



Regional Drug and
Therapeutics Centre

DABIGATRAN[▼]

IN ATRIAL FIBRILLATION

BNF Category: 2.8.2
NICE: Due December 2011
PBR Status: In tariff

Dabigatran is a thrombin inhibitor indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Unlike warfarin, it does not require regular monitoring using blood tests. Dabigatran 110mg has been shown to be non-inferior to warfarin in the prevention of stroke and systemic embolism, while dabigatran 150mg has been shown to be superior. Both are associated with lower or comparable levels of bleeding. The adverse effect profile is similar to that of warfarin, but cost, lack of an antidote and relatively short-term safety data are disadvantages.

What is it?

Dabigatran (Pradaxa[▼]) is a potent, competitive, reversible, direct thrombin inhibitor, already marketed for prevention of venous thromboembolic events in adults following elective hip or knee replacement surgery.¹ A license extension was recently granted for the prevention of stroke and systemic embolism (SEE) in adult patients with non-valvular atrial fibrillation (AF) and one or more of the following risk factors: left ventricular ejection fraction <40%, symptomatic heart failure, age ≥75 years, or age ≥65 years associated with one of diabetes mellitus, coronary artery disease, or hypertension.¹ For prevention of stroke and SEE, dabigatran is administered at a dose of 150mg twice daily, but this may be reduced to 110mg twice daily in patients with risk factors for bleeding.¹ Dabigatran does not require any monitoring or regular dose adjustment.²

How effective is it?

The RE-LY non-inferiority study (n = 18,113) is the only published phase III trial to evaluate dabigatran as a thrombo-prophylactic agent in AF.³ Patients were included if they had documented AF and at least one additional risk factor as described in the licensed indication. Participants were randomised to receive dabigatran 110mg or 150mg twice daily in a blinded fashion, or open-label warfarin titrated to achieve an International Normalised Ratio (INR) of 2.0 – 3.0. The primary endpoint was a composite of stroke and SEE, and the median follow-up was two years.

Dabigatran 110mg was found to be non-inferior to warfarin (relative risk of stroke or SEE [RR] 0.90, 95% confidence interval [CI] 0.74 to 1.10, p<0.001 for non-inferiority, number needed to treat to prevent one stroke or SEE [NNT] 321 at two years). Dabigatran 150mg was found to be superior to warfarin (RR 0.65, 95% CI 0.52-0.81, p<0.001 for superiority, NNT=87 at two years). Dabigatran 150mg was also found to be superior to dabigatran 110mg (RR 0.72, 95% CI 0.58-0.90, p=0.004 for superiority, NNT=119).⁴

In several published subgroup analyses of the RE-LY trial no difference in the primary endpoint was observed when patients were stratified by need for cardioversion, previous use of vitamin K antagonists, or prior stroke or transient ischaemic attack.⁵⁻⁷ One subgroup analysis found that dabigatran was more beneficial in populations where INR control had been poor, due to a reduction in vascular events, non-haemorrhagic events and death.⁸

Trial limitations

RE-LY was appropriately designed and powered to determine non-inferiority of dabigatran to warfarin. The subsequent superiority testing was pre-specified, but no statements were made regarding statistical power. The study groups were well balanced at baseline, and the inclusion criteria for the trial match the licensed indication.

Although difficult to avoid, the non-blinded administration of warfarin may have introduced some bias in the reporting of both

outcome events and adverse events (AEs) during the trial. In an attempt to reduce this potential bias, each primary and secondary outcome event was scrutinised by two blinded adjudicators. While dabigatran has been available since 2008 for prevention of venous thromboembolism, experience of its efficacy and safety as a thromboprophylactic agent in AF is limited to the two year duration of RE-LY. An extension study is currently ongoing, and will attempt to address this issue.⁹

The European Society of Cardiology (ESC) published guidance on the management of AF in 2010, recommending use of the CHADS₂ scale to evaluate risk of stroke in AF. The guidance states that an oral anticoagulant such as warfarin should be given to those with a CHADS₂ score of two or more.¹⁰ Around one third of RE-LY participants had a CHADS₂ score of one or less, which may not reflect UK practice.

How safe is it?

