What do we know about dabigatran (Pradaxa®▼)?

This special supplement to our Newsletter looks at the use of dabigatran for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) and summarises the issues associated with the introduction of dabigatran prior to NICE consideration.

Dabigatran (Pradaxa®▼) has been recently licensed for stroke prevention in people with non-valvular AF with one or more of the following risk factors:
- Previous stroke, TIA or systemic embolism
- LVEF < 40%
- Symptomatic heart failure ≥ NYHA Class 2
- Age ≥ 75 years
- Age ≥ 65 years with either diabetes, coronary artery disease or hypertension

Dabigatran has been available for some time with a licence for prevention of venous thromboembolism following knee- or hip-replacement surgery.

AF is the most common clinically significant sustained cardiac arrhythmia. Stroke and thromboembolism are the main complications of AF. Overall, people with AF have a 4 to 5-fold greater risk of stroke and thromboembolism than people without AF. AF is thought to cause a fifth of all strokes in the UK, and thus it’s detection and treatment, particularly in older patients, is very important. The most effective treatment to prevent stroke in patients with AF is anticoagulation.

The 2006 NICE Clinical Guideline on AF currently advises that people with AF should undergo assessment to ascertain their stroke-risk.1 People at high risk of stroke should be offered warfarin; those at moderate risk of stroke should be offered aspirin or warfarin; and those at low risk should be offered aspirin.1

What do we know about dabigatran?

Dabigatran is a direct thrombin inhibitor. It received it’s licence for use in AF on the basis of the results from the RE-LY trial.2 Other new oral anticoagulants (factor Xa inhibitors) are likely to be licensed for the same indication within the next 1-2 years.

Our advice

NICE is expected to publish a Technology Appraisal on dabigatran for stroke prevention in AF in December 2011.3 Until NICE publishes guidance, we recommend that warfarin should remain first line for anticoagulation with dabigatran being reserved for those patients:
- In whom warfarin is contraindicated
- Who cannot tolerate warfarin
- Who cannot achieve a stable INR, despite best efforts
- Who are at increased risk of drug interactions with warfarin

Please note: Sub-optimal compliance with warfarin alone is not an indication for changing therapy to dabigatran as many of the causes of non-compliance with warfarin may also result in non-compliance with dabigatran (e.g. alcoholism, chaotic lifestyle, wilful non-compliance). Indeed, given the short half-life of dabigatran, poor compliance could lead to worse anticoagulation.

Patients on warfarin with good INR control will derive little benefit by switching to dabigatran.4

Prescribers should fully document the reasons for using dabigatran in preference to warfarin.

Patients should NOT be referred to secondary care in order to obtain the drug.

Why should we be cautious about the prescribing of dabigatran?

1. Dabigatran is a black triangle drug so all adverse effects should be reported to the CSM on Yellow Cards.
2. No long-term (> 2 years) safety data is currently available for dabigatran.
3. Dabigatran is a potent anticoagulant, thus caution should still be exercised in those at elevated bleeding risk, particularly very elderly or frail patients in whom bleeding complications may be serious.5,6
4. RE-LY excluded patients with artificial heart valves, previous severe stroke< 6 mths, high bleeding risk, previous GI haemorrhage< 12 mths, severe hypertension> 180/100mmHg, contraindications to warfarin and eGFR< 30mls/min. Thus safety data in such populations are not available.
5. Although intra-cranial haemorrhage was reduced by dabigatran compared with warfarin, GI bleeding was
more common with the 150mg bd dose and dyspepsia was more common with both doses (likely due to the tartaric acid core within the dabigatran pellets).

6. Serious bleeding secondary to anticoagulation is the greatest safety concern for patients and prescribers. Unlike warfarin which can be reversed by vitamin K or PCC, at present there is no specific antidote to dabigatran (specialist haematology advice +/-dialysis may be required).

7. As yet, there are no published studies on the cost-effectiveness of dabigatran for the prevention of stroke and systemic embolism in AF. This will be considered by NICE.

