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## Oral anticoagulation strategies after a first idiopathic venous thromboembolic event

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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 study examined six strategies for the treatment of 40- to 80-year-old men and women after their first idiopathic venous thromboembolic event or pulmonary embolism (PE) and after a standard 3-month course of conventional-intensity anticoagulation therapy with warfarin.

Strategy 1 was the discontinuation of anticoagulation (i.e. the 3-month strategy).

Strategy 2 was conventional-intensity anticoagulation for 3 additional months (i.e. the 6-month strategy).

Strategy 3 was conventional-intensity anticoagulation for 9 additional months (i.e. the 12-month strategy).

Strategy 4 was conventional-intensity anticoagulation for 21 additional months (i.e. the 24-month strategy).

Strategy 5 was conventional-intensity anticoagulation of unlimited duration.

Strategy 6 was low-intensity anticoagulation of unlimited duration.

### Type of intervention

Secondary prevention.

### Economic study type

Cost-utility analysis.

### Study population

The study population comprised a hypothetical cohort of 40- to 80-year-old men and women, 3 months after a first episode of idiopathic deep vein thrombosis or PE.

### Setting

The setting was secondary care. The economic study was carried out in the USA.

### Dates to which data relate

The effectiveness data and some resource use data came from studies published between 1992 and 2004. The price year was 2002.

### Source of effectiveness data

The effectiveness evidence was derived from a synthesis of completed studies and experts' opinions.

### Modelling

A Markov model was constructed to simulate the clinical and economic outcomes associated with the six treatment options examined in the study. The health states considered were:

well, with or without oral anticoagulation;

recurrent deep vein thrombosis or PE;

severe post-thrombotic syndrome;

minor and major bleeding complications;

permanent disability after haemorrhagic stroke;

vena cava filter treatment; or

death from recurrent PE, major bleeding, filter implantation or natural causes.

Several assumptions were made in the model. First, recurrent venous thromboembolism was always followed by conventional-intensity anticoagulation of unlimited duration. Second, a major bleeding episode always led to permanent discontinuation of anticoagulation. Third, patients who experienced intracerebral bleeding became permanently disabled and died at high rates. Finally, if venous thromboembolism recurred while the patient was receiving conventional-intensity warfarin, two scenarios were possible. In one scenario, if venous thromboembolism recurred when the INR was in the therapeutic range (2 - 3), anticoagulation therapy was continued and a vena cava filter was implanted. In the other scenario, if the disease recurred when the INR was sub-therapeutic (less than 2), anticoagulation therapy was continued and no filter was implanted. The time horizon was the patients' lifetime. The cycle length, although not reported, might have been 1 year. A simplified structure of the model was not reported.

### **Outcomes assessed in the review**

The outcomes estimated from the literature were risk of recurrence, risk of bleeding, mortality, efficacy of vena cava filter, and estimates of quality of life. Life expectancy was also estimated.

### **Study designs and other criteria for inclusion in the review**

A review of the literature was undertaken to identify primary studies. No details of the review were reported. Both clinical trials and observational studies were included, but no further information was provided. Life expectancy was derived from US life tables.

### **Sources searched to identify primary studies**

The authors stated that the peer-reviewed literature was searched to identify primary studies.

### **Criteria used to ensure the validity of primary studies**

Not stated.

### **Methods used to judge relevance and validity, and for extracting data**

Not stated.

### **Number of primary studies included**

Twenty-eight primary studies provided clinical data.

### **Methods of combining primary studies**

The data from clinical trials were pooled to estimate the probability of venous thromboembolism recurring as PE and its case-fatality rate. A narrative method appears to have been used to combine the other primary estimates.

### **Investigation of differences between primary studies**

Not stated.

### **Results of the review**

The risk of recurrence with conventional-intensity anticoagulation was 0.7 per year (range: 0.7 - 1.3).

The relative risk of low- versus conventional-intensity anticoagulation was 2.8 (range: 1.1 - 7).

In terms of the risk of recurrence after anticoagulation is stopped, the early risk (in year 1) was 10% per year (range: 7 - 27) and the late risk (after year 1) was 5% per year (range: 2 - 8). The relative risk of recurrence of women versus men was 0.7 (range: 0.3 - 1).

The likelihood of venous thromboembolism recurring as PE was 32% (range: 25 - 38).

