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A model based cost-effectiveness analysis of opportunistic screening for identifying atrial fibrillation with a single lead handheld electrocardiogram monitor in general practices in Scotland

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Contents

1 Abstract

Background

Atrial fibrillation (AF) is the most common arrhythmia in elderly persons and a major risk factor for stroke. In the elderly population AF is often asymptomatic or produces mild symptoms which do not prompt self-referral. At present there is no systematic manner to identify AF in primary care in Scotland. This study aimed to assess the potential cost-effectiveness of opportunistic screening for AF in a high risk population using a hand-held single lead ECG device (AliveCor) compared to usual care.

Methods

A de-novo decision-analytic Markov model was developed to simulate the risk of stroke and bleeding events with standard case finding of newly identified AF (i.e. no screening/usual care) and to then assess the impact that screening with single lead ECG would have on the downstream costs and health outcomes over a 30 year time horizon. The analysis was conducted from the UK NHS and Personal Social Services (PSS) and included the costs of screening /diagnosis, treatments being given to prevent stroke (e.g. warfarin, NOACs), acute and post-acute stroke care. Effectiveness was measured using life-years and quality-adjusted life-years (QALYs). Future benefits and costs were discounted at an annual rate of 3.5%. Model inputs were based on a number of available evidence sources including the main pilot study. Extensive deterministic sensitivity analysis along with probabilistic sensitivity analysis was undertaken to investigate model assumption and parameter uncertainty on robustness of the results.

Results

Screening with AliveCor costs £22.02 per patient screened. In the base case analysis, usual care (i.e. no screening) was £83.051 more costly and generated -0.0160 fewer QALYs compared with AliveCor over a 30 year's time horizon. The deterministic sensitivity analyses showed that variables having the most impact on results included the estimates for sensitivity and specificity of screening and hazard rates and ratios for events (e.g. systemic embolism, stroke). The probabilistic sensitivity analysis showed that, in 79.5% of simulations, the costs per QALY gained was less than £30,000.

Conclusions

Preliminary results from the simulation model indicate that a move to screening for AF in a high risk population using a single lead ECG compared to standard practice has the potential to be cost-effective. However, the study results are somewhat uncertain and should be considered with a few issues and limitations in mind including the uncertainty around some parameter estimates and availability of data (or variability in) standard AF case finding in routine clinical practice.

2 Introduction

Atrial fibrillation (AF) is a major risk factor for stroke. In the elderly population AF can go undetected as it is often asymptomatic or produces mild symptoms. New ECG screening technologies offer potential for easier identification of patients with AF, many of whom could benefit from oral anticoagulant drugs for stroke prevention. We undertook a health economic modelling project to run alongside the main AF screening pilot study conducted across five Scottish regions.[1] The aim of this study was to assess the clinical and cost-effectiveness of opportunistic screening for AF in primary care using a single lead ECG monitor (AliveCor®) in a Quality and Outcomes Framework (QOF) chronic disease population, compared to standard practice (usual case finding). The specific objectives are to: 1) assess the short term costs and of AF screening; and 2) model the longer term costs and consequences of opportunistic screening (in terms of AF diagnosis rates, eligibility & uptake of OACs, quality-adjusted life years (QALYs), and health and social care costs). We developed a decision model to perform the analyses and used clinical and economic data from the screening pilot study, published literature, previous economic evaluations and routine sources of UK National Health Service (NHS) cost data. This study will help to inform decisions on the potential costs and health benefits of rolling-out a national AF screening programme in primary care in Scotland, and help identify any gaps in the evidence base requiring further research.

Background

Atrial fibrillation (AF) is the most common arrhythmia in elderly persons and a major risk factor for stroke. The prevalence of AF in Scotland is ~1.6% (atrial fibrillation QOF register in 2013/14 or around 88,058 patients), ranging from 1.5% to 3.1% across NHS Boards.[2] These figures are likely to underestimate the true prevalence of AF, and it has been estimated that the number of people living with AF in the UK may be 31% higher than the number diagnosed with the condition.[3]

Atrial fibrillation is associated with a five-fold increase in stroke risk and it is especially prevalent in patients with heart failure, diabetes, hypertension, and vascular disease. Importantly, strokes attributable to AF are associated with greater morbidity, mortality and healthcare costs. Stroke risk is modifiable through the use of warfarin and novel oral anticoagulants (NOACs).

At present, AF is not identified in a systematic manner in primary care in Scotland. Cases are detected every year through pulse checking and subsequent referral for 12-lead ECG (the reference (gold) standard for confirming this diagnosis). However clinical experience indicates that pulse checking is not carried out routinely in the QOF chronic disease population. In addition, pulse checking may be less reliable and less accurate compared to new low-cost technologies for identifying patients with AF.[1,4] Scope exists to use this device to opportunistically screen patients for AF in Scotland, to improve diagnosis rates, increase the uptake/use of anticoagulant drugs, and ultimately reduce the risk of stroke in AF patients.[3]

The overall goal of the Scottish AF screening pilot is to ascertain the acceptability of a large scale deployment of the (AliveCor®) screening tool, it aimed to screen 250 patents per practice (5 practices from each of 5 Scottish regions: Lothian, Greater Glasgow and Clyde, Tayside, Grampian, and Fife), equating to an expected minimum sample of 5000 ECGs over a

one-year period. Based on pilot trial data the AF prevalence rate among this high risk category is 5.5%. In the context of this Scottish pilot project, the aim of this sub-study is to assess the cost of implementing opportunistic screening, and to inform potential cost-effectiveness by making projections of the down-stream impact on the uptake of treatment and the incidence of stroke.

To date, no studies have assessed the potential cost-effectiveness of screening for AF using a single lead ECG based on data relevant to the Scottish GP primary care chronic disease population.

3 Methods

A de novo cost–utility Markov model was developed using TreeAge Pro 2015 (TreeAge Software, Inc., Williamstown, MA, USA, 2015) to assess the cost-effectiveness of using AliveCor iPhone ECG to screen for AF, compared with no routine screening. The alternative pathways were embedded in a Markov model simulating the progression of undiagnosed AF, the downstream impact of diagnosis, treatment and modifying stroke risk on survival and health related quality of life. A Markov model considers patients in a discrete health state and allows the consequences of treatment strategies in terms of prevalence rates, complications avoided, health-related quality of life and costs to be captured for a particular patient population, over the adopted time horizon.

