

## RESEARCH

# Dabigatran etexilate versus warfarin in management of non-valvular atrial fibrillation in UK context: quantitative benefit-harm and economic analyses

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## Abstract

**Objectives** To determine the incremental net health benefits of dabigatran etexilate 110 mg and 150 mg twice daily and warfarin in patients with non-valvular atrial fibrillation and to estimate the cost effectiveness of dabigatran in the United Kingdom.

**Design** Quantitative benefit-harm and economic analyses using a discrete event simulation model to extrapolate the findings of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study to a lifetime horizon.

**Setting** UK National Health Service.

**Population** Cohorts of 50 000 simulated patients at moderate to high risk of stroke with a mean baseline CHADS<sub>2</sub> (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack) score of 2.1.

**Main outcome measures** Quality adjusted life years (QALYs) gained and incremental cost per QALY of dabigatran compared with warfarin.

**Results** Compared with warfarin, low dose and high dose dabigatran were associated with positive incremental net benefits of 0.094 (95% central range -0.083 to 0.267) and 0.146 (-0.029 to 0.322) QALYs. Positive incremental net benefits resulted for high dose dabigatran in 94% of simulations versus warfarin and in 76% of those versus low dose dabigatran. In the economic analysis, high dose dabigatran dominated the low dose, had an incremental cost effectiveness ratio of £23 082 (£26 700; \$35 800) per QALY gained versus warfarin, and was more cost effective in patients with a baseline CHADS<sub>2</sub> score of 3 or above. However, at centres that achieved good control of international normalised ratio, such as those in the UK, dabigatran 150 mg was not cost effective, at £42 386 per QALY gained.

**Conclusions** This analysis supports regulatory decisions that dabigatran offers a positive benefit to harm ratio when compared with warfarin.

However, no subgroup for which dabigatran 110 mg offered any clinical or economic advantage over 150 mg was identified. High dose dabigatran will be cost effective only for patients at increased risk of stroke or for whom international normalised ratio is likely to be less well controlled.

## Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, with an estimated prevalence in the United Kingdom of 10% in patients aged 75 or over and an associated fivefold increase in the risk of ischaemic stroke.<sup>1 2</sup> Bed days for patients with a primary or secondary diagnosis of atrial fibrillation cost the National Health Service (NHS) £1.9bn (£2.2bn; \$2.9bn) in 2008, with outpatient and other inpatient costs totalling £329m.<sup>3</sup>

Warfarin is the mainstay of oral thromboprophylactic anticoagulation treatment.<sup>4</sup> However, patients show considerable variability in their response to warfarin, which, coupled with a narrow therapeutic range, necessitates frequent monitoring and adjustment of dosage to ensure optimal anticoagulation. Deviations outside the therapeutic range (international normalised ratio (INR) 2.0-3.0) increase the risk of both strokes and haemorrhagic events.<sup>5</sup>

Dabigatran etexilate is a new oral direct thrombin inhibitor that may provide an alternative to warfarin; it has the advantage of not requiring regular monitoring. In the multinational, Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, 18 113 patients with non-valvular atrial fibrillation and at least one risk factor for stroke were randomised to one of two doses of dabigatran (110 mg or 150 mg, twice daily) or dose adjusted warfarin.<sup>6</sup> After a median follow-up of two years, the rates of the primary outcome (stroke or systemic embolism) were similar to those for warfarin among

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patients assigned the lower dose but were lower among patients assigned the higher dose (1.11% v 1.71% per year; relative risk 0.66, 95% confidence interval 0.53 to 0.82;  $P=0.0001$ ).

Compared with warfarin, the annual rate of major bleeding was lower among patients assigned dabigatran 110 mg (2.71% v 3.36%; relative risk 0.80, 0.69 to 0.93;  $P=0.003$ ) but similar among those assigned 150 mg. Dabigatran was associated with higher rates of myocardial infarction, but these were not statistically significant.<sup>7</sup>

The US Food and Drug Administration (FDA) was satisfied of the positive benefit to harm balance of dabigatran but failed to identify a subgroup of patients in which the benefit-harm profile was superior for the 110 mg dose compared with the 150 mg dose and consequently approved only the higher dose.<sup>8</sup> However, both doses have been approved by other regulatory authorities, including the European Medicines Agency, which specifies 150 mg twice daily for patients under 80 years of age and 110 mg twice daily for those aged 80 and over or as an option when the thromboembolic risk is considered to be low and the risk of bleeding is high.<sup>9</sup>

Against this background, we describe a quantitative analysis of the trade-off between thrombotic and bleeding risks—events that have differential effects on life expectancy and quality of life—as a basis to guide clinicians' prescribing. We also develop a health economic evaluation to estimate the cost effectiveness of dabigatran in patients with non-valvular atrial fibrillation, given the considerable uncertainty about its cost effectiveness in the UK healthcare setting.

## Methods

We modelled the net benefits and expected lifetime clinical event rates of each dose of dabigatran and warfarin to quantify the benefits and harms of competing treatments, while accounting for uncertainties in parameters.<sup>10 11</sup> We estimated incremental net benefits as the difference between treatments in quality adjusted life years (QALYs), a preference based outcome measure that combines two dimensions of health—life expectancy and health related quality of life.

In the economic analysis, we extended the model to estimate resource use and costs from the perspective of the UK NHS. The primary outcome was the incremental cost per QALY gained.

We developed a discrete event simulation model that considers individual patients, their characteristics, and their experience of clinical events and outcomes according to the passage of time.<sup>12</sup> After each event, a patient's health profile is updated, leading to a new set of probabilities for future events. Costs and QALYs are accrued from the patient's health states and the events that occur.

For each treatment, we generated identical cohorts of 50 000 patients, each assigned an age and health profile defined by the presence/absence (according to the trial protocol<sup>13</sup>) of any of the following characteristics at baseline: hypertension, diabetes mellitus, congestive heart failure, previous stroke, previous transient ischaemic attack, previous myocardial infarction, and previous intracranial haemorrhage (table 1).<sup>6</sup> We assumed health characteristics to be independent in the base case analysis but did a sensitivity analysis to assess the effect of correlation. We used R for all analyses.

