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Dabigatran etexilate for stroke prevention in patients with atrial fibrillation

Contents

Background	5
Current treatments	5
Dabigatran etexilate	7
Clinical efficacy	9
Critical appraisal of RE-LY	13
Guidelines and guidance on use of dabigatran	15
Budgetary implications	18
References	21

Summary

The drug and the review

- Dabigatran etexilate (as mesilate) is an oral antithrombotic agent.
- Dabigatran etexilate 110 mg and 150 mg was approved for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF) with one or more risk factors in August 2011.
- A NICE single technology appraisal for dabigatran etexilate ('dabigatran') is expected in December 2011.
- This review evaluates the evidence to support the use of dabigatran for this indication, and summarises issues associated with introduction of the drug prior to NICE consideration.

Background

- The prevalence of AF is about 1,300 per 100,000 people.
- Current antithrombotic treatments for AF are warfarin, aspirin or clopidogrel; warfarin is the most effective treatment with NNTs to prevent 1 stroke of 33 and 13 for primary and secondary prevention respectively.
- Warfarin requires regular blood monitoring: time in therapeutic range (TTR) is a crucial determinant of effectiveness.

Literature

- Medline, Embase and IDIS databases were searched and Boehringer Ingelheim was contacted for information.
- There is 1 phase III randomised controlled: RE-LY.

Efficacy studies

- The RE-LY study was a phase III clinical trial with a prospective, randomised, open-label, blinded endpoint (PROBE) design. It evaluated non-inferiority of two doses of dabigatran (110mg and 150mg twice daily) compared with warfarin in people with AF at increased risk of stroke.
- The primary efficacy endpoint was the incidence of stroke (including haemorrhagic) and systemic embolism. The primary safety endpoint was major bleeding.

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- Over a median two-year follow-up, dabigatran 110mg was non-inferior to warfarin for stroke and systemic embolism (1.54% per year vs. 1.71% per year respectively, $p < 0.001$). The higher dose was found to be statistically significantly more effective (superior) than warfarin (1.11% per year vs. 1.71% per year, $p < 0.001$). Low dose dabigatran was associated with a reduced risk of major bleeding, whereas there were no significant differences in overall bleeding rates between the high-dose dabigatran and warfarin.
- GI bleeding occurred significantly more frequently compared to warfarin at the 150mg dose only. (110mg: 1.15% per year ($p = 0.52$) and 150mg: 1.56% per year ($p < 0.001$) vs. 1.07% per year). Dyspepsia occurred in 11.8% and 11.3% of patients on dabigatran 110mg and 150mg doses respectively vs. 5.8% for warfarin ($p < 0.001$).
- There was a non-significant increase in the number of myocardial infarctions in patients taking dabigatran compared to warfarin (0.82% for 110mg and 0.81% for 150mg vs. 0.64% ($p = 0.12$)).

Critical evaluation

- The annualised NNTs from the RE-LY trial to prevent 1 systemic embolism or stroke, including haemorrhagic stroke, are 167 for twice daily dabigatran 150mg (superior to warfarin) and 588 for twice daily 110mg (non-inferior to warfarin) for 1 year.
- A network meta-analysis and indirect comparison of dabigatran with warfarin, aspirin and clopidogrel for stroke prevention in AF calculated that dabigatran and warfarin had similar NNTs for stroke prevention compared to no stroke prophylaxis. The NNTs were smaller compared to those for aspirin and clopidogrel.
- For patients who are at high risk of bleeding, GI tolerability may be an issue. The NNHs for a major GI bleed with dabigatran compared to warfarin are 204 with 150mg and 1250 with 110mg.
- The average time in therapeutic range (TTR) with warfarin in the RE-LY study was 64%, although the specific data for the UK centres was 72%. This figure was based on 111 patients in UK centres out of 6022 patients given warfarin so may not be representative. Other UK based studies for TTR in AF patients has ranged from 52% to 63.6%.
- More patients discontinued treatment with dabigatran than warfarin (21% vs. 17% respectively) during the study, which might indicate poorer tolerability or be an artefact of the open-label trial design. There was a slightly higher incidence of discontinuations as a result of serious side effects with dabigatran compared to warfarin.
- The results of this study are not directly applicable to those patient groups who were excluded from the study (e.g. those with recent strokes). RE-LY recruited approximately 2% of patients with a CHADS₂ score of 0 and 30% with a score of 1, as well as those who had a score of 2 and above.
- The study only considered dabigatran treatment for a median period of two years, and thus long-term effectiveness and safety is not yet known.

Safety

- The only adverse event that was significantly more common with both doses of dabigatran than warfarin in the RE-LY study was dyspepsia ($p < 0.001$).
- The rate of GI bleeding occurred significantly more frequently with dabigatran 150mg compared to warfarin.
- Patients taking dabigatran 110mg and 150mg had significantly fewer intracranial bleeds than those on warfarin, including haemorrhagic strokes (0.23% and 0.32% vs. 0.76%, $p < 0.001$) and less life threatening bleeding (1.24% ($p < 0.001$) and 1.49% ($p = 0.03$) vs. 1.85%).
- There is currently no clinical management guideline for bleeding with dabigatran, although a prescriber guide and the Summaries of Product Characteristics have informa-

tion on managing overdose. Dabigatran has a shorter half life than warfarin, it has to be taken twice a day and the coagulopathy is present for a shorter time. Unlike warfarin, dabigatran has no direct reversal agent. However, similar to a bleeding event with warfarin, fresh frozen plasma, prothrombin complex concentrate or recombinant factor VIIa may be given in the case of overdose or life threatening bleeding.

- Dabigatran is a P-glycoprotein substrate and should be used with caution with P-glycoprotein inhibitors (e.g. amiodarone, verapamil) and inducers (e.g. rifampicin, carbamazepine, St Johns Wort), and should not be taken concomitantly with ketoconazole, cyclosporin, itraconazole and tacrolimus.
- Present data does not indicate that dabigatran causes hepatotoxicity. Approximately 2% of patients taking either dose of dabigatran or warfarin in the RE-LY study had ALT or AST >3 times upper limit of normal.

Potential benefits over existing technologies

- INR monitoring is not required.
- Dabigatran has a shorter half life than warfarin (12-14 hours vs. 40 hours) which means that no bridging therapy is required.
- Use of dabigatran may result in easier peri-operative care of AF patients.
- Dabigatran has fewer clinically important food and drug interactions compared to warfarin and has no involvement with CYP450 enzymes.
- Dabigatran has a fixed daily dose compared to a variable dose with warfarin.

Potential disadvantages over existing technologies

- Dabigatran has no direct reversal agent.
- Dabigatran requires twice daily dosing where as warfarin is taken once a day.
- Dabigatran lacks the long term experience of use and safety data that is present with warfarin. The ongoing RELY-ABLE study will gather data on continued use of dabigatran and real world safety data will be collected through GLORIA-AF.
- Whilst the lack of the need to monitor therapy has advantages, it may also create potential problems: the ability to objectively measure anticoagulation and determine adherence with therapy is lost and any currently unknown drug interactions will be hard to assess and could have potentially serious consequences given the inability to monitor the extent of anticoagulation.

