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
Three treatments for stroke prophylaxis in patients with chronic atrial fibrillation were investigated. The treatments were aspirin, adjusted-dose warfarin with an international normalised ratio (INR) of 2 to 3, and fixed-dose ximelagatran (36 mg twice per day).

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 70-year-old patients with chronic atrial fibrillation, varying risk of stroke, and no contraindications to anticoagulation therapy.

Setting
The setting was primary care. The economic study was conducted at Washington University School of Medicine, St. Louis (MO), USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1991 and 2005. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies, supplemented by the authors’ own assumptions and by expert opinion.

Modelling
A semi-Markov model was performed to compare each of the three treatments. The permanent health states in the model included healthy with atrial fibrillation, ischaemic stroke (fatal, major, mild, or reversible), transient ischaemic attack (TIA), haemorrhage (fatal, intracranial, or major or minor non-cerebral), recurrent or combined events, and death. For all treatments, quality-adjusted life expectancy, risk of adverse events, and net cost were quantified over a maximum of 20 years.

Outcomes assessed in the review
The outcomes assessed were:
the rate of stroke with aspirin;

the proportions of ischaemic strokes which were fatal, major, minor, or with no residua with warfarin, ximelagatran, or aspirin treatment;

the relative risk (RR) of stroke with warfarin compared with aspirin;

the RR of stroke with ximelagatran compared with warfarin;

the annual rate of intracranial haemorrhage, major haemorrhage and minor haemorrhage in patients receiving warfarin;

the RR of haemorrhage with ximelagatran compared with warfarin;

the RR of haemorrhage with aspirin compared with warfarin;

the rate of elevated liver function test results with ximelagatran;

the monthly risk of elevated liver function test results with warfarin;

the annual rate of permanent hepatic damage with ximelagatran;

the RR of non-stroke and non-haemorrhage death;

the RR reduction in all-cause mortality in patients on warfarin or ximelagatran compared with aspirin; and

the quality of life values associated with patients in healthy states receiving aspirin or warfarin, patients suffering a mild, moderate-to-severe or recurrent neurological event, and patients suffering a major haemorrhage other than intracranial haemorrhage.

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
Approximately 30 studies were included in the review.

Methods of combining primary studies
Although the authors did not report how the primary studies were combined, it would appear that the results of different primary studies were pooled using a meta-analysis.

Investigation of differences between primary studies
Results of the review
The annual rate of stroke with aspirin was 4.5% (range: 0.8 - 13.7).

The proportions of ischaemic strokes that were fatal, major, minor, or with no residua with warfarin or ximelagatran were:

fatal 8.2% (range: 8.2 - 10.1), major 40.2% (range: 40.2 - 41.7), minor 42.5% (range: 34.8 - 42.5), and with no residua 9.1% (range: 9.1 - 13.3).

The proportions of ischaemic strokes that were fatal, major, minor, or with no residua with aspirin treatment were:

fatal 17.9% (range: 10.1 - 17.9), major 30.0% (range: 30.0 - 41.7), minor 41.0% (range: 34.8 - 41.0), and with no residua 11.0% (range: 11.0 - 13.3).

The RR of stroke with warfarin compared with aspirin was 0.48 (range: 0.37 - 0.63).

The RR of stroke with ximelagatran compared with warfarin was 1.0 (range: 0.74 - 1.31).

In patients receiving warfarin, the annual rate of intracranial haemorrhage was 0.4% (range: 0.4 - 1.2), major haemorrhage 2.5% (range: 2.0 - 4.0), and minor haemorrhage 35.7% (range: 30 - 40).

The RR of haemorrhage with ximelagatran compared with warfarin was 0.74 (range: 0.57 - 0.97).

The RR of haemorrhage with aspirin compared with warfarin was 0.59 (range: 0.50 - 0.70).

The monthly rate of elevated liver function test results with ximelagatran was 1.0% (range: 0 - 2) during the first 6 months and 0.08% (range: 0 - 1) after the first 6 months.