The case-fatality rate of PE was 16% (range: 7 - 29).

The lifetime risk of severe post-thrombotic syndrome was 9.3% (range: 5.6 - 12.8) and the relative risk following recurrence after deep vein thrombosis was 6.4 (range: 3.1 - 13.3).

For warfarin therapy, the risk of major bleeding with conventional-intensity anticoagulation according to age group was:

40 - 49 years, 1.0 (range: 0.5 - 1.5);

50 - 59 years, 1.5 (range: 0.8 - 2.3);

60 - 69 years, 2.3 (range: 1.5 - 3.4);

70 - 79 years, 3.4 (range: 2.3 - 5.1); and

80 years or older, 5.1 (range: 3.4 - 7.6).

The risk of major bleeding without warfarin was 0.4% per year (range: 0 - 1).

The risk of minor bleeding with conventional-intensity anticoagulation was 7.7% per year (range: 2.9 - 9.6).

The risk of minor bleeding without warfarin was 1.4% per year (range: 1.0 - 6.7).

The relative bleeding risk for low- versus conventional-intensity anticoagulation was 1 (range: 0.4 - 3).

The case-fatality rate of major bleeding was 13% (range: 9 - 17).

The rate of haemorrhagic stroke was 9% (range: 6 - 13).

The mortality following haemorrhagic stroke was 18% per year (range: 17 - 52).

The likelihood of sub-therapeutic INR was 28% (range: 14 - 47).

For vena cava filter, the efficacy in preventing PE was 78% (range: 10 - 95), while the case-fatality rate of filter placement was 0.2% (range: 0 - 0.4).

The quality of life measures were:

for permanent disability following haemorrhagic stroke, 0.60 (range: 0.02 - 1);

for warfarin therapy, 0.99 (range: 0.92 - 1); and

for severe post-thrombotic syndrome, 0.95 (range: 0.79 - 1).

The disutilities for acute complications (in days lost from quality-adjusted life expectancy because of hospitalisation or disease) were:

for recurrent PE, 6.7 (range: 3.4 - 10.1);

for recurrent deep vein thrombosis, 5.5 (range: 2.8 - 8.3);

minor bleeding, 1 (range: 0.5 - 1.5);

for bleeding while hospitalised, 2.4 (range: 1.2 - 3.6) in the case of noncerebral major bleeding; and

for bleeding after discharge, 4.8 (range: 2.4 - 7.2) in the case of noncerebral major bleeding.

### **Methods used to derive estimates of effectiveness**

The authors made some assumptions that were used in the decision model.

### **Estimates of effectiveness and key assumptions**

In patients with major bleeding episodes, it was assumed that the frequency of fatal bleeding and haemorrhagic stroke was constant, regardless of anticoagulation intensity.

The proportion of patients undergoing outpatient treatment for deep vein thrombosis was 30% (range: 0 - 100).

### **Measure of benefits used in the economic analysis**

The summary benefit measure used was the number of quality-adjusted life-years (QALYs). These were calculated by combining the utility values and survival derived from the literature. Decreases in utility due to acute complications were estimated as days of utility lost because of hospitalisation (taken from mean length of stay for each complication). Life expectancy was also reported but was not combined with the costs. Expected survival was discounted at an annual rate of 3%.

### **Direct costs**

The perspective adopted in the study was unclear. The health services included in the economic evaluation were drugs, hospitalisations, office visits, INR measurements, medical procedures, and time spent obtaining care and for transportation. The unit costs were presented separately from the quantities of resources used for some cost items but, in general, the costs were expressed as macro-categories. The drug costs came from average wholesale prices, hospitalisations, office visits and INR measurements, while the costs of medical procedures were derived from Medicare reimbursement rates. An extra hospital stay was added if noncerebral major bleeding or haemorrhagic stroke occurred during hospitalisation for venous thromboembolism. If major bleeding occurred after hospital discharge or in patients with deep vein thrombosis treated at home, patients incurred the full costs of hospitalisation for this complication. The occurrence of minor bleeding led to an office visit and an additional INR measurement. Other resource use information appears to have been based on authors' opinions. Discounting was relevant, owing to the long timeframe of the analysis, and an annual discount rate of 3% was applied. The costs were inflated to 2002 values using the medical component of the Consumer Price Index.

### **Statistical analysis of costs**

No statistical analyses of the costs were performed.