## Clinical parameter estimates

We searched Medline, Embase, the Cochrane library, and the FDA and ClinicalTrials.gov websites during July 2010 to

identify relevant trials of dabigatran in atrial fibrillation. We used “dabigatran,” “BIBR 1048,” and “atrial fibrillation” as search terms and identified three phase II trials (PETRO,<sup>26</sup> PETRO-Ex,<sup>14</sup> and NCT01136408<sup>14</sup>) and a single phase III trial (RE-LY).<sup>6</sup> The phase II studies included too few patients receiving the licensed dose and were of too limited a duration (12 weeks) to provide useful data on reduction in stroke event rate. The five year, open label extension to PETRO did not include warfarin as a comparator. We therefore used the RE-LY study for annualised clinical event rates (table 2),<sup>6 14</sup> and the patients modelled consequently represented those of RE-LY (box 1).

Our analysis considered the probability of (and reasons for) discontinuation of treatment to better reflect the “real world” use of oral anticoagulants. At two years, this had occurred in 21% of patients randomised to dabigatran and 17% of those randomised to warfarin.<sup>6 14</sup> We assumed that patients who discontinued dabigatran because of a bleed or who discontinued warfarin (for any reason) had been switched to aspirin. We assumed that patients who discontinued dabigatran for reasons other than bleeds were switched to warfarin, but we tested this in a sensitivity analysis.

Incidence rates for hypertension and diabetes mellitus came from general population data,<sup>29 30</sup> as did age specific mortality rates from non-vascular causes,<sup>31</sup> all with the assumption that these adequately reflect the RE-LY population (table 2). The relative risks of thromboembolic events and bleeds with aspirin (versus warfarin) came from a published meta-analysis of comparative trials.<sup>27</sup> Box 2 lists key modelling assumptions.

## Utility estimates

We took the permanent utility decrement associated with stroke from the results of the European Stroke Prevention Study, using the proportions of disabling and non-disabling strokes from RE-LY (45% of non-fatal strokes are non-disabling). The baseline health state utility for a person with atrial fibrillation (adjusted for age), as well as the decrements associated with other cardiovascular sequelae and haemorrhagic adverse events, came from a report of EQ-5D utility scores elicited from several thousand respondents to the US Medical Expenditure Panel Survey.<sup>15 17</sup> Utility losses in patients receiving warfarin (for example, as a consequence of regular monitoring) and aspirin (assumed to be the same for dabigatran; for example, because of gastrointestinal upset) came from a study of 83 patients with atrial fibrillation.<sup>16</sup> Table 1 shows all utility values; multiple utility decrements for an individual patient are assumed to be additive.

## Resource use and cost estimates

All costs (besides those of dabigatran) are reported in 2009 GBP (£). We inflated costs incurred during the first and subsequent years after stroke or myocardial infarction from 2006/7 prices.<sup>18</sup> Costs included in this figure were ward costs (staffing, equipment, consumables, and overheads) and procedure costs (which also included the cost of hospital drugs), inpatient and outpatient costs, costs of general practitioners' and district nurses' visits, and the costs of other drugs.<sup>18</sup> The costs of pulmonary emboli and transient ischaemic attacks came from NHS reference costs,<sup>19</sup> as did those for managing major and minor bleeds, following the methods and definitions of a report by the National Institute for Health and Clinical Excellence (NICE) on the costing of atrial fibrillation.<sup>20</sup>

Incidences of other adverse events did not differ significantly between treatment groups, so we did not deem attaching a cost

**Box 1: Population modelled**

The population modelled reflected patients in the RE-LY study,<sup>6</sup> who were 63.6% male and 70% white, with a mean age of 71.5 years, a mean weight of 82.6 kg, and no contraindication to anticoagulation. Mean baseline CHADS<sub>2</sub> (Congestive heart failure, Hypertension, Age $\geq$ 75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack) score was 2.1, and 32.4% of patients had a score of 3 or more; 50.4% of patients were naive to vitamin K antagonists.

**Box 2: Assumptions made in constructing model**

- The risk of future cardiovascular events for each simulated patient, at any given time, is determined by their age, current treatment, and CHADS<sub>2</sub> score (a stroke risk index based on age, diagnosis of hypertension, diabetes or congestive heart failure, and previous stroke or transient ischaemic attack,<sup>34</sup>) according to probabilities determined from RE-LY (table 2 $\downarrow$ )
- Clinical event rates (including for myocardial infarction) would remain constant over time, unless a change occurred in one or more of the risk factors
- The rates of discontinuation of treatment in the second year of the RE-LY study persisted for the lifetime of treatment
- The incidence (though not the prevalence) of hypertension and diabetes was the same in patients with atrial fibrillation as in the general population, as were deaths from non-vascular causes

to such events to be necessary. The exception to this is the higher incidence of dyspepsia in the dabigatran groups—11.8% for 110 mg and 11.3% for 150 mg, compared with 5.8% for warfarin—which we accounted for by including the cost of proton pump inhibitors. The proportion of patients taking proton pump inhibitors came from RE-LY, and the number of capsules per patient came from a published cost effectiveness analysis.<sup>21</sup> The relative proportion of patients using proton pump inhibitors in conjunction with aspirin came from a randomised controlled trial of antithrombotic treatments.<sup>28</sup>

We based the costs of warfarin and associated monitoring on a micro-costing analysis of 165 patients with atrial fibrillation included in a six month prospective cohort study, with the cost of starting warfarin excluded from the long term maintenance cost.<sup>22</sup> The average use of aspirin in practice came from a published costing study.<sup>32</sup>

Drug acquisition costs came from the *British National Formulary* and the NICE appraisal consultation document for dabigatran.<sup>23 24</sup> Table 1 $\downarrow$  shows all costs.

**Discounting**

We applied an annual discount rate of 3.5% to costs, life years, and QALYs to reflect time preference but not to discrete clinical events.<sup>25 33</sup>

**Age adjusted dosing**

In age adjusted dosing, patients initially below the age of 80 years start on the 150 mg dose of dabigatran, and those aged 80 or above start on the 110 mg dose. If a person reaches 80 and is still continuing with the 150 mg dose, he or she is then switched to the 110 mg dose. We modelled this regimen in two different ways. Our primary method used the results of a post hoc subgroup analysis,<sup>14</sup> which subdivided people by age. The secondary method used the event rates from the full trial for patients taking either dose.

**Sensitivity and scenario analyses**

We did univariate sensitivity analyses of each parameter in the model to assess the stability of the results when key assumptions are tested. We based ranges for parameters on 95% confidence intervals where available, or, alternatively, on plausible percentage ranges (web extra table A). We tested the possibility that the cost of managing intracranial haemorrhage and gastrointestinal bleeding may be higher with dabigatran than with warfarin, because of the lack of an appropriate reversal agent, by increasing the costs to consider the potential use of

prothrombin complex concentrates (non-activated or activated).<sup>35 36</sup>

Our base case assumes that the benefit of treatment persists for the lifetime of patients. We tested two further scenarios: one in which the benefit persisted for two years and a second in which the benefit decreased linearly to zero over the 10 years after the trial.

