

Drug Trends in Cardiology

New insights and results from the RE-LY trial

The RE-LY trial with dabigatran has provided clinicians worldwide with a new benchmark standard for anticoagulation and stroke prevention in atrial fibrillation. This view was presented at the 2011 European Society of Cardiology (ESC) congress by Dr Gregory Lip, professor of cardiovascular medicine at the University of Birmingham, who is well placed to evaluate clinical expectations for these new agents. He has acted as clinical advisor to the UK Institute of Health and Clinical Excellence (NICE) Guidelines on Atrial Fibrillation (AF) Management and has served as stroke prevention head for the 2010 ESC guidelines on AF management.

‘There is an urgent need for clinicians to adjust to this paradigm shift in stroke prevention, based on the insights and results from RE-LY with dabigatran, currently the only registered anticoagulant for AF.^{1,2} In addition, the emerging data on the oral factor Xa inhibitors, Apixaban and Rivaroxaban will also influence clinical approaches to the use of anticoagulants in a wide variety of clinical settings.’

Two new RE-LY sub-studies were released at the ESC and showed that dabigatran provided consistent benefits in reducing stroke in AF, regardless of whether the patients were on aspirin, clopidogrel or other concomitant therapies, such as the anti-arrhythmics, amiodarone and verapamil.^{3,4} Dr Lip pointed out that the antiplatelet agent, aspirin has little benefit in stroke prevention in AF, and may in fact be less safe than warfarin, especially in the elderly.⁵

Co-chair of this special ESC symposium, Dr Elaine Hylek, of Boston University, USA, pointed out that warfarin and other vitamin K antagonists (coumarin) are very effective, reducing overall risk of strokes by 68%. This benefit dwarfs the benefit shown in statin trials in the early 1990s.

‘Despite this, warfarin is under-used, with only 50% of patients in the USA and Swedish registries being treated with warfarin. The perception of bleeding risk and difficulties around availability with food and other drugs seems to discourage

warfarin use’, she noted. This under-use is aggravated by the fact that in the ACTIVE-W trial, it was shown that patients on warfarin need to be within the target INR (2–3) for 58 to 65% of the time in order to achieve these benefits.

Also, some patients have low INR variability, in contrast to other individuals who show high variability. INR variability is therefore highly individualised, a factor that clinicians and patients must understand.

‘Dabigatran in the RE-LY trial of stroke in non-valvular atrial fibrillation showed that dabigatran etexilate 150 mg bid further reduced the risk of stroke or systemic embolism by an additional 35% compared to well-controlled warfarin’, Dr Lip stressed. This was achieved with a similar rate of bleeding compared to warfarin.

The 110-mg bid dose of dabigatran was non-inferior to warfarin with a lower bleeding risk. Interestingly, there is a suggestion, on further analysis of the RE-LY data, of an age interaction with dabigatran, such that dabigatran 110 mg twice daily was associated with a lower risk of major bleeding compared to warfarin in patients under 75 years of age, and with a similar risk in those older than 75 years.

The higher dose was associated with a trend towards a higher risk of bleeding in those older than 75 years. Importantly, this was due to the rate of extracranial haemorrhages being slightly higher, rather than being due to intracranial haemorrhages, which were consistently reduced with dabigatran compared to warfarin, irrespective of age.⁶

‘This can give reassurance for the use of the 75-mg bid dose in the super-elderly (≥ 75 years)’, Dr Lip noted. ‘There is also some data to suggest that patients with paroxysmal AF do better on the 110-mg dose’, Dr Lip added.

In conclusion, Dr Lip noted that the advent of dabigatran has moved the pivot point of oral anticoagulant benefit versus bleeding to a lower CHADS₂ score of above 0, and if using the newer CHA₂DS₂-VASc score, of 1 and above. This means

that oral anticoagulation should be used more widely to the benefit of more patients, thereby effectively reducing their risk of stroke.

Comments from attending South African experts

Dr Adri Kok, private practice physician, Benoni, Gauteng

As a physician, I am very aware that atrial fibrillation is still a poorly diagnosed risk factor for arterial embolisation and stroke. It is a preventable cause of stroke and the availability of a safer-than-warfarin anticoagulant in the form of dabigatran, a direct thrombin inhibitor, is an important development.

The effective level of anticoagulation with warfarin is difficult to attain in the majority of patients and often results in bleeding complications and hospitalisation for treatment of excessive anticoagulation. Apart from the inadequate stroke prevention due to poor INR control, these hospitalisation events significantly contribute to cost, as do the INR determinations and bleeding complications.

To have a safer and effective alternative is extremely useful and will improve the successful management of these high-risk patients. At present we are very careful of exposing an older patient to warfarin therapy as the bleeding risk may outweigh the potential benefit. With the results of the RE-LY trial, dabigatran provides us with a safe, effective and reliable alternative for these patients.

Dr Jeff King, specialist physician, private practice, Gauteng

Now, for the first time, we have a complement of drugs that can be used effectively to more safely reduce the risk of stroke in AF. While warfarin is cheap, tried and tested, it still has potential cost-ineffective life-threatening complications, of which clinicians are well aware.

There is a clinical need to give earlier and greater attention to the AF co-morbidities as risk managed by the CHA₂DS₂-VASc score. These AF patients that I typically see are identified but not

completely, by the CHA₂DS₂-VASc score, including the middle-aged and elderly patients in whom rhythm disturbances, with lone atrial fibrillation, are a consequence of the ageing process. Secondly, I see diabetics, hypertensives, obese patients, ischaemic heart patients with myocardial dysfunction and idiopathic dilated cardiomyopathy, with or without cardiac failure.

It is important to manage under-recognised aggravating risks such as excessive alcohol intake and obstructive sleep apnoea. Trials are awaited for the treatment of non-valvular associated AF.

A matter of great concern to me is the delayed access or denial of access to these scientifically superior agents for South African patients, due to lack of Medicines Control Council (MCC) approval and consequent non-reimbursement from medical aid funders. The MCC should be proactive in fast tracking the approval of

these highly beneficial drugs, which are already internationally available; circumventing any consequent beguiled health-care funding constraints.

While we are able to consider the use of the 110-mg bid dabigatran dose 'off South African label/registration approvals', there is greater benefit to be derived from the 150-mg bid dose. Sooner MCC approval of these medications would facilitate the enhanced ischaemic stroke protection especially associated with the higher dabigatran dose, with fewer bleeding complications, and with a 59% reduction in ischaemic stroke compared to warfarin.

1. Connolly SJ, *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139–1151.
2. Connolly SJ, Ezekowitz Md, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. *N Engl J Med* 2010; **363**(19): 1875–1876.
3. Dans A, *et al.* Concomitant use of anti-platelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial. Presented at the European Society of Cardiology Congress 2011, 28 August 2011.
4. Reilly P, *et al.* Concomitant use of P-glycoprotein inhibitors with dabigatran or warfarin in the Randomised Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial. Presented at the European Society of Cardiology Congress 2011, 28 August 2011.
5. Lip GY. The role of aspirin for stroke prevention in atrial fibrillation. *Nat Rev Cardiol* 2011; e-pub DOI: 10.1038/nrcardio.2011.112.
6. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healy JS, *et al.* Risk of bleeding with 2 doses of dabigatran versus warfarin in older and younger patients with atrial fibrillation – an analysis of the randomised evaluation of RE-LY trial circulation. *Circulation*; **123**(21): 2363–2372. Epub 16 May 2011.