### Indirect Costs

The indirect costs were not considered. However, days lost due to hospitalisation were included as disutilities in the estimation of QALYs.

### Currency

US dollars (\$).

### Sensitivity analysis

Univariate sensitivity analyses were carried out on all model inputs in order to assess the robustness of the cost-utility ratios. The ranges were derived from the literature or set by the authors. A probabilistic sensitivity analysis was also performed by running 1,000 Monte Carlo simulations.

### Estimated benefits used in the economic analysis

The results were presented for sub-groups by gender and age group (40, 60 or 80 years).

The estimated QALYs for 40-year-old men were 16.566 with strategy 1, 16.572 with strategy 2, 16.577 with strategy 3, 16.587 with strategy 4, 16.648 with strategy 5 and 16.527 with strategy 6.

The estimated QALYs for 60-year-old men were 10.088 with strategy 1, 10.092 with strategy 2, 10.093 with strategy 3, 10.089 with strategy 4, 10.040 with strategy 5 and 9.989 with strategy 6.

The estimated QALYs for 80-year-old men were 4.487 with strategy 1, 4.486 with strategy 2, 4.482 with strategy 3, 4.471 with strategy 4, 4.432 with strategy 5 and 4.419 with strategy 6.

The estimated QALYs for 40-year-old women were 17.546 with strategy 1, 17.549 with strategy 2, 17.550 with strategy 3, 17.551 with strategy 4, 17.489 with strategy 5 and 17.356 with strategy 6.

The estimated QALYs for 60-year-old women were 11.335 with strategy 1, 11.338 with strategy 2, 11.335 with strategy 3, 11.324 with strategy 4, 11.194 with strategy 5 and 11.134 with strategy 6.

The estimated QALYs for 80-year-old women were 5.182 with strategy 1, 5.179 with strategy 2, 5.173 with strategy 3, 5.155 with strategy 4, 5.087 with strategy 5 and 5.071 with strategy 6.

The same trends were found for life expectancy among all age groups and gender.

### Cost results

The estimated costs for 40-year-old men were \$23,740 with strategy 1, \$23,816 for strategy 2, \$24,053 with strategy 3, \$24,514 with strategy 4, \$32,615 with strategy 5 and \$33,020 with strategy 6.

The estimated costs for 60-year-old men were \$17,172 with strategy 1, \$17,284 with strategy 2, \$17,567 with strategy 3, \$18,123 with strategy 4, \$24,314 with strategy 5 and \$24,640 with strategy 6.

The estimated costs for 80-year-old men were \$10,579 with strategy 1, \$10,764 with strategy 2, \$11,132 with strategy 3, \$11,844 with strategy 4, \$15,094 with strategy 5 and \$15,286 with strategy 6.

The estimated costs for 40-year-old women were \$22,589 with strategy 1, \$22,711 with strategy 2, \$23,008 with strategy 3, \$23,582 with strategy 4, \$33,846 with strategy 5 and \$34,252 with strategy 6.

The estimated costs for 60-year-old women were \$16,903 with strategy 1, \$17,060 with strategy 2, \$17,394 with strategy 3, \$18,065 with strategy 4, \$25,932 with strategy 5 and \$26,272 with strategy 6.

The estimated costs for 80-year-old women were \$10,602 with strategy 1, \$10,828 with strategy 2, \$11,250 with strategy 3, \$12,071 with strategy 4, \$16,251 with strategy 5 and \$16,461 with strategy 6.

### **Synthesis of costs and benefits**

Incremental cost-utility ratios were calculated to combine the costs and benefits of the alternative strategies. Dominated options were eliminated. Strategy 1 was the reference strategy for all sub-groups (less costly).

For 40-year-old men, the incremental cost per QALY gained was \$11,168 with strategy 2, \$48,534 with strategy 3, \$48,805 with strategy 4 and \$132,396 with strategy 5.

For 60-year-old men, the incremental cost per QALY gained was \$29,878 with strategy 2 and \$225,654 with strategy 3.

For 80-year-old men, strategy 1 was dominant (more effective and less costly than the remaining strategies).

For 40-year-old women, the incremental cost per QALY gained was \$35,977 with strategy 3 and \$512,337 with strategy 4.

For 60-year-old women, the incremental cost per QALY gained was \$155,033 with strategy 2.