We did a probabilistic sensitivity analysis, implementing a Monte Carlo simulation of 2000 sets of simulated parameters (table 1 $\downarrow$ , web extra table B), to estimate the 95% central ranges for clinical event rates and net health benefits. In the economic analysis, we used the probabilistic sensitivity analysis to consider the joint uncertainty in costs and QALYs to estimate the probabilities of dabigatran being cost effective at different thresholds, presented as a cost effectiveness acceptability curve, and in different clinical scenarios.

We did subgroup analyses to calculate the net health benefits (and associated 95% central ranges), the incremental cost effectiveness ratios, and the probability of cost effectiveness, in the following pre-specified populations<sup>14 37-39</sup>: patients aged 75 or older; patients with a CHADS<sub>2</sub> (Congestive heart failure, Hypertension, Age $\geq$ 75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack) score of 2, or a CHADS<sub>2</sub> score of 3 or more; patients who have previously had a stroke or transient ischaemic attack; patients attending trial centres (clinics) reporting mean INR time within the therapeutic range of more (or less) than 65.5%; patients on warfarin whose time within the therapeutic range was more (or less) than 66.8%, compared with the full dabigatran populations (only summary information was available for this calculation); patients with poor renal function as indicated by a low (30-50 mL/min) creatinine clearance; and patients who were naive to vitamin K antagonist treatment.

**Results**

The results of our simulation at two years matched the results of the trial. No value deviated by more than 2.1% (data not shown), a level of variability that would be expected given the stochastic nature of the simulation.

**Clinical outcomes and net health benefit**

In the base case analysis, dabigatran 110 mg and 150 mg twice daily extended life by 1.1 and 2.4 months compared with warfarin (table 3 $\downarrow$ ). The corresponding incremental net benefits were 0.094 (95% central range -0.083 to 0.267) and 0.146 (-0.029 to 0.322) QALYs. Compared with the low dose of

dabigatran, the higher dose was associated with a positive incremental net benefit in 76% of simulations and with a mean value of 0.052 (−0.122 to 0.228) QALYs. Compared with warfarin, dabigatran 110 mg and 150 mg twice daily were associated with positive incremental net benefits in 86% and 94% of simulations.

Lifetime incidences of stroke or systemic embolism were 12.5% lower with dabigatran 110 mg twice daily than with warfarin and 27.4% lower with dabigatran 150 mg twice daily. Incidences of major haemorrhagic events were lower for low dose dabigatran (by 4.0%) but higher for high dose dabigatran (by 8.8%). We found no discernible differences in lifetime incidences of myocardial infarction between the two doses of dabigatran, but these were about 19% higher than for warfarin. Although age adjusted dabigatran dosing was associated with lower bleeding rates, the higher rates of thrombotic events resulted in it being inferior to the 150 mg dose with respect to QALYs and life years gained.

### Costs and cost effectiveness

Total discounted lifetime costs for dabigatran 110 mg and 150 mg twice daily and warfarin were £10 529, £9850, and £6480. These were made up mainly of drug and monitoring costs, which accounted for 47.3% and 44.2% of the overall costs of the two doses of dabigatran compared with 22.4% for warfarin. The costs of managing strokes or systemic emboli accounted for 39.1%, 40.2%, and 57.6% of total costs; the remainder was accounted for by the costs of managing other events.

The incremental cost effectiveness ratio (ICER) for low dose dabigatran versus warfarin was £43 074 per QALY gained; that for high dose dabigatran was £23 082 per QALY gained (table 4). Dabigatran 110 mg twice daily was dominated as a strategy by dabigatran 150 mg twice daily, as it was associated with a worse health outcome (−0.052 QALYs) and higher cost (£679).

### Age adjusted dosing

The use of dabigatran 110 mg twice daily from the age of 80 years was dominated by the 150 mg twice daily dose under both possible modelling methods. In the models based on the post hoc subgroup analysis and using full RE-LY data, the use of the lower dose accrued 0.005 and 0.017 fewer QALYs and cost £62 and £234 more over a lifetime. Compared with warfarin, the ICERs for use of low dose dabigatran in the over-80s were £24 340 and £27 940 per QALY gained for the two methods.

### Sensitivity analysis

The tornado plot (fig 1) indicates the sensitivity of incremental net benefits to stroke rates and the duration of effect of dabigatran. Dabigatran 150 mg twice daily was cost effective at the lower threshold of £20 000 per QALY when we assumed decreases (or increases) in the rates of stroke or vascular death in patients receiving dabigatran (or warfarin) or increases in either clinical event costs or utility losses. Compared with warfarin, the ICER for dabigatran 110 mg twice daily exceeded £32 415 per QALY in all sensitivity analyses (data not shown).

The probabilistic sensitivity analysis (fig 2) indicates that warfarin had the highest probability of being cost effective at thresholds of £24 400 or lower. Dabigatran 150 mg twice daily was the most probable cost effective option at thresholds above that value. Considering a pair-wise comparison between warfarin and dabigatran 150 mg twice daily, warfarin was the most cost effective treatment at thresholds of £22 800 and below.

### Subgroup analyses

Among the subgroups analysed, the mean incremental net health benefit consistently favoured both doses of dabigatran over warfarin and dabigatran 150 mg twice daily over 110 mg twice daily (fig 3).

Dabigatran 150 mg twice daily was within the £30 000 per QALY cost effectiveness threshold for all subgroups of patients other than in centres with mean time within the therapeutic range for INR of at least 65.5% (table 4). Dabigatran 150 mg twice daily was most cost effective in patients at high risk of stroke (CHADS<sub>2</sub> score ≥3), but even here the probability of it being cost effective was only 68%. Dabigatran 110 mg twice daily, when used for all ages or restricted to patients aged 80 or over, was dominated by the higher dose in all subgroups (data not shown).

