The Newcastle upon Tyne Hospitals
NHS Foundation Trust

Economic evaluation of KardiaMobile for detecting atrial fibrillation

Work package ref	RX290
Work package name	Economic evaluation of KardiaMobile for detecting atrial fibrillation
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Version no.	Date	Author	Purpose
0.01	28/07/2021	K Keltie	Report template created
0.02	11/08/2021	K Keltie	Updated report based on modified model structure
0.03	12/08/2021	AJ Sims	Reviewed and edited
0.04	12/08/2021	K Keltie	Addressing comments
1.00	12/08/2021	K Keltie	Clean version for NICE review
1.01	13/08/2021	K Keltie	Adding responses from experts, responding to NICE comments
		AJ Sims	Review
1.02	01/09/2021	K Keltie	Editing model structure and parameters based on expert responses
1.03	03/09/2021	K Keltie	Clean version
2.00	03/09/2021	K Keltie	Version shared for NICE review
2.01	08/09/2021	AJ Sims K Keltie	Responding to NICE comments
2.02	09/09/2021	K Keltie	Updating narrative in methodology (adding diagnostic yield)
2.03	09/09/2021	K Keltie	Removing diagnostic yield
2.04	10/09/2021	K Keltie AJ Sims	Adding number needed to treat
2.05	10/09/2021	E Belilios	Pre-submission checklist (sections 1-3 only)
2.06	10/09/2021	K Keltie	Review
2.07	10/09/2021	AJ Sims	Review, adding to conclusions
2.08	10/09/2021	K Keltie AJ Sims	Adding AF recurrence univariate analysis, adding latest output from model
3.0	10/09/2021	K Keltie	Clean version for NICE
3.01	12/09/2021	AJ Sims	Review

3.02	13/09/2021	K Keltie AJ Sims	Updating PSA results, adding utilities throughout
3.03	13/09/2021	K Keltie AJ Sims	Updating conclusions
4.0	13/09.2021	K Keltie	Final draft for submission
4.1	15/09/2021	AJ Sims	Minor edits
4.2	17/09/2021	AJ Sims, K Keltie	Additional QA, Adding utilities to AF recurrence model
5.0	17/09/2021	K Keltie	Clean version for NICE
5.1	27/09/2021	K Keltie, AJ Sims	Responding to company fact-check and NICE comments
5.2	29/09/2021	K Keltie	Adding latest model results, final formatting, review.
6.0	29/09/2021	K Keltie	Versions for NICE

Contents

Abbreviations

Term	Definition
AF	Atrial fibrillation
CI	Confidence interval
DG	Diagnostic Guidance
DOAC	Direct acting anticoagulation
DSA	Deterministic sensitivity analysis
EAC	External Assessment Centre
ECG	Electrocardiogram
ESC	European Society of Cardiology
GBP	British Pounds Sterling
GI	Gastrointestinal
IFU	Instructions for use
IQR	Interquartile range [Q1,Q3]
MTAC	Medical Technologies Advisory Committee
MTCD	Medical Technologies Consultation Document
MTG	Medical Technology Guidance
NG	NICE Guideline
PMG	Process and Methods Guide
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
TIA	Transient ischaemic attack

1. Background and objectives

GID-MT554 KardiaMobile for detecting atrial fibrillation was presented at MTAC1 on 18th June 2021. The current recommendations presented in the MTCD state:

1.1 KardiaMobile shows promise for improved detection of atrial fibrillation and atrial fibrillation recurrence. However, there is not enough good-quality economic evidence to support the case for routine adoption in the NHS.

1.2 Research is recommended to address uncertainties about the cost impact of KardiaMobile for detecting atrial fibrillation and atrial fibrillation recurrence.

The rationale for this was that the clinical evidence shows that more people had their AF detected using the KardiaMobile single-lead device compared with standard care, however the cost impact of KardiaMobile for detecting AF was uncertain due to the quality of the economic evidence assessed.

The economic evidence considered by the committee presented a case for KardiaMobile being cost saving when compared with standard care. This consisted of 3 published economic analyses of varying relevance and robustness, a company cost model and a simple cost calculator developed by the EAC. The EAC was unable to validate the company model and also considered it was limited by its relevance to the current care pathway in the NHS, not being able to replicate the model, and by the data and methods used. The EAC presented an elementary cost calculator to provide the MTAC with a more certain cost figure, but this was also limited by its relevance to the current care pathway and methods used. Therefore the committee was not able to recommend KardiaMobile based on the evidence presented although they felt that KardiaMobile is likely to be a cost saving technology in the NHS.

The committee requested that additional cost modelling be carried out to address the decision-problem, and the limitations of the current cost models presented at MTAC1. Any additional economic evidence that is relevant to the case for adoption will be considered at MTAC2.

The aim of this work is to develop a cost model that evaluates the costs of diagnosing and managing AF using KardiaMobile for detection and ongoing monitoring, compared with the current standard(s) of care in the NHS in people presenting with undiagnosed palpitations and people who need to monitor AF recurrence post-treatment. The cost model will address the limitations of the current cost models presented to the committee.

2. Economic model

The description of the economic evaluation has been described following the principles of the Drummond checklist, Appendix 1. A cost-consequence model was developed in R programming language (R Core Team, 2020) using the *rdecision* package (version 1.1.0) from the perspective of the NHS in England. Output from the model are described in Appendix 3 (including tables of transition probabilities).

2.1 Model structure

Previous economic models of AF diagnosis considered by NICE have focused on a screening population and have utilized a decision tree leading into a Markov model structure (MTG13: WatchBP; DG35: Lead I ECG devices for detecting symptomatic AF using single time point testing in primary care). However, such an approach is not directly applicable to a decision problem when events repeat (*i.e.* when there is repeat testing) or when the time to diagnosis may benefit a new technology. The model presented in this report takes the form of a single Markov model, in which patients start in a state where they are waiting for a test. The per-cycle transition probabilities from that state determine the mean waiting time for a test and allow the effect of the time to detection of AF to be modelled. In addition, the model includes a further state in which patients wait for a repeat test, representing a pathway for those patients referred for repeat testing (those who are undiagnosed but remaining symptomatic), and allowing the effect of time to detection for a repeat test to be modelled.

The model structure and parameters were informed using input from clinical experts (previous input summarised in EAC Communications Log 2021, additional questions sent to eight experts on 12/08/2021, and 7 responses received in Appendix 2). The model contains 14 states including 2 tunnel states (representing GI bleed in both treated and untreated AF), and 2 absorbing states (excess death in treated and untreated AF patients). The model structure reflects the decision problem because it has two waiting states (for a first test and a repeat test) and four post-test states (AF and treated with a DOAC; AF but not treated, no AF but prescribed a DOAC, and no AF and not treated) reflecting diagnostic test outcomes (true positive, false negative, false positive, true negative, respectively). Those with AF are at increased risk of an adverse event (e.g. stroke), a repeat adverse event and death from the adverse event (3 states each for those with treated and untreated AF). Those taking a DOAC are at increased risk of a GI bleed (one state each for those taking a DOAC with and without

AF). Other health events common to all scenarios (e.g. death from other causes) are not included in this model because the outcomes represent excess events due to AF.

The starting position of the model has all patients referred for a test (Kardia Mobile or Holter). The outcome of the diagnosis phase is the occupation of AF treated with a DOAC (true positive), AF untreated (false negative), no AF treated (false positive) and no AF untreated (true negative) states as determined by the prevalence of AF, diagnostic yield and the diagnostic accuracy of the monitoring test. As the diagnostic accuracy of KardiaMobile and Holter monitoring is unknown (there is no reference standard for paroxysmal AF, with previous studies reporting sensitivity and specificity on a per-ECG recording basis and not a per-patient basis), in the base case scenario the EAC have assumed that the sensitivity and specificity are the same for both KardiaMobile and Holter and that the diagnostic yield is the same for both. However increased sensitivity is incorporated within sensitivity analysis to model increased AF detection.

The time taken to transition to the four diagnostic outcome states, represents the total time from referral to time of diagnosis, with longer wait times modelled for standard care (Holter monitoring).

Each of the four diagnostic outcome states represents a different patient pathway. The model assumes that all patients with AF detected by a monitoring device (both true positives and false positives) are given direct-acting anticoagulation (DOAC) treatment, and are at risk of gastrointestinal bleeding as an adverse event of treatment. It is assumed that the time for clinician review of test results and initiation of DOACs (if appropriate) is included in the mean waiting time for each diagnostic monitoring arm. Patients with AF (true positive and false negative) are also assumed to be at risk of stroke, subsequent stroke and death (death is represented as an absorbing state in the model), with those receiving treatment (true positive) at reduced risk.

The same overall model approach is applicable to two populations:

1) Patients with undiagnosed palpitations (following positive pulse palpation but negative 12-lead ECG) referred for ambulatory monitoring to detect AF (Figure 1a), and

2) Patients with previously diagnosed AF who received medical/surgical treatment who then requiring ongoing monitoring to detect AF recurrence (Figure 1b).

It is important to note that the use of KardiaMobile in this economic evaluation focuses on increased AF detection only (for undiagnosed palpitation and recurrence post-treatment). There was a lack of clinical evidence to support the use of KardiaMobile in monitoring AF to inform medication choice or titrate medication dose (EAC Assessment Report, 2021), and therefore this was not included in this economic evaluation.

In the general model structure (applicable to both modelled populations), only patients in the undetected AF state (representing patients with false negative initial tests or tests for which no diagnosis was possible, but who remain symptomatic) are considered to be eligible for referral for retesting. Due to lack of robust data, within the model retesting assumes the same diagnostic monitor is used, and that those referred for retesting experience the same waiting time as those referred for their first round of diagnostic monitoring. The model assumes that only a proportion of patients who are false negatives (undiagnosed AF with recurring symptoms) require retesting. In the undiagnosed palpitations population, retesting is permitted in both standard care and intervention arms (Figure 1a).

In the AF recurrence model, variation across the NHS in AF recurrence monitoring was highlighted by the clinical experts (Appendix 2). Two experts reported that Holter monitoring would only be offered post-AF treatment if the patient became symptomatic, one expert reported that at least one Holter within the 12 months post-treatment would be conducted, one expert reported that annual Holter post-treatment was an appropriate, one expert commented that further monitoring would vary by centre and may be influenced by staffing levels at hospital sites, and one expert did not comment further. A simplification of this was incorporated into the standard care arm of the AF recurrence model as a single round of monitoring within one year post-treatment. As such further rounds of retesting were only applicable for the KardiaMobile arm (represented by the red arrow in Figure 1b) and not the standard care (Holter monitoring) arm. The experts noted that there was variable practice in relation to whether patients would be offered repeated further Holter tests. However, the experts advised that most patients in the recurrence scenario would remain on anticoagulation after their initial treatment, and therefore offering routine further testing would be of little benefit.

The undiagnosed palpitations model was run separately for each CHA_2DS_2-VASc score (from 1 to 6) with each score representing a different risk of stroke, and only excess strokes being included in the model. However only patients with a CHA_2DS_2-VASc score≥2, and males with CHA_2DS_2-VASc score=1 received a DOAC (simplification of section 1.6.3 of NICE NG196, 2021). Clinical experts confirmed that CHA_2DS_2-VASc score is widely used in the NHS practice to determine risk of stroke, Appendix 2. Results from each CHA_2DS_2-VASc are aggregated by weighted average.

For the AF recurrence model, only CHA_2DS_2-VASc score of 1 was modelled. This reflects clinical practice (highlighted by two clinical experts, Appendix 2), where high-risk patients are maintained on anticoagulation regardless of recurrence of AF detection in subsequent monitoring. This is consistent with NICE NG196 (2021; section 1.11): "*In people with a diagnosis of atrial fibrillation, do not stop anticoagulation solely because atrial fibrillation is no longer detectable. Base decisions on a reassessment of stroke and bleeding risk using CHA_2DS_2-VASc and ORBIT and a discussion of the person's preferences".* Therefore, anticoagulation would be continued regardless of the outcome of subsequent diagnostic monitoring and therefore no benefit (in terms of reduction of stroke) between Holter monitoring or KardiaMobile in patients with CHA_2DS_2-VASc score≥2, hence why these were excluded from modelling.

For the modelled undiagnosed palpitations population, a two year time horizon with a three month time cycle was used. In common with the (semi-) Markov approach used widely in health economics, each patient is limited to one health event per cycle. The chosen duration of each time cycle was considered appropriate to the timescales of the decision problem (referral for repeat tests, minimum interval between adverse events, period to resolve GI bleeding). This short time horizon will provide a conservative estimate of the cost savings from avoidance of stroke, however beyond two years additional routine monitoring (for example, manual pulse palpation conducted at annual health reviews) may identify instances of AF applicable in both arms. Four of seven experts agreed that the two year time horizon for this model was appropriate, two experts advised that time to diagnosis would be shorter than two years for KardiaMobile, and one expert did not comment further.

For the modelled AF recurrence population, a 10 year horizon and 1 year time cycle (to represent an annual health review) was used. A 1 year time horizon was chosen as applicable to the decision problem, with patients typically expected to be reviewed annually following their initial treatment. Thee longer time horizon was intended to model the burden in managing AF as a chronic condition. The EAC originally suggested a 20-year time horizon, and two of the seven experts agreed that the 20-year time frame for this model was appropriate. However two experts stated that 10 years may be more appropriate and one expert stated that AF recurrence can occur within days, weeks, months or years later and that within 20 years a patient may undergo multiple procedures. The nationwide analysis of the hospital (inpatient and outpatient) attendances in Norway by Kjerpeseth *et al.* (2020) reported a mean (SD) age at AF diagnosis of 79.1 (11.2) in women and 72.1 (13.0) in men, and found that only 19% of patients were less than 65 year old at the time of AF diagnosis. Therefore a 20-year time horizon was deemed inappropriately long because of uncertainty in the long-term persistence of all model variables and model assumptions over 20 years. The model does not include the facility of incrementing the age of the cohort, and assumes that the risks of an adverse event (AE) remain constant over time. For example, as the cohort ages, they will acquire more comorbidities, and the median CHA_2DS_2-VASc score will increase. The EAC felt that a time horizon of greater than 10 years would weaken the validity of the assumption of constant AE rates, and require time-dependent probabilities, which would increase the complexity of the model.

In line with NICE methods of technology appraisal, a discounting rate of 3.5% was applied to both modelled populations (NICE PMG9, 2013).

Figure 1a: Model structure for undiagnosed palpitation population repeated separately for CHA_2DS_2-VASc scores 1 to 6 (tunnel states indicated by dashed outline, absorbing states indicated by shading)

