Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective
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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 investigated the cost-effectiveness of dabigatran etexilate versus warfarin (trial data) or usual care (warfarin, aspirin, or no treatment) for stroke prevention in patients with atrial fibrillation. The authors concluded that dabigatran etexilate was very cost-effective, compared with the usual prevention in Canada. The methods and results were appropriate and generally clearly reported. Some key model parameters were not tested in the sensitivity analysis, which would have been useful, but the conclusions reached by the authors appear to appropriate.

Type of economic evaluation
Cost-utility analysis

Study objective
The aim was to examine the costs and health outcomes of the anticoagulant dabigatran etexilate, for the prevention of stroke and systemic embolism, in patients with atrial fibrillation.

Interventions
The interventions were dabigatran etexilate, warfarin (trial data), and usual care (real-world warfarin). The usual care consisted of prevention with warfarin or aspirin, or no treatment. This was examined using real-world data, with suboptimal therapeutic outcomes, according to those observed in clinical practice. The dose of dabigatran etexilate was 150mg for patients under 80 years old, or 110mg for patients aged 80 years or older.

Location/setting
Canada/primary care.

Methods
Analytical approach:
A decision-analytic Markov model was used to synthesise the evidence. Its structure was based on a developed model (Sorensen, et al. 2009, see ‘Other Publications of Related Interest’ below for bibliographic details). It modelled a hypothetical cohort of adults with a mean age of 69 years, a diagnosis of atrial fibrillation, and at least one additional risk factor for stroke or embolism, or an impaired left ventricular ejection fraction, who were eligible for anticoagulation treatment. The time horizon was lifetime and the authors stated that a Canadian provincial health payer perspective was taken.

Effectiveness data:
The clinical data were mainly from published studies and one pivotal clinical trial; the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial (Connolly, et al. 2009, 2010, see ‘Other Publications of Related Interest’ below for bibliographic details). This trial compared the two doses of dabigatran etexilate with adjusted-dose warfarin, for 18,113 patients. The key clinical outcomes were disability measured on the modified Rankin Scale or the Glasgow Outcome Scale, mortality, quality of life, risk of future cardiac events, and changing treatment status. Other published studies, including a network meta-analysis of up to 20 trials, provided the efficacy data for warfarin and aspirin in trial and real-world settings. The efficacy for all three therapies was assumed to be constant over time. Discontinuation rates of 22% for warfarin and 30% for dabigatran etexilate were modelled.

Monetary benefit and utility valuations:
The utility estimates were from the 2000 to 2002 Medical Expenditure Panel Survey, which used the European Quality of life (EQ-5D) questionnaire, for chronic conditions, adjusted for age, sex, race, income, education, and comorbidity, and from a published systematic review.

Measure of benefit:
The measure of benefit was quality-adjusted life-years (QALYs), which were discounted annually at 5%.

Cost data:
The direct medical costs included those of the drugs, monitoring for warfarin, events (ischaemic stroke, systemic embolism, intracranial haemorrhage, haemorrhagic stroke, extracranial haemorrhage, minor bleed, or myocardial infarction), and follow-up. The drug costs per day were from the Ontario Drug Benefit Formulary, and the other costs were from expert advice and published literature. The price year was 2010 and all costs were presented in Canadian dollars (CAD). They were discounted at 5% annually.

Analysis of uncertainty:
The model parameters were examined in one-way and probabilistic sensitivity analyses. The one-way analyses were performed on most parameters, and Monte Carlo simulations were run for the probabilistic sensitivity analysis, with beta, gamma, and log-normal distributions. The results were illustrated in cost-effectiveness acceptability curves and tables, which were available online.

Results
In the base case, the total discounted costs were CAD 45,124 for dabigatran etexilate sequential dosing (with age), compared with CAD 42,946 for trial data warfarin, or CAD 44,020 for real-world warfarin. The QALYs for were 7.29 for dabigatran etexilate, 7.08 for trial warfarin, and 7.01 for real-world warfarin. The incremental cost per QALY gained for dabigatran etexilate was CAD 10,440 versus trial warfarin or CAD 3,962 versus real-world warfarin.

The one-way sensitivity analyses showed that the incremental cost per QALY gained was sensitive to changes in the control of the international normalised ratio (INR) for patients on warfarin (therapeutic dose control), the long-term disability from ischaemic stroke with dabigatran etexilate versus warfarin, the follow-up costs, and the time horizon, but it did not exceed CAD 30,521 per QALY gained.

The probabilistic sensitivity analyses showed that the cost-utility of dabigatran etexilate was below CAD 30,000 per QALY in 82% of simulations versus trial warfarin or 99% of simulations versus real-world warfarin.

Authors' conclusions
The authors concluded that dabigatran etexilate was highly cost-effective, compared with the usual prevention for strokes and systemic embolisms, in patients with atrial fibrillation in Canada.

CRD commentary
Interventions:
The therapies were described well and the analyses included medication discontinuation rates. Dabigatran etexilate might be available in other settings.

Effectiveness/benefits:
The clinical effectiveness estimates were mainly from a large randomised controlled trial that directly compared dabigatran etexilate against warfarin. This was likely to have produced valid estimates for comparative efficacy and safety, but few details of the trial were reported and the trial publications should be consulted to assess their validity (Connolly, et al. 2009, 2010). The analyses included treatment discontinuation, dose changes with age, and adherence to warfarin in clinical practice versus trials. The authors assumed constant efficacy over time, while on treatment, but this was not tested in the sensitivity analyses.

Costs:
The resource quantities and unit costs were clearly presented and referenced. Some assumptions were necessary for the measurement of these resources, but they appear to have been reasonable and comprehensive. The unit costs were from
publicly available published sources or expert advice.

Analysis and results:
The modelling approach was described briefly and a diagram was provided. The authors discussed their findings, in relation to therapeutic dose control for warfarin, and the consequences of under treatment. Selected results from the one-way sensitivity analyses were reported. The authors acknowledged some limitations, such as the assumptions made during modelling to keep the relative risks of events constant and that the efficacy levels were sustainable over time.

Concluding remarks:
The methods and results were appropriate and generally clearly reported. Some key model parameters were not tested in the sensitivity analysis, which would have been useful, but the conclusions reached by the authors appear to appropriate.

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