### Discussion

Our quantitative benefit-harm analysis found that dabigatran was associated with positive net health benefits when compared with warfarin. High dose dabigatran was the most clinically effective option. Greatest benefits were evident in patients in whom control of INR is poorest (patients' time within the therapeutic range <66.8%) and fewest benefits in centres that achieve good INR control (centre time within therapeutic range ≥65.5%). We were unable to identify a subgroup of patients in which the lower dose of dabigatran—when used for all ages or restricted to patients aged 80 or over—was superior to the higher dose. The benefits of reduced bleeding rates with the lower dose were offset by reduced efficacy in preventing stroke. These findings are in accordance with the results of the RE-LY study,<sup>6</sup> and related subgroup analyses,<sup>14 37-39</sup> and lend support to the FDA's rationale for not licensing the 110 mg dose.<sup>8</sup>

The economic analysis indicated that for the overall RE-LY study population, dabigatran 150 mg twice daily is potentially a cost effective alternative to warfarin, at £23 082 per QALY gained. However, its probability of being cost effective at a threshold of £20 000 per QALY is only 45%. This uncertainty is driven largely by rates of stroke and, to a lesser extent, vascular death and the cost of managing strokes. NICE's criteria for decision making state that "above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of . . . the degree of certainty around the ICER. . . NICE will be more cautious about recommending a technology when it is less certain about the ICERs presented."<sup>25</sup> Dabigatran 110 mg twice daily is not a cost effective option, and the age adjusted dosing regimen was dominated in all scenarios by the 150 mg dose.

High dose dabigatran was more cost effective in patients at a greater risk of stroke (baseline CHADS<sub>2</sub> score ≥3). However, at centres that achieve good INR control (centres' time within therapeutic range ≥65.6%), dabigatran 150 mg twice daily is no longer cost effective, at £42 386 per QALY gained. Although the mean time within the therapeutic INR range in the UK of 72% in the RE-LY study may be higher than routine practice,<sup>22 37</sup> so too might adherence to dabigatran, which requires twice daily dosing compared with warfarin's once.

### Comparison with other studies

We are not aware of any quantitative benefit-harm analyses of dabigatran in atrial fibrillation. However, two economic evaluations of dabigatran in non-valvular atrial fibrillation have

been published. Both used Markov models to estimate lifetime cost effectiveness on the basis of the RE-LY trial.

The US study, which adopted the costing perspective of a health insurer,<sup>40</sup> yielded a quality adjusted life expectancy of 10.28 with warfarin, 10.70 with low dose dabigatran, and 10.84 with high dose dabigatran. These are considerably higher than our estimates, primarily because of patients' starting age which, at 65 years, was 6.1 years younger than in our analysis based on the RE-LY population. Nevertheless, despite this difference, similar results were obtained with respect to dabigatran 150 mg twice daily being associated with positive incremental net health benefits across a range of risks for stroke and intracranial haemorrhage, compared with dabigatran 110 mg twice daily and warfarin. A similar economic outcome also resulted; the ICER fell just below the cost effective threshold but had a high level of uncertainty, driven mostly by drug costs and stroke rates.

The Canadian study,<sup>41</sup> sponsored by the manufacturer of dabigatran and based on RE-LY patient level data (though not listed as a pre-specified analysis),<sup>13</sup> assessed its cost effectiveness according to the same age adjusted dosing schedule as approved in Europe. In contrast to the US study and our study, however, dabigatran was deemed to be cost effective compared with warfarin, at \$10 440 (£6466; €7468; \$10 026) per QALY gained. Differences relate largely to costs, which were proportionally much greater for the management of events and long term care in the Canadian analysis. Considering a patient taking dabigatran who has an acute stroke and five years of follow-up costs, in our analysis the cost of stroke is about five times higher than the cost of drugs whereas in the Canadian study it is more than 15 times higher.

## Strengths and weaknesses

Our analysis benefited from application of a discrete event simulation method, which is the method of choice for conditions in which no obvious discrete disease states exist into which patients can be classified, a necessary assumption for a Markov model.<sup>12</sup> It allows for a much larger number of potential health states to be modelled and removes the need to define the additional structural parameters necessary for a Markov model (such as cycle length). A discrete event simulation also operates in continuous rather than discrete time, thus more naturally approximating actual patients' histories and allowing continuous parameters (such as age) to be more appropriately modelled.

Our analysis counters the concerns raised by NICE in its appraisal of the manufacturer's submission,<sup>24</sup> through the inclusion of the age adjusted dosing regimen, use of reliable estimates of INR monitoring cost, continuation of dyspepsia throughout the duration of dabigatran treatment, and independence from treatment of the risks of disability and death after stroke. We had no access to data on the quality of life sub-study of RE-LY, and we made no attempt at modelling a typical UK population with atrial fibrillation, who are typically older, with proportionately more women, and have a different risk profile for stroke than the RE-LY trial population.<sup>42</sup> Patients are also less likely to persist with anticoagulant treatment in routine practice than in a clinical trial setting,<sup>42</sup> but we had no additional data for more elaborate modelling.<sup>43</sup>

Several caveats exist. Firstly, the reliance on the RE-LY study as the sole source of clinical data is a potential cause for concern. Although RE-LY is one of the largest trials of atrial fibrillation, this makes assessing the effect of any possible weaknesses in the design of the RE-LY study difficult (for example, its open label design, a significant proportion of patients taking aspirin

concomitantly, and only about a third of patients with a baseline CHADS<sub>2</sub> score  $\geq 3$ ). We were further limited by not having access to data for individual patients. Our a priori decision to base our analysis on the entire RE-LY study population may limit the generalisability of the base case estimates to a UK context. Subgroups, defined by centres achieving better INR control and patients in the higher categories of risk for stroke, may result in more relevant estimates of ICER.

Secondly, the necessity of bringing together data from a wide variety of sources has the potential to introduce bias into the analysis. For example, relative event rates for aspirin treatment came from a separate study, which will have had different demographics and different warfarin dosing schedules from RE-LY. Extrapolation of a two year trial to a lifetime horizon also raises questions, as does the assumption that utility decrements for events derived from the general population are appropriate for patients with atrial fibrillation. However, approximations such as these are unavoidable in economic modelling. Thirdly, we did not include the possibility that widespread use of dabigatran might affect the provision of anticoagulation clinic services, as we considered displacement of warfarin by dabigatran to such an extent to be unlikely.

