Cost-Effectiveness of Anticoagulation in Nonrheumatic Atrial Fibrillation in the Primary Prevention of Ischemic Stroke

Sara Lightowlers, MRCP, MSc; Alistair McGuire, PhD

Background and Purpose—A number of clinical trials have shown the value of anticoagulating patients with nonrheumatic atrial fibrillation to prevent ischemic stroke. The purpose of this study was to assess the cost-effectiveness of anticoagulation in nonrheumatic atrial fibrillation with particular reference to the very elderly (aged >75 years) who have a higher incidence of bleeding events while undergoing anticoagulation.

Methods—We calculated the incremental costs per life-year gained for 4 base cases using efficacy data from the Boston Area Anticoagulation Trial for Atrial Fibrillation, the meta-analysis of the 5 nonrheumatic atrial fibrillation trials, cost data from a district general hospital, and review of the literature.

Results—The cost per life-year gained free from stroke over 10 years ranged from £400.45 (ie, a resource saving achieved for each life-year gained free from stroke) to £13 221.29. The results were most sensitive to alteration in the frequency of anticoagulation monitoring.

Conclusions—For medical and economic reasons, anticoagulation treatment in the prevention of ischemic stroke is justified. Although older patients are more at risk of adverse events, anticoagulation is more cost-effective in this group. (Stroke. 1998;29:1827-1832.)

Key Words: atrial fibrillation ■ cost-benefit analysis ■ stroke

A number of clinical trials have shown the value of anticoagulating patients with nonrheumatic atrial fibrillation (NRAF) to prevent occurrence of ischemic stroke.1-5 The 5 trials all had a similar broad approach. Patients with NRAF who had no contraindications to anticoagulation were randomized to treatment with warfarin or treatment with placebo or no treatment. In 2 of the trials there was also a group randomized to treatment with aspirin. The mean age of the subjects was 69 years. All 5 trials showed a statistically significant decrease in the number of strokes in those treated with warfarin. A meta-analysis of these 5 trials revealed the same trends, obtained a more precise estimate of efficacy and risk, and showed an increased risk of stroke with increasing age.6

There is no debate regarding the clinical effectiveness of anticoagulation with warfarin in decreasing stroke incidence. However, there is some concern about the incidence of adverse events, particularly in the very elderly (aged >75 years). The 5 trials did not show a statistically significant increase in the number of major hemorrhagic events, but there is debate regarding how closely a clinical trial, which enforces strict entry criteria, reflects routine clinical practice. A later trial (Stroke Prevention in Atrial Fibrillation [SPAF] II), which included a larger subgroup of very elderly patients, showed an increasing tendency to adverse events with increasing age.7

Because stroke is the third most common cause of death in most developed countries and one of the most common causes of adult physical disability, the potential benefits of preventing strokes are great. Thus, the economic question is as follows: Given the cost of treating adverse events, is treatment with anticoagulants in NRAF cost-effective? This issue is of greater importance in the very elderly, in whom the incidence of adverse events would appear to be greater. To address this issue further, a cost-effectiveness analysis was performed with data from the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) and the meta-analysis of the 5 NRAF trials.

Subjects and Methods

Cost-effectiveness analysis is a common method of evaluating the resource costs incurred in achieving a predefined clinical outcome. Although a number of perspectives may be adopted, this evaluation has considered the view of the third-party payer (the National Health Service [NHS]) and has calculated only direct costs.

Principal Outcome

The principal outcome measure was the incremental cost per life-year gained free from stroke. This was derived as follows: (total cost of treatment with warfarin—total cost of no treatment)/life-years gained free from stroke.

The costs of the warfarin group were calculated as the costs incurred by treatment with warfarin, the cost of treatment of the side
Cost-Effectiveness of Anticoagulation in Stroke Prevention

The cost of anticoagulation was calculated during a 10-year period and the cost of monitoring anticoagulation effects of warfarin (bleeding events), and the cost of treatment of strokes that occurred. The costs of the control group were the costs of treatment of bleeding events and the cost of treatment of stroke. The measure of effectiveness, life-years gained free from stroke, was obtained from BAATAF and the meta-analysis data.