For 80-year-old women, strategy 1 was dominant.

The sensitivity analysis showed that variables that increased the risk of recurrent venous thromboembolism or decreased the risk of major bleeding from conventional-intensity anticoagulation favoured anticoagulation strategies of extended duration. Parameters that decreased the risk of venous thromboembolism or increased the risk of major bleeding favoured the 3-month strategy. The base-case results were also sensitive to variations in the discount rate and some utility values. The probabilistic sensitivity analysis suggested that the 6-month strategy was most likely to be cost-effective in 40-year-olds and in 60-year-old men, while the 3-month strategy was most favoured in 60-year-old women and in all patients aged 80 years or older.

### **Authors' conclusions**

Twenty-four months of conventional-intensity anticoagulation could be cost-effective in 40-year-old men, while 3 months of conventional-intensity anticoagulation was the best option in 80-year-old men. Six-months of conventional-intensity anticoagulation was preferred in all other patients.

### **CRD COMMENTARY - Selection of comparators**

The selection of the comparators was appropriate as a wide range of warfarin treatments was considered. You should decide whether they are valid comparators in your own setting.

### **Validity of estimate of measure of effectiveness**

The effectiveness evidence came from published studies. However, the methods and conduct of the review were not clearly reported. Moreover, little information on the design and characteristics of the primary studies was provided. Thus, it was not possible to assess the validity of the primary estimates, although some data came from randomised controlled trials. Some primary estimates were pooled but the methods used to extract other data from the primary studies were not described. Some opinions were used to derive clinical data when there was a lack of published evidence. Sensitivity analyses were performed to assess the robustness of the final cost-utility estimates to variations in the clinical data.

### **Validity of estimate of measure of benefit**

The benefit measure used in the analysis was appropriate as QALYs capture the impact of the interventions on the most relevant dimensions of care (i.e. survival and quality of life). A further advantage of QALYs is that they are comparable with the benefits of other health care interventions. Discounting was applied, as suggested by US guidelines for

economic evaluations. Limited information on the source of the utility weights and the approach used to calculate QALYs was provided.

### **Validity of estimate of costs**

The economic analysis focused on the direct medical costs. Although the authors stated that a societal perspective was adopted, they indirect costs were not included in the analysis, possibly because they were included as utility decrements in the estimation of QALYs. The unit costs and the quantities of resources used were presented separately for only some cost items. In general, the costs were expressed as macro-categories and a detailed breakdown of items was not reported. This limits the possibility of replicating the cost analysis in other settings. The costs were treated deterministically in the base-case analysis, but extensive sensitivity analyses were performed. The source of the data was reported for all costs, whereas resource consumption was mainly based on authors' assumptions. The price year was reported, which will simplify reflation exercises in other time periods.

### **Other issues**

The authors stated that their findings were consistent with those from a prior cost-effectiveness analysis. The issue of the generalisability of the study results to other settings was not explicitly addressed, although extensive sensitivity analyses were performed. This enhances the external validity of the analysis since variability in key clinical and economic inputs was investigated. The authors noted that the results of the analysis were affected heavily by model assumptions. They acknowledged a further limitation in that the model did not take the frequency of rare events, such as chronic thromboembolic pulmonary hypertension, into consideration.

### **Implications of the study**

The study results suggested that longer initial conventional-intensity anticoagulation is cost-effective in younger patients, while 3 months of anticoagulation is preferred in elderly patients. The authors pointed out that future studies should incorporate patient age, gender, clinical factors and patient preferences into medical decision-making when selecting the optimal anticoagulation strategy.

### **Source of funding**

None stated.

### **Bibliographic details**

Aujesky D, Smith K J, Roberts M S. Oral anticoagulation strategies after a first idiopathic venous thromboembolic event. *American Journal of Medicine* 2005; 118(6): 625-635

### **Other publications of related interest**

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Eckman MH, Singh SK, Erban JK, Kao G. Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: a cost-effectiveness analysis. *Med Decis Making* 2002;22:108-24.

### **Indexing Status**

Subject indexing assigned by NLM

### **MeSH**

Adult; Aged; Aged, 80 and over; Anticoagulants /administration & dosage; Cost-Benefit Analysis; Decision Support

Techniques; Female; Humans; Male; Markov Chains; Middle Aged; Pulmonary Embolism /prevention & control;  
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