# Abstract

**Background :** Atrial fibrillation is a progressive condition affecting up to one person in fifty in the UK. It raises lifetime stroke risk, and is treated by prescribing oral anticoagulants (OACs), which reduces the risk of stroke, but could cause severe haemorrhages which can be fatal. Our objective was to assess the clinical and cost effectiveness of using transthoracic echocardiography (TTE) to help make the decision whether to prescribe OACs.

**Methods:** A discrete event simulation mathematic model was developed in order to simulate the lifetime patient experience resulting from using TTE alongside CHADS2, a standard clinical decision tool, to decide whether to prescribe an OAC (warfarin, dabigatran or rivaroxaban) compared with using CHADS2 alone. Both males and females were considered, aged either 50 or 65 years, and with different existing risk profiles. A lifetime horizon and an NHS perspective was adopted. The cost per QALY of the addition of TTE was estimated.

**Results:** Depending on factors such as patient age, gender, clinical characteristics and choice of OAC, it may or may not be cost-effective to use TTE to help inform the decision to prescribe an OAC. In particular, it may be cost-effective to use TTE to inform the decision whether to prescribe warfarin in patients with a CHADS2 score of one, or to prescribe dabigatran in older patients.

**Conclusions:** The estimated incremental cost effectiveness of using TTE to make the decision to prescribe depends on patient characteristics and OAC being considered.

## Introduction

Atrial fibrillation (AF) is a progressive condition affecting around 1-2% of the UK population, disproportionately older people, and is a significant risk factor for stroke.(1) Effective management of AF and the associated stroke risk is important for reducing additional mortality and morbidity risks that result from the condition. Oral anticoagulants (OACs) reduce the risk of stroke, but can cause major bleeding events which may result in death or severe disablement. (2)

OACs impose a cost burden, either directly due to drug acquisition costs in the case of newer drugs like dabigatran or rivaroxaban, or indirectly due to monitoring costs in the case of warfarin. As a result of this, it is important to identify those patients for whom the benefits are most likely to outweigh the risks, and so a range of diagnostic tools are used to identify patients higher risk patients, including clinical prediction rules using patient history and characteristics. It should be noted that even where an intervention is clinically effective it does not necessarily follow that the intervention is also cost effective.

The decision to prescribe OACs depends on clinical judgement about whether the decreased risk of stroke outweighs the increased risk of severe side effects, in particular potentially fatal major bleeding events. Presently, the assessment about the balance of risks is made using a clinical prediction rule, such as CHADS2, which use demographic and clinical characteristics to produce a stroke risk score.(3) If this score is at or exceeds a threshold, the decision to prescribe OACs is made.

The populations to be modelled are patients with newly diagnosed AF. Based on clinical history, they will either have an initial CHADS2 risk score of zero or one point. This study assesses whether performing an additional, slightly more expensive diagnostic test in the population of interest would lead to better clinical outcomes on average (clinical effectiveness). If such additional testing is clinically effective, it is also important to evaluate whether the additional health benefits are proportionate to the additional costs accrued, and whether the additional testing is cost effective at standard NICE decision-making thresholds. The additional diagnostic test of interest is transthoracic echocardiography (TTE), a non-invasive procedure that allows imaging of the heart and blood flow.

In this study a discrete event simulation (DES) model was developed to simulate the long-term implications of performing TTEs in the population of interest when deciding whether to prescribe OACs. Patients whose CHADS2 scores are below the threshold at which the OAC would be prescribed are additionally assessed using TTE. If TTE identifies at least one type of left atrial abnormality (LA ABN), which has been shown to lead to an increased stroke risk,(4) then they are also prescribed OACs. As a result of this, more people will be prescribed OACs when TTE is included in the diagnostic package than when it is not, so any potential cost savings would be as a result of preventing strokes and the costs to the NHS that result from them.

## Methods

The mathematical model developed estimated the effect of performing TTE in making the decision to prescribe an OAC in eight separate patient cohorts, in making the decision to prescribe any one of three OACs. Because some of these patient cohorts would automatically receive some but not each of the OACs, a total of twelve scenarios were considered. This is described in more detail below. The health economic outcome of interest is the quality adjusted life year (QALY). An NHS perspective is adopted, therefore costs incurred by the patient or wider society are not considered. Standard NICE discount rates for utilities and costs of 3.5% per annum are used. (5) A lifetime horizon is adopted. In order to incorporate the effect of uncertainty on predicted outcomes, a probabilistic model is used, meaning that where possible model parameter estimates are drawn from distributions rather than assumed to be fixed values. The central estimates were derived by taking mean values from probabilistic sensitivity analyses, rather than from a deterministic model run, in order to incorporate nonlinearities between model parameters and outcomes.