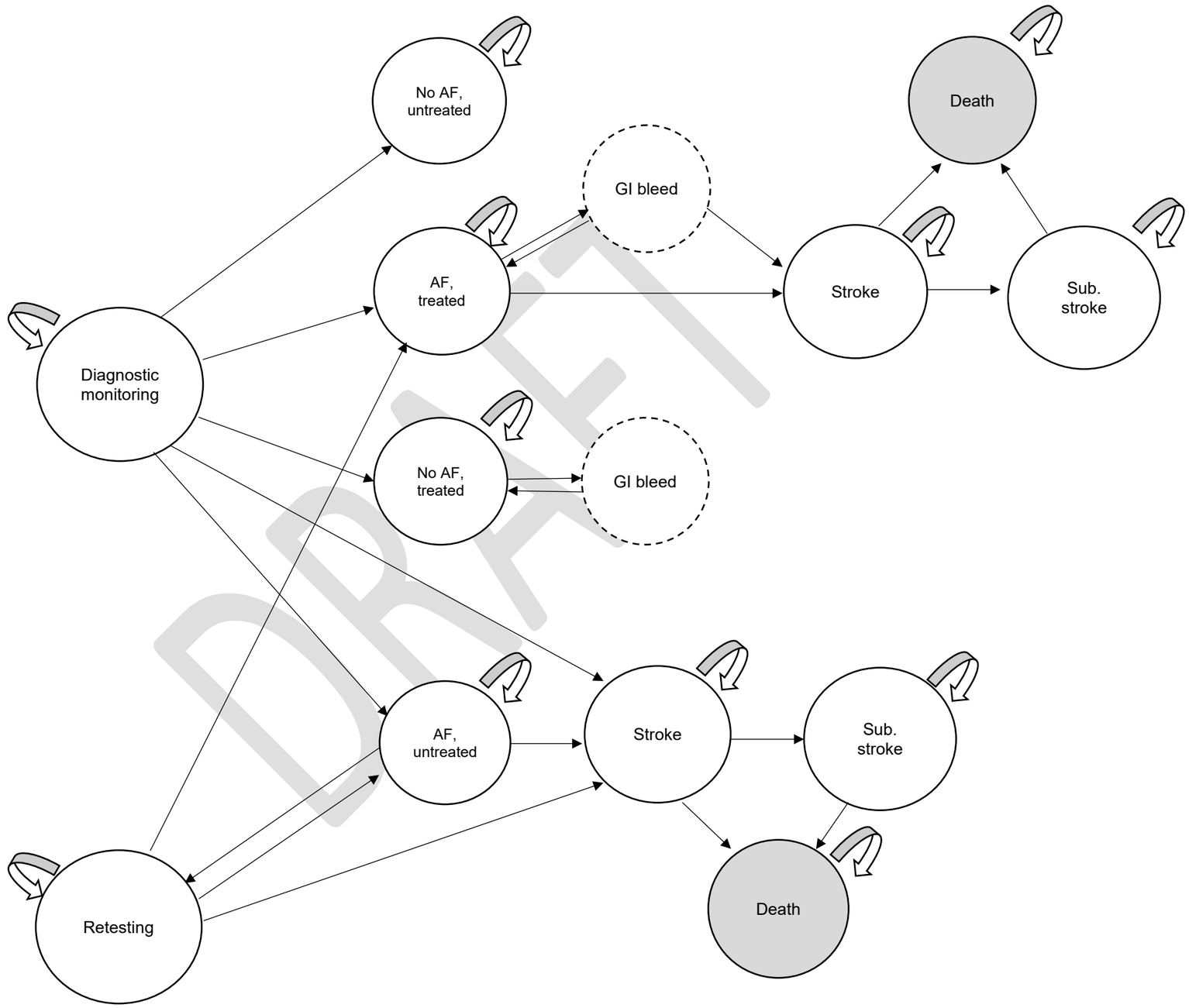
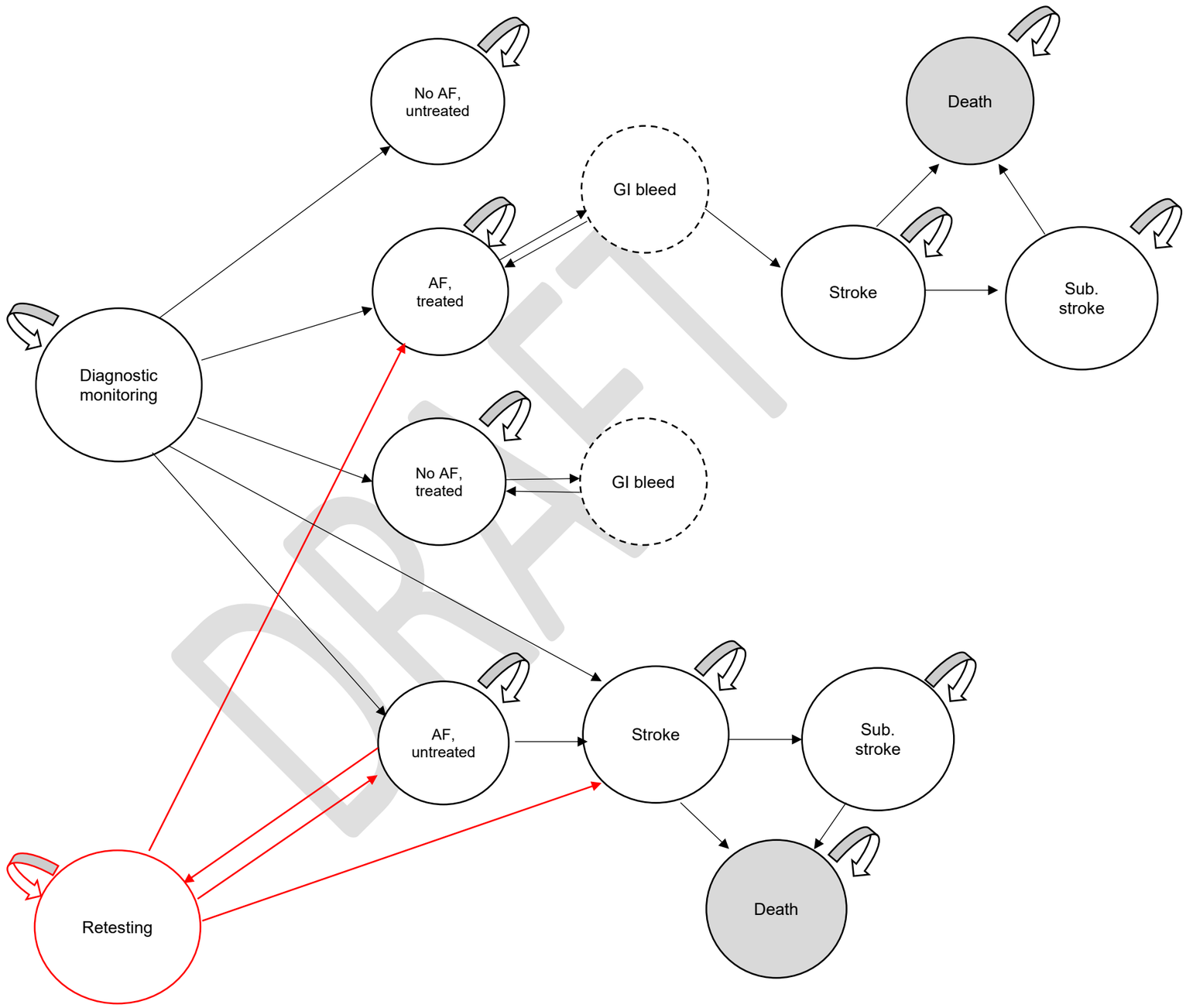


Figure 1b: Model structure for AF recurrence population applied to CHA_2DS_2-VASc score 1 only (tunnel states indicated by dashed outline, absorbing states indicated by shading) [Red arrow and state represents subsequent retesting conducted with KardiaMobile, but retesting is not applied in the standard care arm].



2.2 Setting

Both modelled populations are assumed to have diagnostic monitors issued from an NHS hospital outpatient setting.

2.3 Populations

Two populations will be modelled separately using the same economic model structure: 1) patients with undiagnosed palpitations referred for ambulatory monitoring following negative 12-lead ECG, and 2) patients who have had AF detected, have received treatment and who require monitoring for AF recurrence post-treatment (because their symptoms recur). The difference between populations being the underlying prevalence of AF, and frequency of retesting following initial diagnostic monitoring. Screening in an asymptomatic population and single time point are out of scope for this economic model (NICE Final Scope, 2021).

Despite the known increase in AF risk with age and male gender, these variables are not explicitly defined in the model. The prevalence of AF for the two modelled populations was derived from published literature (EAC Assessment Report 2021). The risk of stroke due to AF is determined solely from CHA_2DS_2-VASc score, which incorporates age and sex as contributory risk factors. CHA_2DS_2-VASc score 1 was the only score modelled separately for males and females (with the model assuming equality gender distribution for this score).

2.4 Intervention

Due to the lack of clinical evidence to support the use of the KardiaMobile six lead device (KardiaMobile-6L), this economic model will focus on the KardiaMobile single lead device only (KardiaMobile-1L), referred to as KardiaMobile for the remainder of this report, and its accompanying software (Kardia app). As the device instructions for use state that the output of Kardia app cannot be used as a clinical diagnosis, the sensitivity and specificity for KardiaMobile is assumed to be that of the classification made by the Kardia app followed by clinical review of the single lead ECG trace. The clinical experts reported an average duration of KardiaMobile use between 14 days and 3 months (EAC Correspondence Log, 2021) meaning that the device could be used by 52 and 8 different patients respectively over the 2 year device lifetime, thus reducing the overall per patient device cost. For the undiagnosed palpitations base case model the EAC have assumed an average KardiaMobile use of 45 days; meaning each device is used by 16 patients during its lifetime. Staff time to set up the

device and provide training to the patient, and staff time to review ECG traces for each patient is combined with the device cost.

2.5 Comparator

From NICE guidelines (NICE NG196, 2021), patients with suspected atrial fibrillation undetected by 12-lead ECG are referred for ambulatory ECG monitoring. The use of 24-hour ambulatory monitoring is recommended if asymptomatic episodes are suspected or is symptomatic episodes are less than 24 hours apart. The use of ambulatory ECG monitor, event recorder or other ECG technology for a period appropriate to detect atrial fibrillation is recommended if symptomatic episodes are more than 24 hours apart. The clinical experts previously advised that 24 hour Holter monitoring was the most common ambulatory monitoring conducted across the NHS (EAC Correspondence Log, 2021). Each Holter monitor is assumed on average to be used by a total of 1000 patients before being replaced (NICE DG35, 2018). Duration of Holter monitoring will be varied in sensitivity analysis by changing the number of device uses. Staff time to set up the device and provide training to the patient (assumed to be shorter for Holter monitoring), and staff time to review ECG traces for each patient (assumed to be longer for Holter monitoring) is combined with the device cost to give a test cost.

2.6 Outcomes

Only excess adverse events related to AF were modelled: gastro-intestinal bleeding due to direct-acting anticoagulant (DOAC) treatment, stroke, subsequent stroke and mortality. A maximum of two strokes is permitted in both undiagnosed palpitations and AF recurrence modelled populations. However given the low risk of stroke, the EAC considered this an appropriate simplification.

Other outcomes, such as myocardial infarction, pulmonary embolism, deep vein thrombosis and systemic embolism in people with AF may depend on the type of medication given for AF. For example the health technology assessment by Sterne *et al.* (2017) compared treatment effects for several DOACs with warfarin, which was later used in the preparation of guidance NG196. For MI, there was weak evidence that in people with AF, apixaban reduced rates of MI compared with warfarin. However, evidence for the effect of a DOAC versus no treatment in this group is likely to be lacking, because in most people with undiagnosed palpitations, there would be no indication for a DOAC until AF is confirmed, and in those

confirmed, anticoagulation would be offered. Thus, other outcomes were considered to be secondary and were not included in the model because of lack of data (or at least, lack of a systematic search of data) to support them.

2.7 Model parameters

Model parameters and incorporated costs (all expressed in GBP) are described in Table 1 and Table 2 respectively.

Table 1: Model parameters

Parameter	Value	Distribution (PSA)	Source
AF prevalence (undiagnosed palpitations)	6.5%	Beta parameters: α=8, β=116	Reed *et al.* 2019: 8/124 had AF detected in intervention arm; 6.5 [95%CI 3.0 to 12.7]%.
AF prevalence (AF recurrence)	25.2%	Beta parameters: α=29, β=86	Hermans *et al.* 2021: 29/115 had AF detected in intervention arm; 25.2 [95% CI 17.8 to 34.3]%
Proportion of people having more than 1 diagnostic test *within 12 months*	27%	Not included in PSA because the numbers used to calculate 27% for MTG52 are not available.	Originally from NICE MTG52, 2020, however the EAC of MTG52 advised that as this was derived from Hospital Episode Statistics data, that this would include stress testing, and likely an upper estimate. Interpreted as the proportion of patients with no AF detected but where symptoms remain to warrant further testing. Value was deemed appropriate by clinical experts (Appendix 2) and applied to both KardiaMobile and Holter monitoring arms. Univariate uncertainty in parameter varied across range 15 to 27%, with the base-case representing the upper limit.
Mean wait time for KardiaMobile, months	1	Gamma parameters Range: 2 weeks to 6 weeks. Approximated by shape (k) = 18.8, scale (θ) =1.62, which has mean 30.45 days and 95% confidence intervals 18.3 to 45.7 days (1 month; 2.6 to 6.5 weeks).	Total wait time represents the time between referral and diagnosis (including receiving device, using device, having ECG interpreted, receiving diagnosis and medication where applicable). Variation in NHS practice as highlighted by clinical experts (Appendix 2, and MT544 EAC Correspondence Log, 2021). Uncertainty in parameter varied in PSA across range 2 to 6 weeks in line with expert responses. The Gamma distribution is the conjugate prior for the mean of the Exponential distribution, which is normally used to model waiting times,
Mean wait time for Holter, months	1.5	Gamma parameters Range: 4 weeks to 8 weeks. Approximated by shape (k) = 42.3, scale (θ) =1.08, which	Wait time assumed to be longer with Holter monitoring due to availability of devices and need for interpretation of results. Variation in NHS practice as highlighted by clinical experts (Appendix 2, and MT544 EAC Communication Log, 2021). Uncertainty in parameter

Parameter	Value	Distribution (PSA)	Source
		has mean 42.3 days and 95% confidence intervals 32.9 to 60.4 days (1.5 months; 4.7 to 8.6 weeks).	varied in PSA across range 4 to 8 weeks in line with expert responses.
Diagnostic accuracy (Holter monitor, 24 hours)	Sensitivity: 80% Specificity: 80%	Not included in PSA	The true prevalence of AF is unknown, patients may not be in AF at the time of diagnostic monitoring (paroxysmal). As per patient pathway, patients with suspected paroxysmal AF undetected by 12-lead ECG are referred for ambulatory monitoring. Therefore no true gold standard. Diagnostic accuracy values stated are interpreted as the combined likelihood of patient being in AF at time of measurement and the device picking it up. Values advised by clinical experts.
Diagnostic accuracy (KardiaMobile)	Sensitivity: 80% Specificity: 80%	Not included in PSA	The diagnostic accuracy of KardiaMobile in AF detection in a referral pathway is still unknown; this is due to published evidence reporting sensitivity and specificity on a per-ECG measurement basis, and not on a per-patient basis. Multiple ECG traces from each patient cannot be treated as independent and therefore cannot be translated into diagnostic accuracy. Combining results for an indirect comparison is not possible due to lack of standard care and range of diagnostic monitoring devices available for AF detection. Furthermore, as reported in DG35, test sensitivity and specificity may be affected by prevalence, with the use of a test in a more severely diseased population associated with better performance of the test (Leeflang *et al.* 2013). However published evidence reviewed within the EAC assessment report (2021) does suggest that KardiaMobile detects more AF (i.e. higher sensitivity).Values of sensitivity and specificity in base case model deemed appropriate by clinical experts (Appendix 2). However increased AF detection (through increased test sensitivity) will be modelled in sensitivity analysis.

Parameter	Value	Distribution (PSA)	Source
Risk reduction of stroke in treated AF (warfarin vs. no treatment)	68%	Not included in PSA	Hobbs *et al.* (2005); risk reduction associated with warfarin: The annual rate of stroke was 4.5% for the control group and 1.4% for the warfarin group; 68% [95%CI 50 to 79%].
Relative risk of stroke in treated AF (DOAC vs. warfarin)	0.81	Not included in PSA	Meta-analysis by Ruff *et al.* 2014: 29,312 patients taking DOAC, 29,229 patients taking warfarin, events included stroke or systemic embolic events; 0.81 [0.73 to 0.91]. Source identified by clinical expert (Appendix 2).
Stroke rate or other thromboembolism event in untreated AF, *per year*	Varies by CHA_2DS_2-VASc score: 0 (n=1): 0% 1 (n=422): 1.3% 2 (n=1,230): 2.2% 3 (n=1,730): 3.2% 4 (n=1,718): 4.0% 5 (n=1,159): 6.7% 6 (n=679): 9.8%	Not included in PSA	CHA_2DS_2-VASc score derived from 7329 patients. Clinical experts agreed that CHA_2DS_2-VASc is most widely used in NHS practice, Appendix 2.
Pooled cumulative risk of stroke recurrence at 1 year after initial stroke [Undiagnosed palpitations model only]	11.1%	Not included in PSA	Meta-analysis by Mohan *et al.* 2011 included 13 studies. Pooled cumulative risk of stroke recurrence was 11.1% [95%CI 9.0 to 13.3] at 1 year after initial stroke. (Note that DG35, 2018 also cited Mohan et al. 2011 as the source of stroke recurrence; however the EAC is unable to verify the value of this parameter applied in the model of DG35: 0.065).
Pooled cumulative risk of stroke recurrence at 10 years after initial stroke [AF recurrence model only]	39.2%	Not included in PSA	Meta-analysis by Mohan *et al.* 2011 included 13 studies. Pooled cumulative risk of stroke recurrence was 39.2% [95%CI 27.2 to 51.2] after initial stroke. (Note that DG35, 2018 also cited Mohan et al. 2011 as the source of stroke recurrence). A clinical expert also identified another source for stroke recurrence (Khanevski *et al.* 2019); however this only included 220 patients from Norway and therefore was considered to lack generalisability to the UK.
Risk of death at 1 year [Undiagnosed palpitations model only]	36.5%	Not included in PSA	Hankey *et al.* 2000; converted to an annual rate and applied to the 10-year time horizon of the AF recurrence model.
Cumulative risk of death at 5-years [AF recurrence model only]	60.1%	Not included in PSA	Hankey *et al.* 2000; converted to an annual rate and applied to the 10-year time horizon of the AF recurrence model.

Parameter	Value	Distribution (PSA)	Source
Hazard ratio of mortality in patients with AF receiving treatment (DOAC)	0.89	Not included in PSA	Sterne *et al.* 2017 (applied in NICE DG35, 2018) 0.89 [95%CI 0.80 to 0.99] assuming Apixaban 5mg
Hazard ratio of mortality in patients with AF but untreated	1.178	Not included in PSA	Applied in NICE DG35, 2018 (the EAC unable to verify data from primary evidence; Sterne *et al.* 2017)
GI bleed rate (only in patients treated with Apixaban) *per patient per year*	0.0213	Not included in PSA	Granger *et al.* 2011 (cited in the Stroke Prevention in Atrial Fibrillation Risk Tool (SPARC) tool)

Table 2: Cost parameters

Parameter	Value	Distribution (PSA)	Source
KardiaMobile device	£82.50	Not included in PSA	The company confirmed that £82.50 represents the cost of KardiaMobile-1L device (VAT removed), Kardia app free of charge.
No. of patients using each KardiaMobile device [Undiagnosed palpitations]	16	The cost per use was modelled with a Gamma distribution with shape (k) = 5.59 and scale (θ) = 0.92, which has mean 5.2 (16 uses) and 95% confidence interval £1.80 to £10.20 (45 uses to 8 uses).	Assumption based on 2 year expected device life, and maximum of 45 days monitoring per patient (730/45=16). This parameter will be varied in sensitivity analysis to model the device being reused every 14 days (used by 52 different patients) to 90 days (used by 8 other patients) in line with clinical feedback (Appendix 2 & MT544 EAC Communication Log).
Staff time (Technician Band 4) minutes; preparation of KardiaMobile and patient training	15	Not included in PSA	Advised by clinical advice (Appendix 2, and MT544 EAC Communications Log, 2021). Training and set-up was considered longer for KardiaMobile than for Holter monitoring due to training patient how to use the Kardia app.
ECG review time (KardiaMobile), minutes ECG technician (Band 4), per patient	20	Not included in PSA	Based on 30 second ECG trace from KardiaMobile taken 3 times a day, for 45 days in the base case. Value deemed appropriate by clinical experts (Appendix 2).
Holter monitor diagnostic monitoring	£1755	Not included in PSA	NICE DG35 (citing MIB101, 2017): £1632.14 and then inflated to 2020 prices Consumer Price Index (Table 9, L528 Health: 112.6/104.7); Note a cost of £168.12 for Holter monitoring was included in MTG52 Zio based on HRG bundle cost (which included stress testing, appointment and staff time costs) as well as information gained via FOI. For fairer comparison, a micro costing based on device costs and number of uses were included in this economic model for both KardiaMobile and Holter monitoring.
No. of uses per Holter device	1000	Not included in PSA	NICE DG35, 2018. This parameter will be varied in sensitivity analysis to model the device with assumed 10 year lifetime being reused every 2 days (used by 1825 different patients) to 5 days (used by 730 different patients) in line with clinical feedback (Appendix 2 & MT544 EAC Communication Log).