Health Economics

- A single cost-utility analysis has been produced to date based on the results of the RE-LY study. The incremental cost per QALY for dabigatran etexilate compared to warfarin is £2,800 if TTR is <56.9%; £5,165 for a TTR between 56.9% and 65.4% and £29,365 if TTR is between 65.4-72.4%. If TTR is >72.4%, warfarin dominates and it is not cost effective to switch to dabigatran. The average incremental cost per QALY was £12,640.

Estimated cost per 100,000 population

- The cost per day is £2.52. The annual cost per patient would be £920.
- The NICE clinical guideline on AF estimates that per 100,000 population about 47% of people with AF receive anticoagulant therapy (611/100,000), whilst another 30% who are eligible (390/100,000) do not.
- Current annual expenditure per 100,000 population on AF patients at risk of stroke who take warfarin and need to attend an anticoagulant clinic is estimated at approximately £250,000 (£409 per patient).
- If the patients with AF who are currently not receiving treatment were to receive dabigatran, the increase in annual expenditure would be £358,000 based on full compliance.

- To prevent 1 systemic embolism or stroke (including haemorrhagic stroke), 167 patients need to be treated with dabigatran 150mg instead of warfarin for 1 year, this would equate to a spend of £153,640.
- The estimated hospitalisation costs for an AF patient admitted with a non-fatal stroke and the mean annual costs of stroke after discharge is £16,641.

Commissioner and provider approaches in the pre-NICE period

- NICE published its preliminary recommendations on 16th August 2011. The Appraisal Committee is minded not to recommend the use of dabigatran etexilate for the prevention of stroke and systemic embolism in people with atrial fibrillation. The Committee requests further information about the licensed regimen, in which people under 80 years begin treatment with dabigatran etexilate 150 mg twice daily, and at 80 years switch to dabigatran etexilate 110 mg twice daily. Boehringer Ingelheim have been asked to provide further information for the second Appraisal Committee meeting in September 2011.
- The cost effectiveness of dabigatran in comparison to drug and non-drug costs for warfarin needs to be considered carefully.
- Despite the potential advantage of dabigatran there remain a number of unknowns related to uptake such as the confidence clinicians and patients will have in an anticoagulant for which efficacy cannot be monitored, and the effectiveness in the real world of an anticoagulant for which adherence cannot be determined.
- In the period between launch of dabigatran and the publication of a NICE single technology appraisal, various approaches are being taken to manage the introduction of the therapy. These include limiting use to groups including those contraindicated to warfarin (as per the SPC), those unable to take warfarin, and those with poor control (defined as TTR<65%). The cost pressures associated with each approach are being mapped by cardiac networks, but there are a number of generic points:
 - It is possible (but not yet demonstrated) that there could be a reduction in non-drug costs associated with use of the dabigatran. However, the fixed costs associated with anti-coagulation services will remain for the foreseeable future given the need to maintain AF patients stable on warfarin and groups with indications other than AF.
 - A cost of £400 per patient per year is stated by NICE for running anticoagulant clinics in primary/secondary care. The costs may be greater if patients are not stable or have to attend anticoagulant clinics more frequently, although given that block contracts are often in place, this may be an overestimate and actual costs could be significantly less than this.
 - Commissioners and providers have differing views as to whether prescribing for patients pre-NICE should be initiated only in secondary care, or whether tailored introduction is possible in primary care.
 - A significant patient lobby for dabigatran is expected at launch and commissioners and providers need to consider how best to handle this development.
- Commissioners need to consider how flexibility is built into anticoagulant clinic contracts for next year, so if patients are prescribed dabigatran, money can be extracted from warfarin services (often block contracted) to assist in paying for the increased drug costs. There are also many anticoagulant services in primary care provided either via GP local enhanced services or community health provider services.
- There are a variety of approaches to managing the use of dabigatran for AF. Any approach which seeks to implement early introduction of dabigatran will cost additional money.

Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the UK. More than 46,000 new cases of AF are diagnosed each year. The prevalence of AF increases with age - at 50-59 years of age, the prevalence is around 0.5%, by 80-89 years of age, the prevalence is around 9%. More men than women have AF, when data are adjusted for age. In UK hospitals, 3-6% of people admitted with acute medical conditions have AF. [1]

Stroke and thromboembolism are the main complications of AF. People with AF have a five-fold greater risk of stroke and thromboembolism than people without AF. Ischaemic strokes in association with AF are often fatal, and those patients who survive are left more disabled by their stroke and more likely to suffer a recurrence than patients with other causes of stroke. [2] The annual incidence of stroke attributable to AF increases from 1.5% in people 50-59 years of age to 23.5% in people 80-89 years of age. Stroke risk is influenced by associated comorbidities, not by the type of AF. Comorbidities include hypertension, diabetes mellitus, congestive heart failure and prior stroke, and the risks are cumulative. [1, 3]

Current treatments

Warfarin, aspirin and clopidogrel are the current antithrombotic treatments for AF. People at low risk of stroke should be offered aspirin, people at high risk of stroke should be offered warfarin and those at moderate risk of stroke should be offered aspirin or warfarin depending on risk factors. [1]

Another method of stroke risk stratification is the CHADS₂ criteria. CHADS₂ is an acronym derived from individual stroke risk factors - see below. Adding together the points from each risk factor provides the total score.

- **Congestive heart failure** = 1 point
- **Hypertension** = 1 point

- **Age older than 75** = 1 point
 - **Diabetes mellitus** = 1 point
 - **Previous Stroke or TIA** = 2 points
- If the total score is 0 (low risk) or 1 (moderate risk) the recommended treatment is aspirin, if the score is 2 or more, then warfarin should be prescribed (if there are no contraindications). [1]

The European Society of Cardiology published updated guidelines for the management of AF in October 2010. [2] In these guidelines they have modified the CHADS₂ criteria to give a more detailed risk assessment. The more refined tool clarifies the most appropriate antithrombotic if the CHADS₂ score is 1. CHA₂DS₂-VASc is a risk factor based approach that can be used for patients with non-valvular AF, it can be used in conjunction with CHADS₂. The score (out of 9) determines whether or not to anticoagulate.

- **Congestive heart failure/LV dysfunction** = 1 point
- **Hypertension** = 1 point
- **Age ≥ 75** = 2 points
- **Diabetes mellitus** = 1 point
- **Stroke/TIA/thromboembolism** = 2 points
- **Vascular disease** (prior myocardial infarction; peripheral artery disease, aortic plaque) = 1 point
- **Age 65-74** = 1 point
- **Sex: female** = 1 point

The scores for deciding whether or not to use antithrombotic therapy have remained the same, however the recommendations have changed - see table 1.

An assessment of bleeding risk should also be undertaken before starting anticoagulation. A simple bleeding risk score has been developed for use in AF patients - HAS-BLED, to help guide choice of therapy. [2]

- **Hypertension** = 1 point
- **Abnormal renal and liver function** = 1 point each.