### Model Overview

An overview of the model is presented in Figure 1. The model comprises a short-term diagnostic stage and a long-term patient outcome stage. In the short-term stage the clinical characteristics of a patient are generated, and whether or not to OAC were prescribed is determined. In the long-term simulation the patient’s clinical outcomes are simulated. Over the patient lifetime the patient may experience a stroke or major bleeding event, both of which are assumed could lead to death, or death from another cause. Each of these events has associated cost and utility implications. By simulating the outcomes for a large number of patients, the average associated costs and utilities following alternative diagnostic strategies (with and without the use of TTE) were estimated, allowing estimation of the mean costs and mean QALYs for both strategies, and from these the incremental cost effectiveness ratio (ICER) of including TTE in the diagnostic package.

### Patient cohorts, OAC indications, and scenarios modelled

Warfarin, dabigatran and rivaroxaban are all recommended for use in patients. Warfarin is commonly prescribed in patients with a CHADS2 score of two or more; the recent NICE recommendations for rivaroxaban are equivalent to stating that patients with a CHADS2 score of one or more should receive it; and recent NICE recommendations for dabigatran are equivalent to stating that patients with a CHADS2 score of one or more should receive it if they are also aged 65 years or more. Eight different patient cohorts were considered in order to assess the effect of patient heterogeneity on the cost-effectiveness of various decisions. Table 1 below shows the CHADS2 scores at which different OACs are recommended, and which patient cohorts were simulated for each OAC. In total 14 separate scenarios were simulated.

It was assumed that some proportion of each patient cohort would have (LA ABN that predisposes the patient to a high risk of stroke(4). LA ABN is defined as a patient having either a left atrial appendage thrombi, a dense spontaneous echo contrast, or left atrial appendage low flow velocities. (6) This feature can be identified by TTE. In the baseline strategies, none of these LAABN patients were treated with the OAC even though their high stroke risk means they should have been. In the comparator strategy, some of these high risk patients would receive the OAC due to TTE correctly identifying the feature. However, due to less not all patients with the feature would receive the OAC, and some patients without LA ABN would receive it due to misdiagnosis. This is discussed in more detail below.

### Modelling of decision

The short term model assesses the effect of including TTE in the diagnostic strategy on the proportion of newly diagnosed AF patients from four mutually exclusive and exhaustive patient groups. These groups are defined as: 1) true positives (TPs): patients where the high risk feature LA ABN was correctly identified, and as a result the patient would receive the OAC. 2) true negatives (TNs): who do not have an LA ABN, and in whom TTE does not misclassify as having LA ABN. These patients would not receive the OAC. 3) False positives (FPs): Patients whom TTE misclassifies as having a LA ABN. As a result of this, using TTE would lead to these patients being given OACs even though for them this would be the wrong decision under current clinical guidelines. 4) False negatives (FNs): Patients with a LA ABN that TTE has failed to identify. These patients would not receive OACs.

The clinical effectiveness and cost-effectiveness of using TTE is a function of the mixture of these four patient groups within the patient population, which is itself a function of 1) the true proportion of patients with a clinical prediction score of zero who have LA ABN and are thus at substantially higher stroke risk than predicted (‘True Proportion High Risk’ or TPHR); and 2) the sensitivity and specificity of TTE in identifying TPHR individuals. The derivation of these four patient groups in the population mix is defined in Table 2. Within the context of the model, the baseline strategy (no TTE) can be considered a diagnostic strategy with a sensitivity of zero and a specificity of one, so the baseline population mix is comprised of TPHR% false negative and 1-TPHR% true negative.

### Data sources used in model

A full list of the information used to populate the parameters in the model, including event risks, costs and utilities, is presented in Table 3.

### Modeling long-term events

Prescribing an OAC means reducing the risk to the patient of suffering a stroke, but introducing the risk of causing a potentially fatal major bleeding event. Three mutually exclusive outcomes could result from a stroke: death, a dependent state, and an independent state. Each outcome has different utilities, probabilities and costs. Similarly, three mutually exclusive outcomes could result from a major bleeding event: death, an intracranial (IC) bleeding event, or a non-intracranial (NIC) bleeding event (assumed to be a gastrointestinal bleed). The severity of an IC bleed can vary substantially, and this variation of outcomes was itself simulated using data based on outcomes categorized by GOS score following traumatic brain injury. The full methodology used to produce these estimates is presented elsewhere. (7)

