# 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 potentially fatal haemorrhages. 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. Cohorts were simulated where the CHADS2 scores alone would not lead to a decision to prescribe OACs. Both males and females were considered, assumed to be aged either 50 or 65 years of age, and with different existing risk profiles. A lifetime horizon and a UK perspective were adopted. The cost per QALY of the addition of TTE was estimated.

**Results:** At conventional willingness-to-pay thresholds of £20,000/QALY or £30,000/QALY, using TTE rather than no TTE appears to be the optimal strategy when the patients have a CHADS2 score of one rather than zero points when used to make the decision whether to prescribe warfarin; or in patients aged 65 rather than 50 years when used to make the decision to prescribe dabigatran or rivaroxaban.

**Conclusions:** It appears that, irrespective of the OAC, scenarios exist where the use of TTE is both clinically effective and cost-effective.

# Introduction

## Background

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 could result in death or severe disablement. (2)

As well as exposing patients to a risk of major bleeding events, 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. It should be noted that even where an intervention is clinically effective it does not necessarily follow that it is also cost effective. If the risk of stroke in the patient is low, then the increased health risks associated with OACs may outweigh the benefits, and so a range of diagnostic tools are used to identify higher-risk patients, including clinical prediction rules using patient history and characteristics.

## The CHADS2 clinical risk prediction algorithm

A commonly used risk prediction rule for assessing stroke risk is 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 CHADS2 risk prediction algorithm assigns a risk score of between zero and six points to patients based on five risk factors. It assigns a score of one point each to a patient if they have a history of: (C) congestive heart failure, (H) hypertension, or (D) diabetes mellitus; or if they are (A) aged 75 years or older. It assigns a risk score of two points if the patient had a prior stroke (S2), transient ischemic attack or thromboembolism.(3)

## Transthoracic Echocardiography and the decision problem

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). The populations to be modeled are patients with newly diagnosed AF. Based on clinical history, they will either have an initial CHADS2 risk score of zero or one point. If additional testing in these patients 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.

An important risk factor not included in CHADS2 is whether an individual has a left atrial abnormality (LA ABN), which has been shown to lead to an increased stroke risk,(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. (5) LA ABNs can be detected by TTE, and so can be used to identify patients with a higher risk of stroke who otherwise may not receive OACs. 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 a LA ABN 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. However, potential cost savings could arise as a result of preventing strokes and the costs to the NHS that result from them.

# Methods

The mathematical model developed estimated the consequences of using TTE to inform the decision whether to prescribe an OAC in a range of patient populations. Eight distinct cohorts were modeled, and separate scenarios were performed for each of three potential OACs: warfarin, dabigatran, and rivaroxiban. The health economic outcome of interest is the quality adjusted life year (QALY). A UK 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. (6) 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.

## Scenarios included

Warfarin, rivaroxiban, and dabigatran are each recommended in patients with different clinical characteristics, with warfarin recommended at a higher CHADS2 threshold than the newer OACs. Warfarin is typically 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(7,8). Because of this some patient cohorts would automatically receive some but not each of the OACs, and so TTE would not contribute to the OAC decision. Because of this, a total of twelve scenarios were considered. These are described in .

## Model Overview

An overview of the model is presented in . 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 the OAC was 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 they may die 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.

In the baseline strategies, none of the patients with LA ABN were treated with the OAC even though their high stroke risk means that the benefits would on average outweigh the risks. In the comparator strategy, some of these patients with LA ABN would receive the OAC due to TTE correctly identifying the feature. However, not all patients with the feature would receive the OAC, and some patients without LA ABN would also receive it. This is discussed in more detail below.

In the short-term diagnostic stage of the model the population are divided into true positives (TPs), true negatives (TNs), false positives (FPs) and false negatives (FNs). The relative size of each of the four groups is a function of the proportion of the population with LA ABN, referred to here as the true proportion high risk (TPHR); and as sensitivity and specificity of the diagnostic technology, and defined as follows:

* Proportion of true positives = TPHR x sensitivity;
* Proportion of true negatives = (1 –TPHR) x specificity;
* Proportion of false positives = (1 – TPHR) x (1 – specificity);
* Proportion of false negatives = TPHR x (1 – sensitivity).

