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MODELLING SCREENING AND TREATMENT DECISIONS IN ATRIAL FIBRILLATION: A REVIEW AND PROPOSED EMPIRICAL ANALYSIS

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Introduction

Atrial fibrillation (AF) is an abnormal heartbeat rhythm whose incidence increases with age.[1] The condition occurs in approximately 5% of individuals aged 65 and over,[1] and those with AF have a five fold increased risk of having a stroke.[2] AF is diagnosed by means of an electrocardiogram (ECG), and once a diagnosis has been made, a patient can be treated with antiplatelet drugs (e.g. aspirin) or anticoagulants (e.g. warfarin) in order to reduce the risk of stroke.

Uncertainties currently exist in terms of the most appropriate and cost-effective approaches to the diagnosis and treatment of patients with AF. Data are being generated through two randomised controlled trials (detailed below) in order to address these issues. However, due to the unavoidable limitations of the scope and follow up duration of the trials, cost-effectiveness estimates will be generated using decision analytic modelling approaches. The purpose of this paper is to review previous modelling work undertaken by others in this area and to report on the models that have been constructed as part of our work.

Clinical Issues

Previous research has indicated that long-term antithrombotic therapy with warfarin or aspirin reduces the risk of stroke of those with AF by 68% and 22% respectively.[3] However, the benefits of warfarin in some patients may be offset by the increased risk of bleeding complications. Most bleeding is not life threatening and does not result in any permanent morbidity, but deaths can occur and some bleeding events are serious enough to warrant hospitalisation. Serious bleeding complications include upper gastrointestinal bleeding especially in patients taking non-steroidal anti-inflammatory drugs (NSAIDs), and those who have had previous bleeds are particularly at risk. Intra-cranial bleeds can also arise, usually after a fall, putting those with poor mobility at a greater risk.

Patients on warfarin are required to attend an anticoagulation clinic regularly, either at hospital outpatients or at their GP surgery, as a blood test is required to determine the INR (International Normalised Ratio), which measures the therapeutic effect of the drug. Therefore, the cost of treating a patient with warfarin is much higher than that for aspirin therapy. However, previous economic evaluations have shown that

warfarin is a cost-effective therapy for stroke risk reduction, particularly in patients with additional risk factors for stroke.[4,5] The costs of warfarin therapy are offset by savings, where strokes are averted or postponed.

National guidelines have recommended that elderly patients with AF should be considered for long term warfarin,[6] but it has been demonstrated, with less than half of patients treated with warfarin, there is a reluctance to prescribe the drug, particularly in patients over 75.[7] In addition to presence of contraindications in this age group such as high risk of falls and problems with compliance, little evidence is available for patients 75 and over, as existing trial data for the effectiveness of warfarin under-represent this age group.[3]

AF is a condition well suited for the application of decision analytic modelling.[8] Markov modelling is useful in depicting the natural history of diseases, especially those involving events such as strokes, that may occur repeatedly and over a long period of time. Screening for AF by means of an ECG may lead to an important reduction in stroke incidence, resulting in a potential health gain and a reduction in NHS expenditure. Modelling can provide estimates for the cost and benefit consequences of AF screening, and help assess the subsequent implications for service provision, particularly anticoagulant care. A modelling framework can also be utilised to determine the preferred treatment strategy for AF. Decisions about whether to use anticoagulant therapy in a patient with AF involve consideration of stroke risk reduction, risk of bleeding, quality of life and cost of the treatment.

The Trials

We are currently undertaking two studies to present evidence for the issues of screening for AF, and treatment of AF in patients aged 75 and over.

SAFE (Screening for Atrial Fibrillation in the Elderly) is a randomised controlled trial investigating different intensities of screening for AF, using patients aged 65 and over. Patients in intervention practices are randomly allocated to systematic (targeted and population screening) or opportunistic screening. The primary objective of the study is to determine the baseline prevalence and incidence of AF based on a variety of screening strategies, and in doing so, to evaluate the incremental cost-effectiveness,

in terms of cost per case identified, of different screening strategies compared with routine clinical practice. Using modelling to extrapolate beyond the period of the trial, the incremental cost per life year gained, incremental cost per QALY and impact on service provision will also be estimated.