The model is updated when events occur that affect an individual’s stroke or bleed risk. Examples of such events are: becoming 75 years of age: experiencing a stroke:. withdrawal of an OAC following a major bleed It was assumed that If a patient experiences a stroke and is not already taking an OAC, they are prescribed OACs, provided they have not experienced a previous bleeding episode. If a patient suffers a severe intracranial haemorrhage (Glasgow outcome scale category 2) as a result of taking OACs, their life expectancy was reduced to a maximum of 3.6 years with no QALY gain. (8) Additionally, the risk of a major bleeding event when taking dabigatran (150mg twice daily) was also assumed to change at the age of 75, as indicated by recent evidence comparing dabigatran with warfarin. (9)

The estimated costs and QALYs associated with the simulated patient experiences following baseline (without TTE) and comparator (with TTE) strategies were used to calculate the incremental cost effectiveness ratio (ICER) of the comparator strategies compared with the baseline strategies, and so the cost-effectiveness of TTE in this context. The probability that the addition of TTE is cost-effective at a wide range of maximum acceptable incremental cost effectiveness ratios (MAICERS) is presented in the form of cost-effectiveness acceptability frontiers (CEAFs). (10)

The expected value of perfect information (EVPI) was calculated. This provides the maximum level of investment that a funding body would be prepared to pay to eliminate all uncertainty in the decision problem.(11) In calculating EVPI an estimation of the number of patients who will be affected by the decision is required. Assuming that: there are 6.7 million people aged between 55 and 64 years in England and Wales;(12) the incidence of AF was 1 per 1,000 person years (approximately the pooled rate for women and men aged 55 to 64 years reported by the Renfrew Paisley study);(13) 6% of people are in the CHADS2 0 category;(6) and that the information is relevant for 10 years, then around 70,000 people would benefit from there being no uncertainty regarding whether TTE is cost effective.

Sensitivity analyses were also undertaken on two key parameters, the TPHR, and the joint uncertainty in the sensitivity and specificity of TTE in detecting LA ABN.

## Results

Due to the large number of scenarios run, only the results for two scenarios are presented in detail here for illustration. The full results are available in the online appendix [LINK]. These two scenarios are: fifty year old males with an initial CHADS2­ score of zero; and fifty year old males with an initial CHADS2 score of one. In these scenarios the OAC assumed was warfarin.

Table 3 compares the simulated patient experience when TTE is added to the decision making process either for fifty year old males with either an initial CHADS2 score of zero, or an initial CHADS2 score of one point. For both cohorts the effect of using TTE to inform the decision is to increase the number of life years, decrease the proportion of patients dying of strokes, but increase the proportion dying of major bleeding events. The increase in life years gained is more modest in the cohort with an initial CHADS2 score of zero points than in the cohort with an initial CHADS2 score of one point. The proportion of patients suffering strokes is decreased in the TTE arms compared with the no TTE arms, but the proportion experiencing either incracranial haemorrhages (ICH) or nonintracranial haemorrhages (NICH) is increased.

For the cohort with an initial CHADS2 score of zero points, Table 6 presents a) a scatterplot of one thousand probabilistic sensitivity analysis runs; b) the cost effectiveness acceptability frontier, which shows the probability that the optimal option is cost-effective; c) the mean cost and mean QALY associated with each option, and the ICER associated with these mean values. Table 7 presents the equivalent information for the cohort with an initial CHADS2 score of one point.

For the cohort with an initial CHADS2 score of zero points (Table 6), it is clear from the scatterplot (a) that the majority of the estimates are in the North West quadrant, indicating that the TTE strategy is dominated by the No TTE strategy. Likewise, the TTE strategy has a lower mean QALY and higher mean cost than the no TTE strategy (c). The mean ICER is negative, which in this case means the TTE strategy is dominated by the no TTE strategy. The CEAF indicates that the no TTE strategy is the adoption strategy at all willingness-to-pay thresholds between £0 and £50,000/QALY.

By contrast, for the cohort with an initial CHADS2 score of one point (Table 7), it is clear from the scatterplot (a) that all estimates are in the North West quadrant, indicating that the TTE strategy is both more costly but also confers greater health benefits than the no TTE strategy. The mean costs and QALYs associated with each arm (c) indicate that the TTE strategy confers an average of 0.5 additional QALYs, but costs on average more than £3,000 more per patient. The estimated mean ICER (c) of £7,197 per QALY suggests that, for this scenario, TTE has a high probability of being cost effective at a standard NICE willingness to pay threshold of £20,000 per QALY. The CEAF (b) indicates that the TTE strategy becomes the adoption strategy at £7,197 per QALY,.