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.

## Modeling long-term events

Prescribing an OAC means that the risk to the patient of suffering a stroke is reduced, but the risk of causing a potentially fatal major bleeding event is introduced. 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. (9)

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. (10) 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. (11)

## 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 .

## Expected value of perfect information

The individual level expected value of perfect information (EVPI) was calculated. In order to convert this into a population level EVPI, an estimate of the population affected is required. The population EVPI provides the maximum level of investment that a funding body would be prepared to pay to eliminate all uncertainty in the decision problem.(12) The population EVPI assuming population sizes of 25,000, 50,000 and 75,000 were calculated. These population sizes were selected as being approximately the correct size based on a rough calculation considering the following factors: that there are 6.7 million people aged between 55 and 64 years in England and Wales;(13) that 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);(14) that 6% of people are in the CHADS2 0 category;(5) and that the information is relevant for 10 years. This calculation suggested a population size of around 70,000 people in the CHADS2 0 category, and as it can be expected that fewer people would have CHADS2 1, this was considered an upper population estimate overall.

## Estimating cost effectiveness

The probabilities that the addition of TTE is cost-effective at maximum acceptable incremental cost effectiveness ratios (MAICERS) ranging from £0/QALY to £50,000/QALY were calculated. This information was used to create cost-effectiveness acceptability frontiers (CEAFs) for each of the scenarios. CEAFs, unlike cost-effectiveness acceptability curves (CEACs), show the probability of the adoption decision alone being cost-effective. (15)

## Deterministic sensitivity analyses

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. The results for the joint uncertainty for two scenarios are presented in the main article. The remainder of these analyses are presented in the associated appendix.

# 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.

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 of fifty year old males with a CHADS2 score of zero, presents a) a scatterplot of one thousand probabilistic sensitivity analysis runs; b) the cost effectiveness acceptability frontier, which shows the probability that the adoption option is cost-effective; c) the mean cost and mean QALY associated with each option, and the ICER associated with these mean values. 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 (), 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. These results suggest that TTE can harm patients due to higher bleed risks, because of misdiagnosis of those without LA ABN. The CEAF indicates that the no TTE strategy is the adoption strategy at all willingness-to-pay thresholds between £0 and £50,000/QALY. The estimated probability of TTE being cost effective is only 7.8% at a MAICER of £20,000/QALY, and 9.6% at a MAICER of £30,000/QALY.

By contrast, for the cohort with an initial CHADS2 score of one point (), it is clear from the scatterplot (a) that all estimates are in the north east 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. These results suggest that the reduction in strokes resulting from using TTE in this population group outweighs the additional risk of bleeding events. The CEAF (b) indicates that the TTE strategy becomes the adoption strategy at £7,197 per QALY. It has an estimated probability of being cost effective of 99.3% at a MAICER of £20,000/QALY and 99.9% at £30,000/QALY.

## Expected value of perfect information

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.

## Deterministic sensitivity analyses

shows how the mean ICER estimated depend on sensitivity and specificity of the technology, assuming all other 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. For the cohort with a CHADS2 score of zero (a), TTE only appears cost effective where both sensitivity and specificity are very high, near the bottom right hand corner of the table.

## Overview of results for other scenarios

The results for all 14 scenarios considered are presented in the associated online 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 . 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 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), and it may be borderline cost effective, if assuming a relatively high MAICER of £30,000/QALY, 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(16,17). 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.(7,8) 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.

Within the reference used to derive the sensitivity and specificity of TEE, transoesophageal echocardiography (TOE), was used assumed to be a perfect gold standard, and so our model also made this assumption. (5) Using TOE as the gold standard, 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 the true benefits of TTE in improving patient management would be underestimated. This relatively small study, of fewer than 400 patients, also formed the basis of our estimates of the TPHR. (5) 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. As b indicates, the structural sensitivity analyses for this scenario indicate that even a diagnostic strategy with a joint sensitivity of one and and specificity of zero may be cost effective. The implications of this result require further research.

## Implications for Research

For some scenarios 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. The extent to which these cost-effectiveness estimated relate to healthcare in the US depends on how similar the populations and healthcare systems are, which could be a matter for further research.