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study is a randomised controlled trial in which patients aged 75 are treated either with aspirin (75 mg daily) or warfarin (target INR 2.5). Patients are recruited from general practice, and followed up for an average of three years. This will enable us to compare the occurrence of strokes (ischaemic or haemorrhagic) in the two groups, as well as the impact in terms of other important side-effects (major extra-cranial haemorrhage), cost and quality of life.

Drawing on data from the trials, decision analytic modelling is being undertaken to explore the most appropriate method for screening, the frequency of screening, the impact on service provision and the most cost-effective therapy for stroke risk reduction. In the first instance a review of the literature is being undertaken to populate the model with data from previous work on AF and stroke, treatment, costs and utility values. Using this data, a model investigating treatment options for patients in AF has been developed. The structure of the model incorporating screening and treatment has been completed and will be populated with trial data once the studies end. In addition, a modelling exercise will be undertaken to identify the most appropriate method of screening to investigate the incremental cost per case detected as screening intensifies.

Literature review

A literature review was carried out to establish modelling work already undertaken on AF. Relevant papers were identified through searching of two electronic bibliographic databases: MEDLINE and the National Health Service Economic Evaluation Database (NHS EED). A search strategy was devised using appropriate keywords to identify all relevant AF modelling papers. All identified papers were initially screened and only included in the main review if some form of modelling was undertaken. Letters, review papers, methodology papers and foreign language papers were omitted. A paper was excluded from the review if it did not describe a decision

tree, Markov model or Discrete Event Simulation, or if the modelling did not address issues of screening or a choice between therapies which included long term anticoagulant or antiplatelet therapy.

A total of 82 papers were identified from the searches, 12 of which were relevant (all 12 identified by MEDLINE and 4 identified by NHS EED). The bibliographies of the selected papers were also searched but no additional relevant studies were identified. Tables 1, 2 and 3 contain details of the study rationale, methods and results of the 12 papers reviewed.

In many cases, decision analytical modelling has been used to explore the preferred treatment for patients with AF to provide guidance on therapeutic choices. Many of the previous model-based analyses used QALYs as the measure of effectiveness. Two studies concentrated on specific bleeding risks, in order explore the suitability of anticoagulant use in patients at risk. [13, 17]

Three cost-effectiveness studies considered wider treatment options for AF, looking at cardioversion and antiarrhythmic drugs as well as long term anticoagulant and antiplatelet therapy.[10, 12, 14] Electrical cardioversion is a procedure used to restore a normal heartbeat rhythm, and evidence suggests that it is more successful in younger patients who have only recently developed AF and have little or no heart disease. After cardioversion, patients may be given an anti-arrhythmic drug to maintain sinus rhythm. Antithrombotic therapy may also be administered whilst a patient is in sinus rhythm or if a patient reverts back to AF.

Eleven studies used a Markov modelling process, with the remaining study reporting a decision tree.[16] Most Markov models had a short cycle length (i.e. 1-3 months), where temporary morbidity from events such as bleeds could be taken into account. Those studies where a cost utility analysis was undertaken tended to follow patients through for longer time periods (e.g. 10 years or remaining life expectancy). In general, sensitivity analyses tended to be very simple – one way or multiway sensitivity analyses were carried out in the majority of studies. The focus for sensitivity analyses tended to be the rate of stroke or bleeding, and the effectiveness or utility associated with therapy.

Reviewing previous modelling in AF has illustrated that although modelling has been conducted on AF, it has concentrated on patients already diagnosed with AF and considers the optimal treatment strategies. None of the previous models included the development of AF nor the issue of screening. It is evident that modelling work needs to be conducted on the progression to AF, the impact of the introduction of a screening programme and the effects on patients and service delivery. The next section of the paper describes the modelling we have undertaken to date.

Treatment decision model

A Markov decision analysis model was constructed using the TreeAge DATA software (version 3.5) to describe the possible outcomes of treatment for patients diagnosed with atrial fibrillation. A hypothetical cohort of male patients aged 65, was simulated over 30 time cycles of length one year, to represent remaining life expectancy. At the decision node (Figure 1a) the patient follows one of the two treatment strategies: 1) anticoagulation (warfarin) or 2) antiplatelet therapy (aspirin). Transitions can occur from one state to another, for example when a patient has a stroke, dies, or changes treatment due to a major bleed, or a patient remains in the same state. There were thirteen possible model health states, dead and twelve combinations of treatment and stroke status (Figure 1b). The antiplatelet arm contained all health states excluding those referring to anticoagulants. Figure 1c illustrates the pathway a patient takes through the model in one typical cycle, from the initial health state through stroke (Figure 1d) and major bleed (Figure 1e) subtrees.

