Ximelagatran cost effectiveness 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.

Health technology
The use of ximelagatran, a new oral antithrombotic, for stroke prevention in non-valvular atrial fibrillation (AF). Ximelagatran was compared with warfarin and aspirin. The dosages assessed were 7.5 mg/day for warfarin, 100 mg/day for aspirin and 36 mg twice daily for ximelagatran.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The hypothetical study population comprised patients aged between 65 and 75 years with chronic non-valvular AF.

Setting
The setting was primary care. The economic study was carried out in Australia.

Dates to which data relate
The effectiveness data related to 1991 to 2003. The resource use data related to 1993 to 2002. The price year was not stated.

Source of effectiveness data
The effectiveness data were derived from a review of published studies, Australian governmental data, local sources and expert opinion.

Modelling
A decision tree model was used to synthesise data from multiple studies and to estimate the costs and clinical outcomes associated with ximelagatran, warfarin and aspirin. The model included the health states of moderate to severe strokes and major bleeds.

Outcomes assessed in the review
The review assessed the risks of moderate to severe stroke with warfarin, aspirin and ximelagatran, and the probability of adverse drug reactions in the form of major bleeds. The review also assessed the quality of life for the health states "well", "stroke" and "bleeding".
Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Eight primary studies were included in the review.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
No differences between the primary studies were investigated.

Results of the review
The proportion of strokes was 1.4 (range: 0.40 to 2.5) for warfarin, 3.6 (range: 1.00 to 6.3) for aspirin and 1.3 (range: 1.00 to 1.6) for ximelagatran.

The proportion of major bleeding was 1.3 (range: 0.40 to 4.2) for warfarin, 0.9 (range: 0.80 to 1.6) for aspirin and 1.3 (range: 1.00 to 1.6) for ximelagatran.

It should be noted that these data were extracted from Table 2 of the study, which does not match the data provided in Table 1 of the study. This discrepancy hinders the interpretation of the study results.

Measure of benefits used in the economic analysis
The main measure of benefits used in the economic analysis was strokes avoided.

Direct costs
The authors reported the medication resource use quantities and costs separately. They reported only the aggregated costs of stroke and major bleeds obtained from published studies. The direct costs were those incurred by a third-party payer, in this case the government in Australia. The medication cost data for warfarin and aspirin were obtained from the Pharmaceutical Benefits Scheme (PBS), while such data for ximelagatran were based on authors’ assumptions. The costs therefore represented those incurred by the Australian government, which may not represent the true opportunity cost of the resources. This may limit the generalisability of the study results to settings outside Australia. Other resource use data for warfarin were obtained from published studies. The time horizon of the model was not stated explicitly, so it was difficult to ascertain whether discounting was relevant. Discounting does not appear to have been conducted. The price year was not stated. The study reported the average costs.
Statistical analysis of costs
Individual patient level data were not available, so a statistical analysis of the costs was not possible.

Indirect Costs
The indirect costs were not included in the analysis, which the authors stated was appropriate given the third-party payer perspective adopted.

Currency
Australian dollars (AUD).

Sensitivity analysis
A univariate sensitivity analysis was undertaken to explore uncertainty in the effectiveness and cost data. The ranges tested were obtained from the review of the literature. In addition, a threshold analysis was undertaken to determine the price at which ximelagatran would be considered cost-effective.

Estimated benefits used in the economic analysis
Warfarin was estimated to prevent 0.748 strokes per patient per year. Aspirin was estimated to prevent 0.546 strokes per patient per year. Ximelagatran was estimated to prevent 0.757 strokes per patient per year. The time horizon for the model was unclear and discounting does not appear to have been undertaken. The model considered only the side effect of major bleeding.

Cost results
Warfarin was estimated to cost AUD 1,677.42 per patient per year, compared with AUD 1,286.01 for aspirin and AUD 4,041.68 for ximelagatran. Again, the time horizon of the model was unclear.