Costs incorporated in the model included those associated with screening, drugs to offset the risk of stroke (i.e. warfarin or NOACs), adverse events (e.g. systemic embolism, stroke) and the potential complications of warfarin and NOAC treatment (e.g. intracranial haemorrhage, clinically relevant bleed). Health-state utilities associated with pre and post treatment were incorporated in the model to calculate QALYs. The alternative strategies were ranked incrementally in terms of their costs and the incremental cost-effectiveness ratio (ICER) was calculated. A ceiling ratio of £30,000 per QALY to delineate the cost-effectiveness of opportunistic screening was applied. Costs and benefits (QALYs) were discounted at the NICE recommended rate of 3.5% per annum in line with the NICE reference case.[5]

Allowance for uncertainty

Sensitivity analysis is a method of testing the robustness of the analysis. To explore the robustness of the study results to changes in the value of key parameter estimates, we performed extensive deterministic sensitivity analyses (varying one parameter at a time) as well as comparing the use of AliveCor with other possible comparators (i.e. including manual pulse palpation as a screening option). To address shortcomings in performing only univariate sensitivity analysis, we also performed probabilistic sensitivity analysis using Monte Carlo simulation (1000 iterations) in which the values of key variables and areas of uncertainty associated with estimates were simultaneously varied by replacing parameter (point) estimates with appropriate distributions for hazard rates (lognormal), health utilities (beta) and disease event costs (gamma). Output from this multiway sensitivity analysis can also take into account uncertainty with respect to maximal cost-effectiveness that decision makers would consider acceptable (e.g. £30,000 per QALY) by generating a cost-effectiveness acceptability curve (CEAC). CEACs assist the decision-making process by depicting the ceiling costs per extra unit of effect values on the x axis against the probability of these values being achieved on the y axis.

Relevant patient population

The modelled cohort consisted of patients with a chronic disease (e.g. cerebrovascular disease, diabetes, hypertension, vascular disease and chronic kidney disease, stage 3 and above) presenting for their annual Quality and Outcomes Framework check-up. All patients had a CHA_2DS_2-VAS_c (congestive heart failure, prior hypertension, age, diabetes, stroke/TIA, vascular disease and gender) score of 2 or above. We considered a cohort of patients aged ≥65, 60% male/40% female, and considered costs and benefits over a 30 year time horizon.

Diagnostic strategy to be evaluated

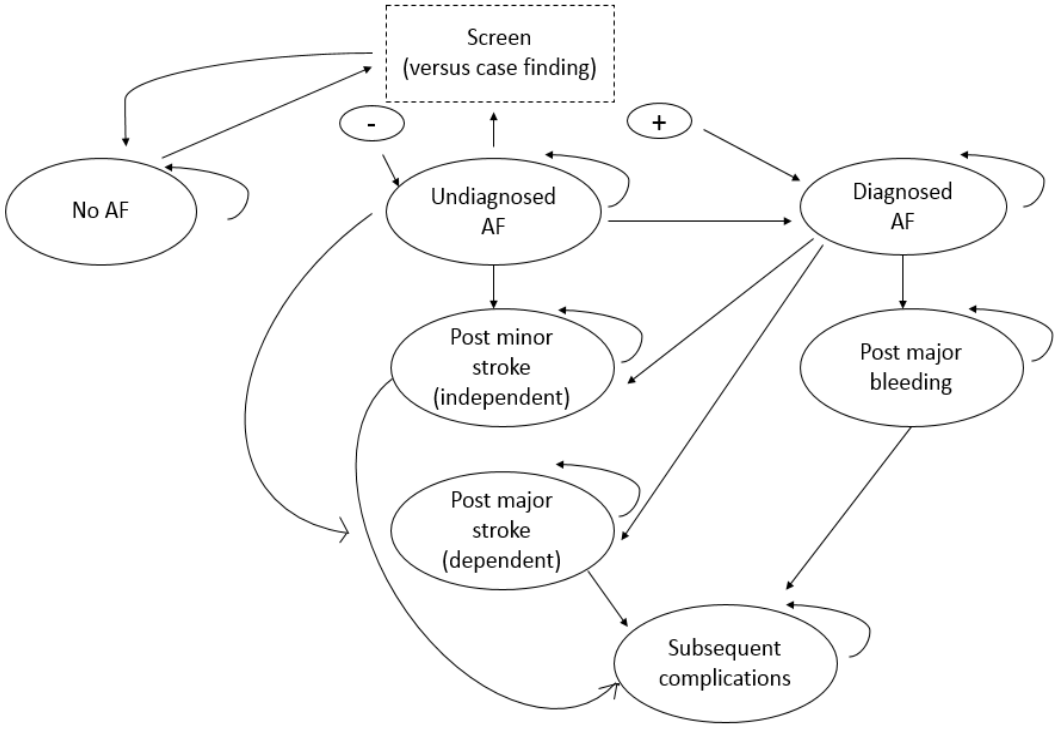
Lack of easy access to ECG or to reporting of ECG is a barrier to systematic screening for AF in primary care. New screening technologies enable an easier (and potentially earlier) identification of patients with AF. The 12 lead ECG remains the reference (gold) standard for confirming AF diagnosis, but for screening a simple single lead ECG can be used to identify P-waves and to assess the regularity of the rhythm. The diagnostic device evaluated in this study is an adapter unit developed for smartphones and handheld computing devices (AliveCor®) which allows recording of such ECG waveforms. These devices are primarily used as event recorders for patients with palpation, but can also be used to record ECG data for screening for silent arrhythmias. The ECG recording can be annotated with an identifier number such as CHI number, and depending on the security of the network used for data transfer, patient-identifiable details. ECG recordings can be queued for transfer by email or via a wireless network for remote interpretation by a cardiologist.

