Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular 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
Warfarin sodium, for the prevention of stroke in patients who have nonvalvular atrial fibrillation (NVAF), with or without additional stroke risk factors.

Type of intervention
Primary prevention and secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
In the base case analysis, patients were 65 years old, had NVAF and were 'good candidates for warfarin and aspirin therapy'.

Setting
The economic study was carried out in California, USA.

Dates to which data relate
Effectiveness and resource use data were taken from a range of studies published between 1989 and 1995. Costs were given in 1994 prices.

Source of effectiveness data
Estimates of effectiveness were obtained from a review of the previously published studies.

Modelling
A Markov model was used to combine the expected outcomes of each treatment alternative with their respective costs over a 10-year period.

Outcomes assessed in the review
The outcomes assessed in the review were the probabilities of stroke, haemorrhage and death, associated with each therapy. Outcomes were analysed by three stroke risk categories: (1) high-risk patients, who had multiple risk factors; (2) medium-risk patients, who had NVAF and one additional risk factor; and (3) low-risk patients, who had no risk factors.
Study designs and other criteria for inclusion in the review
Criteria for inclusion in the review were not explicitly specified, although the NVAF trials were all randomised, controlled trials.

Sources searched to identify primary studies
Not specified.

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

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

Number of primary studies included
Eight randomised-controlled trials (NVAF trials), two cohort studies, two case-control studies and one longitudinal study were included in the review.

Methods of combining primary studies
Primary studies were combined in a narrative fashion, with existing meta-analyses used to derive baseline values, where possible. However, the rate of major haemorrhage was based on data taken directly from NVAF trials, in order to take account of a range of different rates. The method of combination was not explicitly stated.

Investigation of differences between primary studies
Differences between studies in terms of the definition of major haemorrhage, age groups and risk factors were considered.

Results of the review
With no therapy, the annual rate of stroke in high-risk patients was estimated to be 5.3% (range: 4.9 - 17.7), in medium-risk patients, 3.6% (range: 2.6 - 4.6) and in low-risk patients, 1.6% (range: 1.1 - 2.1). The stroke risk reduction with warfarin was estimated to be 68% (range: 50 - 79) and with aspirin 22% (range: 1 - 36). The annual rate for major haemorrhage with warfarin was 1.4% (range: 1.3 - 2.8), with aspirin 0.9% (range: 0.8 - 1.0) and with no therapy 0.8% (range: 0.7 - 1.0). The relative risk (RR) of major haemorrhage for warfarin versus no therapy, was 1.8 and the RR for warfarin versus aspirin was 1.5. The overall decrease in mortality was estimated to be 33% with warfarin and 17% with aspirin.

Measure of benefits used in the economic analysis
Quality adjusted life years (QALYs) were used as the measure of benefit for the economic analysis. Firstly, quality of life estimates were derived by the time trade-off method. 74 patients, with a history of atrial fibrillation, were interviewed with the aid of a computerised utility-assessment tool. 86% of these patients were male, the mean age was 70 years and half were currently receiving warfarin therapy. The results from 57 interviews, which were complete and internally consistent, were combined with probabilities of adverse events to determine QALYs.

Direct costs
Costs and quantities were reported separately and were estimated from the perspective of the health care system. The treatment cost for three types of acute neurological event was obtained from the Medicare DRG Handbook. The annual cost of medical care, following a neurological event, was approximated from the literature. The treatment cost of
haemorrhage without residua and of other causes of death was also calculated from the DRG Medicare handbook. The annual cost of prophylaxis (including the monitoring of warfarin therapy) was estimated from telephone surveys to eight pharmacies and eight laboratories across the USA. Net costs were estimated for a 10-year period, with costs discounted annually at 5%. The cost of routine medical care was excluded as being common to all therapies. Costs related to 1994 prices.

**Statistical analysis of costs**
Not applicable.

**Indirect Costs**
Indirect costs were not included in the study because of the difficulties in estimating them and because they were considered to be relatively small in this patient group.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analysis was used to investigate the cost-effectiveness of warfarin prophylaxis, relative to aspirin prophylaxis. The impact of changes in stroke, haemorrhage and mortality parameters, as well as in quality of life estimates and cost, were investigated using one-way sensitivity analyses.