### Expected value of perfect information

Table 7 presents the estimated expected value of perfect information (EVPI) at individual level for both the cohort with an initial CHADS2 score of zero points (a) and one point (b). This information is presented in tabular form at MAICERs of £20,000/QALY and £30,000/QALY, and translated into population EVPI costs when assuming populations of 25,000, 50,000 or 75,000 people. The results indicate that EVPI is monotonically increasing with MAICER over the range of MAICERs considered for the cohort with an initial CHADS2 score of zero. However, for the cohort with the initial CHADS2 score of one point EVPI peaks at the point where the TTE strategy becomes the adoption strategy, then rapidly decreases, being small at MAICERS of £20,000 and £30,000 per QALY.

### Sensitivity of results to sensitivity and specificity of TTE

Table 8 shows how the mean ICER estimated depend on sensitivity and specificity of the technology, assuming all over values are held at their mean levels. These results indicate that the greatest possible cost-effectiveness of TTE in this context could be around £3,600/QALY in the cohort with a CHADS2 score of zero (a), and £3,300/QALY in the cohort with an initial CHADS2 score of one (b). This is seen by considering the bottom right cells, where both sensitivity and specificity are 1, i.e. a perfect test. In the CHADS2 of one point cohort, TTE remains a cost-effective strategy compared with No TTE, almost irrespective of the sensitivity and specificity of the test. A test specificity of one combined with a sensitivity of zero is equivalent to a strategy of assuming that everyone has LA ABN and should be treated with the OAC. This is indicated in the bottom left cells of the tables. For a CHADS2 score of one (b), even this scenario appears cost effective. By contrast, for the cohort with a CHADS2 score of zero (a), TTE only appears cost effective where both sensitivity and specificity are very high (the bottom right hand corner)

### Overview of results for other scenarios

The results for all 14 scenarios considered are presented in the associated appendix. A brief summary, indicating whether the results suggest TTE appears the optimal strategy at MAICERs of £20,000 /QALY or £30,000/QALY, is shown in Table 9 below. These results suggest that using TTE to make the decision whether to prescribe warfarin may be cost-effective in all patients with a CHADS2 score of one or more point. It also suggests that it may be cost effective to use TTE to help make the decision whether to prescribe dabigatran in older patients (aged 65 years). If a relatively high MAICER of £30,000/QALY is assumed, then it may also be cost effective to use TTE to make the decision whether to prescribe rivaroxaban in older patients (age 65 years). Gender has a slight effect on these results, but the choice of OAC, initial CHADS2 risk score, and patient age appear to have much greater influence.

### Summary

These results indicate that it may be cost effective to use TTE to help make the decision to prescribe warfarin in patients with a CHADS2 score of one point. It may also be cost effective in aiding the decision whether to prescribe dabigatran in older patients.

## Discussion

Prior to producing this model, a systematic literature review was conducted to identify, summarise and appraise existing economic studies for evaluating the cost-effectiveness of TTE in patients with AF. This review identified no economic evaluations of TTE in AF patients, so it is believed that this is the first.

The model has a range of limitations and a number of assumptions have been made within the modelling. For example, only the CHADS2 clinical risk prediction tool was used as the baseline strategy. An alternative to this tool is CHA2DS2-VASc, which is considered to be better at distinguishing low risk from very low risk patients [REFERENCE]. CHA2DS2-VASc was not used in these analyses as CHADS2 is the more established instrument, and the recent NICE recommendations for the use of dabigatran and rivaroxaban both map onto specific CHADS2 risk scores, but not specific CHA2DS2-VASc risk scores. The dose of dabigatran was set at 150mg twice daily, rather than allowing some patients to receive a lower dose of 110mg twice daily. The stroke risk associated with patients with left atrial abnormalities is assumed to be drawn from a constant distribution (8.0% (95% CI: 7.26 – 8.31)) and does not change as a patient ages; ideally differential rates by age or by the number (and type) of abnormalities would be used but these data were not identified.

Perhaps a stronger assumption made in producing the model is that TOE is a perfect gold standard against which the sensitivity and specificity of TTE should be derived. Using this assumption, TTE was estimated to have a very high sensitivity but a specificity of only around 35%. Within this model, this low specificity corresponds to an increased proportion of ‘false positives’ being included in the patient population mix, and so TTE results in more people effectively experiencing increased risks of bleed without the increased benefits in terms of stroke risk reduction seen in higher-risk patients. If TTE were found to be superior to TOE at identifying certain types of LA ABN which expose patients to increased stroke risks, then this modeling assumption would be inaccurate, and the true benefits of TTE in improving patient management would be underestimated. The key data on which this economic evaluation is based – sensitivity, specificity, and TPHR – is derived from a relatively small study, of fewer than 400 patients. This has made the assessment of the benefits of TTE uncertain. A further limitation is that the risk of death unrelated to bleeding or stroke events was taken from lifetables and were not adjusted for the probability of bleeding or stroke mortality.