The comparator chosen for evaluation was selected based on responses to a questionnaire we sent to participating GPs in the main pilot study. The vast majority of the respondents reported that they do not routinely test for AF, therefore for the basecase analysis we assumed that practices do not test routinely (i.e. no screening). We carried out several alternative scenarios to test this assumption which assumed that different proportions of the cohort received pulse palpation.

Pathways

The diagnostic and care pathways were determined based on expert opinion and a review of the literature. Figure 1 below shows the graphical representation of the model structure.

Figure 1: Schematic representation of the economic model structure



The pathways were embedded in a Markov model developed to simulate the progression of diagnosed (treated and untreated) and undiagnosed AF. A number of clinical events and health states were used to model the care pathways including: 1) No AF; 2) Undiagnosed AF; 3) Diagnosed AF not on treatment; 4) Diagnosed AF on treatment; 5) Post single complication states ; 6); Post two complication states.
To begin with, patients on the QOF register were spread across the 'No AF' (94.5%) and 'Undiagnosed AF' (5.5%) health states. In the first cycle of the model, patients in the AliveCor arm undergo a one-off screen with a single lead ECG while patients in the comparator arm did not receive screening. Patients who were correctly identified in the first cycle with underlying, undiagnosed, AF were modelled to transit to the appropriate diagnosed AF state for the subsequent model cycle. Those without AF or AF undetected in the first cycle remained in the appropriate 'no AF' or 'undiagnosed state'. Patients who remained either undiagnosed or opted not to receive warfarin or NOAC treatment (proportions based on the NICE costing report for clinical guideline CG180 on atrial fibrillation)[6] faced a higher risk of experiencing an ischaemic stroke or systemic embolism (based on rates observed for patients without treatment). Undiagnosed or untreated patients were more likely to experience a major stroke (no treatment: 60%, NOAC: 48% warfarin: 51%).[7]

Patients who opted for treatment were assumed the appropriate stroke and SE rates observed for patients receiving warfarin or NOAC treatment. In addition to the AF related complications, patients on treatment could experience a clinically relevant bleed (CRB) or Intracranial haemorrhage (ICH). The model was cycled on a three monthly basis, such that probabilities of incidence, costs of screening and treatment, and health state utility values (quality of life weights) were expressed in terms of this constant cycle length. The age- and sex-specific risk of death from all causes was also incorporated in the model based on interim UK life tables, i.e. using estimates of mortality in the general population and applied to our modelled QOF population.

Patients without AF were modelled to remain in a 'no AF' health state, however new cases of AF could develop based on incidence rates observed in the literature.[8] We made an assumption that if an undiagnosed patient experienced any AF related complication (stroke or SE) they would transit to an appropriate 'diagnosed AF on treatment' health state. We didn't consider in the model strokes in patients without AF.

In order to accurately capture the downstream impact of warfarin and NOAC treatment we modelled an inflated risk of past events on future events.[10] For example, if a patient experienced a stroke they had an increased risk of experiencing any further event (SE, stroke, CRB, ICH and death). We made a simplifying assumption that patients who experienced two complications entered into a semi-absorbing state where they continued to accumulate a lower quality-of-life value, an appropriately inflated risk of death and ongoing costs for the remainder of the model. Also, of particular note, is that we assumed that baseline events (e.g. morality) in AF patients on warfarin were based on (and comparable with) those reported in the warfarin arms of NOAC trials, and further we made the assumptions that this data would be applicable to a Scottish QOF population.

Costs associated with adverse events were incorporated in the model based on the application of unit costs to procedures and treatment. Health utility values associated with the different AF states were used to quality adjust the time spent by patients in each state, and utility decrements associated with adverse events were also applied. Thus the model enabled cumulative costs, life years, QALYs and incidence of first strokes to be tracked over the lifetime of the modelled cohort.

Decision analytical model

Screening

We assumed that all patients who were offered screening as part of their QoF annual appointment would accept it.[7] We also made an assumption that all patients found to have an irregular beat would proceed for a single lead ECG. Lau et al (2013) reported the sensitivity and specificity of iPhone ECG recordings by two independent cardiologists. We took the average sensitivity and specificity values of the two cardiologists and used these data as the estimates in our model, 97.5% and 92% respectively.[9] We tested the proportion of screening uptake and the sensitivity and specificity extensively through sensitivity analyses.

Transition probabilities

An in press HTA monograph conducted a cost-effectiveness analysis of anticoagulant drugs for the prevention of stroke in patients with AF.[10] A systematic literature review was conducted with a network meta-analysis of RCTs considering stroke prevention in patients with AF. We used these reported hazard ratios to estimate transition probabilities in our model. Mean hazards of events (stroke, SE, CRB, ICH, death) were reported for warfarin and hazard ratios of warfarin versus no treatment and NOACs versus warfarin were reported (Appendix 1, Tables 1a and 1b). We estimated three monthly transition probabilities from the reported mean hazard of events for warfarin. We then combined the mean hazard of events on warfarin with the reported hazard ratios of NOACs and no treatment relative to warfarin to calculate three monthly transition probabilities for patients on NOAC treatment, no treatment and undiagnosed.

Resource use and unit cost estimation

Unit costs for all resources used were obtained for the financial year 2014/15 and were acquired, where possible, from national sources including the *British National Formulary,* NHS Reference Costs (2015) and the Unit Costs of Health and Social Care [Personal Social Services Research Unit (PSSRU) 2015].[11,12,13] Where national sources were not available, other published sources were utilised.

Cost of screening

The cost of AliveCor screening includes the initial training of GP practices to use the device, the incremental cost associated with performing a screen during a routine GP consultation, the cost per patient use of the device and, a consultants' time to interpret the results. The total cost per patient screened was estimated using a 'bottom-up' approach. Costs were collected via a GP practice-specific resource use and costing questionnaire, allowing us to estimate a cost of the screening procedure in a practice-specific manner. Information collected included location of the training, number of training minutes, length of time to record and upload ECGs, staff present at training and their corresponding salary band. We

estimated 1) the average cost of training for each practice and; 2) the average incremental cost of conducting the screen, we then divided by the target number of patients (250) in each practice to estimate a training and screening cost per patient. In addition we collected information from participating consultants regarding the duration of time to 1) determine if the ECG is of interpretable quality; 2) identify if AF is present; 3) login and find patient on database and; 4) write and send the brief report. Staffing information and duration times were combined with national unit cost data (Appendix 1, Table 2) to estimate the total cost of consultant time.[13]

Capital equipment was costed from the reported costs per device of an AliveCor portable ECG monitor smartphone adapter and an apple iphone smartphone with data only sim and installed AliveCor application. The initial outlay costs of these devices were annuitized over the expected serviceable working life of these devices (assumed to be 5 years), using an annual depreciation rate of 3.5% to account for the opportunity cost of the investment over time. The estimated equivalent annual cost was then divided by the target number of patients per practice (250) to give an estimated cost per use.