Table 1 – scores and risk factors for deciding whether or not to use antithrombotic therapy

Number of risk factors	Recommended anticoagulant
Score is ≥ 2 1 major risk factor (prior stroke, TIA, thromboembolism or ≥ 75 years) or ≥ 2 clinically relevant non-major risk factors (heart failure, hypertension, diabetes, female sex, age 65-74 years or vascular disease)	Oral anticoagulation, such as warfarin adjusted to INR 2-3 is recommended.
Score is ≥ 1 1 clinically relevant non-major risk factor	Oral anticoagulation or aspirin 75-325mg daily. The preferred choice is to use oral anticoagulation rather than aspirin.
Score is 0 No risk factors	Use either aspirin 75-325mg daily or no antithrombotic therapy. The preferred choice is to use no antithrombotic therapy rather than aspirin.

- **Stroke** = 1 point
 - **Bleeding** = 1 point
 - **Labile INRs** = 1 point
 - **Elderly (>65 years)** = 1 point
 - **Drugs or alcohol** = 1 point each
- A score of ≥ 3 indicates 'high risk' and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with warfarin or aspirin. Many of the risks for stroke and bleeding are the same, so it is important to separate GI bleeding as a potential risk factor, rather than the HAS-BLED score alone.

In patients with AF, warfarin prevents 64% of strokes, however due to several factors it is prescribed to only two thirds of appropriate candidates. Factors precluding use include drug and dietary interactions, inconvenience of INR monitoring and risk of haemorrhage. [4] Time within the therapeutic INR range (TTR) with warfarin varies widely among individuals, centres and countries. In a post-hoc analysis of a clinical trial comparing warfarin with clopidogrel and aspirin involving 526 centres in 15 countries, the mean TTR in the UK centres was 75% (range 46%-78%), however, this study was stopped early. [5] A record linkage study in 1,513 UK patients with non-valvular AF treated with warfarin for a minimum of 6 months, showed that maintaining an INR within the range 2.0

3.0 for 6 months was only achieved by 52% of patients. [6] A systematic review and meta-analysis looking at the effect of setting, monitoring intensity and patient experience on anticoagulation control worldwide, considered 22 studies where target INR was 2.0 to 3.0 and found the mean TTR was 61.3%. [7] A systematic review and meta-regression study reviewed published randomised or cohort clinical trials that measured INRs serially in anticoagulated patients and reported the proportion of time patients spent between within the range 1.8-2.0 and 3.0-3.5. Overall, patients were in their therapeutic range 63.6% of the time (range 61.6-65.6%). The study authors concluded that patients who receive anticoagulation therapy spend a significant proportion of their time out of the therapeutic range. [8]

Antiplatelet treatment with aspirin is much less effective than warfarin, it reduces the risk of stroke by about a fifth compared with placebo. [9] Adding clopidogrel to aspirin improves the effectiveness of antiplatelet treatment to prevent stroke (although the combination remains significantly less effective than warfarin), however the significant increase in major bleeding with the combination is such that it is not recommended routinely within national and

international guidance. [10, 11] Current guidelines recommend warfarin for patients with atrial fibrillation at high risk of stroke (previous stroke or embolism or more than one of the following risk factors: age ≥ 75 years, hypertension, diabetes, or congestive cardiac failure), either aspirin or warfarin for those at moderate risk (only one stroke risk factor), and aspirin for patients at low risk for stroke (no stroke risk factors). [12]

Dabigatran etexilate

Dabigatran etexilate (as mesilate) is an orally active antithrombotic agent which is a prodrug. It is converted to its active form dabigatran by a serum esterase which is independent of cytochrome P450. Dabigatran is a specific and reversible direct thrombin inhibitor. Thrombin is a key enzyme in blood clot formation at the end of the coagulation cascade. [3, 13, 14] Dabigatran has a half life of 12-14 hours and approximately 85% is excreted by the kidney. [13, 14]

Dabigatran etexilate (as mesilate) 75mg and 110mg capsules are already licensed in the UK at doses of 150mg and 220mg once daily for the primary prevention of venous thromboembolic events (VTE) post (elective) total hip and knee replacement surgery but not stroke prevention in patients with AF. [13, 15] In August 2011 the European Commission approved a new indication for dabigatran etexilate 110mg and 150mg twice daily for prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

- previous stroke, transient ischemic attack, or systemic embolism (SEE),
- left ventricular ejection fraction $< 40\%$,
- symptomatic heart failure, \geq New York Heart Association (NYHA) Class 2,
- age ≥ 75 years,
- age ≥ 65 years associated with

one of the following: diabetes mellitus, coronary artery disease, or hypertension. [13, 14]

The recommended dose of dabigatran is 300mg taken as 150mg twice daily. [14] Patients aged 80 years or above should be treated with 220mg taken as 110mg twice daily due to the increased risk of bleeding in this population. [13] Patients who are concomitantly taking verapamil should also use 110mg twice daily. Dabigatran and verapamil should be taken at the same time. [13]

The FDA and Health Canada licensed dabigatran etexilate 150mg but not 110mg for stroke prevention in patients with AF in October and November 2010 respectively. [16, 17] The reasons for the FDA decision were explained in an article in the New England Journal of Medicine in April 2011. The authors summarise all the analyses and considerations that took place and state that the decision to only approve the higher dose was taken because they could not find any subgroup in which use of the lower dose would represent an advantage. [18] The review that the FDA prepared on dabigatran also highlighted that a superiority claim over warfarin should not be granted. This is because there were concerns about granting a superiority claim based on the results of a single, open-label study. Much of the evidence for reduction in stroke/systemic embolism in the 150 mg arm vs. warfarin arm is driven by subjects at sites with poorer INR control. The review states that although the findings in subjects at centres achieving levels of INR control above the median are still supportive of efficacy, they are not supportive of superiority over warfarin. [17, 19]

There is no experience of dabigatran use in children or adolescents, therefore it can not be recommended due to lack of data on safety and efficacy. Women of child bearing potential should avoid pregnancy during treatment with dabigatran. Studies in animals have shown

reproductive toxicity. There are no clinical data on the effect of dabigatran on infants during breast feeding. Breast feeding should be discontinued during treatment with dabigatran. [13, 14]

Use of dabigatran is contraindicated in patients who have –

- Hypersensitivity to the active substance or to any of the excipients.
- Severe renal impairment (CrCL <30 ml/min).
- Active clinically significant bleeding.
- An organic lesion at risk of bleeding.
- Spontaneous or pharmacological impairment of haemostasis.
- Hepatic impairment or liver disease expected to have any impact on survival.
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole or tacrolimus. [13, 14]

The Summary of Product Characteristics states there is no antidote to dabigatran. [13, 14] Doses of dabigatran beyond those recommended, expose the patient to increased risk of bleeding. In case of an overdose suspicion, coagulation tests can help to determine a bleeding risk. A calibrated quantitative (dTT) test or repetitive dTT measurements allow prediction of the time by when certain dabigatran levels will be reached, also in case additional measures e.g. dialysis have been initiated. Excessive anticoagulation may require interruption of dabigatran treatment. There is no specific antidote to dabigatran. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. Appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescrib-

ers discretion. As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies. [13, 14, 20-22]

Comments received from reviewers highlighted that warfarin is a safe drug other than the bleeding risk and the reversibility of warfarin can be overemphasised. Often by the time warfarin patients with life threatening bleeding reach hospital, and are given appropriate treatment for reversal, many hours have elapsed.