Life-Years Gained

Reported information on cumulative survival rates for the warfarin and no-treatment groups was taken from the BAATAF (terminated after 4 years of follow-up). The underlying hazard rate for each group was calculated from this information. The reported hazard rates from the meta-analysis data were also used. The estimated within-trial hazard rates were then used to extrapolate the cumulative survival curves beyond the end of the clinical trial, so that the life-years gained free from stroke over a 10-year period were calculated, a realistic life expectancy for the meta-analysis– and BAATAF-type populations. External validation of this posttrial modeling is difficult because of lack of natural history studies in patients of this type.

Four base cases were examined: cases 1 and 2 with BAATAF data and cases 3 and 4 with the meta-analysis data. In case 1, the within-period hazard rates remained constant from the end of the fourth year to the 10th year in both treatment groups. In case 2, the mean of the within-period hazard rates from years 1 to 4 was used from years 5 to 10 in both treatment groups. In case 3, hazard rates for stroke of 0.045 for the control group and 0.015 for the warfarin group were used. These are the reported hazard rates for the whole of each treatment group from the meta-analysis data. In case 4, hazard rates for stroke of 0.045 for the control group and 0.015 for the warfarin group were used. These are the reported hazard rates for the whole of each treatment group from the meta-analysis data. In case 4, hazard rates for stroke of 0.081 for the control group and 0.012 for the warfarin group were used, which were the reported hazard rates for the group aged >75 years in the meta-analysis data. The BAATAF was a small trial (420 subjects), and there were very few stroke events over the follow-up period of the trial; therefore, the hazard rates calculated were imprecise estimates of the true hazard functions. The extrapolated hazard rates were calculated by 2 different methods because the within-period hazard rate for year 4 was greater in the warfarin group than in the control group, which would not be expected and reflects that the trial was small. However, BAATAF data were used because there was some information available on individual subjects in the trial.

The meta-analysis data were used for cases 3 and 4. There was less information from the meta-analysis on individual cases, but because there was a larger number of subjects (3691), hazard rates were likely to be more accurate, and the effects of treatment on subgroups of patients could be analyzed (in this case the group aged >75 years).

Life-years gained were then estimated as the difference between the extrapolated cumulative survival curves for the warfarin treatment group and the no-treatment group in the 4 different base cases and were then used to derive the cost per life-year gained ratios.

Cost Estimates

Cost of Anticoagulation

The cost of anticoagulation was calculated during a 10-year period from the cost of warfarin and the cost of monitoring anticoagulation every 3 weeks (the intensity of monitoring in the BAATAF). All of the costs of anticoagulation are for a UK-based anticoagulation clinic, where services are already well established.

Cost of Stroke

The cost of stroke is complex. A model for routine management of stroke patients was devised. Data on severity of and fatality from stroke in the first 3 months were derived from the BAATAF. Epidemiological data for the longer-term outcome from stroke were taken from the Oxfordshire Community Stroke Project (OCS). The BAATAF, epidemiological data from the South of England Study, the OCS, and the Royal College of Physicians report on stroke were used to determine the probabilities of patients being admitted to the hospital after a stroke and the probability of being discharged to the community or to hospital continuing care. Treatment received while in the hospital or at home and length of stay were modeled from the Royal College of Physicians report, the South of England Study, and data from a district general hospital.

In the BAATAF, there were a total of 15 strokes (the warfarin and no-treatment groups) over the follow-up period: 8 (53.3%) were of mild to moderate severity, 6 (40%) were severe, and 1 (6.7%) was fatal within 3 months of follow-up. The mortality of 6.7% at 3 months from stroke was not representative of data from epidemiological studies. In the OCS, those subjects with ischemic stroke, the 30-day mortality was 10% as opposed to 16% in the Rochester Study and 15% in the Framingham Study.