A key uncertainty is whether there are other benefits that are accrued from a TTE other than identifying LA ABN. If these exist, and produce even small net QALY gains (> 0.0033) then TTE would be cost effective in all scenarios.

### Implications for Research

Sensitivity analyses indicated that the cost effectiveness estimates generated by the model depend heavily on sensitivity and specificity estimates, as well as the true proportion of genuinely high risk (LA ABN positive) patients in this sub-population of apparently ‘low risk’ patients. The model depends strongly on data reported in a single, relatively small study conducted outside of the UK, and so may misrepresent the true values of the sensitivity of TTE, the specificity of TTE, and TPHR. Having a more robust source of evidence for these parameters is likely to significantly improve the accuracy and validity of the mathematic models.

Additional research that would improve the validity of the model include identifying any additional net benefits to the management of newly diagnosed AF patient that could result from routine screening with TTE at time of diagnosis.

### Implications for clinical practice

The direct burden of routinely screening all newly diagnosed TTE patients is likely to be low. The additional resources required are relatively small, at an estimated £66 per TTE performed. It is likely that additional bed days are made available due to the reduction in stroke following appropriate management, although there is likely to be an increase in bleed related admissions. Should TTE be recommended for those patients with CHADS2 scores of 0 or 1, this is unlikely to place a great burden on hospitals who are likely to have staff trained in the use of TTE machines. TTEs are relatively easily available as well as both safe and non-invasive for patients, with staff trained in their use likely to be already available in hospitals.

### Conclusion

This model considers TTE as part of a diagnostic strategy. As such, TTE can only affect clinical outcomes indirectly, through its effect on the treatment options selected as a result of it. As the results in this paper and the associated appendix indicate, our estimates of the cost effectiveness of the treatment depend on the choice of OAC, as well as patient-level factors such as initial stroke risk and age. Because dabigatran and rivaroxaban appear safer than warfarin, but non-inferior in terms of stroke risk reduction, they are recommended at a lower stroke risk threshold (one CHADS2 point rather than two for warfarin), and so information from TTE makes a difference for fewer AF patients, who are less likely to be of a genuinely high risk of stroke. This moving of the ‘tipping point’ (14) has meant that TTE has become less valuable in this context even as the technology has improved. However, TTE may have value for this population in other decision-making contexts which this model has not explored. Given the very small one-off cost of a single TTE test in the context of large ongoing costs of lifelong patient management for people with AF, TTE may represent a cost-effective use of resources overall even if not when making the OAC decision.

# References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA : the journal of the American Medical Association [Internet]. 2001 May 9 [cited 2012 Mar 8];285(18):2370–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11343485

2. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. American heart journal [Internet]. 2010 Mar [cited 2012 Apr 4];159(3):340–347.e1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20211293

3. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J [Internet]. 2010/08/31 ed. 2010;31(19):2369–429. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20802247

4. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. Ann Intern Med [Internet]. 1998/12/16 ed. 1998;128(8):639–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9537937

5. NICE. Guide to the methods of technoloy appraisal. 2008 p. 80.

6. Providencia R, Botelho A, Trigo J, Quintal N, Nascimento J, Mota P, et al. Possible refinement of clinical thromboembolism assessment in patients with atrial fibrillation using echocardiographic parameters. Europace [Internet]. 2011/08/27 ed. 2012;14(1):36–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21868410

7. Simpson EL, Stevenson MD, Scope A, Poku E, Minton J, Evans P. Echocardiography in newly diagnosed atrial fibrillation patients: a systematic review and economic evaluation. 2012 p. 303.

8. PVS TM-STF on. Medical aspects of the persistent vegetative state: second of two parts. The New England Journal of Medicine [Internet]. 1994;330(22). Available from: http://www.nejm.org/doi/full/10.1056/NEJM199406023302206

9. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation [Internet]. 2011/05/18 ed. 2011;123(21):2363–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21576658

10. NICE. Guide to the methods of technology appraisal [Internet]. 2008. Available from: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

11. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. Health Economics [Internet]. John Wiley & Sons; 1996;5(6):513–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9003938

12. Office for National Statistics. Population Estimates by Marital Status, Mid-2010. 2012 [Internet]. Available from: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm:77-231283

13. Stewart S. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart [Internet]. 2001 Nov 1 [cited 2012 Mar 17];86(5):516–21. Available from: http://heart.bmj.com/cgi/doi/10.1136/heart.86.5.516

14. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes [Internet]. 2010/12/09 ed. 2011;4(1):14–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21139092

15. ONS. Interim Life Tables [Internet]. Cardiff: ONS; 2011. Available from: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables

16. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. European heart journal [Internet]. 2012 Jan 13 [cited 2012 Mar 5]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22246443

17. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med [Internet]. 2009/09/01 ed. 2009;361(12):1139–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19717844

18. Lip GYH, Edwards SJ. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. Thrombosis research [Internet]. 2006 Jan [cited 2012 Apr 5];118(3):321–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16198396

19. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the Modified Rankin Scale (mRS) Measurement into the Generic EuroQol (EQ-5D) Health Outcome. Medical Decision Making [Internet]. 2010;30(3):341–54. Available from: <Go to ISI>://000277892800009

20. Simpson EL, Stevenson MD, Rawdin A, Papaioannou D. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. Health Technology Assessment. 2009;13(2).

21. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research [Internet]. 2010 Aug [cited 2012 Apr 4];13(5):509–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20230546

22. NICE. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: Final appraisal determination [Internet]. 2011. Available from: http://www.nice.org.uk/nicemedia/live/12225/56899/56899.pdf

23. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, et al. A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. Health Technology Assessment. 2002;6(26).

24. DoH. NHS Reference Costs 2009-2010 [Internet]. London: Crown; 2011. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\_123459

25. NHS. National Stroke Strategy Impact Assessment [Internet]. 2007. Available from: http://www.dh.gov.uk/prod\_consum\_dh/groups/dh\_digitalassets/documents/digitalasset/dh\_081054.pdf

26. Curtis L. Unit Costs of Health and Social Care 2010 [Internet]. Kent; 2010 p. 257. Available from: http://www.pssru.ac.uk/archive/pdf/uc/uc2010/uc2010.pdf



Figure 1 Graphical representation of the mathematical model

|  |  |  |  |
| --- | --- | --- | --- |
| **CHADS2 score** | **Prescribe Dabigatran** | **Prescribe Warfarin** | **Prescribe Rivaroxaban** |
| 0 | No | No | No |
| 1 | Yes (age 65 or over) | No | Yes |
| 2 or more | Yes | Yes | Yes |
| **Cohorts simulated** | **Simulated for Dabigatran** | **Simulated for Warfarin** | **Simulated for Rivaroxaban** |
| Males, age 50, CHADS2 score of zero | No | Yes | Yes |
| Females, age 50, CHADS2 score of zero | No | Yes | Yes |
| Males, age 65, CHADS2 score of zero | Yes | Yes | Yes |
| Females, age 65, CHADS2 score of zero | Yes | Yes | Yes |
| Males, age 50, CHADS2 score of one | No | Yes | No |
| Females, age 50, CHADS2 score of one | No | Yes | No |
| Males, age 65, CHADS2 score of one | No | Yes | No |
| Females, age 65, CHADS2 score of one | No | Yes | No |

Table 1 Simplified OAC indications by OAC, and patient cohorts run for each OAC

|  |  |
| --- | --- |
| Population Type | Proportion of total population |
| True Positive | TPHR x sensitivity |
| True Negative | (1 – TPHR) x specificity |
| False Positive | (1 – TPHR) x (1 – specificity) |
| False Negative | TPHR x (1 – sensitivity) |

Table 2 Defining the population mix.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Category** | **Description** | **References** |
| **Risks/Probabilities** | Death from other causes | Nonparametric | UK Lifetables. (15) |
| Sensitivity and Specificity of TTE in detecting LA ABN | Jointly estimated from Dirichlet distribution  (FN, TP, TN, FP) =  (5, 87, 83, 159) | Table 2 of Providencia et al 2012 (6) |
| Proportion of patients with LA ABN | Beta(2.5, 22.5) for CHADS2  Beta(0.5, 11.5) for CHA2DS2-VASc  (Both with prior of 0.5 added to both cell counts.) | Table 2 of Providencia et al 2012 (6) |
| Annual stroke risk by CHADS2 score | Simulated from Lognormal distribution | Friberg 2012(16) |
| Annual stroke risk in those with LA ABN | Simulated from Lognormal distribution | Connolly et al 2009 (17) |
| Relative risk (RR) of stroke in patients receiving dabigatran | Indirect comparison simulation approach | Lip et al 2006 for RR of warfarin compared with placebo (18)  Eikelboom et al 2011 for RR of dabigatran compared with warfarin  (9) |
| Annual major bleeding risk for patients receiving dabigatran | Statified by age. Credible interval calculated using simulation approach | Eikelboom et al 2011  (9) |
| Outcome following stroke | Simulation & mapping based approach | Method described in report using results published in  Rivero-Arias et al 2010 (19) |
| Outcome following a major bleeding event | Previous estimates | Simpson et al 2010 (20) |
| **Utilities** | Baseline utilities by age and gender | Regression based approach | Ara et al 2010 (21) |
| Utility multiplier following stroke, utility multiplier following major non-fatal intracranial bleed | Simulation & mapping based approach | Method described in report results published in  Rivero-Arias et al 2010 (19) |
| **Costs** | Annual cost of dabigatran | £821.25 | NICE FAD, 2011 (22) |
| Cost of TTE | £66 | NHS Reference Costs |
| Cost of death due to stroke | £7,019 (95% CrI £6,975 to £7,064) | Sandercock et al 2002 (23) |
| Costs in stroke survivors | Various. Differing according to dependent and independent states. Subdivided into ongoing and continuing costs | NHS Reference Costs (24)  NHS Stroke Strategy Impact Assessment (25)  Unit Costs of Health and Social Care 2010 (26) |
| Costs of fatal bleed | Assumed identical to costs of death due to stroke | |
| Costs of nonfatal bleed | Various  Depends on whether bleed is gastrointestinal or intracranial. If intracranial, depends on severity of resulting disability | NHS Reference Costs (24) |