Two case reports published in Archives of Internal Medicine in July 2011 discuss 2 cases of serious bleeding with dabigatran, one fatal, in low body weight elderly patients. [23]

The first case was a woman aged 84, with a body weight of 40kg and poor renal function (CrCl 32ml/min/1.73m²), who was being treated with dabigatran 75mg twice daily for AF; she was also receiving amiodarone. She was admitted with abdominal pain and rectal bleeding, and during the course of her admission developed massive rectal bleeding that was fatal. The second case was also a woman, aged 89, with a body weight of 45kg and CrCL 29 mL/min/1.73 m². She was admitted for removal of a cochlear implant, but reported a 1-week history epistaxis. The surgery was postponed, dabigatran was stopped, and her outcome was favourable. The authors comment that dabigatran is excreted mainly by the kidneys, thus impaired renal function will cause accumulation and is likely to have resulted in the overdoses in both these patients. They note also that there is an interaction between dabigatran and amiodarone that markedly increases dabigatran bioavailability. Finally, they highlight that there is not currently an easy test for dabigatran overdose and no antagonist available. They suggest a need for great caution in giving dabigatran to elderly patients, and encourage reporting of bleeding events.

An accompanying Commentary discusses the report and its implications, calling for further analysis of trial data to clarify the risks and benefits in frail elderly people and those with impaired renal function. Meanwhile, dabigatran and related drugs should be used with caution in such patients. [24]

Interactions/cautions

There is comprehensive information on special warnings, precautions for use and interactions with other medicinal products in the Summary of Product Characteristics. [13, 14] Some of the points are set out briefly below.

- The following treatments are not recommended for concomitant use with dabigatran – unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, prasugrel, dextran, sulfapyrazone and vitamin K antagonists.
- Dabigatran is not metabolised by the cytochrome P450 system and has no effect on human cytochrome P450 enzymes.
- Dabigatran is not recommended in patients with elevated liver enzymes > 2 ULN because no treatment experience is available.
- As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding. Factors, such as decreased renal function (30-50 ml/min CrCL), age ≥ 75 years, low body weight < 50 kg, or strong P-gp inhibitor co-medication (e.g. amiodarone, quinidine or verapamil) are associated with increased dabigatran plasma levels.
- Surgical interventions may require the temporary discontinuation of dabigatran.
- Dabigatran capsules contain the colorant sunset yellow (E110) which may cause allergic reactions.

- NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50% on both dabigatran and warfarin. Therefore, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended.
- Amiodarone, verapamil, quinidine, ketoconazole and clarithromycin are inhibitors of the efflux transporter P-glycoprotein and dabigatran is a substrate of this transporter. Concomitant use is expected to result in increased dabigatran plasma concentrations.
- Rifampicin, St Johns wort, carbamazepine and phenytoin are P-glycoprotein inducers and may reduce the systemic exposure of dabigatran; caution is advised if these products are taken together.
- Dabigatran capsules must be retained in their original packaging until the point of consumption and are therefore unsuitable for repackaging into monitored dosage systems.

Clinical efficacy

The **PETRO study** was a 12 week, phase II, randomised, open label, active control study conducted in Europe and the USA which enrolled 502 adults with paroxysmal persistent or permanent non-rheumatic AF with 1 or more of: hypertension, diabetes, heart failure, previous stroke or TIA, age > 75 yrs, left ventricular dysfunction. Mean age was 71 yrs and 81.9% were men. The study compared several fixed doses of dabigatran (50mg, 150mg or 300mg twice daily) with and without aspirin (81mg or 325mg daily) to warfarin alone in patients with AF to establish a dose response for bleeding events and an upper limit of tolerability based on the frequency of major and clinically significant bleeding events. [25]

Dabigatran 300mg with aspirin had significantly more clinically relevant major bleeding events than dabigatran 300mg without aspirin ($p=0.03$). Dabigatran 50mg had significantly fewer bleeding events than warfarin ($p=0.044$). Increasing dabigatran dose was associated with increased bleeding.

The results also showed that based on bleeding rates and anticoagulant activity, dabigatran 150mg twice daily was well tolerated and effective. Serious liver toxicity was not seen.

The **RE-LY study** was a Phase III clinical trial with a prospective, randomized, open-label, blinded endpoint (PROBE) design. [26] It evaluated the non-inferiority of two doses of dabigatran (110mg and 150mg twice daily) compared with warfarin in people with AF who were at increased risk of stroke. Patients were randomly assigned to treatment by an interactive, automated telephone system. Patients had to have at least one of the following –

- Previous stroke or transient ischaemic attack.
- Congestive heart failure or reduced left ventricular ejection fraction (<40%).
- At least 75 years of age or at least 65 years of age with diabetes mellitus, hypertension or coronary artery disease.

Exclusions from the RE-LY study included –

- Presence of a severe heart-valve disorder.
- Stroke within 14 days or severe stroke within 6 months.
- Increased risk of haemorrhage.
- Creatinine clearance less than 30ml/min or active liver disease.
- Pregnancy.

The primary efficacy endpoint of the trial was incidence of stroke (including haemorrhagic) and systemic embolism. The primary safety endpoint was major bleeding. [26]

Over a median two-year follow-up, the study found that the lower dose of dabigatran was non-inferior to warfarin at reducing the risk of stroke and systemic embolism in people with AF. The higher dose was found to be statistically significantly more effective than warfarin. Low dose dabigatran was associated with a reduced risk of major bleeding, whereas there were no significant differences between the high-dose dabigatran and warfarin.

The RE-LY trial was first published in September 2009. [26] Revised data for the efficacy outcomes was published in November 2010. [27] The detailed results of the RE-LY trial are set out in table 2.

An editorial in the New England Journal of Medicine relating to the RE-LY study reasons that because of dabigatran's twice daily dosing and a greater risk of non-haemorrhagic side effects, patients already taking warfarin with excellent INR control have little to gain by switching to dabigatran. However, many other patients who have AF and at least one additional risk factor for stroke could benefit from dabigatran. [4] Excellent INR control is not defined.

An assessment of the RE-LY trial compared the safety and efficacy of dabigatran with warfarin at different levels of INR control for stroke prevention in AF. The mean time in therapeutic range (TTR) for warfarin patients in the RE-LY ranged from 44% to 77% across 951 centres in 44 countries. The mean TTR for the UK study centres was 72%. This figure was derived from 111 patients from 16 UK centres, out of 6022 patients (1.8%) randomised to warfarin. The benefits of 150 mg dabigatran at reducing stroke, 110 mg dabigatran at reducing bleeding, and both doses at reducing intracranial bleeding versus warfarin were consistent irrespective of centres' quality of INR control. For all vascular events, non-haemorrhagic events, and mortality, advantages of dabigatran were greater at sites with

Table 2 – Efficacy and safety outcomes from the RE-LY trial.