We summated the average cost per patient of GP practice training, conducting the screen, device usage and consultant time which gave us a cost per patient screened of £22.02.

Follow-up and adverse event costs
The proportion of patients receiving warfarin, NOAC and no treatment (50.23%, 20.77% and (28.99%, respectively) was derived from the National Institute for Health and Care Excellence costing report of AF CG180 (2014).[6] We tested the proportional split on AF treatments through sensitivity analysis. Average drug costs for the NOACs were estimated from the British National Formulary (BNF, 2015)[11] while warfarin costs were estimated from the NICE costing report of AF[6] (Table 3, Appendix 1).

Adverse events associated with AF and its respective treatment included in our model were SE, stroke, ICH and CRB. We assumed that SE and CRB are transient in nature, meaning patients incur an acute cost of care but do not accumulate ongoing healthcare costs. In contrast, stroke and ICH incur both an acute and long-term follow-up management costs (Table 4, Appendix 1).

Health measurement and valuation
The model was used to estimate cumulative costs and life years over a 30 year horizon of the simulated cohort. This does not account for changes in the quality of life for screened versus unscreened patients as a result of treatment related adverse events (e.g. ICH) nor the impact of offsetting stroke risk. Therefore, appropriate utility weights were identified for the different health states and combined with survival to enable the estimation of QALYs. Utility weights are anchored on a scale where 0 represents death and 1 denotes full-health. QALYs were computed by assuming that changes in utility between measures at adjacent time points follow a straight line between the points. The average utility over each three-monthly cycle was calculated and multiplied by the duration of that time to compute the corresponding QALYs. Utility values (Table 5, Appendix 1) were identified from a previous NICE technology appraisal submission on Rivaroxaban.[14]

As CRB and SE are transient in nature we applied an acute utility value for the duration of one cycle length, after this patients revert to the utility value of stable AF. Stroke and ICH also received an appropriate acute utility value for three months but in addition, post adverse event they received a lower utility value to reflect the downstream impact that stroke and ICH has on health related quality of life. Where patients experienced more than one adverse event, utility values were assumed to be multiplicative. All utility values were adjusted to account for quality of life in a population decreasing with age.

4 Results and Discussion

Projected costs at one year are £77.21 for AliveCor and £29.81 for usual care. It is important to note that while these costs account for the cost of AliveCor screening, the downstream impact of identifying undiagnosed AF (e.g. strokes avoided) is not yet evident. For this reason it is important to project long-term costs and outcomes over a longer time-frame. In the base case analysis we model the costs and outcomes over a 30 year time horizon.

Table 1 presents the mean costs, mean QALYs and incremental cost per QALY associated with screening versus no screening. Table 2 presents the same analysis using life-years as the measure of effect. The base case results show AliveCor to be less costly and more effective than no screening. The ICERs for usual care versus AliveCor are dominated (usual care is more costly and less effective). Therefore screening is favourable from a cost-effectiveness perspective. Figure 2 presents the findings of cost per QALY graphically on the cost-effectiveness frontier. Strategies that do not fall on the line (the cost-effectiveness frontier) are strategies that are absolutely dominated (more costly and less effective than other strategies) and, therefore, they do not have the potential to be considered cost-effective.

Table 1 Base-case analysis (QALYs)

Strategy	Cost, £	Incremental cost, £	QALYs	Incremental QALYs	ICER
AliveCor	1,922.93	-	9.5496	-	-
Usual Care	2,005.98	83.05	9.5336	-0.0160	Dominated

Figure 2 Cost-effectiveness frontier (QALYs)

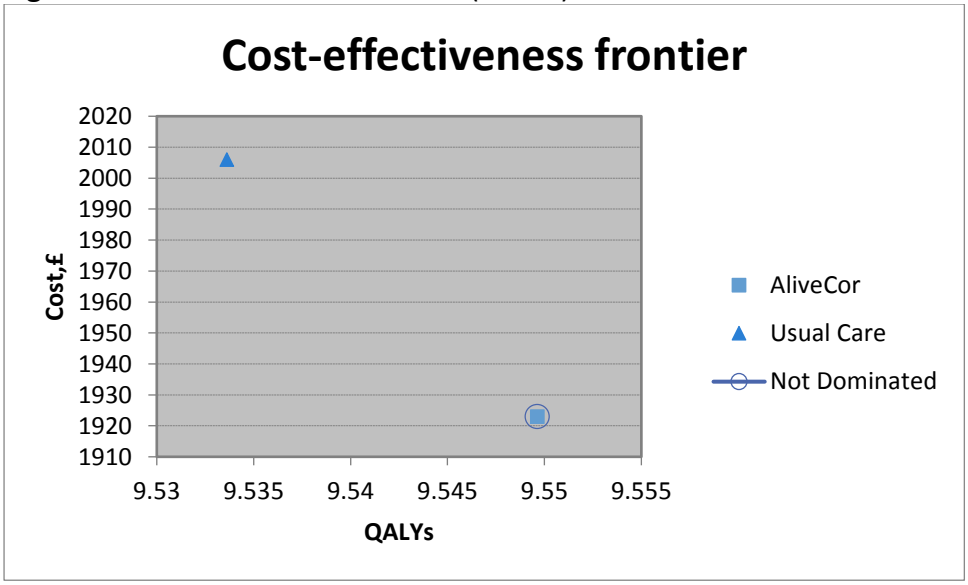


Table 2 Base-case analysis (life-years)

