Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation

Richard Thomson, David Parkin, Martin Eccles, Mark Sudlow, Angela Robinson

Summary

Background Clinical guidelines are needed on whether or not to use anticoagulant therapy to prevent stroke in patients with non-valvular atrial fibrillation. We did a Markov decision analysis to model decision-making with regard to warfarin treatment in patients with atrial fibrillation, and used the model to develop evaluative guidelines.

Methods The decision analysis involved a systematic literature review supplemented by patients’ estimates of the quality of life associated with different states of health, secondary analysis of stroke-registry data, and estimation of service costs; it also incorporated a sensitivity analysis. The derived guidelines were subsequently applied to a cohort of patients with atrial fibrillation.

Findings We constructed decision tables for 12 age and sex groups. For most risk combinations, warfarin treatment would have decreased health-care costs and increased quality-of-life years, although the clinical decision was sensitive to patients’ preferences and to the estimate of warfarin’s effectiveness. 97% of women with atrial fibrillation older than 75 years, and 69% aged 65–74 would have been recommended for treatment; for men, the corresponding figures would have been 75% and 53%. With the upper quartile for the loss of quality of life associated with being on warfarin treatment (1·00), all but two of the 116 patients without contraindications would have been treated, whereas with the lower quartile (0·92), only 27 of 116 would have been treated.

Interpretation Decision analysis is useful in the incorporation of complex probabilistic data into informed decision-making, the identification of factors influencing such decisions, and the subsequent development of evaluative guidelines.


Introduction

Non-valvular atrial fibrillation increases the risk of stroke, but anticoagulant therapy decreases this risk by about two thirds. However, few clinicians have acted on this evidence—a finding that is reflected in the underuse of anticoagulant therapy in patients with atrial fibrillation.

Clinical guidelines can change medical practice and improve health. Previous studies have shown not only demand for guidelines in this area, but also variation in the content and implications of those available. Guidelines have been classified into a hierarchy ranging from informal and formal consensus guidelines, through evidence-based guidelines, to evaluative guidelines. The evaluative method may offer the most comprehensive approach since it incorporates data on quality of life and allows explicit quantitative comparison of the benefits and risks of different therapies. However, it has not been widely used.

Decision analysis permits explicit quantitative comparison of the benefits and risks of different therapies. Previous use of decision analysis has taken a rigorous approach to the synthesis of data from randomised controlled trials, but has not used similarly careful techniques in the assessment of epidemiological evidence, nor has it made the critical step of translating the results of this synthesis into practical tools for making clinical decisions.

We used a Markov decision analysis to model decision-making about warfarin treatment in patients with atrial fibrillation. The analysis included a systematic literature review followed by the development of evaluative guidelines. We then applied the guidelines to a cohort of patients with atrial fibrillation.

Methods

Data acquisition

We did a systematic search of published studies on: effectiveness of anticoagulant and antiplatelet therapies; natural history and risk of stroke in patients with atrial fibrillation; adverse effects of warfarin; utility of relevant health states; and costs of treatment. Titles and abstracts were read, and potentially relevant articles retrieved for full appraisal. Our basic tools were MEDLINE and BIDS, the Cochrane Search Strategies and, for appraisal, the Evidence-Based Medicine Working Group’s, Criteria.

For studies on the effectiveness of anticoagulation and antiplatelet therapies, we added search strategies for atrial fibrillation, warfarin, aspirin, or other anticoagulant or antiplatelet agents. 340 papers were identified, of which 21 were retrieved for appraisal. Meta- Analyst software with a fixed-effects model was used to produce an overall estimate of effectiveness of the combined data.

For studies on absolute risks of stroke and stroke outcomes after atrial fibrillation, we used the McMaster prognosis and aetiology strategies combined with the Cochrane Collaboration Stroke Strategy and the strategy on atrial fibrillation. MEDLINE was searched for 1966–96. Of 710 references, 171 were retrieved for appraisal. We sought a community inception cohort study which would provide absolute rates of stroke for different combinations of risk factors.
For studies on the risk of adverse effects in patients treated with anticoagulants, we searched MEDLINE for 1966–96 using Mcmaster strategies adapted for anticoagulant complications. We sought inception cohorts of unselected (or at least a broad range of) patients with atrial fibrillation, treated with anticoagulants for an average of 6 months or more and monitored by the international normalised ratio. Studies in which high therapeutic ranges of anticoagulation were used were excluded. Of 1968 references, 274 were retrieved.

