-LY study that explored the treatment effects of dabigatran versus warfarin in patient population who had a prior stroke or TIA. In the overall RE-LY patients, the rate of the primary outcome was 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% CI, 0.74 to 1.11; p<0.001 for noninferiority) and 1.11% per year in the group that received 150 mg of dabigatran (relative risk [RR], 0.66; 0.53 to 0.82; p<0.001 for superiority; Figure 1).

A consistent finding was found in patients with prior stroke or TIA (RR, 0.85; 95% CI, 0.59 to 1.22; p=0.37 for dabigatran 110 mg vs warfarin; RR, 0.76; 95% CI, 0.53 to 1.10; p=0.14 for dabigatran 150 mg vs warfarin; Figure 2).

Overall, both dabigatran treatments were superior to warfarin with regard to hemorrhagic stroke (p<0.001) Likewise, in the subgroup of patients with prior TIA or stroke, there was an 89% and 73% relative risk reduction in the incidence of hemorrhagic stroke in the dabigatran 110 mg (p=0.003) and dabigatran 150 mg (p=0.009) groups, respectively, compared with warfarin. Intracranial bleeding rates for all patients were lower in the dabigatran groups than in the warfarin group (p<0.001 superior for both dabigatran doses). Intracranial bleeding rates were also lower in patients with prior stroke or TIA compared with warfarin (p<0.001 for dabigatran 110 mg; p=0.007 for dabigatran 150 mg). There was no increase in bleeding rate that was associated with dabigatran and concomitant aspirin use.

The RE-LY study was a large trial that evaluated two dabigatran dose strategies using rigorous adjudication