A patient's initial state is 'no stroke', where no previous stroke has occurred. During a cycle a patient is at a specified risk of having a stroke. The stroke can be mild (modified Rankin score 0-2) or disabling (modified Rankin score 3-5) and the patient moves to the corresponding health state. If in a subsequent cycle, the patient suffers another stroke, the transition is to a health state indicating a second stroke. A further stroke in a subsequent cycle results in a patient's death.

When on a particular treatment, a patient has a risk of suffering a major bleed, which can be fatal. If the bleed is non-fatal then treatment is changed to one with a lower

risk of bleeding or no treatment at all, and the patient continues in a health state for that treatment for subsequent cycles.

Model assumptions

Several assumptions were made when developing the model.

1. A mild stroke has a Rankin score of 0 to 2 and a disabling stroke has a score of 3 to 5. The level of disability is after one year.
2. The first stroke can be mild or disabling, a second stroke disabling and a third stroke resulting in death.
3. Stroke outcomes are the same for all treatment strategies.
4. Risk reduction by anticoagulants is constant across all risks and severities of stroke.
5. Only major bleeds are considered, defined as bleeds requiring hospitalisation.
6. If a patient is on anticoagulant therapy and has a bleed, then treatment is switched to antiplatelet therapy or no treatment. If a patient is on antiplatelet therapy and has a bleed, the patient is taken off treatment completely.
7. The added risk of bleeding of starting anticoagulation is ignored as the model is being run over a long enough time period.
8. Warfarin does not protect against other causes of death.

Data required

A comprehensive literature review will be carried out to provide data on probabilities for risk and severity of stroke, risk of major bleeds and all cause mortality. In addition, utility values for mild and disabling stroke, major bleeds and being on warfarin and aspirin will be obtained for the calculation of QALYs. Data on costs will be acquired from the literature and from studies undertaken by the authors. Table 4 gives the baseline estimates for each variable in the treatment model. The current baseline estimates have been obtained from the literature reviewed so far. Using these estimates, the results showed quality-adjusted life expectancy for patients was 10.68 QALYs for the anticoagulant arm and 9.78 QALYs for the antiplatelet arm. Life expectancy was 11.57 years for the anticoagulant arm and 11.04 years for the antiplatelet arm. Once a full literature review has been conducted, final baseline estimates will be determined, and interpolation of probabilities of stroke and major

bleed as age increases will be incorporated. In addition, ranges from the literature will be used in sensitivity analyses.

Screening model

A Markov decision analysis model was constructed using the DATA software (version 3.5) to describe the possible outcomes of a screening programme for AF and subsequent treatment decisions. The purpose of the model is to extrapolate over a longer period of time in order to determine the effect of different screening strategies on life expectancy and quality adjusted life expectancy. The model will also attempt to estimate the effect on cost and services of identifying AF patients and treating them, particularly with anticoagulation.

A hypothetical cohort of patients, baseline age 65, will be simulated up over 30 time cycles of length one year, to represent remaining life expectancy. Figure 2a displays the combinations of AF status, treatment and stroke status, which, in addition to death, make up the 21 health states for the model. Figure 2b illustrates the pathway a patient takes through the model in a cycle, dependent on AF status. The subtrees for development of AF, diagnosis of AF, and treatment are illustrated in Figures 2c, 2d and 2e respectively. The subtrees for stroke and bleeding are identical to those in the treatment model (see Figures 1d and 1e).

The initial health state for a patient is No AF/No Stroke, and during a cycle a patient has a probability of developing AF. If AF develops during a cycle, the patient will be in an undiagnosed AF health state at the beginning of the next cycle if they do not suffer a stroke. However, if a stroke event takes place, it is assumed their condition will be diagnosed in the course of post-stroke tests and they may receive subsequent treatment with anticoagulant or antiplatelet therapy or no treatment at all. Their diagnosed AF health state at the beginning of the next cycle will be dependent on their stroke and treatment status.

