Economic evaluation of dabigatran etexilate for the prevention of venous thromboembolism in patients aged over 75 years or with moderate renal impairment undergoing total knee or hip replacement
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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 compared oral dabigatran etexilate with subcutaneous enoxaparin, for patients undergoing total knee or hip replacement, who were over 75 years old or had moderate renal impairment. The authors concluded that dabigatran etexilate was superior to enoxaparin because it produced cost savings, with comparable efficacy and safety. The reporting was variable, but the analysis tends to support the authors’ conclusions, based on the evidence available.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
The aim was to assess the cost-effectiveness of dabigatran etexilate, a thrombin inhibitor, for the prevention of venous thromboembolism in patients undergoing total knee or hip replacement. A hypothetical cohort of patients, over 75 years old or with moderate renal impairment, was assessed.

Interventions
Oral dabigatran etexilate once daily (150mg) was compared with subcutaneous enoxaparin once daily (40mg) for patients undergoing total knee or hip replacement, who were over 75 years old or had moderate renal impairment. Dabigatran etexilate had no special monitoring requirements. Moderate renal impairment was defined as a creatinine clearance of from 30ml per minute up to under 50ml per minute.

Location/setting
UK/in-patient care.

Methods
Analytical approach:
A decision analytic model, with Markov chains, was adapted from a similar model constructed by the same authors (Wolowacz, et al. 2009, see ‘Other Publications of Related Interest’ below for bibliographic details). The model synthesised published data from key randomised controlled trials and epidemiological and national reports and studies. The authors stated that the perspective was that of the UK National Health Service (NHS) and the analysis had a lifetime horizon.

Effectiveness data:
The main clinical endpoints were total venous thromboembolism and all-cause mortality; major bleeds; and minor bleeds. The clinical event data were primarily from subgroup analyses of patients over 75 years from two pivotal randomised controlled trials; RE-MODEL (Thromboembolism Prevention After Knee Surgery) and RE-NOVATE (Dahl, et al. 2008a and 2008b, and Eriksson, et al. 2007a and 2007b, see ‘Other Publications of Related Interest’ below for bibliographic details). These trial data were combined in fixed-effect meta-analysis to obtain the relative risks. Other published studies and epidemiological reports were used for the remaining model probabilities.

Monetary benefit and utility valuations:
The health state values were based on those reported by the authors for the previous model (Wolowacz, et al. 2009).
Measure of benefit:
The measures of benefit were venous thromboembolisms avoided, life-years saved, and quality-adjusted life-years (QALYs). Discounting was applied at an annual rate of 3.5%.

Cost data:
The direct medical costs included those of: dabigatran etexilate and enoxaparin acquisition; nursing time for injections; length of hospital stay; and district nurse visits. The resource estimates were from a selection of relevant published studies. Their values were from national sources, such as the UK Hospital Episode Statistics, British National Formulary, and NHS reference costs, or the previous model (Wolowacz, et al. 2009). The costs were discounted at 3.5% per annum and were reported in 2008 UK pounds sterling (£).

Analysis of uncertainty:
One-way sensitivity analyses and a probabilistic sensitivity analysis were undertaken. Beta distributions were assigned to the patient probabilities and normal distributions were assigned for treatment duration, costs, and the relative risk of venous thromboembolism and bleeding. One thousand Monte Carlo simulations were performed and 95% confidence intervals were generated. The results were illustrated on cost-effectiveness planes.

Results
For patients over 75 years, who were undergoing total knee replacement, the discounted mean cost per patient over a lifetime was £475 with dabigatran etexilate and £572 with enoxaparin. The QALYs were 8.256 with dabigatran etexilate and 8.225 with enoxaparin. For those who were undergoing total hip replacement, the discounted mean cost was £410 with dabigatran etexilate and £565 with enoxaparin. The QALYs were 8.388 with dabigatran etexilate and 8.372 with enoxaparin.

For patients with moderate renal impairment, who were undergoing total knee replacement, the discounted mean cost was £540 with dabigatran etexilate and £602 with enoxaparin. The QALYs were 7.656 with dabigatran etexilate and 7.635 with enoxaparin. For those undergoing total hip replacement, the discounted mean cost was £474 with dabigatran etexilate and £748 with enoxaparin. The QALYs were 8.394 with dabigatran etexilate and 8.372 with enoxaparin.

Dabigatran etexilate dominated enoxaparin as it was less costly and produced more QALYs. This was consistent across the different patient scenarios and endpoints. The probabilistic sensitivity analysis indicated that there was a 91 to 99% chance that the incremental cost per QALY would fall below a willingness-to-pay threshold of £20,000, for patients over 75 years, and a 76 to 93% chance, for patients with moderate renal impairment.

Authors' conclusions
The authors concluded that, compared with enoxaparin, dabigatran etexilate was cost saving and had comparable safety and efficacy, for patients undergoing total knee or hip replacements, who were over 75 years old or had moderate renal impairment.

CRD commentary
Interventions:
The authors' provided clear descriptions of the treatment options and these might be appropriate comparators in other settings.

Effectiveness/benefits:
The model structure was not described nor illustrated, but all the inputs and data sources were reported and the model was externally validated. The valuation methods for the utilities were also not reported, but should be available in the original model publication (Wolowacz, et al. 2009). The two randomised controlled trials that provided the main effectiveness data were not described and their publications need to be consulted to assess their quality (Dahl, et al. 2008a and 2008b, and Eriksson, et al. 2007a and 2007b). It appears that these two trials provided the best available evidence. The model inputs were well presented and referenced, but it was not possible to determine their internal validity.

Costs:
The direct medical costs were included and they appear to have been appropriate for the perspective. Thorough details of the resource types, how these were measured and valued, and their unit costs were provided.

Analysis and results:
The analyses were comprehensive and reported in full. It is unclear why normal distributions were assigned to the hospital stay and the cost estimates, which are typically right-skewed and fit gamma or log normal distributions. It is difficult to determine the impact that this would have on the results, but it unlikely that all the parameter uncertainty was captured. The authors’ interpretation of the results for the two options was reasonable as the costs and QALYs were virtually equivalent or not significantly different, in the base analyses, but the probabilistic sensitivity analysis clearly showed the superiority of dabigatran etexilate. The authors reported a number of limitations, including assumptions for data derived from post-hoc subgroup analyses, where the randomisation was not stratified and the samples were small, and the possible imbalance of confounding factors in the two treatment groups. The reporting of the analysis and results was far superior to the reporting of the inputs and how they were obtained.

Concluding remarks:
There were some limitations to the transparency of the model structure and the utility estimates, but the methods and analyses seem to have been appropriate and comprehensive. The conclusions reached by the authors reflect the scope of the analysis undertaken.

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Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Aged, 80 and over; Anticoagulants /economics; Arthroplasty, Replacement, Hip /adverse effects; Arthroplasty, Replacement, Knee /adverse effects; Benzimidazoles /economics /therapeutic use; Cost-Benefit Analysis; Dabigatran; Enoxaparin /economics /therapeutic use; Great Britain; Health Care Costs; Hemorrhage /chemically induced; Humans; Kidney Diseases /complications; Postoperative Complications /prevention & control; Pyridines /economics /therapeutic use; Venous Thromboembolism /prevention & control

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