# 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.

Objective: 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 either an OAC prescription decision using a standard clinical decision tool (CHADS2 or CHA2DS2-VASc) alongside TTE, compared to a standard clinical decision tool alone. From this, incremental costs and utilities were estimated in order to calculate an incremental cost effectiveness ratio. (ICER)

Target Population: Sixty year old males with newly diagnosed atrial fibrillation and without a previous history of coronary heart disease or stroke.

Time Horizon: lifetime.

Perspective: NHS

Interventions: Dabigatran 150mg twice daily if the decision to prescribe an OAC was made, and no pharmaceutical intervention was modeled otherwise.

Outcome Measures: Quality adjusted life years (QALYs).

**Results:** Adding TTE to the decision to prescribe OACs appears cost-effective when CHADS2 is modeled as the comparator, but not when CHA2DS2–VASc is used. The mean respective ICERs are £5847 per QALY for CHADS2 and £49491 per QALY for CHA2DS2-VASc.

**Limitations:** Data used to populate many important parameters in the model were either missing or limited.

**Conclusions:** The estimated incremental cost effectiveness of using TTE to make the decision to prescribe depends on whether the comparator is CHADS2 or CHA2DS2-VASc. Whilst TTE does not appear cost effective when added to CHA2DS2-VASc, this conclusion is uncertain due to data limitations.

## 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) They are also relatively expensive, either directly due to drug acquisition costs in the case of newer drugs like dabigatran, 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.

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 and CHA2DS2-VASc, 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.

This study assesses whether performing an additional, slightly more expensive diagnostic test in all newly diagnosed AF patients 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 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 model the long-term implications of performing TTEs in all newly diagnosed AF patients without a history of coronary heart disease or stroke when making the decision whether to prescribe OACs. Dabigatran was selected as the OAC to model, as it has recently been recommended for use in this population group by NICE (4), and carries a lower bleed risk than warfarin.(5) Patients whom the prediction rule would suggest are of lowest stroke risk, and so would not normally be prescribed OAC, are also 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,(6) 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 all newly diagnosed 60 year old males with AF, on the decision to prescribe dabigatran and outcomes following this decision, compared with just using one of two related clinical prediction rules (described later) to make this decision. Males aged under 65 were considered because being female and being aged 65 or older are risk factors according to the more sensitive of the two clinical prediction rules (CHA2DS2­-VASc), and so would lead to a decision to prescribe OACs even in the absence of information from TTE. The health economic outcome of interest is the quality adjusted life year (QALY). An NHS perspective is adopted, so that 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. (7) A lifetime horizon is adopted. In order to incorporate the effect of uncertainty on predicted outcomes, a probabilistic model is used, so 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 involves both a short-term diagnostic stage and long-term patient outcome stage. In the short-term stage the clinical characteristics of a patient are generated, and the decision whether or not to prescribe OAC is made. 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, or a death from another cause. Each of these events have associated costs and utility implications. By simulating the outcomes for a large number of patients, the average associated costs and utilities following both diagnostic strategies (within and without the use of TTE) were estimated, allowing estimation of the mean costs and mean QALYs for both strategies, and so the incremental cost effectiveness ratio (ICER) of including TTE in the diagnostic package.



Figure 1 Graphical representation of the mathematical model

### Comparison of Diagnostic Instruments

The criteria and scoring systems used by the two baseline strategies are shown in Table 1 below. The CHADS2 instrument produces a risk score for each patient ranging from zero to six points inclusive, and CHA2DS2-VASc assigns patients a score ranging from zero to nine points inclusive. In both cases, it is assumed a patient assigned a risk score of one or more point would be prescribed dabigatran. As a result of this, CHA2DS2-VASc will recommend treatment to more people than CHADS­2.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| CHADS2 | | | CHA2DS2-VASC | | |
| Code | Condition | Points | Code | Condition | Points |
| C | Congestive heart failure | 1 | C | Congestive heart failure | 1 |
| H | Hypertension | 1 | H | Hypertension | 1 |
| A | Age ≥ 75 years | 1 | A2 | Age ≥ 75 years | 2 |
| D | Diabetes mellitus | 1 | D | Diabetes mellitus | 1 |
| S­­­2 | Prior stroke or TIA | 2 | S­­­2 | Prior stroke or TIA | 2 |
|  | | | V | Vascular disease | 1 |
| A | Age 65-74 years | 1 |
| Sc | Sex category (female) | 1 |