A patient with undiagnosed AF as a starting state may be diagnosed in a subsequent cycle if a stroke event occurs. If no stroke occurs, the patient may have their AF diagnosed depending on the screening method employed, and it's sensitivity. Once AF has been diagnosed, the patient can either receive no treatment or receive

treatment with anticoagulant or antiplatelet therapy. In subsequent cycles patients progress through the stroke and bleed subtrees as described in the treatment model.

Assumptions

In addition to those made for the treatment modelling exercise, additional assumptions have been made for the screening model.

1. When a patient with undiagnosed AF has a stroke, their AF will be diagnosed during post-stroke investigations.
2. Increasing age is a risk factor for developing AF.
3. Patients without AF who suffer a stroke will have the same progression to AF as a non-stroke patient.
4. If a patient develops AF and has a stroke in one cycle, they can receive anticoagulant or antiplatelet therapy within that cycle, but will not proceed through the bleed subtree until subsequent cycles.

Data required

The literature review will also provide data on probabilities for risk and severity of stroke, risk of major bleeds and all cause mortality, utilities for the calculation of QALYs, and data on costs of stroke and major bleeds. On completion of the SAFE study, the screening model will be run to incorporate data on the sensitivity of alternative screening strategies and the incidence of AF. Cost data is also being collected alongside the trial. The results of the BAFTA trial will provide data on the incidence of stroke and major bleeds in patients aged 75 and over, on warfarin or aspirin, and the cost of each therapy will be estimated. Cost data from previous work carried out by the authors will also be considered.

Discussion

This study is the first to address cost-effectiveness issues in screening for AF, and incorporates new trial data on the effectiveness of warfarin and aspirin in patients 75 and over. Initial analyses demonstrate that the modelling framework used for the treatment model is broadly in line with work carried out in other studies.

The literature review did not identify any previous modelling conducted on screening for AF. The screening model we have constructed can be used to estimate the effect

of introducing a screening programme on both survival and the quality of life of patients with AF, dependent on the subsequent therapy received. If more patients are diagnosed with AF and are subsequently put on antithrombotic therapy, cost savings may be seen if stroke incidence decreases. However cost savings may be offset if a greater number of patients are being treated, particularly if the majority are prescribed anticoagulation; the location of anticoagulant care (primary or secondary care based) will possibly influence the results. Previous work has suggested that although practice based care is more expensive per patient, if there are sufficient and increasing numbers attending a practice clinic, cost per patient decreases.[32]

A possible weakness of the paper is the sole focus on a Markov model. We are initially exploring the adequacy of the Markov modelling process in this clinical area, but will carry out future work taking a broader view of decision analytic modelling. The first author is currently undertaking a PhD to explore the different modelling approaches available, and will carry out a parallel modelling exercise using Discrete Event Simulation.

In contrast with the short cycle length of most published models, a cycle length of one year has been chosen for our model, in order to incorporate screening. A limitation of this approach is the inability to incorporate short term events (e.g. bleeds) into the models. However, this lack of accuracy in the timing of events may not be important compared with other uncertainties in the data. Major bleeds requiring hospitalisation are considered as one overall risk and we need to investigate if this simplifying assumption is adequate, or if we need to consider specific bleeds. The model also considers the average risk of stroke and major bleed for patients 65 and over, but could also be run taking into consideration the increasing risk with age. These issues highlight that the model should be used to ascertain whether a simple model is adequate, and if the model more complex has any dramatic impact on results.

The current model has been set to use data for an average cohort. Consideration of how the model is to be used should be taken into account when deciding whether to run the model for the average cohort, or for different cohorts of patients, taking into account age, gender, and other risk factors. If required, the model may be run to make

a decision for an individual patient by incorporating specific figures for their characteristics.