## Implications for practice and future research

Dabigatran has advantages over warfarin; the most important are that monitoring is not needed, that anticoagulation for a given dose is more predictable, and that fewer drug-drug interactions are likely. However, it also has disadvantages.<sup>44</sup> Firstly, the lack of monitoring provides little ability to objectively monitor adherence, which in the real world setting is likely to be worse with dabigatran given the need for twice daily dosing and its associated higher incidence of dyspepsia. Secondly, if the patient has a serious bleed, no proven antidotes exist.<sup>45</sup> Thirdly, some uncertainty exists about dosing in certain clinical settings such as renal failure, old age, and concomitant intake of amiodarone, which may lead to either underdosing or overdosing given that no pharmacodynamic marker for monitoring exists. Fourthly, the safety and efficacy of thrombin inhibitors in the longer term (beyond two years) are uncertain, although the follow-up study of RE-LY patients should yield valuable information.<sup>46</sup>

An important finding from the cost effectiveness analysis is that dabigatran is not cost effective when compared in patients whose INR is well controlled or in centres that achieve good INR control. Part of the reason for such variability in the time within the therapeutic range with warfarin is the presence of genetic polymorphisms in the *CYP2C9* and *VKORC1* genes.<sup>22 47</sup> At least four randomised trials are running globally in which genotype guided prescribing of warfarin, which is predicted to improve the time within the therapeutic range, is being tested against current clinical care. Whether dabigatran would be cost effective against genotype guided prescribing of warfarin is unclear and needs further evaluation. Furthermore, other competitors to dabigatran are due to be evaluated for licensing soon, such as rivaroxaban and apixaban, which have shown similar clinical effectiveness to warfarin but have not been tested against dabigatran.<sup>48</sup> Thus, although the arrival of new anticoagulants should be welcomed, their place in the prevention of strokes in patients with atrial fibrillation in comparison with warfarin (perhaps genotype guided) needs further evaluation. In the end, a stratified approach may represent the best approach to maximise both the clinical effectiveness and cost effectiveness of anticoagulation in patients with atrial fibrillation.

**What is already known on this topic**

Dabigatran etexilate is an alternative thromboprophylactic agent to warfarin for patients with non-valvular atrial fibrillation. However, uncertainty exists about its dose, balance of benefits and harms, and cost effectiveness. Previous cost effectiveness analyses of dabigatran for this indication have shown conflicting results and have not used appropriate modelling approaches.

**What this study adds**

Dabigatran was associated with positive incremental net benefits versus warfarin, but dabigatran 110 mg twice daily did not offer clinical or economic advantage over 150 mg twice daily in any subgroup. Dabigatran is unlikely to be cost effective in clinics, such as those in the UK, able to achieve good control of the international normalised ratio (INR) with warfarin. Dabigatran 150 mg twice daily, and an age adjusted dosing regimen, will be cost effective only for patients at increased risk of stroke or for whom INR is likely to be less well controlled.

**Contributors:** DAH had the idea for the study, oversaw its design, contributed to the interpretation of the data, and redrafted the paper. JP did all the analyses, interpreted the results, and drafted the paper. SL and MP assisted in the design of the study, interpretation of results, and discussion of the findings. All authors revised the paper for important intellectual content. All authors have approved the final version of the paper. DAH is the guarantor.

**Funding:** The study was funded by the Medical Research Council, as part of the North West Hub in Trial Methodological Research (NWHMTR). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

**Competing interests:** All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: JP and DAH have support from the Medical Research Council for the submitted work; no relationships that might have an interest in the submitted work in the previous three years; no non-financial interests that may be relevant to the submitted work.

**Ethical approval:** Not needed.

**Data sharing:** No additional data available.

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**Accepted:** 08 September 2011

Cite this as: [BMJ 2011;343:d6333](https://doi.org/10.1136/bmj.d6333)

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## Tables

**Table 1 | Patients' baseline characteristics, costs, health state utilities, and discount rate parameters used in model**

Parameter	Value	Probabilistic sensitivity analysis distribution	References
<b>Baseline characteristics*</b>			
Hypertension	14 283/18 113	$\beta$ (14 283, 3830)	6, 14
Diabetes	4221/18 113	$\beta$ (4221, 13 892)	6, 14
Heart failure	5793/18 113	$\beta$ (5793, 12 320)	6, 14
Previous stroke	2273/18 113	$\beta$ (2273, 15 840)	6, 14
Previous transient ischaemic attack	1663/18 113	$\beta$ (1663, 16 450)	6, 14
Previous myocardial infarction	3005/18 113	$\beta$ (3005, 15 108)	6, 14
Previous intracranial haemorrhage	713/18 113	$\beta$ (713, 17 400)	6, 14
<b>Health state utilities</b>			
Atrial fibrillation (age 67)	0.774	$1-\gamma$ (43.06, 0.0052)	15
Stroke (permanent disutility)†	0.233	Normal (0.233, 0.0032)	16
Stroke (temporary disutility)†	0.1385	Normal (0.1385, 0.01)	15, 17
Stroke (temporary duration, years)†	1/12	Uniform (0, 0.183)	17
Myocardial infarction (permanent disutility)	0.0409	Normal (0.0409, 0.002)	15
Myocardial infarction (temporary disutility)	0.1247	Normal (0.1247, 0.01)	15, 17
Myocardial infarction (temporary duration, years)	1/12	Uniform (0, 0.183)	17
Intracranial haemorrhage (permanent disutility)	0.0524	Normal (0.0524, 0.001)	15
Pulmonary embolism (temporary disutility)	0.1385	Normal (0.1385, 0.01)	15, 17
Pulmonary embolism (temporary duration, years)	1/12	Uniform (0, 0.183)	17
Transient ischaemic attack (temporary disutility)	0.1032	Normal (0.1032, 0.01)	15, 17
Transient ischaemic attack (temporary duration, years)	5/365	Uniform (0, 0.027)	17
Major bleed (temporary disutility)	0.1385	Normal (0.1385, 0.01)	15, 17
Major bleed (temporary duration, years)	1/12	Uniform (0, 0.183)	17
Minor bleed (temporary disutility)	0.06	Normal (0.06, 0.01)	17
Minor bleed (temporary duration, years)	5/365	Uniform (0, 0.027)	17
Warfarin disutility	0.013	$\gamma$ (1.3, 0.01)	16
Dabigatran disutility	0.002	$\gamma$ (0.2, 0.01)	Assumption
Aspirin disutility	0.002	$\gamma$ (0.2, 0.01)	16
<b>Costs</b>			
Stroke—year 1†	£10 543.36	$\gamma$ (102.68, 102.68)	18
Stroke—subsequent years†	£2781.22	$\gamma$ (52.74, 52.74)	18
Myocardial infarction—year 1	£2357.13	$\gamma$ (58.26, 40.46)	18
Myocardial infarction—subsequent years	£828.90	$\gamma$ (34.55, 23.99)	18
Pulmonary embolism	£1543.27	NA	19
Transient ischaemic attack	£839.62	NA	19
Major bleed	£1684.58	NA	20
Minor bleed	£93.17	NA	20
Proton pump inhibitors (1 year)	£185.20	NA	21
Warfarin—drugs (1 year)	£41.23	Uniform (32.98, 49.48)	22, 23
Warfarin—monitoring (1 year)	£198.39	$\gamma$ (202.59, 0.979)	22
Dabigatran—both doses (1 year)	£919.80	NA	24
Aspirin (1 year)	£7.39	$\gamma$ (73.9, 0.1)	17, 23
<b>Discount rate</b>			
Utilities	3.5%	NA	25
Costs	3.5%	NA	25

Table 1 (continued)

Parameter	Value	Probabilistic sensitivity analysis distribution	References
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NA=not applicable.