Table 1 CHADS2 and CHA2DS2-VASc

In the comparator strategy, information from TTE is used in addition to that from the standard clinical prediction rule, and so the decision to coagulate can also be made as a result of TTE identifying a structural feature of left atrial abnormality (LA ABN) that predisposes an individual to a high risk of stroke(6). 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. (8)

### Modeling of decision

The short term model looks at 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 would receive dabigatran. 2) true negatives (TNs): patients with a clinical prediction score of zero, who also do not have an LA ABN, and whom TTE does not misclassify as having LA ABN. These patients currently do not receive the OAC, and for this patient group this is the correct decision under current clinical guidelines. 3) False positives (FPs): Patients with a clinical prediction score of zero 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 clinical prediction score of zero, but a LA ABN that TTE has failed to identify. These patients would not receive OACs even though for them prescribing OACs would be the correct decisionhad the LA ABN been identified. 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 below. 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.

|  |  |
| --- | --- |
| 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.

### 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 below.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Category** | **Description** | **References** |
| **Risks/Probabilities** | Death from other causes | Nonparametric | UK Lifetables. (9) |
| 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 (8) Providencia et al 2012 |
| 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 (8) Providencia et al 2012 |
| Annual stroke risk by CHADS2 score | Simulated from Lognormal distribution | Gage et al 2004(10) |
| Annual stroke risk by CHA2DS2-VASc score | Assumed identical to risk by CHADS2 score | Gage et al 2004 (10) |
| Annual stroke risk in those with LA ABN | Simulated from Lognormal distribution | Connolly et al 2009(11) |
| Relative risk (RR) of stroke in patients receiving dabigatran | Indirect comparison simulation approach | Lip et al 2006 (12) for RR of warfarin compared with placebo  Eikelboom et al 2011(5) for RR of dabigatran compared with warfarin |
| Annual major bleeding risk for patients receiving dabigatran | Statified by age. Credible interval calculated using simulation approach | Eikelboom et al 2011(5) |
| Outcome following stroke | Simulation & mapping based approach | Method described in companion paper [Ref], using results published in  Rivero-Arias et al 2010(13) |
| Outcome following a major bleeding event | Previous estimates | Simpson et al 2010(14) |
| **Utilities** | Baseline utilities by age and gender | Regression based approach | Ara et al 2010(15) |
| Utility multiplier following stroke, utility multiplier following major non-fatal intracranial bleed | Simulation & mapping based approach | Method described in companion paper [Ref], using results published in  Rivero-Arias et al 2010(13) |
| **Costs** | Annual cost of dabigatran | £821.25 | NICE FAD, 2011 (16) |
| Cost of TTE | £66 | NHS Reference Costs (17) |
| Cost of death due to stroke | £7,019 (95% CrI £6,975 to £7,064) | Sandercock et al 2002 (18) |
| Costs in stroke survivors | Various. Differing according to dependent and independent states. Subdivided into ongoing and continuing costs | NHS Reference Costs(17)  NHS Stroke Strategy Impact Assessment (19)  Unit Costs of Health and Social Care 2010(20) |
| 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(17) |

Table 3 Parameters used in model

### Modeling the long-term implications of decision

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 (21)

The model is dynamically updated when events occur that affect an individual’s CHADS2 or CHA2DS2-VASc score, or other characteristics that affect their stroke or bleed risk. For example, when the patient reaches an age of 65, their CHA2DS2-VASc score increases by one; at age 75 their score increases by one CHADS2 point, and their CHA2DS2-VASc score by an additional point. A stroke leads to an increment of two points on the CHADS2/CHA2DS2-VASc score. If a patient suffers a major bleeding event after taking OACs, they stop being prescribed the OACs, leading to the risk of bleeds reducing to zero, but the risk of stroke increasing. If a patient experiences a stroke and are 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 3.4 years with no QALY gain.[[1]](#footnote-1) 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. (5)

The costs and QALYs associated with the simulated patient experiences following both baseline (without TTE) and comparator (with TTE) strategies were used to estimate 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 comparator strategy is cost-effective at a wide range of maximum acceptable incremental cost effectiveness ratios (MAICERS) is presented in the form of cost-effectiveness acceptability curves (CEACs) and cost-effectiveness acceptability frontiers (CEAFs), and the probability of being cost-effective at the commonly quoted threshold of £20,000 per QALY is reported.