The full literature review will enable comprehensive sensitivity analyses to be conducted to test the robustness of the model, and the impact of changing particular variables, in particular, the disutility of anticoagulation, which was an important variable in many of the other models. Probabilistic sensitivity analyses will be conducted to examine the effect of joint uncertainty in the variables used in the analysis. The review will also enable us to include costs in order to calculate the cost utility of different treatment options, and compare values with those from previous models. The cost of anticoagulation will be important, as costs may be dependent on the location of monitoring. The utility of being on anticoagulation therapy may also differ with the location, with previous research demonstrating stronger preferences for practice based care. [15, 33]

Areas for further discussion

- Treatment model structure
- Screening model structure
- Use of models for individual decision making
- How comprehensive is the literature review?
- Next steps

Table 1. Review of modelling studies in AF - study rationale

Paper, country of origin, sponsor(s)	Purpose of modelling	Comparison	Model population
Naglie (1992) [9] Canada. Ontario Ministry of Health Research. Health and Welfare Canada.	To determine the preferred treatment strategy for AF to assist with treatment decisions for specific patient subgroups using QALYs.	Warfarin, aspirin and no treatment.	4 cohorts, male and female aged 70 and 75. No reference to risk factors.
Disch (1994) [10] USA. Veterans Affairs. National Library of Medicine.	A comparison of the relative risk and benefits of antithrombotic therapy (warfarin) with cardioversion with antiarrhythmic drugs (quinidine or amiodarone) in AF patients.	No treatment, warfarin, and cardioversion plus quinidine or amiodarone.	Base case 65 year old (50% male).
Gage (1995) [4] USA. Palo Alto Institute for Research & Education. Veterans Affairs.	An examination of the cost-effectiveness of prescribing warfarin in AF patients with or without additional risk factors using decision analysis.	Warfarin, aspirin and no treatment.	Base case of 65 year old patients with no contraindications for warfarin, at 3 risk levels (high, medium, low). Sensitivity analyses were also carried out for patients aged 55 and 75 years.
Gage (1998) [11] USA. Palo Alto Institute for Research & Education. Veterans Affairs.	Using the same model from Gage's previous work, the cost-effectiveness of preference based treatment versus warfarin-for-all treatment was investigated. Preference based treatment involved eliciting patient utilities and projecting individual QALYs for each therapy.	Warfarin, aspirin and no treatment.	Base case of 65 year old patients with no contraindications for warfarin, at 3 risk levels (high, medium, low). Sensitivity analyses were also carried out for patients aged 75 years.
Eckman (1998) [5] USA. Not stated.	To investigate the cost-effectiveness of anticoagulant therapy for heart disease, using AF as an example.	Anticoagulant and no treatment. Antiplatelet therapy included in the sensitivity analysis.	Base case of 35 year old woman with mitral stenosis and AF. Sensitivity analyses were also carried out for male AF patients aged 69 and 80 year old AF patients at low and high risks of stroke.
Eckman (1998) [12] USA. National Library of Medicine. Pfizer Inc.	An examination of the cost-effectiveness of antithrombotic (warfarin or aspirin) and antiarrhythmic treatment strategies for AF. Patients can have cardioversion to restore sinus rhythm and may receive antiarrhythmic drugs for maintenance. Antithrombotic drugs can be administered whilst in sinus rhythm, or when the patient reverts to atrial fibrillation.	No treatment, warfarin, aspirin, cardioversion followed by 4 antithrombotic strategies, cardioversion followed by 4 antithrombotic strategies and the addition of 3 antiarrhythmic therapy strategies.	Base case 65 year old male.