8. Dabigatran carries a significant cost impact.

**FAQs about dabigatran**

**How does dabigatran work?**

Dabigatran (Pradaxa®) is an anticoagulant. It is formulated as the pro-drug dabigatran etexilate and is converted to dabigatran in the plasma and liver. Dabigatran binds directly and reversibly to thrombin to inhibit its actions and interrupts the formation of blood clots. The recommended dose is 150mg twice daily (110mg twice daily in patients over 80 years, or >75 years at increased bleeding risk). Dabigatran is 80% excreted by the kidney.

**What guidance is already available about dabigatran?**

NICE is expected to publish a Technology Appraisal on dabigatran for stroke prevention in AF in December 2011. The NICE appraisal Committee published its preliminary recommendations in August 2011 and was “minded NOT TO RECOMMEND the use of dabigatran for the prevention of stroke and systemic embolism in people with AF” but requested several further cost effectiveness analyses.

The Scottish Medicines Consortium (SMC) accepts the use of dabigatran in the NHS in Scotland in patients with non-valvular AF with one or more of the risk factors stated above.

**What is known about using dabigatran in elderly patients or those with co-morbidities?**

- Reduce the dose to 110mg twice daily for patients ≥ 80 years.
- Dabigatran is contraindicated in severe renal impairment (CrCl ≤ 30ml/min).
- Consider prescribing the lower dose (110mg twice daily) for patients with moderate renal impairment (CrCl 30-50ml/min) or those at higher risk of major bleeding.
- Patients with conditions associated with a very high risk of bleeding, particularly GI bleeding, should not receive dabigatran.
- Dabigatran should not be used by patients with liver disease or severe hepatic impairment.

**Is dabigatran easier to take than warfarin?**

Dabigatran is a twice daily dose, whereas warfarin is taken once daily. Dabigatran capsules should be swallowed whole with water. Breaking, chewing or emptying the contents increases the dose absorbed and the risk of bleeding.

**Are there any storage requirements for dabigatran capsules?**

Dabigatran capsules should be stored and dispensed in the manufacturer’s original packaging. Repackaging dabigatran capsules increases the risk of exposure to moisture or humidity, causing product breakdown and loss of potency.

**Do patients on dabigatran require regular testing/monitoring?**

There is no routine monitoring with dabigatran.

**Are there fewer side-effects with dabigatran?**

The following adverse events were noted in the RE-LY study:

- Very common (≥ 1/10): Dyspepsia
- Common (≥ 1/100, < 1/10): dizziness, dyspnoea, peripheral oedema, fatigue, cough, chest pain, back pain, arthralgia, nasopharyngitis, diarrhoea, AF, urinary tract infection, upper respiratory tract infection, ALT or AST > 3 times upper limit of normal, non-serious hepatobiliary disorder.

At the lower dose (110mg twice daily) dabigatran shows a lower risk of bleeds than warfarin; however patients generally require the higher dose to reduce their risk of stroke and at this higher dose (150mg twice daily) the risk of bleeding is the same as that of warfarin.

**What about drug interactions with dabigatran?**

Although dabigatran interacts with a number of medicines, it has fewer clinically important food and drug interactions than warfarin.

- Dabigatran should not be used concomitantly with ketoconazole, ciclosporin, itraconazole and tacrolimus.
- Inadequate clinical data are available regarding the co-administration of dabigatran and dronedarone, and their co-administration is not recommended.
- Dabigatran should be used cautiously in patients taking amiodarone. HIV-protease inhibitors, verapamil, quinidine and clarithromycin. These agents can increase dabigatran plasma levels, and therefore, the risk of bleeding. If co-administering with verapamil, the dose should be reduced to 110mg bd.
- Rifampicin, St John’s wort, carbamazepine and phenytoin may reduce serum dabigatran levels; caution should be exercised.