The monthly risk of elevated liver function test results with warfarin was 0.035% (range: 0 - 1).

The annual rate of permanent hepatic damage with ximelagatran was 0.04% (range: 0.012 - 0.113).

The RR of non-stroke and non-haemorrhage death was 1.3 (range: 1.0 - 1.5) for patients with atrial fibrillation, and 2.3 (range: 1.3 - 3.0) for atrial fibrillation patients with a history of stroke.

The RR reduction in all-cause mortality in patients on warfarin or ximelagatran compared with aspirin was 19% (range: 0 - 33).

The quality of life estimates were as follows:

for patients in healthy states, receiving aspirin 0.998 (range: 0.994 - 1) and receiving warfarin 0.987 (range: 0.953 - 1);

for patients suffering neurological events, mild neurological event 0.75 (range: 0 - 1), moderate-to-severe neurological event 0.39 (range: 0 - 1), and recurrent neurological event 0.12 (range: 0 - 1); and

for patients suffering a major haemorrhage other than intracranial haemorrhage 0.8 (range: 0.5 - 0.99).

Methods used to derive estimates of effectiveness
Utility estimates were supplemented by the authors' own assumptions and by expert opinion. To derive the quality of life estimates associated with ximelagatran treatment, the authors conducted a one-time e-mail survey of the Anticoagulation-Thromboembolism Research Consortium, a group of approximately 30 physicians involved in antithrombotic clinical management and research. Twelve of these physicians responded. Seven decision-analysts, who had published in the area of antithrombotic therapy, were also surveyed. Three of these responded.
Estimates of effectiveness and key assumptions
The utility associated with ximelagatran treatment was 0.989 (range: 0.986 - 0.991) during the first 6 months of therapy, and 0.994 (range: 0.993 - 0.996) after the initial 6 months.

The utility associated with minor haemorrhage was 0.8 (range: 0.5 - 0.99), liver function test elevation 0.98 (range: 0.9 - 1.0) and initiation of warfarin therapy, and initiation of warfarin therapy, 0.98 (range: 0.9 - 1.0).

Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs). The authors obtained the utility for warfarin and aspirin from a prior survey of 83 patients with atrial fibrillation. Other utility values were derived from expert opinion, or from the authors’ own assumptions.

Direct costs
The resource quantities and the costs were not reported separately. However, the authors provided detailed costs, broken down by category. The direct costs included were those of the third-party payer. These comprised the costs of adverse events such as haemorrhage, stroke, TIA, intracranial haemorrhages and hepatic failure, and drug costs. The costs of a minor haemorrhage were based on remuneration for an expanded problem-focused physician visit. The costs of a major extra cranial haemorrhage were based on Medicare remuneration for the diagnosis-related group associated with gastrointestinal haemorrhage. The costs for other adverse events were calculated using the median value of published studies and Medicare remuneration. The annual costs of warfarin therapy were calculated by combining the annual prescription cost with Medicare reimbursement information. The cost of ximelagatran was based on the cost of clopidogrel and the cost of ximelagatran in Germany. The authors reported that medical costs unrelated to antithrombotic therapy, haemorrhage or neurological ischaemia were excluded as they were interested in the incremental cost-effectiveness of one option versus another, rather than the absolute costs. Discounting was necessary, as the costs could be incurred during 20 years, and was appropriately performed at a rate of 3% per annum. The study reported the average costs. The price year was 2003.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
The authors performed one-way sensitivity analyses of the variables in the decision model over their plausible ranges. In a two-way sensitivity analysis, the authors calculated the cost-effectiveness ratios of ximelagatran for combinations of stroke and intracranial haemorrhage risk. The authors also performed first-order Monte Carlo simulations, by randomly sampling 10,000 times a series of utilities from the 70 patients who had atrial fibrillation and usable utility values, and simulated outcomes using uniform distributions in all variables.

