Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation
Harrington AR, Armstrong EP, Nolan PE, Malone DC

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 evaluated the cost-effectiveness of new oral anticoagulants, for stroke prevention, in patients with nonvalvular atrial fibrillation, compared with warfarin. The authors concluded that the anticoagulants were more cost-effective than warfarin, and apixaban was preferred. The study was generally well reported, but had some unclear and potentially inappropriate costs. The analysis was not fully incremental, and there were questions around the costing methods, so the validity of the authors' conclusions is unclear.

Type of economic evaluation
Cost-utility analysis

Study objective
This study evaluated the long-term cost-effectiveness of new oral anticoagulants, for stroke prevention, in patients with nonvalvular atrial fibrillation, compared with the standard treatment of warfarin.

Interventions
The four interventions were warfarin, apixaban 5mg twice daily, dabigatran 150mg twice daily, and rivaroxaban 20mg once daily. Warfarin dose was assumed to be adjusted to achieve the patient's target international normalised ratio (INR).

Location/setting
USA/in-patient and out-patient care.

Methods
Analytical approach:
A Markov model, with one-month cycles, combined the published data. The time horizon was 30 years and the authors stated that the perspective was societal.

Effectiveness data:
Several types of effectiveness data were used. Adverse events were from three trials; one for each drug. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial was used for apixaban. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial was used for dabigatran. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism (ROCKET-AF) was used for rivaroxaban. Warfarin adverse events were pooled from the three trials. Transition probabilities, and increases in death risk were from other published economic evaluations. Multiple classifications of ischaemic stroke, intracranial haemorrhage, and myocardial infarction (MI) were used, with probabilities derived from the literature.

Monetary benefit and utility valuations:
The baseline utility scores were from US chronic-condition EQ-5D generic preference-based utility data, for atrial fibrillation. Utility decrements were applied for aging, anticoagulation treatment, model states, and adverse events, based on values from the literature.

Measure of benefit:
The summary measure of benefit was quality-adjusted life-years (QALYs). QALYs were discounted at 3% annually.

Cost data:
One-time event costs for stroke, intracranial haemorrhage, MI, gastrointestinal haemorrhage, and dyspepsia were from an online US cost and utilisation database, using International Classification of Diseases (ICD)-9 codes and Medicare diagnosis-related group (DRG) data. The costs of additional events were from Current Procedural Terminology (CPT) codes and Medicare reimbursement rates. Drug costs, for dabigatran, rivaroxaban, and warfarin, were their wholesale acquisition costs, from the Medi-Span database. Costs for apixaban were from UK guidance issued by the National Institute for Health and Clinical Excellence (NICE), converted from £ to 2012 $. The long-term costs were from a 1996 study on the use of acute care services 12 months before and after an ischaemic stroke or intracranial haemorrhage. Patient time costs were from a published warfarin study. All costs were presented in 2012 $. If necessary, costs were inflated using the medical care component of the US Bureau of Labor Statistics, Consumer Price Index. Costs were discounted at 3% annually.

Analysis of uncertainty:
One-way sensitivity analyses and probabilistic sensitivity analysis were undertaken. Some results of the one-way analyses were presented in a tornado diagram. The probabilistic sensitivity analysis used gamma distributions for the costs, and beta distributions for probabilities, transition probabilities, and utilities. The results were presented in a table, and a cost-effectiveness acceptability curve.

Results
Apixaban had the highest QALYs and the highest costs. Compared with warfarin, apixaban had an incremental cost-effectiveness ratio of $15,026 per QALY gained, which was below the assumed willingness-to-pay threshold of $50,000.

In the one-way sensitivity analysis, the most influential parameters were the age-adjusted probability of ischaemic stroke, the yearly cost of apixaban, and the age-adjusted probability of intracranial haemorrhage, followed by the costs of dabigatran and rivaroxaban.

The probabilistic sensitivity analysis indicated that at a willingness-to-pay threshold of $50,000 for a QALY, apixaban was most cost-effective in 45.1% of simulations, and dabigatran was most cost-effective in 40% of simulations, while warfarin was most cost-effective in no simulations. When the threshold was raised to $100,000 per QALY, apixaban was most cost-effective in 60.7% simulations.

Authors’ conclusions
The authors concluded that the new oral anticoagulants were more cost-effective than warfarin, and apixaban was preferred.

CRD commentary
Interventions:
The interventions were well described, but the rationale for their choice was not completely clear. There may have been other interventions available for patients with nonvalvular atrial fibrillation.

Effectiveness/benefits:
The means of the parameters in the model were clearly reported, but their variances were not, which limits the validation of the results of the analyses of uncertainty. It was not clear how the effectiveness data were identified and chosen, so it was unclear if the best available data were used. The warfarin adverse events were pooled from the three trials, but the method was not described. All trials had a common comparator, warfarin, so a mixed-treatment meta-analysis should have been undertaken. The model used a multiplication for the death risk after stroke, intracranial haemorrhage, and MI, and this factor was constant over time, which may have overestimated mortality for patients having these events, as over time the difference between mortality from the events, and that from age, lessens. It is unclear what effect this had on the cost-effectiveness. The utility scores appear to have been appropriately derived from US sources, using preference-based methods.

Costs:
The mean costs for resource use items were well reported, but the variances were not, which makes it difficult to validate the results of the uncertainty analyses. The costs were detailed and seem to have been appropriate, but the selection of the sources was not explained. The costs for apixaban were from the UK and converted to US $; the drug costs vary between countries, and drugs can be more expensive in the USA than they are in the UK. Its cost could have been adjusted based on the differences between the UK and the USA, for the other drugs. It was not clear how the costs of monitoring the patient's INR were incorporated in the model, and it was unclear how patient time was valued. An analysis excluding the patient time costs would have been useful, as the authors indicated that other evaluations had not considered them, and including them favoured the anticoagulants.

Analysis and results:
The authors clearly presented the results of the economic evaluation, but did not conduct a full incremental analysis. All the main and probabilistic sensitivity results were presented as comparisons with warfarin. Each treatment should have been compared with the next least costly. The most influential inputs were those that were modified by a factor associated with aging, and this factor was not varied in the analyses. The authors reported a thorough comparison of their results, with those of other economic evaluations of the drugs.

Concluding remarks:
The study was generally well reported, but had some unclear and potentially inappropriate costs. The analysis was not fully incremental, and there were questions around the costing methods, so the validity of the authors' conclusions is unclear.

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