**Estimated benefits used in the economic analysis**
In the base case analysis, warfarin improved survival by 0.24 QALYs compared with aspirin and by 0.50 QALYs compared with no therapy, for high-risk patients. Warfarin improved survival by 0.14 QALYs compared with aspirin and by 0.37 QALYs compared with no therapy in medium-risk patients. In low-risk patients warfarin improved survival by 0.01 QALYs compared with aspirin and by 0.19 QALYs compared with no therapy. Benefits were discounted at 5% per annum.

**Cost results**
Over the 10-year period, the expected total per-patient cost for the high-risk group was estimated to be $12,500 for warfarin, $13,200 for aspirin, and $15,300 for no therapy. In the medium-risk group, the cost for warfarin was $10,900, for aspirin $9,700, and for no therapy $11,400. For low-risk patients the cost was estimated to be $9,000 for warfarin, $5,400 for aspirin and $6,300 for no therapy.

**Synthesis of costs and benefits**
Warfarin was the dominant strategy (yielding cost savings and increased QALYs) for high-risk patients. For medium-risk patients the incremental cost-effectiveness ratio (ICER) for warfarin, relative to aspirin, was estimated to be $8,000 per QALY gained (range: $200 - $30,000); both warfarin or aspirin were dominant to no therapy. For the low-risk group, the ICER of warfarin was estimated to be $370,000 per QALY gained compared to aspirin and $14,000 (range: 7,700 - 24,000) per QALY gained compared with no therapy. Aspirin therapy was found to be dominant to no therapy for all categories of stroke risk.

Sensitivity analysis revealed that the cost-effectiveness of warfarin, relative to aspirin, was directly related to the rate of stroke. For example, if the annual rate of stroke were 4.6% or higher, warfarin would be dominant, relative to aspirin. The utility of warfarin, the cost of medical care and the patient age at which therapy began were also found to be directly related to cost-effectiveness: if warfarin therapy were used for a 75-year-old, low-risk individual, then the ICER of warfarin would fall to $110,000 per QALY gained. The ICER was found to be inversely related to the rate of haemorrhage during warfarin therapy, the discount rate and the effectiveness of aspirin therapy: if aspirin were
ineffective for preventing both cardiovascular deaths and strokes, then warfarin was found to have an ICER of $14,000

**Authors’ conclusions**
Warfarin prophylaxis prolongs quality-adjusted survival and yields cost savings for NVAF patients with high-risk of stroke. Treatment of medium-risk NVAF patients with warfarin is inexpensive relative to other existing health technologies. In low-risk patients, warfarin prophylaxis is expensive relative to other health interventions. Aspirin is more cost-effective than no therapy for all risk groups.

**CRD COMMENTARY - Selection of comparators**
The reason for the authors’ choice of comparators is clear, namely that they represented common clinical practices. You, the user of the database, should decide if these are widely used practices in your own setting.

**Validity of estimate of measure of benefit**
Measures of effectiveness were based on a literature review, but no detail was given regarding the criteria for inclusion, the sources searched or the criteria used to ensure validity of primary studies. Although some data came from randomised controlled trials, the validity of the randomisation process was not demonstrated. However, a comprehensive sensitivity analysis was performed to investigate uncertainties in the base case estimates.

The measures of QALY used in the economic analysis were derived from a sample of patients with NVAF. The utility values assigned by these patients may not be representative of those that society might place on such events. Variations in utility values were found to ‘considerably affect’ cost-effectiveness estimates and the authors acknowledged the need for further research in this area.

**Validity of estimate of costs**
Costs and quantities were reported separately, were discounted and the year to which they relate was clearly specified. However, since all costs related to the US setting, they should be interpreted with care, when generalised to other settings.

**Other issues**
The authors conducted their analysis with reference to the level of risk of stroke, which improved the accuracy of their cost-effectiveness estimates. They acknowledge the limitations of their research, such as the generalisability of the findings to other age groups, and conducted an extensive sensitivity analysis to investigate the implications of uncertainty in the estimates used in their model.

**Implications of the study**
To improve the accuracy of the estimate for the cost-effectiveness of warfarin therapy, further research on quality of life estimates is needed.

**Source of funding**
None stated

**Bibliographic details**

**PubMedID**
7500532
Other publications of related interest


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Subject indexing assigned by NLM

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