In the OCSP, the 1-year mortality from stroke was 31%. The annual risk of death after the first year was 9.1% up to 5 years.

In the South of England Study (which only examined patients aged <75 years), 71% were admitted to the hospital after a stroke. This figure was only 54% in the OCS. Very few of the patients who were not admitted to the hospital received investigation or treatment for stroke.

According to the Royal College of Physicians report, 20% of those who initially survive from stroke never improve sufficiently to return home and are discharged to residential or nursing homes or to hospital continuing care. Thirty-three percent of survivors return to a restricted life at home, and the rest make a good functional recovery.

Figure 1 shows the probability of being admitted to the hospital after a stroke, the probability of discharge to the community or hospital continuing care, and the probability of survival from years 1 to 10.

From the model of admission and survival after stroke, it was determined that 6 different pathways of stroke outcome and management exist: the patient is (1) admitted to the hospital and discharged to the community; (2) admitted to the hospital and discharged to hospital continuing care; (3) admitted to the hospital and dies in the hospital; (4) not admitted to the hospital and remains in the community; (5) not admitted to the hospital but eventually admitted to hospital continuing care; or (6) not admitted to the hospital and dies in the community.

The costs for each pathway were determined over a 10-year period, and thus the average cost of stroke treatment could be calculated.

<table>
<thead>
<tr>
<th>Year</th>
<th>Stroke</th>
<th>Admit</th>
<th>Alive</th>
<th>p=0.06</th>
<th>Alive</th>
<th>p=0.93</th>
<th>Home</th>
<th>p=0.34</th>
<th>p=0.34</th>
<th>p=0.28</th>
<th>p=0.28</th>
<th>p=0.24</th>
<th>p=0.24</th>
<th>p=0.22</th>
<th>p=0.21</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stroke</td>
<td>p=0.71</td>
<td>Admit</td>
<td>p=0.66</td>
<td>Alive</td>
<td>p=0.34</td>
<td>p=0.34</td>
<td>p=0.28</td>
<td>p=0.28</td>
<td>p=0.24</td>
<td>p=0.24</td>
<td>p=0.22</td>
<td>p=0.22</td>
<td>p=0.20</td>
<td>p=0.20</td>
</tr>
<tr>
<td>2</td>
<td>Stroke</td>
<td>p=0.05</td>
<td>Dead</td>
<td>p=0.27</td>
<td>Alive</td>
<td>p=0.243</td>
<td>p=0.17</td>
<td>p=0.14</td>
<td>p=0.13</td>
<td>p=0.11</td>
<td>p=0.11</td>
<td>p=0.097</td>
<td>p=0.088</td>
<td>p=0.08</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Stroke</td>
<td>p=0.29</td>
<td>Not adm</td>
<td>p=0.027</td>
<td>Alive</td>
<td>p=0.015</td>
<td>p=0.014</td>
<td>p=0.013</td>
<td>p=0.012</td>
<td>p=0.011</td>
<td>p=0.0098</td>
<td>p=0.0089</td>
<td>p=0.0089</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Stroke</td>
<td>p=0.01</td>
<td>Dead</td>
<td>p=0.01</td>
<td>Alive</td>
<td>p=0.009</td>
<td>p=0.009</td>
<td>p=0.009</td>
<td>p=0.009</td>
<td>p=0.009</td>
<td>p=0.009</td>
<td>p=0.009</td>
<td>p=0.009</td>
<td>p=0.009</td>
<td>p=0.009</td>
</tr>
</tbody>
</table>

Figure 1. Admission and survival after stroke. HCC indicates hospital continuing care.
**TABLE 1. Unit Cost Data**