Staff time (technician Band 4) minutes; preparation of Holter and patient training	10	Not included in PSA	Values advised by clinical experts (Appendix 2).
ECG review time (Holter), minutes ECG technician (Band 4), per patient	60	Not included in PSA	Based on 24 hour ECG trace from Holter monitor. Value deemed appropriate by clinical experts (Appendix 2).
ECG review time, minutes specialist nurse (Band 6) *per patient per positive finding (AF detected)*	5	Not included in PSA	Second ECG review only conducted for patients where AF is detected (combining true and false positives). Values advised by clinical experts (Appendix 2).
Cost of ECG technician (Band 4) to conduct set-up/training and initial ECG review, per hour	£34	Not included in PSA	PSSRU 2019/20 Assumed same as hospital based radiographer (Band 4).
Cost of nurse specialist (Band 6) to review AF detected results, per hour	£50	Not included in PSA	PSSRU 2019/20 Hospital-based nurse (Band 6)
Cardiology outpatient appointment	£154.43	Not included in PSA	NHS reference costs 2018/19 for consultant-led cardiology outpatient appointment (service code: 320); £151. The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/110.1); £154.43. The cost of a cardiology appointment is only applied to patients where AF is detected and for retesting. [All patients would require a cardiology appointment to get the initial diagnostic monitoring device, and therefore applied to all patients and excluded from the model for simplicity.]
DOAC: Apixaban (per day)	£1.90	Not included in PSA	BNF (Drug tariff price is the same for 2.5mg and 5mg); twice daily recommended in NICE TA275 (2013). Applied as a state occupancy cost (accrued with each cycle).
Stroke (subsequent years)	£1183.77	Not included in PSA	Xu et al. 2018; difference between year 5 and year 1 £4511, assume £1128 accrued linearly each year. Inflated to 2020 prices (112.6/107.3). Same approach applied in NICE DG35, 2018. Applied as a state occupancy cost (accrued with each cycle)
Stroke (first year)	£12,932.68	Not included in PSA	Xu et al. 2018; £13,452 mean healthcare costs in year 1 from SSNAP audit. This cost of stroke is treated as an entry cost therefore cost of stroke in subsequent years removed, and then inflated to 2020 prices (112.6/107.3). Applied as an entry cost (applied during transition only) therefore cost of stroke in subsequent years (£1183.77) removed from entry cost to avoid double counting.
GI bleed	£784.84	Not included in PSA	TA607 Major non-fatal extracranial bleed (which used NHS Reference costs 2017/18): £747.90

			The EAC inflated to 2020 using Consumer Price Index (Table 9, L528 Health: 112.6/107.3); £784.84. Applied as an entry cost (applied during transition only)

2.8 Number needed to treat

For the annual stroke rates predicted by CHA_2DS_2-VASc scores and the treatment effect of taking a DOAC (apixaban) the number needed to treat (NNT) can be calculated. For example, for a CHA_2DS_2-VASc score of 2, the annual rate of stroke in people with untreated AF is 2.2%. The risk of stroke in those taking warfarin relative to no treatment is 0.686 and the risk in those taking apixaban versus those taking warfarin is 0.81; which combined give a treatment effect of 0.55. Therefore the expected annual rate of stroke in people with AF taking a DOAC is 1.21%. The NNT to save one stroke per year is 101.2. The annual cost of treatment is the annual cost of a DOAC (£693.50) plus the annual cost of treating GI bleeds in the proportion affected (2.13% costing £784.84 each; £16.72), a total of £710.22. The annual cost of treatment needed to save one stroke per year for those with CHA_2DS_2-VASc score of 2 is therefore £71,867. This exceeds the cost of stroke in the first year (£12,933).

The NNT and annual costs of anticoagulation needed to save one stroke in those with different risk factors are described in Table 3. All exceed the first year cost of stroke (£12,933), and thus *any* technology which detects and leads to the treatment of more AF cases will be cost incurring when compared with standard care over a short time horizon, assuming that treatment is with a DOAC. Note that the number needed to treat and the cost needed to treat will be greater if anticoagulants are given to those without AF (false positives) and not given to those with AF (false negatives).

Table 3: Number needed to treat (NNT) and annual cost of anticoagulation required to avoid one stroke.

CHA_2DS_2-VASc	NNT	Annual cost of anticoagulation required to avoid one stroke
1	171.2	£121,621
2	101.2	£71,867
3	69.6	£49,408
4	55.7	£39,527
5	33.2	£23,598
6	22.7	£16,133

For all CHA_2DS_2-VASc scores combined, assuming the distribution of prevalence reported by Lip *et al.* (2010), the NNT is 67.3 and the annual cost needed to save one stroke is £47,767. This approach excludes the clear patient benefit of more AF detected, less strokes and reduced mortality, and therefore the EAC added incorporate utilities into the developed model, Table 4.

Table 4: Utility values utilised in the base-case

Parameter	Value	Source
Diagnostic monitoring, and diagnostic outputs	1	
Stroke	-0.272	DG35 (2018). The same decrement in utility is assumed for the first and subsequent strokes.
GI bleed	N/A	In line with approach taken in DG35, bleeding is assumed to be an acute event that fully resolves and has no long-term impact on HRQoL
Death	0	

2.9 Model assumptions

- The model includes excess events only (that is, strokes due to AF, and GI bleeds due to medication for AF). The risks of stroke, bleeding and death not associated with AF have not been included in the model.
- The cost of stroke is the same for AF treated and AF untreated patients. Five of the seven clinical experts reported that this assumption was reasonable, however five also stated that this will underestimate cost benefit because strokes as the result of untreated AF would like be more severe and more disabling. Note that DG35 did not apply a different cost of stroke between AF treated and untreated groups. The EAC has noted this as a limitation, therefore cost savings in stroke avoidance will likely represent a lower estimate.
- The model assumes that users will already have a compatible mobile device for using the KardiaMobile device and Kardia app and does not account for the cost of a loan mobile device for patients who do not have a compatible device. Patients lacking a compatible device would require training on how to use the mobile phone as well as training on how to use the Kardia app, and therefore other monitoring devices may be deemed more suitable in this patient group, therefore excluded from the model. Clinical experts advised approximately 80% of patients would have a smart device compatible for use with KardiaMobile (EAC Communications Log, 2021).
- The model does not account for unreadable ECGs in either KardiaMobile or Holter monitoring arms. The proportion of unreadable ECGs is small and has reduced over time (between 0.6% and 1.9% in the published clinical evidence, EAC Assessment Report, 2021). Similarly, the model does not account for the failure of Kardia app to classify ECGs recorded by the KardiaMobile device. This is due to the assumption that the majority of ECG traces can be classified by a reviewing clinician (Hermans *et al.* 2021) and clinical review of ECG prior to diagnosis is a requirement of the KardiaMobile instructions for use.
- The diagnostic accuracy of KardiaMobile reported in the literature is on a per-ECG recording basis. Due to non-independence of ECGs from the same patient, with IFUs recommending three ECGs daily, the published diagnostic accuracy for KardiaMobile cannot be translated to a per-patient basis. Furthermore, as the prevalence of AF is unknown (patients can be asymptomatic), and some patients not being in AF at the time of recording (paroxysmal AF) the true diagnostic accuracy of Holter Monitoring is

unknown. Therefore the sensitivity and specificity of Holter monitoring are both assumed to be 80%, which was deemed appropriate by clinical experts. For KardiaMobile the published clinical evidence does confirm the ability for KardiaMobile to identify *more* cases of AF than standard care (which included Holter monitoring). Therefore the specificity of KardiaMobile has been fixed at 80%, however variable sensitivity and diagnostic yield have been incorporated into the model. These will be explored further within the sensitivity analysis.

- Staff time cost for ECG review is included within device costs and is assumed to be quicker with KardiaMobile (20 minutes to review three 30 second ECG recorded daily across 45 days) than 24-hour Holter monitoring (60 minutes review).
- The total wait time is modelled using a single transition rate from the time of referral to the occupation of the diagnostic accuracy states (true positive, false positive, false negative, true negative), and assumed to be shorter with KardiaMobile due to remote ECG interpretation.
- In line with ESC guidelines, interpretation of single lead ECG can be used to diagnose AF. However the additional cost of a 12-lead ECG will be explored during sensitivity analysis in the undiagnosed palpitations population to represent use of KardiaMobile in a primary care setting.
- For the undiagnosed palpitations model, patients with AF detected (true and false positives) and those requiring additional round of monitoring (*i.e.* retesting) will incur the cost of an additional follow-up cardiology outpatient clinic appointment.
- Patients requiring additional diagnostic monitoring (retesting) will undergo monitoring with the same device again (that is, those using KardiaMobile will use KardiaMobile again, those using Holter monitoring will use Holter again).
- All patients with AF detected (true and false positives), with CHA_2DS_2-VASc score ≥2 and all males with CHA_2DS_2-VASc score =1, receive medical therapy with a single DOAC (apixaban); simplification of NG196, 2021. Exclusion of warfarin and anticoagulation clinic costs was adopted in similar economic modelling conducted in NICE DG35 (2018).
- Due to uncertainty in the proportion of patients requiring cardioversion/ablation (i.e. the proportion of patients where drug therapy is ineffective or not tolerated), the timing of surgical intervention (i.e. how long DOAC treatment would be used before intervention considered), and the impact of surgical intervention on adverse events (i.e. reduction

in stroke risk versus medical therapy) only medical treatment costs and their associated reduction in stroke risk have been considered within this economic evaluation. The implication of not including surgical intervention as a treatment option in the model, is that AF treatment costs and management of adverse events will represent a lower estimate, as it is likely that ablation will offer higher reduction of stroke in some patients but not realised in the economic evaluation.

- The entry point of the AF recurrence model is post-treatment (that is, patients have previously been diagnosed with AF and have received surgical intervention or medical treatment). As this is applied to all patients, and across both arms, for simplicity the cost of initial treatment has been excluded as an entry fee in the AF recurrence model.

2.10 Uncertainty

Univariate deterministic sensitivity analysis (DSA) will include the following:

- Change in baseline AF prevalence; in the undiagnosed palpitation cohort between 6.5% (Reed et al. 2019) and 18.2% (Narasimha *et al.* 2018) and in the AF recurrence cohort between 25.2% (Hermans *et al.* 2021) and 60.9% (Hickey *et al.* 2017) in the AF recurrence cohort.
- Sensitivity of KardiaMobile will be varied between 80% and 100% in deterministic sensitivity analysis to model increased AF detection with KardiaMobile versus Holter monitoring.
- The number of uses per KardiaMobile device (2 year lifetime) will vary between 8 (used by a different patient every 3 months) and 52 (14 days) to reflect variation in practice across the NHS.
- The number of uses per Holter device (10 year lifetime) will vary between 730 (used by a different patient every 5 days) and 1825 (2 days) to reflect variation in practice across the NHS.
- For the undiagnosed palpitations cohort the proportion of patients requiring an additional round of diagnostic monitoring (retesting) will vary between 15% and 27% to reflect variation in population.
- For the undiagnosed palpitation population, variation in mean wait times for both KardiaMobile and Holter will be varied using ranges advised by clinical experts; 2-6 weeks for KardiaMobile and 4-8 weeks for Holter to reflect variation across hospitals in

the NHS. [Note that mean wait times of weeks will have no impact on long-term modelling for AF recurrence where the cycle length is 1 year].

Uncertainty in input parameters will be modelled through probabilistic sensitivity analysis (PSA) including KardiaMobile sensitivity in AF detection, number of KardiaMobile uses, number of Holter monitor uses, mean wait times for KardiaMobile and Holter monitoring as hyper parameters. A total of 1000 simulations were run in PSA.

3. Results: patients presenting with undiagnosed palpitations

Detailed output of results from the model are provided in Appendix 3.
The report was shared with the company (AliveCor) on 21/09/2021 and fact-check comments received on 27/09/2021, Appendix 4.

3.1 Base case

In the base-case scenario the diagnostic accuracy (sensitivity and specificity) of KardiaMobile is assumed to be the same as Holter monitoring. The total incremental cost of KardiaMobile over 2 years was £422.64 compared with £435.87 for Holter monitoring, resulting in a cost saving of £13.22 per patient over 2 years, Table 5. This is driven by reduced waiting time (i.e. patients being diagnosed and treated faster) in the KardiaMobile arm when compared with Holter monitoring. The shorter waiting time assumed for KardiaMobile leads to more patients receiving a DOAC, more strokes saved, and fewer deaths from stroke.

Table 5: Base-case model results from undiagnosed palpitations population

Device	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000
KardiaMobile	£422.64	1.998604	325.5	79.2
Holter	£435.87	1.998525	333.8	83.6
Difference	**-£13.22**	**0.000078**	**-8.3**	**-4.4**

3.2 Univariate sensitivity analysis

3.2.1 Sensitivity of KardiaMobile

Increasing test sensitivity for KardiaMobile up to 95% still results in an absolute cost saving versus Holter monitoring, Table 6. However the magnitude of saving reduces as test sensitivity increases; this is a consequence of the increasing number of patients with AF detected resulting in increased treatment (DOAC) costs. See also the Number Needed to Treat analysis.

Table 6: Univariate analysis: increased test sensitivity for KardiaMobile (KM) when compared to base case (*)

Sensitivity	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000	Cost difference (KardiaMobile – Holter)
*80%	£422.64	1.998604	325.5	79.2	-£13.23
85%	£425.55	1.998641	317.8	76.3	-£10.22
90%	£428.39	1.998679	310.2	73.5	-£7.48
95%	£431.16	1.998716	302.7	70.7	-£4.71

3.2.2 AF prevalence

The total incremental costs of KardiaMobile and Holter arms were sensitive to changes in AF prevalence (Table 7a), however the absolute cost saving remained when varying the AF prevalence even up to an unrealistic AF prevalence of 52% (Table 7b).

Table 7a: Univariate analysis – Impact of changing AF prevalence when compared to base case (*)

Device	AF prevalence	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000
Holter	3.25%	383.59	1.999263	166.9	41.8
Holter	*6.5%	435.87	1.998525	333.8	83.6
Holter	13%	540.37	1.997052	667.3	167.2
Holter	26%	749.12	1.994109	1333.4	334.1
Holter	52%	1165.64	1.988239	2662	667
KardiaMobile	3.25%	370.63	1.999302	162.8	39.6
KardiaMobile	*6.5%	422.64	1.998604	325.5	79.2
KardiaMobile	13%	526.62	1.997208	650.9	158.3
KardiaMobile	26%	734.4	1.99442	1301	316.5
KardiaMobile	52%	1149.31	1.988853	2598.7	632.2

Table 7b: Univariate analysis – Difference in outcomes between KardiaMobile and Holter monitoring when changing AF prevalence when compared to base case (*)

	Difference in outcomes (KardiaMobile – Holter)

AF prevalence	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000
3.25%	-£12.95	0.000039	-4.1	-2.2
*6.5%	-£13.22	0.000078	-8.3	-4.4
13.0%	-£13.75	0.000156	-16.4	-8.8
26.0%	-£14.72	0.000311	-32.4	-17.6
52.0%	-£16.34	0.000615	-63.2	-34.8

3.2.3 Number of KardiaMobile uses (patients per device)

Increasing the number of patients using each KardiaMobile device, increases the potential cost saving as expected, Table 8. It is only when each KardiaMobile device is only used by 4 patients that the device becomes cost incurring when compared to Holter monitoring.

Table 8: Univariate analysis – Impact of changing the number of patients using each KardiaMobile device (reuses)

Number of KardiaMobile uses	Total cost per patient	QALY	Stroke per 100,000	Deaths per 100,000	Cost difference (KM-H)
4	£438.04	1.998604	325.5	79.2	£2.17
5	£433.93	1.998604	325.5	79.2	-£1.94
8	£427.78	1.998604	325.5	79.2	-£8.09
*16	£422.64	1.998604	325.5	79.2	-£13.23
52	£419.09	1.998604	325.5	79.2	-£16.78

3.2.4 Number of Holter uses (patients per device)

Varying the number of patients using each Holter device between 730 and 1825 made little significant difference to the absolute cost saving between KardiaMobile and Holter monitoring, Table 9.

Table 9: Univariate analysis – Impact of changing the number of patients using each Holter device (reuses)

	Difference (KardiaMobile – Holter)	

Holter uses	Total cost per patient	QALY	Stroke per 100,000	Deaths per 100,000	Cost difference (KM-H)
730	£436.51	1.998525	333.8	83.6	-£13.87
*1000	£435.87	1.998525	333.8	83.6	-£13.23
1825	£435.08	1.998525	333.8	83.6	-£12.44

3.2.5 Subsequent diagnostic monitoring

Varying the proportion of patients requiring subsequent diagnostic monitoring (retesting applied only to false negatives) between 15 and 27% (Table 10a) results in no change in absolute cost difference (Table 10b). This is a consequence of both having the same test accuracy at baseline.

Table 10a: Univariate analysis – Impact of changing the proportion of patients requiring subsequent diagnostic monitoring (retesting)

Device	Retesting	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000
Holter	15%	£435.24	1.99851	338.5	84.7
Holter	20%	£435.50	1.998517	336.5	84.2
Holter	*27%	£435.87	1.998525	333.8	83.6
KardiaMobile	15%	£422.03	1.998587	330.5	80.3
KardiaMobile	20%	£422.29	1.998594	328.4	79.9
KardiaMobile	*27%	£422.64	1.998604	325.5	79.2

Table 10b: Univariate analysis – difference in outcomes when changing the proportion of patients requiring subsequent diagnostic monitoring (retesting)

	Difference in outcomes (KardiaMobile – Holter)			
Retesting	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000
15%	-£13.21	0.000077	-7.9	-4.3
20%	-£13.22	0.000078	-8.1	-4.4
*27%	-£13.22	0.000078	-8.3	-4.4

3.2.6 Wait time

Paradoxically, increasing the wait time for KardiaMobile reduces the total incremental costs for KardiaMobile arm and thus increases the absolute cost saving versus Holter monitoring (Table 11; see also Number Needed to Treat analysis).

Table 11: Univariate analysis – Impact of changing the wait time for KardiaMobile and Holter monitoring

Device	Device wait time (days)	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000
Holter	28.1	£439.29	1.998618	324.1	78.4
Holter	42.1	£436.74	1.998542	332	82.7
Holter	56.2	£432.88	1.998479	338.7	86.3
KardiaMobile	14	£422.99	1.998714	313.9	73.1
KardiaMobile	28.1	£422.93	1.998618	324.1	78.4
KardiaMobile	42.1	£420.40	1.998542	332	82.7

3.3 Multivariate sensitivity analysis

When PSA was applied to the undiagnosed palpitations model (n=1000 simulations), the cost difference between KardiaMobile and Holter monitoring was -£13.34 [95% CI -£18.78 to -£6.49] per patient over 2 years.