Table 1 continued. Review of modelling studies in AF - study rationale

Paper, country of origin, sponsor(s)	Purpose of modelling	Comparison	Model population
Man-son-Hing (1999) [13] Canada. Ontario Ministry of Health Research. Medical Research Council of Canada.	To determine whether the risk of falling (which may increase the chance of a bleeding episode) should influence the choice of antithrombotic therapy in AF patients using QALYs.	Warfarin, aspirin and no treatment.	Base case of 65 year old patients, with an average risk of stroke (6%) and falling (33%), with no other contraindications for antithrombotic therapy. Patients with different risks of stroke and falling were also modelled. Sensitivity analyses were carried out for patients aged 75.
Catherwood (1999) [14] USA. Not stated.	A comparison of the cost-effectiveness of cardioversion, with or without antiarrhythmic drugs, with that of rate control plus warfarin or aspirin. Aspirin or warfarin may be administered on relapse to AF.	Cardioversion, cardioversion plus amiodarone or quinidine, warfarin or aspirin plus rate controlling agent.	Cohort of 70 year old patients (50% male) with different baseline risks for stroke. Sensitivity analyses were carried out for patients aged 65 and 75.
Thomson (2000) [15] UK Northern & Yorkshire Region NHS R&D	To model decision making of warfarin treatment in AF patients, and to use the model in the development of evaluative guidelines, taking into account health-care costs and patient preferences.	Warfarin and aspirin.	1512 combinations of age (60-64, 65-69, 70-74, 75-79, 80-84, 85+), gender, systolic blood pressure and risk factors (smoking, cardiovascular disease, hypertension, diabetes, left ventricular hypertrophy).
* Protheroe (2000) [16] UK. Wellcome. NHS R&D.	An investigation of patients' own treatment preferences with decision analysis using individual utility assessments and probabilities which were assigned to a decision tree. Preferences were compared with published treatment guidelines. Results: 59 patients preferred anticoagulation – fewer than the number recommended treatment by guidelines. Almost half of patients were not being prescribed warfarin although they showed a preference for the treatment. There was marked disagreement between decision analysis and guideline recommendations.	Warfarin and no treatment.	Randomly selected patients aged 70-85 with AF, from 8 general practices. 97 patients with a mean age of 77 participated in the decision making, 55% of which were female.
Man-son-Hing (2002) [17] Canada. Not stated.	Using the same model from Man-son-Hing's previous work, the preferred treatment strategy for AF patients was determined, taking into account the risk of upper gastrointestinal tract bleeding.	Warfarin, aspirin and no treatment.	Base case of 65 year old patients, with an average risk of stroke (6%) and major upper GI tract bleeding (1.17%), with no other contraindications for antithrombotic therapy. Patients with different risks of stroke and upper GI bleed were also modelled. Sensitivity analyses were carried out for patients aged 70 and 75.

* the paper describes a decision tree and will not be referred to in the subsequent tables

Table 2. Review of modelling studies in AF - methodology

Paper	Model used	Cycle length	Time frame	Nature of economic analysis	Nature of sensitivity analysis
Naglie (1992) [9]	Markov decision analysis	1 month	5 years	None	One way, multiway
Disch (1994) [10]	Markov decision analysis	3 months	5 years	None	One way, multiway
Gage (1995) [4]	Markov decision analysis	1 month	10 years	Cost utility analysis	One way
Gage (1998) [11]	Markov decision analysis	1 month	10 years	Cost utility analysis	One way, multiway
Eckman (1998) [5]	Markov decision analysis	1 month	Remaining life expectancy	Cost utility analysis	One way, multiway
Eckman (1998) [12]	Markov decision analysis	6 weeks	Remaining life expectancy	Cost utility analysis	One way, multiway
Man-son-Hing (1999) [13]	Markov decision analysis	3 months	1 year	None	One way
Catherwood (1999) [14]	Markov decision analysis	3 months	Remaining life expectancy	Cost utility analysis	One way
Thomson (2000) [15]	Markov decision analysis	12 months	Remaining life expectancy	Cost utility analysis	One way
Man-son-Hing (2002) [17]	Markov decision analysis	3 months	1 year	None	One way