Strategy	Cost, £	Incremental cost, £	Life-years	Incremental life-years	ICER
AliveCor	1,922.93	-	12.5317	-	-
Usual Care	2,005.98	83.05	12.5224	-0.0093	Dominated

Deterministic sensitivity analysis

The process of populating the model required a number of parameter and structural assumptions. To assess the sensitivity of the base case results to these assumptions, several deterministic sensitivity analyses were conducted (Appendix 2, Table 1). Sensitivity analyses were conducted on the following:

- the adopted time horizon,
- the starting age of the cohort,
- the prevalence of AF,
- the frequency of screening,
- the proportion screened with pulse palpation in the usual care arm (sensitivity and specificity values for pulse palpation from a HIQA report (2015)),[7]
- screening uptake of AliveCor (based on estimates from the SAFE study),[16]
- the sensitivity and specificity of AliveCor (varying reported cardiologists sensitivity and specificity estimates),[9]
- utilising automated AF detection software (i.e. based on optimized algorithm and therefore consultant time not included)
- hazard rate of SE for no treatment,
- the risk of stroke with no treatment (based on the lowest, mean and highest CHA_2DS_2-VAS_c scores reported in the main pilot study)[15] and,
- the proportion of patients receiving warfarin, NOAC and no treatment.
- the cost per patient screened assuming 500 ECG screens/patients screening per practice (base case = 250)
- in those with undetected AF assume new case finding through a percentage with symptomatic referral (extra GP visit + outpatient visit for 12-lead ECG procedure)

Table 1 in Appendix 2 shows the results of the deterministic sensitivity analysis in terms of their impact on the cost per QALY findings base case analysis. These analyses demonstrate that screening dominates (less costly and more effective than the comparator option) in the majority of scenarios tested. In the analyses where usual care is not dominated (e.g. shorter model time horizon (10 years), older starting cohort age (75, 80), the risk of stroke with no treatment based on the lowest CHA_2DS_2-VAS_c score (2) reported in the main pilot study) the ICER for AliveCor remains substantially below the adopted threshold of £30,000 per QALY gained.

The results of the probabilistic sensitivity analysis showed that when varying key selected input model parameters simultaneously (hazard rates, event costs, health utilities), AliveCor was the dominant strategy in 79.5% of Monte Carlo simulations for a willingness to pay £30,000 per QALY. This can be interpreted as the probability that AliveCor is the dominant strategy compared to usual care (Figure 3). The incremental cost-effectiveness scatterplot (Figure 4) graphically represents the results of the 1000 simulations (each dot is one iteration); most (but not all) of simulations resulted in AliveCor having a lower cost and offered greater effectiveness (more QALYs) than usual care (i.e. the 795 out of the 1000) of simulations in the south east quadrant.

Figure 3 Cost-effectiveness acceptability curve

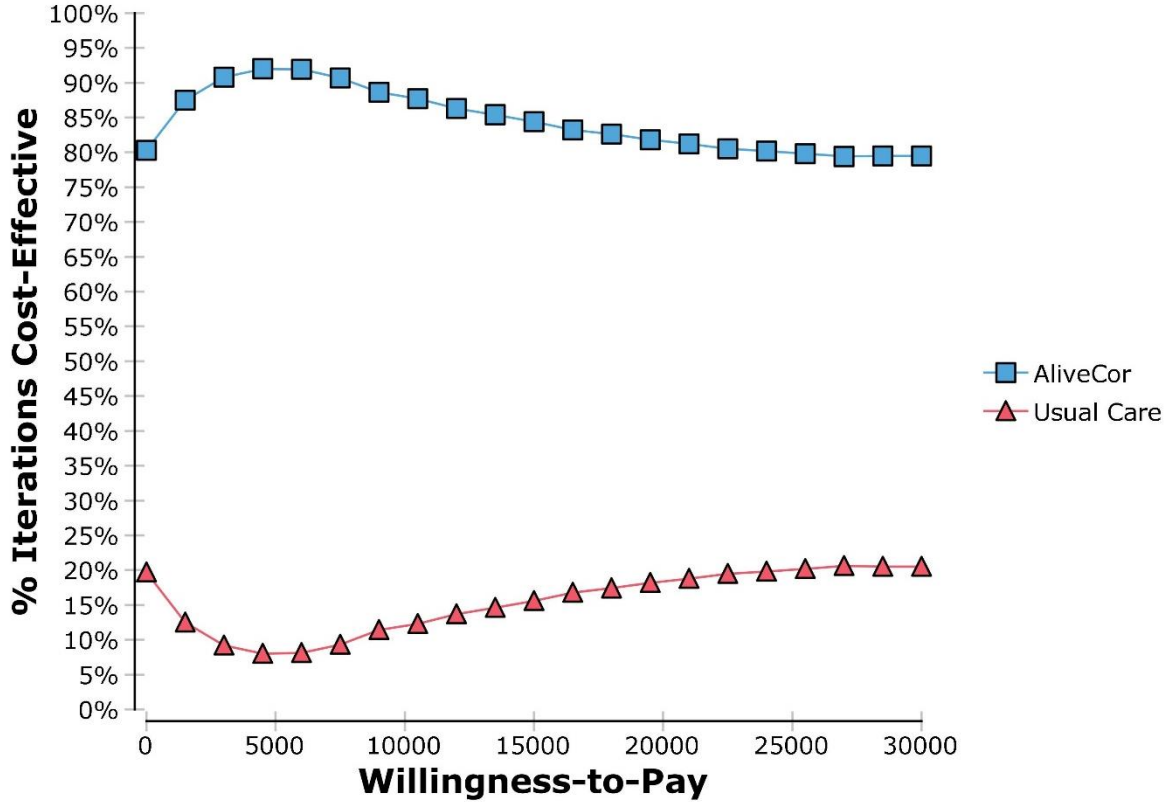
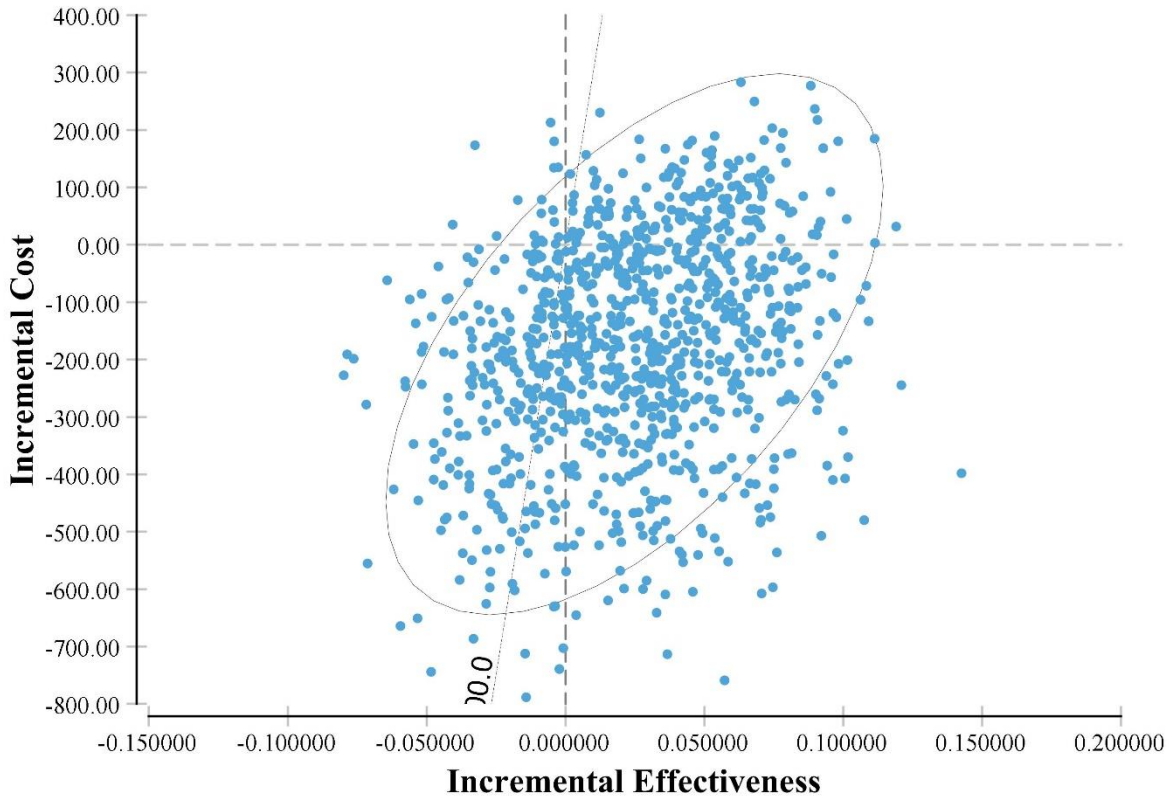