4. Results: AF recurrence

4.1 Base case

The incremental cost over a 10 year time horizon of using KardiaMobile to detect AF recurrence at one year post-treatment and in those referred for repeat testing in the low risk group (CHA_2DS_2-VASc=1) was £2477.09, compared with £2391.18 for with a single round of Holter monitoring at 1 year post-treatment, Table 12. Patients with higher risk (CHA_2DS_2-VASc>1) were not included in the model because guidance recommends that these patents continue taking a DOAC after their treatment and additional tests were not required to inform a treatment decision concerning DOACs. Further tests may have value in other aspects of patient management, but this was not considered in the model. This model represents the ease of use and accessibility of using KardiaMobile to monitor AF recurrence post-treatment, however does result in a small cost expenditure of only £85.91 per patient across a 10-year period. The increase is a direct consequence of KardiaMobile detecting more AF and thus incurring additional treatment (DOAC) costs which do not offset the cost from stroke prevention (due to low risk of stroke) which was highlighted in early NNT analysis. More frequent retesting with KardiaMobile in this population would increase the cost of the KardiaMobile arm, given the other assumptions in the model. However, additional analysis incorporating utilities would demonstrate the patient benefit of KardiaMobile over standard care.

Table 12: Base-case model results from AF recurrence population

Device	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000
KardiaMobile	£2477.09	9.956278	1640.9	745.2
Holter	£2391.18	9.950311	1853.8	860.2
Difference	**£85.91**	**0.005968**	**-212.8**	**-115**

4.2 Univariate sensitivity analysis

4.2.1 Sensitivity of KardiaMobile

Increasing test sensitivity for KardiaMobile up to 95% increasing the cost expenditure of KardiaMobile, Table 13. This is a consequence of the increasing number of patients with AF

detected and the costs of treatment (DOAC) costs not outweighing the cost avoidance of stroke. See Number Needed to Treat analysis.

Table 13: Univariate analysis: increased test sensitivity for KardiaMobile (KM) when compared to base case (*)

Sensitivity	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000
*80%	£2477.09	9.956278	1640.9	745.2
85%	£2519.48	9.956963	1627.8	732.1
90%	£2559.07	9.957624	1615.6	719.6
95%	£2596.03	9.958262	1604.3	707.7

4.2.2 AF prevalence

The total incremental costs of KardiaMobile and Holter arms were sensitive to changes in AF prevalence (Table 14a), however the higher the AF prevalence the more cost expending KardiaMobile became (Table 14b).

Table 14a: Univariate analysis – Impact of changing AF prevalence when compared to basecase (*)

Device	AF prevalence	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000
Holter	13%	£1837.86	9.974361	956.5	443.8
Holter	26%	£2391.18	9.950311	1853.8	860.2
Holter	52%	£3605.9	9.897511	3823.5	1774.3
KardiaMobile	13%	£1874.48	9.977442	846.6	384.5
KardiaMobile	26%	£2477.09	9.956278	1640.9	745.2
KardiaMobile	52%	£3800.28	9.909807	3385	1537.2

Table 14b: Univariate analysis – Difference in outcomes between KardiaMobile and Holter monitoring when changing AF prevalence when compared to base case (*)

	Difference in outcomes (KardiaMobile – Holter)

AF prevalence	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000
13.0%	£36.62	0.003081	-109.9	-59.4
26.0%	£85.91	0.005968	-212.8	-115
52.0%	£194.38	0.012295	-438.5	-237

4.2.3 Number of KardiaMobile uses (patients per device)

Increasing the number of patients using each KardiaMobile device decreases the cost expenditure associated with KardiaMobile, Table 15. Even if each KardiaMobile device was used by 500 different patients, KardiaMobile is still cost incurring when compared to Holter monitoring.

Table 15: Univariate analysis – Impact of changing the number of patients using each KardiaMobile device (reuses) when compared to base case (*)

	Total per patient cost, over 2 years		
Number of KardiaMobile uses	KardiaMobile	Holter	**Cost difference (KardiaMobile – Holter)**
*16	2477.09	2391.18	£85.91
52	2473.49	2391.18	£82.31
500	2472.05	2391.18	£80.87

4.2.5 Subsequent diagnostic monitoring

Decreasing the proportion of patients undergoing subsequent diagnostic monitoring (retesting) from 27% to 15%, reduced the cost difference between KardiaMobile and Holter monitoring (Table 16a), however KardiaMobile was cost incurring in all cases (Table 16b). This inverse relationship (between decreasing testing and increased cost benefit) is a consequence of increased AF detection resulting in increased treatment which is not offset by the cost of stroke avoidance (see Number Needed to Treat analysis).

Table 16a: Univariate analysis – Impact of changing the proportion of patients requiring subsequent diagnostic monitoring (retesting)

Device	Retesting	Total cost per patient	QALY	Strokes per 100,000	Deaths per 100,000

KardiaMobile	15%	£2443.23	9.954501	1699.8	780.2
KardiaMobile	20%	£2459.15	9.955314	1671.3	764
KardiaMobile	*27%	£2477.09	9.956278	1640.9	745.2
Holter	0%	£2391.18	9.950311	1853.8	860.2

Table 16b: Univariate analysis – difference in outcomes when changing the proportion of patients requiring subsequent diagnostic monitoring (retesting)

	Difference in outcomes (KardiaMobile – Holter)			
AF prevalence	Total cost per patient	QALY	Stroke per 100,000	Deaths per 100,000
15%	£52.05	0.004191	-153.9	-80
20%	£67.96	0.005003	-182.4	-96.2
*27%	£85.91	0.005968	-212.8	-115

4.3 Multivariate sensitivity analysis

When PSA was applied to the AF recurrence model, KardiaMobile was associated with a cost expenditure of £85.93 [95% CI £55.70 to £123.02] per patient over 10 years when compared to Holter monitoring.

5. Discussion

5.1 Key findings

The EAC independently developed a model where the base case scenario confirms the potential for KardiaMobile to be cost saving versus standard care when used in undiagnosed palpitations population (referred for ECG). The modelled cost savings were relatively small (£13.22 per patient over 2 years) but were sustained over univariate analysis (only becoming cost incurring when each KardiaMobile device was reused by as few as 4 patients which the EAC would consider unlikely) and PSA (cost saving -£13.34 [95%CI -£18.78 to -£6.49]. Additional analysis incorporating utilities demonstrates the patient benefit of KardiaMobile over standard care.

The EAC also demonstrated that KardiaMobile versus Holter monitoring in AF recurrence detection post-AF treatment in a low risk population (CHA_2DS_2-VASc score of 1 only as anticoagulation is likely to continue in an AF population) was cost incurring by £85.91 per patient over 10 years, with PSA results also confirming cost expenditure £85.93 [95%CI £55.70 to £123.02]. However the generalisability of this specific AF recurrence model is unclear. The increased cost is a direct consequence of KardiaMobile detecting more AF (because re-testing is allowed for in the Kardia Mobile arm) and thus incurring additional treatment (DOAC) costs which do not offset the cost from stroke prevention (due to low risk of stroke) which was highlighted in early NNT analysis.

5.2 Strengths & Limitations

Strengths include:

- The model was developed independently.
- It reflects the use of KardiaMobile in an NHS setting, and is informed by UK-based evidence and expert opinion.
- The model is transparent and reproducible.
- It captures the diagnostic phase (including diagnostic yield, device test performance) and the management phase of AF (treatment with DOACs and its consequences of reduced risk of stroke and increased GI bleeding).

Limitations include:

- There were several assumptions made due to the lack of data. Opinion was sought from clinical experts throughout model development, including ranges on hyper-parameters included in PSA.
- The model assumes independence of test results (that is, an individual's probability of testing positive is independent of previous diagnostic test results).
- In the AF recurrence population, only people with a CHA_2DS_2-VASc score of 1 were included in the modelled population because those at higher risk are assumed to continue to be prescribed a DOAC (NG196), and testing would be of no benefit to the decision to prescribe a DOAC. However, in practice, some patients who report further symptoms of AF following their treatment may be offered further testing in relation to other aspects of their management. This is not captured in the model.
- The model assumes that repeat tests use the same diagnostic tool, with the same associated costs, as the first test. In practice, some patients without a diagnosis of AF and who report ongoing symptoms may progress to more costly investigations, such as implantable loop recorders. The choice of further investigation will depend on the time interval between symptoms and severity of symptoms. This is not captured in the model.
- Rates of adverse events (e.g. strokes, repeat strokes, death from stroke, GI bleeds) were assumed to be constant over time for the modelled cohort. For the undiagnosed palpitations scenario, this is reasonable assumption. But for the AF recurrence scenario, this is a model limitation. For example, as the cohort ages, there will be additional comorbidities which will alter the risks of adverse events; that is, the median CHA_2DS_2-VASc score would increase over time. Including time dependent probabilities into the model would increase its complexity, and would require more extensive systematic review and meta-analysis to identify the effects of ageing on adverse event rates.
- The model did not include secondary outcomes, for example MI, DVT, TIA. This was because data on the treatment effect of a DOAC versus no treatment was lacking in these outcomes for people with AF. It is thus a limitation of the model that it does not include these effects, which could be either beneficial (that is, a DOAC may reduce the risk of a particular AE compared with no treatment), or deleterious (that is, the DOAC may increase the risk of the AE compared with no treatment).

- Cost saving due to stroke avoidance from this economic evaluation is likely to represent a lower estimate due to the following reasons:
    - strokes due to untreated AF and treated AF were given same cost however this is unlikely in clinical practice (clinical experts advised that strokes due to untreated AF are likely more disabling, and more costly to NHS). This would be appropriate in cost-utility analysis.
    - Only medical AF treatment was considered in this economic evaluation due to uncertainty in transition probabilities following surgical (ablation, cardioversion) intervention.
- A range of univariate sensitivity analysis also highlights a number of paradoxical outcomes:
    - Increasing the KardiaMobile test sensitivity results in KardiaMobile being *less* cost saving;
    - Increasing AF prevalence results in KardiaMobile being *less* cost saving (due to faster testing);
    - Increasing the patient wait time for KardiaMobile increases cost savings per patient;

  This highlights the limitation of using a cost-consequence analysis in AF detection, in that the cost of anticoagulation is not outweighed by the cost of strokes avoided. However the use of KardiaMobile does decrease the number of strokes and deaths, therefore the economic model of AF detection devices must include utilities in order to demonstrate the patient benefit.

5.2 Conclusions

The EAC developed a transparent and reproducible model that reflected a simplified view of the diagnostic pathway for two situations. Firstly, symptomatic patients (palpitations), suspected of having AF, who are referred for testing with Holter monitoring or a comparator device, after having a negative 12-lead ECG. Secondly, people who have received interventional treatment for AF who are being tested for recurrence with a Holter monitor or a comparator device. The model included a diagnosis phase and a management phase. The former incorporated diagnostic test performance and the latter incorporated anticoagulation treatment and its consequences. The outcome of the model was the incremental costs

associated with the technology (Kardia Mobile) and standard care (Holter), the number of additional AF cases detected, and the number of strokes saved.

For the undiagnosed palpitations situation, Kardia Mobile was found to be cost saving in all scenarios. The cost saving was modest (base case saving of £13.22 per patient over 2 years, saving 8.3 strokes/100,000 patients tested and 4.4 deaths/100,000 tested) and was driven by both the faster time to diagnostic monitoring (shorter wait time to receive KardiaMobile than Holter monitoring) and the lower cost of the diagnostic phase. For the recurrence situation, Kardia Mobile was found to modestly cost incurring (base case £85.91 per patient over 10 years, saving 212.8 strokes/100,000 patients tested and 115 deaths/100,000 tested).

NICE Guidance NG196 recommends offering a DOAC to people with AF and a CHA_2DS_2-VASc score of 2 or more. However, by an elementary number-needed-to-treat analysis which was independent of diagnostic device and assuming an ideal situation of 100% prevalence, the direct cost of DOACs and their bleeding consequences exceeds the cost of stroke for all CHA_2DS_2-VASc scores over all plausible time horizons. This represents a challenge for novel detectors of AF, such as KardiaMobile, because superiority in AF detection compared with standard care will inevitably lead to increased cost compared with standard care, assuming the parameters take the values assumed in this model. In the situation of undiagnosed palpitations, there is plausible evidence from a large UK RCT (Reed 2019) that KardiaMobile is associated with shorter waiting times (more rapid times to diagnosis) and higher diagnostic yield than Holter monitoring. In detecting AF recurrence there is evidence from diagnostic accuracy studies (*Hermans et al.* 2021) that Kardia Mobile leads to increased AF detection rates. The model presented in this report permits exploration and evaluation of these benefits, including utilities, but the additional cases detected will lead to extra treatment costs which will not outweigh savings in the diagnostic phase.

The model developed by the EAC demonstrated a small cost saving of using KardiaMobile when compared to Holter monitoring (as representative of standard care), confirmed by univariate and PSA in an undiagnosed palpitation population. However the model does demonstrate the clear patient benefit (reduction in strokes and deaths) for which KardiaMobile has increased utility. In detecting AF recurrence, the model developed by the EAC showed that Kardia Mobile was modestly cost incurring over 10 years, but led to a large

reduction in number of strokes and deaths thus confirming the utility of KardiaMobile in this population also.

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Acknowledgements

Ruth Chambers, Ex-Staffordshire clinical lead for technology enabled care services programme, digital workstream and Honorary Professor Keele University, Visiting Professor Staffordshire University.

David Ferguson, Arrhythmia Advanced Nurse Practitioner, University Hospitals Morecambe Bay NHS Foundation Trust

Shouvik Haldar, Consultant Cardiologist and Electrophysiologist, Royal Brompton and Harefield Hospitals

Shona Holding, Cardiovascular Specialist Nurse Practitioner, Affinity care

Kevin McGibbon, Arrhythmia Clinical Nurse Specialist, University Hospitals of North Midlands NHS Trust

Lis Neubeck, Professor of Cardiovascular Health, Edinburgh Napier University.

Matthew Reed, Consultant, NRS Clinician and RCEM Professor of Emergency Medicine, NHS Lothian.

Appendices

Appendix 1– Drummond checklist 1996

Item	Judgement	EAC Comment
Study design		
1* The research question is stated.	Yes	The aim of this work is to develop a cost model that evaluates the costs of diagnosing and managing AF using KardiaMobile for detection and ongoing monitoring, compared with the current standard(s) of care in the NHS in people presenting with undiagnosed palpitations and people who need to monitor AF recurrence post-treatment. The cost model will address the limitations of the current cost models presented to the committee.
2* The economic importance of the research question is stated.	Yes	To assist committee decision at MTAC2.
3* The viewpoint(s) of the analysis are clearly stated and justified.	Yes	The model was developed from the perspective of the NHS England.
4* The rationale for choosing alternative programmes or interventions compared is stated.	Yes	Intervention section 2.4: KardiaMobile-1L
5* The alternatives being compared are clearly described.	Yes	Comparator section 2.5: Holter 24 hour
6* The form of economic evaluation used is stated.	Yes	Cost consequence analysis stated in Section 2
7* The choice of form of economic evaluation is justified in relation to the questions addressed.	Yes	Previous models in AF detection summarised, different approach taken due to screening being out of scope for this economic evaluation. Model structure and parameters informed from clinical input.
Data collection		
8* The source(s) of effectiveness estimates used are stated.	Yes	Source of model parameters in Table 1.
9 Details of the design and results of effectiveness study are given (if based on a single study).	Not applicable	
10 Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	Not applicable	
11* The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Outcomes section 2.6: Excess adverse events including gastro-intestinal bleeding, stroke due to AF and fatal stroke. Single stroke permitted in undiagnosed palpitations model, multiple within AF recurrence model.

Item	Judgement	EAC Comment
12 Methods to value benefits are stated.	Not applicable	Cost consequences – no utility included in model.
13 Details of the subjects from whom valuations were obtained were given.	Yes	Named experts in Acknowledgements section, experts responding to queries listed in Appendix 2.
14 Productivity changes (if included) are reported separately.	Not applicable	
15 The relevance of productivity changes to the study question is discussed.	Not applicable	
16*Quantities of resource use are reported separately from their unit costs.	Yes	Duration and cost of staff time to train patients and to review ECG included in Table 2.
17*Methods for the estimation of quantities and unit costs are described.	Yes	Source of all model parameters and costs provided in Tables 1 and 2 respectively.
18*Currency and price data are recorded.	Yes	Costs described (GBP), section 2.7
19*Details of currency of price adjustments for inflation or currency conversion are given.	Yes	All inflation (and source of inflation) provided in Table 2 where used.
20 Details of any model used are given.	Yes	Model structure (section 2.1) and separate illustrations for undiagnosed palpitations and AF recurrence models.
21 The choice of model used and the key parameters on which it is based are justified.	Yes	Source of all model parameters and costs provided in Tables 1 and 2 respectively.
Analysis and interpretation of results		
22*Time horizon of costs and benefits is stated.	Yes	Time horizon of both models described (section 2.1). Costs tabulated in Table 2.
23 The discount rate(s) is stated.	Yes	*A discounting rate of 3.5% was applied to both modelled populations.*
24 The choice of discount rate(s) is justified.	Yes	Reference to NICE Guide to the methods of technology appraisal 2013.
25 An explanation is given if costs and benefits are not discounted.	Not applicable	
26 Details of statistical tests and confidence intervals are given for stochastic data.	Not applicable	
27 The approach to sensitivity analysis is given.	Yes	Uncertainty analysis section 2.9: univariate, PSA and scenario analysis explored.
28 The choice of variables for sensitivity analysis is justified.	Yes	Hyperparameters included in PSA are summarised in Table 1.

