

### **What are the emerging therapeutic alternatives to Warfarin in Stroke patients? How would the results of RE-LY benefit Pakistanis?**

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#### **Randomized Evaluation of Long-Term Anticoagulation (RE-LY)**

##### **Why is this study important and noteworthy?**

Warfarin is currently the gold standard for stroke prevention in patients with atrial fibrillation. Therapy with Warfarin requires frequent International Normalized Ratio (INR) monitoring due to its low therapeutic index. Furthermore, multiple food and drug interactions lead to non-compliance and frequent dose adjustment.

Dabigatran, the active form of the prodrug Dabigatran etexilate, is a competitive inhibitor of thrombin. This new anticoagulant does not require frequent monitoring and had been evaluated in a pilot trial with promising results.

RE-LY was a randomized study which tested two fixed doses of Dabigatran (110 and 150 mg twice daily) given in a blinded manner, with open label use of Warfarin in patients with atrial fibrillation and an increased risk of stroke.

##### **Who were the participants?**

A total of 18,113 patients from 951 clinical centers across 44 countries were recruited for this non-inferiority trial and followed for a median duration of 2 years. There was a fair representation from Asia, with patients being recruited from India, China, Korea and Japan. All patients had documented atrial fibrillation on electrocardiography at the time of screening or within 6 months beforehand and, a risk of stroke. 63.6% of the patients were men and the mean age was 71 years.

##### **What was the intervention?**

Patients were assigned randomly to one of three treatment groups. Two groups received either 110 mg or 150 mg twice daily dose of Dabigatran in a blinded fashion. The third group received Warfarin in 1, 3 or 5 mg tablets adjusting to an International Normalized Ratio (INR) of 2.0 to 3.0 in an unblinded fashion. Concomitant use of Aspirin at a dose of <100 mg per day or any other antiplatelet agent was permitted. All three groups were comparable in terms of age, gender, type of atrial fibrillation, co-morbidities and CHADS2 scores.

##### **What was the outcome?**

Primary outcome (stroke or systemic embolism) in the 110 mg Dabigatran group was 1.53% per year compared with 1.11% per year in 150 mg Dabigatran group and 1.69% per year in the Warfarin group. This rendered both doses of Dabigatran to be noninferior to Warfarin.

There were significantly fewer haemorrhagic strokes in the Dabigatran arms at both doses compared to Warfarin with RR of 0.31 with 110 mg and 0.26 with 150 mg ( $p < 0.001$  in both cases) dose. Rates of major bleeding were 3.36%, 2.71% and 3.11% per year for Warfarin, Dabigatran 110 mg (relative risk 0.80,  $p = 0.003$ ) and Dabigatran 150 mg (relative risk 0.93,  $p = 0.31$ ) respectively.

A subgroup analysis compared the two doses of Dabigatran with Warfarin in secondary prevention of stroke in a subset of patients with prior stroke or transient ischaemic attack. They found a higher annual rate of stroke in this subgroup. A significant reduction in all-cause mortality was found with 110 mg Dabigatran but not 150 mg Dabigatran compared with Warfarin in this subgroup. The 150 mg dose of Dabigatran was superior to Warfarin for the primary outcome in this subgroup analysis of patients with previous stroke or transient ischaemic attack (RR reduction 25%).

##### **What were the conclusions?**

The authors concluded that both doses of Dabigatran were noninferior to Warfarin. The 150 mg dose of Dabigatran was superior to Warfarin as far as stroke or systemic embolism prevention was concerned both in patients with or without prior stroke or transient ischaemic attack. The 110 mg dose of Dabigatran was superior to Warfarin with respect to major bleeding.

##### **How does this impact our clinical practice?**

There are considerable difficulties with the practical administration of warfarin in Pakistan. Dabigatran may be a welcome future alternative particularly in a population which is already at a higher risk of haemorrhagic strokes compared to the rest of the world.

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### **Recommended Reading:**

1. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, Oldgren J, Themeles E, Wallentin L, Yusuf S. Rationale and design of RE-LY:

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