<table>
<thead>
<tr>
<th>Service</th>
<th>Cost, £</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin, per tablet</td>
<td>0.0125*</td>
</tr>
<tr>
<td>Anticoagulation clinic attendance</td>
<td>35.00*</td>
</tr>
<tr>
<td>Medical bed-day</td>
<td>155.00*</td>
</tr>
<tr>
<td>Full blood count</td>
<td>3.50*</td>
</tr>
<tr>
<td>U&amp;E, LFT, cholesterol, glucose</td>
<td>5.30*</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>3.50*</td>
</tr>
<tr>
<td>Serology</td>
<td>16.40*</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>13.50*</td>
</tr>
<tr>
<td>ECG</td>
<td>10.70*</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>64.00*</td>
</tr>
<tr>
<td>Carotid Doppler</td>
<td>23.40*</td>
</tr>
<tr>
<td>CT brain scan</td>
<td>93.40*</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>162.00</td>
</tr>
<tr>
<td>Blood transfusion, per unit</td>
<td>33.59</td>
</tr>
<tr>
<td>Hospital outpatient attendance</td>
<td>84.00*</td>
</tr>
<tr>
<td>Continuing care bed-day</td>
<td>75.04*</td>
</tr>
<tr>
<td>Sudden death</td>
<td>388.00</td>
</tr>
<tr>
<td>General practice consultation</td>
<td>11.90*</td>
</tr>
</tbody>
</table>

U&E indicates urea and electrolytes; LFT, liver function test.

*Unit costs needed to calculate the cost of stroke.

It was determined that the unit costs described in Table 1 and marked with an asterisk were needed to calculate the cost of stroke. The unit costs were taken from literature review and data from a district general hospital. Any data that were not published in 1997 were multiplied by the gross domestic product deflator at market prices with figures from the treasury for June 1997. All costs were discounted at the recommended UK treasury rate of 6% to convert to net present value.

**Cost of Bleeding Events**

It was also necessary to model the management of bleeding events. Data from BAATAF were used for the number, type, and severity of bleeding events. The treatment of major bleeding events was modeled from review of the literature and data from a district general hospital. There were 4 major bleeding events in the warfarin group and 2 in the no-treatment group in the follow-up period of the BAATAF. It was assumed that there was 1 bleeding event per year in the warfarin group and 0.5 event per year in the no-treatment group. Figure 2 shows the probability of each type of major bleeding event in the trial. The costs for each type of bleeding event were determined, and thus the average cost of bleeding event treatment could be calculated. The unit costs were taken from review of the literature and a district general hospital and are shown in Table 1. All costs were discounted to net present value.

**Figure 2. Probability of different bleeding events from BAATAF.**

**TABLE 2. Life-Years Gained Free From Stroke Over a 10-Year Period**

<table>
<thead>
<tr>
<th>Case</th>
<th>Life-Years Gained (Not Discounted)</th>
<th>Life-Years Gained (Discounted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.41879</td>
<td>0.33061</td>
</tr>
<tr>
<td>2</td>
<td>0.73249</td>
<td>0.5349</td>
</tr>
<tr>
<td>3</td>
<td>1.312</td>
<td>0.9349</td>
</tr>
<tr>
<td>4</td>
<td>2.662</td>
<td>1.908</td>
</tr>
</tbody>
</table>

**Sensitivity Analysis**

Given that the basic analysis adopts a modeling approach, it is sensible to apply a sensitivity analysis to judge how robust the results are to assumptions made. The following data were subjected to sensitivity analysis: (1) cost of monitoring anticoagulation less frequently (every 6 weeks); (2) length of stay for stroke; (3) percentage of patients admitted to the hospital after a stroke; (4) percentage of patients discharged to hospital continuing care; (5) unit costs for hospital bed-days; and (6) incidence of bleeding events in base case 4.

Monitoring of anticoagulation every 6 weeks was considered to be a closer reflection of routine practice. Length of stay was varied over a range from review of the literature. No data were available on patients discharged to hospital continuing care beds, but assumptions were varied over a feasible range. Variations in cost data for bed-days were taken from review of the literature. The incidence of bleeding events was varied with the use of data from the SPAF II trial, which was a follow-up study of SPAF I, which included a larger subgroup of patients aged >75 years.