Item	Judgement	EAC Comment
29 The ranges over which the variables are varied are justified.	Yes	PSA distributions summarised in Table 1, largely informed by clinical expert advice.
30 Relevant alternatives are compared.	Yes	NNT analysis added. PSA and utility to be added
31 Incremental analysis is reported.	Yes	Univariate analysis conducted and difference referred to base-case.
32*Major outcomes are presented in a disaggregated as well as aggregated form.	Yes	End state occupancy and total costs broken down in base-case scenario.
33*The answer to the study question is given.	Yes	Key findings in Discussion. PSA and utility added
34*Conclusions follow from the data reported.	Yes	Key findings in Discussion
35*Conclusions are accompanied by the appropriate caveats.	Yes	Strengths and limitations stated section 5.2
* Not justified is not considered an available option		

Appendix 2 – Questions for clinicians (sent 12/08/2021)

1) Two populations will be modelled separately:
    a. Is a 2-year horizon appropriate when modelling patients presenting with undiagnosed palpitations referred for ambulatory monitoring?

#	Response
1	Sorry I don't really understand the question. If you're asking if 2 years is a reasonable time to diagnose palpitations the answer is no, we can do it within 3 months with alivecor
2	Yes I think that's fine.
3	agree
4	If this time scale is to reach diagnosis, using ambulatory monitoring (Holter) then it may take longer than 2 years,,, would be much shorter time frame using kardia
5	YES – this is an appropriate time frame
6	No additional comment
7	Agree [with expert 5]
8	

    b. Is a 20-year time horizon appropriate when modelling patients post-AF treatment who are monitoring for AF recurrence?

#	Response
1	Again I don't understand the question. We may monitor patients for AF recurrence at any time and at any age.
2	Yes I think that's fine/justified.
3	agree
4	High risk of recurrence of AF with days, weeks, months of procedure , or can be 3-4 years later. Within 20 year timeframe, patient may have had repeat procedures done
5	Yes – to be honest there is some date on 5 years post AF ablation and sparse data on 5-10 years post ablation outcomes. 20 years would be excellent but 10 years would also be more than adequate
6	No additional comment
7	Agree [with expert 5] 10 years probably sufficient
8	

2) A KardiaMobile device costs (VAT removed) are £82.50. Previous costs for Holter monitor have included aggregated bundle costs, therefore we are microcosting. Is a device cost of £1400 appropriate for a Holter monitor (as we are unable to identify a device cost on NHS Supply Chain)?

#	Response
1	Yes but there are other factors that come into play, especially the analysis time and the licence required to use the monitoring system, some companies also charge per patient for analysis making holter monitoring a very expensive option when compared to interpreting an alivecor trace
2	I trialled epatch (cardiologic) in 2020 using 20 patches per practice (2 practices) – cost was circa [redacted] each inc VAT(inc patch device/ analysis/report) I trialled zio patch (irhythm) in 2019/20 using 20 patches per practice (3 practices) – cost was circa [redacted] each patient (inc patch device/analysis/report) inc VAT Both patches were worn for up 14 days (ie epatch arrangement can have less days for holter wear)
3	Don't know
4	Approximate cost of a holter is [redacted] Kardia: £82.50 plus VAT
5	Yes – from my sources the holter monitor cost is between [redacted] - [redacted].
6	No additional comment
7	No additional comment
8	

3) In the model we have assumed that patients wait approximately 1 month to receive a KardiaMobile device and 2 months to receive a Holter monitor. Is this broad assumption representative of wait times for diagnostic monitoring in the NHS? (Are wait times longer during COVID, if so how much so?)

#	Response
1	Our average waits at the moment are 2 weeks or less for kardiamobile, 4-6 weeks for a holter monitor, it varies tremendously with staff availability and was worse during the worst peaks of COVID
2	In our pilot practice held the 20 patches from each company & set up patient soon after identified by clinician – eg 1-5 days later; but in COVID times, e-patch/cardiologic devised way to do by sending epatch to patient via post so didn't need to come into surgery for nurse to set up/train patient. So depending on local arrangements, 2 months for holter seems too long.
3	Agree COVID-no change
4	Yes theses timescales similar to a community service COVID has not depayed these timeframes
5	At my trust RBH – patients currently would be able to get a holter done in 2 months. There is probably a lot of variation throughout the UK however.
6	Huge variation across UK
7	Agree huge variation across UK, also depends on where patient referred (i.e. which specialty)
8	

4) We assume it takes a nurse 10 minutes to train patients how to use a Holter monitor and 15 minutes for KardiaMobile device+app. Is this appropriate?

#	Response
1	On average yes, doesn't have to be a nurse, we use band 3 ECG technicians in that role. Those teaching patients about kardiamobile need to be tech savvy and aware of the different platforms that mobile phone companies use, so usually the younger the better!
2	Yes- unless switch to online – as above for holter; and we've produced webinars for patients showing them how to use AliveCor as one of several remote monitoring kits
3	Agree
4	Agree 10mins to set up holter and educate patient Kardia may take longer than 15 mins.we used to book in for 30 min slot: If patient not used to technology or if they have their own device, needs to be set up with email for results to be sent
5	Yes - I would say 10 -15 minutes for Kardia device and app maximum.
6	There would be no training to use a holter monitor. It is applied and removed by a cardiac physiologist. There may be a button to press to record symptoms. The patient will usually have to return to the clinic to get the holter monitor removed. By contrast, patients could post Kardia back. It is intermittent monitoring however, and has to be patient activated. Depending on the individual it could be very quick to demonstrate, but probably safe to assume 15 mins, also requires installation of the app and registration
7	Agree with both comments [experts 5&6], even though Holter applied by CP would still require CP time to train patient? Kardia probably nearer 15 unless app already downloaded by patient before call/visit
8	

5) We have assumed that a single KardiaMobile device is reused every 2 months, and a single Holter monitor is reused every 14 days. Is this appropriate?

#	Response
1	Again very variable, we do give patients kardiamobile for up to 2 months but if we get a diagnosis in the first week it comes back to be used again. A holter can be used for between 1-7 days, is cleaned and can be used on the next day if required.
2	I think you could recycle KardiaMobile every 4 weeks; and the holter query not right- as patch is disposable so all patients in parallel possible.
3	Agree
4	Kardia used every 1-2 months. 'single ' holter has 24 hour turn around for cleaning , eg 24 hour holter turnaround every 2 days, 7 day holter longest duration would also have 24 hour turnaround.

5	Yes – seems reasonable although Kardia Mobile device may be re-used sooner if a diagnosis is made sooner which is one of its strengths – then it is down to hospital logistics as to how quick turnaround is for reuse.
6	Holter monitors are used frequently, maybe every 2-4 days. They have the actual device and then the tapes are separate, usually clinics will have more tapes than devices and these will be retained, while the device is cleaned and reused quickly. Kardia will very much depend on individual need and when or if an abnormal rhythm is detected. Unlike the holter monitor, the rhythm is available in real time and can be viewed remotely
7	We turned around Kardia in 90 days initially in study but in clinic setting it more like 1/12 with some patients who haven't recorded a symptomatic rhythm hanging onto it for 2-3 months. Agree 2 months probably a good average 'wear'
8	

6) The proportion of patients requiring more than 1 diagnostic test within 12 months (i.e. retested) is assumed to be 27% at base case [MTG52 Zio]. We have also assumed in the model that only false negatives will be retested, as they remain symptomatic to warrant further testing. Is both the proportion and the population requiring retesting appropriate?

#	Response
1	I really don't know but that sounds reasonable, I would say we get less false negatives than implied here.
2	Seems so
3	Agree
4	Unsure of stats on this Not sure what is meant by false negatives in this context If patient has recurrent holters with no symptoms and assuming no dysrhythmia, then a kardia would be offered to capture rhythm during symptoms. If no dysrhythmia captured during symptomatic period, then this is a valid result demonstrating symptoms not caused by a dysrhythmia
5	Difficult to quantify - % could be higher but 27% not unreasonable. I think by false negative you mean no arrythmia was found with first test – in which case population is correct.
6	Agree, you would do a retest only if there was a negative first test, but still a high suspicion of arrhythmia, in which case you may test for longer, or consider an implantable loop recorder
7	Agree with above
8	

7) For the AF recurrence population (i.e. patients with previously diagnosed AF who have received surgical/medical treatment, but then undergo diagnostic monitoring for AF

recurrence), all patients are retested to simulate an annual review. For the Holter arm this would mean patients receive a Holter every year. Is this representative of NHS practice?

#	Response
1	Not in our practice, that is quite a wasteful way to approach it. For patients who are symptomatic with their AF a kardiamobile use is invaluable here and we might encourage patients to buy their own if they can afford to. For asymptomatic patients its more difficult but giving someone a kardiamobile for 2 weeks and asking them to do 4-5 traces a day will probably pick up more silent AF than a holter monitor over 24 hours.
2	I can only give primary cae initiated practice- holter use rare – so assume only relevant in secondary care?
3	Agree
4	No, further holter/kardia monitoring would only be needed if symptomatic Pulse check should be done annually and if irregular would lead to a 12 lead ECG
5	Yes generally they would have two holters post ablation treatment but at least one within the year of treatment. Some trusts will just discharge at 3 months and say only come back if there are symptoms.
6	Will vary depending on local policy. Because interpreting a holter requires a cardiac physiologist, it may also depend on staffing levels at local site
7	No additional comment
8	

8) ECG review timings and staffing varies across centres. However for simplification, we have assumed that ECG review time (minutes of specialist nurse) is broadly 1 hour (Band 6 nurse specialist) per patient for Holter monitoring and 30 minutes (Band 6 nurse specialist) per patient for KardiaMobile. We have also assumed that all positive results (i.e. AF detected) will be reviewed by a medical consultant for approximately 5 minutes per patient. Are these timings broadly representative of the NHS?

#	Response
1	I would say less ECG technicians at band 4 and band 5 review our holter for 30 minutes and kardiamobile traces in 15 minutes. Nurse practitioners at band 7 & 8 review the positive results in approx 10 minutes, although we do ring patients to give the results at that time so this can take longer. Other areas vary practice but consultant cardiologists are becoming less involved and few band 6 nurses I would argue interpret the holter/kardia traces, although this may happen more in general practice.
2	As the two types of holter we've tried are analysed by the cardio-analysts in the companies owning holter products, and our extra element asking local consultant cardiologist if he agreed with companies' analysis generated his agreement with one

	extra suggestion but no disagreement for one in 40 patients, then time for nurse is just setting up patient with holter for following 2 weeks- which took up to 20 minutes- from a health care assistant band 3 in our pilots. For KardioMobile's the 400 clinicians to whom we gave KardioMobile over last few years just added to their consultation opportunistically - or to flu vaccination screening clinics to all without AF diagnosis - so I guess took 2-3 minutes in all to do ECG lead one tracing on average. Then if needed review by GP would have been 10 mins- with review tracing/patient history.
3	Agree
4	Probably not up to 1 hour for holter 1 trace from kardia would take 3-5 mins to interpret if a good trace. If multipe tracings sent in one sitting, this will multiply the above . band 6 nurse or equivalent trained HCP can confirm positive results. It is not necessary to have confirmation from consultant or another colleague unless there is uncertainty about the result . it is good practice to seek a second opinion if there is doubt about interpretation
5	Yes although 30 mins for Kardia mobile seems too long – perhaps 15-20 mins.
6	Interpretation of Holter done by cardiac physiologist, probably band 5. It would take 15-30 mins depending on length of holter (24-72 hours). On screen algorithm gives highly sensitive and specific diagnosis of AF in only 30 seconds. If you did want an expert to verify this, they would be able to do a single time point ECG in seconds. It will really depend how many of the kardia mobile ECGs have been recorded by the patient. A usual protocol would be 4 times a day plus any time they feel symptoms. I would think a cardiac physiologist could flip through 1 days ECGs in a few minutes
7	Agree
8	

9) A 68% reduction in strokes was been well documented (HTA by Hobbs et al. 2015), however this risk reduction associated with warfarin. Are you aware of any published evidence stating the risk reduction due to NOAC/DOACs?

#	Response
1	The DOAC companies will be able to help you there as they have both trial and real world evidence, I suspect the percentage is higher with DOACS
2	No, sorry
3	All of the DOACs were equivalent or better than warfarin in their clinical trials for stroke reduction.
4	Each DOAC trial demonstrated equivalent risk reduction in stroke compared to warfarin (ReLy, ROCKET-AF, ARISTOTLR , ENGAGE) In meta-analyses of all four Novel OACs studied in phase III trials for stroke/SE prevention in patients with AF vs.

	warfarin, Novel OACs had a favourable risk-benefit profile[1] Novel OACs reduced stroke vs. warfarin[1,2] Ruff CT et al. Lancet. 2014;383(9921):955–962; 2. Hankey G. Lancet Neurol. 2014;13(2):178–194
5	Yes – have given one example below: Risks of Stroke and Mortality in Atrial Fibrillation Patients Treated With Rivaroxaban and Warfarin Mark Alberts , Yen-Wen Chen , Jennifer H. Lin , Emily Kogan , Kathryn Twyman , Dejan Milentijevic Originally published31 Dec 2019https://doi.org/10.1161/STROKEAHA.119.025554Stroke. 2020;51:549–555
6	Yes there are many and NOACs added to the Essential medicines List in 2019 -Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-World Setting Comparison of Nonvitamin-K Antagonist Oral Anticoagulants Versus Vitamin-K Antagonists for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis. Stroke. 2017 Sep;48(9):2494-2503. doi: 10.1161/STROKEAHA.117.017549. Epub 2017 Jul 17. PMID: 28716982. -Zaidel, E. J., Leng, X., Adeoye, A. M., Hakim, F., Karmacharya, B., Katbeh, A., … Di Cesare, M. (2020). Inclusion in the World Health Organization Model List of Essential Medicines of Non-Vitamin K Anticoagulants for Treatment of Non-Valvular Atrial Fibrillation: A Step Towards Reducing the Burden of Cardiovascular Morbidity and Mortality. Global Heart, 15(1), 52. DOI: http://doi.org/10.5334/gh.608
7	No additional comment
8	

10) Risk of stroke has been determined by CHA_2DS_2-VASc score derived from 7329 patients. However risk drops after score 6 due to small numbers. Is this source of "risk of stroke in AF population" data the most appropriate?

#	Response
1	Yes. Anyone with a CHA2DS2VASc score of 2 is deemed at risk of stroke so going higher is of little value
2	Sorry not familiar with this evidence
3	I would say that most clinicians would assume the risk continues to rise after score 6 as it would seem likely
4	I believe it's the only evidence we have
5	Yes I think so although Helen Williams may be able to point to larger cohorts
6	There are criticisms of CHA2DS2-VASc score but for now it remains in all guidelines, and is the tool most used by HCPs.
7	
8	

11) For the undiagnosed palpitations cohort (time horizon 2 years), we have simplified the model such that patients can only experience 1 stroke. Given low frequency of AF patients experiencing multiple strokes within this short time frame, is this simplification of the model appropriate?

#	Response
1	It depends how you define stroke, do you include TIA's if so people can have multiple TIA's in 2 years
2	Seems okay
3	Agree
4	Not sure we can say how many strokes patients may have in this cohort. They could have a severe stroke or one or multiple TIAs (mini strokes)
5	Yes
6	This study suggests that cumulative recurrence rate for ischemic strokes was 5.4% at 1 year, 11.3% at 5 years, and 14.2% at the end of follow-up. 30% of all ischaemic strokes are thought to be due to AF. Therefore if you have a stroke you have at least a 5% chance of having another one in 2 years Khanevski AN, Bjerkreim AT, Novotny V, Naess H, Thomassen L, Logallo N, Kvistad CE; NOR-STROKE study group. Recurrent ischemic stroke: Incidence, predictors, and impact on mortality. Acta Neurol Scand. 2019 Jul;140(1):3-8. doi: 10.1111/ane.13093. Epub 2019 Apr 11. PMID: 30929256; PMCID: PMC6594196.
7	No additional comment
8	

12) For the AF recurrence cohort (time horizon 20 years). What proportion of patients will have multiple strokes?

#	Response
1	I don't know and I doubt its been studied in detail
2	Sorry not familiar with this evidence
3	There will be a very low proportion on multiple strokes. Repeat monitoring will help with symptom treatment but the patient will be anticoagulated according to their CHADSVASc score, so if the risk is high, anticoagulation will continue even if recurrent AF is not documented.
4	Difficult to say but those at high risk will still be taking oral anticoagulation to reduce their risk of stroke and it should reduce the severity of stroke if it occurs.
5	I honestly don't know answer to this question.
6	If you say that AF patients have a five fold increased risk of stroke, stroke incidence in the UK is currently 113000 PA of which around 30% will be AF related, also see above study
7	No additional comment
8	

13) In the model we have simplified adverse events and included a single stroke state. Is this assumption reasonable? We have also included the same cost of stroke resulting from treated and untreated AF, is this assumption reasonable?

#	Response
1	I would say that untreated AF related strokes can be more disabling than those that are treated, you would be best asking a stroke physician's opinion on that
2	Sorry not familiar with this evidence but I'd have thought that as those having stroke related to AF get more severe strokes/least chance of recovery need to be clear these comparisons don't include an undiagnosed AF when had an earlier stroke few years before etc
3	Agree
4	YES As mentioned above, severity of stroke may be reduced if taking OAC
5	Yes but cost of stroke likely to be higher with untreated AF as stroke may be more severe.
6	Agreed, AF strokes more likely fatal or severely debilitating and cost is approx. 3 times as high in first year
7	Sounds reasonable for clinical review
8	

14) Due to device instructions for use, KardiaMobile categorisation of ECG cannot be used for diagnosis of AF. Therefore every ECG requires clinical review. Sensitivity and specificity of Holter monitoring is fixed at 80% and 80%. Sensitivity and specificity of KardiaMobile will be varied between 80% and 100% in deterministic sensitivity analysis. Are these ranges appropriate?

#	Response
1	I wouldn't give kardiamobile 100%, maybe 90%
2	I don't think you can use a generic specificity & sensitivity rating for 'holter' when there are several different types; and they vary between 2-14 days wear, with many diagnoses of AF via holter being on days 3-4. KardioMobile also needs to define if sensitivity/specificity relate to lead 1 or lead 6 types; and if it is opportunistic one minute screening; or patient using it for say 7 days on/off
3	Agree
4	Kardia sensitivity 96.6%, and specifity of 94% 24 hour holter in a clinical study demonstrated a 93% sensitivity and 96.8% specificty
5	Yes this is probably reasonable.
6	Yes, this is ok
7	Sounds reasonable
8	

15) Prevalence of AF in undiagnosed palpitation cohort varied between 6.5% and 18.2%. Prevalence of AF in the AF recurrence cohort varied between 25.2% and 60.9%. These were sources from the literature identified in the company clinical submission. Are these ranges appropriate?