Table 3 Parameters used in model

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Strategy |  | Cause of Death (%) | | | Average Number of Events | | | |
| Life Years | Stroke | Bleed | Other | Dependent Strokes | Independent Strokes | ICH | NICH |
| CHADS2 of zero | No initial treatment | 28.840 | 11.7 | 1.3 | 87.1 | 0.120 | 0.242 | 0.010 | 0.075 |
| TTE with those diagnosed with LA ABN treated | 28.928 | 10.8 | 1.8 | 87.4 | 0.111 | 0.223 | 0.014 | 0.112 |
| CHADS2 of one | No initial treatment | 28.294 | 24.6 | 3.1 | 72.4 | 0.259 | 0.496 | 0.021 | 0.181 |
| TTE with those diagnosed with LA ABN treated | 28.660 | 22.8 | 3.8 | 73.4 | 0.243 | 0.459 | 0.027 | 0.234 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | | |

Table 4 Simulated patient experience: patients with a clinical prediction rule score of 0

Table 5 Cost effectiveness information for the scenario where TTE is used to inform the decision whether to prescribe Warfarin to fifty year old males with an initial CHADS2 score of zero (Dashed lines in the cost-effectiveness acceptability frontier indicate that the No TTE strategy is optimal, and solid lines indicate that the TTE strategy is optimal)

|  |  |
| --- | --- |
| X:\EchoAF\R\Figures\W_50_0_M__PSA.jpeg | X:\EchoAF\R\Figures\W_50_0_M__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_50\_0\_M*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | | *No TTE* | £ 2,459 | 13.60 |  | ***ICER (£/QALY)*** | -£ 26,489 | -£ 26,552 | to | | -£ 26,408 | |  | | *TTE* | £ 4,712 | 13.51 |  | *Interpretation:* | *Dominated* | | |  | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

Table 6 Cost effectiveness information for the scenario where TTE is used to inform the decision whether to prescribe Warfarin to fifty year old males with an initial CHADS2 score of one (Dashed lines in the cost-effectiveness acceptability frontier indicate that the No TTE strategy is optimal, and solid lines indicate that the TTE strategy is optimal)

|  |  |
| --- | --- |
| X:\EchoAF\R\Figures\W_50_1_F__PSA.jpeg | X:\EchoAF\R\Figures\W_50_1_F__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_50\_1\_F*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | *No TTE* | £ 8,308 | 12.54 |  | ***ICER (£/QALY)*** | £ | £ 7,192 | to | £ 7,202 | |  | | *TTE* | £ 11,919 | 13.04 |  | *Interpretation:* | *Neither dominated nor dominating* | | | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

|  |  |
| --- | --- |
| X:\EchoAF\R\Figures\W_50_0_M__EVPI.jpeg | C:\Users\Jon Minton\Google Drive\EchoAF\R\Figures\W_50_1_M__EVPI.jpeg |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **25,000** | **50,000** | **75,000** | | *£20,000/QALY* | 111 | 2.78 | 5.55 | 8.33 | | *£30,000/QALY* | 244 | 6.09 | 12.18 | 18.26 | | |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **25,000** | **50,000** | **75,000** | | *£20,000/QALY* | 4 | 0.10 | 0.20 | 0.30 | | *£30,000/QALY* | 2 | 0.04 | 0.08 | 0.12 | |
| 1. **Initial CHADS2 score of zero points** | 1. **Initial CHADS2 score of one point** |

Table 7 Expected value of perfect information at a range of maximum acceptable incremental cost effectivneess ratios (MAICERs), for scenarios involving fifty year old males and the decision whether to prescribe warfarin