For studies that assessed the utility values of health states (ie, patients’ perceived quality of life with regard to different health states), we searched MEDLINE for 1966–96. We looked for studies on outcome (using the UK Clearing House Health Outcomes search), bleeding, stroke, and anticoagulation. These factors were combined to identify all papers on outcome, plus stroke, anticoagulation, or bleeding. Of 2350 papers, 99 were retrieved. However, only one study included relevant health-state values, and this involved a population we thought not representative of the UK.

Therefore, we did a utility assessment exercise using the standard-gamble method:24 health states were ranked and anchored to “normal health” (value of one) and “immediate death” (value of zero).25 We interviewed elderly volunteers from a representative sample of community-based patients with atrial fibrillation to derive utility measures for health states.

For studies that attached costs to outcomes, we searched MEDLINE (1980–96) to identify papers on the costs of stroke, bleeding, and anticoagulation, using the search strategy recommended by the UK Centre for Reviews and Dissemination.26 From 2233 papers, 75 were retrieved. Only one27 allowed costs (inpatient only) to be broken down according to stroke severity. These costs were inflated to account for outpatient and primary care.28 Local cost data were derived from a hospital-based, pharmacy-led anticoagulation service. The cost of a gastrointestinal bleed was based on mean length of stay and mean daily cost.

**Decision model**

The treatment decision model was developed as a Markov process by use of DATA software (version 2.6). A hypothetical cohort of patients is followed up over several time “cycles”. Patients can move between health states according to the risk of a clinical event. Transitions may be from one state to another (eg, whenever a patient has a stroke or major bleed, or dies), or from one state back to that same state (eg, if the patient remains well or remains disabled with a mild or severe stroke). Data on effectiveness of warfarin, absolute risk of stroke, risk of recurrent stroke, outcome of stroke, and risk of major (non-cerebral) bleed were derived from systematic review, with point estimates used in the model. Since utility values were not normally distributed, median values were used.

**Assumptions within the decision model were:** that the model covered remaining life expectancy; that patients are on warfarin for the first year only; that the relative risk reduction afforded by warfarin is constant across different absolute risks of stroke and across severities of stroke; that the outcome of stroke is constant across different absolute risks of stroke; that warfarin offers no protection against mortality from other causes; that minor bleeds are not significant and that all events occur 6 months into the year. Life expectancy was taken from official statistics.29 The mean daily cost.

**Table 1: Utility values for relevant health states derived from standard-gamble study in patients with atrial fibrillation**

<table>
<thead>
<tr>
<th>Health state</th>
<th>Utility value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>On warfarin managed by general practitioner</td>
<td>0.948 (0.089)</td>
</tr>
<tr>
<td>On warfarin managed in hospital outpatient clinic</td>
<td>0.941 (0.101)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>0.841 (0.172)</td>
</tr>
<tr>
<td>Mild stroke</td>
<td>0.641 (0.275)</td>
</tr>
<tr>
<td>Severe stroke</td>
<td>0.189 (0.278)</td>
</tr>
</tbody>
</table>