Figure 4 Incremental cost-effectiveness scatterplot, AliveCor v Usual Care



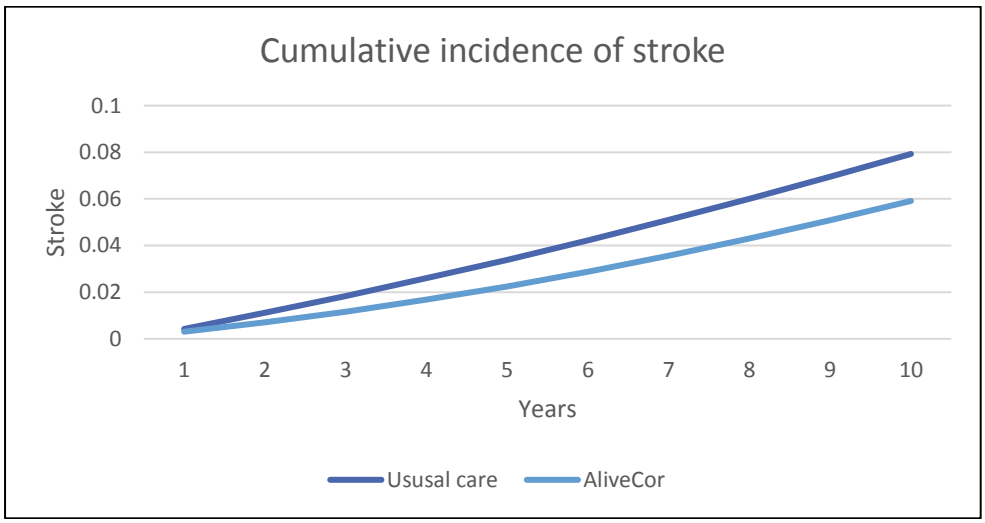
Secondary analysis

We conducted a secondary analysis to estimate a cost per stroke avoided at 10, 20 and 30 year timeframes. The cost per stroke avoided due to opportunistic screening at these time points is £45,835, £9,458 and £11,469, respectively. The number of strokes avoided in the opportunistic arm per 1,000 people are also reported in Table 3, as expected the number of strokes avoided increases overtime. Figure 5 shows the resultant modelled cumulative incidence of stroke in screened and unscreened patients over a 10 year timeframe. This figure clearly shows the downstream impact of identifying and treating AF has on offsetting the risk of stroke.

Table 3 Cost per stroke avoided

Timeframe	Incremental cost	Incremental Effectiveness	Cost per stroke avoided	Number of strokes avoided per 1,000
10 years	-£24	0.00516	£4,587	5.164
20 years	£66	0.00702	£9,458	7.028
30 years	£83	0.00724	£11,469	7.241

Figure 5 Cumulative incidence of stroke at 10 years



Discussion and conclusion

This analysis combined the best available data on the downstream impact of identifying high risk patients with AF. The results of our specific economic modelling study suggest that opportunistic screening for AF in primary care has potential to be cost-effective. The ICER for the single lead handheld ECG AliveCor device dominated usual care in the majority of scenarios presented and remained under the cost-effectiveness threshold of £30,000 cost per QALY gained in all other scenarios.