Trial design	2 year, phase III, prospective, randomized, open-label, blinded endpoint study. Conducted worldwide.			
Trial population	18,113 adults with AF and at least one other risk factor for stroke Mean age = 71 yrs 64% were men, mean CHADS ₂ = 2.1			
Treatments	Dabigatran 110mg, n=6015 Dabigatran 150mg, n=6076 Dabigatran given twice daily, blinded treatment Warfarin, n=6022, adjusted to INR of 2 to 3, unblinded treatment Aspirin used by ~40% of patients at baseline and ~20% of patients in all 3 groups by the end of the study.			
Primary efficacy outcome	Stroke or systemic embolism			
Dabigatran 110mg	1.54%/yr p<0.001 vs. warfarin; NNT = 588 Non-inferiority to warfarin shown but not superiority			
Dabigatran 150mg	1.11%/yr p<0.001 vs. warfarin; NNT = 167 Non-inferiority and statistical superiority to warfarin shown			
Warfarin	1.71%/yr			
Other efficacy outcomes				
	Haemorrhagic stroke	Ischaemic or unspecified stroke	Myocardial infarction	Pulmonary embolism
Dabigatran 110mg	0.12%/yr P<0.001 vs. warfarin	1.34%/yr P=0.35 vs. warfarin	0.82%/yr P=0.09 vs. warfarin	0.12%/yr P=0.71 vs. warfarin
Dabigatran 150mg	0.10%/yr P<0.001 vs. warfarin	0.92%/yr P=0.03 vs. warfarin	0.81%/yr P=0.12 vs. warfarin	0.15%/yr P=0.30 vs. warfarin
Warfarin	0.38%/yr	1.21%/yr	0.64%/yr	0.10%/yr
Primary safety outcome	Major bleeding			
Dabigatran 110mg	2.87% per year, p=0.003 vs. warfarin			
Dabigatran 150mg	3.32% per year, p=0.31 vs. warfarin			
Warfarin	3.57% per year			
Other safety outcomes				
	Life threatening bleeding	Intracranial bleeding	Gastrointestinal bleeding	
Dabigatran 110mg	1.24% per year, p<0.001 vs. warfarin	0.23% per year, p<0.001 vs. warfarin	1.15% per year, p=0.52 vs. warfarin	
Dabigatran 150mg	1.49% per year, p=0.03 vs. warfarin	0.32% per year, p<0.001 vs. warfarin	1.56% per year, p<0.001 vs. warfarin	
Warfarin	1.85% per year	0.76% per year	1.07% per year	
Discontinuations	17% of warfarin group (n=1024), 21% on dabigatran etexilate (n=2539)			
Adverse effects	Very common (≥ 1/10): Dyspepsia Common (≥ 1/100, <1/10): dizziness, dyspnoea, peripheral oedema, fatigue, cough, chest pain, back pain, arthralgia, nasopharyngitis, diarrhoea, atrial fibrillation, urinary tract infection, upper respiratory tract infection, ALT or AST >3 times upper limit of normal, non serious hepatobiliary disorder			

Table 3 – Efficacy and safety outcomes in warfarin naïve and experienced patients

	Dabigatran 110mg	Dabigatran 150mg	Warfarin
Primary efficacy outcome			
Warfarin naïve – rate of stroke & systemic embolism	1.57% P=0.65 vs. warfarin	1.07% P=0.005 vs. warfarin	1.69%
Warfarin experienced – rate of stroke & systemic embolism	1.51% P=0.32 vs. warfarin	1.15% P=0.007 vs. warfarin	1.74%
Primary safety outcome			
Warfarin naïve – major bleeding rate	3.11% P=0.19 vs. warfarin	3.34% P=0.55 vs. warfarin	3.57%
Warfarin experienced – major bleeding rate	2.66% P=0.003 vs. warfarin	3.30% P=0.41 vs. warfarin	3.57%
Other safety outcome			
Warfarin naïve – intracranial bleeding rate	0.19% P<0.001 vs. warfarin	0.33% P=0.005 vs. warfarin	0.73%
Warfarin experienced – intracranial bleeding rate	0.26% P<0.001 vs. warfarin	0.32% P=0.001 vs. warfarin	0.79%

poor INR control than at those with good INR control. [28]

A pre-specified substudy of the RE-LY trial compared the results in patients naïve to and experienced with warfarin. 50.4% (9,123) of the trial population were warfarin-naïve and 49.6% (8,989) were warfarin-experienced. The data showed that for patients starting dabigatran without prior warfarin experience and for those switching from warfarin, there was benefit from dabigatran at either dose compared to warfarin. The rate of the primary efficacy outcome (stroke and systemic embolism) was lower with dabigatran, this was statistically significant with 150mg dabigatran. The rate of the primary safety outcome was also reduced with dabigatran. For the patients assigned to warfarin, TTR was 62% for warfarin naïve patients and 67% for those experienced on warfarin. Detailed results are set out in table 3. [29]

A posthoc analysis of patients who underwent cardioversion in the RE-LY study has been published. Data from before, during and 30 days after cardio-

version were analysed. A total of 1983 cardioversions were performed in 1270 patients. Detailed results are set out in table 4. The frequencies of stroke and major bleeding on the 2 doses of dabigatran were low and comparable to those on warfarin with or without transesophageal echocardiography guidance. There was no significant difference in the rate of the primary outcome within 30 days of cardioversion with either dose of dabigatran and warfarin. Dabigatran 110mg significantly reduced the rate of major bleeding whilst the rate of bleeding with dabigatran 150mg was similar to warfarin. The study authors conclude that dabigatran is a reasonable alternative to warfarin in patients requiring cardioversion. [30]

A comment from the reviewers highlighted that there is no data for atrial fibrillation ablation with dabigatran. This procedure is normally performed while patients are fully anticoagulated on warfarin as this improves the embolic stroke risk.

RELY-ABLE is a long term extension of the RE-LY trial focusing on drug safety,

Table 4 - Efficacy and safety outcomes in patients undergoing cardioversion

	Dabigatran 110mg	Dabigatran 150mg	Warfarin
Number of cardioversions performed	647	672	664
Transesophageal echocardiography (positive for left atrial thrombi)	25.5% (1.8%)	24.1% (1.2%)	13.3% (1.1%)
Continuous treatment with study drug \geq 3 wks before cardioversion	76.4%	79.2%	85.5%
Rate of stroke & systemic embolism at 30 days	0.8% P=0.71 vs. warfarin	0.3% P=0.4 vs. warfarin	0.6%
Rate of major bleeding	1.7% P=0.06 vs. warfarin	0.6% P=0.99 vs. warfarin	0.6%

primarily occurrence of major bleeding. Estimated enrolment is 6,200 patients with expected completion of data collection in July 2011. [31]

Critical appraisal of RE-LY

The RE-LY trial has been reviewed and critically appraised. [26, 31-33] The National Prescribing Centre (NPC) produced a review of the RE-LY study and suggests that dabigatran may be an appropriate option for those patients who cannot take warfarin, or undergo the monitoring required, or where control of anticoagulant status is poor, despite best efforts. Dabigatran, unlike warfarin, does not require regular anticoagulant monitoring and it appears to have fewer clinically important food and drug interactions. [26, 32] The same conclusion was reached by the Canadian Agency for Drugs and Technologies in Health in March 2010 which reviewed the clinical trials for dabigatran and rivaroxaban for stroke prevention in patients with AF. [31]

The NPC review of the RE-LY study provides a critical appraisal of the trial [32]:

- More patients discontinued treatment with dabigatran than warfarin (21% vs. 17% respectively) during the study, which might be due to poorer tolerability or be due to the

open-label trial design. A higher incidence of discontinuations that were a result of serious side effects supports this view (2.7% for both doses of dabigatran and 1.7% for warfarin). However, as patients and physicians knew which treatments (dabigatran or warfarin) were being received this may have raised their perception of possible side effects from the newer drug, and decisions to discontinue may have been taken more readily.