**Results**

**Life-Years Gained**

The calculated life-years gained free from stroke over a 10-year period for the 4 base cases are shown in Table 2. The fewest life-years free from stroke were gained in base case 1. This reflects that the survival analysis data were probably inaccurate because so few subjects had strokes in the follow-up period of the trial, so that the estimated stroke rate (hazard rate) for the warfarin group from years 5 to 10 was greater than in the control group. In case 2, because the mean (hazard rate) for the warfarin group from years 5 to 10 was greater than in the control group. In case 2, because the mean (hazard rate) for the warfarin group from years 5 to 10 was greater than in the control group. In case 3 the hazard rates from the meta-analysis were used to calculate the life-years gained free from stroke. More life-years were gained in base case 3 than when the BAATAF data were used, and this may be a more accurate reflection of the true state because the result was derived from examining a larger group of subjects. The most life-years were gained in base case 4, reflecting the higher incidence of stroke in this group.

**Costs**

**Anticoagulation**

The costs of anticoagulation of 1 subject for 1 year with anticoagulation checks every 3 weeks (the frequency of monitoring in the BAATAF cohort) was £610.06. Therefore, the discounted cost of anticoagulation of 1 subject for 10 years was £4759.56.

**Stroke**

The discounted total average cost for treatment of a stroke over a 10-year period was £17 819.58. We used the survival analysis data from the 4 base cases to estimate the expected...
number of strokes in each case. Table 3 shows the discounted cost of stroke treatment over 10 years in each of the 4 base cases.

**Bleeding Events**
The average cost of a bleeding event was calculated as £2064.12. If we assumed a constant rate of bleeding events throughout the 10 years of 0.5 event per year in the control group and 1 event per year in the warfarin group, the discounted cost of bleeding events over 10 years was £8051.93 in the control group and £16 103.86 for the warfarin group.

**Cost-Effectiveness Ratios**
The cost-effectiveness ratios derived from attaching the incremental costs to the increases in life expectancy free from stroke are shown in Table 4. The discounted costs per life-years gained free from stroke range from £400.45 to £13 221.29. In base case 4 there is a cost saving in base case 1 and 4 events per year in the control group and 1 event per year in the warfarin group, the discounted cost of bleeding events over 10 years was £8051.93 in the control group and £16 103.86 for the warfarin group.

**Sensitivity Analysis**
The results of the sensitivity analysis are shown in Table 5. The results of the cost-effectiveness analysis were most sensitive to alteration in the frequency of monitoring of anticoagulation. In the BAATAF, anticoagulation was monitored every 3 weeks, which does not accurately reflect clinical practice. In the sensitivity analysis, monitoring every 6 weeks was assumed, and anticoagulation with warfarin was found to be more cost-effective, so that in base case 3 there was a saving of £774.98 per life-year gained free from stroke. Of the variables that affected the cost of stroke, which were varied over a range from review of the literature, reducing the length of stay to 18.5 days and reducing the number of patients who went into hospital continuing care beds resulted in a net cost of anticoagulation in base case 4. There is a trend to discharge patients from the hospital earlier. However, these data were from a study that examined a population of stroke patients aged <75 years, which may partly account for much shorter lengths of stay. If patients were discharged earlier into the community, one might expect that they would need to receive rehabilitation at home (which did not appear to be the case in this study), since recovery from stroke occurs for up to 6 months. This would of course increase the cost of community medical treatment of stroke. There are certainly examples of community-based treatment of stroke that have not been found to be cheaper than hospital-based treatment. There has been a decline in discharge to NHS-funded continuing care, although health authorities do have a statutory obligation to provide continuing care beds.

**Discussion**
The cost per life-year gained free from stroke with data from the BAATAF and the meta-analysis varied from £1751.05 in base case 3 to £13 221.29 in base case 1. Base case 4 attempted to examine a specific subgroup of patients (ie, the group aged >75 years) from the meta-analysis and resulted in a cost-effectiveness ratio of −£400.45 per life-year gained free from stroke. In relation to other similar healthcare interventions, the cost is moderate; for example, estimates of the cost of screening for hypertension are on the order of £6000 to £30 000 per quality-adjusted life-years saved.