\*Proportion in initial population.

†Includes both strokes and systemic emboli, excluding pulmonary emboli.

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Table 2 | Clinical parameters used in model

Parameter*	Aspirin	Warfarin	Dabigatran 110 mg	Dabigatran 150 mg	References
<b>Clinical event rates</b>					
Stroke (CHADS <sub>2</sub> score ≤1)†‡	0.0177	0.0109	0.0112	0.0068	6, 14, 27
Stroke (CHADS <sub>2</sub> score 2)†‡	0.0222	0.0138	0.0145	0.0084	6, 14, 27
Stroke (CHADS <sub>2</sub> score ≥3)†‡	0.0441	0.0273	0.0212	0.0189	6, 14, 27
Pulmonary embolism†	0.0016	0.0010	0.0012	0.0015	6, 14, 27
Transient ischaemic attack†	0.0135	0.0084	0.0062	0.0072	6, 14, 27
Congestive heart failure†	0.0062	0.0062	0.0070	0.0048	6, 14
Probability of death from stroke‡	0.1887	0.1887	0.1887	0.1887	6, 14
Probability of death from pulmonary embolism	0.1591	0.1591	0.1591	0.1591	6, 14
Vascular death (excluding stroke and systemic and pulmonary embolism)†	0.0228	0.0228	0.0216	0.0208	6, 14
Probability that major bleed is intracranial haemorrhage	0.2191	0.2191	0.0839	0.0960	6, 14
<b>Adverse events</b>					
Major bleed (CHADS <sub>2</sub> score ≤1)†	0.0127	0.0290	0.0188	0.0220	6, 14, 27
Major bleed (CHADS <sub>2</sub> score 2)†	0.0145	0.0331	0.0298	0.0304	6, 14, 27
Major bleed (CHADS <sub>2</sub> score ≥3)†	0.0202	0.0461	0.0380	0.0486	6, 14, 27
Minor bleed†	0.0718	0.1637	0.1316	0.1485	6, 14, 27
Non-bleed adverse events	NA	0.4600	0.4596	0.4725	6, 14
Proportion of patients using proton pump inhibitor	0.2317	0.1840	0.2126	0.2164	6, 14, 28
Myocardial infarction†	0.0064	0.0064	0.0082	0.0081	6, 14, 18
<b>Comorbidities</b>					
Diabetes†	0.0122	0.0122	0.0122	0.0122	29
Hypertension†	0.0271	0.0271	0.0271	0.0271	30
<b>Discontinuations</b>					
Probability that major bleed leads to discontinuation	NA	0.1425	0.1801	0.2133	6, 14
Probability that adverse event leads to discontinuation	NA	0.0194	0.0298	0.0292	6, 14
Probability that discontinue year 1 (other reasons)	NA	0.0832	0.1160	0.1226	6, 14
Probability that discontinue year 2 onwards (other reasons)	NA	0.0459	0.0475	0.0432	6, 14

CHADS<sub>2</sub>=Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack; NA=not applicable.

\*See web extra table B for parameters specifying distributions for probabilistic sensitivity analysis.

†Presented as rates per 100 person years.

‡Includes both strokes and systemic emboli but not pulmonary emboli.

**Table 3| Lifetime estimates of event rates, net benefits, and incremental differences versus comparator, derived from probabilistic sensitivity analysis**