**Results**

**Data acquisition**

There were six randomised, controlled trials of warfarin anticoagulation,3,32,33 and a pooled analysis of five of them. One trial32 reported only an on-treatment analysis and was excluded. Four were not double-blind.3,31,33,34 The pooled study34 analysed the data by intention-to-treat, which overcame the problem of on-treatment results, but included trials that were not double-blind. The two double-blind trials of warfarin and placebo32,35 were terminated early, and only one showed statistical and clinical significance35. Where possible, we reanalysed trials that were not double-blind using only objective endpoints (ie, moderate and severe strokes, and fatal events)3,31,34 and combined the data with those of the two double-blind trials. Three double-blind, randomised trials compared aspirin with placebo.3,31,34 We excluded one which reported only on-treatment analysis,31 and combined the other two. The outcome for both analyses was all stroke, haemorrhagic or ischaemic. Anticoagulant-treated patients had 42% (95% CI 26–66) of the risk of stroke of placebo-treated patients (p<0.001). Aspirin-treated patients had 81% (95% CI 65–102) the risk of stroke of placebo-treated patients, but this value was not significant. We decided to limit our decision analysis to the decision on whether to anticoagulate with warfarin, given the clear benefit of warfarin over aspirin.
Of 17 community cohort studies (full list of references available from the authors), only one allowed predictive stratification of patients with atrial fibrillation into different levels of absolute stroke risk. We used this study to calculate the probability of having a first stroke within 12 months. The absolute risk of recurrent stroke (11% per annum in those who survived 30 days from their first stroke) could be derived from only one community cohort study—the Oxfordshire Community Stroke Project. No valid published studies reported the risk of different outcomes after stroke associated with atrial fibrillation. Original data from the Oxfordshire project were provided by the investigators (Martin Dennis, personal communication). The modified Rankin scale was used to grade outcome as 5 (death), 3–4 (disability sufficient to prevent independent existence), or 0–2 (less severe disability). The proportions who had had a stroke with atrial fibrillation in these categories were 45%, 23%, and 32%, respectively. From this finding, and from the risks of stroke from the Framingham model, we derived the risk of first stroke of differing severities. We assumed the same case-fatality rate for recurrent stroke as for first stroke, but that a non-fatal recurrent stroke always left a patient dependent.

Figure 1: Flowchart showing guidelines for treatment of patients with atrial fibrillation with warfarin

Additional notes: address reversible risk factors (eg, smoking or uncontrolled hypertension) and consider whether addressing them might alter the need for anticoagulation; review patients annually to reassess advice; since tables are derived from average values, remember the importance of individual patient’s preferences (eg, if patients have little or no aversion to warfarin treatment, threshold for advising treatment will fall, whereas patients particularly averse to treatment may have a higher threshold. In the latter case, a trial of therapy may be justified).

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Risk of adverse effects
We found only one large prospective community cohort study in which anticoagulation was monitored using the international normalised ratio. This study reported on 2745 patients (mean follow up 267 days [2011 patient-years]). Bleeding rates were similar to those in the trials of warfarin for atrial fibrillation: fatal bleeding rate 0·25 per 100 patient-years (all due to cerebral bleeding), major bleeding rate 1·1, and minor bleeding rate 6·2. From this study, only patients’ age could be associated with bleeding risk. The results were adjusted to include only the absolute risk of non-cerebral haemorrhage, because the estimate of effectiveness of anticoagulants in our model was of the effect on the occurrence of all stroke, including haemorrhagic stroke. Only major or fatal bleeding was included. The overall proportion of non-cerebral major bleeds to all major bleeds was applied to the total major bleeding rates for each age group, giving rates of 0·55% and 1·74% for those aged 50–69 years and 70 years or older, respectively. These estimates were further smoothed for use in the model by assumption that the risks of 0·55% and 1·74% held for the median age within the relevant cohort. We interpolated risks assuming linear risk with age, which gave estimates for non-cerebral major bleeds ranging from 0·47% for a 60-year-old to 2·51% for a person aged 85 years or older.

Utility values of health states
180 patients in atrial fibrillation were invited to be interviewed in the derivation of utility measures for health states. 64 agreed, and 57 completed the interview. Patients who agreed to take part were slightly younger (mean age 73 years) than those who declined (mean age 76 years), but the sex distribution was the same. 31 (54%) were men. 28 (49%) were on warfarin, and 13 (23%) had suffered a stroke. Utility values of these health states are given in table 1.

Costs
Estimated mean costs for mild, severe, and fatal stroke were £5476, £15 472, and £7089, respectively. The annual cost of warfarin treatment and the average cost of admission for gastrointestinal bleed were estimated at £82·88 and £963, respectively.