Table 3. Review of modelling studies in AF - results

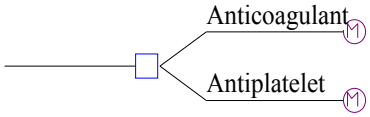
Paper	Main results
Naglie (1992) [9]	5 year QALYs calculated for the four cohorts showed little difference between warfarin and aspirin. For a 70 year old male, warfarin produced 4.03 QALYs, aspirin 4.02 QALYs and no treatment 3.95 QALYs. However the effectiveness of aspirin was overestimated at 45%. Sensitivity analyses showed results were sensitive to the effectiveness of aspirin and utility of being on warfarin.
Disch (1994) [10]	Warfarin resulted in less disabling events than no treatment, but more than with cardioversion plus amiodarone or quinidine. In terms of 5 year mortality and QALYs, warfarin was the most favourable option (4.72 QALYs) after amiodarone (4.75 QALYs). A reduction in the risk of stroke resulted in warfarin becoming the optimal therapy, however increasing the rate of bleeding or reducing the utility of being on warfarin made warfarin less favourable.
Gage (1995) [4]	Warfarin was a cost-effective treatment relative to aspirin or no therapy if one or more risk factors were present. Warfarin was the dominant therapy in patients with a high risk of stroke and cost $8000/QALY in moderate risk patients. In patients 65 years old with no risk factors, costs increased significantly with minimal improvement in QALYs ($370000/QALY). Aspirin was preferred to no treatment in terms of cost and QALYs, regardless of risk factors. Sensitivity analyses showed that the rate of stroke, effectiveness of aspirin, estimates of major haemorrhage and utility of warfarin all affected the cost-effectiveness estimates significantly.
Gage (1998) [11]	Preference based treatment improved QALYs by 0.05 QALYs and reduced costs by $670 where there were no additional risk factors and by 0.02 QALYs and $90 with one risk factor. Where patients had more than one risk factor, preference based therapy increased cost but only marginally increased QALYs ($11000/QALY). Sensitivity analyses showed that preference based therapy was cost-effective compared with aspirin-for-all therapy.
Eckman (1998) [5]	Anticoagulation was more expensive and more effective for base case analysis ($1826/QALY) and 69 year old males ($1907/QALY). For 80 year old patients, anticoagulation was dominated by no therapy in both low and high risk patients. Sensitivity analyses determined that the optimal strategy of therapy changes with different risks of stroke, major bleed and efficacy of anticoagulation and also if antiplatelet therapy is an option.
Eckman (1998) [12]	Any intervention resulted in a QALY gain compared with no therapy. The most effective strategies were cardioversion, and the use of amiodarone and warfarin together. Marginal cost-effectiveness ratios demonstrated that only 3 strategies were not dominated, all involving cardioversion. Reduction in the effectiveness of aspirin led to domination by other strategies. Aspirin was cheaper than warfarin however the latter gave higher QALYs ($10667/QALY).
Man-son-Hing (1999) [13]	For an average risk of stroke and falling, the utility adjusted life expectancy for warfarin therapy was 12.90 QALYs, aspirin therapy 11.17 QALYs, and no therapy 10.15 QALYs. Sensitivity analyses showed the probability of falls had no influence on the choice of optimal therapy, as the benefits of warfarin outweighed the risks of a fall. Results were sensitive to the probability of other types of bleed, effectiveness of aspirin and warfarin, and the risk of stroke.
Catherwood (1999) [14]	Strategies involving cardioversion alone were more effective and less costly. After relapse to AF, warfarin therapy was cheaper than aspirin and more effective for high and medium stroke risk groups but not low risk groups. Sensitivity analysis demonstrated that the optimal strategy and incremental cost-effectiveness were most influenced by risk of stroke, rate of stroke in sinus rhythm, efficacy, cost and utility of warfarin and cost and utility of amiodarone.
Thomson (2000) [15]	Decision tables were constructed for 12 age and sex groups for different risk combinations. For most patients with risk factors, warfarin decreased health care costs and increased QALYs. Clinical decisions were sensitive to utility of being on warfarin, and the effectiveness of warfarin.
Man-son-Hing (2002) [17]	Where patients had an average risk of stroke and upper GI bleed, the utility adjusted life expectancy for warfarin therapy was 12.10 QALYs, aspirin therapy 10.8 QALYs, and no therapy 10.1 QALYs. Sensitivity analyses for this patient group demonstrated that altering the effectiveness of warfarin or aspirin, risk of upper GI bleeding and utility of warfarin, resulted in warfarin no longer being the preferred therapy. For patients with much higher risks of upper GI bleeding and/or lower risks of stroke, warfarin was no longer the clear optimal therapy choice.

Table 4. Treatment model variables for base case

Probability/rate	**Value**	**Source**
Stroke	0.05	20-22
Death from stroke	0.25	24-29
Disabling non-fatal stroke	0.35	30
Further stroke	0.10	23
Death from further stroke	0.25	15
Effectiveness of warfarin	0.68	3
Effectiveness of aspirin	0.22	3
Major bleed on warfarin	0.015	4, 5, 9-17
Major bleed on aspirin	0.01	4, 5, 9-17
Death from major bleed	0.2	4, 5, 9-17
Change to aspirin post-bleed	1.0	4, 5, 9-17
AF Mortality Relative Risk (male)	1.5	19
Utilities		
Mild stroke	0.7	15, 31
Disabling stroke	0.2	15, 31
Taking warfarin	0.987	31
Taking aspirin	0.998	31
Major bleed	0.7	9, 15, 31