Referent	Mean (95% central range) estimate	Mean (95% central range) difference*	Comparator
<b>Quality adjusted life years (QALYs)†</b>			
Warfarin	6.390 (6.265 to 6.517)	-0.094 (0.083 to -0.267)	Dabigatran 110 mg bid
Dabigatran 110 mg bid	6.484 (6.360 to 6.634)	-0.049 (0.126 to -0.221)	Dabigatran age adjusted‡
Dabigatran age adjusted‡	6.531 (6.401 to 6.664)	-0.005 (0.171 to -0.180)	Dabigatran 150 mg bid
Dabigatran 150 mg bid	6.536 (6.413 to 6.662)	0.146 (-0.029 to 0.322)	Warfarin
<b>Life years†</b>			
Warfarin	10.851 (10.687 to 11.018)	-0.089 (0.142 to -0.323)	Dabigatran 110 mg bid
Dabigatran 110 mg bid	10.940 (10.776 to 11.111)	-0.102 (0.129 to -0.338)	Dabigatran age adjusted‡
Dabigatran age adjusted‡	11.042 (10.873 to 11.221)	-0.009 (0.243 to -0.232)	Dabigatran 150 mg bid
Dabigatran 150 mg bid	11.051 (10.885 to 11.220)	0.200 (-0.035 to 0.429)	Warfarin
<b>Stroke or systemic embolism (excluding pulmonary emboli)</b>			
Warfarin	0.2408 (0.2010 to 0.2841)	0.0302 (-0.0260 to 0.0875)	Dabigatran 110 mg bid
Dabigatran 110 mg bid	0.2107 (0.1698 to 0.2538)	0.0308 (-0.0268 to 0.0893)	Dabigatran age adjusted‡
Dabigatran age adjusted‡	0.1799 (0.1401 to 0.2245)	0.0044 (-0.0476 to 0.0511)	Dabigatran 150 mg bid
Dabigatran 150 mg bid	0.1755 (0.1354 to 0.2196)	-0.0654 (-0.0092 to -0.1226)§	Warfarin
<b>Ischaemic stroke</b>			
Warfarin	0.1718 (0.1484 to 0.1982)	-0.0045 (-0.0565 to 0.0493)	Dabigatran 110 mg bid
Dabigatran 110 mg bid	0.1763 (0.1507 to 0.2067)	0.0331 (-0.0189 to 0.0822)	Dabigatran age adjusted‡
Dabigatran age adjusted‡	0.1432 (0.1167 to 0.1708)	0.0044 (-0.0502 to 0.0570)	Dabigatran 150 mg bid
Dabigatran 150 mg bid	0.1388 (0.1121 to 0.1662)	-0.0330 (0.0261 to -0.0803)	Warfarin
<b>Transient ischaemic attack</b>			
Warfarin	0.1643 (0.1281 to 0.2074)	0.0218 (-0.0280 to 0.0712)	Dabigatran 110 mg bid
Dabigatran 110 mg bid	0.1425 (0.1057 to 0.1791)	0.0273 (-0.0237 to 0.0762)	Dabigatran age adjusted‡
Dabigatran age adjusted‡	0.1152 (0.0791 to 0.1509)	0.0042 (-0.0449 to 0.0580)	Dabigatran 150 mg bid
Dabigatran 150 mg bid	0.1110 (0.0744 to 0.1476)	-0.0533 (-0.0035 to -0.1027)§	Warfarin
<b>Intracranial haemorrhage</b>			
Warfarin	0.0756 (0.0655 to 0.0835)	0.0479 (0.0347 to 0.0614)§	Dabigatran 110 mg bid
Dabigatran 110 mg bid	0.0277 (0.0240 to 0.0308)	-0.0062 (-0.0191 to 0.0077)	Dabigatran age adjusted‡
Dabigatran age adjusted‡	0.0339 (0.0298 to 0.0372)	-0.0017 (-0.0133 to 0.0116)	Dabigatran 150 mg bid
Dabigatran 150 mg bid	0.0356 (0.0322 to 0.0391)	-0.0400 (-0.0271 to -0.0578)§	Warfarin
<b>Major bleed (including intracranial haemorrhage)</b>			
Warfarin	0.3313 (0.2942 to 0.3766)	0.0133 (-0.0409 to 0.0673)	Dabigatran 110 mg bid
Dabigatran 110 mg bid	0.3180 (0.2811 to 0.3623)	-0.0379 (-0.0902 to 0.0257)	Dabigatran age adjusted‡
Dabigatran age adjusted‡	0.3559 (0.3180 to 0.3985)	-0.0048 (-0.0561 to 0.0512)	Dabigatran 150 mg bid
Dabigatran 150 mg bid	0.3607 (0.3233 to 0.4017)	0.0294 (0.0835 to -0.0247)	Warfarin
<b>Non-fatal myocardial infarction</b>			
Warfarin	0.0612 (0.0434 to 0.0813)	-0.0109 (-0.0346 to 0.0126)	Dabigatran 110 mg bid
Dabigatran 110 mg bid	0.0721 (0.0560 to 0.0895)	-0.0006 (-0.0251 to 0.0256)	Dabigatran age adjusted‡
Dabigatran age adjusted‡	0.0727 (0.0560 to 0.0914)	-0.0003 (-0.0250 to 0.0255)	Dabigatran 150 mg bid
Dabigatran 150 mg bid	0.0730 (0.0561 to 0.0934)	0.0119 (0.0356 to -0.0116)	Warfarin

bid=twice daily.

\*Difference from comparator group.

†Discounted at 3.5% per annum.

‡Age adjusted dabigatran dosing regimen (110 mg bid for patients aged ≥80 years) based on post hoc subgroup analysis.

§95% central range for incremental difference does not cross zero.

Table 4| Cost effectiveness results for subgroups, based on probabilistic sensitivity analysis

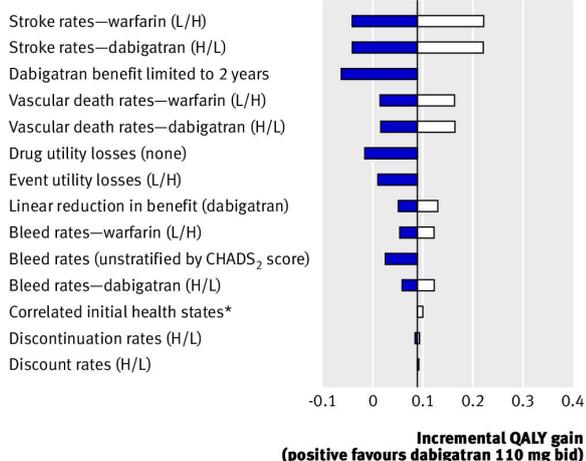
Subgroup	Warfarin cost (£)	Warfarin QALYs	Dabigatran 150 mg bid cost (£)	Dabigatran 150 mg bid QALYs	ICER (£/QALY)	Probability of cost effectiveness*	
						At £20 000 per QALY	At £30 000 per QALY
RE-LY population	6480	6.390	9850	6.536	23 082	0.449	0.596
CHADS <sub>2</sub> score 2	7412	6.283	10 443	6.433	20 207	0.475	0.615
CHADS <sub>2</sub> score ≥3	9912	6.224	12 646	6.396	15 895	0.565	0.683
Centres' time in therapeutic range ≥65.5%	6247	6.517	9977	6.605	42 386	0.137	0.309
Centres' time in therapeutic range <65.5%	6617	6.261	9656	6.410	20 396	0.469	0.636
Patients' time in therapeutic range ≥66.8%	6302	6.401	9850	6.536	26 281	0.393	0.511
Patients' time in therapeutic range <66.8%	6694	6.360	9850	6.536	17 932	0.519	0.643
Creatinine clearance <30-50 mL/min	7991	6.310	10 788	6.460	18 647	0.501	0.631
Previous stroke or transient ischaemic attack	10 004	6.217	12 787	6.378	17 286	0.525	0.649
Vitamin K antagonist naive	6437	6.396	9792	6.545	22 517	0.446	0.587
Age ≥75 years	4612	4.275	7362	4.429	17 857	0.498	0.635

bid=twice daily; CHADS<sub>2</sub>=Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; RE-LY=Randomized Evaluation of Long-Term Anticoagulation Therapy.

