

Dabigatran: A look before we leap

Naseer A Masoodi and Bilal Ahmad

Warfarin is the most commonly used oral anticoagulant and has established efficacy for more than 50 years for the prevention of thromboembolic events, but its use is limited by fear of bleeding, drug-drug and drug-food interactions, and routine monitoring of international normalized ratio (INR). In patients with atrial fibrillation (AF), warfarin prevents 64% of strokes in research studies but the real-world effectiveness drops to 35% because of various factors leading to its suboptimal use.¹ In October 2010 the United States (US) Food and Drug Administration (FDA) approved Pradaxa capsules (dabigatran etexilate) as the first new agent to prevent stroke and systemic emboli in patients with non-valvular AF. In this article we will discuss some of the evidence for and against the use of dabigatran.

In the RE-LY study² (Randomized Evaluation of Long-term Anticoagulant Therapy), high-dose dabigatran (150mg twice a day) was found to be superior to warfarin for the prevention of stroke and systemic emboli, required no routine INR monitoring, and had few food and drug interactions. James Freeman and colleagues,³ using data from the RE-LY trial, found that high-dose dabigatran (150mg twice a day) was the most efficacious and cost-effective strategy compared with adjusted-dose warfarin among adults older than 65 with AF.

Dabigatran has been shown to specifically and reversibly inhibit thrombin, the key enzyme in the coagulation cascade. Studies in healthy volunteers⁴ and in patients undergoing orthopaedic surgery have indicated that dabigatran has a predictable pharmacokinetic/pharmacodynamic profile, allowing for a fixed-dose regimen. Peak plasma concentrations of dabigatran are reached approximately two hours after oral administration in healthy volunteers, with no unexpected accumulation of drug concentrations upon multiple dosing. Excretion is predominantly via the renal route as unchanged drug. Dabigatran is not metabolized by cytochrome P450 isoenzymes. Though use of dabigatran for non-valvular AF and venous thromboembolism (VTE) is gaining practice,⁵ it remains far from being the standard of care.

What are the concerns with use of dabigatran? In the RE-LY study the INR control was relatively poor (64% TTR (time in the therapeutic range)) but, probably more importantly, the

relationship between events and individual's INR control was not reported. The use of centre's time in therapeutic range (cTTR) in the RE-LY study as a surrogate for INR control may not truly reflect TTRs for individual patients. Also in RE-LY study, randomization was stratified for centre and by the centre-based analyses, and the quality of oral anticoagulant services was the basis for the comparisons in this report. A subgroup analysis⁶ concluded that relative effectiveness of dabigatran versus warfarin was mainly seen at centres with poorer INR control. For example, Swedish centres had good TTR and the relative effectiveness and safety of dabigatran was virtually the same as with warfarin; thus, it is only the price difference that counts. It also highlights how local standards of care affect the benefits of use of new treatment alternatives and hence further limits the generalizability of any 'overall average' cost-effectiveness of dabigatran, raising the question that if an intervention does not do more, why should a payer pay more for it? There are several other factors that could impact on the cost-effectiveness⁷ of dabigatran such as patient medication adherence, dosing frequency, and the potential effect of new efficient methods of warfarin management improving INR control by patient self-testing.

The other shortcomings of dabigatran include lack of antidotes when patients do bleed and lack of any alert to physicians that patients are not compliant with dabigatran (INR serves this purpose for warfarin). Additionally, in the RE-LY trial, dabigatran was used twice daily thus raising compliance issues compared to once daily warfarin (the rates of discontinuation of dabigatran were higher at 15% and 21% at one and two years, respectively); 11.3% reported dyspepsia (twice the rate of warfarin group); high rate of gastrointestinal bleed compared with warfarin; patients in the dabigatran cohort were at slightly higher risk of myocardial infarction (not sure how it will translate in real world practice); and contraindication of dabigatran in severe renal dysfunction raises some more questions about its use and cost effectiveness. In addition, the RE-LY trial excluded patients who had: contraindications to anticoagulation, severe heart-valve disorder, stroke within 14 days or severe stroke within six months before screening, a condition that increased risk of haemorrhage, creatinine clearance of less than 30ml per minute, active liver disease, and pregnancy. Clinicians will need to use their judgement to

weigh and balance the risk for bleeding with this new agent in a setting of an acute stroke versus the risk of having another ischaemic stroke in someone with AF if not given anti-coagulation therapy immediately. Safety and efficacy at extremes of body weight is not well established with current FDA approved doses of dabigatran either.

In summary dabigatran is a very exciting new agent with significant advantages over warfarin. However, in view of dabigatran's higher non-adherence rate and greater risk of non-haemorrhagic side effects, patients already taking warfarin with excellent INR control have little to gain by switching to dabigatran.¹ Until more studies and post-marketing data become widely available, we should advocate tight INR control for which there is a wealth of evidence for benefits, and promote strategies to improve the management of therapy with warfarin.

Competing Interests

None Declared

Author Details

NASSEER A MASOODI MD, MBA, FACP, CMD, CPE, Associate Professor Clinical Sciences, FSU College of Medicine, Tallahassee, FL-32060, USA; Medical Director Health Services, ACV Inc., Dowling Park, FL-USA BILAL AHMAD MD, Clinical Instructor, Internal Medicine/Geriatrics, Wake Forest University School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157, USA

CORRESPONDENCE: NASSEER A MASOODI, Associate Professor Clinical Sciences, FSU College of Medicine, Tallahassee, FL-32060, USA

REFERENCES

1. Gage BF. Can we rely on RE-LY? *N Engl J Med.* 2009; 361:1200-1202.
2. Connolly SJ, Ezekowitz MD, Yusuf S et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009; 361:1139-1151.
3. Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, Wang PJ, Turakhia MP. *Ann Intern Med.* 2011 Jan 4;154(1):1-11.
4. Stangier J, Rathgen K et al. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol.* 2007 September; 64(3):292-303.
5. Clayville LR, Anderson KV et al. New options in anticoagulation for the prevention of venous thromboembolism and stroke. *P T.* 2011 February; 36(2):86-88, 93-99.
6. Wallentin L, Yusuf S, Ezekowitz MD et al; RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet.* 2010; 376:975-83.
7. Masoodi NA. Compared with warfarin, high-dose dabigatran might be cost-effective for preventing stroke in older patients with nonvalvular AF (Comment). *ACP Journal Club.* 2011 Jun 21; 154:JC6-12.