Synthesis of costs and benefits
The costs and benefit were combined to calculate the cost per stroke averted. The study reported average cost-effectiveness ratios for all three drugs, and incremental cost-effectiveness ratios (ICERs) for ximelagatran versus either aspirin or warfarin. The ICER was AUD 272,000 per additional stroke avoided per patient per year for ximelagatran compared with warfarin, and AUD 13,000 per additional stroke avoided per patient per year for ximelagatran compared with aspirin.

The sensitivity analysis showed that ximelagatran was more cost-effective in patients who experienced warfarin-related adverse drug events. Ximelagatran would need to be priced at $1.28 per 36-mg tablet for the ICER to be zero when compared with warfarin.

Authors' conclusions
Warfarin is cost-effective when compared with aspirin or ximelagatran for stroke prevention in atrial fibrillation (AF). Ximelagatran appears to be cost-effective in a small group of patients, particularly those with a high risk of bleeding with warfarin. This conclusion could not be drawn from the data reported in the study, as the authors did not conduct an incremental analysis that simultaneously compared all three alternatives. In addition, the authors did not discuss what threshold should be considered appropriate when assessing incremental cost-effectiveness ratios (ICERs) based on the cost per stroke avoided.

CRD COMMENTARY - Selection of comparators
The authors selected warfarin and aspirin as the comparators since they are commonly used therapies for AF in the study setting. The study also included a new comparator, ximelagatran. The study did not include other potentially...
relevant comparators such as clopidogrel. You must decide whether aspirin and warfarin are commonly used in your own setting.

**Validity of estimate of measure of effectiveness**

The authors did not state that a systematic review of the literature had been undertaken. It was unclear whether the review had been conducted in a systematic way to identify relevant research and minimise bias. Details of the primary studies and the methods used to combine the primary estimates were not provided. Estimates from multiple studies do not appear to have been combined. The authors stated that the included trials had strict selection criteria, which may mean the effectiveness results are not representative of the general population. The authors also acknowledged that the age range in the included trials was 65 to 75 years, so the results may not be generalisable to older patients. Uncertainty around the outcome parameters was investigated in sensitivity analyses.

**Validity of estimate of measure of benefit**

The estimation of health benefits was modelled. The authors employed estimates of utility, which could have been used to calculate quality-adjusted survival, in an outcome measure and chose to use a disease-specific measure of strokes avoided, which may make it difficult to compare the results from this study with cost-effectiveness analyses in other disease areas.

**Validity of estimate of costs**

It appears that all the categories of cost relevant to the perspective adopted were included in the analysis. While the resource use quantities were reported separately from the costs for medication, the authors presented only aggregated costs for the main health outcomes of stroke and major bleed. As these are likely to be quite important costs in the analysis, this may limit the generalisability of the study results. The authors performed one-way sensitivity analyses around the medication costs, using ranges that appear to have been appropriate. The authors do not appear to have adjusted the costs for inflation, or adjusted them to the same price year. They acknowledged that the cost of stroke was estimated in 1998 to 1999 and is likely to be an underestimate of the current cost of stroke. This limits the validity of the study results. Discounting might have been relevant, as the time horizon for the model was unclear, but it was not undertaken.

**Other issues**

The authors compared their findings with those from other studies. They discussed the potential use of ximelagatran in other disease areas. They also discussed the possibility that ximelagatran may be cost-effective in patients who are intolerant to warfarin or aspirin, or if the bleeding rate on warfarin is very high. However, they did not discuss how likely it is that the bleeding rate on warfarin would reach the upper limit of the range tested. The authors appear to have presented their results selectively since they did not present the cost per quality-adjusted survival, even though the outcome measure was specified in the study. The authors acknowledged that the study was based on limited data for ximelagatran, and that the results might change as more data on effectiveness and price become available.

**Implications of the study**

The authors suggested that more data are required to fully evaluate the pharmacoeconomic implications of ximelagatran.

**Source of funding**

None stated.

**Bibliographic details**

Indexing Status
Subject indexing assigned by CRD

MeSH
Anticoagulants; Aspirin; Atrial Fibrillation; Azetidines; Comparative Study; Cost-Benefit Analysis; Costs and Cost Analysis; Sensitivity and Specificity; Stroke /etiology /prevention & control; Warfarin

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