Decision model
There were four distinct outcomes from the model. In the first, treatment produced QALY gains and cost savings, leading to an unequivocal decision to “definitely treat”. In
the second, treatment lead to both QALY losses and higher costs, and the unequivocal decision was “definitely do not treat”. In the third, treatment yielded more QALYs than did no treatment, but with higher costs. The decision in this case would be “treat if the cost per QALY gained is acceptable”. In the fourth, there was a QALY loss as a result of treatment, but at a lower cost (ie, a cost per QALY by not treating). The implication here is that money could be saved by treating someone, but their quality of life would be lower. We thought this was unethical, so the decision was also “definitely do not treat”. Using this classification, we constructed a table for each of 12 age and sex groups (for example, see figure A, www.thelancet.com). In most cases, treatment led to lower costs—in only 12 of the 1512 cells (0.8%) was there a cost per QALY gain; values ranged from £250 to £6000 using the basic assumptions in the model.

Sensitivity analysis showed that the model was more sensitive to change in some variables than others. In particular, the model was sensitive to variation in the patient’s utility for being on warfarin. It was also sensitive to the estimate of warfarin effectiveness derived from the meta-analysis. For reasons of space, the sensitivity analyses of these variables are available in tables on The Lancet website (figures B and C, www.thelancet.com) or from the authors. However, the sensitivity to patients’ utilities is addressed below in the assessment of the impact of different utilities on application of the model to representative patients in the community.

Evaluative guidelines

Our guidelines-development group raised issues of heart-rate control, cardioversion, and contraindications for warfarin. Although not included in the model, we produced introductory statements, guided by group consensus, on these issues (figure 1).

We calculated that all patients with atrial fibrillation and three or more risk factors for stroke, and men with atrial fibrillation, left ventricular hypertrophy, and any one other risk factor, should be treated with warfarin (figure 1). For treatment of patients not in these categories, clinicians should refer to the associated tables (figures 2 and 3). We grouped patients into 5-year age-bands, in a few of which the recommendation to treat with warfarin would apply only to those towards the upper end of the age group.

The increased risk of cerebral bleed associated with warfarin has been taken into account in the model, with the effectiveness of warfarin estimated for all strokes, both haemorrhagic and ischaemic. However, for patients with a
The baseline risk of stroke less than 50% greater than the risk of cerebral bleed on warfarin, the reduction in the risk of stroke afforded by warfarin could be outweighed by this increased risk (assuming that warfarin affords a reduction of about two-thirds). Using an analogous method to that used to estimate the risk of a non-cerebral bleed (above), the risk of cerebral bleed on warfarin was estimated, and ranged from 0.15% in patients aged 60 years, to 1.6% in patients aged 85 years and older. This finding suggests that it may be prudent not to treat patients with risks below 0.23% (0.15/1.5) at 60 years, and 2.4% (1.6/1.5) at age 85 years and older. In only 10 of the 1512 cells (all women aged 80 years or more) did the results of the model based on median values for patient utilities.
Table 2: Proportion of patients (from a representative community sample of patients with atrial fibrillation) having no contraindications to warfarin treatment and above the risk threshold for treatment for three different utilities

<table>
<thead>
<tr>
<th>Age (years) and sex of patients</th>
<th>Utility of warfarin=1.000</th>
<th>Utility of warfarin=0.986</th>
<th>Utility of warfarin=0.920</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>13/13 (100%)</td>
<td>9/13 (69%)</td>
<td>2/13 (15%)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>33/33 (100%)</td>
<td>32/33 (97%)</td>
<td>13/33 (39%)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>19/19 (100%)</td>
<td>10/19 (53%)</td>
<td>1/19 (5%)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>49/51 (96%)</td>
<td>36/51 (71%)</td>
<td>11/51 (22%)</td>
</tr>
</tbody>
</table>

We have produced evaluative guidelines from this decision analysis. Such guidelines raise issues of application—eg, the sensitivity of the decision to variations in patients’ preferences. We used measures of central tendency to produce the guidelines from the model. The mean of warfarin effectiveness, for example, is appropriate given that the relative risk reduction is constant across different risk groups. We can estimate the absolute risk of stroke for an individual by means of the Framingham equation. At present, we cannot assess individual risk or likely response to treatment other than by applying such probabilistic population-based measures. However, patients’ preferences are quintessentially an individual, rather than a population, attribute. It would theoretically be possible to determine these measures for an individual patient at clinical consultation, but to produce practical recommendations, we used median utilities in the model to derive the summary guidelines. However, we qualified the derivation of such recommendations with associated guidance on their use when faced with differing patient preferences. This problem is shared by any guideline producing recommendations without explicitly assessing each individual’s preferences. Indeed, the problem is likely to be considerably greater for guidelines which do not make any explicit attempt to incorporate or advise on the effects of patients’ values.