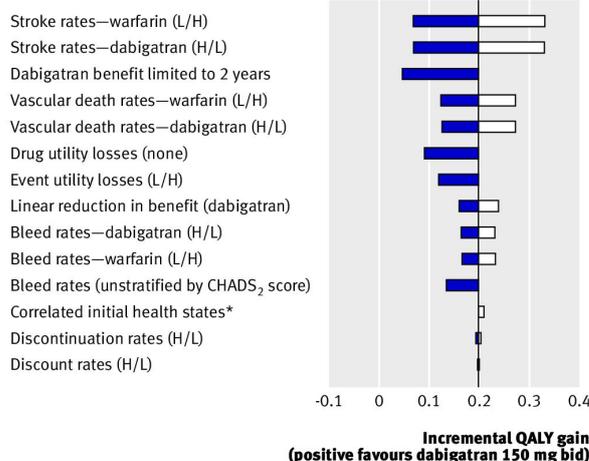
\*Proportion of simulations in which dabigatran 150 mg twice daily is cost effective versus warfarin.

# Figures

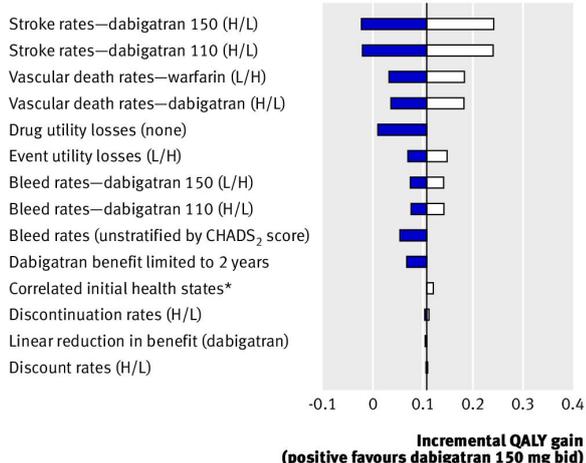
**Warfarin v dabigatran 110 mg twice daily**



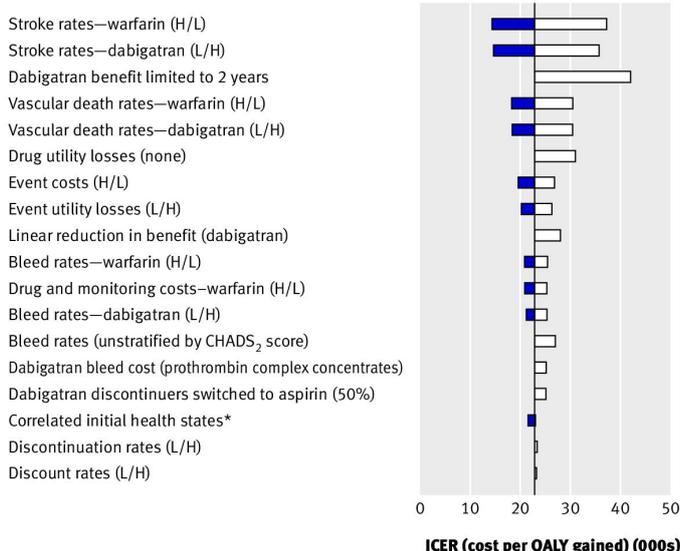
**Warfarin v dabigatran 150 mg twice daily**



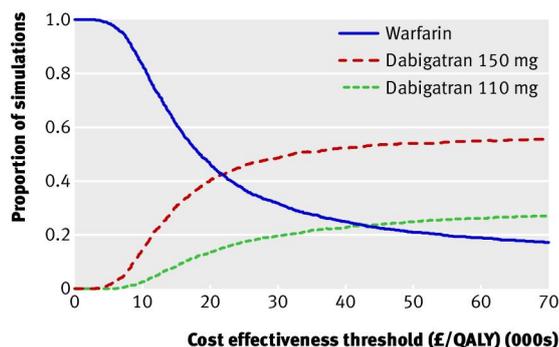
**Dabigatran 110 mg twice daily v dabigatran 150 mg twice daily**



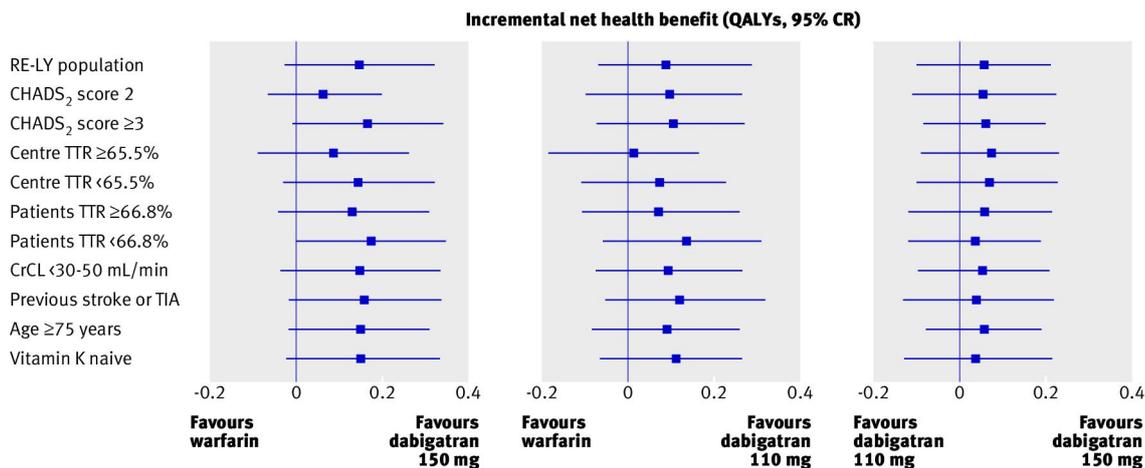
**Dabigatran 150 mg twice daily v warfarin**



**Fig 1** Tornado plot of univariate sensitivity analyses. First three panels relate to benefit-harm analyses; lower right panel relates to economic comparison of dabigatran 150 mg twice daily and dose adjusted warfarin. L=lower end of 95% CI for parameter set; H=higher end of 95% CI for parameter set (see web extra table A). bid=twice daily; CHADS<sub>2</sub>= Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year. \*Maximum deviation from all correlation structures tested, which occurred when all patients with hypertension were assumed to have diabetes and all patients with previous myocardial infarction were assumed to also have previous stroke



**Fig 2** Cost effectiveness acceptability curve for base case analysis. QALY=quality adjusted life year



**Fig 3** Results of probabilistic sensitivity analysis on efficacy and safety end points, expressed as incremental QALYs. Values are means and 95% central ranges from 2000 simulations. CHADS<sub>2</sub>= Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack; CrCl=creatinine clearance; QALY=quality adjusted life year; RE-LY= Randomized Evaluation of Long-Term Anticoagulation Therapy; TIA=transient ischaemic attack; TTR=time within therapeutic range