The Royal Australasian College of Physicians

Review of Anticoagulation Therapies in Atrial Fibrillation

Submission by the Royal Australasian College of Physicians

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Executive Summary

The Royal Australasian College of Physicians (the College) welcomes the opportunity to comment on the review of anticoagulation therapies in atrial fibrillation.

The dabigatran data used for the Pharmaceutical Benefits Advisory Committee (PBAC) submission in 2011 is based upon one clinical trial of dabigatrin versus warfarin in 18,113 patients with atrial fibrillation[1], the RE-LY study (Randomised Evaluation of Long–term anticoagulant therapy) a multi-centre, multinational, randomised parallel group study of two blinded doses of dabigatran (110 mg twice daily and 150 mg twice daily) compared to open-label warfarin in patients with non-valvular atrial fibrillation at moderate to high risk of stroke or systemic embolism. Mortality rates are similar; 4.13% on Warfarin; 3.75% on 110 mg dabigatrin and 3.64% on 150 mg dabigatrin.[2]

There are a number of identified limitations:

- the trial sample size is relatively small and may not be representative of the Australian population.
- the full safety profile is yet to emerge including the effects of concomitant drugs in a trial setting, as they have been extensively studied for warfarin.
- including that gastrointestinal haemorrhage is more frequent compared to warfarin, there is no antidote like vitamin K and the anticoagulant effects are not as easy to monitor routinely compared to warfarin.
- the listing of dabigatran may result in low risk patients currently managed on aspirin or no treatment being unnecessarily transferred to dabigatran at a much higher cost.

Recommendations:

The College recommends that:

- dabigatran may be beneficial in a number of patients who are reluctant to take warfarin because of the stringent monitoring requirements and who find it difficult to maintain a therapeutic INR and interactions with other drugs and foods, but who should be taking oral anticoagulation, and this would likely lead to additional benefits and costs not measured in the trial.

- kidney function and risk of bleeding require monitoring in high risk patients such as the elderly[ii]. The College suggests use of risk scores such as HAS-BLED to predict patients at high risk to have an understanding of the risk predictors for bleeding before making a decision re drug use. At present, there are no evidence based recommendations to adjust drug dose for newer anticoagulants but the lower dose regimen 110mg twice daily for Dabigatran should be used in patients considered at risk. The dose reduction suggestions are mentioned in the company product information sheet. There is a paucity of data in high risk groups and more studies are required.
- caution must be exercised when prescribing based on the fact that there is no antidote to dabigatran, no readily available and validated test of effect and no reversal agent. In patients with urgent surgery dabigatran would need to be ceased and surgery deferred if possible. Also caution would be advised in re introducing these medications post-surgery in patients at high risk of bleed or where bleeding poses a risk such as neurosurgery or TURP. In some of these patients bridging therapy with unfractionated heparin might be advised.
- dabigatran should only be available on authority for patients where warfarin is contraindicated as listed above.
- an adequate monitoring and a continued multidisciplinary education campaign needs to be in place. For example: the hospital discharge summaries must adequately communicate with general practitioners on the continuing treatment regimens with respect to dose and individual patient risk factors.
- an adequate education campaign is launched that captures the entire multidisciplinary team responsible for the post discharge patient. Educational initiatives might include those aimed at the primary care Physician to improve compliance with guidelines, including improved understanding of guidelines and correct use of risk scoring systems for stroke and bleed. Educational initiatives may be directed to patients to improve acceptance of need for treatment and adherence to treatment.
- multidisciplinary team hospital initiated home medication reviews (HIMR) should be implemented for these patients. Education and monitoring with information in discharge summaries should include a summary of the main differences between warfarin and dabigatran. The importance of careful drug adherence is key to minimising the risks of stroke and bleed (particularly given dabigatran will be used twice daily). Links with other multidisciplinary teams such as pharmacy educational resources post hospital and in the community are required.
- dabigatran is only available on authority for patients where warfarin is contraindicated until more data is available in a larger cohort of patients with co morbidities and co medications.

Introduction

Since the 1960s, warfarin has been the only oral anticoagulant drug in regular use for treating patients with thromboembolic disease. In November 2008, the Therapeutic Goods Administration (TGA) approved two new oral anticoagulant drugs – rivaroxaban and dabigatran etexilate – for the prevention of venous thrombosis in patients having elective knee or hip replacement. Dabigatran etexilate is an oral direct thrombin inhibitor that provides anticoagulation at a fixed dose without the need for routine INR ratio tests. The main advantages of dabigatran etexilate and rivaroxaban are a rapid onset of anticoagulant effect, more predictable pharmacokinetics, and a lower potential for clinically important interactions

with food, lifestyle and other drugs. These drugs do not require routine monitoring and dose adjustment as required with warfarin.

Commonly, on the Pharmaceutical Benefits Scheme (PBS), warfarin is prescribed for high-risk patients to prevent strokes, and either aspirin or warfarin is prescribed for moderate-risk patients. However, the disadvantage of warfarin is that it has a narrow therapeutic index and in practice patients must be monitored regularly to ensure their treatment is titrated to an optimum International Normalized Ratio (INR) to balance the risks of stroke and warfarin-related bleeding. In practice, patients achieve optimum control only 50-60% of the time and warfarin remains a major contributor to drug-related hospitalisations in Australia. Treatment with less expensive vitamin K antagonists, such as warfarin, can reduce the risk of stroke in patients with atrial fibrillation.