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.(22) In calculating EVPI an estimation of the number of patients who will be affected by the decision is required. Assuming 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);(23) that there are 6.7 million people aged between 55 and 64 years in England and Wales;(24) that 6% of people are in the CHADS2 0 category;(8) 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

Table 3 shows the shows the simulated patient experience when TTE is added to either CHADS2 or CHA2DS2-VASc, in terms of clinical events. These suggest that using information from TTE increases the expected life of patients, and increases the proportion of patients that die of non stroke- or bleed-related causes. An initial TTE reduces the estimated number of strokes but at the expense of a greater number of bleeds.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  | Cause of Death (%) | | | Average Number of Events | | | |
|  | Strategy | Life Years | Stroke | Bleed | Other | Dep. Strokes | Ind. Strokes | ICH | NICH |
| CHADS2 | No initial treatment | 20.024 | 12.2 | 1.4 | 86.4 | 0.115 | 0.262 | 0.011 | 0.082 |
| TTE with those diagnosed with LA ABN  treated | 20.175 | 10.9 | 1.8 | 87.3 | 0.104 | 0.235 | 0.014 | 0.109 |
| CHA2DS2-VASc | No initial treatment | 19.777 | 14.6 | 1.6 | 83.9 | 0.140 | 0.311 | 0.012 | 0.092 |
| TTE with those diagnosed with LA ABN  treated | 19.823 | 14.0 | 1.9 | 84.1 | 0.136 | 0.298 | 0.014 | 0.111 |
| 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

Where a new intervention is estimated to be both more costly and more clinically effective than standard practice, the ratio of additional cost to additional benefit can be meaningfully described using an incremental cost effectiveness ratio (ICER). Where the new intervention is both more efficacious and less costly than standard practice, the new intervention is described as having ‘simple dominance’ over standard practice, as no trade-off between additional cost and additional clinical effectiveness is required to make the decision to move to the new treatment. Where the new intervention is both less efficacious and less costly decision, the new treatment is described as being ‘simply dominated’ by standard practice. Due to the uncertainty in the true values of the model input parameters, there exists a range of joint estimates of the incremental cost and incremental effectiveness of the new treatment compared with existing treatment, from which a 95% credible interval can be calculated. Table 4 shows the costs, QALYs, and ICERs associated with the simulated patient experiences presented in Table 3. For CHADS2, the mean cost per QALY of below £6000 indicates that TTE is likely to be a cost effective use of resources. For CHA2DS2-VASc, the mean cost per QALY of almost £50,000 suggests TTE is not likely to be cost-effective in this context. The 95% credible intervals for the ICERs range from dominating to almost £30,000 per QALY for CHADS2, and from less than £6,000 to dominated for CHA2DS2-VASc. These correspond directly to the joint estimation of costs and QALYs resulting from the PSA, as shown in figure 2(a) and figure 2(b). For figure 2(a) (CHADS2), a significant proportion of the estimates are in the south east quadrant, indicating simple dominance over the baseline strategy. For figure 2(b) (CHA2DS2-VAsc), a significant proportion of the estimates are in the north-west quadrant, indicating that the comparator strategy (CHA2DS2-VASc with TTE) is dominated by the baseline strategy (CHA2DS2-VASc alone).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Strategy | | Cost | QALYs | Incremental Cost | Incremental QALYs | Cost per QALY  (2.5th and 97.5th percentiles) |
| CHADS2 | No initial treatment | £13,792 | 10.185 |  |  |  | |
| TTE with those diagnosed with LA ABN treated | £15,646 | 10.502 | £1,854 | 0.317 | £5847  (Dominating -£28,939) | |
| CHA2DS2-VASc | No initial treatment | £15,249 | 10.077 |  | | | |
| TTE with those diagnosed with LA ABN treated | £19,729 | 10.168 | £4480 | 0.091 | £49,491  (£5604 - Dominated) | |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality | | | | | | |

Table 5 Cost effectiveness of the use of TTE in patients with a CHADS2 or CHA2DS2-VASc score of 0

|  |  |
| --- | --- |
| Dab_C0_PSA.jpeg | Dab_CV0_PSA.jpeg |
| CHADS2 | CHA2DS2-VASc |

Figure 2 PSA scatterplot

|  |  |
| --- | --- |
| Dab_C0_ceac.jpeg | Dab_CV0_ceac.jpeg |
| CHADS2 | CHA2DS2-VASc |

Figure 3 Cost Effectiveness Acceptability Curves

|  |  |
| --- | --- |
| Dab_C0_ceaf.jpeg | Dab_CV0_ceaf.jpeg |
| CHADS2 | CHA2DS2-VASc |

Figure 4 Cost Effectiveness Acceptability Frontiers

Figures 4a and 4b shows the cost-effectiveness acceptability frontiers (CEAFs) associated with CHADS2 and CHA2DS2-VASc respectively. Figure 4a indicates that the comparator strategy (CHADS2 + TTE, shown as a solid line) becomes the optimal strategy, compared with CHADS2 alone (the dashed line) at a willingness to pay threshold of £5847 or more per QALY gained. Conversely, figure 4b indicates that the baseline strategy (CHA2DS2-VASc alone) has a high likelihood of being the optimal decision at threshold of lower than £50,000 per QALY gained, compared with CHA2DS2-VASc + TTE.

Figures 5a and 5b show, respectively, the per patient EVPI of TTE compared with CHADS2 alone and CHA2DS­2-VASc alone. It is seen that there is most uncertainty at maximum acceptable incremental cost effectiveness ratios (MAICERs) close to the value at which TTE becomes cost effective. As the MAICER increases the value of EVPI falls substantially. Assuming that there are 70,000 people who would benefit from no uncertainty in the decision problem, the expected value of perfect information would be in the region of £5 million assuming a MAICER of £20,000 per QALY when using CHADS2 alone; the equivalent figure for CHA2DS2-VASc is in the region of £28 million.

|  |  |
| --- | --- |
| Dab_C0_evpi.jpeg | Dab_CV0_evpi.jpeg |
| CHADS2 | CHA2DS2-VASc |

Figure 5 Expected Value of Perfect Information per patient

Figure 6a and 6b indicate the effect that different assumptions about the TPHR within the subgroup of the population with CHADS2 scores of zero and CHA2DS2-VASc scores of zero, respectively. For CHADS2 (Figure 6a) it is seen that at low proportions of patients with LA ABN that TTE is cost effective; even at zero percent TTE is cost effective indicating that there is an apparent benefit in treating those with a CHADS2 score of zero even when the patient does not have LA ABN. Conversely, for CHA2DS2-VASc (Figure 6b) it is seen that the proportion of patients with LA ABN needs to be close to 12.5% in order for the cost per QALY of TTE to be near £20,000. At present there are very little data on this parameter with 0 of 11 patients with a CHA2DS2-VASc score of 0 having LA ABN.

|  |  |
| --- | --- |
| C:\Users\User\AppData\Local\Temp\HR_Dab_C0.jpeg | C:\Users\User\AppData\Local\Temp\HR_Dab_CV0.jpeg |
| CHADS2 | CHA2DS2-VASc |

Additional analyses were undertaken to identify the effect of different sensitivity and specificity assumptions on the expected ICERs. These indicated that, when CHADS2 was the comparator strategy, incorporating TTE appeared cost effective or even dominating for almost all possible sensitivity and specificity values except where specificity tends to one and sensitivity tends to zero (i.e. where TTE is assumed to add very little benefit to the clinical rule alone). However, where CHA2DS2-VASc was the comparator strategy, including TTE in the diagnostic decision only appeared cost effective at a threshold of £20,000 or less where both sensitivity and specificity were assumed to be close to perfect.