Estimated benefits used in the economic analysis
The discounted QALYs gained with each of the three strategies were 8.58 with aspirin, 9.39 with warfarin and 9.51 with ximelagatran.
**Cost results**
The discounted costs associated with each of the three treatments were $17,000 with aspirin, $19,000 with warfarin and $32,000 with ximelagatran.

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the extra cost per QALY gained). The associated incremental cost-utility ratios were:

for warfarin versus aspirin, $2,000 per QALY;

for ximelagatran versus aspirin, $16,200 per QALY; and

for ximelagatran versus warfarin, $116,000 per QALY.

The results from the sensitivity analysis showed that for ximelagatran to be cost-effective over warfarin at the $50,000 per QALY threshold, it would have to cost less than $1,100 per year or be prescribed to patients who had an elevated risk of intracranial haemorrhage of more than 1% per year of warfarin, or a low quality of life with warfarin therapy (i.e. less than 0.97).

**Authors' conclusions**
Assuming equal effectiveness in stroke prevention and decreased haemorrhage risk, ximelagatran was unlikely to be cost-effective in patients with atrial fibrillation unless they had a high risk of intracranial haemorrhage or a low quality of life with warfarin.

**CRD COMMENTARY - Selection of comparators**
The justification for using warfarin and aspirin as the comparators was clear in that these two treatments represented current practice in stroke prophylaxis. You should decide if these comparators represent current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The authors did not report that a systematic review of the literature was undertaken to identify relevant research and minimise biases. Nor did they report the methodology of their review. Despite this, the authors used data from approximately 30 studies, all of which appeared to be relevant and up to date. The authors did not explicitly report how the estimates of effectiveness from primary studies were combined. However, it would appear that results from different studies were combined using some form of meta-analysis. The authors did not report whether differences between the studies used to derive the same measure of effectiveness were investigated. To derive utility values for certain health states the authors used expert opinion and their own assumptions. All effectiveness and utility data used to populate their model were varied using appropriate sensitivity analyses, the ranges used appear to have been adequate.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled using a semi-Markov model, which was appropriate. As the benefits could be incurred during a 20-year period, the QALYs were appropriately discounted at a rate of 3% per annum.

**Validity of estimate of costs**
All the categories of cost relevant to the perspective adopted were included in the analysis. The authors reported that costs not related to antithrombotic therapy, haemorrhage, or neurological ischaemias were excluded from the analysis. It is unlikely that these omissions would have affected the authors' results, as they would appear to be common to all treatment groups. Although the costs and the quantities were not reported separately, which will limit the
generalisability of the authors' results, the authors appropriately separated the costs into different categories. The costs were derived from Medicare and the published literature. Appropriate sensitivity analyses of the costs were performed, using ranges that appear to have been appropriate. Discounting was necessary, as the costs could be incurred over a 20-year period, and was appropriately performed. Medicare reimbursements were used to proxy prices, which may not reflect the true cost of the intervention. The price year was appropriately reported, which will facilitate any possible inflation exercises.

Other issues
The authors did not compare their findings with those from other studies. As ximelagatran is a relatively new drug, it is unlikely that any other cost-effectiveness analysis had been undertaken at the time of this study. The issue of generalisability to other settings was addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively, and their conclusions reflected the scope of the analysis. The authors reported a number of further limitations to their study. First, the efficacies used in the base-case were based on a randomised, controlled trial in which compliance, monitoring and follow-up were better than in general practice, hence overestimating the benefits of both anticoagulants. In addition, since ximelagatran has a shorter half-life than warfarin and aspirin, noncompliant patients taking ximelagatran may be especially susceptible to lapses in adherence. Second, extrapolations were made from the results of clinical trials lasting only 1 to 3 years, and thus did not account for the fact that rates of adverse events could vary over the long term.

Implications of the study
The authors recommended that, if additional randomised trials with ximelagatran are conducted in the atrial fibrillation population, they should preferentially recruit patients with very low utility values whilst on warfarin, or patients with a high risk of intracranial haemorrhage.

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