Warfarin places a considerable burden on patients and prescribers through:

- the need for frequent blood monitoring especially for patients living in rural or regional areas;
- fear of treatment-related bleeding, including difficult to treat and disabling stroke and major bleeds;
- requirements for patients to follow specific and consistent diets due to drug-food interactions; and
- interactions between warfarin and many common medicines.

Dabigatran etexilate was TGA registered on 24 November 2008 for the prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement).

As at 29 April 2011, dabigatran etexilate TGA registered indications were extended to include for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke**.**

The PBAC has raised some concerns about listing dabigatrin on the PBS based on results of only 18,113 patients (~9000 in each arm) that may not reflect the Australian population and may lead to the medicine being over prescribed without an adequate education campaign. Moreover; the effects of concomitant drugs are yet to be evaluated for dabigatran as they have been for warfarin. These risks are expanded upon below.

Risks and Adverse Events of warfarin vs. dabigatrin

There needs to be caution before the newer anticoagulants are freely prescribed on the PBS like warfarin. The potential pitfalls and considerations until more extensive data are available include:

- dabigatran is a new medicine and like all new medicines the full range of side effects is not yet known.
- the rate of major bleeds on warfarin is 3.57% versus 2.87% on 110 mg Dabigatrin and 3.32 % on 150 mg Dabigatrin. The higher doses are required to reduce the rate of stroke but expose the patient to the risk of bleeding. Although, specialised coagulation tests can be used to determine bleeding risk. The full safety profile of dabigatran is yet to be established in patients at high risk of bleeding, and follow-up data is limited to 2 years.[2]

- gastrointestinal bleeding was lower with warfarin. Gastrointestinal (GI) haemorrhage occurred at a higher frequency with dabigatrin etexilate compared to warfarin. The underlying mechanism of the increased rate of GI bleeding has not been established.

- dabigatran etexilate subjects had a lower incidence of fatal adverse events (AEs), life-threatening AEs, and events that required hospitalisation as compared to warfarin subjects. The incidence of AEs was similar between subjects treated with dabigatran etexilate 110 mg twice daily and dabigatran etexilate 150 mg twice daily (78.6% and 78.3%, respectively) versus 75.9% of subjects treated with warfarin[3].

- the incidence of SAEs was similar across treatment groups. However, dabigatran etexilate subjects had a lower incidence of fatal AEs, life-threatening AEs, and events that required hospitalisation as compared to warfarin subjects.

- the INR test is unreliable in patients taking dabigatran and false positive INR elevations have been reported. Therefore, INR tests should not be performed. Tests of anticoagulant activity such as thrombin time (TT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) are available to detect excessive dabigatran activity.

- there is increased risk of bleeding relating to the use of dabigatran (Pradaxa®) the TGA therefore advises that kidney function should be assessed in all at risk patients (e.g.>75 years).[4]

- dabigatran is associated with an increased risk of myocardial infarction or acute coronary syndrome.[5]

In summary, dabigatran is of similar overall safety to adjusted-dose warfarin, i.e. superior in terms of life-threatening and minor bleeds and inferior in terms of gastrointestinal adverse events. Dabigatran also causes reduced intracranial bleeding, an important benefit for patients.[2] The safety and efficacy of dabigatran in the prevention of venous thrombosis, however, in patients other than those having arthroplasty remains to be established in clinical trials with a larger cohort of patients.

Cost Implications

First-ever strokes specifically due to atrial fibrillation in 2011 are estimated to cost $314.4 million in the first year and $562.7 million over five years. Treatment is essential to reduce the risk of stroke in people with atrial fibrillation.

The predicted utilisation of dabigatran in the Australian population may be underestimated, particularly if lower risk patients are prescribed the drug. The financial implications were predicted to be greater than $100 million in Year 5, although there would be some savings to with a reduction in INR testing. Dabigatran may be beneficial in non-compliant patients reluctant to take warfarin; those who are rural and INR testing is problematic.

Warfarin monitoring and bleeding in atrial fibrillation costs patients and the Australian health care system over $95 million annually, including costs of INR testing, treatment of bleeds and patient travel/time costs. There are additional associated travel costs for patients in rural and regional areas.

References

[1]Connolly SJ., et al; Dabigatrin versus warfarin in patients with atrial fibrillation. N Engl J Med 361: 1139-51,2009.
[2] Wallentin L., et al;[2] Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. The Lancet 376: 975-983, 2010.[2]
[3] http://www.nps.org.au/health_professionals/publications/nps_radar/2011/august_2011/dabigatran_af (accessed Feb 15, 2012)

[4] http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111005.htm (accessed 15 February 2012).
[5] Uchino K, Hernandez A. Dabigatran Association With Higher Risk of Acute Coronary Events Meta-analysis of Noninferiority Randomized Controlled Trials. Arch Intern Med. 2012.