- The results of this study are not directly applicable to those patient groups who were excluded from the study (e.g. those with recent strokes). In general, the patients included, who were at moderate to high risk of stroke, are the types of patients for which warfarin can be considered according to the NICE AF clinical guideline. [34] RE-LY recruited approximately 2% of patients with a CHADS₂ score of 0 and about 30% with a score of 1, as well as patients with a CHADS₂ score of 2 and above. The average CHADS₂ score in RE-LY was 2.1.
- In the study, the mean time the INR was in the therapeutic INR range was 64%. This is similar to other contemporary trials of warfarin. An analysis looking at the time the INR was in therapeutic range is discussed above. [28]
- Although, major bleeding was no

more frequent between groups overall, the higher risk of GI side effects (both doses) and GI bleeding with dabigatran at the 150mg dose compared with warfarin raises questions about its use in people who are at high risk of these side effects.

- The study only considered dabigatran treatment for a median period of two years, and thus long-term safety is not yet known. Serious hepatic side-effects were the reason for the withdrawal of the licence for ximelagatran (another thrombin inhibitor) for a similar indication. There were no indications of a difference between treatments with regard to hepatic side effects in the present study, and use in patients with moderate-severe renal impairment is unclear because patients with a creatinine clearance of less than 30ml/min were excluded.
- The numerically greater rate of MIs with high-dose dabigatran serves as a signal of potential long-term safety which will need to be considered. The absolute differences in this study were small; nevertheless, this raises particular concerns about the use of dabigatran in people who are at high risk of coronary heart disease. There are approximately 600,000 adults with AF in England, and a substantial number of myocardial infarctions might therefore result from long-term use of dabigatran in place of warfarin. While the mechanism remains to be ascertained, dabigatran has been reported to increase urinary thromboxane excretion in patients not receiving aspirin, suggesting a paradoxical platelet activation effect. Alternatively, the difference could reflect a protective effect of warfarin against MI. [35, 36] The results of substudy of the RE-LY trial presented at the 2011 International Society on Thrombosis and Haemostasis Congress indi-

cated that there is no evidence that dabigatran is associated with platelet aggregation in patients with AF. [37]

An editorial in the BMJ highlighted that although dabigatran has some benefits over warfarin, evidence on long term efficacy and safety is lacking. [33] A Canadian review of the RE-LY trial published early in 2011 provides a critical appraisal of the data. Based on a number of concerns around absence of blinding in the trial, the increased annualised incidence of intracranial haemorrhage with warfarin and the concomitant use of antiplatelets, the conclusions were –

- Licensing of dabigatran 150 mg BD for atrial fibrillation is premature, pharmacologically irrational and unsafe for many patients.
- The optimal dose of dabigatran for non-valvular atrial fibrillation is not yet clear.
- An independent audit of RE-LY is needed to check for irregularities in conduct, sources of bias and the cause of the unusually high incidence of intracranial haemorrhage in the warfarin arm. In comparable trials with warfarin in AF patients, annualised incidence of intracranial haemorrhage has ranged from 0.28% to 0.53%.
- An independently conducted double-blind RCT comparing dabigatran with warfarin in patients with non-valvular atrial fibrillation is required.
- Taking antiplatelet drugs in combination with oral anticoagulants doubles the incidence of major bleeding events. [17]

Although the RE-LY study continued for a median of 2 years, the NNTs have been annualised. The NNTs for twice daily 150mg dabigatran (superior to warfarin) and 110mg dabigatran (non-inferior to warfarin) are set out in table 5. [26, 27]

Table 5 – Annualised NNTs for twice daily 150mg and 110mg dabigatran

	Dabigatran 150mg	Dabigatran 110mg
Prevent 1 systemic embolism or stroke (including haemorrhagic stroke)	167	588
Prevent 1 non-haemorrhagic stroke	345	769
Prevent 1 haemorrhagic stroke	357	385
Prevent 1 major bleed	400	143

A systematic literature review and network meta-analysis to synthesise the efficacy and safety data of treatments used in the prevention of stroke and systemic embolism in AF patients was published in 2010. This approach was taken as assessing the safety and efficacy of dabigatran in a head to head study versus aspirin with or without clopidogrel and placebo in a clinical trial would be unethical given the existing evidence base. The statistical analyses calculated NNTs for stroke, systemic embolism, mortality and acute myocardial infarction for dabigatran with other antiplatelet agents and placebo – see table 6. [38]

The results indicate that one stroke of any type will be avoided for every 16, 18 or 19 patients treated with dabigatran 150mg, 110mg and warfarin respectively compared with patients not

receiving any stroke prophylaxis. The results show there is indirect evidence that treatment with dabigatran reduces the risk of stroke, systemic embolism and mortality compared with aspirin, aspirin plus clopidogrel and placebo in patients with AF. [38]

Guidelines and guidance on use of dabigatran

Review of the NICE AF guidance is under discussion and use of dabigatran in England and Wales will be addressed by the NICE single technology appraisal guidance expected by December 2011. NICE will produce criteria for use based on clinical and cost effectiveness. The Appraisal Committee's preliminary recommendations were published on 16 August 2011. [39]

Table 6 – NNT point estimates and 95% confidence intervals for stroke, systemic embolism, mortality and acute myocardial with dabigatran, warfarin, aspirin and clopidogrel over placebo

	Dabigatran 150mg	Dabigatran 110mg	Adjusted dose warfarin	Aspirin	Aspirin + clopidogrel
All stroke	16 [10, 37]	18 [11, 51]	19 [11, 56]	36 [16, -143]	33 [15, -159]
Ischaemic stroke	18 [13, 33]	21 [14, 43]	20 [14, 38]	27 [16, 107]	37 [18, -3,498]
Systemic embolism	112 [61, 762]	116 [62, 998]	121 [63, 1363]	156 [68, -544]	477 [87, -137]
Mortality	27 [15, 117]	29 [16, 150]	35 [18, 524]	43 [19, -141]	36 [17, -299]
Acute MI	294 [58, -97]	324 [59, -93]	147 [51, -163]	548 [61, -78]	933 [61, -70]

The Committee is minded not to recommend the use of dabigatran etexilate for the prevention of stroke and systemic embolism in people with atrial fibrillation.