#	Response
1	This is so difficult to analyse, in the general population (all ages including children) it will vary between 2-4%. However we know AF is age related and so if you target high risk populations for screening of AF in undiagnosed palpitations you get approx 10%. The variability in the the recurrence cohort will again vary with age and depend who you target and when and whether or not they are symptomatic and treated appropriately, the complexities are huge so as an average that figure of between 25 – 60% may be right, to me its almost irrelevant.
2	Sorry not familiar with this evidence
3	Agree
4	Prevalance of AF is strongly age dependent: 0.1-2% age under 55; 3.8% >60 yrs; 10% >80 year olds Unable to comment on prevalence in AF recurrent cohort
5	Yes
6	Yes
7	In IPED, 125 patients received and used the device for 3 months. Number of recordings ranged from 0-177, median was 0 (IQR 0-6) and mean 8 in 3 months
8	

16) For the undiagnosed palpitation population, the number of uses per KardiaMobile device over its 2 year lifetime in the basecase is 12 uses (patients keep for 2 months before used by another patient) and will vary between 5 uses (patients keep for 4.8 months) and 25 uses (patients keep for 1 month) in sensitivity analysis. Is this range appropriate?

#	Response
1	Its reasonable yes
2	You seem to assume AliveCor device not being used opportunistically by clinicians; when they might try it on 5 patients a week say. I'd have thought lending to a patient would be for up to one month; as much PAF happens every few days
3	Agree
4	Yes this seems appropriate… timeline will be dictated by frequency of symptoms and when /if a diagnosis is made … maybe with days or months of prescribing kardia.

5	These use figures seem too low. I think most patients would use it much more than these figures – also you seem have the 4.8 months and 1 months the wrong way round. My estimate for 1 month would be 15-20 uses and for 4.8 months 50-60 uses (patients will likely use less the longer they have it especially if does not yield a diagnosis).
6	As above, most studies have reported 4 times a day plus with symptoms. Assuming the patient keeps for 2 weeks (again based on study populations) that would be 56 uses minimum over a 2 week period
7	No additional comment
8	

17) For the undiagnosed palpitation population, the number of uses per Holter device over its 5 year lifetime in the basecase is 130 uses (each patient keeps for 14 days before used by another patient) will vary up to 912 uses (patient keeps for 48 hours only). Is this range appropriate?

#	Response
1	yes
2	As above – holter patches disposable – so no idea what your data relates to
3	Agree
4	Holter monitoring is normally set up for 24hr, 48hr, 72hr and longest is 7 days.
5	Yes seems appropriate.
6	Yes, agree, but see my comments before about reuse of devices
7	No additional comment
8	

18) For the AF recurrence group, treatment by ablation and cardioversion are excluded as the transition probabilities following these treatments to AF recurrence, subsequent stroke and fatal stroke are unknown. Is this simplification of the model reasonable?

#	Response
1	No because most patient with symptomatic AF recurrence will be treated with cardioversion/abaltion. If you're only talking about asymptomatic patients then yes.
2	Sorry not familiar with this evidence
3	Agree
4	Unsure of this, however patients are still assessed for their risk of stroke post treatment and OAC is recommended in those with high stroke risk, whether they stay in normal rhythm or not due to risk of recurrent AF
5	Post AF ablation there is quite a lot of data on AF recurrence is known and there is data on subsequent stroke from the CABANA (ref below). Not sure about fatal stroke. Perhaps too simplified if this data is available.

	Packer DL , Mark DB , Robb RA , et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding and cardiac arrest among patients with atrial fibrillation. JAMA 2019;321:1261–1274.
6	No additional comment
7	No additional comment
8	

Appendix 3 – Output from model

Introduction

The aim of this project was to develop an economic model to determine the cost consequences of using the KardiaMobile device in detecting atrial fibrillation when used in two distinct populations: 1) those with undiagnosed palpitations referred for ambulatory ECG, and 2) those with previously diagnosed AF who received treatment and use KardiaMobile to monitor recurrence.

Undiagnosed palpitations

Model structure

The structure of the model is shown in Figure 1. Each patient began in state A (awaiting a test) and moved to one of states B, C, D, or E after their test depending on their AF status and the performance of the test. Those with positive tests were assumed to be offered an oral anticoagulant (DOAC), and those with AF were assumed to be at increased risk of stroke. A proportion of patients with undetected AF (state E) were assumed to be referred for re-testing (state G) if their symptoms recurred. Patients waiting for a test and who had AF (the prevalence proportion in A and everyone in G) were assumed to be at risk of stroke (transitions A to J and G to J).

For states in which more than one type of event was possible (A, C, E, G, J, K), the per-cycle event probability was calculated from the sum of the individual event rates, and the conditional probabilities of the transitions were assumed to be equal to the proportions of individual rates to the total event rate. This assumed that no more than one event per person per cycle was possible.

The time horizon was 2 years, the cycle length was 3 months and the annual discount rate was 3.5%.

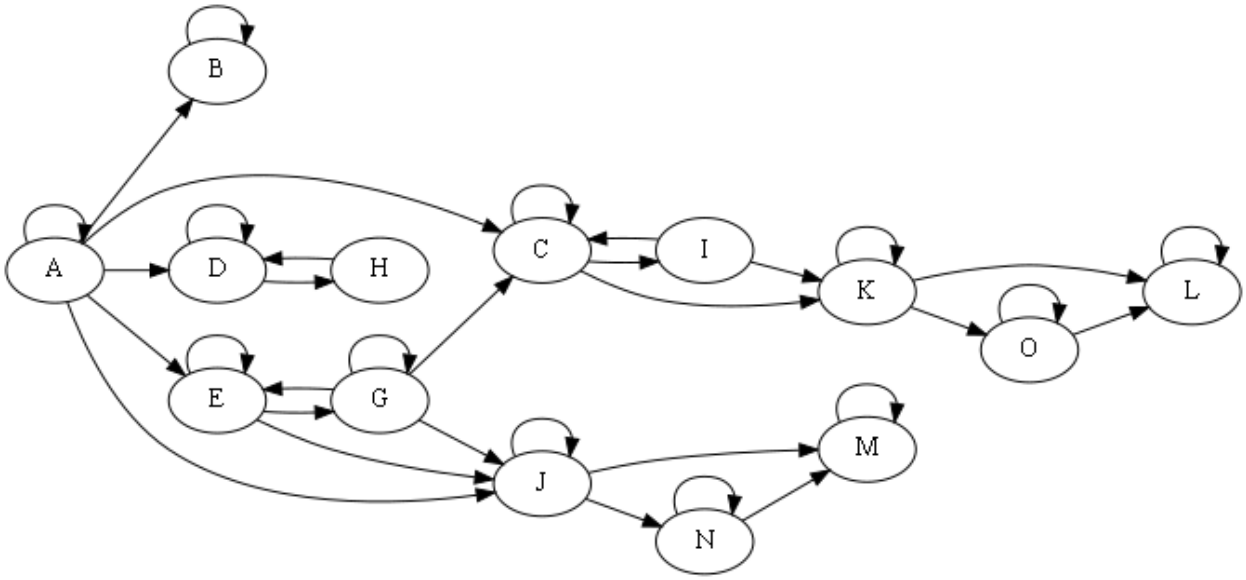

Figure 1. Markov model for undiagnosed palpitations A: Symptomatic and awaiting test; B: No AF, not treated (TNs and those with no diagnosis); C: AF, treated (TPs); D: No AF, treated (FPs); E: AF, not treated (FNs and those with no diagnosis); G: AF, awaiting re-test; H: GI bleed (FP); I: GI bleed (TP); J: AF stroke (FN and those with no diagnosis); K: AF stroke (TP); L: Dead (TP); M: Dead (FN); N: Subsequent stroke (FN); O: Subsequent stroke (TP)

Population

The eligible population were people with symptoms of AF (palpitations) who had tested negative on 12 lead ECG and were referred for Holter or similar test. The prevalence of AF in this population was assumed to be constant (6.5%). People were considered to have additional risk factors for stroke that would result in CHA_2DS_2-VASc scores of 1 to 6 if AF were diagnosed. The prevalence of CHA_2DS_2-VASc scores in the population was assumed to follow Lip.[1]

Patients at low risk (CHA_2DS_2-VASc score of 0 for male, or 1 for female) are not recommended to take anticoagulation therapy because the annual stroke risk for this group is considered to be zero.[1] The modelled population did not include those with CHA_2DS_2-VASc scores of 0. For those with a score of 1, 50% of patients were assumed to receive no DOAC (representing female patients), and 50% were assumed to take a DOAC (representing male patients) because NICE Guideline NG196 recommends clinicians to consider anticoagulation for male patients with a score of 1.[2]

Utilities

The utility of stroke (states J, K, N, O) was 0.728.[3] The utility of a GI bleed (states H and I) was 1 because bleeding was considered as an acute event which fully resolves and has no effect on health-related quality of life.[3] The utility of states L and M was zero. All other states had a utility of 1.

Treatment costs

The annual incremental occupancy costs of states A (awaiting a test), B (true negative), E (false negative), L and M (dead) were considered to be zero. The annual cost of treatment with a DOAC (states C, I, D, H, K), assumed as apixaban, was 1.90 GBP per day.[4] The annual incremental occupancy cost of stroke (states J and K) was 1183.77 GBP.[5] The cost of stroke in the first year was modelled as a transition cost (transitions from E to J, C to K and I to K), which incurred a one-off cost of 12932.68 GBP[5] for all patients who made such a transition (this is the annual cost of first year of stroke minus the annual cost in subsequent years). Subsequent strokes were assumed to incur the same cost as a first stroke (transitions J to N and K to O) and the annual occupancy cost assumed to be the same in states N and O as states J and K. The cost of a GI bleed, due to taking a DOAC (assumed as apixaban), was 784.84 GBP[6] and was accrued as a cost for each transition from D to H and C to I. The states, their occupancy costs (per year) and utilities are shown in Table 1. The transition costs (excluding diagnostic-related costs) are shown in Table 2.

Table 1. Model states, occupancy costs (GBP) and utilities

State	Cost	Utility
A: Symptomatic and awaiting test	0	1
B: No AF, not treated (TNs and those with no diagnosis)	0	1
C: AF, treated (TPs)	693.5	1
D: No AF, treated (FPs)	693.5	1
E: AF, not treated (FNs and those with no diagnosis)	0	1
G: AF, awaiting re-test	0	1
H: GI bleed (FP)	693.5	1
I: GI bleed (TP)	693.5	1
J: AF stroke (FN and those with no diagnosis)	1183.77	0.73
K: AF stroke (TP)	1183.77	0.73

L: Dead (TP)	0	0
M: Dead (FN)	0	0
N: Subsequent stroke (FN)	1183.77	0.73
O: Subsequent stroke (TP)	1183.77	0.73

Table 2. Transition costs, excluding diagnostic costs (GBP).

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
A	0	0	0	0	0	0	0	0	12933	0	0	0	0	0
B	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	785	0	12933	0	0	0	0
D	0	0	0	0	0	0	785	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0	12933	0	0	0	0	0
G	0	0	0	0	0	0	0	0	12933	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	12933	0	0	0	0
J	0	0	0	0	0	0	0	0	0	0	0	0	12933	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	12933
L	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0
O	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Diagnostic costs

The per-use cost of a diagnostic device was modelled as the cost to purchase a device (82.5 GBP for Kardia Mobile, 1755 GBP for a Holter recorder), divided by the number of times a device is issued in its lifetime (16 for Kardia Mobile, 1000 for Holter). For each diagnostic episode, it was assumed that the device would be issued by a Band 4 technician who would instruct the patient in its use (15 minutes for Kardia Mobile and 10 minutes for Holter). It was assumed that a Band 4 technician would review the recordings once per issue (20 minutes for Kardia Mobile and 60 minutes for Holter). The hourly cost of a Band 4 technician is 34 GBP.

In the case of tests that were positive after nurse review, it was assumed that the trace would be reviewed by a nurse specialist (5 minutes) at an hourly rate of 50 GBP, and that the patient would be offered a cardiology outpatient appointment (154.43 GBP).

People with AF referred for a re-test (those in state G) were assumed to be subject to the same waiting time as those in state A and those with AF to have the same stroke risk as those in state A (noting that all people in state G have AF). The costs associated with retesting (G to C and G to E) were assumed to incur the same costs as transitions A to C and A to E.

Adverse event probabilities

The rate of untreated stroke varies with CHA_2DS_2-VASc score[1] (0.013 per patient per year for a score of 1; 0.022 for a score of 2; 0.032 for a score of 3; 0.04 for a score of 4; 0.067 for a score of 5; 0.098 for a score of 6). These rates apply to transitions from states E to J (people with undiagnosed AF). The risk of stroke in those taking warfarin relative to no treatment is 0.68[7] and the risk in those taking apixaban versus those taking warfarin is 0.81.[8] These relative risks were combined (0.55) and applied

to the untreated risk of stroke to estimate the rate of stroke in those with AF and taking apixaban compared with those left untreated (C to K and I to K). The annual rate of recurrent stroke was modelled as 11.1%;[9] transitions J to N and K to O.

The risk of death, following a stroke, after 1 year was assumed to be 36.5%.[10] This was assumed to be relative to warfarin, and for those untreated, a hazard ratio of 1.178 [DG35] was applied, and for those treated with a DOAC, a hazard ratio of 0.89 applied [DG35].

The rate of major bleeding (ISTH criteria) in people taking apixaban for AF was reported as 2.13%/year (0.0213 per patient per year) from the ARISTOTLE study.[11] In total 327 events were observed from 9120 patients with a median follow-up of approximately 1.8 years. This rate applies to those in states C and D who are treated with apixaban and transition to states I and H respectively.

Number needed to treat analysis

For the annual stroke rates predicted by CHA_2DS_2-VASc scores and the treatment effect of taking a DOAC (apixaban) the number needed to treat (NNT) can be calculated. For example, for a CHA_2DS_2-VASc score of 2, the annual rate of stroke in people with untreated AF is 2.2%. The treatment effect is 0.55 (see previous section), and the expected annual rate of stroke in people with AF taking a DOAC is 1.21%. The NNT to save one stroke per year is 101.2. The annual cost of treatment is the annual cost of a DOAC (693.50 GBP) plus the annual cost of treating GI bleeds in the proportion affected (0.0213 times 784.84; 16.72 GBP), a total of 710.22 GBP. The annual cost of treatment needed to save one stroke per year for those with CHA_2DS_2-VASc score of 2 is therefore 71,867 GBP. This exceeds the cost of stroke in the first year (12,933 GBP).

The NNT for those with different risk factors are 171.2 (score of 1), 69.6 (score of 3), 55.7 (score of 4), 33.2 (score of 5), 22.7 (score of 6). The annual costs needed to save one stroke in those with different risk factors are 121,621 GBP (score of 1), 49,408 GBP (3), 39,527 GBP (4), 23,598 GBP (5), 16,133 GBP (6). For all CHA_2DS_2-VASc scores combined, assuming the prevalences reported by Lip,[1] the NNT is 67.3 and the annual cost needed to save one stroke is 47,767 GBP.

All these exceed the first year cost of stroke, and without further modelling it is clear that a technology which detects, and leads to the treatment of, more AF cases will be cost incurring compared with standard care over a short time horizon (one or two years), assuming that treatment is with a DOAC. Note that the number needed to treat and the cost needed to treat will be greater if anticoagulants are given to those without AF (false positives) and not given to those with AF (false negatives).

Diagnostic test performance and rates

It was assumed that the mean waiting time for a test (state A to state A) was 1 month (Kardia Mobile) and 1.5 months (Holter). The proportion of people who were false negatives being re-tested within 12 months was assumed to be 0.27. The diagnostic test performance of Kardia Mobile was 80% (sensitivity) and 80% (specificity) and Holter was 80% (sensitivity) and 80% (specificity) .

Diagnostic yield

The relative proportions of people transitioning to states B, C, D and E from state A in each cycle depends on the diagnostic yield of the device, its diagnostic performance (sensitivity and specificity), and the prevalence of AF. Figure 2 is the probability tree illustrating the situation. For those in whom a sympomatic rhythm is captured, the performance of the subsequent rhythm classification leads to

the conventional TP, FN, FP and TN outcomes (leafs C, E, D, B in the upper branch). For those in whom the device yields no symptomatic rhythm, the number with AF left untreated (leaf E, lower branch) or those without AF and correctly untreated (leaf B in the lower branch) depends on the AF prevalence only.

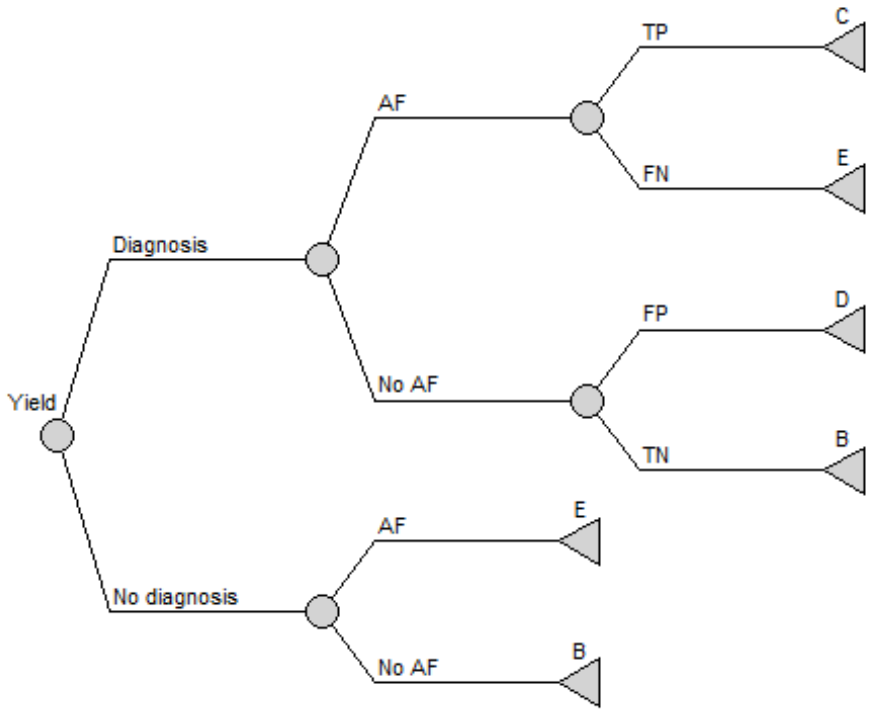

Figure 2. Probability tree for diagnosis. B: No AF, no anticoagulation; C: AF, anticoagulation; D: No AF, anticoagulation; E: AF, no anticoagulation;

For modelling outcomes, the two E leafs (AF, no anticoagulant) are equivalent and are combined to give the relative probability of transitioning to state E. Similarly for the two B leafs (no AF, no anticoagulant).