Figure 1. Treatment model

a) Treatment decision

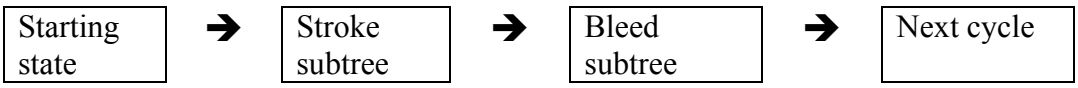


b) Health states (excluding dead)

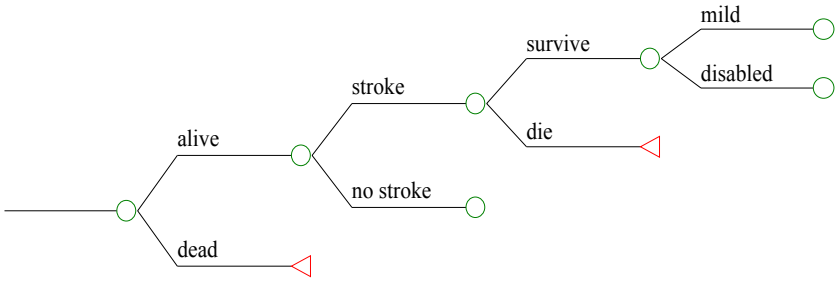
Treatment	Stroke
Anticoagulant*	No stroke
Antiplatelet	First stroke (mild)
No treatment	First stroke (disabled)
	Second stroke

* Anticoagulant arm only

c) Model pathway



d) Stroke subtree



e) Bleed subtree

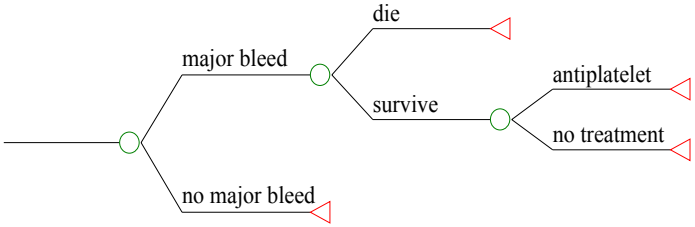


Figure 2. Screening model

a) Health states (excluding dead)

AF Status and treatment		**Stroke**
No AF*		No stroke
Undiagnosed AF*		First stroke (mild)
Diagnosed AF	Anticoagulant	First stroke (disabled)
	Antiplatelet	Second stroke
	No treatment	

* Where AF is not present or has not been diagnosed, the health state is a combination of the AF status and stroke status.

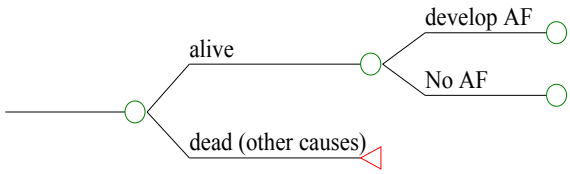
b) Possible model pathways

Starting state: No AF → AF development subtree → Stroke subtree → Treatment subtree → Next cycle

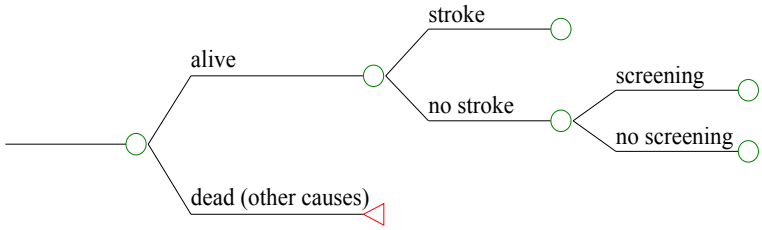
Starting state: Undiagnosed AF → AF diagnosis subtree → Stroke subtree → Treatment subtree → Bleed subtree → Next cycle

Starting state: Diagnosed AF → Stroke subtree → Bleed subtree → Next cycle

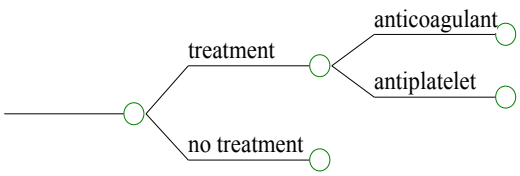
c) AF development subtree



d) AF diagnosis subtree



e) Treatment subtree



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