The Committee requests further information about the licensed regimen, in which people under 80 years begin treatment with dabigatran etexilate 150 mg twice daily, and at 80 years switch to dabigatran etexilate 110 mg twice daily. The manufacturer of dabigatran etexilate should provide the following for the second Appraisal Committee meeting (20 September 2011):

- A cost-effectiveness analysis of the sequential regimen outlined above, comparing dabigatran etexilate with warfarin using relative risks from the whole RE-LY trial population rather than from the post hoc subgroup analysis. The analysis should include sensitivity analyses using a range of assumptions of international normalised ratio (INR) monitoring costs such as those used by the Evidence Review Group (ERG) (£279.36, £241.54 and £115.14) in addition to the cost stated in the manufacturer's submission (£414.90).
- A cost-effectiveness analysis of the sequential regimen outlined above, comparing dabigatran etexilate with warfarin and including sensitivity analyses using a range of assumptions of INR monitoring costs and the assumptions suggested by the ERG:
 - a patient cohort representing people with AF in the UK. [40]
 - a variable (per patient) cost of £115.14 for anticoagulant monitoring.
 - people have dyspepsia throughout dabigatran etexilate treatment, not just in the first 3 months of treatment.
 - disability & mortality risks after stroke are treatment-independent.
 - disutility associated with dabiga-

tran etexilate during the first 12 months of treatment as used in the RE-LY quality of life sub-study (the details are academic-in-confidence).

- Further comment and consideration of the cost effectiveness of dabigatran etexilate in the subgroup of people who are already well controlled on warfarin. [39]

In anticipation of dabigatran being licensed and launched, recommendations for the use of dabigatran were incorporated into the most recent European Society of Cardiology updated guidelines for the management of AF - see table 7. [2] Following a CHADS₂ score of >1 and then a CHA₂DS₂-VASc assessment where an oral anticoagulant is recommended, dabigatran may be considered as an alternative to adjusted dose warfarin therapy.

The 2010 Canadian Cardiovascular Society AF guidelines make similar recommendations to the European guidance - see table 8. One major difference is in patients who have stable coronary artery disease. The guidelines state that given the benefits of warfarin for the reduction of coronary events, which can be substantial in those patients at higher risk, when oral anticoagulation is indicated to prevent stroke in those who have AF and are also at high risk of a coronary event (e.g. those without evidence of coronary artery disease whose Framingham risk is 2% per year, those with stable coronary artery disease with high risk features and those with or ACS in recent months) it seems prudent to recommend warfarin in preference to dabigatran. [41]

The NHS North East Treatment Advisory Group (NETAG) produced guidance on use of dabigatran for prevention of stroke in non-valvular AF in July 2011. [42] NETAG recommended use for the following patient groups -

Table 7 – European Society of Cardiology guidelines for dabigatran use

Risk factors / Risk of bleeding	Use of dabigatran
Low risk of bleeding (e.g. HAS-BLED score of 0-2)	Dabigatran 150 mg twice daily may be considered, in view of the improved efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and similar rates of major bleeding events, when compared with warfarin).
Measurable risk of bleeding (e.g. HAS-BLED score of ≥ 3)	Dabigatran 110 mg twice daily may be considered, in view of a similar efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and of major bleeding compared with warfarin).
One 'clinically relevant non-major' stroke risk factor	Dabigatran 110 mg twice daily may be considered, in view of a similar efficacy with warfarin in the prevention of stroke and systemic embolism but lower rates of intracranial haemorrhage and major bleeding compared with the warfarin and (probably) aspirin.
No stroke risk factors (e.g. CHA ₂ DS ₂ -VASc = 0)	Either aspirin 75–325 mg daily or no antithrombotic therapy is recommended. Where possible, no antithrombotic therapy should be considered for such patients, rather than aspirin, given the limited data on the benefits of aspirin in this patient group (i.e. lone AF) and the potential for adverse effects, especially bleeding

Table 8 – Canadian Cardiovascular Society guidelines for dabigatran use

Risk factors / Clinical setting	Use of dabigatran
Low or moderate risk of stroke (CHADS ₂ = 1 or ≥ 2).	Warfarin [INR 2 to 3] or dabigatran recommended. Dabigatran is preferred to warfarin and dabigatran 150mg BD is preferred to 110mg BD.
Haemodynamically stable patients with AF or atrial flutter of ≥ 48 hours or uncertain duration for whom cardioversion is planned.	Warfarin [INR 2-3] or dabigatran for 3 weeks before and at least 4 weeks post cardioversion.
Patients with AF or AFL with stable coronary artery disease should have antithrombotic therapy based on the risk of stroke.	Aspirin if CHADS ₂ = 0. Warfarin or dabigatran if CHADS ₂ ≥ 1 . Warfarin is preferred over dabigatran.

- Patients with a clinical contra-indication to warfarin that is not otherwise a contra-indication to anti-coagulant therapy in general. Note that a bleeding risk that would lead to contra-indication of warfarin would also contra-indicate dabigatran.
- Patients who cannot achieve an INR TTR with warfarin of at least 50%. The TTR should only be calculated using a minimum of 5 consecutive months of warfarin therapy. The first month of warfarin therapy following initiation should not be included in TTR calculations.

The UK Clinical Pharmacy Association (UKCPA) published a position statement on the introduction of new oral anticoagulants (NOACs, dabigatran and rivaroxaban) for stroke prevention in AF in July 2011. [43] UKCPA provide the following view –

- Patients with a CHADS₂ / CHA₂DS₂VASc score ≥ 2 should be initiated on warfarin in the first instance stance, unless contraindicated. Selected patients with a score of 1 may also be considered appropriate for oral anticoagulation, under specialist advice.
- until NICE publishes guidance.

- Warfarin remains the agent of choice for stroke prevention in AF
- In the short-term, NOACs should only be considered as an alternative to warfarin for stroke prevention in AF in patients who are:
 - unable to take warfarin due to allergy or contraindications (including active gastrointestinal ulceration, uncontrolled hypertension, liver failure, coagulation disorders, aneurysm, confirmed intracranial or intraspinal bleed, pregnancy);
 - unable to adhere to the monitoring requirements associated with warfarin therapy;
 - unable to achieve an INR within the target therapeutic range (TTR) for a satisfactory period of time after a suitable trial of warfarin.
- Patients currently stable on warfarin therapy should not be considered for a switch to NOACs.
- Prescribing of NOACs should be undertaken only by primary or secondary care clinicians specialising in stroke prevention in AF.

The Midlands Therapeutics Review and Advisory Committee issued commissioning guidance on the use of dabigatran in August 2011. [44] Their recommendations are that warfarin remains the first line option for anticoagulation in patients with AF at a high risk of stroke. Commissioners should ensure optimal existing warfarin therapy services including access to INR clinics, use of computerised decision-support software, and access to drugs such as acenocoumarol for patients allergic to warfarin. In view of the considerable financial implications, dabigatran treatment should only be prescribed for –

- Those patients with co-morbidities who are adherent to warfarin monitoring and lifestyle requirements but need frequent co-prescribed medications that interact with warfarin and affect the patients TTR.