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.(18) 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 zero or one point, this is unlikely to place a great burden on the majority of hospitals who are likely to have staff trained in the use of TTE machines, which are both safe for patients and non-invasive.

## Conclusion

This paper presented the results of mathematical models which simulated the effects of using TTE to help make the decision whether to prescribe an OAC in a range of patient types. It found that using TTE in this way appears cost effective when the OAC of choice is warfarin and the patient population has a CHADS2 risks score of one point rather than zero points. It also found that when rivaroxaban or dabigatran is the OACs of choice then it appears cost-effective to use TTE in this way in patients aged 65 years. As higher CHADS2 scores represent increased estimated stroke risk, and stroke risk is also known to increase with age, these results suggest that, irrespective of the OAC, it may be both clinically effective and cost effective to use TTE to help inform the decision in all but the patients with the lowest stroke risk.

# 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. 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

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

7. NICE. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation [Internet]. NICE technology appraisal guidance 256. 2012 [cited 2012 Sep 28]. Available from: http://www.nice.org.uk/nicemedia/live/13746/59295/59295.pdf

8. NICE. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation [Internet]. NICE technology appraisal guidance 249. 2012 [cited 2012 Sep 28]. Available from: http://www.nice.org.uk/nicemedia/live/13677/58470/58470.pdf

9. 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.

10. 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

11. 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

12. 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

13. 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

14. 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

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

16. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest [Internet]. 2009/09/19 ed. 2010;137(2):263–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19762550

17. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ [Internet]. 2011 Jan 31 [cited 2012 Mar 27];342(jan31 1):d124–d124. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.d124

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

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

20. 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

21. 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

22. 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

23. 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

24. 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).

25. 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

26. 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

27. 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).

28. 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

29. 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

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Category** | **Description** | **References** |
| **Risks/Probabilities** | Death from other causes | Nonparametric | UK Lifetables. (19) |
| 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 (5) |
| 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 (5) |
| Annual stroke risk by CHADS2 score | Simulated from Lognormal distribution | Friberg 2012(20) |
| Annual stroke risk in those with LA ABN | Simulated from Lognormal distribution | Connolly et al 2009 (21) |
| Relative risk (RR) of stroke in patients receiving dabigatran | Indirect comparison simulation approach | Lip et al 2006 for RR of warfarin compared with placebo (22)  Eikelboom et al 2011 for RR of dabigatran compared with warfarin(11) |
| Annual major bleeding risk for patients receiving dabigatran | Statified by age. Credible interval calculated using simulation approach | Eikelboom et al 2011 (11) |
| Outcome following stroke | Simulation & mapping based approach | Method described in report using results published in Rivero-Arias et al 2010 (23) |
| Outcome following a major bleeding event | Previous estimates | Simpson et al 2010 (24) |
| **Utilities** | Baseline utilities by age and gender | Regression based approach | Ara et al 2010 (25) |
| 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 (23) |
| **Costs** | Annual cost of dabigatran | £821.25 | NICE FAD, 2011 (26) |
| 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 (27) |
| Costs in stroke survivors | Various. Differing according to dependent and independent states. Subdivided into ongoing and continuing costs | NHS Reference Costs (18)  NHS Stroke Strategy Impact Assessment (28)  Unit Costs of Health and Social Care 2010 (29) |
| 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 (18) |

Table 2 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 3 Simulated patient experience: patients with a clinical prediction rule score of 0

Table 4 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 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 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. Appears cost effective at £20,000/QALY* | | | |  |  | | |
| 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 6 Expected value of perfect information at a range of maximum acceptable incremental cost effectiveness ratios (MAICERs), for scenarios involving fifty year old males and the decision whether to prescribe warfarin

Table 7 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. The four cells with sensitivity and specificity values closest to the empirical values are underlined. (Amounts in £1000 / QALY; >99; Over £99,000/QALY; D: Dominated)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***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 | ∞ |
| **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 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***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 | ∞ |
| **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 |

Table 8 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 | No [[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 a MAICER of £30,400/QALY. [↑](#footnote-ref-1)