Overall the key drivers in the model results are the sensitivity and specificity of screening with AliveCor and the hazard rates and ratios of adverse events for patients on warfarin, NOACs and no treatment. There is uncertainty regarding the hazard rate for SE in the no treatment group. In the base case we assumed that it was equivalent to SE in the warfarin arm. This assumption is conservative in nature and it may be reasonable to expect that rates of SE in an untreated group would be higher than those in a treated group. We tested this assumption through sensitivity analysis, where we assumed that the rate of SE among untreated patients was equivalent to the stroke rate in an untreated group. The ICER for usual care remained dominated. There is also a degree of uncertainty regarding the long-term diagnosis of patients who were not opportunistically screened, it is probable that some patients would experience AF symptoms which would lead to an attendance for a 12 lead ECG and a possible diagnosis of AF. We explored the potential identification of patients in usual care by pulse palpation, which again produced favourable results for AliveCor gives us some confidence that the impact of uncertainty would be small.

As a secondary analysis we estimated the cost per stroke avoided at 10, 20 and 30 years and the number of strokes avoided per 1,000 high risk patients. The number of strokes avoided due to opportunistic screening increased overtime. In conclusion, screening with AliveCor provided potentially favourable cost-effectiveness estimates, owing to the offset of strokes compared to usual care at an apparently modest implementation cost. Screening offers a cost-effective use of scarce healthcare resources. However, that being said, the study results are somewhat uncertain and should be considered with a few issues and limitations in mind including the uncertainty around some parameter estimates and availability of data (or variability in) on standard AF case finding in routine clinical practice.

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Appendix

Appendix 1 – Model input parameters

Table 1a Hazard ratios[10]

Event	Hazard ratios used to calculate 1 year model probability for no treatment and NOAC
NOAC vs warfarin	
Ischaemic stroke	0.90 (0.72, 1.11)
CRB	0.82 (0.70,0.94)
Systemic embolism	0.65 (0.33, 1.18)
ICH	0.46 (0.36, 0.58)
Death all cause	0.89 (0.80, 0.99)
Warfarin vs no treatment	
Ischaemic stroke	0.359 (0.213)
Systemic embolism	1 (assumption that hazard ratio is same as warfarin)
Death all cause	0.849

Table 1b Transition probabilities[10]

Event	1 year probability
Warfarin	
Ischaemic stroke	0.0119
CRB	0.0639
Systemic Embolism	0.0169
ICH	0.0094
Death all cause	
NOAC vs warfarin	
Ischaemic stroke	0.0107
CRB	0.0527
Systemic embolism	0.0110
ICH	0.0043
Death all cause	0.0205
Warfarin vs no treatment	
Ischaemic stroke	0.0329
Systemic embolism	0.0169
Death all cause	0.0270

Table 2 Unit cost of staff time inputs[13]

Staff	Unit cost per hour	Cost per minute
Nursing staff		
Band 2	£23	£0.38
Band 3	£25	£0.42
Band 4	£28	£0.47
Band 5	£43	£0.72
Band 6	£51	£0.85
Band 7	£60	£1.00
Band 8a	£70	£1.17
GP		
Per hour GMS	£129	£2.15
Consultant		
Medical consultant	£105	£1.75

Table 3 Cost of treatment

Drug	Dose per day (mg)	Mg per tablet	Number in pack	Cost per pack	Cost per day	Cost per 3 month cycle	Annual cost
Apixaban[11]	10	5	56	61.5	£2.20	£200.42	£801.70
Warfarin[6]					£0.78	£70.75	

Table 4 Unit cost estimates for treatment pathways

Event	Unit cost	Assumption
Minor Ischaemic stroke[17]	£ 3,790.94	Inflated to 2014/15 values
Major Ischaemic stroke[17]	£ 21,374.62	Weighted average of moderately and totally disabling Inflated to 2014/15 values
ICH[17]	£ 12,113.39	Assumed weighted average of stroke costs
SE[12]	£ 2,035.16	Weighted average HRG YQ50A, YQ50B, YQ50C, YQ50D, YQ50E

CRB[12]	£ 1,422.89	Weighted average of HRG FZ38G-P to estimate cost of extracranial bleeds, AA23C-G to cost non-intracerebral intracranial bleeds.
Post minor stroke[17]	£ 2,379.79	Inflated to 2014/15 values
Post major stroke[17]	£ 5,055.08	Weighted average of moderately and totally disabling. Inflated to 2014/15 values
Post ICH[17]	£3756.78	Assumed weighted average of stroke costs. Inflated to 2014/15 values

Table 5 Health state utilities

Health State	Utility	Notes
Stable AF[18]	0.7790	
Acute minor stroke[19]	0.6410	
Acute major stroke[19]	0.1890	
Post minor stroke[20]	0.7189	
Post major stroke[20]	0.4819	
Acute Systemic embolism[21]	0.6601	
Post systemic embolism	0.7790	Assumption
Acute CRB[19]	0.7787	
Post CRB	0.7790	Assumption
ICH[22]	0.6000	
Post ICH[23]	0.7400	

Appendix 2 – Sensitivity Analyses

Table 1 Deterministic sensitivity analyses

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER
Base-case					
AliveCor	£1,922.93	-	9.5496	-	-
Usual Care	£2,005.98	83.05	9.5336	-0.0160	Dominated
1) QALYs over a 10 year time horizon					
Usual Care	£692.11	-	6.1715	-	
AliveCor	£715.80	£23.69	6.1799	0.0084	£2,833
2) QALYs over a 20 year time horizon					
AliveCor	£1,625.71	-	8.9388	-	-
Usual Care	£1,692.18	£66.47	8.9236	-0.0151	Dominated
3) Starting cohort age 70					
AliveCor	£1,718.66	-	7.8028	-	-
Usual Care	£1,759.99	£41.33	7.7812	0.0216	Dominated
4) Starting cohort age 75					
Usual Care	£1,224.60	-	6.1690	-	-
AliveCor	£1,238.60	£14.00	6.1901	0.0211	£664
5) Starting cohort age 80					
Usual Care	£796.60	-	4.6834	-	-
AliveCor	£842.18	£45.58	4.7032	0.0197	£2,308
6) 3% prevalence AF					
AliveCor	£1,642.03	-	9.5959	-	-
Usual Care	£1,685.40	£43.36	9.5851	-0.0108	Dominated
7) 7% prevalence AF					
AliveCor	£2,190.13	-	9.5057	-	-
Usual Care	£2,310.93	£120.80	9.4846	-0.0210	Dominated
8) 25% of patients in usual care have pulse palpation					
AliveCor	£1,922.93	-	9.5496	-	-
Usual Care	£1,986.63	£63.70	9.5373	-0.0124	Dominated
9) 50% of patients in usual care have pulse palpation					
AliveCor	£1,922.93	-	9.5496	-	-