For this model, the diagnostic yield for the Kardia Mobile device was assumed to be 100% and 100% for Holter devices.[12] With the prevalence of AF and diagnostic performance described, the relative proportions who transition from state A for Kardia Mobile are: 0.748 (B), 0.052 (C), 0.187 (D), 0.013 (E) and for Holter the relative proportions are: 0.748 (B), 0.052 (C), 0.187 (D), 0.013 (E). For re-testing (transitions G to C and G to E) all patients are assumed to have AF, and the transition probability from G to C is the per-cycle probability of re-testing multiplied by the sensitivity of the test and the diagnostic yield.

KardiaMobile

Example scenario: risk score of 2

Here, we consider a single scenario to illustrate a single run of the model. In this case, we include patients with two stroke risk factors having a test with the KardiaMobile device (i.e. people with a CHA_2DS_2-VASc score of 2 if they are diagnosed with AF). The per-cycle transition probabilities are shown in Table 3 and the per-cycle transition costs in Table 4.

Table 3. Per-cycle probabilities (%), Kardia Mobile, risk score 2.

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
A	4.98	71.07	4.94	17.77	1.24	0	0	0	0.01	0	0	0	0	0
B	0	100	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	99.16	0	0	0	0	0.53	0	0.31	0	0	0	0
D	0	0	0	99.47	0	0	0.53	0	0	0	0	0	0	0
E	0	0	0	0	91.92	7.55	0	0	0.53	0	0	0	0	0
G	0	0	75.9	0	18.97	4.95	0	0	0.18	0	0	0	0	0
H	0	0	0	100	0	0	0	0	0	0	0	0	0	0
I	0	0	99.69	0	0	0	0	0	0	0.31	0	0	0	0
J	0	0	0	0	0	0	0	0	87.35	0	0	10.05	2.6	0
K	0	0	0	0	0	0	0	0	0	92.02	7.69	0	0	0.29
L	0	0	0	0	0	0	0	0	0	0	100	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	100	0	0
N	0	0	0	0	0	0	0	0	0	0	0	10.19	89.81	0
O	0	0	0	0	0	0	0	0	0	0	7.8	0	0	92.2

Table 4. Transition costs (GBP), Kardia Mobile, risk score 2.

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
A	0	25	184	184	25	0	0	0	12933	0	0	0	0	0
B	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	785	0	12933	0	0	0	0
D	0	0	0	0	0	0	785	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0	12933	0	0	0	0	0
G	0	0	184	0	25	0	0	0	12933	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	12933	0	0	0	0
J	0	0	0	0	0	0	0	0	0	0	0	0	12933	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	12933
L	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0
O	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 5. Markov trace, Kardia Mobile, risk score 2.

Years	A	B	C	D	E	G	H	I	J	K	L	M	N	O	Cost
0	10000	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.25	498	7107	494	1777	124	0	0	0	1	0	0	0	0	0	99.78
0.5	25	7461	515	1856	120	9	9	3	2	2	0	0	0	0	47.41
0.75	1	7478	521	1860	112	9	10	3	2	3	0	0	0	0	44.7
1	0	7479	527	1860	105	9	10	3	2	4	0	1	0	0	44.33
1.25	0	7479	532	1860	98	8	10	3	3	6	1	1	0	0	44.06
1.5	0	7479	537	1860	92	8	10	3	3	7	1	1	0	0	43.78

1.75	0	7479	541	1860	86	7	10	3	3	8	2	1	0	0	43.49
2	0	7479	545	1860	80	7	10	3	3	9	2	2	0	0	43.2

The Markov trace for 8 cycles of the simulation for CHA2DS2-VASc score of 2, across a time horizon of 2 years is given in Table 5 (rounded to whole patients). The total incremental cost per patient was 410.76 GBP. Note that the number of people with AF (states C, I, K, O, L and E, G, J, N, M) is 651, which is the number expected (10000 times prevalence; 650).

Example scenario: females with a risk score of 1

In this scenario, patients are not given anticoagulants, do not incur DOAC costs, do not benefit from reduced risk of stroke, and are not at increased risk of GI bleed (Tables 6, 7, 8). The total incremental cost per patient was 83.66 GBP.

Table 6. Per-cycle probabilities (%), Kardia Mobile, risk score 1, females.

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
A	4.98	71.07	4.94	17.77	1.24	0	0	0	0.01	0	0	0	0	0
B	0	100	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	99.67	0	0	0	0	0	0	0.33	0	0	0	0
D	0	0	0	100	0	0	0	0	0	0	0	0	0	0
E	0	0	0	0	92.13	7.55	0	0	0.31	0	0	0	0	0
G	0	0	75.95	0	18.99	4.96	0	0	0.1	0	0	0	0	0
H	0	0	0	100	0	0	0	0	0	0	0	0	0	0
I	0	0	99.67	0	0	0	0	0	0	0.33	0	0	0	0
J	0	0	0	0	0	0	0	0	87.35	0	0	10.05	2.6	0
K	0	0	0	0	0	0	0	0	0	92	7.69	0	0	0.31
L	0	0	0	0	0	0	0	0	0	0	100	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	100	0	0
N	0	0	0	0	0	0	0	0	0	0	0	10.19	89.81	0
O	0	0	0	0	0	0	0	0	0	0	7.8	0	0	92.2

Table 7. Model states and occupancy costs

State	Cost
A: Symptomatic and awaiting test	0
B: No AF, not treated (TNs and those with no diagnosis)	0
C: AF, treated (TPs)	0
D: No AF, treated (FPs)	0
E: AF, not treated (FNs and those with no diagnosis)	0
G: AF, awaiting re-test	0
H: GI bleed (FP)	0
I: GI bleed (TP)	0
J: AF stroke (FN and those with no diagnosis)	1184
K: AF stroke (TP)	1184
L: Dead (TP)	0
M: Dead (FN)	0

N: Subsequent stroke (FN)	1184
O: Subsequent stroke (TP)	1184

Table 8. Transition costs (GBP), Kardia Mobile, risk score 1, females.

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
A	0	25	184	184	25	0	0	0	12933	0	0	0	0	0
B	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	12933	0	0	0	0
D	0	0	0	0	0	0	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0	12933	0	0	0	0	0
G	0	0	184	0	25	0	0	0	12933	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	12933	0	0	0	0
J	0	0	0	0	0	0	0	0	0	0	0	0	12933	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	12933
L	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0
O	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 9. Markov trace, Kardia Mobile, risk score 1, females.

Years	A	B	C	D	E	G	H	I	J	K	L	M	N	O	Cost
0	10000	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.25	498	7107	494	1777	124	0	0	0	1	0	0	0	0	0	60.13
0.5	25	7461	517	1865	120	9	0	0	1	2	0	0	0	0	5.604
0.75	1	7479	524	1870	113	10	0	0	1	3	0	0	0	0	3.056
1	0	7479	529	1870	106	9	0	0	1	5	0	0	0	0	2.956
1.25	0	7479	534	1870	99	8	0	0	2	6	1	0	0	0	2.967
1.5	0	7479	539	1870	93	8	0	0	2	7	1	1	0	0	2.977
1.75	0	7479	543	1870	87	7	0	0	2	8	2	1	0	0	2.984
2	0	7479	547	1870	82	7	0	0	2	10	2	1	0	0	2.986

Base case: combining different stroke risks

Table 10 shows the combined Markov trace for six cohorts of people with CHA_2DS_2-VASc scores of 1 to 6 (N=6938; 422 with score of 1 half of whom were female, 1230 with a score of 2, 1730 with a score of 3, 1718 with a score of 4, 1159 with a score of 5 and 679 with a score of 6). The total incremental cost was 422.64 GBP and the incremental utility was 1.9986037.

Table 10. Markov trace for Kardia Mobile, combined risks.

Years	A	B	C	D	E	G	H	I	J	K	L	M	N	O	Cost
0	6938	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.25	345	4930	343	1233	86	0	0	0	2	0	0	0	0	0	100.1
0.5	17	5176	356	1288	83	6	6	2	2	2	0	0	0	0	49.1
0.75	1	5188	359	1290	77	7	7	2	3	4	0	0	0	0	46.43

1	0	5188	362	1290	72	6	7	2	3	6	0	1	0	0	46.04
1.25	0	5188	365	1290	67	6	7	2	4	8	1	1	0	0	45.73
1.5	0	5188	367	1290	62	5	7	2	4	9	2	1	0	0	45.42
1.75	0	5188	368	1290	58	5	7	2	4	11	2	2	0	0	45.09
2	0	5188	370	1290	54	5	7	2	4	12	3	2	0	0	44.74

Standard care (Holter Monitor)

Example scenario: risk score of 2

Here, we consider a single scenario to illustrate a single run of the model. In this case, we include patients with two stroke risk factors having a test with a Holter device (i.e. people with a CHA_2DS_2-VASc score of 2 if they are diagnosed with AF). The per-cycle transition probabilities are shown in Table 11 and the per-cycle transition costs in Table 12. Note that the proportion remaining in state A is greater than for Kardia Mobile, reflecting the increased waiting time for a test.

Table 11. Per-cycle probabilities (%), Holter, risk score 2.

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
A	13.5	64.7	4.5	16.2	1.1	0	0	0	0	0	0	0	0	0
B	0	100	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	99.2	0	0	0	0	0.5	0	0.3	0	0	0	0
D	0	0	0	99.5	0	0	0.5	0	0	0	0	0	0	0
E	0	0	0	0	91.9	7.5	0	0	0.5	0	0	0	0	0
G	0	0	69	0	17.3	13.5	0	0	0.2	0	0	0	0	0
H	0	0	0	100	0	0	0	0	0	0	0	0	0	0
I	0	0	99.7	0	0	0	0	0	0	0.3	0	0	0	0
J	0	0	0	0	0	0	0	0	87.4	0	0	10.1	2.6	0
K	0	0	0	0	0	0	0	0	0	92	7.7	0	0	0.3
L	0	0	0	0	0	0	0	0	0	0	100	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	100	0	0
N	0	0	0	0	0	0	0	0	0	0	0	10.2	89.8	0
O	0	0	0	0	0	0	0	0	0	0	7.8	0	0	92.2

Table 12. Transition costs (GBP), Holter, risk score 2.

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
A	0	41	200	200	41	0	0	0	12933	0	0	0	0	0
B	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	785	0	12933	0	0	0	0
D	0	0	0	0	0	0	785	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0	12933	0	0	0	0	0
G	0	0	200	0	41	0	0	0	12933	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	12933	0	0	0	0
J	0	0	0	0	0	0	0	0	0	0	0	0	12933	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	12933
L	0	0	0	0	0	0	0	0	0	0	0	0	0	0

M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
O	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 13. Markov trace, Holter, risk score 2.

Years	A	B	C	D	E	G	H	I	J	K	L	M	N	O	Cost
0	10000	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.25	1353	6467	450	1617	112	0	0	0	2	0	0	0	0	0	105.6
0.5	183	7342	507	1827	119	8	9	2	2	1	0	0	0	0	52.85
0.75	25	7460	519	1855	112	10	10	3	3	3	0	0	0	0	45.66
1	3	7476	525	1859	105	10	10	3	3	4	0	1	0	0	44.49
1.25	0	7478	531	1860	99	9	10	3	3	5	1	1	0	0	44.1
1.5	0	7479	535	1860	92	9	10	3	3	7	1	1	0	0	43.8
1.75	0	7479	540	1860	86	8	10	3	3	8	2	2	0	0	43.51
2	0	7479	544	1860	81	8	10	3	3	9	2	2	0	0	43.21

The Markov trace for 8 cycles of the simulation for CHA2DS2-VASc score of 2, across a time horizon of 2 years is given in Table 13. The total incremental cost was 423.18 GBP.

Base case: combining different stroke risks

Table 14 shows the combined Markov trace for six cohorts of people with CHA_2DS_2-VASc scores of 1 to 6 (N=6938; 422 with score of 1 half of whom were female, 1230 with a score of 2, 1730 with a score of 3, 1718 with a score of 4, 1159 with a score of 5 and 679 with a score of 6). The total incremental cost was 435.87 GBP and the incremental utility was 1.9985254.

Table 14. Markov trace for Holter, combined risks.

Years	A	B	C	D	E	G	H	I	J	K	L	M	N	O	Cost
0	6938	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.25	938	4486	312	1122	78	0	0	0	2	0	0	0	0	0	106.5
0.5	127	5093	351	1267	82	6	6	2	3	2	0	0	0	0	54.53
0.75	17	5175	358	1287	77	7	7	2	4	4	0	1	0	0	47.41
1	2	5186	361	1290	72	7	7	2	4	6	0	1	0	0	46.22
1.25	0	5188	364	1290	67	6	7	2	4	8	1	1	0	0	45.8
1.5	0	5188	366	1290	62	6	7	2	4	9	1	2	0	0	45.46
1.75	0	5188	368	1290	58	5	7	2	5	11	2	2	0	0	45.13
2	0	5188	369	1290	54	5	7	2	5	12	3	3	1	0	44.78

Comparison of tests

Univariate sensitivity analysis

Base case

Table 15. Base case.

Device	Cost	QALY	Strokes.per.100k	Deaths.per.100k
Kardia Mobile	422.64	1.998604	325.5	79.2
Holter	435.87	1.998525	333.8	83.6

Difference	-13.22	0.000078	-8.3	-4.4

KardiaMobile sensitivity

Table 16. Diagnostic sensitivity.

Sensitivity	Cost	QALY	Strokes.per.100k	Deaths.per.100k
0.8	422.64	1.998604	325.5	79.2
0.85	425.55	1.998641	317.8	76.3
0.9	428.39	1.998679	310.2	73.5
0.95	431.16	1.998716	302.7	70.7

AF prevalence

Table 17a. AF prevalence.

Device	Prevalence	Cost	QALY	Strokes.per.100k	Deaths.per.100k
Holter	3.25	383.59	1.999263	166.9	41.8
Holter	6.5	435.87	1.998525	333.8	83.6
Holter	13	540.37	1.997052	667.3	167.2
Holter	26	749.12	1.994109	1333.4	334.1
Holter	52	1165.64	1.988239	2662	667
KardiaMobile	3.25	370.63	1.999302	162.8	39.6
KardiaMobile	6.5	422.64	1.998604	325.5	79.2
KardiaMobile	13	526.62	1.997208	650.9	158.3
KardiaMobile	26	734.4	1.99442	1301	316.5
KardiaMobile	52	1149.31	1.988853	2598.7	632.2

Table 17b. Effect of AF prevalence on difference (KM-Holter).

Prevalence	Cost	QALY	Strokes.per.100k	Deaths.per.100k
3.25	-12.95	0.000039	-4.1	-2.2
6.5	-13.22	0.000078	-8.3	-4.4
13	-13.75	0.000156	-16.4	-8.8
26	-14.72	0.000311	-32.4	-17.6
52	-16.34	0.000615	-63.2	-34.8

Number of uses

Table 18a. Number of uses of KardiaMobile.

nUses	Cost	QALY	Strokes.per.100k	Deaths.per.100k
4	438.04	1.998604	325.5	79.2
5	433.93	1.998604	325.5	79.2
8	427.78	1.998604	325.5	79.2
16	422.64	1.998604	325.5	79.2
52	419.09	1.998604	325.5	79.2

Table 18b. Number of uses of Holter.

nUses	Cost	QALY	Strokes.per.100k	Deaths.per.100k

730	436.51	1.998525	333.8	83.6
1000	435.87	1.998525	333.8	83.6
1825	435.08	1.998525	333.8	83.6

Repeat testing

Table 19a. Probability of retest.

Device	P.retest	Cost	QALY	Strokes.per.100k	Deaths.per.100k
Holter	0.15	435.24	1.99851	338.5	84.7
Holter	0.2	435.5	1.998517	336.5	84.2
Holter	0.27	435.87	1.998525	333.8	83.6
KardiaMobile	0.15	422.03	1.998587	330.5	80.3
KardiaMobile	0.2	422.29	1.998594	328.4	79.9
KardiaMobile	0.27	422.64	1.998604	325.5	79.2

Table 19b. Effect of retest probability on difference (KM-Holter).

P.retest	Cost	QALY	Strokes.per.100k	Deaths.per.100k
0.15	-13.21	0.000077	-7.9	-4.3
0.2	-13.22	0.000078	-8.1	-4.4
0.27	-13.22	0.000078	-8.3	-4.4

Waiting time

Table 20. Waiting time.

Device	wait.days	Cost	QALY	Strokes.per.100k	Deaths.per.100k
Holter	28.1	439.29	1.998618	324.1	78.4
Holter	42.1	436.74	1.998542	332	82.7
Holter	56.2	432.88	1.998479	338.7	86.3
KardiaMobile	14	422.99	1.998714	313.9	73.1
KardiaMobile	28.1	422.93	1.998618	324.1	78.4
KardiaMobile	42.1	420.4	1.998542	332	82.7

Probabilistic sensitivity analysis

Base case

The prevalence of AF was modelled with Be(8,116) (mean 0.0645161, 95%CI 0.028 to 0.114). The waiting time for KardiaMobile was modelled with Ga(18.778,1.621) (mean 30.4, 95%CI 18.3 to 45.7) days. The waiting time for Holter was modelled with Ga(42.25,1.081) (mean 45.7, 95%CI 32.9 to 60.4) days. The cost per use for KardiaMobile was modelled with Ga(5.587,0.923) (mean 5.2, 95%CI 1.8 to 10.2). From 1000 simulations, the mean cost saving (KM minus Holter) was -13.34 GBP, 95% confidence interval -18.78 to -6.49 GBP.