### Summary

These results indicate that the cost effectiveness of TTE in this context depends on the baseline strategy assumed, with results indicating TTE is cost effective when compared with CHADS2 alone, but not when compared with CHA2DS2-VASc alone, although this latter conclusion is subject to considerable uncertainty.

## Discussion

This model indicates that, when it was assumed that the CHADS2 tool was used, the addition of TTE with the aim of identifying patients with LA ABN was deemed cost effective with the mean cost per QALY below £20,000 for all analyses and a low probability of the cost per QALY being greater than £20,000. Conversely, when the CHA2DS2-VASc tool was used, the addition of a TTE was not considered cost effective with the mean cost per QALY being greater than £30,000 for all analyses, and often considerably higher. However, there is considerable uncertainty in this conclusion due to the dearth of data, particularly in the proportion of patients with LA ABN and a CHA2DS2-VASc score of 0, as there were only 11 patients with a CHA2DS2-VASc of zero.

The model has a range of shortcomings and limitations. Assumptions have been made within the modelling. For example, the risk of stroke associated with a CHA2DS2-VASc score was assumed to be equal to that associated with the identical CHADS2 score, which is incorrect as the CHA2DS2-VASc is incremented by one when the person is 65 years, with the corresponding age for a unit increment in the CHADS2 score is 75 years. 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 constant at 8.0% (95% CI: 7.26 – 8.31) 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 OACs in terms of bleed risks without corresponding increased benefits in terms of stroke risk reduction. 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 may 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 a relatively small study, of fewer than 400 patients, and in the group of interest, those patients who would be given a CHADS2 or CHA2DS2-VASc score of 0, fewer than 25 patients. This has made the assessment of the benefits of TTE uncertain, particularly in addition to the use of CHA2DS2-VASc, which had the fewer number of patients.

Other limitations include that there were no data relating the risk of stroke with CHA2DS2-VASc score, and this was approximated using the risk of stroke associated with CHADS2 score; 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; and that the patient groups analysed within the model was limited, being males aged 60 with a CHADS2 or CHA2DS2-VASc score of 0 or 1.

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.

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.

### Implications for Research

Sensitivity analyses indicated that the model’s cost-effectiveness estimates 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 under-represent the true level of uncertainty we have about sensitivity, specificity 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: producing evidence linking each CHA2DS2-VASc score with an underlying annual stroke risk, as currently the assumption has had to have been made that CHA2DS2-VASc risks correspond exactly with CHADS2 risks; and 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 or CHA2DS2-VASc 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. Recent changes in the recommended OAC for AF patients, from warfarin to dabigatran, have led to changes in the added value of TTE in this context, as it has changed the proportion of patients where the new information from TTE is likely to make a difference to clinical management. Because dabigatran appears safer than warfarin, but is noninferior in terms of stroke risk reduction, the OAC is prescribed 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’ (25) 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.

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;31(19):2369–429. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20802247

4. NICE. Final appraisal determination – Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation [Internet]. 2012. Available from: http://www.nice.org.uk/nicemedia/live/12225/56899/56899.pdf

5. 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;123(21):2363–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21576658

6. 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;128(8):639–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9537937

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

8. 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]. 2012;14(1):36–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21868410

9. ONS. Interim Life Tables [Internet]. 2011;2012(12 January). Available from: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables

10. Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BS, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation [Internet]. 2004;110(16):2287–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15477396

11. 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;361(12):1139–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19717844

12. 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

13. 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

14. 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).

15. 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

16. NICE. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: Final appraisal determination [Internet]. 2011;2012(12 January). Available from: http://www.nice.org.uk/nicemedia/live/12225/56899/56899.pdf

17. DoH. NHS Reference Costs 2009-2010 [Internet]. 2011;2012(12 January). Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\_123459

18. 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).

19. NHS. National Stroke Strategy Impact Assessment [Internet]. 2007;2012(13 January). Available from: http://www.dh.gov.uk/prod\_consum\_dh/groups/dh\_digitalassets/documents/digitalasset/dh\_081054.pdf

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

21. 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.

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

23. 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

24. 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

25. 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]. 2011;4(1):14–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21139092

1. Personal communication to Mike Holmes from a clinician he was working with in the TTE for stroke project. Not sure how to cite this… simply remove sentence? [↑](#footnote-ref-1)