Dabigatran 110mg was associated with less frequent major bleeding (RR 0.80, 95% CI 0.70-0.93, p=0.003), major or minor bleeding (RR 0.78, 95% CI 0.73-0.83, p<0.001), and intracranial bleeding (RR 0.30, 95% CI 0.19-0.45, p<0.001) compared with warfarin. Dabigatran 150mg was associated with similar levels of major bleeding to warfarin (RR 0.93, 95% CI 0.81-1.07, p=0.31), but less major or minor bleeding (RR 0.91, 95% CI 0.85-0.96, p=0.002), or intracranial bleeding (RR 0.41, 95% CI 0.28-0.60, p<0.001). Gastrointestinal bleeding was reported more often for dabigatran 150mg than warfarin (RR 1.48, 95% CI 1.18-1.85, p=0.001).

The net clinical benefit outcome (a composite of stroke, SEE, pulmonary embolism, myocardial infarction, death or major bleeding) showed no statistical difference between dabigatran 110mg and either warfarin or dabigatran 150mg. However, dabigatran 150mg showed some benefit over warfarin (RR 0.90, 95% 0.82-0.99, p=0.02).

Other than bleeding the only AE with a significant difference between groups was dyspepsia, which was twice as common with dabigatran 110mg and 150mg than warfarin (11.8% & 11.3% vs. 5.8%, p<0.001). This may be due in part to the tartaric acid content of dabigatran capsules.¹ Dabigatran-treated patients were also more likely to discontinue treatment after one year (Kaplan-Meier estimates 15% & 16% vs. 10% for warfarin, p<0.001) or two years of treatment (21% & 21% vs. 17%, p<0.001).

Boehringer Ingelheim, in agreement with the EMA and MHRA, has issued a [letter](#) to inform healthcare professionals of new recommendations to assess renal function in patients being considered for, or already being treated with dabigatran.¹¹ This follows reports of a number of cases of fatal bleeding, some of which occurred in elderly patients with severe renal impairment, which constitutes a contraindication for this treatment.

There are potential concerns regarding the lack of an antidote for dabigatran, and the potential difficulties in treating any uncontrolled bleeding that may occur.¹²

What other options are there?

In clinical guideline 36 NICE recommends treatment with warfarin for patients with AF who are at high risk of stroke, and warfarin or aspirin in those with moderate risk.¹³ This guideline was first published in 2006 and an update is now planned. A NICE appraisal of the use of dabigatran in AF is currently underway and is expected to be published in December 2011; the preliminary recommendation of the appraisal committee is to not recommend dabigatran for this indication.¹⁴

The factor Xa inhibitors rivaroxaban and apixaban are currently in development for the prevention of stroke in AF, and may represent significant competition for dabigatran if approved. They are expected to launch in late 2011 and late 2012 respectively.¹⁵

Economic Impact

The prevalence of AF is 1,300 per 100,000 people.¹⁶ NICE estimates that about 47% currently receive anticoagulant therapy, with an additional 30% eligible, but not receiving therapy.¹⁷ Every year in England and Wales 130,000 people experience a stroke episode, more than 20% of which are caused by AF.¹⁸

Dabigatran is considerably more expensive than therapy with warfarin or aspirin (see chart below). The difference in cost may be offset to some degree by the reduced need for INR monitoring, which was estimated recently at £426 per patient per year.¹⁹ However warfarin clinics will still need to be maintained, and the cost of running them may not be significantly reduced by switching a proportion of patients to dabigatran.