Table 8 Illustration of the effect of different levels of sensitivity and specificity on ICER of TTE compared with no TTE in cohorts of male patients aged fifty in making the decision whether to prescribe warfarin. (Amounts in £1000 / QALY; >99; Over £99,000/QALY; D: Dominated)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***a) CHADS2*** | | *Sensitivity* | | | | | | | | | | |
| ***of zero*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** |
| *Specificity* | **0** | D | D | D | D | D | D | D | D | D | D | Inf |
| **0.1** | D | D | D | D | D | D | D | D | D | D | 8.4 |
| **0.2** | D | D | D | D | D | D | D | D | D | D | 5.7 |
| **0.3** | D | D | D | D | D | D | D | D | D | 70.7 | 4.9 |
| **0.4** | D | D | D | D | D | D | D | D | D | 26.2 | 4.4 |
| **0.5** | D | D | D | D | D | D | D | D | >99 | 17.1 | 4.2 |
| **0.6** | D | D | D | D | D | D | D | D | 65.6 | 13.1 | 4.0 |
| **0.7** | D | D | D | D | D | D | D | D | 35.0 | 10.9 | 3.8 |
| **0.8** | D | D | D | D | D | D | D | >99 | 24.5 | 9.5 | 3.8 |
| **0.9** | D | D | D | D | D | D | D | 63.9 | 19.2 | 8.5 | 3.7 |
| **1** | D | D | D | D | D | D | >99 | 40.2 | 16.0 | 7.8 | 3.6 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***b) CHADS2*** | | *Sensitivity* | | | | | | | | | | |
| ***of one*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** |
| *Specificity* | **0** | 9.8 | 9.8 | 9.9 | 9.9 | 9.9 | 10.0 | 10.1 | 10.3 | 10.6 | 11.6 | Inf |
| **0.1** | 9.3 | 9.3 | 9.3 | 9.2 | 9.1 | 9.1 | 9.0 | 8.8 | 8.5 | 7.8 | 5.6 |
| **0.2** | 8.9 | 8.8 | 8.7 | 8.6 | 8.5 | 8.4 | 8.1 | 7.8 | 7.3 | 6.4 | 4.3 |
| **0.3** | 8.5 | 8.4 | 8.3 | 8.2 | 8.0 | 7.8 | 7.5 | 7.1 | 6.5 | 5.6 | 3.9 |
| **0.4** | 8.2 | 8.1 | 8.0 | 7.8 | 7.6 | 7.3 | 7.0 | 6.6 | 6.0 | 5.1 | 3.7 |
| **0.5** | 7.9 | 7.8 | 7.6 | 7.4 | 7.2 | 7.0 | 6.6 | 6.2 | 5.6 | 4.8 | 3.6 |
| **0.6** | 7.7 | 7.5 | 7.4 | 7.2 | 6.9 | 6.7 | 6.3 | 5.9 | 5.3 | 4.6 | 3.5 |
| **0.7** | 7.4 | 7.3 | 7.1 | 6.9 | 6.7 | 6.4 | 6.0 | 5.6 | 5.1 | 4.4 | 3.4 |
| **0.8** | 7.2 | 7.1 | 6.9 | 6.7 | 6.4 | 6.2 | 5.8 | 5.4 | 4.9 | 4.3 | 3.4 |
| **0.9** | 7.0 | 6.9 | 6.7 | 6.5 | 6.2 | 6.0 | 5.6 | 5.2 | 4.7 | 4.1 | 3.4 |
| **1** | 6.9 | 6.7 | 6.5 | 6.3 | 6.1 | 5.8 | 5.5 | 5.1 | 4.6 | 4.0 | 3.3 |

Table 9 Qualitative summary of results of all 14 scenarios

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Age | Gender | CHADS2 score of 1 | OAC | Ruled out by simple dominance | TTE optimal | |
| at £20,000  /QALY | At £30,000  /QALY |
| 50 | male | no | warfarin | yes | No | No |
| 50 | female | no | warfarin | yes | No | No |
| 65 | male | no | warfarin | no | No | No |
| 65 | female | no | warfarin | no | No | No |
| 50 | male | yes | warfarin | no | Yes | Yes |
| 50 | female | yes | warfarin | no | Yes | Yes |
| 65 | male | yes | warfarin | no | Yes | Yes |
| 65 | female | yes | warfarin | no | Yes | Yes |
| 50 | male | no | rivaroxaban | yes | No | No |
| 50 | female | no | rivaroxaban | yes | No | No |
| 65 | male | no | rivaroxaban | no | No | Switch-over [[1]](#footnote-1) |
| 65 | female | no | rivaroxaban | no | No | Yes |
| 65 | male | no | dabigatran | no | Yes | Yes |
| 65 | female | no | dabigatran | no | Yes | Yes |

1. The optimal strategy switches from no TTE to TTE at this MAICER. [↑](#footnote-ref-1)