Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
This study assessed the cost-effectiveness of low- or high-dose dabigatran, compared with warfarin, for the prevention of ischaemic stroke in patients aged 65 years or older, with non-valvular atrial fibrillation and risk factors for stroke. The authors concluded that dabigatran, particularly at a high dose, could be cost-effective compared with warfarin, but this depended on the price of dabigatran. The methods were generally valid and the authors’ conclusions appear to be robust.

Type of economic evaluation
Cost-utility analysis

Study objective
This study assessed the cost-effectiveness of low- or high-dose dabigatran, compared with warfarin, for the prevention of ischaemic stroke in patients aged 65 years or older, with non-valvular atrial fibrillation and risk factors for stroke.

Interventions
The interventions were low-dose dabigatran at 110mg twice daily, high-dose dabigatran at 150mg twice daily, and warfarin at a dose adjusted to achieve a target international normalised ratio (INR) of between 2.0 to 3.0.

Location/setting
USA/hospital.

Methods
Analytical approach:
The analysis was based on a Markov model, with a lifetime horizon. The authors stated that it was carried out from a societal perspective.

Effectiveness data:
The clinical data were from a selection of relevant studies. Most of the evidence for the short-term treatment efficacy and safety was from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, which was an international, multicentre, randomised, non-inferiority trial comparing the three treatments. Additional long-term data were from other published sources and well-known algorithms. The key input for the model was the annual risk of ischaemic stroke, in the three model arms, and this was from the RE-LY trial.

Monetary benefit and utility valuations:
The utility values were from published sources. The utility for warfarin therapy was from patient preferences, while the values for dabigatran were from a survey of physicians.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary benefit measure and they were discounted at an annual rate of 3%.

Cost data:
The economic analysis included the costs of drugs, INR laboratory test, and management of neurologic events,
intracranial haemorrhage, myocardial infarction, and minor or major haemorrhage. Both in-patient and out-patient hospital costs were considered. These were from official US sources, including Medicare and Medicaid, average wholesale prices, the Healthcare Cost and Utilization Project, and published studies. The price of dabigatran was based on its UK price as it was not sold in the USA at the time of the study. On the basis of cost ratios for other on-patent cardiovascular medications, it was assumed that the retail price in the USA would be 1.5 times higher than that in the UK. The costs were in US dollars ($) and the price year was 2008. A 3% annual discount rate was applied.

Analysis of uncertainty:
One-way sensitivity analyses were carried out on all the inputs for the model, using plausible ranges of values, from published sources. Alternative scenarios were considered for the price of dabigatran and the risks of stroke and intracranial haemorrhage. A probabilistic sensitivity analysis was conducted, using Monte Carlo simulation, with predetermined probability distributions for the model inputs.

Results
The projected costs were $143,193 with warfarin, $164,576 with low-dose dabigatran, and $168,398 with high-dose dabigatran. The QALYs were 10.28 with warfarin, 10.70 with low-dose dabigatran, and 10.84 with high-dose dabigatran.

Compared with warfarin, the incremental cost per QALY gained was $51,229 with low-dose dabigatran and $45,372 *** with high-dose dabigatran. Low-dose dabigatran was extendedly dominated, as it was less effective and less cost-effective than high-dose dabigatran.

The sensitivity analysis showed that the cost of dabigatran was the key driver of the model. The incremental cost per QALY gained exceeded the threshold of $50,000 at a daily cost greater than $9.36, for low-dose dabigatran, and greater than $13.70, for high-dose dabigatran.

Variations in the other inputs changed the incremental cost-utility ratio, for high-dose dabigatran, by less than $15,000, and it remained under $85,000.

The probabilistic analysis found that high-dose dabigatran was cost-effective in 53% of simulations at a threshold of $50,000, and 68% at $100,000 per QALY. Either high- or low-dose dabigatran was preferred to warfarin in more than 80% of iterations, at a threshold of $50,000, and in more than 95% of iterations, at a threshold of $100,000.

*** Following the publication of this abstract, the authors informed us that they had revised this estimate to reflect: "actual drug price; and minor changes in event probabilities based on republished event rates upon re-adjudication of the RE-LY trial during study closure". The revised estimate is $12,386 per QALY. More detail on the revision can be found in a letter published in Annals of Internal Medicine 2011;154(8):570-571 which can be accessed here:

http://www.annals.org/search?fulltext=turakhia&submit=yes&x=0&y=0

Authors' conclusions
The authors concluded that dabigatran, especially at a high dose, could be cost-effective, compared with warfarin, but this depended on the price of dabigatran.

CRD commentary
Interventions:
The selection of the comparators appears to have been appropriate. The treatments were the comparators in the clinical trial that was the basis for the analysis. The authors stated that high-dose dabigatran was approved in the USA, in October 2010, while low-dose dabigatran (110mg) was not approved; a dose of 75mg was approved, but was not analysed.

Effectiveness/benefits:
Most of the clinical benefits were from a large randomised clinical trial that directly compared the treatments. This should have ensured high internal validity, but might be difficult to generalise to clinical practice. The follow-up of this
trial was two years and other studies were needed to extrapolate clinical outcomes to the long-term. Little information on these studies was provided, but standard equations were used and extensive sensitivity analysis was conducted on all the clinical inputs. QALYs were an appropriate benefit measure. They capture the impact of the disease on both survival and quality of life, which are relevant for patients with cardiovascular events. Little information on the derivation of the utility values was provided; the authors did not mention the instrument used to elicit the preferences. Different populations were used for the utilities for warfarin and for dabigatran, but sensitivity analyses were conducted on these values.

**Costs:**
The authors stated that a societal perspective was used, but they did not justify the exclusion of non-medical costs and productivity losses. The analysis therefore reflected a health care payer perspective. Most of the costs were from third-party payers in the USA, and these are often presented as category totals. The unit costs and most of the resource quantities were not reported. The price year and discount rate were clearly stated. The impact of variations in the cost estimates was extensively tested in the sensitivity analyses. As dabigatran was not available in the USA at the time of the study, its cost was assumed to be 1.5 times higher than in the UK. Once the US price is available, the analysis should be conducted using that value.

**Analysis and results:**
The estimated costs and benefits were extensively presented and were appropriately synthesised, using an incremental approach. The uncertainty was satisfactorily investigated, using both deterministic and probabilistic analyses, and the findings were clearly illustrated. The model was clearly described. The authors did not explicitly discuss the generalisability of their results and they should be considered to be US specific.

**Concluding remarks:**
The methods were generally valid and the authors' conclusions appear to be robust.

**Funding**
Supported by grants from the American Heart Association, and the Veterans Affairs Health Services Research and Development Service.

**Bibliographic details**

**PubMedID**
21041570

**DOI**
10.7326/0003-4819-154-1-201101040-00289

**Original Paper URL**
http://www.annals.org/content/early/2010/11/01/0003-4819-154-1-201101040-00289.abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Aged; Aged, 80 and over; Anticoagulants /administration & dosage /adverse effects /economics; Atrial Fibrillation /complications; Benzimidazoles /administration & dosage /adverse effects /economics; Cost-Benefit Analysis; Dabigatran; Fibrinolytic Agents /administration & dosage /adverse effects /economics; Hemorrhage /chemically induced; Humans; Intracranial Hemorrhages /chemically induced; Ischemic Attack, Transient /prevention & control; Markov Chains; Myocardial Infarction /chemically induced; Quality-Adjusted Life Years; Risk Factors; Sensitivity and Specificity; Stroke /prevention & control; Warfarin /administration & dosage /adverse effects /economics; beta-Alanine
NHS Economic Evaluation Database (NHS EED)
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