

## Dabigatran for Atrial Fibrillation

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### Clinical Scenario:

A 62 year old, female is diagnosed with new onset atrial fibrillation. She has a family history of atrial fibrillation and stroke. She will need anticoagulation therapy prescribed today.

### Clinical Question:

In patients with atrial fibrillation, is the use of dabigatran a safe and effective alternative to warfarin in the prevention of stroke?

### Articles:

Connolly, S. J., Ezekowitz, M. D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., et al. (2009). Dabigatran versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine*, 361(12), 1139-1151. doi: 10.1056/NEJMoa0905561

Diener, H.-C., Connolly, S. J., Ezekowitz, M. D., Wallentin, L., Reilly, P. A., Yang, S., et al. (2010). Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischemic attack or stroke: a subgroup analysis of the RE-LY trial. *The Lancet Neurology*, 9(12), 1157-1163. doi: 10.1016/S1474-4422(10)70274-X

### Critical Review of Study:

Connolly et al. (2009) explained the results of a PROBE (prospective randomized, open-label, blinded endpoint) trial (level of evidence 1b) completed in March 2009. Diener et al. (2010) provided a subgroup analysis of the same randomized controlled trial (level of evidence 2b).

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial measured fixed doses of dabigatran (110 mg or 150 mg twice daily) and adjusted-doses of warfarin (to maintain INR 2.0-3.0) in the prevention of stroke or systemic embolism in 18,113 patients with atrial fibrillation and a risk of stroke. Patients were not blinded to whether dabigatran or warfarin was administered, but the patients who received dabigatran were blinded to the dose they received. The median duration of follow-up was 2 years which included 99.9% of patients. Primary outcomes measured included the risk of stroke and systemic embolism. The primary safety outcome was major hemorrhage (Connolly et al., 2009).

Diener et al. (2009) performed a subgroup analysis of patients in the RE-LY trial who had a history of previous stroke or transient ischemic attack. This consisted of 3,623 patients, with 1195 from the 110 mg dabigatran group, 1233 from the 150 mg dabigatran group, and 1195 from the warfarin group. Primary outcomes measured included the risk of stroke, systemic embolism, and major hemorrhage.

Results of the RE-LY trial indicated that stroke or systemic embolism occurred in 182 patients receiving 110 mg dabigatran (1.53%/yr.), 134 patients receiving 150 mg dabigatran (1.11%/yr.), and 199 patients receiving warfarin (1.69%/yr.). Both doses of dabigatran were noninferior to warfarin ( $P < 0.001$ ). The 150 mg dose of dabigatran was also superior to warfarin ( $P < 0.001$ ), but the 110 mg dose was not ( $P = 0.34$ ). The rates of hemorrhagic stroke were less in the dabigatran groups than in the warfarin groups: 0.38%/year in the warfarin group, 0.12%/year in the 110 mg dabigatran group ( $P < 0.001$ ), and 0.10%/year in the 150 mg dabigatran group ( $P < 0.001$ ). The rate of major hemorrhage was less in the 110 mg dabigatran

group (2.71%/year) as compared to the warfarin group (3.36%/year) (P=0.003). The 150 mg dabigatran group had similar rates of hemorrhage (3.11%/year) as the warfarin group (P=0.31). Rates of life-threatening bleeding, intracranial bleeding, and major or minor bleeding were higher with warfarin than with either dose of dabigatran (P<0.05). There was a significantly higher rate of major gastrointestinal bleeding with 150 mg dabigatran than with warfarin (P<0.001) (Connolly et al., 2009).

In the subgroup analysis of the RE-LY trial by Diener et al., (2010), patients with a history of stroke or transient ischemic attacks had a statistically significant increased rates of stroke or transient ischemic attacks (P<0.001) as compared to those patients without a history. However, there was no significant interaction between previous stroke and transient ischemic attack on the primary outcome with either 110 mg dabigatran (P=0.62) or 150 mg dabigatran (P=0.34).

### **Clinical Bottom Line:**

Dabigatran is a new oral direct thrombin inhibitor indicated for use in patients with atrial fibrillation as a non-inferior alternative to warfarin. According to the RE-LY trial, when compared with warfarin, the 110 mg dose of dabigatran is associated with similar rates of stroke and systemic embolism and lower rates of major hemorrhage. The 150 mg dose of dabigatran is associated with lower rates of stroke and hemorrhage, but with a similar rate of major hemorrhage as compared to warfarin. In patients with a history of stroke or transient ischemic attack, there is no greater risk with dabigatran than with warfarin (Connolly et al., 2009; Diener et al., 2010). The metabolism of dabigatran is independent of the cytochrome P450 enzyme system, making drug-drug and drug-diet interactions less likely. It also does not require frequent laboratory monitoring to determine therapeutic effectiveness.

As a result of the large RE-LY trial findings, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) practice guidelines on the management of patients with atrial fibrillation were updated in 2011 to include the use of dabigatran:

Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance 15 mL/min) or advanced liver disease (impaired baseline clotting function) (Class of recommendation: I; Level of Evidence: B) (ACCF/AHA Task Force on Practice Guidelines, 2011).

Since dabigatran is a newly-approved medication by the Food & Drug Administration (approved October 2010), there is a need for further trials to evaluate its safety and effectiveness in the prevention of stroke for patients with atrial fibrillation. Currently, the RE-LY trial is the only trial utilizing a high level of evidence for this population. Further follow-up with the study participants will be important in order to determine long term effects of dabigatran. Further investigation of a dose in between the 110 mg and 150 mg dose would also be beneficial since the higher dose has been proven superior to warfarin in regards to stroke and systemic embolism prevention, but it has been associated with increased risks of gastrointestinal bleeding.

American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Task Force on Practice Guidelines. (2011). 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Update on dabigatran). *Journal of the American College of Cardiology*, 57(11), 1-9. doi: 10.1016/j.jacc.2011.01.010. Retrieved from <http://content.onlinejacc.org/cgi/reprint/j.jacc.2011.01.010v1.pdf>

Oxford Centre for Evidence-Based Medicine. (2009). Levels of evidence. *University of Oxford*. Retrieved from <http://www.cebm.net/index.aspx?o=1025>