The results were explored with the use of sensitivity analysis. The results were sensitive to reducing the frequency of anticoagulation monitoring. In the BAATAF, anticoagulation was monitored every 3 weeks, which does not accurately reflect clinical practice. In the sensitivity analysis, monitoring every 6 weeks was assumed, and anticoagulation with warfarin was found to be more cost-effective, so that in base case 3 there was a saving of £774.98 per life-year gained free from stroke. Of the variables that affected the cost of stroke, which were varied over a range from review of the literature, reducing the length of stay to 18.5 days and reducing the number of patients who went into hospital continuing care beds resulted in a net cost of anticoagulation in base case 4. There is a trend to discharge patients from the hospital earlier. However, these data were from a study that examined a population of stroke patients aged <75 years, which may partly account for much shorter lengths of stay. If patients were discharged earlier into the community, one might expect that they would need to receive rehabilitation at home (which did not appear to be the case in this study), since recovery from stroke occurs for up to 6 months. This would of course increase the cost of community medical treatment of stroke. There are certainly examples of community-based treatment of stroke that have not been found to be cheaper than hospital-based treatment. There has been a decline in discharge to NHS-funded continuing care, although health authorities do have a statutory obligation to provide continuing care beds.

**Table 3. Discounted Cost of Stroke Treatment Over 10 Years in the 4 Base Cases**

<table>
<thead>
<tr>
<th>Case</th>
<th>Warfarin Group</th>
<th>No-Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>£743 974.58</td>
<td>£818 488.39</td>
</tr>
<tr>
<td>2</td>
<td>£316 422.81</td>
<td>£696 531.87</td>
</tr>
<tr>
<td>3</td>
<td>£386 456.50</td>
<td>£1 036 393.30</td>
</tr>
<tr>
<td>4</td>
<td>£334 527.87</td>
<td>£1 484 875.90</td>
</tr>
</tbody>
</table>

**Table 4. Cost-Effectiveness Ratios**

<table>
<thead>
<tr>
<th>Case</th>
<th>Cost per Life-Years Gained, £ (Benefits Not Discounted)</th>
<th>Cost per Life-Years Gained, £ (Benefits Discounted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 437.43</td>
<td>13 221.29</td>
</tr>
<tr>
<td>2</td>
<td>4014.61</td>
<td>5497.59</td>
</tr>
<tr>
<td>3</td>
<td>1247.76</td>
<td>1751.05</td>
</tr>
<tr>
<td>4</td>
<td>−287.20</td>
<td>−400.45</td>
</tr>
</tbody>
</table>
literature, there was little effect on the cost-effectiveness of anticoagulation.

The effects of rare events (such as systemic embolism) or relatively insignificant events (minor hemorrhage) were not considered but were not likely to affect the cost-effectiveness ratio significantly because even major hemorrhage had little effect on the analysis. Mortality from events other than stroke was not considered in the analysis. This is much more likely to have an effect on the analysis because 37 patients died during the BAATAF (11 deaths in the warfarin group and 26 in the control group, a significant difference).

There were also problems with the survival analysis from the BAATAF data. There were very few stroke events over the follow-up period of the trial, so that the hazard rates are imprecisely estimated. However, the analysis of the 4 base cases probably covers the range of effectiveness seen in clinical practice.

The unit cost data were mainly collected from a district general hospital. However, even when costs were varied in the sensitivity analysis from review of the literature, there was little effect on the cost-effectiveness of anticoagulation. It should also be remembered, however, that prices do not always reflect costs because of imperfect information in the healthcare market.

In summary, anticoagulation in the primary prevention of ischemic stroke is cost-effective in patients aged >65 years. Although subjects in the group aged >75 years are more at risk of adverse events while undergoing anticoagulation, anticoagulation is more cost-effective in this group, presumably because the subjects have a higher incidence of stroke.

Acknowledgment

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References

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