- Those patients who are adherent to monitoring and lifestyle requirements but whose TTR remains unacceptable despite attempts to optimise treatment with warfarin. Commissioners should set the TTR threshold at an affordable level for their local health economy.

Budgetary implications

The cost per day is £2.52. The annual cost per patient is £920.

The West Yorkshire Cardiac Network have conducted an economic appraisal of dabigatran 150mg compared to warfarin or aspirin in patients with atrial fibrillation. [45] The information for dabigatran vs. warfarin was taken from the RE-LY study. The evidence for the efficacy and safety of dose adjusted warfarin (target INR 2.5), compared to 75mg aspirin, came from the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) study. The BAFTA study recruited 973 patients from 260 general practices in England and Wales with AF or atrial flutter aged 75 years or over and followed them for a mean of 2.7 years. The study showed that warfarin was more effective than aspirin in prevention of stroke in people with atrial fibrillation who are aged 75 or over. The frequency of major stroke, arterial embolism, and intracranial haemorrhage (primary events) was significantly lower in patients on warfarin than in those on aspirin (24 vs. 48 primary events, yearly risk 1.8% vs. 3.8%, relative risk 0.48, 95% CI 0.28–0.80, $p=0.003$). [46]

When compared to aspirin, dabigatran 150mg resulted in an incremental cost per QALY of £4,820. This indicates that the higher drug costs are offset by the cost of strokes avoided and dabigatran 150mg is cost effective for patients aged 75 years and over with AF. The appraisal showed that if a patient taking warfarin was able to maintain a TTR of >72.4% or more, then it was not cost-effective

Table 9 - Incremental cost per QALY for dabigatran 150mg compared to warfarin

TTR	Incremental cost per QALY for dabigatran 150mg compared to warfarin
<56.9%	£2,800
56.9%-65.4%	£5,165
65.4%-72.4%	£29,365
>72.4%	Warfarin dominates lower cost and higher QALYs
Study total	£12,640

to switch to dabigatran 150 mg and there is no health gain to offset the higher drug costs. The results for different TTRs are in table 9.

This suggests that prior to a NICE recommendation, it would not be appropriate to switch patients with a TTR >72.4% to dabigatran 150 mg. Patients in the 65.4-72.4% quartile are very close to the NICE cost effectiveness threshold of £30,000 and it may not be appropriate to switch them. The analyses suggest it is cost effective to switch patients with TTR <65.4% to dabigatran 150 mg.

The authors of the document highlight that there are a number of limitations – the analysis is based on subgroup analyses using point estimates for secondary endpoints, together with one way sensitivity analyses. The measure of warfarin control, TTR, is taken as a measure of the clinical effectiveness of warfarin, however, it may reflect differences in overall care between centres. The impact of institutional factors was not addressed but could be very important. Numerous assumptions were made to generalise the data from two clinical studies to the English AF population. [45]

As dabigatran does not require regular anticoagulant monitoring, there could be a reduction in non-drug costs associated with use of the medicine. However, what is uncertain is if dabigatran will require additional consultation time to ensure that patients understand the need to adhere to therapy. Should specific patient

education take place during a normal GP consultation or would this be in the context of an anticoagulant clinic and what would the costs of this be? Good patient information and counselling are crucial with warfarin and this will also apply to dabigatran especially in relation to the lack of long term safety data and uncertainty around reversibility. The costs associated with the current warfarin service will continue due to the need to maintain the existing infrastructure for patients well established on warfarin. Warfarin and anticoagulant clinics will still be required as warfarin has a number of uses aside from atrial fibrillation. The following indications include treatment of deep-vein thrombosis and pulmonary embolism, cardioversion, dilated cardiomyopathy, mural thrombus, coronary artery thrombosis, paroxysmal nocturnal haemoglobinuria as per recommendations by the British Society for Haematology. [47, 48] One view is that it seems unlikely that there will be real cost savings until the evidence for alternatives to warfarin becomes more established. [32]

The prevalence of AF is about 1,300 per 100,000 population. The NICE clinical guideline on AF estimated that about 47% of people with AF receive anticoagulant therapy (611/100,000) however another 30% (390/100,000) are eligible for therapy but do not receive treatment. [34] The average cost of running primary/secondary care anticoagulant clinics is approximately £400 per annum per patient. [34, 49]

The costs may be greater if patients are not stable or have to attend anticoagulant clinics more frequently. There are data that says the setting and model of an anticoagulant clinic plays a big part in the quality and level of anticoagulant control achieved by patients, commissioners need to decide locally how much of the work in introducing dabigatran appropriately is around providing support to clinics achieving lower levels of anticoagulation control, redesigning services and patient pathways, dispelling myths around warfarin use and improving uptake of warfarin to manage their budget. Dabigatran is unlikely to be the solution for poorly performing clinics or non-adherent patients.

Based on the figures above, the following may apply:
 Current annual expenditure on AF patients at risk of stroke -
 611 per 100,000 population on warfarin at a cost of £14/yr = £8,554,
 611 people attending an anticoagulant clinic = £244,400,
 Total costs are therefore approximately £250,000 (£409 per patient).
 If the additional 30% of patients with AF who are currently not receiving treatment were to receive warfarin, the extra cost would be about £161,400. If they received dabigatran instead, the increase in annual expenditure would be around £358,000 based in a fully compliant patient. However, this figure does not include the off-set of acute care costs for stroke, rehabilitation and disability.

To prevent 1 systemic embolism or

stroke (including haemorrhagic stroke), 167 patients need to be treated with dabigatran 150mg instead of warfarin for 1 year, this would equate to expenditure of £153,640. This figure does not include the potential savings through the prevention of acute events nor subsequent rehabilitation and disability costs or cost reduction due to withdrawals from dabigatran.

The West Yorkshire Cardiac Network economic appraisal estimated the costs for non-fatal stroke and other events in AF patients – see table 10. [45]

The estimated hospitalisation costs for an AF patient admitted with a non-fatal stroke and the mean annual costs of stroke after discharge is £16,641.

Commissioners need to consider how flexibility is built into anticoagulant clinic contracts so if patients are prescribed dabigatran, money can be extracted from warfarin services (often block contracted) to assist in paying for the increased drug costs. A reduction in the number of people attending anticoagulant clinics in the short term is not anticipated. As well as anticoagulant clinics in acute hospital trusts, there are also many anticoagulant services in primary care provided either via GP local enhanced services or community health provider services.

Commissioners need to plan to control the introduction of the medicine as patient and clinician expectations are already high and any approach which seeks to implement early introduction of dabigatran will cost additional money.

Table 10 – Estimated costs of hospitalisation due to non-fatal stroke and clinical events in AF patients

Clinical event	Cost
Hospitalisation due to non-fatal stroke	£11,863
Annual costs of stroke	£4,778
Myocardial infarction	£5,141
Systemic embolism	£1,462
Major extracranial bleeds	£1,573
Minor bleeds	£87

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Search strategy:

MEDLINE: DABIGATRAN

EMBASE: DABIGATRAN ETEXILATE/ AND HEART ATRIUM FIBRILLATION/

IDIS: "DABIGATRAN ETEXILATE 20120449" and "FIBRILLATION, ATRIAL 427.3"

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