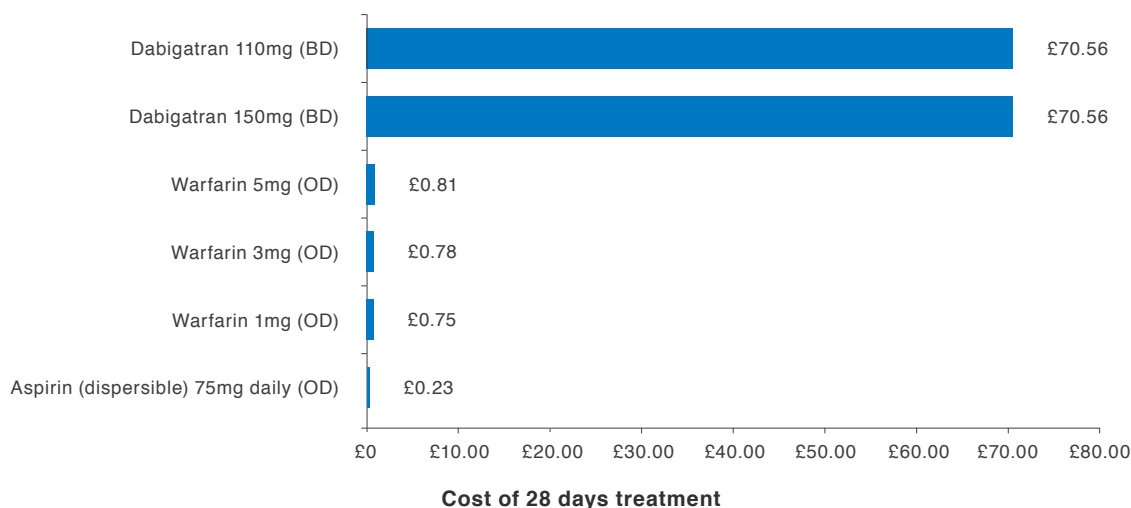
Several cost-effectiveness analyses have been published, with results varying from finding dabigatran highly cost effective to being cost effective only in patients at high risk of stroke or haemorrhage, or whose INR is often outside the therapeutic range.¹⁹⁻²¹ No analyses in UK populations have yet been published.

When should it be used?

Dabigatran may be appropriate for patients who require thromboprophylaxis due to high stroke risk, but for whom warfarin is contraindicated, or who cannot undergo the necessary monitoring. It may also be useful for patients who are currently treated with warfarin but who have difficulty maintaining their INR in the therapeutic range.

How much does it cost?

Cost for 28 days treatment (Drug Tariff/eMIMS October 2011)



REFERENCES

- Boehringer Ingelheim. Summary of Product Characteristics - Pradaxa 110mg hard capsules. Date of revision of text 08/2011.
- Gage BF. Can we rely on RE-LY? The New England Journal of Medicine 2009;361:1200-2.
- Connolly SJ et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. The New England Journal of Medicine 2009;361:1139-51.
- Connolly S et al. Supplementary Appendix to: Newly identified events in the RE-LY trial. N Engl J Med 2010;363:1875-6.
- Nagarakanti R et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation 2011;123:131-6.
- Ezekowitz MD et al. Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation. Circulation 2010;122:2246-53.
- Diener H-C et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurology 2010;9:1157-63.
- Wallentin L et al. 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. Lancet 2010;376:978-83.
- ClinicalTrials.gov. RELY-ABLE Long Term Multi-center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed RE-LY Trial. NCT00808067.
- Camm AJ et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). European Heart Journal 2010;31:2369-429.
- MHRA. Information sent to healthcare professionals in October about the safety of medicines. (Pradaxa) Dabigatran. 28 October 2011. <http://www.mhra.gov.uk/home/groups/pl-p/documents/websitesources/con134763.pdf>.
- del Zoppo GJ et al. New Options in Anticoagulation for Atrial Fibrillation. The New England Journal of Medicine 2011;Epub ahead of print, August 2011.
- NICE. CG36 The management of atrial fibrillation. 2006.
- NICE. Atrial fibrillation - dabigatran etexilate. <http://guidance.nice.org.uk/TA/Wave21/10>.
- UKMI. New Drugs Online. <http://www.ukmi.nhs.uk/>.
- England Level QOF Tables 2008/09 - prevalence. <http://data.gov.uk/>
- NICE. Assumptions used in estimating a population benchmark <http://www.nice.org.uk/usingguidance/commissioningguides/anticoagulationtherapyservice/popbench.jsp>. Accessed 25/08/11.
- NICE. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. Final scope. June 2011.
- West Yorkshire Cardiac Network. Economic Appraisal of Dabigatran Etxilate 150 mg Compared to Warfarin or Aspirin in Patients with Atrial Fibrillation. Updated report February 2011.
- Sorensen SV et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. Thrombosis and Haemostasis 2011;105:908-19.
- Shah SV et al. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. Circulation 2011;123:2562-70.

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