See the Summary of Product Characteristics for full details of drug interactions with dabigatran (www.medicines.org.uk).

**How much does dabigatran cost?**

Dabigatran costs over £900 per patient per year compared to a cost of approximately £400 per patient per year of warfarin therapy (including monitoring costs). The cost effectiveness of dabigatran in comparison to drug and non-drug costs for warfarin needs to be considered carefully.

**Will we be able to do away with warfarin clinics?**

Warfarin and anticoagulant clinics will still be required as warfarin has a number of uses and dabigatran currently has only a limited licence.
A bit about the RE-LY trial

The Randomised Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial is the only large-scale trial of dabigatran. RE-LY was a drug company-funded phase-III clinical trial that evaluated the non-inferiority of two doses of dabigatran (110mg twice daily and 150mg twice daily) compared with warfarin in people with AF who were at moderate to high risk of stroke. The primary efficacy endpoint of the trial was incidence of stroke and systemic embolism. The primary safety endpoint was major bleeding. The mean age of study participants was 71 years. Over a median 2-year follow-up, the study found that:

- Dabigatran 110mg twice daily was associated with a similar rate of stroke and systemic embolism compared with warfarin, but a lower rate of major haemorrhage.
- Dabigatran 150mg twice daily, as compared with warfarin, was associated with a lower rate of stroke and systemic embolism but a similar rate of major haemorrhage (less intracranial haemorrhage but more gastrointestinal haemorrhage than with warfarin).

Some figures from RE-LY:

In a RE-LY type population, with moderately increased risk of stroke:

172 people would need to be treated with dabigatran 150mg twice daily, instead of warfarin, for one year in order to prevent one stroke or systemic embolism.

625 people would need to be treated with dabigatran 110mg twice daily, instead of warfarin, for one year in order to prevent one stroke or systemic embolism.

Limitations of the RE-LY study:

- RE-LY was open-label so both the participants and the physicians were aware of the treatment allocated (although allocation of dabigatran doses was blinded).
- Treatment for AF may be life-long and currently long-term safety data for dabigatran is lacking. The long-term effects of dabigatran are being evaluated in an ongoing follow-up study (RELY-ABLE). Patients in the study were at moderate to high risk of stroke and so the results are not directly applicable to patient groups at lower risk.

Summary

- Warfarin remains the first-line anticoagulant for the prevention of stroke in patients with AF who are at moderate to high risk of stroke.
- The RE-LY study found that dabigatran 150mg twice daily was associated with a 35% reduction in the primary efficacy endpoint of stroke or systemic embolism compared with warfarin. Dabigatran 110mg twice daily was non-inferior to warfarin.
- The bleeding risk with the 150mg dose of dabigatran was equivalent to that of warfarin therapy (with less intracranial haemorrhage but more gastrointestinal haemorrhage). The 110mg dose of dabigatran had a slightly lower risk of bleeding than warfarin.
- The RE-LY study excluded patients at significant risk of haemorrhage or with contraindications to warfarin thus caution should be exercised in patients at higher bleeding risk especially if frail or elderly.
- Dyspepsia was significantly more common with both dabigatran doses.
- Important differences in the effectiveness of dabigatran were related to the quality of INR control in trial patients. Patients with good INR control did not show reduction in the primary endpoint.
- Dabigatran carries a significant cost impact.
- Unlike warfarin, at present there is no specific antidote for dabigatran.
- No long-term (> 2 years) safety data is currently available for dabigatran.

This newsletter has been produced for GPs and Pharmacists by the Regional Pharmacy and Medicines Management Team. If you have any queries or require further information on the contents of this newsletter, please contact one of the Medicines Management Pharmacists in your local HSCB office.

Eastern Area Office: 028 9055 3784
Northern Area Office: 028 2531 1049
Southern Area Office: 028 3741 4622
Western Area Office: 028 7186 0086
1. NICE. Atrial fibrillation. NICE Clinical Guideline 36 2006;