Cost-effectiveness of warfarin: trial versus "real-world" 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.

CRD summary
This study examined the cost-effectiveness of warfarin treatment in patients with atrial fibrillation, who were at moderate-to-high risk of ischaemic stroke, and considered various scenarios for treatment adherence and discontinuation. The cost-effectiveness of warfarin and its beneficial effect deteriorated with poorer control of the international normalised ratio, as shown when real-world data for replacement with aspirin and discontinuation were used. The study was based on valid methodology and was well conducted and reported. The authors' conclusions appear to be robust.

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

Study objective
The objective was to examine the cost-effectiveness of warfarin treatment for patients with non transient, non valvular atrial fibrillation, who were at moderate-to-high risk of ischaemic stroke. Various scenarios for treatment adherence and discontinuation, comparing real practice with trial data, were considered.

Interventions
The four scenarios for warfarin control were perfect control, trial-data control, real-world control, and combination control.

In perfect control, all patients on warfarin stayed within the target range of international normalised ratio (INR) and this was the ideal treatment according to official guidelines.
In trial-data control, patients on warfarin reflected clinical trial conditions, where the INR remained within target range only 68% of the time.
In real-world control, patients on warfarin stayed within the INR target range as they would do in routine out-patient clinical practice, which was 48% of the time.
In combination control, a proportion of warfarin-eligible patients were prescribed either aspirin (12%), or neither warfarin nor aspirin (23%), and the remainder received warfarin, as in clinical prescription practice.

Location/setting
USA/secondary care.

Methods
Analytical approach:
The analysis was based on a semi-Markov model that represented the clinical events associated with primary and recurrent ischaemic stroke and both intracranial and extracranial haemorrhage. A lifetime horizon was considered. The authors stated that the perspective of the US health care system was adopted.

Effectiveness data:
The clinical data came from a selection of known, relevant sources, including meta-analyses, clinical trials, observational studies, and official databases. The INR control for trial-data control was taken from a randomised controlled trial (RCT) and that for real-world control was from a retrospective study of US out-patient practices. The
risk of future events and transition probabilities were mainly from RCTs and meta-analyses of RCTs. The key details of each source were provided. The primary clinical input was the probability of ischaemic stroke under each scenario.

Monetary benefit and utility valuations:
The utility valuations were derived from two sources: a nationally representative catalogue of European Quality of life (EQ-5D) questionnaire scores for chronic conditions from the 2000 to 2002 Medical Expenditure Panel Survey, and a systematic review of quality of life in stroke patients.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary benefit measure and were discounted at an annual rate of 3%. Life-years (LYs) and other model outputs were also reported.

Cost data:
The economic analysis included the costs of drugs, medical services associated with acute events, long-term medical services, which depended on the level of disability, management of adverse events, and INR tests and follow-up. The costs and resource use data were derived from published studies, wholesale acquisition prices, and a national database of 1,000 hospitals. A cost-to-charge ratio was applied when only charges were available. All costs were in US dollars ($) and a 3% annual discount rate was applied. The price year was not reported.

Analysis of uncertainty:
A probabilistic sensitivity analysis was undertaken on most of the model inputs, which were assigned stochastic distributions. Univariate analyses were performed on the key inputs, which were the baseline stroke risks, anticoagulation discontinuation, and time in therapeutic range, and on other inputs that could not be included in the probabilistic analysis.

Results
The expected costs were $68,039 with perfect control, $77,764 with trial-data control, $84,518 with real-world control, and $87,248 with combination control. The LYs were 9.70 with perfect control, 9.44 with trial-data, 9.28 with real-world, and 9.21 with combination control. The QALYs were 7.21 with perfect, 6.92 with trial-data, 6.75 with real-world, and 6.67 with combination control.

Real-world control was more costly and less effective than trial-data control, showing that trial conditions might have been too favourable compared with real practice. This was due to the higher number of strokes found with real-world data compared with trial data.

The probabilistic sensitivity analysis showed that real-world and combination control resulted in higher costs and lower benefits compared with trial-data control in most of the simulations, while perfect control was generally more beneficial and less expensive than trial-data control.

The deterministic sensitivity analysis indicated that the costs were affected by changes in stroke history, while QALYs were influenced by changes in patient age.

Authors' conclusions
The authors concluded that the cost-effectiveness of warfarin and its beneficial effect deteriorated with poorer control of INR levels, as shown when real-world levels of replacement with aspirin and discontinuation were used.

CRD commentary
Interventions:
The selection of the comparators was consistent with the objective, which was to identify the impact of different levels of treatment adherence on the cost-effectiveness of warfarin treatment.

Effectiveness/benefits:
The authors selected their data sources, which varied in their validity, ranging from randomised controlled trials and systematic reviews, which are generally considered to be robust sources of evidence, to retrospective and observational
studies, which have some methodological drawbacks due to their non-rigorous study design. The use of the observational data was justified by the need to evaluate real-world situations and the sources appear to have been appropriate. The key details of each data source were reported, which enhances the transparency of the clinical estimates. The main benefit measure was appropriate given the impact of the disease on both quality of life and survival. Conventional discounting was applied. The sources of the utility values were described and the instruments used to derive them were appropriate.

Costs:
The analysis of costs was carried out from a relatively broad perspective and included a wide range of economic inputs. The authors noted the importance of including long-term medical costs, which were the key driver of the analysis. Most of the costs were derived from published studies and official reports, which means that some cost categories were not broken down into individual items. A large database was used to estimate the hospital costs. The price year was not explicitly reported, which limits the possibility of making reflation exercises in other time periods.

Analysis and results:
The costs and benefits were reported for all scenarios, but they were not synthesised into cost-utility ratios because the objective was to compare the total costs and benefits between scenarios. The issue of uncertainty was addressed well in the sensitivity analysis, which used various approaches to investigate the impact of changes in all the model inputs. A diagram of the decision model and its assumptions were clearly reported. The authors pointed out the strengths and limitations of their analysis, such as the strengths of the appropriate comparator selections (different levels of treatment adherence rather than various therapies), and the limitations of using observational data and simplifying assumptions.

Concluding remarks:
The study was based on valid methodology and was well conducted and reported. The authors' conclusions appear to be robust.

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