Usual Care	£1,967.28	£44.35	9.5409	-0.0087	Dominated
10) 75% of patients in usual care have pulse palpation					
AliveCor	£1,923.45	-	9.5496	-	-
Usual Care	£1,948.46	£25.00	9.5446	-0.0050	Dominated
11) 100% of patients in usual care have pulse palpation					
AliveCore	£1,922.93	-	9.5483	-	-
Usual Care	£1,928.583	£5.65	9.5496	0.0014	£4,085
12) Annual screening for AliveCor and 0% of patients receive pulse palpation					
AliveCor	£1,899.91	-	9.5336	-	-
Usual Care	£2,005.98	£106.08	9.6318	0.0982	Dominated
13) Annual screening for AliveCor and 25% of patients receive annual pulse palpation					
AliveCor	£1,899.91	-	9.6318	-	-
Usual Care	£1,961.07	£61.16	9.5739	-0.0580	Dominated
14) Annual screening for AliveCor and 50% of patients receive annual pulse palpation					
AliveCor	£1,899.91	- -	9.6318	-	-
Usual Care	£1950.43	£50.53	9.5963	-0.0355	Dominated
15) Annual screening for AliveCor and 75% of patients receive annual pulse palpation					
AliveCor	£1,899.91	-	9.6318	-	-
Usual Care	£1,955.51	£55.60	9.6145	-0.0173	Dominated
16) Annual screening for AliveCor and 100% of patients receive annual pulse palpation					
AliveCor	£1,899.91	-	9.6318	-	-
Usual Care	£1,968.12	£68.22	9.6312	-0.0007	Dominated
17) AliveCor screening uptake of 69.2% - based on SAFE study[15]					
AliveCor	£1,948.51	-	9.5447	-	-
Usual Care	£2,005.98	£57.47	9.5336	-0.0111	Dominated
18) AliveCor screening uptake of 54.7% - based on SAFE study[15]					
AliveCor	£1,960.55	-	9.5424	-	-
Usual Care	£2,055.98	£45.43	9.5336	-0.0088	Dominated
19) AliveCor sensitivity of 0.95 and specificity of 0.90 [9]					
AliveCor	£1,928.27	-	9.5493	-	-
Usual Care	£2,005.98	£77.71	9.5336	-0.0157	Dominated
20) AliveCor sensitivity of 1 and specificity of 0.94[9]					
AliveCor	£1,917.60	-	9.5500	-	-

Usual Care	£2,005.98	£88.39	9.5336	-0.0164	Dominated
21) AliveCor sensitivity (0.98) and specificity (0.97)- based on optimized algorithm[9] and excluding consultant time cost					
AliveCor	£1,896.70	-	9.5493	-	-
Usual Care	£2,000.88	£104.18	9.5332	-0.0162	Dominated
22) Hazard rate for SE off treatment assumed equivalent to hazard rate of stroke off treatment					
AliveCor	£1,961.15	-	9.5530	-	-
Usual Care	£2,050.00	£88.85	9.5385	-0.0145	Dominated
23) CHA_2DS_2-VAS_c score of 2 - rate of stroke 2.2 for those undiagnosed and not on treatment[16]					
Usual Care	£1,442.37	-	9.5509	-	-
AliveCor	£1,519.67	£77.30	9.5616	0.0107	£ 7,215
24) CHA_2DS_2-VAS_c score of 4 - rate of stroke 4 for those undiagnosed and not on treatment[16]					
AliveCor	£2,137.46	-	9.5432	-	-
Usual Care	£2,303.72	£166.26	9.5244	-0.0188	Dominated
25) CHA_2DS_2-VAS_c score of 7 - rate of stroke 9.6 for those undiagnosed and not on treatment[16]					
AliveCor	£3,570.81	-	9.5000	-	-
Usual Care	£4,251.84	£681.03	9.4637	-0.0363	Dominated
26) All patients receive treatment post diagnosis – NOACs: 49.77% and warfarin: 50.23%					
AliveCor	£1,907.93	-	9.5596	-	-
Usual Care	£2,009.61	£101.68	9.5361	-0.0236	Dominated
27) All patients receive NOAC treatment - post diagnosis (71% on NOAC and 29% on no treatment) and post event (100% on NOAC)					
AliveCor	£2,087.33	-	9.5510	-	-
Usual Care	£2,115.59	£28.26	9.5387	-0.0123	Dominated
28) Equal uptake of warfarin and NOACs post diagnosis (NOACs: 35.5%; warfarin: 35.5%, no treatment: 29%) and post event (NOAC: 50%; warfarin: 50%)					
AliveCor	£1,964.27	-	9.5530	-	-
Usual Care	£2,038.13	£73.87	9.5351	-0.0179	Dominated
29) Average cost per patient screened assuming 500 ECGs per practice (base case: 250 ECG)					
AliveCor	£1,922.56	-	9.5496		
Usual Care	£2,005.98	£83.42	9.5336	-0.0160	Dominated
30) In those with undetected AF assuming a case finding through 1% symptomatic referral					
AliveCor	£1,923.06	-	9.550861		

Usual Care	£2,022.98	£79.92	9.535663	-0.015198	Dominated
31) In those with undetected AF assuming a case finding through 5% symptomatic referral					
AliveCor	£1,922,77	-	9.555015		
Usual Care	£1,991.77	£68.40	9.542454	-0.012561	Dominated
32) In those with undetected AF assuming a case finding through 10% symptomatic referral					
AliveCor	£1,921.35	-	9.558949		
Usual Care	£1,977.54	£56.19	9.548638	-0.010311	Dominated