AF recurrence

Model structure

The model structure is identical to the one used for undiagnosed palpitations (Figure 1). The time horizon is 10 years, the cycle time is 1 year and the discount rate is 3.5%.

Population

The eligible population are people with symptoms of AF (palpitations) who have have had previous interventional treatment for AF and are at risk of recurrence. The prevalence of AF in this population was assumed to be constant (25.2%). In this population, most are routinely given anticoagulation, and a decision to start anticoagulation only applies to people with a CHA_2DS_2-VASc scores of 1. We assume that all patients (male and female) with a score of 1 are eligible for a DOAC in this scenario.

Treatment costs

The treatment costs are identical to the ones used for the undiagnosed palpitations model.

Diagnostic costs

The diagnostic costs are identical to the ones used for the undiagnosed palpitations model.

Adverse event probabilities

The adverse event probabilities are identical to the ones used for the undiagnosed palpitations model, apart from the following:

- The risk of stroke recurrence is calculated from the 10 year cumulative probability of recurrence (39.2%).[9]
- The mortality rate from stroke is calculated from the cumulative rate after 5 years (60.1%).[10]

Diagnostic test performance and rates

These are identical to the ones used in the undiagnosed palpitations model. In the Holter arm, it is assumed that there are no retests; this is achieved by setting the retest rate to zero.

Diagnostic yield

This is modelled identically to the undiagnosed palpitations model.

Kardia Mobile

For people with a CHA_2DS_2-VASc score of 1 the per-cycle transition probabilities are shown in Table 21 and the per-cycle transition costs in Table 22.

Table 21 Per-cycle probabilities (%), Kardia Mobile, recurrence.

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
A	0	59.8	20.2	15	5	0	0	0	0	0	0	0	0	0
B	0	100	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	97.2	0	0	0	0	2.1	0	0.7	0	0	0	0
D	0	0	0	97.9	0	0	2.1	0	0	0	0	0	0	0
E	0	0	0	0	72.1	26.8	0	0	1.1	0	0	0	0	0
G	0	0	79.9	0	20	0	0	0	0.1	0	0	0	0	0
H	0	0	0	100	0	0	0	0	0	0	0	0	0	0
I	0	0	99.3	0	0	0	0	0	0	0.7	0	0	0	0
J	0	0	0	0	0	0	0	0	76.6	0	0	19	4.4	0
K	0	0	0	0	0	0	0	0	0	84.6	14.7	0	0	0.6
L	0	0	0	0	0	0	0	0	0	0	100	0	0	0

M	0	0	0	0	0	0	0	0	0	0	0	100	0	0
N	0	0	0	0	0	0	0	0	0	0	0	19.5	80.5	0
O	0	0	0	0	0	0	0	0	0	0	15.1	0	0	84.9

Table 22. Transition costs (GBP), Kardia Mobile, recurrence.

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
A	0	25	184	184	25	0	0	0	12933	0	0	0	0	0
B	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	785	0	12933	0	0	0	0
D	0	0	0	0	0	0	785	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0	12933	0	0	0	0	0
G	0	0	184	0	25	0	0	0	12933	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	12933	0	0	0	0
J	0	0	0	0	0	0	0	0	0	0	0	0	12933	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	12933
L	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0
O	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 23. Markov trace, Kardia Mobile, recurrence.

Years	A	B	C	D	E	G	H	I	J	K	L	M	N	O	Cost
0	10000	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	0	5982	2015	1496	504	0	0	0	3	0	0	0	0	0	316.9
2	0	5982	1959	1464	363	135	32	42	8	14	0	1	0	0	258.5
3	0	5982	2054	1465	289	97	31	41	10	26	2	2	0	0	257.5
4	0	5982	2115	1465	227	77	31	43	11	37	6	4	1	0	253.5
5	0	5982	2160	1465	179	61	31	44	11	47	12	6	1	0	248.3
6	0	5982	2192	1465	141	48	31	45	11	55	18	9	1	1	242.3
7	0	5982	2214	1465	111	38	31	46	10	63	27	11	2	1	235.7
8	0	5982	2228	1465	88	30	31	46	9	69	36	13	2	1	228.7
9	0	5982	2235	1465	69	24	31	47	8	75	46	15	2	1	221.6
10	0	5982	2238	1465	55	19	31	47	7	79	58	17	2	2	214.3

The Markov trace for 10 cycles of the simulation for CHA2DS2-VASc score of 1, across a time horizon of 10 years is given in Table 23. The total incremental cost per patient was 2477.09 GBP. Note that the number of people with AF (states C, I, K, O, L and E, G, J, N, M) is 2522, which is the number expected (10000 times prevalence; 2520).

Holter

For people with a CHA_2DS_2-VASc score of 1 the per-cycle transition probabilities are shown in Table 24 and the per-cycle transition costs in Table 25.

Table 24. Per-cycle probabilities (%), Holter, recurrence.

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
A	0	59.8	20.1	14.9	5	0	0	0	0	0	0	0	0	0
B	0	100	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	97.2	0	0	0	0	2.1	0	0.7	0	0	0	0
D	0	0	0	97.9	0	0	2.1	0	0	0	0	0	0	0
E	0	0	0	0	98.7	0	0	0	1.3	0	0	0	0	0
G	0	0	79.8	0	20	0	0	0	0.2	0	0	0	0	0
H	0	0	0	100	0	0	0	0	0	0	0	0	0	0
I	0	0	99.3	0	0	0	0	0	0	0.7	0	0	0	0
J	0	0	0	0	0	0	0	0	76.6	0	0	19	4.4	0
K	0	0	0	0	0	0	0	0	0	84.6	14.7	0	0	0.6
L	0	0	0	0	0	0	0	0	0	0	100	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	100	0	0
N	0	0	0	0	0	0	0	0	0	0	0	19.5	80.5	0
O	0	0	0	0	0	0	0	0	0	0	15.1	0	0	84.9

Table 25. Transition costs (GBP), Holter, recurrence.

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
A	0	41	200	200	41	0	0	0	12933	0	0	0	0	0
B	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	785	0	12933	0	0	0	0
D	0	0	0	0	0	0	785	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0	12933	0	0	0	0	0
G	0	0	200	0	41	0	0	0	12933	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	12933	0	0	0	0
J	0	0	0	0	0	0	0	0	0	0	0	0	12933	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	12933
L	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0
O	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 26. Markov trace, Holter, recurrence.

Years	A	B	C	D	E	G	H	I	J	K	L	M	N	O	Cost
0	10000	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	3	5980	2014	1495	504	0	0	0	4	0	0	0	0	0	334.5
2	0	5982	1959	1464	497	0	32	42	10	14	0	1	0	0	259.9
3	0	5982	1946	1465	491	0	31	41	14	26	2	3	1	0	252
4	0	5982	1932	1465	484	0	31	41	17	36	6	5	1	0	244.1
5	0	5982	1918	1465	478	0	31	41	19	45	11	9	2	0	236.2
6	0	5982	1904	1465	472	0	31	40	21	52	18	13	2	1	228.3

7	0	5982	1891	1465	466	0	31	40	22	58	26	17	3	1	220.5
8	0	5982	1877	1465	460	0	31	40	23	63	34	22	3	1	212.8
9	0	5982	1864	1465	454	0	31	39	24	67	44	27	4	1	205.2
10	0	5982	1851	1465	448	0	31	39	24	70	54	32	4	2	197.8

The Markov trace for 10 cycles of the simulation for CHA2DS2-VASc score of 1, across a time horizon of 10 years is given in Table 26. The total incremental cost per patient was 2391.18 GBP. Note that the number of people with AF (states C, I, K, O, L and E, G, J, N, M) is 2523, which is the number expected (10000 times prevalence; 2520).

Comparison

Univariate sensitivity analysis

Base case

Table 27. Base case.

Device	Cost	QALY	Strokes.per.100k	Deaths.per.100k
Kardia Mobile	2477.09	9.956278	1640.9	745.2
Holter	2391.18	9.950311	1853.8	860.2
Difference	85.91	0.005968	-212.8	-115

KardiaMobile sensitivity

Table 28. Diagnostic sensitivity.

Sensitivity	Cost	QALY	Strokes.per.100k	Deaths.per.100k
0.8	2477.09	9.956278	1640.9	745.2
0.85	2519.48	9.956963	1627.8	732.1
0.9	2559.07	9.957624	1615.6	719.6
0.95	2596.03	9.958262	1604.3	707.7

AF prevalence

Table 29a. AF prevalence.

Device	Prevalence	Cost	QALY	Strokes.per.100k	Deaths.per.100k
Holter	13	1837.86	9.974361	956.5	443.8
Holter	25.2	2391.18	9.950311	1853.8	860.2
Holter	52	3605.9	9.897511	3823.5	1774.3
KardiaMobile	13	1874.48	9.977442	846.6	384.5
KardiaMobile	25.2	2477.09	9.956278	1640.9	745.2
KardiaMobile	52	3800.28	9.909807	3385	1537.2

Table 29b. Effect of AF prevalence on difference (KM-Holter).

Prevalence	Cost	QALY	Strokes.per.100k	Deaths.per.100k
13	36.62	0.003081	-109.9	-59.4
25.2	85.91	0.005968	-212.8	-115
52	194.38	0.012295	-438.5	-237

Number of uses

The effect of changing the number of uses per patient of each KardiaMobile device is shown in Table 30. The number of strokes, number of deaths and QALY are as per the base case. Costs are compared with the Holter device for the base case.

Table 30. Number of uses of KardiaMobile.

nUses	KardiaMobile.Cost	Holter.Cost	Cost.Difference
16	2477.09	2391.18	85.91
52	2473.49	2391.18	82.31
500	2472.05	2391.18	80.87

Repeat testing

Table 31a shows the outcomes as the probability of retesting changes for Kardia Mobile, and Table 31b shows the differences in outcome compared with the base case for Holter monitoring.

Table 31a. Probability of retest.

Device	P.retest	Cost	QALY	Strokes.per.100k	Deaths.per.100k
KardiaMobile	0.15	2443.23	9.954501	1699.8	780.2
KardiaMobile	0.2	2459.15	9.955314	1671.3	764
KardiaMobile	0.27	2477.09	9.956278	1640.9	745.2
Holter	0	2391.18	9.950311	1853.8	860.2

Table 31b. Effect of retest probability on difference (KM-Holter).

P.retest	Cost	QALY	Strokes.per.100k	Deaths.per.100k
0.15	52.05	0.004191	-153.9	-80
0.2	67.96	0.005003	-182.4	-96.2
0.27	85.91	0.005968	-212.8	-115

Probabilistic sensitivity analysis

Base case

The prevalence of AF was modelled with Be(29,86) (mean 0.2521739, 95%CI 0.177 to 0.335). The waiting time for KardiaMobile was modelled with Ga(18.778,1.621) (mean 30.4, 95%CI 18.3 to 45.7) days. The waiting time for Holter was modelled with Ga(42.25,1.081) (mean 45.7, 95%CI 32.9 to 60.4) days. The per-use cost KardiaMobile was modelled with Ga(5.587,0.923) (mean 5.2, 95%CI 1.8 to 10.2). From 1000 simulations, the mean cost saving (KM minus Holter) was 85.93 GBP, 95% confidence interval 55.70 to 123.02 GBP.

Report details

Author: “Andrew J. Sims, Kim Keltie” Report generated: Tue Sep 28 10:31:58 2021

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

EAC economic evaluation of KardiaMobile for detecting atrial fibrillation factual check

Please find enclosed the assessment report prepared for this assessment by the EAC economic evaluation of KardiaMobile for detecting atrial fibrillation.

You are asked to check the assessment report from Newcastle External Assessment Centre to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by **midday** (12pm), **24 June 2021** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC economic evaluation report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website.

21 September 2021

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
page 10 in the base case scenario the EAC has assumed that the sensitivity and specificity are the same for both KardiaMobile and Holter and that the diagnostic yield is the same for both	This is not a correct assumption for the base-case analysis. We would refer to it as a “worst-case” analysis. We suggest higher sensitivity and specificity for KardiaMobile compared to Holter, according to the results of clinical studies.	There are some points that the EAC should consider: 1- KardiaMobile's (KM) added value to healthcare is that KM can detect more AF cases in a shorter time than Holter. Many studies have reported this, and we are not aware of any study that shows Holter has the same, or higher, diagnostic yield than KM. Taking this assumption for the base-case ignores the value of KM, and existing evidence from published studies. 2- A base-case analysis usually refers to the **most likely** or preferred set of assumptions and input values. It is not transparent how EAC decided that the same sensitivity and specificity for KM and Holter is the **most likely** assumption. This is not in line with multiple clinical studies which show that more AF cases are detected with KM.	Thank you for your comment. The clinical evidence reports AF on a per-ECG basis (not a per-patient). All evidence suggest that KardiaMobile detects more AF, however there is no evidence to confirm that each diagnosis is correct. The EAC acknowledges that the base-case represents the most robust data. All uncertainties have been addressed in sensitivity analysis (e.g. increased diagnostic sensitivity was altered in univariate analysis). However the EAC is unable to comment on specificity compared with Holter monitoring.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 18: Proportion of people having more than 1 diagnostic test within 12 months (27%) A rate of 27% applied to both KardiaMobile and Holter monitoring arms.	This is not a correct assumption. The proportion of people having more than one round of monitoring should be lower in the KM arm of the model, based on the difference between AF detected cases with KM vs Holter.	This assumption has not taken into account the value of KM in that it leads to higher and faster detection of AF cases. This assumption also results in the addition of unnecessary costs in the KM arm. Therefore, this assumption underestimates the potential cost-saving of KM compared to Holter monitoring. Again, this can be defined as a “worst-case” analysis, where the EAC use the higher value of a range (15-27%) for the base-case analysis.	Thank you for your comment. The model accounts for this effect. Because retesting only applies to (27% of) false negatives, in scenarios where the test sensitivity of KardiaMobile exceeds the test sensitivity of the comparator, there will be a smaller proportion of people moving to the false negative (AF, untreated) state in the KardiaMobile arm. Therefore, fewer people are retested. The effect of this is explored in sensitivity analysis.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 28: Patients requiring additional diagnostic monitoring (retesting) will undergo monitoring with the same device again (that is, those using KardiaMobile will use KardiaMobile again, those using Holter monitoring will use Holter again).	This is not an accurate assumption based on the current care pathway in the NHS and (NICE Final Scope, 2021) for this economic evaluation. An average costs of other monitoring procedures should be applied for re-tested cases in both arms	Other diagnostic approaches may be used after Holter monitoring which are more expensive than Holter. This assumption underestimates the potential cost-saving of KM when it can detect more AF cases in the first round of AF detection, and there is no need for subsequent AF detections. Again, this can be defined as a “worst-case” analysis.	Thank you for your comment. Only a small number of patients have retesting (27% of false negatives), and has little impact on results. As there are no robust data to demonstrate the proportions of patients having different diagnostic monitoring, and in order to remove additional uncertainty in the model, the EAC removed the possibility of retesting with different devices from the model (this simplification was confirmed as appropriate by clinical experts).

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
page 28: KardiaMobile the published clinical evidence does confirm the ability for KardiaMobile to identify more cases of AF than standard care (which included Holter monitoring). Therefore the specificity of KardiaMobile has been fixed at 80%, however variable sensitivity and diagnostic yield have been incorporated into the model. These will be explored further within the sensitivity analysis.	This is not a correct assumption. We suggest higher sensitivity and specificity for KardiaMobile compared to Holter, according to the results of clinical studies.	See issue 1.	See response to comment 1.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 36: Table 13: Base-case model results from undiagnosed **palpitations** population.	The Table title should be corrected (AF recurrence).		Thank you for your comment. This has been amended.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 36: This model represents the ease of use and accessibility of using KardiaMobile to monitor AF recurrence post-treatment, however does result in a small cost expenditure of only £85.91 per patient across a 10-year period. The increase is a direct consequence of KardiaMobile detecting more AF and thus incurring additional treatment (DOAC) costs which do not offset the cost from stroke prevention (due to low risk of stroke) which was highlighted in early NNT analysis.	This interpretation can be changed if the above issues were addressed in the model. We suggest modification of input variable based on clinical studies.	We think this interpretation results from cumulative underestimations of potential cost-saving of KM vs. Holter based on the use of identical sensitivity and specificity for both arms, and similar re-testing rates. Moreover, two questions are raised here: 1- How the model estimates the difference in the proportion of patients with AF in the base-case analysis when: ***a:*** *the model uses the same prevalence for both arms* ***b:*** *the model uses the same sensitivity and specificity for both arms (80%)* ***c:*** *the proportion of patients with repeat monitoring are identical in both arms (27%).* For how long are there undetected cases in both arms? Did the model estimate a proportion of patients with undetected AF over 10 years? Or from a certain year, the AF detected (on treatment) patients would be the same in both arms?	Thank you for your comment. Due to lack of data the diagnostic accuracy is assumed to be the same in both arms in the base-case. The only difference is shorter wait time for testing with KardiaMobile, therefore AF is detected earlier, treatment is offered faster, and there is reduction in the number of stroke. The wait time for testing is included in the model. Each patient starts in a holding area and the rate at which they go to AF detected/undetected is dependent upon the mean wait time assigned. To note that if sensitivity of KardiaMobile is increased, then more AF is detected however more anticoagulation costs are accrued, and these do not offset the stroke costs. Therefore increasing sensitivity increases costs as well as utilities.

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 12: A simplification of this was incorporated into the standard care arm of the AF recurrence model as a single round of monitoring within one year post-treatment. As such further rounds of retesting were only applicable for the KardiaMobile arm (represented by the red arrow in Figure 1b) and not the standard care (Holter monitoring) arm.	This simplification does not provide a fair comparison between KM and Holter. Both arms should follow identical conditions for a fair comparison.	If experts believe that only one Holter per year would be enough for patients with a chance of AF recurrence, then this should be applied to KM as well. Therefore, re-testing only after KM results in an overestimation in costs in the KM arm.	Thank you for your comment. The clinical experts noted variable practice with regards to AF monitoring post-treatment. One single round of retesting after 12 months was deemed appropriate post-treatment by the majority of clinical experts. However the long-term use of KardiaMobile is beneficial for patients, with the ability to capture recurrence of AF and frequency of arrhythmias. However long-term use also requires clinical review of ECG (which incurs additional cost) hence its inclusion in the model.