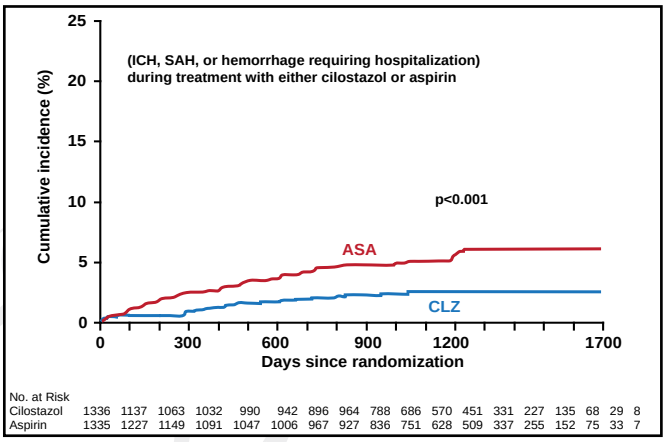
Safety results also demonstrated favorable outcomes with the use of CLZ versus aspirin. Hemorrhagic events occurred less frequently in patients who were treated with CLZ than in those who were treated with aspirin (p<0.001; Figure 1). Adverse drug reactions that resulted in treatment discontinuation 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

of events. Results of both the main study and the subanalysis are promising. However, there are some potential shortcomings in this study, including the fact that the warfarin arm was not blinded. Results of the subgroup analysis were consistent with the findings of the overall patient cohort; however, the subgroup was too small to demonstrate a statistically significant superiority of the higher dabigatran dose over warfarin, as demonstrated in the overall RE-LY cohort. Further evaluations of the long-term safety and efficacy data from RE-LY data are needed to determine the optimal choice of the dabigatran dose for patients with prior TIA or stroke of treatment with dabigatran.

Figure 1. Stroke/SSE All Patients.

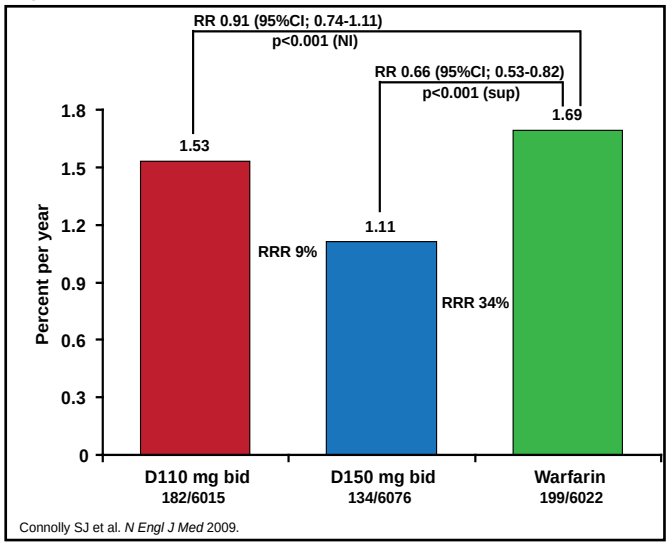

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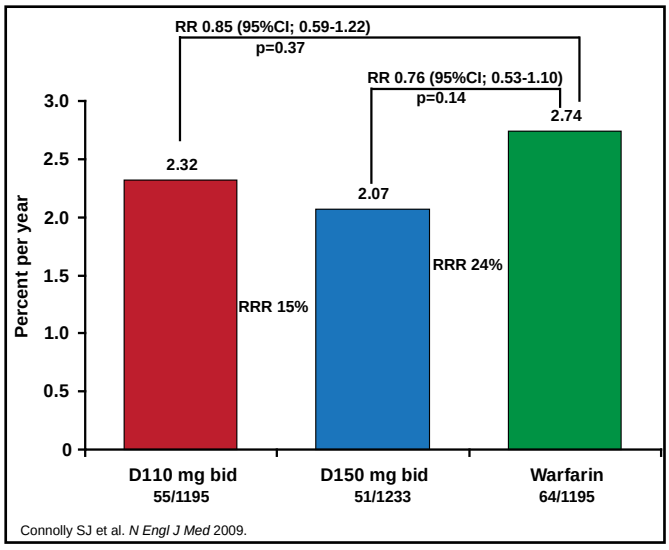
Figure 2. Stroke/SSE Patients with Prior Stroke or TIA.



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Randomized Trial of Robot-Assisted Rehabilitation for Chronic Stroke

Robot-assisted therapy (RT) and intensive comparison treatment (ICT), structured to match that of RT with regard to number of sessions, type, and intensity of movement, were superior to customary chronic poststroke care (usual care – UC) for the treatment of chronic stroke that affected the upper extremities. Extremity function greatly affects the overall outcome of chronic stroke; therefore, improvement of extremity function is a critical aim of rehabilitation [Olsen TS et al. *Stroke* 1990]. Albert Lo, MD, PhD, Providence VA Medical Center, Providence, RI, discussed the use of novel RT as a rehabilitation strategy to improve functionality and quality of life in patients ≥6 months poststroke.

In this study by Lo and colleagues, patients with an index stroke that occurred at least 6 months prior to enrollment (mean time since stroke 4.7 years), resulting in moderate to severe upper extremity impairment as measured by Fugl-Meyer score of 7 to 38 (out of a possible 66 points), were randomized to receive RT (n=49), ICT (n=50), or UC (n=28) for 36 sessions over a 12-week period. Patients who experienced multiple strokes (33%) were also included in this study, provided the index stroke was ≥6 months prior to enrollment. There was no significant difference in baseline characteristics across the groups. RT entailed using a 4-module robotic system, which included a vertical, horizontal, hand, and wrist unit, and produced >1000 intensive movements per session. ICT was equivalent to the RT model (also producing >1000 intensive movements/session), and UC utilized conventional methods, such as a 5-foot pole with a sliding base, a hand odometer, and a horizontal "hand skate."

Evaluations were performed at Weeks 6, 12, 24, and 36. The primary endpoints were motor capacity, as assessed by Fugl-Meyer score, and safety, as determined by spasticity (using modified Ashworth) and pain (using a numerical scale) immediately following the completion of therapy at 12 weeks. Secondary endpoints were the difference in Wolf Motor Function Test and Stroke Impact Scale (composite of hand, mobility, activities of daily life tasks, and participation) over 36 weeks (including treatment and 6 months of follow-up).

There was no significant difference in Fugl-Meyer score between RT and ICT or UC at 12 weeks. However, at 36 weeks, 12 weeks posttreatment, a mean point difference of +2.88 in Fugl-Meyer score was observed in RT patients versus UC (p=0.016). Additionally, the mean change in