There has been much debate on the role of the patient in shared decision-making and the impact that this process may have upon compliance and outcome. In addition, there have been studies on patients’ decision aids, which present data on the benefits and risks of different treatments, the tailoring of information to a particular patient, and the implicit or explicit enabling of patients to express their values. Our work has further emphasised the importance of incorporating patients’ values into decisions: we showed the variations in patients’ preferences and their effects on the model. We believe that our summary guidelines, along with guidance on taking account of patients’ preferences, offer a valuable tool for clinical practice.

**Contributors**
Richard Thomson, Martin Eccles, David Parkin, and Mark Sudlow conceived the study; Angela Robinson led the development of the decision-analysis model and designed and undertook the health-state evaluation study; Mark Sudlow led the literature review and was aided by all investigators; Richard Thomson and Angela Robinson led the analyses and used all strokes as the outcome measure, produced a summary measure lower than that provided by the pooled analysis of the data, and by a meta-analysis. However, despite this finding, our conclusions on treatment are likely to be conservative. The same is true for our assumption that case fatality after recurrent stroke is the same as that after first ever stroke (in the absence of high quality data on recurrent stroke), although we did assume that severity would be greater after recurrent stroke.

Our reanalysis of the data on aspirin failed to show a significant benefit in the prevention of stroke; this finding was in contrast to that of a pooled analysis, which suggested that aspirin was associated with a reduction in stroke risk (relative risk reduction 21% [95% CI 0–38%] p=0.05). Nonetheless, evidence for the effectiveness of aspirin is much less robust than that for warfarin. We therefore excluded aspirin from our model, but used it in the guidelines as the alternative treatment in patients with warfarin contraindications or where warfarin is not indicated.

We recommend treatment for patients below these thresholds. These cells are therefore classified as “do not treat” in the tables.

When we applied the summary guidelines to data from patients without contraindications (116 of 207) in our population sample, 97% of women older than 75 years and 69% aged between 65 and 74 years would be recommended for treatment with warfarin. For men, the corresponding figures would be 75% and 53% (table 2). If we had used the upper quartile value for warfarin disutility (1.00), the model suggests that all but two of the patients without contraindications should be treated, whereas a value set at the lower quartile (0.92) markedly decreases the proportion that would have been treated.

**Discussion**
We have shown that a Markov decision-analysis model can clarify the factors that affect clinical decisions on anticoagulation. Decision analysis explicitly quantifies uncertainty—eg, we showed that the decision on whether to anticoagulate is sensitive to the estimate of the effectiveness of warfarin, which itself is available as a point measure with attendant uncertainty in the form of confidence intervals around this estimate. The incorporation of a patient’s preference also makes explicit the impact of variation in patients’ views.

As well as making the elements of the decision-making process, and their implications, explicit, use of decision analysis has also allowed incorporation of a wider range of available “evidence” (eg, patients’ utilities and the risk of stroke) in guidelines development than is the case with other valid methods, thus going beyond the widely accepted evidence-based approach. Although others have developed decision analyses, they have not used evidence-based estimates as rigorously as we have attempted, nor have they developed these into guidelines.

We selected the Framingham equation for calculation of the absolute risk of stroke. However, this equation has not been validated in any other cohort, and it is derived from data from the entire Framingham cohort, not just from those with atrial fibrillation. Regression equations tend to underestimate risk in those at the higher end of the range, thus this equation may underestimate the absolute risk of stroke in patients with atrial fibrillation. Furthermore, use of the Framingham equation means that the risk-factor profile differs from risk-stratification schemes derived from the trials of warfarin. Nonetheless, we believe that use of this equation is justified by the appraisal criteria applied, and enables risk assessment in routine practice without need for complex investigation.

Our reanalysis of the effectiveness of warfarin, in which we applied strict evidence-based criteria to the published
development of the guidelines and were aided by all investigators; all investigators contributed to the writing of the paper.

Acknowledgments

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